Advanced
Organic Chemistry

Books by

G. W. Wheland

THE THEORY OF RESONANCE AND ITS APPLICATION TO ORGANIC CHEMISTRY

ADVANCED ORGANIC CHEMISTRY, *Second Edition*

Advanced Organic Chemistry

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Second Edition

New York · John Wiley & Sons, Inc.
London · Chapman & Hall, Limited

CHAPTERS 1–10 COPYRIGHTED AS
Syllabus for Advanced Organic Chemistry 321
BY
THE UNIVERSITY OF CHICAGO, 1946

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Syllabus for Advanced Organic Chemistry 322
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SECOND EDITION
SECOND PRINTING, NOVEMBER, 1949

PRINTED IN THE UNITED STATES OF AMERICA

Preface

A student who takes a second course in organic chemistry should not be satisfied with merely memorizing a number of additional isolated facts. He should instead strive also to improve his understanding of the subject as a whole, and to develop a more mature attitude toward it. In particular, he should become familiar with the relationships which exist among the innumerable facts, and he should complete at least the first step toward mastering the theoretical basis of the science. In this book, I have presented the material which is, in my opinion, best suited to the needs of such a student. The book is therefore neither a large introductory textbook nor a monograph on some highly specialized topic, nor even a collection of short monographs on several different, more or less unrelated, topics. It is instead a textbook for a course in advanced organic chemistry; it is designed for students who have had previous training in both elementary organic chemistry and elementary physical chemistry.

The primary guiding and unifying principle of the book is the structural theory in its broadest sense. This one theory underlies the whole of organic chemistry; its different aspects are discussed in the various chapters. Throughout the book, considerable stress is laid upon the theoretical and empirical generalizations that have been found to be most widely applicable; the treatment, however, is kept as concrete and as precise as possible, and frequent references are made to the limitations of the so-called "general reactions." Accordingly, the convenient, but often misleading, use of the letter R is reduced to a minimum; hence, the compounds and reactions which are employed as illustrative examples are in most instances explicitly stated. Although it has not been my intention to deal exhaustively with reaction kinetics as such, I have ordinarily discussed the information that is now available in regard to the mechanisms of the reactions considered. Moreover, I have made a serious (even though not an entirely successful) attempt to provide clear, logical, and mutually consistent definitions of the technical terms that are used. The reader is, of course, assumed to be already familiar with the more elementary facts and theories which are discussed in all modern introductory textbooks of organic and of physical chemistry; consequently, although these facts and theories cannot be entirely ignored, they are not stressed, except in so far as they may profitably be reviewed from a more advanced and more critical point of view.

It is to be expected that many students will wish more information regarding some specific subjects than is contained in this book. Fairly complete references are therefore given to the original literature, to comprehensive review articles, and to monographs. In order, however, that the number of footnotes may be reduced to a reasonable figure, references are not ordinarily given for data that are listed in *Beilsteins Handbuch der organischen Chemie*.

I wish at this time to thank Professors James K. Senior, Henry Taube, Wilbert H. Urry, and Frank H. Westheimer for their invaluable help, inspiration, and advice; Mr. Andrew D. Suttle for his assistance in reading stencils for the earlier mimeographed edition of this book; and the University of Chicago Bookstore both for its cooperation in the publication of this earlier edition and for its permission to use copyrighted material from it. I wish also to acknowledge with thanks that Table 3·1 is here reproduced by permission of Professors W. F. Luder and S. Zuffanti; that, in Chapters 4–9, many passages (which are too numerous to list) are reprinted by permission of the *Encyclopædia Britannica* from my articles Isomerism and Stereochemistry; that Figure 9·2 is here reproduced by permission of Professor L. Ruzicka and the Society of Chemical Industry; that Chapter 11 is based entirely upon a memorandum which was prepared for me by Professor Frank H. Westheimer; and that the translation of the "S. C. H. Windler" letter in Section 15·6 is adapted, with permission, from an earlier translation by Dr. H. B. Friedman.

Since I realize that it is hardly possible for this book to be entirely free either from misprints or from still more serious errors, I will appreciate corrections and criticisms from its readers.

G. W. WHELAND

Chicago, Illinois
June, 1949

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1.

Some Fundamental Concepts

1·1 Introduction. This first chapter is devoted to a critical examination of a few of the fundamental concepts that will be employed throughout the book. The purpose of this examination is not so much to reveal the "true" or "correct" interpretations of these concepts, whatever they may be, as to call attention to the complexity of even the most familiar ideas of chemistry which "everyone understands" but which practically no one ever takes the trouble to define precisely and unambiguously. It will be found that the attempt to define these ideas encounters great difficulties—difficulties which are in no way lightened by the fact that, in many instances, chemists have never reached general agreement as to just what the desired precise meanings are. No claim therefore is made that the definitions formulated in this chapter (and on numerous further occasions in subsequent chapters) are the best and most logical ones that can be devised, or even that they represent the views of all organic chemists. The maximum claim that can be made for them is that they provide a convenient compromise between the desire, on the one hand, to achieve complete precision and self-consistency, and, on the other hand, to adhere as closely as possible to common usage, to the extent that a common usage can be said to exist. In those instances, of which there are several, in which the definitions either leave room for ambiguity or depart considerably from common usage, or both, an attempt will be made to give the reader proper warning.

1·2 Organic Chemistry. The historical reasons which led to the adoption of the word "organic" as a description of the particular branch of chemistry with which this book is concerned are well known. Moreover, the fact that those historical reasons soon lost their validity as the doctrine of "vital force" fell into disrepute is also well known. (See the following paragraph.) Nevertheless, the division of chemistry into "organic" and "inorganic" has continued to be useful, and so has been retained. At the present time, of course, the distinction between organic and inorganic compounds is based not upon their origin in living or nonliving matter, respectively, but rather upon their elementary composition. The most common statement of the distinction which is encountered nowadays is that a substance is organic if it contains carbon, and is inorganic if it does not. Although this statement is probably as nearly satisfactory as any that can be formulated simply, it is still not completely adequate. On the one hand, it classifies elementary carbon, carbon dioxide, and the metal carbonates, for example, as organic, although these substances have been found to be most conveniently grouped with the inorganic substances. Moreover, it classifies molecular hydrogen, water, and ammonia, for example, as inorganic, although an organic chemist might possibly wish to claim them as the simplest paraffin, the simplest alcohol, and the simplest amine, respectively, just as he claims formaldehyde as the simplest aldehyde.

The abandonment of the doctrine of "vital force" presents an interesting example of chemical mythology.[1] It is at present a widely held belief that in 1828 Wöhler synthesized urea from ammonium cyanate;[2] that, by thus preparing an organic substance from an inorganic one, he conclusively proved the nonexistence of any essential difference between organic and inorganic matter; and that the formerly current doctrine of vital force was therefore immediately abandoned by all competent chemists. This belief, which apparently stems from a statement made by Hofmann[3] many years later on the occasion of Wöhler's death, is not, however, entirely correct. At the time of Wöhler's work, no method had as yet been devised for the preparation of either ammonia or cyanic acid from the elements (or from any other definitely inorganic substances); instead, these compounds could then be made only from such typically organic materials as horns, hoofs, or blood. Consequently, Wöhler did not, in the strictest sense, synthesize urea at all (i.e., he did not make it from the elements); moreover, he did not even show that this compound can be prepared from inorganic substances. (The first naturally occurring organic compound that was made artificially from the elements is usually said[1] to have been acetic acid.[4]) These limitations were explicitly recognized by Wöhler, who therefore did not claim either that he had synthesized urea or that his preparation disproved the theory of vital force. There is no evidence that his contemporaries assigned any deeper significance to his work than he himself did; indeed, for a number of years after 1828, many of the leading chemists of the day continued to speak of vital force as an unquestioned fact. Not until the middle of the nineteenth century, or perhaps even later, was the doctrine gradually brought into disrepute by the slow accumulation of chemical knowledge.

Although the usual definition of organic chemistry is completely unambiguous, it does not (as was seen above) always agree perfectly with the way in which the term is actually used in practice, and it sometimes draws a sharp distinction where relatively little chemically important difference exists. A further peculiarity of the definition in question is that it assigns to carbon a unique role which is not shared by any of the

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[1] Cf. D. McKie, *Nature* **153**, 608 (1944).

[2] F. Wöhler, *Ann. Physik* [2] **12**, 253 (1828); *Ann. chim.* [2] **37**, 330 (1828).

[3] A. W. Hofmann, *Ber.* **15**, 3127, 3152 (1882).

[4] H. Kolbe, *Ann.* **54**, 145 (1845).

remaining elements. There is, for example, no separate branch of chemistry which deals exclusively with the compounds of boron, or of zirconium, or of the like. Why then is carbon so honored? A common explanation offered is that carbon forms a much greater number of compounds than does any other element, so that the number of organic compounds reported in the chemical literature is several times as large as is that of all the inorganic compounds combined. This explanation is often supplemented by the further one that the existence of such a tremendous number of carbon compounds is due to the unique ability of carbon atoms to form long chains. Thus, although carbon chains of more than a hundred atoms have been prepared, and have been found to be quite stable, the longest nitrogen chain that is at present known is composed of only eight atoms,[5] and any compound containing it is very unstable.

A consideration of the question whether carbon does indeed possess the unique properties attributed to it will be both interesting and instructive. In the first place, it is probably not true that there are more known compounds of carbon than of any other element. Although there are undoubtedly more organic than inorganic compounds, nevertheless, nearly all the organic substances contain hydrogen as well as carbon (the formula index of *Beilsteins Handbuch der organischen Chemie* lists only about 400 compounds not containing hydrogen), and a very large number of the inorganic compounds contain hydrogen too. It appears rather likely, therefore, that the compounds of hydrogen outnumber those of carbon by a wide margin. A different way of viewing the situation is suggested by Table 1·1, in which are listed the numbers of known binary compounds R_mQ_n, where R is O, Cl, F, and H; and Q is an element of the first short period. The figure given for the hydrides of carbon is doubtless much too low because it is complete only through 1919. The remaining figures, however, are more nearly up to date and should be fairly accurate. From the first row of the table, carbon is seen to be by no means unusual in its ability to form oxides; in fact, there are fewer known oxides of carbon than there are of nitrogen. From the second row, carbon is seen to be somewhat, but not extraordinarily, superior to any of the other first-period elements in its ability to form chlorides. Here, however, it should be noted that several of the chlorides included in this list were poorly characterized by their discoverers and may not actually exist, and also that the relatively large number of reported carbon chlorides can be considered merely to reflect the enormous number of hydrocarbons from which they can conveniently be made. From the

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[5] For example, 1,3,6,8-tetraphenyloctazatriene $C_6H_5{-}N{=}N{-}N(C_6H_5){-}N{=}N{-}N(C_6H_5){-}N{=}NC_6H_5$ [A. Wohl and H. Schiff, *Ber.* **33**, 2741 (1900)].

TABLE 1·1

NUMBERS OF KNOWN BINARY COMPOUNDS R_mQ_n

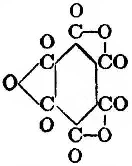
Q R	Li	Be	B	C	N	O	F
O	2[a]	1[b]	1[c]	5[d]	8[e]	3[f]	2[g]
Cl	1[h]	1[i]	2[j]	37[k]	2[l]	6[m]	2[n]
F	1[o]	1[p]	1[q]	40[r]	3[s]	2[g]	1[t]
H	1[u]	0	6[v]	>2000[w]	5[x]	2[y]	1[z]

[a] Li_2O and Li_2O_2.

[b] BeO.

[c] B_2O_3.

[d] CO, CO_2, carbon suboxide $O{=}C{=}C{=}C{=}O$, pentacarbon dioxide $O{=}C{=}C{=}C{=}C{=}C{=}O$ [A. Klemenc and G. Wagner, *Ber.* **70,** 1880 (1937)], and mellitic anhydride



[e] N_2O, NO, N_2O_2, N_2O_3, NO_2, N_2O_4, N_2O_5, and NO_3.

[f] O_2, O_3, and O_4. In regard to the last one of these substances, see G. N. Lewis, *J. Am. Chem. Soc.* **46,** 2027 (1924).

[g] OF_2 and O_2F_2.

[h] LiCl.

[i] $BeCl_2$.

[j] BCl_3 and B_2Cl_4. Evidence for the existence of at least two additional boron chlorides has been obtained by H. I. Schlesinger and coworkers (private communication).

[k] Too numerous to list. Cf. the formula indexes in *Beilsteins Handbuch der organischen Chemie* and in the abstract journals.

[l] NCl_3 and ClN_3.

[m] Cl_2O, ClO, ClO_2, ClO_3, Cl_2O_6, and $(ClO_4)_x$. The last of these substances is possibly the dimer Cl_2O_8.

[n] ClF and ClF_3.

[o] LiF.

[p] BeF_2.

[q] BF_3.

[r] Too numerous to list. Cf. A. V. Grosse and G. H. Cady, *Ind. Eng. Chem.* **39,** 367 (1947).

[s] NF_3, FN_3, and N_2F_2. For the last two substances, see J. F. Haller, Doctoral Dissertation, Cornell University, 1942, and also S. H. Bauer, *J. Am. Chem. Soc.* **69,** 3104 (1947).

[t] F_2.

[u] LiH.

[v] B_2H_6, B_4H_{10}, B_5H_9, B_5H_{11}, B_6H_{10}, and $B_{10}H_{14}$.

[w] Too numerous to list. The figure given here is certainly much too small since it was obtained from the formula index of *Beilsteins Handbuch der organischen Chemie,* which is complete only through 1919.

[x] NH_3, $H_2N{-}NH_2$, HN_3, $NH_4{}^+N_3{}^-$, and $H_2N{-}NH_3{}^+N_3{}^-$.

[y] H_2O and H_2O_2.

[z] Hydrogen fluoride is here considered to be one compound; however, it probably consists, in the gaseous state, of a mixture of HF, $(HF)_2$, $(HF)_3$, and so on. Cf. G. Briegleb, *Z. physik. Chem.* **B51,** 9 (1941); R. A. Oriani and C. P. Smyth, *J. Am. Chem. Soc.* **70,** 125 (1948).

third row of the table, the ability of carbon to form fluorides appears to be little, if any, greater than its ability to form chlorides. There is, however, an important difference which exists between the two types of halide, but which is not brought out in the table; although the number of known carbon chlorides has increased only slowly during the past fifty years, hardly any of the carbon fluorides were known until after about 1940.[6] It can, therefore, be expected that the fluorides will soon outnumber the chlorides by a much greater margin than they do now. (See also below.) Finally, from the last row of the table, carbon is seen to be little short of phenomenal in its ability to form hydrides (i.e., hydrocarbons); in fact, the truth of this statement becomes especially apparent when it is realized that the figure given in the table may easily have been doubled, or more, since 1919. Consequently, even if it is admitted that a great many additional carbon fluorides will doubtless be prepared within the next few years, the hydrides must for a long time, and probably must always, remain by far the most numerous class of compounds containing only carbon and some other single element. The conclusion may therefore be drawn that carbon does indeed possess an extraordinary ability to form a large number of compounds, but that it shows this property to the full extent only in combination with hydrogen. Which is then the unique element, carbon or hydrogen?

The above considerations may seem quite arbitrary since there can be no assurance that the relative numbers of now-known binary compounds have any theoretical significance. Indeed, these relative numbers could conceivably be so drastically altered within, say, the next hundred years that hydrogen would become no more important than any one of a dozen or more other elements. Although such a criticism may be entirely valid, it is, however, not relevant to the discussion; the question here being considered is that of the significance and appropriateness, *at the present time,* of the distinction between inorganic and organic compounds. There can, in fact, be no doubt that now, just as throughout the history of the science, organic chemistry assigns to hydrogen a role which rivals, if indeed it does not equal, that of carbon itself. Moreover, it may well be questioned whether the distinction that is now made between inorganic and organic chemistry might not need to be drastically revised, or even discarded, if at some future time hydrogen should lose its present predominant importance.

Even the ability of carbon atoms to join together into long chains seems to be dependent upon the presence of hydrogen atoms (or of fluorine atoms, see below). For example, if a paraffin hydrocarbon C_nH_{2n+2} is treated with an excess of chlorine, the completely chlorinated product C_nCl_{2n+2} is not obtained if n is greater than 3. Under such

---

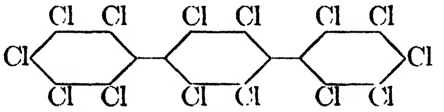
[6] For a discussion of the organic fluorine compounds, see the papers which were presented at the symposium on fluorine chemistry held at the Chicago meeting of the American Chemical Society in September 1946, and which are published in *Ind. Eng. Chem.* **39,** 236–434 (1947). Cf. also F. Smith, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **44,** 86 (1947).

circumstances, either the chlorination is incomplete, so that more or less hydrogen remains in the molecule, or else the molecule breaks up into (often unsaturated) fragments containing no more than about four carbon atoms per molecule. Hexachloroethane, I, and hexachloro-1,3-butadiene, II, are, in fact, often the final products of exhaustive chlorination of many higher aliphatic compounds. The completely chlo-

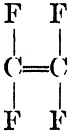
$CCl_3—CCl_3$
I

$Cl_2C{=}CCl—CCl{=}CCl_2$
II

rinated compound, decachloro-*n*-butane C_4Cl_{10}, has been made, however, by an indirect method,[7] as has also dodecachlorocyclohexane C_6Cl_{12};[8] these substances contain the longest chains of completely chlorinated, saturated carbon atoms that have been reported. Among the unsaturated, and especially among the aromatic substances, several completely chlorinated compounds with relatively large numbers of carbon atoms linked to each other are known. Of these may be mentioned a dodecachloroheptadiene C_7Cl_{12} of uncertain structure,[9] and



III


$$\begin{matrix} F & & F \\ | & & | \\ C & = & C \\ | & & | \\ F & & F \end{matrix}$$
IV

the chlorinated terphenyl, III. Still less is known about the analogous bromo and iodo derivatives, although tetrabromoethylene C_2Br_4 is known to be formed from butane. On the other hand, a large number of higher fluorocarbons have been prepared; these include perfluoro-*n*-hexadecane *n*-$C_{16}F_{34}$ and even a completely fluorinated lubricating oil.[6] Moreover, tetrafluoroethylene, IV, can be polymerized to a plastic material which undoubtedly contains extremely long chains of $—CF_2—CF_2—$ groups.[10] The fact that such compounds as these last ones exist (and, moreover, appear to be no less stable than their hydrogen-containing analogs) suggests that long fluorocarbon chains may ultimately become as familiar as the long hydrocarbon chains are now. Any development of this sort will, however, require a great many years for its completion, if indeed it be possible at all.

Throughout this book, structural formulas are designated, as above, by Roman numerals. The numeration starts again with I in each section.

[7] W. T. Miller, *J. Am. Chem. Soc.* **62**, 341 (1940).
[8] T. van der Linden, *Rec. trav. chim.* **55**, 569 (1936).
[9] H. J. Prins, *Rec. trav. chim.* **51**, 1065 (1932).
[10] Cf., for example, M. M. Renfrew and E. E. Lewis, *Ind. Eng. Chem.* **38**, 870 (1946).

In diamond and graphite, extremely long chains of carbon atoms exist without even one hydrogen (or fluorine) atom, except conceivably at the crystal surfaces where some sort of alterations in the regular atomic arrangements must necessarily occur. However, carbon is hardly unique in this respect, since many of the other solid elements, including boron, silicon, and tin, are analogously constituted.

From the foregoing discussion, the unique properties which characterize organic compounds are seen to be due not solely to the carbon atoms, but rather to the combination of carbon and hydrogen atoms. (The possibly very great, but at present only hypothetical, future importance of fluorine is here ignored.) For this reason, organic chemistry might profitably be defined as the chemistry of the hydrocarbons and their derivatives, since thereby the important role of the hydrogen would receive recognition. Actually, however, this definition would not necessarily result in a new classification of substances, since any substance which contains carbon can be considered to be a derivative of a hydrocarbon, and so to be an organic compound from either point of view. Moreover, the definition would not be completely unambiguous until the word "derivative" has been very carefully defined. For example, water is one of the products of combustion of a hydrocarbon. Is it, or is it not, therefore, a derivative of the hydrocarbon, and hence an organic substance? Consequently, to the extent that any need for a definition of organic chemistry exists at all, the conventional one that it is the chemistry of the compounds of carbon will be used in this book. Due recognition should be given, however, to the fact that the importance of carbon is thereby overemphasized and that of hydrogen is underemphasized.

1·3 Forces Acting between Atoms and Molecules.

The problem of the nature of valence can be considered a part of the more general problem of the natures of all the forces, of various types, which act between atoms and molecules. It should be obvious that some of these forces must be attractive and that some must be repulsive. If attractive forces did not exist between individual atoms, then the valence bonds which hold the atoms close together would be impossible; if they did not exist between molecules, then gases could not be condensed to form liquids and solids. On the other hand, if repulsive forces did not also exist, then atoms and molecules would continue to attract one another down to zero interatomic and intermolecular distances, so that the observed relative incompressibility of liquids and solids would be impossible.

At the present time, these attractive and repulsive forces are considered to be almost entirely electrostatic in nature. The magnetic interactions, which exist too, of course, are so much smaller than the electrostatic ones that, for the purposes of this discussion, they can be completely ignored. It may seem strange, however, that a single explanation can account for forces which appear to differ as markedly as do, for example, the strong valence forces, the weak van der Waals attractions, and the more or less strong repulsions between atoms that are not bonded to one another. It will be instructive to consider in some detail just how these various types of force come into being.

A more careful examination of the precise significance of the expression "valence bond" will be made later. (See Section 1·16.) For the present, however, the statement that a valence bond exists between any two atoms which are held together by attractive forces strong enough to withstand molecular collisions will be sufficient. Although, as was pointed out above, all such interatomic forces are presumed to be electrostatic, it has been found convenient to divide valence bonds into two principal classes which, in spite of the resulting confusion in terminology, are called *electrostatic* and *covalent*. These various types of bond will be considered in the following sections.

1·4 The Ionic Bond. The simplest kind of electrostatic bond is the ionic bond in, for example, a molecule of gaseous sodium chloride. As a first approximation, this molecule can be considered to consist of a positive sodium ion plus a negative chloride ion. If the interionic distance is r, and if, for simplicity, the effect of the simultaneously acting repulsive forces is neglected, the energy of the electrostatic attraction between the oppositely charged ions is seen from Coulomb's law to be $-e^2/r$, where e is the magnitude of the electronic charge. In other words, in order to break the bond by dissociating the molecule into its constituent ions, it would be necessary to supply an amount of energy equal to e^2/r. Since this quantity amounts to more than 100 kcal per mole, the bond in question is clearly a very strong one, even when allowance is made for the neglected repulsive forces.

The total electrostatic energy of two isolated sodium chloride molecules, when calculated in the above approximate manner, is found to be $-2e^2/r$. However, if the two molecules are allowed to approach so that the four ions are arranged at the corners of a square as in Figure 1·1, and if the interionic distance is assumed to have the same value r as before, the energy is now found to be $-e^2/r \times [4 - (2/\sqrt{2})]$, or $-2.586\, e^2/r$. The difference of $0.586\, e^2/r$, or of $0.293\, e^2/r$ per NaCl molecule, then measures the amount of energy which would have to be supplied to dissociate $(NaCl)_2$ into 2NaCl. Since this quantity amounts to more than 30 kcal per mole of NaCl, the dimeric $(NaCl)_2$ is seen to be very stable. Similarly, four molecules of sodium chloride have an energy of $-4e^2/r$ when isolated, but of $-e^2/r \times (12 - 12/\sqrt{2} + 4/\sqrt{3})$, or of $-5.825\ e^2/r$, when brought together so that the eight ions occupy the eight corners of a cube, as in Figure 1·2. The difference is now $1.825\ e^2/r$, or $0.456\ e^2/r$ per sodium chloride molecule; hence the tetrameric $(NaCl)_4$ is even more stable than the dimeric $(NaCl)_2$. This trend continues until a complete crystal of the solid is built up. Calculation has shown that, with a set of N molecules of sodium chloride, where N is some very large number like Avogadro's number, the total energy varies from $-Ne^2/r$ for the N isolated molecules to $-1.747558\ Ne^2/r$ for the crystal. (The number 1.747558 is known as the *Madelung constant* for the sodium chloride structure. Each type of crystal has its own characteristic Madelung constant.)[11] Consequently, nearly 75 per cent as much energy would be required to dissociate a crystal of sodium chloride into isolated NaCl molecules (i.e., to vaporize the crystal) as would be required to dissociate the resulting molecules further into ions. (This figure is, of course, only approximate since the repulsive forces, and also the variation in interionic distance, have been neglected.) In this way, the high boiling point of the substance, as well as that of any other similarly constituted substance, finds a ready explanation.

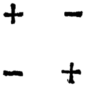


FIGURE 1·1. A schematic diagram representing the relative positions of the cations (+) and anions (−) in dimeric sodium chloride $(NaCl)_2$.

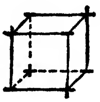


FIGURE 1·2. A schematic diagram representing the relative positions of the cations (+) and anions (−) in tetrameric sodium chloride $(NaCl)_4$.

1·5 Ionic Double Bonds. Just as the formation of the gaseous sodium chloride molecule can be considered dependent upon the transference of one electron from the sodium atom to the chlorine atom, so also that of the gaseous magnesium oxide molecule can be considered dependent upon the transference of two electrons from the magnesium atom to the oxygen atom. If, then, an ionic single bond is said to exist in the sodium chloride molecule, an ionic double bond must similarly be said to exist in the magnesium oxide molecule. On the other hand, ionic triple bonds appear seldom, if ever, to exist.

It is of interest that an isolated oxide ion $O^{=}$ dissociates spontaneously and completely into the univalent anion O^{-} plus an electron. The former ion, with the double negative charge, can in fact exist only when it is stabilized by the presence

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[11] For a table of Madelung constants for different types of structure, see Table 1 of J. Sherman, *Chem. Revs.* **11**, 93 (1932).

of one or more nearby cations, as in molecular (i.e., gaseous) magnesium oxide or in the solid form of this, or other analogous, substance.[12] The stabilization of the anion by the cation can be explained in either of two completely equivalent ways. on the one hand, the comparatively small cation can be assumed to polarize the larger anion; and, on the other hand, the ionic bond can be presumed to have more or less covalent character. (Cf. Section 1·10.)

1·6 Ion-Dipole Bonds. A second type of electrostatic bond results from the interaction, not between two oppositely charged ions, but instead between an ion and a dipole. A brief explanation of what is meant by a dipole is now necessary. Some molecules, such as those of hydrogen chloride, have positive ends and negative ends, whereas others, such as those of hydrogen, do not. The former molecules are said to be *polar* and to have *dipole moments* (or *dipoles*); the latter are said to be *nonpolar* and to have zero dipole moment (or dipole). It should be clear that a positive ion is attracted by the negative end of a polar molecule, just as by a negative ion; and also that a negative ion is attracted by the positive end of a polar molecule, just as by a positive ion. If the attraction is so strong that one may profitably speak of a bond at all, the bond in question is referred to as an *ion-dipole bond.* For example, a sodium ion in aqueous solution is strongly hydrated; the union between the ion and a water molecule may be due to such an ion-dipole bond or, in other words, to the electrostatic attraction between the positive sodium ion and the negative (oxygen) end of the water molecule (An alternative interpretation will be given later, however, in Section 1·12.) Possibly, in most instances, the water of crystallization in salts is attached in this way to the positive, and also to the negative, ions. Moreover, the analogous alcohol, ammonia, etc., of crystallization, possessed by many salts, may be presumed to be attached in completely similar ways. Since ion-dipole interactions are in general weaker than ion-ion interactions, bonds of the former type may be expected to be relatively weak. This expectation is in agreement with the fact that water of crystallization, and the like, can usually be driven out by moderate heating.

1·7 Dipole-Dipole Interactions. A final type of electrostatic interaction is the dipole-dipole interaction, which results from the attraction between the positive end of one dipole and the negative end of a second dipole. Usually, such an attraction is so weak that no bond is considered to be formed at all. However, there is one important type of dipole-dipole interaction which is strong enough to require attention. This is the so-called *hydrogen bond,* or *hydrogen bridge,* the simplest example of which occurs in hydrogen fluoride. In the gas phase, this sub-

[12] The author is indebted to Professor K. Fajans for calling his attention to this fact

stance appears to consist not of simple HF molecules, but of a complex mixture of molecules with the formulas HF, $(HF)_2$, $(HF)_3$, and so on. In the liquid phase, the situation is probably more complicated, but dipole-dipole interactions are doubtless still important. In a single molecule of HF, the hydrogen and fluorine atoms are considered to have, respectively, rather large net positive and negative charges. Consequently, the dimeric form can be represented by structure I, where the broken line indicates the electrostatic interaction that holds the two

H—F- - -H—F

I

parts together. In a similar way, the association of liquid water, alcohol, ammonia, etc., is explained as resulting from the presence of hydrogen (i.e., dipole-dipole) bonds. These hydrogen bonds will be discussed in greater detail later (see Section 2·6) and will be referred to frequently throughout the book.

1·8 Covalent Bonds. The covalent bonds now remain to be considered. Obviously, the formation and stability of the hydrogen molecule, H_2, for example, cannot be related to a simple electrostatic attraction between oppositely charged ions. Since the two hydrogen atoms are equivalent, neither one of them can be assumed to give up its electron entirely to the other, with production of a proton and of a negative hydride ion. Nevertheless, the covalent bond which actually exists is presumed to be due to electrostatic forces. The oppositely charged particles among which the attractive forces operate are now the two positively charged hydrogen nuclei, on the one hand, and the two negatively charged electrons, on the other. A fundamental difference between such a covalent bond and the ionic one in gaseous sodium chloride is that here the negative particles (i.e., the electrons) are extremely light and hence extremely mobile. Consequently, they cannot, even as a rough first approximation, be assumed to occupy fixed positions, like the chloride ions; instead, they must be considered to wander over the whole molecule. Nevertheless, one may still speak of their *average* positions, which are of course at definite points with respect to the protons, and of their average interactions with each other and with the protons. It turns out that these average interactions are not very different from those which would obtain if the electrons were held fixed in some such orientation as that shown in Figure 1·3. (However, see below.) From analogy, then, with the foregoing discussion of the dimeric sodium chloride $(NaCl)_2$, it should be evident that the hydrogen molecule H_2 is more stable than two isolated hydrogen atoms, or, in other words, that in the molecule a bond exists between the two atoms.

It may be asked why the analogy between the ionic and the covalent bonds stops at this point. Thus, as far as the simple electrostatic interactions are concerned, there is no obvious reason why there should not exist a molecule H_4, which is even more stable than $2H_2$, just as $(NaCl)_4$ is more stable than $2(NaCl)_2$. The explanation is that covalence, unlike electrovalence, can be saturated. That is to say, although an ion can attract as many other ions of opposite sign as can find room to come sufficiently close, an atom can form only a definite number of covalent bonds. In particular, a hydrogen atom can form at most one covalent bond, and an atom of the first short period can form at most four covalent bonds. Although this rule is, in the last analysis, merely an empirical generalization required by the facts of chemistry, a more detailed consideration of the question why two hydrogen molecules actually repel each other will be found instructive.

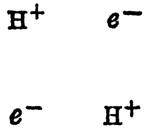


FIGURE 1·3. A schematic diagram representing the relative average positions of the protons (H^+) and electrons (e^-) in a normal hydrogen molecule H_2.

FIGURE 1·4. A schematic diagram representing the relative average positions of the protons (H^+) and electrons (e^-) in a possible "repulsive" state of a system composed of two hydrogen atoms.

In the formation of the stable hydrogen molecule, the attraction between the two atoms may be considered due to the fact that, on the average, the two electrons tend to come into the region between the nuclei. If, on the other hand, the electrons had tended to remain outside that region, in the manner represented schematically by Figure 1·4, the electrostatic interactions would have led to a strong repulsion, and not to the formation of a bond. Now, when two hydrogen molecules H_2 and H_2^* come close together, the two pairs of electrons, which form the covalent bonds in the isolated molecules, tend to occupy the regions between two atoms H and between two atoms H*, but to stay out of the regions between any one atom H and any one atom H*. (The asterisk is used here to distinguish the two pairs of hydrogen atoms from one another.) Consequently, the two atoms H attract each other, as do also the two atoms H*, but the molecules H_2 and H_2^* as a whole repel each other. The four electrons in the system composed of four hydrogen atoms therefore behave in an entirely different way from the four chloride ions in a system composed of four NaCl molecules; for, in the latter system, an overall attraction predominates. In other words, the covalence of the hydrogen atoms is saturated. This difference in behavior finds an "explanation" in quantum mechanics but cannot be discussed further here. In similar ways, the saturation of the valences of the heavier atoms finds its interpretation in the electrostatic interactions of the charged particles.

The representations in Figures 1·3 and 1·4 of the average charge distributions are, of course, extremely crude. In at least one respect, in fact, they can give rise to a false impression. Thus, Figure 1·3 suggests (incorrectly) that, in the normal hydrogen molecule, there are two distinct regions in which the electrons are especially likely to be. The diagram is intended, however, to indicate rather that, although the two electrons tend on the average to be in the region between the nuclei, they nevertheless tend at any given instant to be as far from one another as possible, on account of the electrostatic repulsion of their like charges. A more satisfactory representation of the true average charge distribution, but one which does not suggest the instantaneous separation of the electrons, is given in Figure 1·5. In this figure the closeness of the dots in each small region represents the average density of electronic charge in that region; in other words, it represents the probability that, if the necessary experiment were performed, an electron would be found in that region. The relative closeness of the dots in the space between the

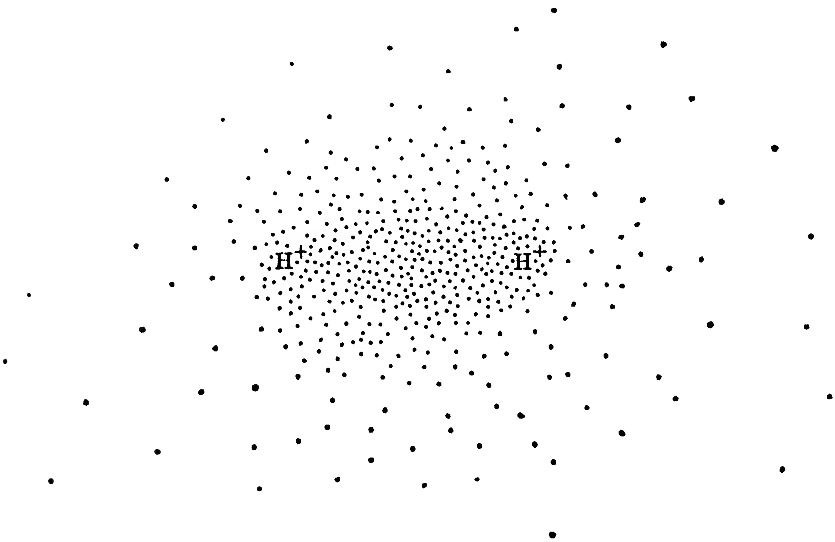


Figure 1·5. The average distribution of electronic charge in the normal hydrogen molecule H_2.

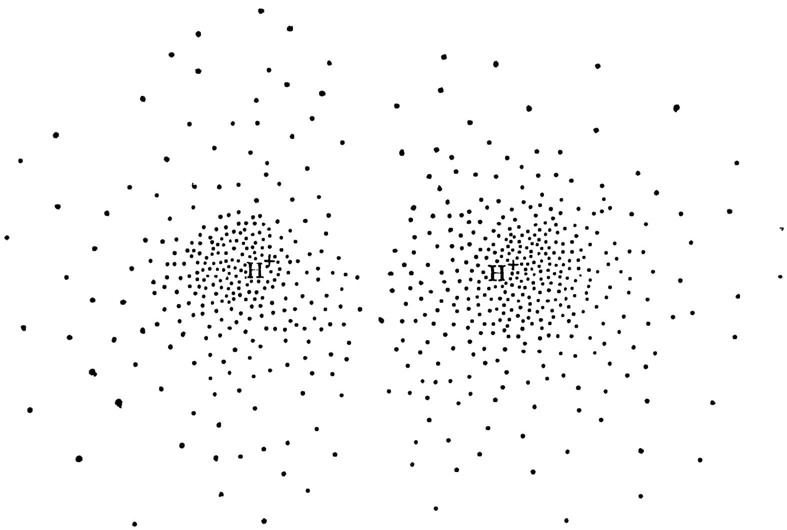


Figure 1·6. The average distribution of electronic charge in the "repulsive" state of a system composed of two hydrogen atoms.

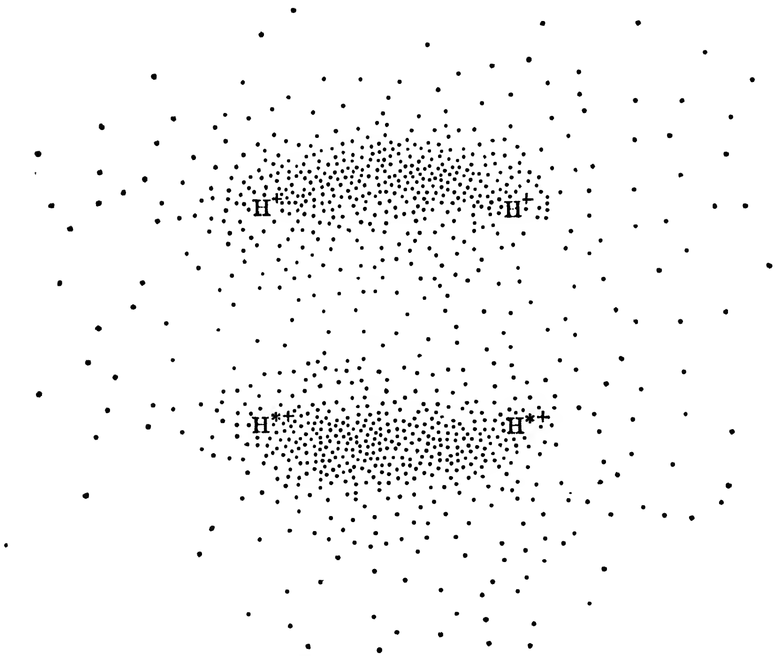
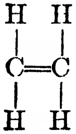


Figure 1·7. The average distribution of electronic charge in a system composed of two hydrogen molecules H_2 and H_2^*.

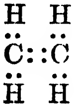
two nuclei corresponds therefore to the concentration of the valence electrons along the bond axis. (Cf. also Section 10·5.) Similarly, Figure 1·6 shows the average charge distribution in the "repulsive" state represented originally by Figure 1·4; Figure 1·7 shows that in a system composed of two rather close hydrogen molecules. (See the preceding paragraph.)

1·9 Double and Triple Covalent Bonds. Many atoms which are heavier than that of hydrogen are able to form double and triple bonds with other atoms by the sharing, respectively, of four and six electrons. Unambiguous multiple bonds involving elements other than carbon, nitrogen, and oxygen are, however, relatively rare. (Cf. pages 359 f., 422, and 425.) In ethylene, for example, either of the two equivalent structures, I and II, implies that two electrons are especially likely to be



$$\begin{array}{cc} H & H \\ | & | \\ C & \!\!=\!\! & C \\ | & | \\ H & H \end{array}$$

I



$$\begin{array}{c} H\ \ H \\ \ddot{C}::\ddot{C} \\ H\ \ H \end{array}$$

II

found in each of the regions between a hydrogen atom and its adjacent carbon atom, and that altogether four electrons are especially likely to be found in the region between the two carbon atoms. Similarly, in acetylene, either of the two corresponding structures III and IV implies that here six electrons, on the average, tend to come into the region between the two carbon atoms. Quadruple, and still higher, covalent bonds

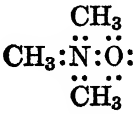
H—C≡C—H
III

H:C:::C:H
IV

are unknown, presumably on account of the tremendous steric strains which would be required. (Cf. Chapter 9.)

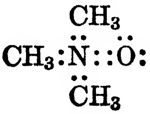
1·10 Bonds of Mixed Type. When even a covalent bond is formed between two dissimilar atoms, one atom usually carries a net positive charge, whereas the other carries a net negative charge. This fact shows that the two electrons which produce the bond by being concentrated in the region between the two nuclei, and which are said to be *shared* by the atoms, are more likely to be near to one nucleus than to the other. In hydrogen chloride, for example, the average positions of the shared electrons are nearer to the chlorine atom than they are to the hydrogen atom; consequently the former atom is negatively charged and the latter is positively charged. The situation is conveniently described by the statement that the sharing is *unequal*. Clearly, it is possible to imagine a sequence of bonds in which the degree of sharing varies by successive small differences all the way from the one extreme represented by, say, the hydrogen molecule to the opposite extreme represented by, say, the sodium chloride molecule. It follows, therefore, that there is no sharp dividing line between covalent and ionic bonds. Any bond between dissimilar atoms may be considered to have at least some ionic character since the sharing cannot be quite equal; and even the bond in sodium chloride must have some covalent character since the electrons on the chloride ion must have a somewhat greater probability of being in the region between the two nuclei than elsewhere, and hence must be shared to some extent. Nevertheless, it is convenient to speak of ionic and covalent bonds as two distinct types, although it must be realized that these are merely the two extremes of a steady progression. Fortunately, since most bonds appear to be fairly near one extreme or the other, little trouble is caused by this inexact terminology. In other words, any given bond is almost certain to be either *essentially* ionic or *essentially* covalent, and the word "essentially" can usually be omitted without danger of confusion. (For further discussion of the theoretical principles involved in the assumption that bonds may be of mixed types, see Chapter 10.)

1·11 The Semipolar Double Bond. There exists still a further type of bond, which may be said to be intermediate, in a somewhat different sense, between the ionic and the covalent extremes. An example is provided by the nitrogen-oxygen bond in trimethylamine oxide. For this substance, the electronic structure I can be written. The "classical" structure II, in which the nitrogen atom forms five covalent bonds



$$\mathrm{CH_3}{:}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{N}}}}}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{O}}}{:}$$

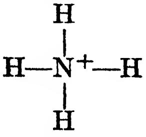
I



$$\mathrm{CH_3}{:}\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{N}}}}}{::}\overset{\cdot\cdot}{\mathrm{O}}{:}$$

II

and is surrounded by ten electrons in its valence shell, is probably impossible since, as was pointed out in Section 1·8, there is reason to believe that, in consequence of the phenomenon of saturation, a nitrogen atom can form no more than four covalent bonds. Since in structure I two electrons are considered to be shared by the nitrogen and oxygen atoms, there appears to be an ordinary single covalent bond between these atoms. However, the nitrogen atom, since it forms altogether four such bonds, is in essentially the same state as is the one in the ammonium ion; and the oxygen atom, since it forms only one such bond, is in essentially the same state as is the one in the hydroxide ion. Now, although the ionic charges of the ammonium and hydroxide ions do not reside entirely upon the nitrogen and oxygen atoms, respectively, the structures can nevertheless conveniently be written as if the charges did reside upon the atoms stated. Thus, the structures for the ammonium and hydroxide ions and, correspondingly, for the trimethylamine oxide molecule become III, IV, and V, respectively. (For simplicity, the bonds are represented here in the "old-fashioned" manner as straight lines, and not as pairs of dots; and the unshared pairs of electrons are not explicitly indicated.)

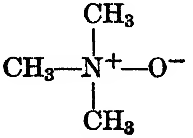


$$\begin{array}{ccc} & H & \\ & | & \\ H- & N^+ & -H \\ & | & \\ & H & \end{array}$$

III

$^-O—H$

IV



$$\begin{array}{ccc} & CH_3 & \\ & | & \\ CH_3- & N^+ & -O^- \\ & | & \\ & CH_3 & \end{array}$$

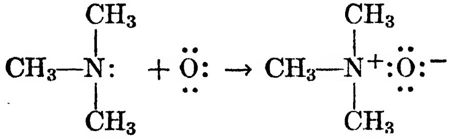
V

As has already been noted, the plus and minus signs in structures III, IV, and V do not correspond exactly to unit positive and negative charges, respectively, upon the atoms concerned. In order that attention may be called to this fact, these signs are said to represent *formal charges*. For example, the nitrogen atom in the ammonium ion or in the amine oxide molecule has a formal charge of plus one, and the oxygen atom in the hydroxide ion or in the amine oxide molecule has a formal charge of minus one. It may be noted that, if all electrons taking part in covalent bonds were shared equally (i.e., if no covalent bond ever had any ionic character), then the formal charges would be equal to the true charges, expressed in electronic units. However, since the sharing between nonequivalent atoms is probably never equal, the formal charges are at best rather rough approximations to the true charges.

A second, equivalent way in which the idea of formal charges can be approached brings out more clearly the significance of the inequality of sharing. In an electronic structure, the symbol for an element (such as H, C, O, N) does not represent the entire atom but instead only the so-called atomic *kernel*. That is, it represents the nucleus together with all the inner electrons, if any, which do not belong to the valence shell. The charge on the kernel is always positive and equal, in electronic units, to the number of valence electrons, since the complete atom composed of kernel plus valence electrons must be electrically neutral. In most, if not in all, of the examples which will be considered in this book, the kernel charge is equal to the number of the group to which the atom belongs in the periodic table. (In order for this statement to be sufficiently general, hydrogen must be considered to belong to the first group.) Thus, the kernel charges of hydrogen, carbon, nitrogen, oxygen, and chlorine are 1, 4, 5, 6, and 7, respectively. Now, in a molecule, all the positive kernels are surrounded by electrons, which tend to cancel their charges. These electrons belong to two main classes: first, those which are not shared by two atoms and so may be said to be "owned outright" by some single atom; and second, those which are shared by two atoms and so may be said to belong partly to each. If the sharing of electrons were always equal, each of these shared electrons would, on the average, belong half to one atom and half to the second. Consequently, if a given atom has a kernel charge of Z (in electronic units), if it owns p electrons outright, and if it shares s electrons with other atoms, then its net charge F would be equal to $Z - p - s/2$ if the sharing were equal. The quantity F is then the formal charge. It is easily seen that this more precise definition leads to the same values of the formal charges as does the more qualitative treatment given originally. Obviously, the algebraic sum of the formal charges in any structure must be equal to the total charge on the corresponding molecule or ion.

With this much in the way of explanation, the nitrogen-oxygen bond in trimethylamine oxide may again be discussed. To the extent that the formal charges on the nitrogen and oxygen atoms can be considered real, this bond is a double one, composed of a single ionic bond plus a single covalent bond. Such a bond has by various authors been called a *semipolar double bond*, a *coordinate covalence*, and a *dative bond*. Throughout this book, however, its method of representation, given above, will ordinarily be found to provide a sufficient description of it; hence only occasionally need it be referred to by a special name.

The essential distinction between a semipolar double bond and an ordinary covalent single bond is frequently said to be that the former type of bond results when one atom contributes both of the binding electrons, whereas the latter type results when each of two atoms contributes one electron. Thus, the molecule of trimethylamine oxide can be considered formed from one of trimethylamine plus an atom of oxygen (equation 1·1), whereas the hydrogen molecule can be considered formed

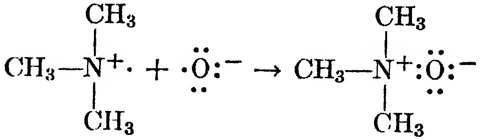


$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{N}}}}: \;+\; \underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}: \;\rightarrow\; CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{N}}}}{}^{+}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}:^{-} \qquad (1\cdot1)$$

from two hydrogen atoms (equation 1·2). It should be noted, however, that there is no necessity to consider these molecules formed in the way

$$H\cdot + \cdot H \rightarrow H{:}H \qquad (1\cdot2)$$

stated. It is, in fact, easily possible to imagine the formation of trimethylamine oxide in a different way (equation 1·3), and also that of



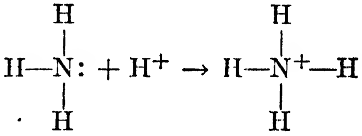
$$CH_3-\underset{CH_3}{\overset{CH_3}{N}}{}^{+}\cdot + \cdot\ddot{\underset{\cdot\cdot}{O}}:^- \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{N}}{}^{+}:\ddot{\underset{\cdot\cdot}{O}}:^- \qquad (1\cdot3)$$

hydrogen (equation 1·4). On the basis of equations 1·1 and 1·2, the

$$H^+ + :H^- \rightarrow H:H \qquad (1\cdot4)$$

definition under discussion requires that the nitrogen-oxygen bond in trimethylamine oxide be a semipolar double bond, and that the hydrogen-hydrogen bond be an ordinary covalent single bond; however, on the basis of equations 1·3 and 1·4, the definition leads to the opposite conclusions. In any event, no great significance can be attached to a definition which classifies bonds by their method of formation, because the nature of a bond is independent of its past history. For example, molecular hydrogen is the same substance whether it has been made by reaction 1·2 or by reaction 1·4.

A further difficulty inherent in the alternative definition of the semipolar double bond can be illustrated by the ammonium ion. From equation 1·5, it follows that, if this definition is adopted, one of the nitrogen-

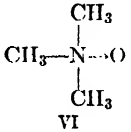


$$H-\underset{H}{\overset{H}{N}}: + H^+ \rightarrow H-\underset{H}{\overset{H}{N}}{}^{+}-H \qquad (1\cdot5)$$

hydrogen bonds in the resulting ion must be called a semipolar double bond, whereas the other three bonds may be called covalent single bonds just as in the original ammonia. Actually, however, no bond here is a semipolar double one, since there is no formal negative charge upon any atom; and actually, all four bonds are completely equivalent. For these several reasons, no use will be made hereafter of this second definition of the semipolar double bond.

As has just been pointed out, the source of the electrons involved in a bond is of no significance in the discussion of the nature of that bond, once it has been formed. The conclusion cannot be drawn, however, that the source of the electrons is of no significance in *any* discussion. In fact, it is easily seen that the nature of any chemical reaction by which a new bond is produced depends upon the number of electrons contributed by each reagent, since the function of each reagent must be determined by the number of electrons which it contributes. Consequently, the source of the electrons taking part in a given bond provides an important method of describing the reactions by which the bond might have been formed and of classifying the respective reagents involved, but not of defining the nature of the bond itself.

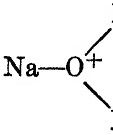
In especially the British chemical literature, a semipolar double bond between atoms A and B is frequently represented by the symbol A→B, rather than by the symbol $A^+—B^-$. Thus, the structure of trimethylamine oxide may be written as VI instead of as V. The arrow here implies that both of the shared electrons are contributed by the nitrogen atom. (See above.) Although these two methods of representation are completely equivalent, the one employing the formal charges seems to be both more illuminating and more convenient; it will be used exclusively throughout this book.



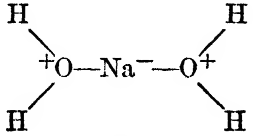
$CH_3{—}\underset{CH_3}{\overset{CH_3}{N}}{\rightarrow}O$

VI

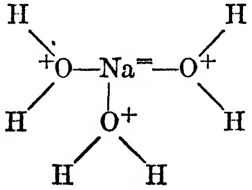
1·12 Further Discussion of Solvated Cations and of Some Related Questions. It was mentioned in Section 1·6 that the hydration of a cation like the sodium ion might be due to an ion-dipole bond between the positive sodium ion and the negative end of the water dipole. An alternative explanation, however, is the following. A sodium ion with one, two, three, and so on molecules of water of hydration could be represented, respectively, by structures I, II, III, and so on. In these structures, the sodium atom is joined to each oxygen atom by a covalent single bond, and formal charges appear on the oxygen and (usually) on the sodium atoms. Of the various sodium-oxygen bonds, therefore, the one in the monohydrate is analogous to the nitrogen-hydrogen bond in the ammonium ion, and those in the higher hydrates are analogous to the semipolar double bond in the amine oxide.



I



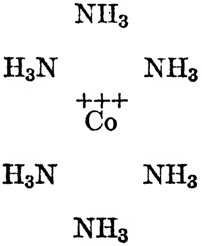
II



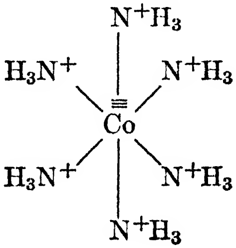
III

The truth probably lies somewhere between these two extremes. That is to say, the actual distribution of charge in a solvated ion is probably intermediate between that corresponding to an ion-dipole bond and that corresponding to the type of bond shown in structures I, II, and III. (Cf. Chapter 10.) The presence of the formal negative charges on the sodium atoms, in fact, makes it seem very unlikely that the above structures could, by themselves, be accurate descriptions of the structures of the ions.

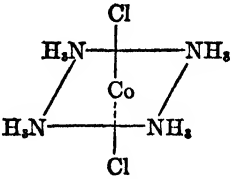
The so-called Werner complexes, although perhaps not strictly describable as solvated cations, nevertheless belong in this present discussion. The hexamminocobaltic ion, for example, doubtless owes its stability to a charge distribution intermediate between the ones represented by structure IV with only ion-dipole interactions and structure V with both covalent and ionic bonds. The bonds in such complexes, however, are rather stronger than are those in, say, the hydrated sodium ion. At any rate, they are strong enough to permit the isolation of stable stereoisomers, like the two dichlorotetramminocobaltic chlorides, which contain the cations represented by the conventionalized projection diagrams VI and VII. Since this difference in strength proves to be a rather important one for the subsequent discussion, the arbitrary convention will be adopted hereafter of using the term "ion-dipole interaction" to describe situations like that in the hydrated sodium ion, in which the "bonds" (whatever their exact nature may be) are too weak to permit the isolation of stereoisomers; and of adopting the term "coordinate bond" for situations like those in the Werner complexes, in which the "bonds" (again, whatever their exact nature may be) are strong enough to permit stereoisomerism.



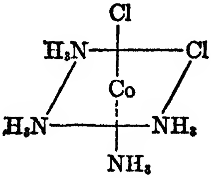
IV



V



VI



VII

On this basis, the distinction between an ion-dipole interaction and a coordinate bond is a rather indefinite one. The relation between two atoms in a given molecule or ion could conceivably pass from the former classification to the latter when additional experimental information is obtained. Such a complication, however, is not likely to cause serious trouble; in any event, some ambiguity is unavoidable since there actually exists no sharp dividing line between true bonds and the weaker interactions which must be described in other terms.

1·13 Intermolecular Forces. According to the preliminary definition stated above on page 8, a bond may be said to exist between two given atoms only if the attraction between the atoms is strong enough to withstand molecular collisions. Attractions which are too weak to be thus described as bonds are, however, well known. These additional forces, which also are considered to be of electrostatic origin, are the ones that act between different molecules, and that are responsible for the deviations of real gases from the perfect gas law and for the condensation of gases to liquids and solids. Similar forces, which act between the more distant parts of even a single molecule, also exist, of course, but need not be separately discussed.

The dipole-dipole interactions, as has already been mentioned, are of this weaker class, since they never lead to the formation of bonds, except in the particular case of the hydrogen bond. They do, however, produce between polar molecules appreciable net attractions which are reflected in the relatively high boiling points of such substances. For example, the highly polar acetone boils at an appreciably higher temperature than does any nonpolar hydrocarbon of comparable molecular weight.

Some justification is required for the above conclusion that the dipole-dipole interactions result in net attraction, since, from the simplest point of view, the attractive and repulsive forces might be expected exactly to cancel each other.[13] In fact, the direction of the force acting between two dipoles is determined by the relative orientation of the dipoles; moreover, there are as many orientations leading to repulsion as there are leading to attraction. This same difficulty arises also with the interaction between an ion and a polar molecule, since the ion could be imagined to approach either the like charged or the oppositely charged end of the molecule. With such a simple system, however, the solution of the problem is too obvious to require comment. In any event, it will be noted that the following discussion could be applied without essential change to an ion-dipole, as well as to a dipole-dipole, interaction. As an example of a dipole-dipole interaction, a system composed of two molecules of hydrogen chloride can be considered. If these molecules are arranged as in diagram I, they obviously attract each other, but, if they are arranged as in diagram II, they obviously repel each other. Each mutual orientation which leads to a force of attraction is thus balanced

H—Cl H—Cl
I

H—Cl Cl—H
II

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[13] F. London, *Trans. Faraday Soc.* 33, 8 (1937).

by a second mutual orientation which appears to lead to an equal force of repulsion. There exist, however, two further factors which have not been considered heretofore and which ensure that the attraction predominates. These may be called the *probability* (or *orientation*) factor and the *polarization* factor.

The first of these factors results from the fact that, although there are as many repulsive as attractive relative orientations, two given molecules are more likely to be in an attractive orientation with respect to each other than in a repulsive one. The reason for this difference is that the energy of the former orientation is lower than is that of the latter, and that, moreover, any system has a tendency to spend as much time as possible in its low-energy (i.e., its most stable) states. Consequently, in a system composed of a large number of molecules, the attraction must at any given time outweigh the repulsion.

The polarization factor arises in a different way. When two polar molecules are so close that any appreciable force of either attraction or repulsion exists between them at all, each molecule must to some extent polarize (or, in other words, alter the distribution of charge in) the other one. For example, the schematic diagrams III and IV may be written

III IV

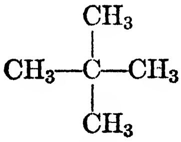
to represent two polar molecules in, respectively, an attractive and a repulsive orientation. Now, in the orientation III, the molecule at the left is nearer to the positive than to the negative end of the molecule at the right. Consequently, in the left-hand molecule, the average positions of the positively charged nuclei will be displaced farther to the left, and those of the negatively charged electrons will be displaced farther to the right, by the electrostatic field due to the right-hand molecule. In other words, the separation of the positive and negative charge in the molecule, and hence the magnitude of the dipole moment, is increased by the presence of the second molecule. In a similar way, the right-hand molecule also is polarized so that its dipole moment is increased. The electrostatic attraction between the two molecules, for a given relative orientation and distance, is proportional to the product of the magnitudes of the two dipoles; hence it is increased by the polarization. In the repulsive orientation IV, on the other hand, similar reasoning shows that the polarization *decreases* the moment of each molecule and hence also the force of repulsion. It follows therefore that, even if the probability factor did not exist, and even though the numbers of attractive and repulsive orientations are equal, the attraction must still predominate since, in consequence of polarization, the attractive orientations, on the average, are more attractive than the repulsive orientations are repulsive.

Attractive forces exist even with nonpolar molecules. The simplest example is the interaction between one polar and one nonpolar molecule, or between one ion and one nonpolar molecule. Here, although the orientation (i.e., the probability) factor is not important, the polarization factor still operates since the nonpolar molecule can be polarized by the polar one (or by the ion). Consequently, there should be appreciable attraction. The principles involved here may be illustrated by the familiar experiment in which an electrically charged object is found to attract an uncharged pith ball, small piece of paper, or other light object. When neither molecule is polar, the discussion becomes somewhat more difficult, but it still proceeds along essentially the same lines. Neither the orientation nor the polarization factor can exist, at any rate in exactly the same form as before; nevertheless attraction must still be assumed present in order that the condensation of even the nonpolar paraffin hydrocarbons, for example, may be explained. A part of the explanation of this remaining attraction is provided by the fact that molecules which carry no ionic charges, and which have no dipole moments, may still give rise to small, but appreciable, electrostatic fields in their neighborhood. This fact is expressed mathematically by the statement that such molecules may have quadrupole, octupole, or still higher electric moments; although the precise significance of these terms need not be considered here, a rough idea of their nature can be obtained in the following way. A molecule of carbon dioxide, V, for example, is nonpolar, as should be evident from the fact that, since the oxygen atoms

$$\mathrm{O{=}C{=}O}$$

V

are equivalent to each other, one cannot be the positive, and the other the negative, end of the linear molecule. Nevertheless, the two oxygen atoms carry fairly large net negative charges (which are balanced by a positive charge on the carbon atom); consequently, a second molecule that is extremely close to one of the oxygen atoms is in an electrostatic field of appreciable magnitude, since the relative effects of the more distant carbon and oxygen atoms are then small. Such electrostatic fields may also, of course, lead to net attraction in much the same way as do those due to dipole moments. The same orientation and polarization factors as before (with suitable modifications) must again be taken into account in order that the predominance of attraction over repulsion may be explained. It is of interest here, that, if a molecule is highly symmetrical (i.e., if it is more or less spherical), the electrostatic field about it is particularly small and, moreover, decreases particularly fast as the distance from the molecule increases. It therefore follows that the forces acting between such symmetrical molecules must be smaller than are those between less symmetrical, but otherwise comparable, molecules. The reason for this conclusion is twofold. In the first place, the forces in question must, of course, decrease as the fields, to which they are due, decrease. In the second place,[14] the forces act only over very short distances; hence, they are most effective between those parts of the different molecules which are actually in contact with each other. Clearly, therefore, the forces between nonpolar molecules are more accurately described as properties of the respective surfaces than as properties of the entire molecules; consequently, the forces must increase (other factors being equal) with the areas of the molecular surfaces. Since, in general, highly symmetrical molecules have smaller surface areas than do less symmetrical ones, the former molecules should, as was stated above, attract one another less strongly than do the latter. These considerations doubtless provide at least a part of the explanation of the fact that, for example, the highly symmetrical neopentane, VI, boils at a so much lower temperature than does the isomeric and still nonpolar, but much less symmetrical, n-pentane, VII. The boiling points are, respectively, 9.5°C and 37°C. Numerous further examples of this striking effect of symmetry upon boiling point are well known throughout organic chemistry.



$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-CH_3$$

VI

$$CH_3-CH_2-CH_2-CH_2-CH_3$$

VII

1·14 van der Waals Forces. The factor that is probably the most important one leading to attraction between electrically neutral and not too highly polar molecules still remains to be considered. That such a factor (or factors) must exist can be seen in several ways. For example, the difference in boiling point between even neo- and n-pentane, striking as it is, is very small compared with the difference between the boiling point of either of these compounds and the absolute zero. In other words, the question why these substances can be condensed at all has been little more than touched. Moreover, the rare gases, like helium and neon, are considered to be surrounded by no electrostatic field at all

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[14] J. H. Hildebrand and T. S. Gilman, *J. Chem. Phys.* **15**, 229 (1947); J. H. Hildebrand, *Proc. Natl. Acad. Sci. U. S.* **33**, 201 (1947).

(however, see below); nevertheless, attractive forces must exist since these substances too can be both liquefied and solidified.

These remaining forces, which are known as *van der Waals forces,* are due to electrostatic interactions, just as are all the ones considered previously. The principles involved can be illustrated by a consideration of the situation with helium. The statement that an atom of helium is surrounded by no electrostatic field means that the average force acting upon a charged point-particle which is in its neighborhood, but which is assumed not to affect its distribution of charge, is zero, even if the average in question is taken over an extremely short period of time, say, 10^{-10} sec. However, at any single instant, the force might not be zero. Indeed, the atom must actually possess a dipole moment at all instants, except at those very rare ones when the nucleus is exactly halfway between the two electrons, as in structure I. It is only because the electrons move so rapidly that the existence of the resulting instantaneous

$$e^- \quad \mathrm{He}^{++} \quad e^-$$

I

field cannot by ordinary means be detected; before any experiment for the measurement of the field could be carried out, the direction of the field would have reversed many times, so that the experiment would necessarily give only the average field, namely, zero. Nevertheless, the very fact that electrons can move so fast means that the motions of the electrons in one molecule can be appreciably influenced by the instantaneous fields produced by the electrons in a second molecule. Consequently, the same polarization factor that leads to attraction between ordinary dipolar molecules can operate here too in essentially the same way, and so again can lead to attraction. (The probability factor also may play a role, but, on account of the special conditions operating, the distinction between it and the polarization factor loses most of its significance; consequently, it need not be discussed further.) The van der Waals forces, like the forces due to the electrostatic fields about nonpolar and highly symmetrical molecules (cf. page 25), are effective over only extremely short distances. Consequently, these forces also should be the smaller, the more symmetrical are the molecules between which they act.

The van der Waals forces are therefore due to modifications in the motions of the electrons in each molecule; these modifications are caused by a very rapidly varying electric field, which is itself caused by the rapidly moving charged particles in all the nearby molecules. A different way in which an atom or molecule may be subjected to a rapidly varying electric field is by illuminating it with infrared, visible, or ultraviolet light, since light of any type is characterized by an electric field that varies with the frequency of the light. (Cf. Section 5·3.) Under these latter conditions, the interaction between the field and the substance is made evident by the phenomenon of refraction, or dispersion. It might be expected, therefore, that a relation should exist between the van der Waals forces and the molecular refraction. The attempt to go further into this relation would lie outside the scope of this book; it may, however, be remarked that, in general, two substances with the same molecular refraction may be expected to have similar van der Waals forces and so, in the absence of ionic charges or strong dipoles, similar boiling points. For a reason which should now be obvious, the van der Waals forces are sometimes referred to as *dispersion* forces. Moreover, since the mathematical theory was first worked out by London,[13,15] they are also sometimes known as *London* forces.

1·15 Repulsive Forces. So far, there have been encountered several kinds of situations in which repulsion predominates over attraction at all internuclear distances. There remains to be considered, however, the fact that, when a bond is formed, the attraction predominates only at relatively great distances, whereas repulsion predominates at shorter distances. For example, in the hydrogen molecule, equilibrium is reached when the distance between the protons is 0.74 A (0.74 angstrom unit, or 0.74×10^{-8} cm). If the protons are at a greater distance, an attraction tends to pull them closer; if they are at a shorter distance, a repulsion tends to push them farther apart. Moreover, this same effect is observed with all other covalent bonds, as well as with ionic bonds like the one in sodium chloride, and with the weaker intermolecular attractions of the dipole-dipole or van der Waals type. It will be instructive to consider how this additional type of repulsion comes into being.

The repulsive forces now under discussion, like the attractive ones considered in the preceding section, are frequently classified as van der Waals forces. When this terminology is used, two distinct classes of van der Waals forces must then, of course, be recognized. The *attractive* van der Waals forces (i.e., the dispersion or London forces) are related to the constant a of the familiar van der Waals equation for an imperfect gas (equation 1·6); the *repulsive* van der Waals forces, on the other hand,

$$\left(p + \frac{a}{v^2}\right)(v - b) = RT \tag{1·6}$$

are related to the constant b of this same equation.

As was pointed out in Section 1·8, the average distribution of charge in the hydrogen molecule can be described very roughly by Figure 1·3, in which H^+ and e^- represent the average relative positions of the pro-

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[15] F. London, *Z. Physik* **63**, 245 (1930).

tons and electrons, respectively. (Cf. also Figure 1·5.) For simplicity, the assumption may be made that the total electrostatic energy of the molecule is the same that it would have been if the particles were stationary and situated at the corners of a square, as shown. Then, just as in the dimeric sodium chloride, the energy is found to be $-2.586\ e^2/r$, where r is the side of the square. On this basis, there can be no equilibrium distance, because the energy continues to decrease (i.e., the molecule continues to become more stable) as r decreases; in fact, the energy approaches minus infinity as r approaches zero. Consequently, if no further factors intervened, the molecule would collapse into a single point. The reason why this catastrophe does not occur is that, as the two protons come closer and closer together, the two electrons tend to be squeezed out of the region between the protons. Consequently, for a very small interprotonic distance, the average distribution of charge would be more nearly that represented by Figure 1·4 or 1·6; hence a very strong repulsion results.

The squeezing out of the electrons is not considered to be the result of the fact that they have a certain definite size and so must occupy a certain definite amount of space. Actually, nothing is known about the exact size of an electron. In fact, it is not even known whether an electron has a size at all, in the usual meaning of the word. The significant point is rather that, according to quantum mechanics, an electron which is contained in a small volume must possess a large amount of kinetic energy. The smaller the volume, the greater must be this kinetic energy. Consequently, if the electrons are held in the region between the two nuclei, then, as the nuclei come closer together, and as the volume of this region decreases, the total energy of the system finally begins to increase because of the extremely rapid increase in the kinetic energies of the electrons. When this situation is realized, the energy of the system as a whole can be made lower if the electrons are allowed to wander over a larger volume, since then the resulting increase in electrostatic energy is more than counterbalanced by the decrease in kinetic energy. However, repulsion still exists in consequence of the electrostatic interactions; hence there is a most stable internuclear distance, where the electrostatic and kinetic-energy factors are just balanced.

1·16 A More Critical Discussion of the Valence Bond. So far, the discussion of interatomic and intermolecular forces has been concerned primarily with their nature and origin, and no need has yet arisen for a precise definition of a valence bond. Now, however, a more careful examination of the underlying concepts is both possible and desirable. This section is devoted to such an examination.

There are several obvious requirements which any definition must impose upon a valence bond. In the first place, the valence forces at moderate distances must be attractive, and not repulsive; in the second place, the resulting bond must be strong enough to withstand molecular collisions. This second requirement implies that an interaction between two given atoms may be describable as a valence bond at certain temperatures, but not at certain higher temperatures. For example, a valence bond may exist between two hydrogen atoms at room temperature, but not at temperatures (say, 5000°C) where elementary hydrogen is almost completely dissociated into atoms. Moreover, there must exist an intermediate temperature range in which no clear-cut decision can be made between the existence and nonexistence of a valence bond. Fortunately, however, this last complication causes little difficulty, because, in most of the examples of interest to this book, there is no such uncertainty.

A further property of a valence bond, which must be recognized in its definition, is that it acts between just two atoms, and neither between one atom and a whole group of other atoms nor between two whole groups of atoms. For example, in tetramethylammonium chloride, the positive charge of the cation resides in the entire tetramethylammonium group; hence there is no one atom which can be considered joined to the chlorine atom by an ionic bond. Similarly, in tetramethylammonium nitrate, neither ion contains a unique atom which can be considered to take part in an ionic bond. To be sure, if formal charges represented actual charges, ionic nitrogen-chlorine and nitrogen-oxygen bonds might be said to exist in the chloride and nitrate, respectively. However, formal charges do not represent actual charges, and so such a procedure could at best be only a rough first approximation. Moreover, in the nitrate there would still be ambiguity as to which one of the three equivalent oxygen atoms was the one bonded to the nitrogen atom of the cation. For these reasons, it seems advisable not to use the concept of the ionic bond in describing the above ammonium salts, but instead to speak only of a general force of electrostatic attraction.

Even with sodium chloride, in which both the cation and the anion consist of single atoms, the nature of the linkage is not easy to define. Although no difficulties arise if there is assumed to be an ionic valence bond between the sodium and chloride ions in the monomeric NaCl, complications appear as soon as the dimeric $(NaCl)_2$ of page 8 is considered. If valence and charge are correlated in the customary way, then the sodium ion with its single positive charge has here a valence of plus one; yet it interacts strongly with *two* chloride ions. If each attraction is called a valence bond, then the univalent sodium ion must be said to form two bonds. The situation is still worse in a macroscopic crystal of sodium chloride, where the still univalent sodium ion must be said to form six bonds with the nearest chloride ions, and in addition a large number of weaker bonds with more distant chloride ions.

The dilemma indicated could be resolved, of course, if the valence of sodium were considered to be one in NaCl, two in $(NaCl)_2$, and six in the crystalline solid (the weaker interactions with the more distant chloride ions in the solid being ignored). However, the present generally accepted relation between valence and charge seems too useful to be given up so readily; moreover, the suggested variations in valence correspond to no real variations in the state of the sodium ion. (Cf., for example, the distinction between univalent and bivalent copper.) As a second alternative, the sodium and chloride ions might be said to be joined by single bonds in NaCl, by half-bonds in $(NaCl)_2$, and by sixth-bonds in the crystalline solid. Then, in each instance, each sodium ion would form altogether only one bond; but the introduction of fractional bonds would make the whole treatment awkward and inconvenient. Moreover, the single bond in monomeric NaCl and the sixth-bond in the crystal do not differ as do, for example, the double bond in ethylene and the single bond in ethane.

Probably, from a purely logical point of view, the least unsatisfactory solution of the difficulty is to give up all attempts to describe any attraction between oppositely charged ions in terms of bonds. The adoption of this suggestion, however, would necessitate a rather fundamental departure from the most generally accepted terminology. In particular, the word "bond" would have to be restricted to mean a covalent bond or, at any rate, an "essentially" covalent bond, since, as was pointed out in Section 1·10, the distinction between covalent and ionic bonds is not a completely sharp one. Thus, it would be necessary to consider that in any form of sodium chloride, just as in tetramethylammonium nitrate, the oppositely charged ions were held together, not by bonds, but instead merely by their mutual electrostatic attractions. This method of avoiding the dilemma suffers from the logically important, but practically rather unimportant, defect that it provides no unambiguous description for a strong interatomic attraction which is neither essentially covalent nor essentially ionic.

Although the just-described definition of a valence bond has been adopted by some chemists,[16] it has never been widely accepted. It will, accordingly, not be employed in this book. Instead, a less extreme procedure will be followed. A valence bond may be defined as any sort of attractive force which is strong enough to withstand molecular collisions

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[16] See, for example, B. Eistert, *Tautomerie und Mesomerie*, Ferdinand Enke, Stuttgart, 1938, pages 20 ff.

at the temperature in question, and which acts between two individual atoms. Thus, covalent bonds, semipolar double bonds, coordinate bonds of the sort in the Werner complexes (Section 1·12), and ionic bonds between individual atoms, as in sodium chloride, are four types of valence bond. On the other hand, ion-dipole interactions of the sort occurring in the solvated ions (Section 1·12) are probably not strong enough to establish valence bonds. An electrostatic interaction between oppositely charged ions, of which at least one is polyatomic, is also not a valence bond because it does not act between two individual atoms; and a dipole-dipole or van der Waals interaction between molecules is not a valence bond because it satisfies neither of the two necessary conditions. This suggested definition of a valence bond does not avoid the difficulties referred to in connection with the nature of the linkages in sodium chloride. Such difficulties remain, but fortunately they do not arise with organic substances. Consequently, although their existence must be recognized, they can be ignored here.

1·17 Molecules. For the further discussion throughout this book, a molecule may be defined as a collection of atoms, which is held together by valence bonds (in the sense of the preceding paragraph), and which retains its identity in the *fluid* state (i.e., in the liquid or gaseous state or in both or in solution in a liquid solvent). A *charged* molecule is called an *ion*. The significance of this definition can be made clearer with the aid of a few examples.

A particle consisting of one sodium and one chloride ion may, as heretofore, be called a gaseous sodium chloride molecule, since it is held together by an electrostatic interaction between two individual atoms. On the other hand, a particle consisting of one tetramethylammonium and one nitrate ion, if indeed such a particle be capable of existence at all, cannot be called a gaseous tetramethylammonium nitrate molecule, since its two ions are not joined by a valence bond. A particle of this sort may instead be called an *ion-pair*. The individual ions which comprise an ion-pair are molecules in the present sense. Thus, the tetramethylammonium and nitrate ions are polyatomic molecules. The salt tetramethylammonium nitrate, therefore, consists of a mixture of dissimilar molecules.

From the viewpoint of the kinetic theory, rather than from that of organic chemistry, an ion-pair should behave in exactly the same way as does a molecule. From the former viewpoint, therefore, an ion-pair can most conveniently be called a molecule.

An important difference exists between the two types of mixture represented, for example, by tetramethylammonium nitrate and by Formalin. In the former mixture the molecular ratio of the two components must be exactly 1:1, and hence no variation in the composition is possible; consequently, an empirical formula can be assigned to this substance, even though a molecular formula cannot be assigned. In Formalin, on the other hand, the molecular ratio of the two components is not uniquely determined, since the composition of the mixture can be varied continuously within wide limits; consequently, not even an empirical formula can be assigned to this solution. A mixture like tetramethylammonium nitrate, in which the molecular ratio is invariant, may be called a *stoichiometric* mixture; one like Formalin, in which the ratio is not invariant, may be called a *nonstoichiometric* mixture.[17] Only the stoichiometric mixtures have unique compositions and empirical formulas; hence, only they can be described as *substances*.

In a diamond crystal each carbon atom is joined to four other carbon atoms by covalent single bonds. However, the crystal as a whole is not a molecule because it does not retain its identity in any fluid state. A crystal of naphthalene, on the other hand, consists of units with the formula $C_{10}H_8$. Each unit is held together by valence bonds, but only van der Waals forces act between different units. When the crystal is melted, dissolved in a liquid solvent, or vaporized, it breaks up into these $C_{10}H_8$ units, which retain their identity and so are the actual molecules of naphthalene. A hydrated sodium ion is not a single molecule but a mixture of a sodium ion and an uncertain number of water molecules. On the other hand, the Werner complex ions, such as the hexamminocobaltic ion, are to be regarded as molecules rather than as mixtures of any kind.

Since the existence of a bond depends upon the temperature, that of a molecule must do likewise. For example, two hydrogen atoms may form a molecule at room temperature but not at 5000°C. Within a certain intermediate temperature range, the existence of the molecule is uncertain. (Cf. Section 1·16.)

1·18 Isomers. Two substances are said to be *isomers* of each other if, first, they are different and, second, they have the same molecular formula. Both parts of this definition require comment.

Ordinarily, there is no ambiguity concerning whether two substances are identical or different, because, if they are different, they must differ in at least one physical or chemical property, even if that property be merely the sign of optical rotation. However, a number of examples are known in which the distinction can be made only with some arbitrari-

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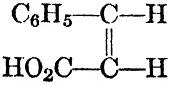
[17] The author is indebted to Professor J. K. Senior, who called to his attention the desirability of making the distinction between the two types of mixture, and who suggested the expression "stoichiometric mixture" here adopted.

ness. For example, *cis*-cinnamic acid, I, can be obtained in three crystalline forms, which melt at 68°C, 58°C, and 42°C. Since these forms



$$\begin{array}{c} C_6H_5\text{—}C\text{—}H \\ \| \\ HO_2C\text{—}C\text{—}H \end{array}$$

I

differ in melting point, they might appear to be different substances; however, they give identical melts and identical solutions. Consequently, the differences among them, since they exist only in the solid phase, must be due to differences in the ways in which the molecules are packed into the crystal, and not to any intrinsic differences in the molecules themselves. Crystallographers, who are interested in the crystal forms, would therefore have to consider that there are three isomeric (more precisely, polymorphic) *cis*-cinnamic acids. However, organic chemists, who are interested rather in the constitution of the individual molecules, would prefer to consider that there is only a single *cis*-cinnamic acid. Consequently, when hereafter the number of isomers is counted, only those substances which retain their differences in the fluid states will be considered different. This convention is justified by the fact that, since most organic compounds are usually put into some fluid state before they are caused to react with other compounds, any differences which exist only in the solid state are chemically rather unimportant; indeed, the structural theory was designed primarily for, and is best suited to, the description of fluid substances.

In view of the somewhat special definition of a molecule which was given above, the significance of the molecular formula will have to be considered. Ordinarily this formula is defined as the one which gives not only the per cent composition of the substance but also its molecular weight. In theoretical, rather than experimental, terms, it may be defined as the formula which states how many atoms of each element are present in a single molecule. Consequently, no molecular formula can be given for the stoichiometric mixture of tetramethylammonium and nitrate ions that is known as tetramethylammonium nitrate, any more than one can be given for the nonstoichiometric mixture of formaldehyde and water molecules that is known as Formalin. Moreover, methylammonium formate, II, is not an isomer of ammonium acetate, III; for, since neither substance has any molecular formula at all, the two cannot have the same one. Each of these salts is a stoichiometric mixture of

$$[H_3N\text{—}CH_3]^+[HCO_2]^- \qquad [NH_4]^+[CH_3CO_2]^-$$

II III

electrically charged molecules (i.e., ions), no one of which is isomeric with any other. Two different stoichiometric mixtures which, like methylammonium formate, II, and ammonium acetate, III, have the same composition and hence the same empirical formula may be called *stoichiomers* of one another.[18]

The foregoing definitions and distinctions may perhaps seem more confusing than helpful, but the following, less trivial examples should serve to show their significance. The two sequences of reactions given in equations 1·7 and 1·8 may first be considered.[19] The substances IV and V cannot be isolated, but they are definitely different since, on decomposition, they are transformed into different products.

$$(CH_3)_3N^+\text{—}O^- + CH_3OH \rightarrow [(CH_3)_3N\text{—}OCH_3]^+OH^- \xrightarrow{NaOC_2H_5}$$

$$\underset{\text{IV}}{[(CH_3)_3N\text{—}OCH_3]^+OC_2H_5^-} \qquad (1\cdot 7)$$

$$\text{evaporate}\Big\downarrow\text{solution}$$

$$(CH_3)_3N + C_2H_5OH + H_2CO$$

$$(CH_3)_3N^+\text{—}O^- + C_2H_5OH \rightarrow [(CH_3)_3N\text{—}OC_2H_5]^+OH^- \xrightarrow{NaOCH_3}$$

$$\underset{\text{V}}{[(CH_3)_3N\text{—}OC_2H_5]^+OCH_3^-} \qquad (1\cdot 8)$$

$$\text{evaporate}\Big\downarrow\text{solution}$$

$$(CH_3)_3N + CH_3OH + CH_3CHO$$

Although, according to the definition given above, they are stoichiomers, and not isomers of one another, it will be instructive to consider the situation which would arise if, on the basis of some other definition, they had to be treated as isomers. Later, a sharp division of all isomers into *structural* isomers and *stereo*isomers will be made. (See Chapters 4–8.) To which class would the substances IV and V then belong? If the nitrogen atoms are considered to be joined by ionic bonds to the oxygen atoms of the alkoxide ions, the isomerism might be called a new type of structural isomerism, in which the two structures differ in the natures of the bonds. Thus, in the substance IV, the methoxyl and ethoxyl groups would be linked to the nitrogen atom by covalent and ionic bonds, respectively; whereas, in the substance V, the opposite would be true. On the other hand, if attention is centered upon the relative positions in space of the methoxyl and ethoxyl groups, the isomerism might instead be called a new type of stereoisomerism. From neither point of view, however, is the situation very closely analogous to any encountered in the more

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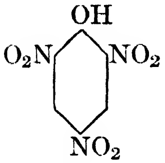
[18] The word "stoichiomer" was suggested by Professor J. K. Senior.

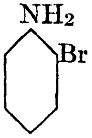
[19] J. Meisenheimer, *Ann.* **397**, 273 (1913).

familiar varieties of structural isomerism and stereoisomerism. It seems simpler and more logical, therefore, to speak of the compounds IV and V as stoichiomers than to try to classify them under the heading of isomeric substances. Indeed, it was just for the purpose of avoiding difficulties like this one and the ones discussed in the next paragraph that the above definitions of isomers and stoichiomers were devised.

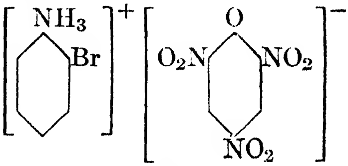
A further example in which the suggested definitions prevent a possible ambiguity is the following.[20] If a mixture of picric acid, VI, and *o*-bromoaniline, VII, is crystallized from ethyl alcohol at the boiling point of the saturated solution, there is obtained a yellow solid product, which is presumably the salt, VIII. On the other hand, if the same mixture is crystallized from chlorobenzene at a temperature above 95°C, there is instead obtained a red solid product, which is presumably an addition compound analogous to naphthalene picrate. (See Section 2·8.) If the yellow form is heated to a temperature above 95°C, it changes without melting into the red form; conversely, if the red form is cooled to a temperature below 95°C, it changes to the yellow form. Moreover, this type of behavior is not restricted to crystalline solids, but has been observed also in the fluid state.[21] Thus, an equimolecular mixture of diethylaniline, IX, and 3,5-dinitrobenzoic acid, X, gives a colorless solution in water, but a yellowish red one in any of several organic solvents, such as alcohol, ether, and chloroform. Since the colorless aqueous solution is a good conductor of the electric current, it presumably contains the salt, XI; on the other hand, the colored solutions



VI



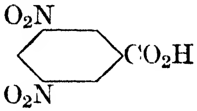
VII



VIII

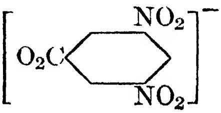
$C_6H_5—N(C_2H_5)_2$

IX



X

$[C_6H_5—NH(C_2H_5)_2]^+$



XI

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[20] E. Hertel, *Ber.* **57**, 1559 (1924).

[21] H. Ley and R. Grau, *Z. physik. Chem.* **100**, 271 (1922).

in the organic solvents presumably contain greater or smaller quantities of the addition compound. According to the definitions given above, the two members of either pair of substances are not isomers of one another but are instead just two different stoichiometric mixtures (i.e., stoichiomers). If, on the other hand, they were considered to be isomers, the same difficulty as before would arise in regard to whether they are structural isomers or stereoisomers.

It has, of course, been known for many years that, if stoichiomers are not distinguished from isomers, the classification of isomers can become very complicated. Werner, for example, recognized several different types of "isomeric" complex salt.[22] Thus, he used the expression "coordination isomers" to describe such pairs of substances as XII and XIII, or as XIV and XV, and the expression "ionization metamers" to describe such further pairs as XVI and XVII. Moreover, he considered

$$[Co(NH_3)_6]^{+++}[Cr(CN)_6]^{\equiv}$$
XII

$$[Cr(NH_3)_6]^{+++}[Co(CN)_6]^{\equiv}$$
XIII

$$[Co(NH_3)_6]^{+++}[Co(NO_2)_6]^{\equiv}$$
XIV

$$[Co(NO_2)_2(NH_3)_4]^{+}[Co(NO_2)_4(NH_3)_2]^{-}$$
XV

$$[CoBr(NH_3)_5]^{++}SO_4^{=}$$
XVI

$$[Co(SO_4)(NH_3)_5]^{+}Br^{-}$$
XVII

that the two hydrated salts XVIII and XIX are "hydration isomers" of one another. Somewhat later, Hertel[20] applied the term "complex isomers" to the two different

$$[CrCl(H_2O)_5]^{++}\,2Cl^{-} + H_2O$$
XVIII

$$[CrCl_2(H_2O)_4]^{+}Cl^{-} + 2H_2O$$
XIX

products obtained from an acidic polynitro compound (like picric acid, VI, or 3,5-dinitrobenzoic acid, X) and an aromatic amine (like *o*-bromoaniline, VII, or diethylaniline, IX, respectively). In this book, however, all these several types of "isomer" are treated not as isomers, but as stoichiomers, and no attempt is made to subdivide the stoichiomers into still smaller classes.

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[22] A. Werner, *Neuere Anschauungen auf dem Gebiete der anorganischen Chemie*, Friedrich Vieweg und Sohn, Braunschweig, 4th ed., 1920, pages 327 ff.

2.

Addition Compounds

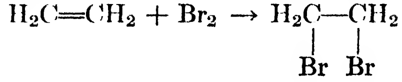
2·1 Distinguishing Characteristics of Addition Compounds. An addition compound can be defined as a substance that is formed by an addition reaction, i.e., by a direct combination of two (or more) simpler substances. The addition compound necessarily contains all the atoms that were present in the original reagents; hence methyl formate, for example, is not an addition compound since, in its preparation from methyl alcohol and formic acid, two hydrogen atoms and one oxygen atom are eliminated as a molecule of water.

Addition compounds in general can be divided into three main classes, the boundaries among which are not always completely sharp and unambiguous. These classes consist, respectively, of those addition compounds which can be interpreted on the basis of the simple structural theory; of those which can be interpreted only on the basis of an extended structural theory; and of those which cannot at the present time be interpreted on any known basis.

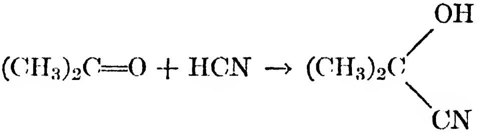
Inasmuch as addition compounds are defined with reference to their method of preparation, rather than with reference to their properties, these substances may appear not to be sharply distinguished, in any really fundamental sense, from all the other substances which are not addition compounds. (Cf. page 19.) This objection is indeed valid when it is applied to the addition compounds that belong to the first of the three classes just defined, since such compounds can usually be formed not only by addition reactions, but also by reactions of entirely different types. (See Section 2·2.) The objection is, however, not entirely valid when it is applied to the addition compounds of the two remaining classes, since such further compounds can usually not be formed except by addition reactions; and since, moreover, these substances can be distinguished structurally by the fact that their existence is explainable (if at all) only with the aid of an extended structural theory.

2·2 Addition Compounds Which Can Be Interpreted on the Basis of the Simple Structural Theory. Innumerable substances of this type are known. An example is provided by ethylene bromide, which is formed by the addition of bromine to ethylene, as in equation

2·1. Similarly, acetone cyanohydrin is formed by the addition of hydrogen cyanide to acetone, as in equation 2·2. In all examples of this kind, at least one of the initial compounds has a multiple linkage, which is changed in the addition compound into one of lower order (often into a single bond). Clearly, addition compounds of this first type are too familiar to require further special comment here. Moreover, for the reason given in the preceding paragraph, such addition compounds do not form a sharply distinguished class of substances; ethylene bromide, for example, can be made not only by the addition of bromine to ethylene (equation 2·1), but also by a substitution reaction between ethyl bromide and bromine (equation 2·3).

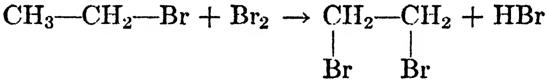


$$H_2C{=}CH_2 + Br_2 \rightarrow \underset{Br}{H_2C}{-}\underset{Br}{CH_2} \qquad (2\cdot1)$$



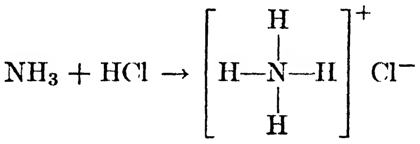
(2·2)

$$(CH_3)_2C{=}O + HCN \rightarrow (CH_3)_2C\begin{matrix}OH\\CN\end{matrix} \qquad (2\cdot2)$$

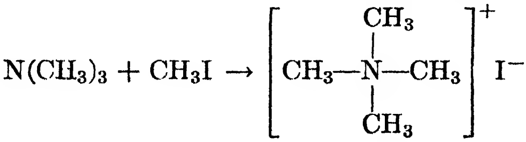


$$CH_3{-}CH_2{-}Br + Br_2 \rightarrow \underset{Br}{CH_2}{-}\underset{Br}{CH_2} + HBr \qquad (2\cdot3)$$

2·3 Onium Salts. The second class of addition compounds consists of those which can be assigned definite structures only on the basis of an extension of the simple valence theory. The most familiar examples of such addition compounds are the ammonium salts, like ammonium chloride (equation 2·4) and tetramethylammonium iodide (equation 2·5). In each of these reactions, the nitrogen atom increases its covalence from three to four and, moreover, acquires a positive formal charge.

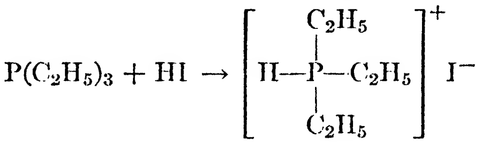


$$NH_3 + HCl \rightarrow \left[\begin{matrix} & H & \\ & | & \\ H{-} & N & {-}H \\ & | & \\ & H & \end{matrix}\right]^+ Cl^- \qquad (2\cdot4)$$

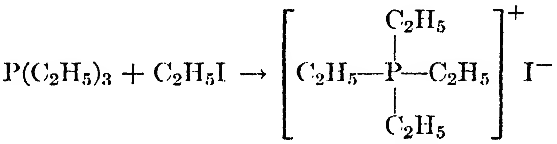


$$N(CH_3)_3 + CH_3I \rightarrow \left[\begin{matrix} & CH_3 & \\ & | & \\ CH_3{-} & N & {-}CH_3 \\ & | & \\ & CH_3 & \end{matrix}\right]^+ I^- \qquad (2\cdot5)$$

The ammonium salts constitute only one of several different classes of substance, which are known collectively as the *onium compounds.* In general, an onium compound can be defined as a substance formed by an addition reaction, in the course of which some atom increases its covalence by one unit and, in doing so, increases its formal charge algebraically by one unit. For example, phosphonium compounds, which are completely analogous to the ammonium ones, are well known; the reactions by which such compounds are formed are illustrated in equations 2·6 and 2·7. Sulfonium compounds also exist; they are produced

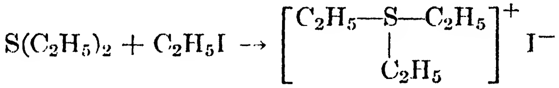


$$\mathrm{P(C_2H_5)_3 + HI \rightarrow \left[\begin{array}{c} C_2H_5 \\ | \\ H{-}P{-}C_2H_5 \\ | \\ C_2H_5 \end{array}\right]^+ I^-} \qquad (2\cdot6)$$



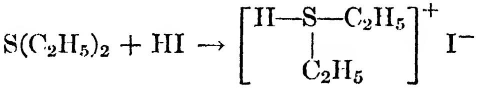
$$\mathrm{P(C_2H_5)_3 + C_2H_5I \rightarrow \left[\begin{array}{c} C_2H_5 \\ | \\ C_2H_5{-}P{-}C_2H_5 \\ | \\ C_2H_5 \end{array}\right]^+ I^-} \qquad (2\cdot7)$$

in reactions like the one illustrated in equation 2·8, but apparently *not*



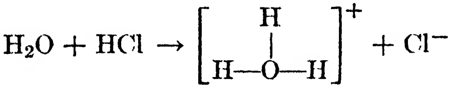
$$\mathrm{S(C_2H_5)_2 + C_2H_5I \rightarrow \left[\begin{array}{c} C_2H_5{-}S{-}C_2H_5 \\ | \\ C_2H_5 \end{array}\right]^+ I^-} \qquad (2\cdot8)$$

in reactions like the one shown in equation 2·9.



$$\mathrm{S(C_2H_5)_2 + HI \rightarrow \left[\begin{array}{c} H{-}S{-}C_2H_5 \\ | \\ C_2H_5 \end{array}\right]^+ I^-} \qquad (2\cdot9)$$

The oxonium compounds are considerably more important than the phosphonium and sulfonium compounds. Almost every substance which contains oxygen has a greater or less ability to form such compounds with acids. For example, the ionization of hydrochloric acid in water (which goes very nearly to completion) must really be represented by



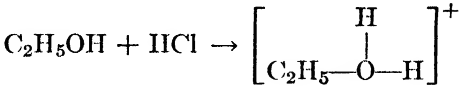
$$\mathrm{H_2O + HCl \rightarrow \left[\begin{array}{c} H \\ | \\ H{-}O{-}H \end{array}\right]^+ + Cl^-} \qquad (2\cdot10)$$

equation 2·10, and not by equation 2·11. (Cf. Section 3·2.) It is the

$$\mathrm{HCl \rightarrow H^+ + Cl^-} \qquad (2\cdot11)$$

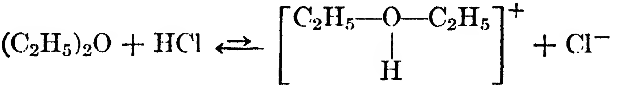
H_3O^+ ion, or hydrated proton, which in discussions of aqueous solutions is often referred to loosely as the hydrogen ion; it can be designated more precisely as either the *oxonium* ion, the *hydroxonium* ion, or the *hydronium* ion.

In alcohols, and in other ionizing solvents, the situation is similar (equation 2·12). Even when the ionization is extremely small, the



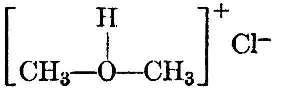
$$C_2H_5OH + HCl \rightarrow \left[\begin{array}{c} H \\ | \\ C_2H_5-O-H \end{array}\right]^+ + Cl^- \qquad (2\cdot 12)$$

formation of some oxonium compound undoubtedly occurs if the solvent contains oxygen, as in equation 2·13. In a few instances, the addition



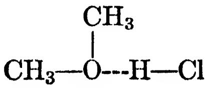
$$(C_2H_5)_2O + HCl \rightleftharpoons \left[\begin{array}{c} C_2H_5-O-C_2H_5 \\ | \\ H \end{array}\right]^+ + Cl^- \qquad (2\cdot 13)$$

compound has been isolated; one such product is formed in the reaction between methyl ether and hydrogen chloride. This substance is a liquid which boils at −2°C and dissociates increasingly into its components as the temperature is raised. In view of its physical properties, it can hardly have the salt-like structure I, analogous to that of ammonium chloride; probably the molecules are held together by hydrogen bonds, as in structure II. This conclusion does not imply, however, that there may not be a small amount of the ionized "salt" I present in equilibrium



$$\left[\begin{array}{c} H \\ | \\ CH_3-O-CH_3 \end{array}\right]^+ Cl^-$$

I



$$\begin{array}{c} CH_3 \\ | \\ CH_3-O{-}{-}H-Cl \end{array}$$

II

in the liquid phase.

Ketones, and especially α,β-unsaturated ketones, are apparently able to form more stable oxonium compounds than are the ethers. Benzalacetophenone, for example, dissolves in concentrated sulfuric acid to form a salt, as is shown in equation 2·14.[1] That a rather significant

$$C_6H_5CH{=}CH{-}CO{-}C_6H_5 + H_2SO_4 \rightarrow$$
$$[C_6H_5CH{=}CH{-}COH{-}C_6H_5]^+HSO_4^- \qquad (2\cdot 14)$$

chemical change, and not merely a physical solution, has occurred is indicated by the fact that, although the original ketone has only a light yellow color when either alone or dissolved in, say, alcohol, its solution in concentrated sulfuric acid is intensely yellow. For this reason, this oxonium compound is called a halochromic salt, as is also every other

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[1] S. v. Kostanecki and G. Rossbach, *Ber.* **29**, 1488 (1896).

one of similar type. (Greek, ἅλς, ἁλός, salt; χρῶμα, color.) Similarly, if the light yellow dibenzalacetone, III, is dissolved in ether and then treated with dry hydrogen chloride, there are formed a yellow and a colorless monohydrochloride, and a red and a colorless dihydrochloride.

$$C_6H_5CH{=}CH{-}CO{-}CH{=}CHC_6H_5$$

III

$$C_6H_5CH{=}CH{-}CO{-}CH_2{-}CHCl{-}C_6H_5$$

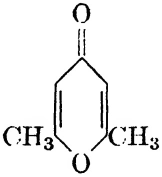
IV

$$C_6H_5{-}CHCl{-}CH_2{-}CO{-}CH_2{-}CHCl{-}C_6H_5$$

V

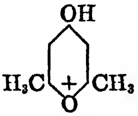
The two colorless addition compounds presumably have the structures IV and V, respectively, whereas the colored products are presumably halochromic salts.

Especially stable salts are formed, but without the appearance of color, by dimethyl-γ-pyrone, VI, and by other substances containing the

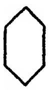


VI

γ-pyrone ring. There has been considerable controversy in regard to the structure of the cation in these salts. The best view at the present time is that the proton is attached to the carbonyl oxygen atom, and that the ring has a pseudo-aromatic character, analogous to that of benzene. The structure can, accordingly, be written as VII, where, as in the con-

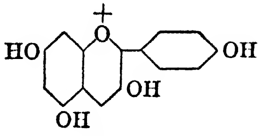


VII

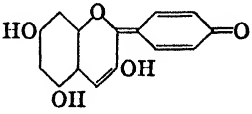


VIII

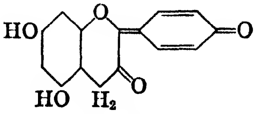
ventional structure, VIII, of benzene, no attempt is made to describe the finer structural details. Presumably the same factors which operate to make the benzene ring itself so stable operate here also to make this cation stable. (See Section 10·10.) A further example of an oxonium cation which owes its relatively great stability to the presence of a pseudo-aromatic ring, and which also can be considered part of an addition compound, is shown by the ion IX.[2] The parent substance from



IX



X



XI

which this ion is derived is the so-called color base, X or XI, of pelargonidin, a common flower-pigment, occurring (as a glycoside) in the corn flower, salvia, some dahlias, and various other flowers. This color base is itself purple; in basic solution it forms blue salts by means of the phenolic hydroxyl groups; and in acid solution it gains a proton to form red salts containing the ion IX. Clearly, therefore, a wide range in color is possible with only this single pigment. (In many instances, of course, variations in the colors of flowers are due to the presence of different pigments of other types, as well as to variations in the acidity or basicity of the sap.)

In a sufficiently acidic medium, even such substances as the simple saturated ethers may be transformed largely into oxonium salts. Ethyl ether, for example, produces nearly twice the lowering of the freezing point of 100 per cent sulfuric acid that would be expected on the basis of its molecular formula.[3] Consequently, under the conditions stated, reaction 2·15 must go nearly, if not quite, completely to the right. The

$$(C_2H_5)_2O + H_2SO_4 \rightarrow [(C_2H_5)_2OH]^+ + [HSO_4]^- \qquad (2\cdot 15)$$

solubility of ether, and of nearly all other substances containing oxygen, in concentrated sulfuric acid is partially, although probably not entirely, due to this salt formation.

The reaction in which an oxonium salt is produced by the addition of an acid to an oxygen-containing substance is entirely analogous to the one in which an ammonium salt is produced by the addition of an acid to an amine. Consequently, the original oxygen-containing substance, like the amine, must be said to neutralize the acid and hence to act as a base in the addition reaction. (See also Chapter 3.) The ionization constants of a few "oxygen bases" in aqueous solution have, in fact, been estimated in ways that cannot be discussed here; some values are listed in Table 2·1. (For the significance of the constant K_b, see equation 3·14 on page 79.) The last three values in this table are given in order

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[2] Cf. K. P. Link in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume II, Chapter 13, 2nd ed., 1943, Volume II, Chapter 18.

[3] A. Hantzsch, *Z. physik. Chem.* **61**, 257 (1907); **65**, 41 (1908).

TABLE 2·1

IONIZATION CONSTANTS OF SOME VERY WEAK BASES IN WATER[a]

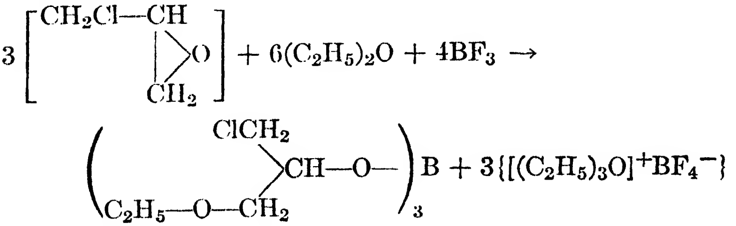
Substance	K_b
Dimethyl-γ-pyrone[b]	2×10^{-14}
p-Methylacetophenone	4.5×10^{-20}
Benzalacetophenone	2.5×10^{-20}
Acetophenone	1×10^{-20}
p-Bromoacetophenone	4×10^{-21}
Anthraquinone	7×10^{-23}
p-Nitroaniline	1.3×10^{-13}
2,4-Dinitroaniline	4×10^{-19}
2,4,6-Trinitroaniline	5×10^{-24}

[a] Except as noted, these values are obtained from L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, New York, 1940, pages 266, 271.

[b] P. Walden, *Ber.* **34,** 4185 (1901).

to show that the oxygen compounds, although extremely weak bases, are not tremendously weaker than certain other substances, the basic characters of which are generally recognized.

An important property of amines is their ability to form ammonium ions not only by the addition of protons, but also by the addition of alkyl cations. In particular, amines lead ultimately to quaternary ammonium compounds in which each nitrogen atom is joined to four hydrocarbon residues. (Cf. equation 2·5.) Moreover, the phosphines and sulfides behave similarly and give the analogous quaternary phosphonium and tertiary sulfonium salts. (Cf. equations 2·7 and 2·8, respectively.) It might be expected, therefore, that the tertiary oxonium compounds also should be obtainable. Only a very small number of such substances are known, however. The cations derived from dimethyl-γ-pyrone and from pelargonidin might be said to belong to this class, but they are rather special in that they do not have three distinct groups joined to the oxygen atom. A more typical example is provided by Meerwein's triethyloxonium cation,[4] which can be made by either of the reactions 2·16 or 2·17. Similar salts with the $SbCl_6^-$, $AlCl_4^-$, and



(2·16)

$$(C_2H_5)_2O + C_2H_5F + BF_3 \xrightarrow[\text{weeks}]{\text{3 or 4}} [(C_2H_5)_3O]^+BF_4^- \qquad (2\cdot 17)$$

---

[4] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. prakt. Chem.* [2] **147,** 257 (1937).

$FeCl_4^-$ anions have also been made, but the cation decomposes if the attempt is made to associate it with less complex anions or to derive from it the corresponding base. That these substances are true salts is shown by the fact that, for example, the one with the $SbCl_6^-$ anion is a good conductor of the electric current when it is dissolved in liquid sulfur dioxide. The substances are all decomposed by water.

The hydrated cations referred to in Sections 1·6 and 1·12 may be said, in at least a purely formal sense, to be parts of oxonium salts or, more generally, of oxonium electrolytes; for, to the extent that a shared-electron bond exists between the metal atom and the oxygen atom, the latter is indeed seen to take part in three covalent bonds and to carry a formal positive charge.

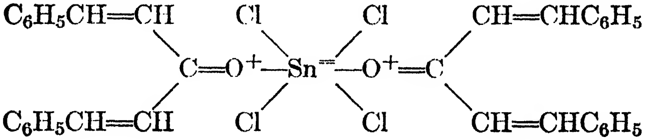
2·4 Onium Compounds Which Are Not Electrolytes.[5] So far, the various (electrically neutral) oxonium compounds that have been discussed have been electrolytes, consisting of distinct cations and anions. Other types of onium compound, however, are not only possible but very common and very important. This statement is especially true of the *oxonium* compounds, to which the following discussion will be restricted. Typical examples are provided by the addition compounds formed between, on the one hand, substances like aluminum chloride, boron fluoride, or stannic chloride, and on the other hand, organic oxygen-containing substances. Some characteristic examples are the ones to which structures I, II, and III may be assigned. Substances of this type are frequently distinguished from the addition compounds of the first class and from the onium electrolytes considered previously, by being called *molecular compounds*. This same term is also used generally for the description of all the remaining types of addition compound to be described below. In general, an addition compound is called a molecular compound if it neither belongs, like ethylene bromide and acetone cyanohydrin, to the simple first class, nor is an onium electrolyte.

$(C_6H_5)_2C{=}O^+{-}Al^-Cl_3$

I

$(CH_3)_2O^+{-}B^-F_3$

II



III

2·5 "Carbonium" Salts. A further type of addition compound, which is commonly, but erroneously, referred to as an onium salt, is

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[5] For numerous further examples, see P. Pfeiffer, *Organische Molekülverbindungen*, Ferdinand Enke, Stuttgart, 1st ed., 1922, 2nd ed., 1927.

represented by the "carbonium" salt I formed from triphenylmethyl chloride and aluminum chloride. This highly colored "halochromic salt"

$$[(C_6H_5)_3C]^{+}AlCl_4^{-}$$

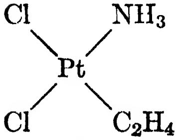
I

has definite salt-like properties, and doubtless it is actually composed of the cation and anion stated. However, the covalence of the central carbon atom of the cation has not increased, but rather has decreased, in the transition from the neutral triphenylmethyl chloride molecule to the positive triphenylmethyl ion; the term "carbonium" is therefore inappropriate. For this reason, the alternative word "carbenium" has been proposed;[6] it has not, however, been widely adopted. Closely related to the salt I are the further halochromic salts[7] such as triphenylmethyl perchlorate, II, and bisulfate, III, which, however, cannot be classified as addition compounds, and so are out of place here.

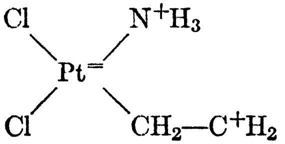
$$[(C_6H_5)_3C]^{+}ClO_4^{-} \qquad [(C_6H_5)_3C]^{+}HSO_4^{-}$$

II III

The platinum compound, IV,[8] would have somewhat more right to be termed a carbonium compound, if its structure could legitimately be written more explicitly as V, and if it could therefore be considered a derivative of a hypothetical, highly polarized ethylene molecule with structure VI. Moreover, the situation is similar in various other complexes that are formed by the addition of unsaturated hydrocarbons to compounds containing metallic atoms or cations; some characteristic examples of such further substances may be represented noncommittally as VII,[9] VIII,[10] IX,[11] and X.



IV



V

$$^{-}\ddot{C}H_2—C^{+}H_2$$

VI

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[6] W. Dilthey and R. Dinklage, *Ber.* **62**, 1834 (1929); B. Eistert, *Tautomerie und Mesomerie*, Ferdinand Enke, Stuttgart, 1938, page 27.

[7] For further discussion of these salts, see L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, New York, 1940, pages 54 f.

[8] For discussion of this and other analogous platinum compounds, see J. Chatt, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **43**, 120 (1946).

[9] W. F. Eberz, H. J. Welge, D. M. Yost, and H. J. Lucas, *J. Am. Chem. Soc.* **59**, 45 (1937); see also S. Winstein and H. J. Lucas, *ibid.* **60**, 836 (1938).

[10] W. C. Gangloff and W. E. Henderson, *J. Am. Chem. Soc.* **39**, 1420 (1917).

[11] I. L. Kondakov, F. Balaš, and L. Vít, *Chem. Listy* **24**, 1, 26 (1930); *Chem. Zentr.* **1930**, I, 3287.

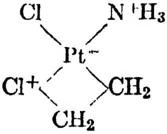
$$[(CH_3)_2C{=}CH_2 \cdot Ag]^+ \qquad (CH_3)_2C{=}CH_2 \cdot AlCl_3 \cdot 2CH_3OH \cdot H_2O$$

VII VIII

$$(CH_3)_2C{=}CHCH_3 \cdot ZnCl_2 \qquad Ni(CN)_2 \cdot NH_3 \cdot C_6H_6$$

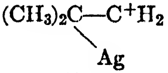
IX X

There is reason to doubt that structure V and its analogs can be accurate descriptions of the respective substances or ions; in fact, a carbon atom with only six electrons in its valence shell, and hence with a positive formal charge, is seldom, if ever, encountered in a stable molecule or ion, unless it is directly linked to several aromatic rings. (Cf. the salts I–III.) For the compounds IV, VIII, and IX, alternative *chloronium* structures can be written; thus, for the first of these three substances, structure XI seems not at all unreasonable. With the remaining compounds VII and X, however, no very closely analogous representations are possible. Still a

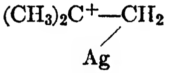


XI

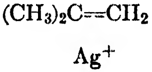
further suggestion, which is of greater generality than the one just discussed, can be illustrated with reference to the ion VII. It is possible that the average distribution of the electrons in this ion is intermediate among the average distributions characteristic of structures XII–XV.[12] (Cf. Chapter 10.) No definite decision



XII

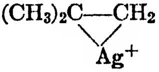


XIII



$$\underset{Ag^+}{(CH_3)_2C{=}CH_2}$$

XIV



XV

among these various possibilities can at present be made. Perhaps no single explanation applies to all the addition compounds here considered.

2·6 The Hydrogen Bond.[13]

A further type of addition compound that can be interpreted only on the basis of an extension of the simple structural theory is presented by those substances in which individual molecules are held together by the particularly strong dipole-dipole interaction known as the *hydrogen bond* or *hydrogen bridge*. The dimeric form of hydrogen fluoride, for example, may be written as in structure I, where the broken line, as before (see Section 1·7), represents the electrostatic attraction between the two monomeric molecules. It should

$$H{-}F{\cdots}H{-}F$$

I

---

[12] H. J. Lucas, R. S. Moore, and D. Pressman, *J. Am. Chem. Soc.* **65**, 227 (1943).

[13] For general discussions of the hydrogen bond, see L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, 1st ed., 1939, 2nd ed., 1940, Chapter IX; G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 44 ff.; M. Davies, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **43**, 5 (1946); L. Hunter, *ibid.* **43**, 141 (1946).

be observed that, on the basis of the definition introduced in the preceding chapter, the linkage between the two fluorine atoms cannot be classified definitely as a bond; for, although it acts between two individual atoms, it is broken with relative ease by molecular collisions. For this reason, the term "hydrogen bridge" might be preferable to "hydrogen bond," since the existence of any bond at all may be questioned. However, present usage favors the latter, less precise expression, which will therefore be used hereafter.

The existence of the hydrogen bond was at one time considered to show that a hydrogen atom can form as many as two covalent bonds; the structure of dimeric hydrogen fluoride was accordingly written in the two equivalent forms II and III. At the present time, however, it is generally believed that a hydrogen atom cannot

$$\underset{\text{II}}{\mathrm{H{-}F{-}H{-}F}} \qquad\qquad \underset{\text{III}}{\mathrm{H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{F}}:H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{F}}:}}$$

have more than two electrons in its valence shell. (Cf. pages 12 and 423.) This earlier interpretation of the hydrogen bond has therefore been completely abandoned. A further and more recent suggestion that the hydrogen bond is due to a resonance effect (cf. Chapter 10) is also unsatisfactory.[13] There is, in fact, no reason to doubt that, as was stated above, the bond or bridge in question is largely, if not entirely, the result of an exceptionally large dipole-dipole interaction.

Historically, the concept of the hydrogen bond seems to have been used first to explain the fact that quaternary ammonium hydroxides are incomparably stronger bases than are ammonia and the primary, secondary, and tertiary amines.[14] An apparently reasonable interpretation of this fact, which had previously been more or less tacitly assumed to be correct, is that, with ammonia, for example, the equilibrium depicted in equation 2·18 is greatly in favor of the free ammonia plus water, so

$$NH_3 + H_2O \rightleftarrows NH_4OH \rightleftarrows NH_4^+ + OH^- \qquad (2\cdot 18)$$

that very little ammonium hydroxide is present in either its ionized or its un-ionized form; consequently, even though the ammonium hydroxide which is present is considered to be highly ionized, the resulting concentration of hydroxide ion must be low. Moreover, according to this same proposed explanation, a quaternary hydroxide, like tetramethylammonium hydroxide, can dissociate only into ions, as in equation 2·19. Consequently, since the hydroxide is again considered to be

$$[(CH_3)_4N]^+OH^- \rightleftarrows [(CH_3)_4N]^+ + OH^- \qquad (2\cdot 19)$$

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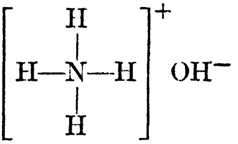
[14] T. S. Moore and T. F. Winmill, *J. Chem. Soc.* **101,** 1635 (1912). For a still earlier and somewhat similar suggestion in connection with the structures of *o*-hydroxyazo compounds, see G. Oddo and E. Puxeddu, *Gazz. chim. ital.* **36,** II, 1 (1906); *Chem. Zentr.* **1906,** II, 1191.

highly ionized, the concentration of hydroxide ion is relatively great.

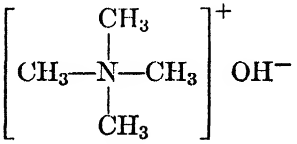
In 1912, however, Moore and Winmill[14] brought forth some experimental evidence which purported to show that the concentration of un-ionized ammonium hydroxide (as well as that of an un-ionized primary, secondary, or tertiary ammonium hydroxide) is far from small enough to account for the low base strength of ammonia (or for that of a primary, secondary, or tertiary amine). Although their experiments might no longer be considered very convincing, the conclusion to which they came is still regarded as, at any rate, qualitatively correct. In other words, it is at the present time commonly assumed that the explanation given in the preceding paragraph is incorrect, and that there really is a marked difference in the degrees of dissociation of the various ammonium hydroxides.

This conclusion is somewhat surprising since, on the basis of the electronic theory of valence, there is no way in which an un-ionized molecule of any ammonium hydroxide can exist at all, no matter how many hydrogen atoms are attached to the nitrogen atom. Structures IV and V are completely analogous to each other and also to those of the intermediate primary, secondary, and tertiary ammonium hydroxides. In none of these structures is the hydroxyl group joined to the ammonium group by a valence bond. There is thus no obvious reason why ammonium hydroxide, IV, should be only partially dissociated, whereas its tetramethyl derivative, V, is almost completely dissociated.



$$\left[\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{N}}{-}H}\right]^+ \mathrm{OH^-}$$

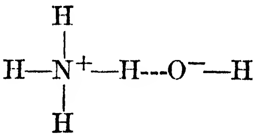
IV



$$\left[\mathrm{CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{N}}{-}CH_3}\right]^+ \mathrm{OH^-}$$

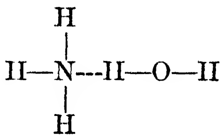
V

Moore and Winmill perceived the difficulty just outlined, although they naturally described it in the language of their day and without the benefit of the more modern electronic theories. In order to explain their data, they therefore proposed that, as long as at least one hydrogen atom remains attached to the nitrogen atom of the ammonium ion, this hydrogen atom can form a link between the nitrogen and oxygen atoms. In ammonium hydroxide, and in the primary, secondary, and tertiary ammonium hydroxides, such links are possible, and so the undissociated molecules can exist; in tetramethylammonium hydroxide, on the other hand, the link is not possible, and so an undissociated molecule cannot exist. In modern terminology, undissociated ammonium hydroxide can thus be written as either VI or VII (it is not certain which structure is preferable), whereas tetramethylammonium hydroxide must still be



$\mathrm{H-\overset{H}{\underset{H}{N}}^{+}-H\cdots O^{-}-H}$

VI

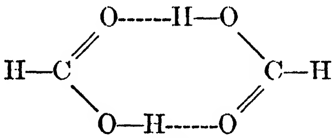


$\mathrm{H-\overset{H}{\underset{H}{N}}\cdots H-O-H}$

VII

written in the original manner, V.

Since 1912 the hydrogen bond has been found to be important in many fields of chemistry.[13] The association of hydrogen fluoride and, in general, of all compounds containing hydroxyl or amino groups is considered due to hydrogen bonds. As should be apparent from the typical structures which have already been given, such association can, in principle, proceed to any desired extent. In other words, there is no natural upper limit to the value of the index n in, say, $(HF)_n$. However, certain of the lower carboxylic acids are known to form stable dimers which are not entirely dissociated even in the gaseous state, and which show little, if any, tendency to come together into still larger aggregates. An example which has been investigated rather carefully is provided by formic acid, the dimeric form of which has been assigned structure VIII.[15]



VIII

From a study of the effect of temperature upon the position of the equilibrium between the monomeric and dimeric forms,[16] the conclusion has been drawn that about 14 kcal is required to break up 1 mole of the dimer into 2 moles of the monomer. It follows, therefore, that each of the 2 equivalent hydrogen bonds has an energy of about 7 kcal per mole. This value, which illustrates the order of magnitude of the energies of all the hydrogen bonds between 2 oxygen atoms for which data are available, may be compared with the energies of 25–100 kcal per mole that are characteristic of most single covalent bonds. Obviously, therefore, the hydrogen bond, although it is very strong for a dipole-dipole interaction, is really a rather weak kind of interaction. Dimeric formic acid may be considered to represent a borderline case between a single molecule and an aggregate composed of two different molecules.

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[15] See, for example, J. Karle and L. O. Brockway, *J. Am. Chem. Soc.* **66**, 574 (1944).
[16] A. S. Coolidge, *J. Am. Chem. Soc.* **50**, 2166 (1928).

Even in the gas phase, this dimer holds together to a certain extent at sufficiently low temperatures; nevertheless, its stability is much less than is that of a typical molecule. The question is, of course, merely another aspect of the previous one whether the hydrogen bond is really a bond or not. (See page 47.)

An important limitation upon hydrogen bonds is that they exist only between the most electronegative elements. In fact, fluorine, oxygen, and (to a smaller extent) nitrogen are the only elements which enter into such unions at all frequently; in general, the more electronegative the atoms that are joined, the stronger is the hydrogen bond between them. Dipole-dipole interactions involving chlorine atoms are ordinarily too weak to be classed as true hydrogen bonds; the ones involving the still less electronegative carbon atoms are ordinarily much weaker still. To be sure, hydrogen cyanide is a highly associated liquid, presumably as a result of hydrogen bonds of the type shown in structure IX. Here, however, the carbon atoms have lost to the nitrogen atoms a considerable part of their share of the valence electrons; hence, on account of their resulting net positive charges, their attraction for electrons must be considerably greater than usual. Consequently, in this respect, they resemble the atoms of a more electronegative element.

$$\mathrm{H{-}C{\equiv}N{--}H{-}C{\equiv}N}$$

IX

The reason for this limitation should be apparent. If, as has been assumed throughout the previous discussion, the hydrogen bond is the result of a dipole-dipole interaction, its strength must certainly increase with the magnitudes of the two dipoles involved. Only if the atoms which are joined by the hydrogen bond are strongly electronegative can these magnitudes be sufficiently great to produce an appreciable binding. It may seem strange, however, that dipole-dipole interactions are never strong enough to cause association unless *hydrogen* atoms are present. For example, the dipole moment of the carbon-nitrogen bond in methyl cyanide is about 3.3 D, whereas that of the hydrogen-oxygen bond in water is only about 1.6 D.[17] (The so-called Debye unit, or debye, which is here represented by the letter D, is defined as 10^{-18} electrostatic unit of electric moment.) The moment of the former bond is therefore approximately twice as great as is that of the latter. Nevertheless, methyl cyanide is not noticeably associated, whereas water is highly associated. The explanation of this apparent discrepancy is possibly geometrical. The energy of interaction between two dipoles de-

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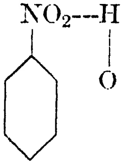
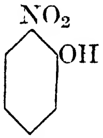
[17] Cf. N. V. Sidgwick, *Some Physical Properties of the Covalent Link in Chemistry*, Cornell University Press, Ithaca, 1933, pages 147 ff.

creases extremely rapidly as the distance between them increases. Consequently, such an interaction cannot be strong unless the two dipoles can come very close to each other. Apparently, only the hydrogen atom is small enough to permit this necessary close approach. The further fact that the hydrogen atom is univalent is doubtless important also in decreasing the geometrical interference to a strong bond, since, with bi- and polyvalent atoms, the repulsions between the additional atoms or groups that are always present should hinder close approach. (Cf. Sections 9·6 and 9·7.)

Hydrogen bonds can exist not only between two different molecules, but also between two parts of the same molecule. Although, in the latter event, the substance can of course no longer be regarded as an addition compound in any useful sense, such *intra*molecular hydrogen bonds will nevertheless, for the sake of continuity, be discussed here. *o*-Nitrophenol, for example, should be written as X and not as XI, since



X



XI

one of the oxygen atoms of the nitro group is "hydrogen-bonded" to that of the hydroxyl group. As a result of this intramolecular hydrogen bond, no free hydroxyl group remains for the production of an *inter*molecular bond. Consequently, the substance differs from its *meta* and *para* isomers in being not associated.[18] The fact that *o*-nitrophenol has a much higher vapor tension than does either of these other two compounds, and, in particular, that it alone is volatile with steam is an immediate consequence of this difference. A further consequence is that (at 60°C) *o*-nitrophenol is only one-fifth as soluble in water as is the *para* compound, but is 127 times as soluble in benzene; clearly these figures show that the former substance is much less polar than the latter. On the other hand, no such striking difference in solubilities exists between *m*- and *p*-nitrophenol; this fact could have been anticipated, inasmuch as an intramolecular hydrogen bond in either compound is geometrically impossible. (See the following paragraph.)

Intramolecular hydrogen bonds of the sort in *o*-nitrophenol are encountered throughout organic chemistry. Their existence has been shown most commonly by a spectroscopic method[19] which cannot be

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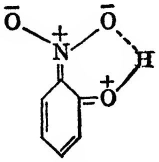
[18] Cf. E. N. Lassettre, *Chem. Revs.* **20**, 259 (1937).

[19] See, for example, G. E. Hilbert, O. R. Wulf, S. B. Hendricks, and U. Liddel, *J. Am. Chem. Soc.* **58**, 548 (1936).

discussed here; studies of solubility, association, and volatility have also provided useful criteria. The following rules governing the occurrence of such intramolecular hydrogen bonds have been found to be fairly general. In the first place, just as with the intermolecular bonds, the atoms joined must be strongly electronegative. Indeed, nearly all recognized intramolecular hydrogen bonds are either between two oxygen atoms or between one oxygen and one nitrogen atom. In the second place, the ring containing the hydrogen atom must contain altogether six atoms, including the hydrogen atom. (A few examples of five- and seven-membered rings are known, but such rings are exceptional.) The reason for this second requirement is probably that smaller rings would be too highly strained (cf. Chapter 9), whereas larger rings would be too flexible. The disadvantage of too much strain should be particularly important here in view of the weakness of the hydrogen bond; that of too much flexibility arises from the fact that ring formation, which naturally presupposes that the two ends of a chain have come together, rapidly becomes less probable as the length of the chain, and hence also its flexibility, increases. (Cf. Section 9·4.) A final rule, which possibly is also related to the flexibility in the ring, is that stable intramolecular hydrogen bonds are seldom formed unless the resulting ring contains two conjugated double bonds. (The two carbon atoms to which the nitro and hydroxyl groups are attached in *o*-nitrophenol may here be considered joined to each other by a double bond, as may also any other pair of adjacent atoms in an aromatic ring of any type.)

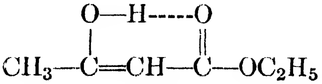
An alternative explanation of the role of conjugated double bonds in the ring is that these bonds permit a displacement of electric charge in such a way that the electrostatic interaction responsible for the bond is increased. Thus, in *o*-nitrophenol, the average distribution of charge may be intermediate between the average distributions represented by structures X and XII. (Cf. Chapter 10.) Only if there



XII

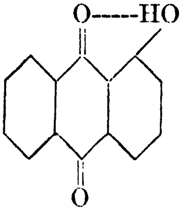
are conjugated double bonds in the ring which contains the hydrogen bond is such a displacement possible.

Some further examples[13,19] of molecules in which all these conditions are satisfied, and in which hydrogen bonds exist, include the enol form of acetoacetic ester, XIII; 1-hydroxyanthraquinone, XIV; 1,8-dihydroxyanthraquinone, XV; methyl salicylate, XVI; and 1-benzeneazo-2-naphthol, XVII. On the other hand, satisfaction of the stated conditions is not sufficient to ensure that an intramolecular hydrogen bond must be formed. Thus, there appears to be no such bond in β-benzilmonoxime, XVIII, and in a few other substances of similar type.

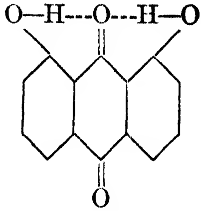


$$\overset{\overset{\displaystyle O-H\text{-----}O}{|\qquad\quad\ \|}}{CH_3-C=CH-C-OC_2H_5}$$

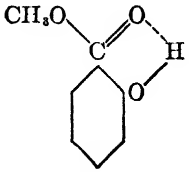
XIII



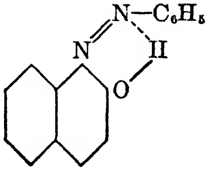
XIV



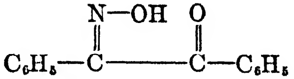
XV



XVI



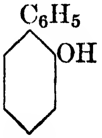
XVII



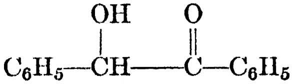
$$C_6H_5-\overset{\overset{\displaystyle N-OH}{\|}}{C}-\!\!-\!\!-\overset{\overset{\displaystyle O}{\|}}{C}-C_6H_5$$

XVIII

Examples [13,19] of molecules in which at least one of the foregoing conditions is violated, and in which no intramolecular hydrogen bond could be expected, include *o*-phenylphenol, XIX (because only one strongly electronegative atom is present); benzoin, XX (because the ring, if formed, would contain only five atoms altogether); *o*-hydroxybenzo-

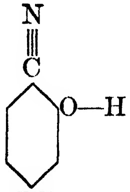


XIX

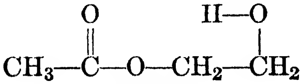


$$C_6H_5-\overset{\overset{\displaystyle OH}{|}}{CH}-\!\!-\!\!-\overset{\overset{\displaystyle O}{\|}}{C}-C_6H_5$$

XX

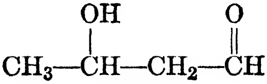


XXI



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_2-\overset{\overset{\displaystyle H-O}{|}}{CH_2}$$

XXII



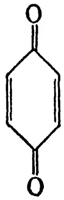
$$CH_3-\overset{\overset{\displaystyle OH}{|}}{CH}-CH_2-\overset{\overset{\displaystyle O}{\|}}{CH}$$

XXIII

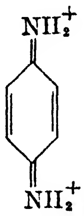
nitrile, XXI (because the ring, although it would contain six atoms, would be highly strained because of the linearity of the cyano group); ethyleneglycol monoacetate, XXII (because the ring would have to contain either five or seven atoms); and aldol, XXIII (because the ring would contain only one double bond).

2·7 Quinhydrones. The quinhydrones form a rather extensive group of substances which, until comparatively recently, were considered to belong to the third class of addition compounds (i.e., to the class of addition compounds for which no structure could be written even with the aid of an extended valence theory). At the present time, however, this view is considerably altered. Several different kinds of quinhydrones are now recognized; some quinhydrones can be assigned definite structures; some are not actually addition compounds at all; and some are still not explainable.

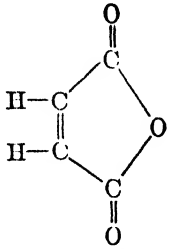
The distinguishing characteristics of a quinhydrone are, first, that it is a highly colored substance that is formed by the combination of two different colorless or, at any rate, less highly colored components; second, that one of its two components either must be a quinone such as *p*-benzoquinone, I, or else must be a substance, like the quinonediimine cation, II, or maleic anhydride, III, with a structure very similar to that of a quinone; and third, that the remaining component must be an aromatic substance, usually with hydroxyl, alkoxyl, or amino groups attached directly to the aromatic ring. The quinhydrone is always obtained readily, either by melting the two components together or by crystallizing a mixture of them from a suitable solvent. (For the significance of the word "suitable," see Section 2·9.)



I



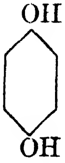
II

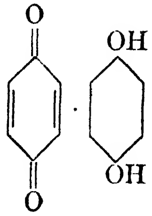


III

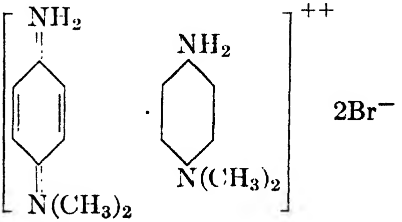
The most familiar type of quinhydrone is the one formed from a quinone and its corresponding hydroquinone. The simplest member of this series is the substance which is often designated merely as quinhydrone, and which is formed from equimolecular quantities of *p*-benzoquinone

I, and its hydroquinone, IV; this substance may be described graphically by the rather noncommittal symbol V.


IV


V

In some mixed quinhydrones of this type, the aromatic component is a hydroquinone other than the one formed by reduction of the quinone component; such more complex examples, however, need not be discussed further here. Closely related in structure to the quinhydrones of type V are the so-called Wurster's salts, of which Wurster's red, VI, is a characteristic example.


VI

For the sake of definiteness, and for the purpose of distinction from the remaining types of quinhydrone, substances of these first two classes will be referred to hereafter as *quinhydrones proper*. As will be explained later, they differ significantly from those other classes of substance to which the name "quinhydrone" has also been applied in the past, and which will be designated below as *quasi-quinhydrones*.

The quinhydrones proper have been carefully studied in recent years,[20] and, as a result, a great deal is at present known about them. It is now recognized that perhaps the majority of them are not actually addition compounds. For definiteness, as well as for simplicity, the following discussion will deal with the simplest representative, V, although, as a matter of fact, not all the details of the complex behavior described have actually been observed with this one substance.

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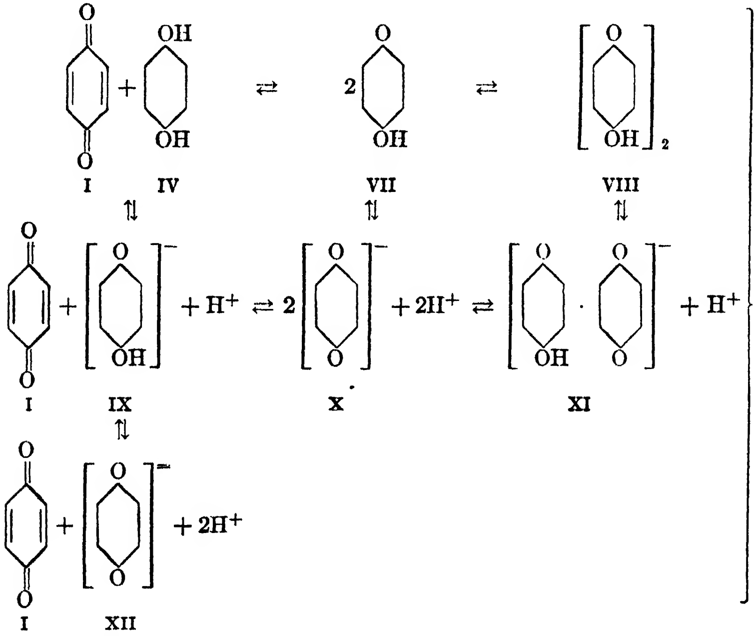
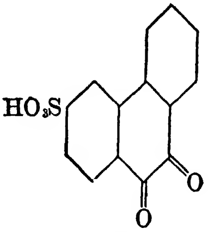
[20] The following discussion of the quinhydrones proper is based upon L. Michaelis, *Chem. Revs.* **16**, 243 (1935); L. Michaelis and M. P. Schubert, *ibid.* **22**, 437 (1938); and numerous further papers by Michaelis and coworkers in *Journal of the American Chemical Society*.

When an equimolecular mixture of *p*-benzoquinone, I, and its hydroquinone, IV, is dissolved in water or alcohol, there is set up a complex equilibrium, which is made even more complex still by the fact that several of the substances present are weak acids and therefore ionize to a greater or less extent. The equilibrium in question is the one shown in the set of equations 2·20. The substance VII, listed at the top of the central column, is called a *semiquinone;* it is a free radical containing either univalent oxygen or trivalent carbon. The ion X, formed from VII by the loss of a proton, is likewise a free radical. (For further details regarding the structures of the semiquinones and of the ions derived from them, see pages 725 f., 738.) The substance VIII, listed at the top of the right-hand column, is called the *dimer,* or the *dimeric form,* of the semiquinone. Only this dimer, or the anion XI derived from it, could with much right be referred to as an addition compound. Neither VIII nor XI is a free radical. In the following paragraphs, the word "quinhydrone" will be used somewhat loosely to mean the complete equilibrium mixture, regardless of its exact composition.

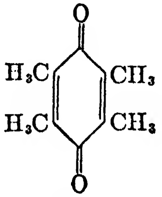


(2·20)

The relative proportions of the several substances present in the solution of a quinhydrone vary tremendously with the concentration of the solution, with its acidity or alkalinity, and with the nature of the particular quinone-hydroquinone pair that is involved. The following generalizations, however, have been established. In acid or neutral solution, the organic solute exists almost entirely, of course, in its unionized forms, so that the only substances which can be present in significant amount are those in the top row of equation 2·20. Under these circumstances, the equilibrium depicted in this row is often so nearly completely to the left that the quinhydrone may be described as merely an equimolecular mixture of the quinone I and hydroquinone IV; only traces of either the semiquinone VII or its dimer VIII then exist. In some instances, however, appreciable quantities of the dimer may be present. In fact, if the total concentration of organic solute is high, so that (in accordance with the law of mass action) the association of the monomer VII is favored, the dimer VIII may be the most important form; usually, however, this situation is encountered only with those semiquinones which are derived from *ortho* quinones, like phenanthrenequinone-3-sulfonic acid, XIII. With the semiquinones derived from *para* quinones, like *p*-benzoquinone, I, on the other hand, dimerization is ordinarily much less extensive; with the one derived from duroquinone, XIV, as an extreme example, no dimer at all can be detected. The concentration of the neutral monomer VII, unlike that of the dimer VIII, is apparently *always* very small.



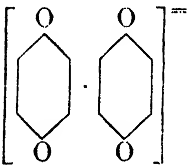
XIII



XIV

If the solution of the quinhydrone is made somewhat basic, the equilibrium constants defining the equilibria among the electrically neutral forms I, IV, VII, and VIII may be presumed to remain essentially unchanged. The overall situation is, however, altered by the fact that these neutral substances are, to a greater or less extent, transformed into the anions shown in the second row of the equations 2·20. (The hydrogen ions are written here only in order that the equations may be balanced; in alkaline media, these ions are of course largely removed by reaction with the base.) The equilibrium among the anions IX, X, and XI (plus the neutral quinone I) is usually much farther to the right than is that between the neutral molecules I, IV, VII, and VIII. The relative proportions of the anions X and XI, like those of the corresponding neutral substances, VII and VIII, respectively, are of course determined by the total concentration of the organic solute and by the identity of the parent quinone.

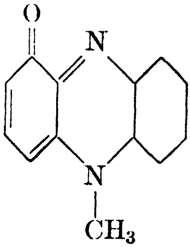
If now this "somewhat basic" solution is made still more basic, the fraction of the solute that exists in the form of the semiquinone anion X is found always to increase. In extremely basic solution, in fact, this ion may become the most important component of the equilibrium mixture. On the other hand, as the solution is made more and more basic, the fraction of the solute that exists in the form of the dimer anion XI first increases to a maximum value and then decreases until it at last becomes negligibly small. Presumably, therefore, the hydroxylic hydrogen atom of the ion XI is somewhat acidic, so that it is removed as a proton in the most strongly basic solutions. Since no evidence has been obtained, however, for the existence of the bivalent anion XV, which


XV

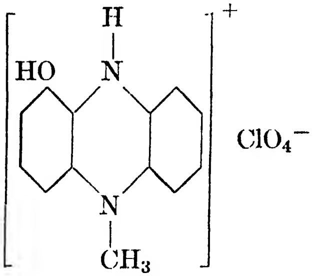
might be expected to be thus produced, the conclusion may be drawn that this ion is unstable, and that it decomposes into two of the univalent ions X. (For theoretical discussions of the observed effects of the basicity upon the several equilibria, see pages 60, 726 f.)

With the analogous Wurster's salts, the situation is similar to that just described; it is, however, modified by the fact that the various electrically neutral substances taking part in the equilibria are weak bases and not weak acids. Consequently, the derived ions are cations and not anions, and they are produced in acidic and not in basic solution. The semiquinone is again more stable as an ion than as a neutral molecule; hence here it is favored by acidity rather than by alkalinity. (Cf. page 738.)

In the *solid* state the complex equilibria which obtain in solution are no longer possible. The solid substance is found to consist sometimes of a simple mixture of quinone and hydroquinone (or, with the nitrogen compounds, of quinoneimine and phenylenediamine), sometimes of semiquinone, and sometimes of dimer (or possibly of some still higher polymer). The first of these possibilities is realized with duroquinone, XIV, the second with pyocyanine, XVI (of which the semiquinone is the salt



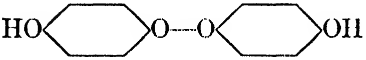
XVI



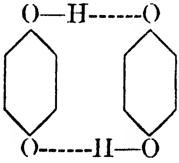
XVII

XVII), and the third with *p*-benzoquinone, I.

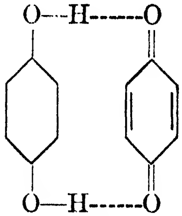
It remains to consider the structure of the dimer which, as was noted above, is the only one of the various electrically neutral substances which can rightfully be called an addition compound. With a quinhydrone derived from a quinone, rather than from a quinoneimine, this dimer might have a peroxidic structure of the type XVIII. However,



XVIII

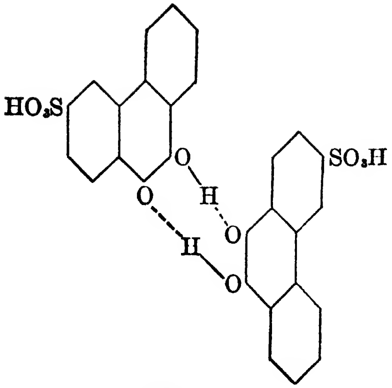


XIX

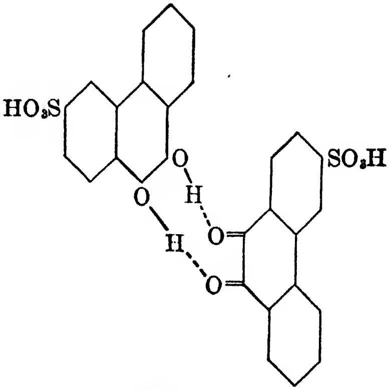


XX

such a structure could hardly account for the intense color of the substance; consequently, Michaelis has proposed structure XIX or XX, in which the two halves of the dimer are held together by hydrogen bonds. The distinction between structures XIX and XX is rather slight, and there is at present no reliable method of deciding which form is preferable. For geometrical reasons, the two rings must here lie so that each is flat against the other. This interpretation then explains why the semiquinone from duroquinone, XIV, forms no dimer; the four methyl groups attached to each ring are so bulky that the necessary relative orientation of the rings is impossible. With an *ortho* quinone, like phenanthrenequinone-3-sulfonic acid, XIII, on the other hand, the corresponding dimer, represented by either XXI or XXII, could exist with the two



XXI



XXII

aromatic ring systems in the same plane; this possibility may contain the explanation of the exceptional stabilities of such dimers. The univalent dimer anion XI (equation 2·20) contains only one hydroxylic hydrogen atom; consequently, it must be held together by only one hydrogen bond. Michaelis's structures of the dimeric semiquinones account also for the fact that the bivalent anion XV dissociates completely into the univalent anions X (see above); obviously, the hydrogen bond which holds the dimer together is impossible when the hydrogen atom which produces it has been removed. Moreover, the dissociation of the bivalent dimer anion XV must be favored also by the electrostatic repulsions of the resulting monomer anions X.

With the nitrogen-containing analogs, such as the Wurster's salts, the situation is somewhat more complicated; apparently, not merely dimerization but also a more extensive polymerization takes place. The individual monomer units can again be considered held together, in the dimer or polymer, by hydrogen bonds. Nothing further will be said here, however, about these more complex substances, since the problem of their constitution is probably not yet completely solved.

The information at present available in regard to the several further classes of addition compound (here grouped together under the heading of quasi-quinhydrones) is much less than is that in regard to the above quinhydrones proper. The discussion of the quasi-quinhydrones can, accordingly, be limited to a listing of the more important types.[5,21] (Cf., however, Sections 2·8 and 2·10.) One class of quasi-quinhydrone, of which a number of representatives have been reported, consists of the so-

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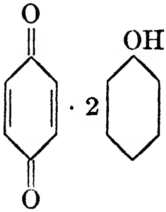
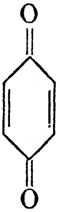
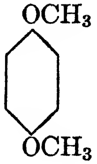
[21] For further examples, see W. Hückel, *Theoretische Grundlagen der Organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, 2nd ed., 1934, Volume I, Chapter 3.

called *phenoquinones.* These substances are composed of one mole of a quinone for every two moles of a monohydric phenol; the simplest example is the one represented by symbol XXIII. In a second class of quasi-quinhydrones, the hydroxyl groups of the aromatic component are alkylated. For example, when *p*-benzoquinone, I, and the dimethyl ether, XXIV, of its hydroquinone are melted together, the resulting liquid is highly colored, but the quinhydrone, which therefore appears to be present in equilibrium with its two components, cannot be obtained in solid form. With the more complicated analog represented by symbol XXV, on the other hand, the solid can be obtained. (The positions of all the substituents on the two naphthalene rings in the diethoxy component have not been established.) A few examples are known in which the aromatic component is a hydrocarbon. Included in this class are the substances represented by formulas XXVI and XXVII. For none of those quasi-quinhydrones is it now possible to write a structure based upon either the simple valence theory or any extension of it. (However, see Section 2·10.)


XXIII


I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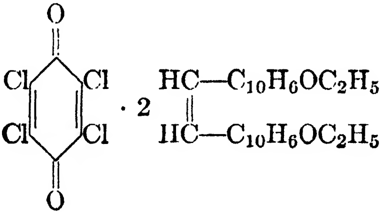
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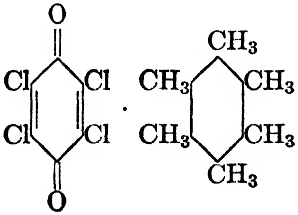
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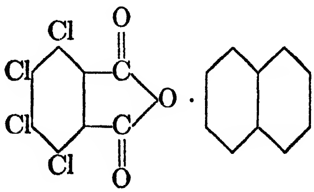
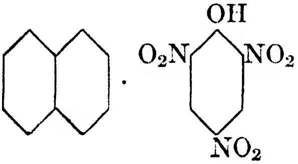

XXVII

2·8 Addition Compounds of Polynitro Compounds. A large number of polynitro compounds enter into addition compounds which, in at least their superficial aspects, resemble the quinhydrones that have just been discussed. That is to say, these addition compounds are highly colored substances that are formed by simple mixing of the two less highly colored components, either in the melted state or in solution in a suitable solvent. (See Section 2·9.) Of the two components, one (namely, the polynitro compound) may be considered to replace the quinoid component of the quinhydrones, whereas the second, just as in the quinhydrones, is an aromatic substance, often with hydroxyl or amino groups as substituents. Indeed, these further addition compounds may with considerable reason be said to constitute merely a special type of quasi-quinhydrone. Of the thousand or so known examples of such addition compounds, the substances I–VI will serve as characteristic illustrations.[5,21] It may be noted that the addition compounds in which picric acid takes part are commonly, but erroneously, called "picrates"; thus, compound I is "naphthalene picrate."



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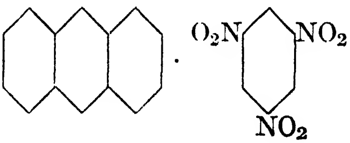

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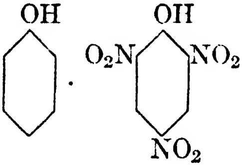

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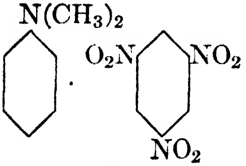

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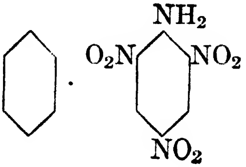

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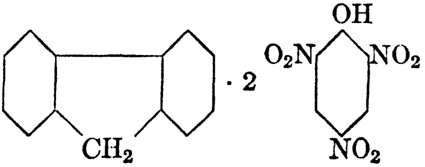

VI

A number of generalizations regarding the stabilities of the addition compounds have been observed. The ability of the nitro component to enter into such complexes increases with the number of nitro groups, and apparently also with that of halogen atoms, hydroxyl groups, and amino groups. On the other hand, it is diminished by methyl substituents. The ability of the second component to enter into such complexes increases markedly with the size of the aromatic ring system, so that, although benzene forms only a relatively small number of rather unstable addition compounds, naphthalene forms a larger number of more stable ones. This trend continues with anthracene, and so on. Moreover, methyl substituents in this second component increase the stabilities of the complexes to such an extent that even hexamethylbenzene forms stable ones. Hydroxyl and amino groups act in the same way as methyl groups, but nitro groups have the opposite effect and decrease the tendency toward the formation of addition compounds. A final generalization, which is of a different type from the foregoing, is that usually, but not always (see the compound VI), the two components enter into the addition compound in a one-to-one molecular ratio.

2·9 The Necessary Conditions for the Precipitation of an Addition Compound from Solution. In each of the two preceding sections, the statement has been made that a certain addition compound can be prepared by crystallization of a mixture of the components from a "suitable" solvent. It will be interesting at this point to consider the criteria which determine whether a given solvent is or is not suitable, since many solvents are found in practice to be unsuitable. The point involved here is that, when a solution of a mixture of the two components is made more concentrated, the identity of the solid phase which first separates is determined by the relative solubilities of the components and of the addition compound, as well as by the position of the equilibrium between the components and the addition compound. In fact, only qualitative reasoning is required to show that if, in the solvent used, one component is much less soluble than is either the other component or the addition compound, and if the equilibrium is such that the addition compound is dissociated to a considerable extent, then the relatively insoluble component, rather than the addition compound, may be expected to precipitate first.

The situation can be treated almost quantitatively in the following manner.[22, 23] For simplicity, the addition compound will be considered to be of the one-to-one type and hence to be representable by the symbol

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[22] O. Dimroth and C. Bamberger, *Ann.* **438**, 67 (1924).

[23] N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, 1937, pages 261 ff.

AB, where A and B are the two components. The equilibrium in question is then the one shown in equation 2·21. The equilibrium constant

$$A + B \rightleftarrows AB \tag{2·21}$$

K_s, which applies to the solution, can be expressed in the form given in equation 2·22. The numerical value of the constant K_s depends, of

$$K_s = \frac{[AB]}{[A][B]} \tag{2·22}$$

course upon the units in which the concentrations [AB], etc., are expressed; in particular, the value obtained when the concentrations are given in moles per liter of solution is different from the one obtained when they are given instead in grams per 100 g of solvent, and so on. Moreover, even with a given unit of concentration, the value of K_s may be expected to vary from one solvent to another. The variation with the solvent can, however, be avoided if the equilibrium in the solution is compared with that in the vapor phase. The vapor tensions of pure AB, A, and B at the temperature of interest may be designated as $p_{AB}{}^0$, $p_A{}^0$, and $p_B{}^0$, respectively; the fact that all these vapor tensions may be, and usually are, exceedingly small does not affect the following derivation.[24] Since a saturated solution of any substance is defined as one in equilibrium with the pure solute, the quantities $p_{AB}{}^0$, $p_A{}^0$, and $p_B{}^0$ must be equal also to the partial pressures of AB, A, and B, respectively, over their saturated solutions; moreover, these equalities must be true regardless of the solvent used. Now, if the solubilities of AB, A, and B are sufficiently small that Henry's law can be assumed to hold for each substance throughout its entire concentration range, then the partial pressures p_{AB}, p_A, and p_B over solutions at concentrations C_{AB}, C_A, and C_B moles per liter, respectively, must be those shown in equations 2·23–2·25, where S_{AB}, S_A, and S_B are the solubilities, in moles per

$$p_{AB} = p_{AB}{}^0 \cdot \frac{C_{AB}}{S_{AB}} \tag{2·23}$$

$$p_A = p_A{}^0 \cdot \frac{C_A}{S_A} \tag{2·24}$$

$$p_B = p_B{}^0 \cdot \frac{C_B}{S_B} \tag{2·25}$$

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[24] Cf. G. N. Lewis and M. Randall, *Thermodynamics*, McGraw-Hill Book Company, New York, 1923, page 128.

liter, of the indicated substances. These equations must be satisfied, within the limits of Henry's law, no matter what solvent is used.

The derivation of equations 2·23–2·25 is as follows. Henry's law states that at a given temperature the partial pressure of any volatile solute X is proportional to its concentration; thus p_X is proportional to C_X, and hence equal to $k_X C_X$, where k_X is the proportionality constant that applies to the particular solute X and solvent employed. Moreover, the proportionality constant k_X is easily shown to be equal to the ratio $p_X{}^0/S_X$, since, when the solution is saturated, C_X is equal to S_X, and p_X is equal to $p_X{}^0$. It therefore follows that p_X is equal to $(p_X{}^0/S_X)C_X$, or to $p_X{}^0(C_X/S_X)$, as in equations 2·23–2·25.

In the strict statement of Henry's law, all concentrations C_X and solubilities S_X should be expressed as mole fractions, and not as moles per liter; since, however, the solutions now under discussion are required to be rather dilute, the mole fractions are so nearly proportional to the concentrations in moles per liter that no significant error is introduced by the use of the latter units instead of the former. In fact, the assumed proportionalities are probably as nearly accurate as is Henry's law itself.

The equilibrium among AB, A, and B (equation 2·21) in the *vapor* phase may be described by the equilibrium constant K_v of equation 2·26; this constant is, of course, independent of the solvent, since it is

$$K_v = \frac{p_{AB}}{p_A p_B} \tag{2·26}$$

defined without reference to any solvent. With the aid of equations 2·23–2·25, equation 2·26 can be put into the equivalent forms 2·27 and 2·28. The quantity G appearing on the left side of equation 2·28 is

$$K_v = \frac{p_{AB}{}^0(C_{AB}/S_{AB})}{p_A{}^0(C_A/S_A)\cdot p_B{}^0(C_B/S_B)} = \frac{p_{AB}{}^0}{p_A{}^0 p_B{}^0}\cdot\frac{C_{AB}}{C_A C_B}\cdot\frac{S_A S_B}{S_{AB}} \tag{2·27}$$

$$G \equiv \frac{p_A{}^0 p_B{}^0}{p_{AB}{}^0} K_v = \frac{C_{AB}/S_{AB}}{(C_A/S_A)\cdot(C_B/S_B)} = \frac{C_{AB}}{C_A C_B}\cdot\frac{S_A S_B}{S_{AB}} \tag{2·28}$$

frequently called the *van't Hoff-Dimroth G;* its value must be at least approximately independent of the solvent since it can be expressed approximately in terms of only $p_{AB}{}^0$, $p_A{}^0$, $p_B{}^0$, and K_v, each of which is itself rigorously independent of the solvent. Comparison of equations 2·22 and 2·28 shows that (regardless of the solvent) G is equal to the equilibrium constant K_s obtained when the concentrations [AB], etc., are expressed, not in any of the conventional units like moles per liter, but instead as the ratios C_{AB}/S_{AB}, etc., of the respective concentrations and solubilities.

The next step in the discussion is to consider the conditions which must be satisfied in order that the addition compound AB, rather than either A or B, may precipitate when the solution is made more concentrated. Clearly, if AB precipitates while both A and B remain in solution, the equation 2·29 and the inequalities 2·30 and 2·31 must be satisfied. By combination of these three expressions with equation 2·28,

$$\frac{C_{AB}}{S_{AB}} = 1 \tag{2·29}$$

$$\frac{S_A}{C_A} > 1 \tag{2·30}$$

$$\frac{S_B}{C_B} > 1 \tag{2·31}$$

the further relation 2·32 can be derived. Moreover, if equimolecular

$$G = \frac{S_A S_B}{C_A C_B} > 1 \tag{2·32}$$

quantities of A and B are taken originally, so that the molar concentrations of A and B are always equal (equation 2·33), and if also the more

$$C_A = C_B \tag{2·33}$$

soluble component is designated as A (inequality 2·34), then expression 2·35 can be derived. In other words, if the solid addition compound AB

$$S_A > S_B \tag{2·34}$$

$$G = \frac{S_A S_B}{C_B C_B} > \frac{S_A}{C_B} = \frac{S_A S_B}{S_B C_B} > \frac{S_A}{S_B} > 1 \tag{2·35}$$

is to precipitate, the ratio S_A/S_B of the solubility of the more soluble component to that of the less soluble component must lie between G and 1. If G, which is at least approximately independent of the solvent, is less than unity, this condition cannot be satisfied in any solvent, and so the addition compound cannot be obtained by precipitation from a solution containing equivalent amounts of the two components. Moreover, if G is greater than unity but less than the ratio S_A/S_B in the particular solvent used, then again the addition compound cannot be obtained. In either event, the solid phase which actually forms must consist of the less soluble component B. It should be obvious that the larger the magnitude of G, the more stable is the addition compound, and the wider is the range of solvents which can be used.

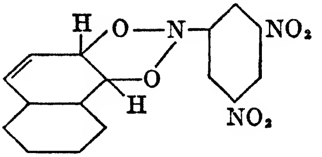
The data of Table 2·2 in regard to anthracene picrate illustrate the situation described above. For this addition compound, G has been found to have the nearly, but not completely, constant value of 2.1–2.47 in the six solvents listed. Clearly, the addition compound can be obtained from ligroin, ether, or chloroform as solvent, but not from carbon tetrachloride, ethyl alcohol, or water. Moreover, once the addition compound has been obtained, it can be decomposed again into its components by extraction with any of these last three solvents. Similar considerations apply equally well, of course, to all other types of one-to-one addition compound, including the above quinhydrones (both proper and quasi).

TABLE 2·2

APPLICATION OF THE VAN'T HOFF-DIMROTH RELATION TO ANTHRACENE PICRATE IN SEVERAL SOLVENTS[22,23]

Solvent	$\dfrac{S_{\text{anthracene}}}{S_{\text{picric acid}}}$	$\dfrac{S_{\text{picric acid}}}{S_{\text{anthracene}}}$	*Solid Phase Formed*
Carbon tetrachloride	7.7	. . . .	Picric acid
Ligroin	1.84	. . . . .	Addition compound
Ether	. . . .	2.0	Addition compound
Chloroform	. . . .	1.14	Addition compound
Ethyl alcohol	. . . .	28	Anthracene
Water	. . . .	Very large	Anthracene

2·10 The Forces Acting between the Components of Quasi-quinhydrones and Their Analogs. There is at present no completely satisfactory theory to account for the forces acting between the components either of the quasi-quinhydrones of Section 2·7 or of the further apparently analogous addition compounds of Section 2·8. The various explanations that have been proposed may be divided into two groups.[23] On the one hand, certain authors have assumed the existence of covalent bonds between the two components, as, for example, in structures I and II. On the other hand, certain other authors have preferred instead to



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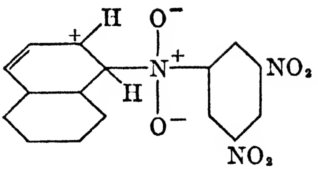
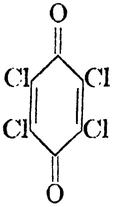


II

speak of electrostatic interactions arising from the polarization of one component by the other. (Cf. Section 1·13.)

What evidence there is seems, by and large, to support the second of these two views. The quinoid and nitro compounds do indeed possess strongly polar groups which could produce the postulated polarizations, and the substances that can act as the second component are indeed highly polarizable. Moreover, the structural changes which are observed to increase the stabilities of the addition compounds are just the changes which would be expected to increase the polar character of the one component and the polarizability of the other. Thus, chloranil, III,



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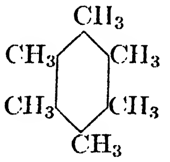

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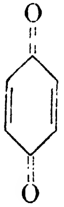

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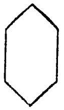

VI

and hexamethylbenzene, IV, form an addition compound, whereas *p*-benzoquinone, V, and benzene, VI, do not; the carbon-chlorine bonds make chloranil a more effective polarizing agent than *p*-benzoquinone, and the methyl groups make hexamethylbenzene more polarizable than benzene. Further evidence pointing to the same conclusion is provided by the great ease with which the addition compounds can be formed and decomposed; much slower reactions would be anticipated if the formation of the addition compounds requires the rupture of some valence bonds and the creation of new ones. And finally, the crystal structures of a few such addition compounds have been investigated;[25] in general, the molecules of the two components are so far apart that no valence bonds between them seem possible.

Nevertheless, there is some evidence which is difficult to reconcile with the hypothesis that only polarization forces are involved. For example, the addition compound between indene, VII, and dimethyl 4,6,4′,6′-

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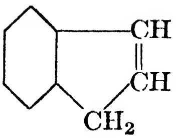
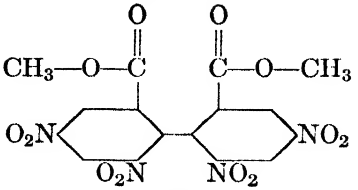
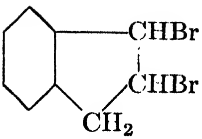
[25] For example, see H. M. Powell, G. Huse, and P. W. Cooke, *J. Chem. Soc.* **1943**, 153; D. H. Saunder, *Proc. Roy. Soc.* (London) **A188**, 31 (1946); **A190**, 508 (1947); R. W. James and D. H. Saunder, *ibid.* **A190**, 518 (1947).



VII

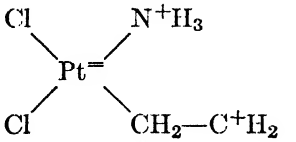


VIII

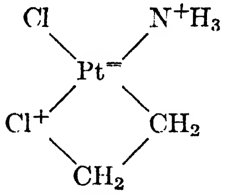


IX

tetranitrodiphenate, VIII, is formed from its components at a measurable rate.[26] This fact strongly suggests that an activation energy is required, and, consequently, that some valence bonds must be broken in the process. Moreover, this addition compound reacts only rather slowly with bromine, although under comparable conditions indene itself adds bromine very rapidly to form the dibromide, IX. This further observation also suggests that the indene in the complex has undergone a more drastic change than a mere polarization by the nitro compound. Finally, it may be mentioned that some complexes of other types, which are formed by unsaturated hydrocarbons, are most simply explainable on the assumption that they are held together by valence bonds. An example of this sort is given by the platinum compound to which a structure like X or XI may perhaps be assigned. (For further discussion of this and some similar compounds, see Section 2·5.) The existence of such substances, of course, does not prove that the complexes formed by quinones, nitro compounds, and the like must have analogous structures; it does, however, provide analogies.



X



XI

In view of the above uncertainties, the quasi-quinhydrones and the addition compounds formed by the polynitro compounds must for the present be put into the group of substances for which no structures can be given.

2·11 Choleic Acids.[27]

A very interesting, and as yet completely unexplained, group of addition compounds consists of the so-called *choleic acids.* These substances are formed by the combination of either

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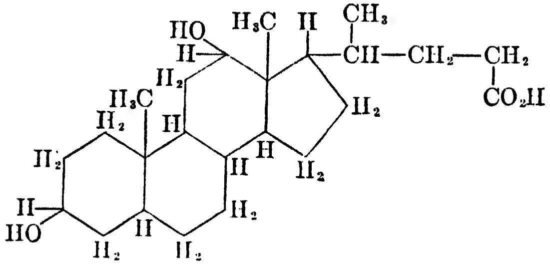
[26] D. L. Hammick and G. Sixsmith, *J. Chem. Soc.* **1935,** 580.

[27] For a general discussion of the choleic acids, see L. F. Fieser, *The Chemistry of Natural Products Related to Phenanthrene*, Reinhold Publishing Corporation, New York, 2nd ed., 1937, pages 129 ff., 368 f.

desoxycholic acid, I, or (much less frequently) apocholic acid, II, with any of a large number of other substances of various types, including



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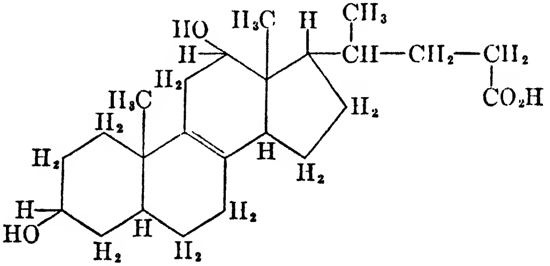
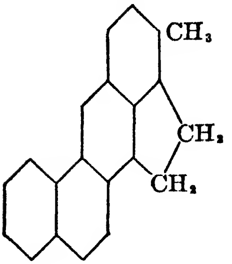


II

carboxylic acids, esters, alcohols, phenols, ethers, alkaloids, and even some hydrocarbons. The resulting addition compounds are occasionally of the 1:1 type, but usually they contain 2, 3, 4, 6, or 8 molecules of the desoxycholic or apocholic acid for each molecule of the second component. In general, the larger a molecule is, the greater is the number of desoxycholic or apocholic acid molecules with which it can combine. Thus, with desoxycholic acid, formic acid does not give a choleic acid at all; acetic acid forms a 1:1 compound; propionic acid forms a 1:3 compound; the normal aliphatic acids with from 4 to 8 carbon atoms per molecule form 1:4 compounds; those with from 9 to 14 carbon atoms per molecule form 1:6 compounds; and the still higher acids form 1:8 compounds. Similar trends are observed also in other series of analogous substances.

The stabilities of the choleic acids vary widely. The one between stearic and desoxycholic acids is so stable that it is decomposed only if the desoxycholic acid is dehydrated or oxidized or transformed chemically in some other way into a substance that cannot combine with stearic acid. On the other hand, some other choleic acids, such as that between methylcholanthrene, III, and desoxycholic acid, are largely dissociated into their components in solution. In general, the question



III

whether a given choleic acid can be precipitated from a given solvent is governed by factors which are analogous to those discussed in Section 2·9 with reference to the quinhydrones and the complexes formed by polynitro compounds.

As is implied by their name, the choleic acids retain the acid character of the desoxycholic or apocholic acid from which they are derived. That is to say, the addition compounds form salts without decomposition into their components. Since these salts are often soluble in water, their formation provides a method of bringing many types of otherwise insoluble substances into solution. Even the fats and the higher aromatic hydrocarbons can thus be made "soluble" in water. Since desoxycholic acid occurs in bile, the suggestion has been made that the dissolving power of bile for fats is due to the formation of choleic acids. This view, however, is probably incorrect,[27] since desoxycholic acid is only a minor constituent of bile, and since the remaining bile acids, which are present in greater amount, do not form choleic acids. Moreover, the desoxycholic acid of the bile is not present as such but is in a combined state in which it apparently does not form stable choleic acids.

Nothing is known about the nature of the forces responsible for the stability of the choleic acids. Any explanation based upon the creation of new covalent bonds in the addition compounds would be difficult in view of the wide range of substances that combine with desoxycholic and apocholic acids, and in view also of the fact that the other bile acids of very similar structure are unable to enter into such complexes. Moreover, no reasonable explanation can be based upon a supposed polarization of one component by the other. Neither desoxycholic nor apocholic acid is characterized either by the presence of especially polar groups or by an especially great polarizability; the same is true also of the various types of substances which act as the second component. All that can be done at present, therefore, is to classify the choleic acids among the addition compounds for which no explanation can be given.[28]

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[28] For an interesting recent suggestion regarding the constitution of the choleic acids and certain other addition compounds, see H. M. Powell, *J. Chem. Soc.* **1948,** 61.

3.

Modern Concepts of Acids and Bases[1]

3·1 Limitations of the Classical Definitions of Acids and Bases. According to the classical definitions, an acid is a substance which ionizes to give a hydrogen ion, and a base is a substance which ionizes to give a hydroxide ion. The question may be asked why hydrogen and hydroxide ions are thus distinguished from all other cations and anions, and why substances which ionize to give, say, sodium ions and chloride ions are not similarly grouped into separate classes. The answer is simply that the hydrogen and hydroxide ions are the ones produced by the self-ionization of the most common solvent, water. As long, therefore, as only aqueous solutions are considered, these two ions play unique roles not shared by any others, such as the sodium and chloride ions. Consequently, hydrogen and hydroxide ions can profitably be used in the definitions of the two opposed classes of compound, acids and bases. In nonaqueous solutions, however, the unique character of either the hydrogen or the hydroxide ion, or of both, is lost, and so the concept of acids and bases, if it is to be retained at all, must be expressed in more general terms.

In the three following sections, three recent generalized treatments of acids and bases will be discussed. It is to be especially noted that the three resulting viewpoints and the classical one differ from each other only in that they are based upon different sets of definitions; they do not presuppose different assumptions in regard to the natures of the chemical reactions involved, and they do not lead to different predictions in regard to the results of experiments. In other words, they are not, as is frequently suggested, different *theories*. Consequently, there is no question of any one of them being more nearly correct than the others. The most that can be said is that, for some particular purpose, one of the points of view may be most convenient.

3·2 The Lowry-Brønsted Definitions of Acids and Bases.[1,2] The most widely adopted of the three above-mentioned attempts to

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[1] Cf. W. F. Luder and S. Zuffanti, *The Electronic Theory of Acids and Bases*, John Wiley and Sons, New York, 1946.

[2] T. M. Lowry, *Chemistry & Industry* **42**, 43 (1923); J. N. Brønsted, *Rec. trav. chim.* **42**, 718 (1923); *Chem. Revs.* **5**, 231 (1928).

generalize the concept of acids and bases is the one due to Lowry and to Brønsted. According to these authors, the proton must be recognized as essentially different from any other cation, since it alone consists of a bare nucleus that is not surrounded by any shielding electrons. Indeed, the proton is different even from the charged particle which exists in solution, and which is commonly known as the hydrogen ion and is represented by the symbol H^+. On account of its minute size, a proton can come extremely close to any molecule in its vicinity, and so the electrostatic attraction between it and the molecule must be very great. (Cf. Section 1·13.) In fact, the attraction must be so great that the proton cannot exist completely free in any solution but must instead be combined in some way with some other molecule or ion.

If the proton is accepted as a unique particle, then, even with respect to a nonaqueous solution, an acid may be defined as a substance that can give up a proton. This Lowry-Brønsted definition does not differ from the classical one in any very important respect, but it alters the viewpoint in a way that will become apparent after the corresponding definition of a base has been discussed.

Unlike the proton, the hydroxide ion is in no sense unique, except as regards its relationship to water. Its importance in the classical definition of a base may be ascribed to its ability to combine with a proton to form water. As a simple and logical generalization of this idea, Lowry and Brønsted define a base as *any* substance which can combine with a proton to form any product. Since the proton which is thus taken up cannot have been initially free but must have been surrendered by a molecule of some acid, and, moreover, since this proton could conceivably be returned with regeneration of the original acid, the general situation can be represented by equation 3·1. According to the Lowry-Brønsted

$$\mathrm{HA} + \mathrm{B} \rightleftarrows \mathrm{A} + \mathrm{HB} \qquad (3\cdot1)$$

definitions, HA and HB are acids, and A and B are bases. Moreover, the base A is said to be *conjugate* to the acid HA, and vice versa; similarly B and HB are also conjugate to each other. No assumption is here made in regard to the charge type of either A or B. In fact, A may have any one of the charges $\cdots, -2, -1, 0, 1, 2 \cdots$, provided, of course, only that HA have the corresponding one of the charges $\cdots, -1, 0, 1, 2, 3 \cdots$; similarly, the only restriction upon the charges of B and HB is that that of B must be algebraically one less than that of HB.

A few specific examples will help to make the situation clearer. The ionization of hydrogen chloride in aqueous solution may be written as in equation 3·2. In this reaction, hydrogen chloride and the hydronium

$$\mathrm{HCl} + \mathrm{H_2O} \rightarrow \mathrm{H_3O^+} + \mathrm{Cl^-} \qquad (3\cdot2)$$

ion H_3O^+ are the acids, whereas water and the chloride ion are the bases. Water and the hydronium ion are conjugate base and acid, as are also chloride ion and hydrogen chloride. If hydrogen chloride is added to aqueous ammonia rather than to water, the most important reaction to occur is the one shown in equation 3·3. The ammonia here is a stronger

$$HCl + NH_3 \rightarrow NH_4^+ + Cl^- \qquad (3\cdot3)$$

base than the water which is also present, and so it gets most of the protons. Correspondingly, the ammonium ion is a weaker acid than the hydronium ion. As before, the reaction may be considered simply the ionization of the hydrogen chloride, since it is identical in type with that of equation 3·2. Classically, however, it would be called a neutralization, and its description would require that the further equilibrium 3·4

$$NH_3 + H_2O \rightleftarrows NH_4^+ + OH^- \qquad (3\cdot4)$$

be also taken into account. From the classical viewpoint, the fact that the solution of ammonia is more strongly basic than is pure water is due to the increased concentration of hydroxide ion; and the base which is neutralized by the hydrogen chloride is ammonium hydroxide, as in equation 3·5. If equations 3·4 and 3·5 are added, the water and the

$$NH_4^+ + OH^- + HCl \rightarrow NH_4^+ + Cl^- + H_2O \qquad (3\cdot5)$$

hydroxide ion cancel out, and equation 3·3 results. Consequently, the Lowry-Brønsted viewpoint is simpler than the classical one, since it leads in a single step to the desired answer and does not require that water and hydroxide ion be introduced just to be canceled out again. Moreover, if the hydrogen chloride is added to liquid ammonia instead of to an aqueous solution of ammonia, then, since no water is present, equations 3·4 and 3·5 cannot be written. Equation 3·3, however, still describes the situation.

The close analogy between equations 3·2 and 3·3 suggests that a solution of ammonium chloride in liquid ammonia should be acidic, just as is one of hydronium chloride (i.e., hydrochloric acid) in water. This supposition is indeed correct, since ammonium chloride in such a solution affects indicators, neutralizes bases, and attacks metals in the ways characteristic of acids.

Even in aqueous solution, ammonium chloride is acidic. Classically, this fact is explained as resulting from the reaction 3·6 (i.e., from the

$$NH_4^+ + H_2O \rightleftarrows NH_3 + H_3O^+ \qquad (3\cdot6)$$

hydrolysis of the ammonium ion). From the Lowry-Brønsted point of view, however, no such explanation is necessary since the ammonium ion is itself an acid, whereas the chloride ion is too weak a base to exert any noticeable effect; the hydrolysis reaction 3·6 is then quite incidental and merely describes the competition of the two bases, water and ammonia, for the proton.

In a similar way the fact that an aqueous solution of sodium acetate is basic is explained classically as the result of the hydrolysis of the acetate ion, as in equation 3·7. On the other hand, from the Lowry-Brønsted point of view, it is the result of the basic character of the acetate ion; again the hydrolysis reaction 3·7 is incidental and merely describes the competition of the two bases (here, hydroxide ion and acetate ion) for the proton.

$$CH_3{-}CO_2^- + H_2O \rightleftarrows CH_3{-}CO_2H + OH^- \qquad (3{\cdot}7)$$

A further way in which the definitions of Lowry and Brønsted alter the classical terminology is with respect to the identity of the actual base that is present under any given set of conditions. Thus, classically, sodium hydroxide and ammonium hydroxide are bases, whereas ammonia is merely a substance which can react with water to form a base. According to Lowry and Brønsted, however, neither sodium hydroxide nor ammonium hydroxide is a base, whereas ammonia is. In sodium hydroxide, the base is the hydroxide ion; the sodium ion has nothing to do with the acid-base reactions. In aqueous ammonia the hydroxide ion (to the extent that any is present) is a base, as is also the uncombined ammonia NH_3. In liquid ammonia, of course, the classical definitions are inapplicable, and so the ammonia itself is necessarily the base.

The Lowry-Brønsted definitions, like the classical ones, permit the existence of *amphoteric* substances, or, in other words, of substances which are both acids and bases at the same time. For example, water acts as an acid in the reactions of equations 3·4 and 3·7, but as a base in those of equations 3·2 and 3·6. Similarly, ammonia, which acts as a base in the reactions of equations 3·3, 3·4, and 3·6, acts instead as an acid when it loses a proton and becomes the amide ion NH_2^-. A further example is the bicarbonate ion HCO_3^-, which is an acid because it can lose a proton to give the carbonate ion $CO_3^=$, but which is also a base because it can absorb a proton to give un-ionized carbonic acid H_2CO_3.

Clearly, no substance can be simultaneously a strong acid and a strong base. Nevertheless, the fact that a given substance is a weak acid does not necessarily imply that it must be a strong base; similarly, the fact that a substance is a weak base does not necessarily imply that it must be a strong acid. Indeed, a substance can be very weak both as an acid and as a base. For example, benzene is an extremely weak acid, since it does not lose a proton and become the phenyl anion $C_6H_5^-$

under any ordinary conditions; on the other hand, it is also a very weak base, since the reaction of equation 3·8 goes only a very small distance

$$HCl + C_6H_6 \rightleftarrows C_6H_7^+ + Cl^- \qquad (3\cdot8)$$

to the right (i.e., since hydrogen chloride is only very slightly ionized in benzene solution), even though the chloride ion is itself only a weak base.

Although a weak acid is not necessarily a strong base, it must have a strong *conjugate* base. For example, the fact that acetic acid is weaker than hydrochloric acid means that the acetate ion is a stronger base than the chloride ion. Moreover, the fact that water is a weaker acid even than acetic acid means that the hydroxide ion must be a stronger base than the acetate ion; and the fact that benzene is an extremely weak acid means that the phenyl anion is an extremely strong base. In a similar way, a weak base must have a strong conjugate acid. For example, the fact that water is a weaker base than ammonia means that the hydronium ion is a stronger acid than the ammonium ion, and the fact that sulfuric acid is a weaker base than even water means that the ion $[H_3SO_4]^+$ is a stronger acid than even the hydronium ion.

A further problem which can conveniently be discussed from the Lowry-Brønsted viewpoint is the *leveling effect* of solvents upon acid and base strengths.[3] As is well known, all so-called strong acids appear (within the limits of measurement) to be completely ionized in aqueous solution and so to be equally strong. Nevertheless, it would be a most extraordinary coincidence if all these acids really do have exactly the same strength. The difficulty arises from the fact that the difference between two strong acids, even though it may actually be very great, is obscured by the leveling effect of the aqueous solvent. If, as a hypothetical example, the acids HA and HB are, respectively, 99.9900 per cent and 99.9999 per cent ionized in solutions of the same concentration, the ionization constant of HA is only about $\frac{1}{100}$ as great as is that of HB. Nevertheless, although the two acids thus differ very markedly in what may be called their intrinsic strengths, their degrees of dissociation, and hence their ionization constants, cannot be distinguished experimentally. In either solution, the only acid present in measurable amount is the hydronium ion H_3O^+; in each solution the concentration of this ion is, within experimental uncertainty, the same.

Information regarding the relative intrinsic strengths of two strong acids can be obtained only from a study of their solutions in a solvent in which their ionizations are not so nearly complete. In reactions 3·9 and 3·10, the water acts as a base in the Lowry-Brønsted sense; the fact

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[3] For further discussion, see L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, New York, 1940, pages 256 f.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^- \qquad (3\cdot9)$$

$$HB + H_2O \rightleftharpoons H_3O^+ + B^- \qquad (3\cdot10)$$

that each reaction goes practically to completion means that water is a much stronger base than is either of the ions A^- and B^-; or, in other words, that HA and HB are much stronger acids than is the hydronium ion H_3O^+. It is evident, therefore, that the degrees of ionization must be less in a solvent which is less basic than water, or, in other words, which has a conjugate acid that is stronger than the hydronium ion.[4] (However, see the paragraph below in fine print.) Methyl and ethyl alcohol satisfy this requirement; in either of these solvents, nitric acid is only slightly ionized, although most of the remaining common strong acids are still completely ionized within the limits of measurement. Formic acid is still less basic than the alcohols; in it, even hydrochloric acid is a weak electrolyte, although sulfuric acid is still a strong one. In acetone and nitrobenzene, all acids are weak electrolytes except perchloric acid $HClO_4$, which is in fact the strongest acid known. In this way the following order of decreasing acid strengths has been established: perchloric acid, sulfuric acid, benzenesulfonic acid, hydrochloric acid, nitric acid. Hydriodic acid is also known to be stronger than hydrobromic acid, which in turn is stronger than hydrochloric acid,[5] but the relation of the first two acids of this group to those of the foregoing group is uncertain.

If solvents which are more basic than water are used, the leveling effect appears with still weaker acids. For example, even acetic acid is indistinguishable from a strong acid in liquid ammonia, since its ionization (equation 3·11) is then essentially complete. (However, see the following paragraph.)

$$CH_3CO_2H + NH_3 \rightarrow NH_4^+ + CH_3CO_2^- \qquad (3\cdot11)$$

An interesting result of the leveling effect of solvents is that any specified acid forms the most acidic solution (i.e., the solution which is the most effective proton donor) in that solvent in which it is least ionized.[4] The justification of this somewhat paradoxical conclusion is that the ionization of an acid is really a more or less complete neutralization by the basic solvent, and that the extent of this neutralization increases with the basicity of the solvent and hence also with the degree of ionization. Thus, a solution of hydrogen chloride in benzene, where the ionization is very slight, is more acidic than is one of the same substance in water,

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[4] L. P. Hammett, *J. Am. Chem. Soc.* **50**, 2666 (1928); *Physical Organic Chemistry* McGraw-Hill Book Company, New York, 1940, page 261.

[5] A. Hantzsch, *Ber.* **58**, 612 (1925).

where the ionization is practically complete; for in benzene the acid actually present is the un-ionized hydrogen chloride, whereas in water it is the weaker hydronium ion. Similarly, acetic acid forms a more acidic solution in water than it does in liquid ammonia, although the ionization is much more extensive in the latter solvent. (Cf. the preceding paragraph). On this basis, a simple interpretation can be given to such facts as the one that the very weakly basic ethyl ether is transformed into a salt by concentrated sulfuric acid, which is largely un-ionized (cf. page 42), but not by dilute aqueous sulfuric acid, which is largely ionized. From the classical point of view, this last fact can still be easily explained, of course, by reference to the hydrolysis of the salt in the aqueous solution. As can readily be verified, the considerations of this paragraph in no way contradict the rule that, in any one solvent, that acid is strongest which is most ionized.

The discussion in the preceding paragraphs is considerably oversimplified, and hence is not entirely correct.[4] Thus, there is fairly conclusive evidence that the *intrinsic* base strengths of methyl alcohol and of ethyl alcohol are not significantly less than is that of water. To be sure, the contrary statement that these alcohols *are* less basic than water may, in a sense, be considered merely a description of the experimental fact that the two former solvents are less able than the latter one to accept a proton from an acid like nitric acid. Such a comparison, however, is not really legitimate, since it is implicitly based on the false assumption that base strengths are independent of solvent. In other words, although it may be true that water *in water* is more basic than is, for example, ethyl alcohol *in ethyl alcohol*, this fact gives little information regarding the relative intrinsic base strengths of the two substances. A valid comparison of base strengths can be made only when the bases that are being compared are, as nearly as possible, in identical states, and, more particularly, when they are surrounded by identical media. There is no evidence that, in a dilute solution of water in ethyl alcohol, the water is appreciably more basic than the alcohol; conversely, there is no evidence that, in a dilute solution of ethyl alcohol in water, the alcohol is appreciably less basic than the water. The relatively small ionization of nitric acid in pure ethyl alcohol is largely, if not entirely, due to the relatively low dielectric constant of this solvent, and to the therefore relatively large electrostatic attraction which acts between the cation $C_2H_5—O^+H_2$ and the anion NO_3^-. (Cf. Section 11·2.) On the other hand, an acid like anilinium ion $C_6H_5—NH_3^+$ is nearly as strong an acid in ethyl alcoholic as in aqueous solution,[6] because its ionization does not require the separation of oppositely charged ions. Similar considerations apply also, of course, to the discussion below of the leveling effect of *acidic* solvents upon *base* strengths.

. Just as all strong acids appear to be equally strong in a sufficiently basic solvent, so also all strong bases appear to be equally strong in a sufficiently acidic solvent. In aqueous solution, for example, the fact that, as has just been discussed, the hydronium ion is the strongest acid that can exist is paralleled by the further fact that the hydroxide ion is

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[6] H. Goldschmidt, *Z. physik. Chem.* **99**, 116 (1921).

the strongest base that can exist. Consequently, if any base B, which has a greater intrinsic strength than the hydroxide ion, is brought into contact with water, it will remove a proton from the water in accordance with reaction 3·12, so that, regardless of what the original base B may

$$B + H_2O \rightarrow BH^+ + OH^- \qquad (3\cdot12)$$

have been, the only base present in appreciable amount in the resulting solution is the hydroxide ion. In general the most familiar bases that are strong enough for this leveling effect to be important in aqueous solution (aside from the hydroxide ion itself, as provided by substances like sodium hydroxide or tetramethylammonium hydroxide) are the anions of extremely weak acids. The amide ion NH_2^-, the phenyl acetylide ion $C_6H_5{-}C{\equiv}C^-$, and the triphenylmethide ion $(C_6H_5)_3C^-$ may be mentioned as examples. Obviously, the base strengths of such ions cannot be compared in aqueous solution since water is too acidic. However, they can be compared in such less acidic solvents as liquid ammonia or ether. In this way, the phenyl acetylide ion is found to be the weakest base, the triphenylmethide ion is found to be somewhat stronger, and the amide ion is found to be the strongest of the three named.[7] All are stronger, of course, than hydroxide ion.

A further important application of the Lowry-Brønsted terminology involves the numerical values of the basic ionization constants of amines and similar bases. From equation 3·13 the classical ionization constant

$$B + H_2O \rightleftarrows BH^+ + OH^- \qquad (3\cdot13)$$

K_b of such a base B is seen to have the value given by equation 3·14.

$$K_b = \frac{[BH^+]\,[OH^-]}{[B]} \qquad (3\cdot14)$$

The symbol [B] here represents the sum of the concentrations of both the uncombined B and the un-ionized hydrate BHOH, since, in general, these two concentrations cannot be measured separately. With the general adoption of the Lowry-Brønsted definitions, however, the custom has arisen of replacing the classical base constant K_b by the acid constant K_a of the conjugate acid BH^+. From equation 3·15, this constant

$$BH^+ + H_2O \rightleftarrows B + H_3O^+ \qquad (3\cdot15)$$

is seen to have the form shown in equation 3·16.

$$K_a = \frac{[B]\,[H_3O^+]}{[BH^+]} \qquad (3\cdot16)$$

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[7] J. B. Conant and G. W. Wheland, *J. Am. Chem. Soc.* **54**, 1212 (1932); C. A. Kraus and R. Rosen, *ibid.* **47**, 2739 (1925).

The two constants K_a and K_b of a given base in a given solvent are closely related to each other. In fact, the value of either is completely determined by that of the other; thus, in aqueous solution, the relation between K_a and K_b is the one stated in equation 3·17. It is to be observed that a strong base with large K_b has a small K_a, whereas a weak base with small K_b has a large K_a.

$$K_a = \frac{[H_3O^+][OH^-]}{K_b} \cong \frac{10^{-14}}{K_b} \qquad (3\cdot17)$$

In place of the constants K_a and K_b themselves, the respective logarithmic functions pK_a and pK_b, defined in equations 3·18 and 3·19,

$$pK_a = -\log K_a \qquad (3\cdot18)$$

$$pK_b = -\log K_b \qquad (3\cdot19)$$

are now fairly commonly used. Thus, a base with K_b equal to 10^{-5} and K_a equal to 10^{-9} would have a pK_b of 5 and a pK_a of 9. As is shown in this example, the pK's are easier to work with than are the K's themselves, since they are of more convenient magnitude and do not involve the awkward exponents. It should be noted that, on account of the minus sign in the defining equations, pK_a increases, and pK_b decreases as the strength of the base increases.

3·3 The Lewis Definitions of Acids and Bases.[1, 8] Almost simultaneously with Lowry and Brønsted, G. N. Lewis made an even more far-reaching generalization of the acid-base concept. Although it is true that the proton, being a bare nucleus, is unique among the known cations, this property is not actually used even in the Lowry-Brønsted scheme. The property of the proton which *is* used is rather that this ion is able to form a covalent bond with an atom by sharing two electrons that are both provided by this atom. In this respect, the proton is by no means unique, since many other atoms and molecules can behave similarly. In general, any substance in which at least one atom has only an "open sextet" of electrons belongs to this class. For example, boron trifluoride BF_3 and aluminum chloride $AlCl_3$ are able to form addition compounds by sharing electrons provided by the second component, as was mentioned in Sections 2·3 and 2·4. Moreover, a number of further substances, such as stannic chloride, $SnCl_4$, in which no open sextet exists, but in which the octet of electrons about some atom can be expanded, are also of the same type. Lewis has proposed that all such substances be called acids, and that the further substances which provide the pairs of electrons for the new bonds be called bases.

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[8] G. N. Lewis, *Valence and the Structure of Atoms and Molecules*, Chemical Catalog Company, New York, 1923, pages 141 f.; *J. Franklin Inst.* **226**, 293 (1938).

The above discussion may seem inconsistent with the view expressed earlier on pages 18 f. that no significance can be attached to the origin of the two electrons which produce a covalent bond. In the earlier section, however, the discussion was concerned with the nature of the bond itself after it has been formed; here, it is concerned instead with the natures of the two reagents before they have reacted, and with the factors which enable these reagents to come together to form a new covalent bond. It is easily seen that no inconsistency exists.

Lewis's definitions require considerable departure from both the classical and the Lowry-Brønsted terminologies. Thus, hydrogen chloride is not itself an acid; instead the proton which it contains, and which it can readily give up, is the acid. Similarly, the hydronium ion also is not an acid. On the other hand, boron trifluoride, aluminum chloride, stannic chloride, and the like are acids. As with Lowry and Brønsted, the hydroxide ion is a base, whereas sodium hydroxide is not. Any substance which is a base according to Lowry and Brønsted is a base also according to Lewis, since the ability to react with a proton is a sufficient criterion from either point of view. The converse is not necessarily true, however. In order to be a base according to Lowry and Brønsted, a substance must react with a *proton*, whereas it may still be a base according to Lewis even if it does not react with a proton, provided that it does react with some other acid, such as aluminum chloride, for example. Thus, the argon atom is not a base according to Lowry and Brønsted, because it does not react with a proton, but it is a weak base according to Lewis, because it forms a rather unstable addition compound with the acid boron trifluoride.[9]

It should be apparent that all the addition compounds of the onium type, which were discussed in Sections 2·3 and 2·4, are classified by Lewis as products of reactions between acids and bases. Thus, the two reactions 3·20 and 3·21 are described in the same terms. No significance

$$NH_3 + H^+ \rightarrow NH_4^+ \tag{3·20}$$

$$(CH_3)_2O + BF_3 \rightarrow (CH_3)_2O^+\text{—}B^-F_3 \tag{3·21}$$

is attached to the fact that, in the first, the product is an ion that forms part of a salt, whereas, in the second, the product is a neutral molecule. In each reaction, a base (ammonia or methyl ether, respectively) shares two electrons with an acid (the proton or boron trifluoride, respectively).

The Lewis definitions of acids and bases have not been so widely adopted as have those of Lowry and Brønsted. At the present time, however, their popularity is increasing rapidly. Their advantage lies not only in the fact that they permit a correlation and systematization of a large number of otherwise unrelated data, but also in the further fact that the substances which they classify as acids do actually possess

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[9] H. S. Booth and K. S. Willson, *J. Am. Chem. Soc.* **57**, 2273 (1935).

most of the usual properties associated with acidity. Thus, in nonaqueous solvents, these substances often affect indicators, catalyze reactions, and neutralize bases in the ways characteristic of ordinary acids. Examples of such behavior will be mentioned in later chapters. Moreover, in aqueous solution, the substances are acidic even in the classical sense of increasing the concentration of hydrogen ion (i.e., of hydronium ion). For example, an aqueous solution of aluminum chloride is strongly acidic. In classical language, this fact is explained as a result of hydrolysis; in the language of Lowry and Brønsted, a more complicated interpretation, based upon the assumed presence of an acid like $[Al(H_2O)_6]^{+++}$, can be given; but, according to Lewis, the acidity of the solution is a direct consequence of the acidity of the aluminum chloride itself, as modified by the basic character of the water.

3·4 The Solvent Concept of Acids and Bases.[1,10] Still a third, much less widely adopted, generalization of the acid-base concept may be described here briefly. As has been mentioned, the hydrogen and hydroxide ions, which form the basis of the classical definitions of acids and bases, are of special importance because they are, respectively, the cation and anion derived from the most common solvent, water. A logical generalization of the classical definitions, applicable to both aqueous and nonaqueous solutions, is therefore obtained if acids and bases are defined as substances which increase the concentrations of the cation and anion, respectively, of the solvent. The application of this new definition to a few specific examples is shown in Table 3·1, which should be self-explanatory.

TABLE 3·1

THE SOLVENT CONCEPT OF ACIDS AND BASES[a]

Solvent	*Acid*	+	*Base*	→	*Salt*	+	*Solvent*
H_2O	$H_3O^+ \quad Br^-$		$K^+ \quad OH^-$		$K^+ \quad Br^-$		$2H_2O$
NH_3	$NH_4^+ \quad Br^-$		$K^+ \quad NH_2^-$		$K^+ \quad Br^-$		$2NH_3$
C_2H_5OH	$C_2H_5OH_2^+ \quad Br^-$		$K^+ \quad OC_2H_5^-$		$K^+ \quad Br^-$		$2C_2H_5OH$
SO_2	$SO^{++} \quad 2Br^-$		$2K^+ \quad SO_3^{=}$		$2(K^+ \quad Br^-)$		$2SO_2$
$COCl_2$	$COCl^+ \quad AlCl_4^-$		$K^+ \quad Cl^-$		$K^+ \quad AlCl_4^-$		$COCl_2$
$SeOCl_2$	$2(SeOCl)^+ \quad SnCl_6^{=}$		$2(K^+ \quad Cl^-)$		$2K^+ \quad SnCl_6^{=}$		$2SeOCl_2$
$SbCl_3$	$Sb^{+++} \quad 3Br^-$		$3(K^+ \quad Cl^-)$		$3(K^+ \quad Br^-)$		$SbCl_3$

[a] Adapted from W. F. Luder and S. Zuffanti, *The Electronic Theory of Acids and Bases*, John Wiley and Sons, New York, 1946, page 12.

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[10] H. P. Cady and H. M. Elsey, *J. Chem. Education* **5**, 1425 (1928); W. F. Luder, *Chem. Revs.* **27**, 547 (1940).

3·5 Nomenclature of Acids and Bases. When one speaks of either an acid or a base, he may have in mind the classical meaning of the word, the meaning proposed by Lowry and Brønsted, the one proposed by Lewis, or the one based upon the solvent concept. This ambiguity in nomenclature is found in practice to lead to little confusion, however, since the four definitions are seldom very widely different, and since the context usually makes the meaning sufficiently clear. Whenever the possibility of a more or less serious misunderstanding exists, this danger can be removed by such obvious circumlocutions as "an acid (or base) in the classical sense," "a Lowry-Brønsted acid (or base)," or "a Lewis acid (or base)." It may be noted also that the Lowry-Brønsted acids and bases are more frequently referred to simply as Brønsted acids and bases, respectively. Moreover, the Lewis acids are commonly called cationoid [11] (kationoid [11]) or electrophilic [12] reagents by many chemists; similarly, the Lewis bases are called anionoid,[11] nucleophilic,[12] or electrodotic [1,13] reagents.

A further matter of terminology is introduced by the question how weak an acid or a base must be before it can no longer be called, respectively, an acid or a base. There is, of course, no precise answer to this question, since there is no sharp separation between, on the one hand, acids or bases and, on the other hand, neutral substances. In fact, when the Brønsted definitions are used, every substance which contains hydrogen is, in one sense, an acid, since the molecule of any such substance is always able, at least in principle, to lose a proton; similarly, every substance (regardless of its composition or structure) is a base, since its molecule must always be able, in principle, to combine with a proton. Benzene, for example, was considered in Section 3·2 to be both an acid and a base; even argon, which was said in Section 3·3 to be not a Brønsted base, would surely, however, be able to accept a proton if only a suitable proton donor (i.e., a sufficiently strong acid) could be found. In an analogous manner, a great many substances which are not now ordinarily regarded as Lewis acids or Lewis bases can be described as exceedingly weak Lewis acids or Lewis bases. Only seldom, however, is it necessary to adopt the extremely general point of view that has just been outlined. A more satisfactory procedure is instead to use the words "acid" and "base" only with reference to fairly definitely specified chemical reactions. Thus, phenol is a (classical or Brønsted) acid when it is dissolved in water and when it reacts with sodium hydroxide;

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[11] A. Lapworth, *Nature* **115**, 625 (1925); R. Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions*, The Institute of Chemistry of Great Britain and Ireland, London, 1932.

[12] C. K. Ingold, *J. Chem. Soc.* **1933**, 1120; *Chem. Revs.* **15**, 225 (1934).

[13] N. F. Hall, *J. Am. Chem. Soc.* **63**, 883 (1941).

aniline is a (Brønsted or Lewis) base when it is dissolved in water and when it reacts with hydrogen chloride; benzene is a (Brønsted or Lewis) base when it combines with a proton that is formed by the ionization of hydrogen chloride (equation 3·8); and so on. On the other hand, neither phenol nor benzene is either an acid or a base when the two substances are merely mixed with one another, since then no chemical reaction takes place.

4.

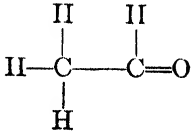
Structural Isomerism

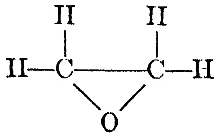
4·1 The Significance of Structure. The field of isomerism is subdivided into *structural* isomerism and *stereo*isomerism. With the definition of the word "isomer" given in Section 1·18, the distinction between these two subdivisions is sharp and unambiguous. Two given isomers are always either structural isomers or stereoisomers of each other; they are never both, and never neither.

Two isomers are said to be structural isomers of each other if they differ in *structure,* and to be stereoisomers of each other if they have identical structure but differ in *configuration.* The meaning of the word "configuration" will be discussed later (see Section 5·1 and also Chapter 6), but that of the word "structure" requires immediate, careful consideration.

Throughout this book, the structure of any given molecule will be considered to consist of a detailed statement of the way in which each atom of the molecule is linked (if at all) to each other atom. In principle, this statement may take any of several superficially different, but equivalent, forms. In practice, however, one of these forms is so much more convenient than any of the others that it is the only one which is at all commonly used. This favored form is, of course, the familiar one, in which each covalent bond is represented by a (usually) straight line drawn between the chemical symbols for the atoms joined, or else, in the so-called electronic structures, by a pair of dots. It should be noted, however, that an *ionic* bond, even though it may act between two single atoms, is usually not similarly represented by a line, since the presence of the plus and minus signs indicating the ionic charges is sufficient to show the existence of such a bond.

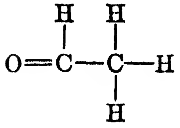
Diagrams I and II are here sufficient to illustrate this most important

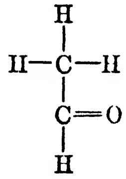

I

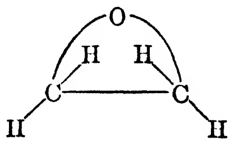

II

method of representing structures. These diagrams are obviously not equivalent since they differ in the ways in which the atoms are linked. Consequently, the existence of the two structurally isomeric substances, acetaldehyde and ethylene oxide, with the molecular formula C_2H_4O, is accounted for.

The conventional diagrams of the foregoing type suffer from the fact that they appear to imply more than they actually do. More particularly, they appear to have geometrical significance. Diagram I, for example, has the two carbon atoms, the oxygen atom, and one of the hydrogen atoms on a horizontal straight line, with the oxygen atom at the extreme right and the hydrogen atom at the extreme left; similarly, diagram II has the oxygen atom below the carbon and hydrogen atoms; and so on. It must be emphasized, however, that the structures, as distinguished from the diagrams under discussion, have no geometrical significance whatever. The geometrical significance which is often assigned to such structures really belongs instead to the associated configurations, as will be discussed in greater detail in the following chapters. One very familiar consequence of this lack of geometrical significance is that, even if diagrams like I and II are moved in the plane in which they are written, or if they are bent or distorted in any arbitrary way, they still correspond to the same structure. For example, diagrams III and IV are not to be distinguished from I; similarly, diagrams V and VI are not to be distinguished from II. Although these examples may seem too simple to require special comment, the situation is not always so obvious. A more complicated example, which has in fact given rise to some confusion in the past, is discussed on pages 108 f.


III


IV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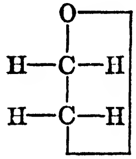
VI

The irrelevance of geometrical considerations in the definition of a structure can be shown most conclusively by a discussion of some of the remaining, less convenient and less familiar, ways in which structures can be specified. One of these ways consists in giving a purely verbal description. Thus, the structure of acetaldehyde (I, III, or IV) can be stated in words as the one in which a carbon atom is joined by covalent single bonds to three hydrogen atoms and to a second carbon atom, which in turn is joined by a covalent single bond to a fourth hydrogen atom and by a covalent double bond to an oxygen atom; similarly, the structure of ethylene oxide (II, V, or VI) can be stated as the one in which each of two carbon atoms is joined by covalent single bonds to the other carbon atom, to a common oxygen atom, and to two hydrogen atoms. These descriptions are clearly unique and different, and they express exactly the same meanings, no more and no less, that are contained in the respective diagrams I (or III or IV) and II (or V or VI). However, they are much too cumbersome to be of practical use.

TABLE 4·1

A NONGEOMETRICAL STATEMENT OF THE STRUCTURE OF ACETALDEHYDE[a]

	C	C	H	H	H	H	O
C	..	1	1	1	1	0	0
C		..	0	0	0	1	2
H			..	0	0	0	0
H				..	0	0	0
H					..	0	0
H						..	0
O							..

[a] Each number in this table represents the number of covalent bonds linking the atom at the left of the row to the atom at the top of the column.

TABLE 4·2

A NONGEOMETRICAL STATEMENT OF THE STRUCTURE OF ETHYLENE OXIDE[a]

	C	C	H	H	H	H	O
C	..	1	1	1	0	0	1
C		..	0	0	1	1	1
H			..	0	0	0	0
H				..	0	0	0
H					..	0	0
H						..	0
O							..

[a] Each number in this table represents the number of covalent bonds linking the atom at the left of the row to the atom at the top of the column.

A further nongeometrical way of describing the structures of acetaldehyde and of ethylene oxide is slightly more illuminating than the verbal one; when this method is adopted, the two structures are expressed as in Tables 4·1 and 4·2, respectively. The numbers in the bodies of these tables represent the numbers of covalent bonds between the corresponding atoms at the left of the rows and at the tops of the columns. The two tables are easily seen to be different from one another, but to be completely equivalent to the respective conventional diagrams and verbal descriptions.

The foregoing alternative ways of describing structures have not been given here with the idea that they would be of practical use, but rather with the hope that they would serve to emphasize the fact that structures, as such, need have no geometrical implications. Since exactly the same information which is contained in a conventional diagram can be given equally well (even though incomparably less conveniently) by an obviously nongeometrical verbal description or table, then the diagram, in spite of its appearance, must also be actually nongeometrical. In other words, all geometrical features of the diagrams which are not contained in either the verbal description or the table must be disregarded as of no significance. (Later, when the discussion is of configuration rather than of structure, this extreme statement will require some modification. See Chapters 6–9.) With this much in the way of explanation and of warning, however, a return may now be made to the familiar diagrams, which will be used exclusively hereafter as the only practical descriptions of the corresponding structures, and which, in accordance with common usage, will be called structural formulas or, more simply, structures.

4·2 The Number of Isomers.[1] A fundamental postulate of the structural theory of chemistry is that two molecules which differ in structure must correspond to different substances with different chemical and physical properties. A corollary of this postulate is that the number of theoretically possible structural isomers which have any given molecular formula must be equal to the number of nonequivalent structures that are permitted by the rules of valence. The application of this assumption to the calculation of isomer numbers should be too familiar to require further comment here.

The postulated equality of the number of structures and of isomers corresponding to each molecular formula is subject to several different types of limitation. The ideal situation would be that exactly one substance exist for each structure which can be drawn; and that, conversely, exactly one structure be associated with each substance which exists. Four types of exception to this ideal can, however, be visualized, and examples of each type have been encountered: first, many structures which can be written correspond to no known substance at all; second, some structures must be associated with two or more different substances; third, some substances cannot be described by any structure of the usual type; and fourth, some apparently single substances behave

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[1] Cf. J. K. Senior, *J. Chem. Education* **12**, 409, 465 (1935).

as if they possess two or more distinct structures. If the prediction of the numbers of isomers is to be considered an essential function of the structural theory, these exceptions must be examined in order that their extent and significance may be evaluated.

1. The fact that there are many structures which can be written, but for which no corresponding substances are known, is often merely the result of the fact that no chemist has as yet been sufficiently interested, or had sufficient time, to prepare samples of all the theoretically possible isomers. Even relatively simple molecular formulas may permit enormous numbers of structures; for example, it has been calculated [2] that the formula $C_{20}H_{42}$ permits 366,319 structures and that the formula $C_{40}H_{82}$ permits 62,491,178,805,831 structures! Actually, of course, such large numbers as especially the second of these are experimentally meaningless, since, even if a sample of each of the substances were available, it would be impossible experimentally to prove that no two of them were identical. At present, only about ten or a dozen different substances with the formula $C_{20}H_{42}$, and about four with the formula $C_{40}H_{82}$, are known. The most complicated molecular formula for which all possible structural isomers have been prepared is probably C_9H_{20}, with altogether thirty-five nonequivalent structures. For other formulas, *incomplete* sets of more than one hundred known isomers are, however, not uncommon. The essential point to be brought out here is that, in those instances in which a serious attempt has been made to prepare all the possible isomers, and in which the factors discussed below do not make success impossible, the theoretical isomer numbers have usually been confirmed experimentally.

The following example will show how enormous the number of theoretically possible structural isomers may become if only the system is sufficiently complex. A hypothetical, relatively simple, protein molecule with a molecular weight of approximately 30,000 may be considered to be built up from 300 amino acid residues in linear order. Twenty of these amino acid residues may be supposed to belong to each of 15 different types, so that there are, for example, exactly 20 glycine residues, exactly 20 alanine residues, exactly 20 lysine residues, etc. If any two nonequivalent residues are interchanged, a structurally isomeric protein molecule is obtained. The total number of isomeric molecules which can be thus obtained *merely by permuting the amino acid residues* is then approximately 5×10^{338}. A sample consisting of only a single molecule (not mole) of each isomer would weigh approximately 3×10^{313} tons and, if it had a density of 1, would occupy a cubic box approximately 3×10^{88} light years on an edge. Obviously, it would be quite impossible for all these isomers to exist.

In some instances, however, attempts to prepare substances with certain structures have been unsuccessful in spite of repeated and varied

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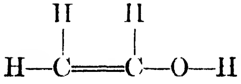
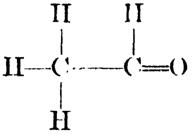
[2] H. R. Henze and C. M. Blair, *J. Am. Chem. Soc.* **53**, 3077 (1931).

attempts. For example, all attempts to prepare vinyl alcohol, I, have



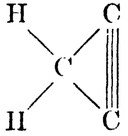
$\mathrm{H-\overset{H}{C}=\overset{H}{C}-O-H}$

I



$\mathrm{H-\overset{H}{\underset{H}{C}}-\overset{H}{C}=O}$

II



III

led instead to the isomeric acetaldehyde, II. Apparently, therefore, a substance with structure I cannot exist or, at any rate, cannot be isolated, because it undergoes a rapid and spontaneous transformation into a different, but isomeric substance. Numerous further examples of this same phenomenon are known; their existence has been explained by the concept of *tautomerism*, which will be discussed in greater detail in Chapter 14. In other instances, certain structures that can be written on paper correspond to molecules which would be so highly *strained* that they could not be expected to exist. A simple example is represented by structure III (of the unknown cyclopropyne); further examples are discussed in Section 9·5. Finally, certain structures correspond to substances for which at present no method of preparation is known. Thus, for perhaps fifty years all attempts to prepare *tert*-butyl ether, IV, for example, led instead to entirely different substances, be-

$$(CH_3)_3C—O—C(CH_3)_3$$

IV

cause the chemical reactions that were carried out failed to follow the desired courses; the products obtained in these reactions were not isomeric and hence were not tautomeric (see above) with the expected ether IV. There is, however, no obvious reason why such a substance as this could not be prepared if only a suitable method of preparation could be devised; in fact, *tert*-butyl ether was finally prepared in 1941 [3] by the action of silver carbonate upon *tert*-butyl chloride. (This problem of the nonexistence of predicted isomers is discussed further from a different point of view on pages 121 f.)

2. The existence of structures which must be assigned to two or more different substances has made necessary a fundamental extension and broadening of the structural theory. The nature of the developments arising from this cause is discussed in considerable detail in Chapters 5–8, which deal with the phenomenon of *stereoisomerism*.

3. For some substances which exist, no structures of the classical type can be written. In nearly all instances, however, such substances have been brought successfully into the structural scheme by suitable ex-

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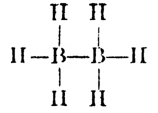
[3] J. L. E. Erickson and W. H. Ashton, *J. Am. Chem. Soc.* **63**, 1769 (1941).

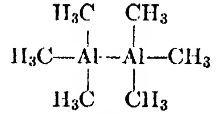
tensions of the theory. Several such extensions have already been mentioned in the previous chapters in which the natures of the coordinate bond, of the hydrogen bond, and of the onium compounds were discussed. Moreover, the existence of still other types of substance has required the recognition of variations in valence. For example, it is now an accepted fact that carbon, although it is quadrivalent in most of its compounds, is occasionally trivalent (see Chapter 15) and that many other elements also have greater or less tendencies to display similarly variable valences. With the aid of this extension of the structural theory, a large number of substances, to which structures could not otherwise have been assigned, can be taken care of without difficulty. Finally, the theory of resonance (see Chapter 10) has served to clear up most of the remaining difficulties by introducing a more generalized concept of structure. Although there are still many substances to which no structures have as yet been definitely assigned, there are now very few (if any) which seem to lie completely outside the structural scheme.

It is perhaps not impossible that the existence of such substances as the boron hydrides (cf. footnote *v* of Table 1·1, page 4) and aluminum methyl $Al_2(CH_3)_6$ may ultimately require that the structural theory be extended still further in some as yet undetermined direction. Thus, the two "obvious" structures V and VI for



$$\begin{array}{ccccccc} & & \mathrm{H} & & \mathrm{H} & & \\ & & | & & | & & \\ \mathrm{H} & - & \mathrm{B} & - & \mathrm{B} & - & \mathrm{H} \\ & & | & & | & & \\ & & \mathrm{H} & & \mathrm{H} & & \end{array}$$

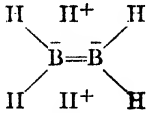
V



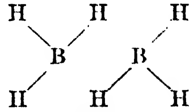
$$\begin{array}{ccccccc} & & \mathrm{H_3C} & & \mathrm{CH_3} & & \\ & & | & & | & & \\ \mathrm{H_3C} & - & \mathrm{Al} & - & \mathrm{Al} & - & \mathrm{CH_3} \\ & & | & & | & & \\ & & \mathrm{H_3C} & & \mathrm{CH_3} & & \end{array}$$

VI

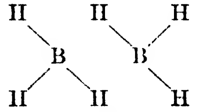
diborane and aluminum methyl, respectively, are impossible because each contains two more electrons than does the molecule which it is designed to represent, and because each therefore corresponds actually to a bivalent anion In these substances, the average numbers of valence electrons per bond are less than two, even though, in general, every covalent bond is supposed to require a complete pair of electrons. One of the earliest proposed explanations of these anomalous compounds was that each contains a number of "one-electron bonds," resulting from the sharing of only one electron, rather than of the customary two electrons, by the atoms concerned.[4] An alternative explanation, which now seems almost definitely established, suggests that the structure of diborane, for example, cannot be expressed by any unique symbol of the classical type, but must instead be described as intermediate among several different structures, of which VII, VIII, and IX are perhaps the



VII



VIII



IX

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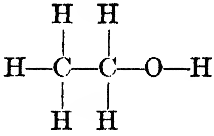
[4] Cf. N. V. Sidgwick, *The Electronic Theory of Valency*, Oxford University Press, Oxford, 1927, page 103; L. Pauling, *J. Am. Chem. Soc.* **53**, 3225 (1931).

most important.[5] (Cf. Chapter 10.) If neither of these proposals should prove to be satisfactory, then (as suggested above) some still more drastic modification of the structural theory may be necessary. In any event, however, substances of the type here discussed are very uncommon and, moreover, mostly inorganic; consequently, although their existence should certainly be recognized, they will not be encountered again in this book.

4. The existence of apparently single substances which act as if they have two or more structures has given rise to the concept of tautomerism. (Cf. paragraph 1, above, and also Chapter 14.) In some instances, however, the interpretation of such substances involves the idea of resonance instead. (Cf. paragraph 3, above, and also Chapter 10.) In any event, the modern structural theory, with the aid of its various extensions, is able without difficulty to accommodate nearly (if not quite) all the anomalous substances of this last type.

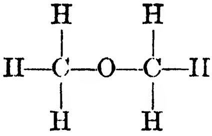
4·3 Use of Chemical Reactions in the Determination of Structure. The structural theory would be of relatively little practical value if it permitted only the calculation of the number of isomers, and not the assignment of a definite structure to each of the isomers in those instances in which more than one structure is possible. So far, however, nothing has been said about the experimental methods by which structures are actually assigned. These methods, although they may vary greatly in detail, usually belong to one of only three main types, or else are combinations of methods belonging to two or perhaps even to all three of these types. The first general method to be discussed here is the one based upon the study of chemical reactions. The second and third methods, which are based, respectively, upon the study of isomer numbers and of physical properties, will be taken up later in this chapter. (See Sections 4·4–4·7.)

One of the first "proofs of structure" to be given in courses in elementary organic chemistry is often that for ethyl alcohol. The argument frequently runs as follows. The molecular formula of ethyl alcohol is found, from its analysis and from a determination of its molecular weight, to be C_2H_6O. By trial and error, one can easily convince himself that there are two and only two structures, namely, I and II,



$$\begin{array}{ccccccc} & & H & & H & & \\ & & | & & | & & \\ H & - & C & - & C & - & O-H \\ & & | & & | & & \\ & & H & & H & & \end{array}$$

I



$$\begin{array}{ccccccccc} & & H & & & & H & & \\ & & | & & & & | & & \\ H & - & C & - & O & - & C & - & H \\ & & | & & & & | & & \\ & & H & & & & H & & \end{array}$$

II

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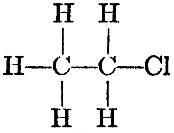
[5] Cf. H. C. Longuet-Higgins and R. P. Bell, *J. Chem. Soc.* **1943,** 250; K. S. Pitzer, *J. Am. Chem. Soc.* **67,** 1126 (1945); R. S. Mulliken, *Chem. Revs.* **41,** 207 (1947); R. E. Dodd and P. L. Robinson, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **44,** 52 (1947). Cf., however, G. Silbiger and S. H. Bauer, *J. Am. Chem. Soc.* **70,** 115 (1948); J. S. Kasper, C. M. Lucht and D. Harker, *ibid.* **70,** 881 (1948).

which correspond to this molecular formula and which satisfy the requirement that the carbon atoms be quadrivalent, that the oxygen atom be bivalent, and that the hydrogen atoms be univalent. (The number of different possible structures satisfying these conditions can, of course, be proved by rigorous mathematical methods, as well as by trial and error.) Consequently, the structure of ethyl alcohol must be either I or II, and the problem is to decide which one of these is right. This conclusion is supported by the fact that there is also known exactly one isomeric substance, methyl ether, to which the other of the structures I and II must be assigned; consequently, the method of treatment, at the very least, correctly predicts the total number of isomers.

The decision between structures I and II for ethyl alcohol is now made on the basis of the chemical reactions of the substance. In the first place, although altogether six hydrogen atoms are present in the molecule, only one can be replaced by an active metal like sodium. The inference is then drawn that one hydrogen atom is essentially different from the other five. Since this condition is satisfied by structure I but not by structure II, ethyl alcohol can therefore be assigned structure I, so that methyl ether must be assigned structure II. Further evidence leading to the same conclusion is provided by the reaction which occurs between ethyl alcohol and hydrogen chloride, and which leads to ethyl chloride C_2H_5Cl. For this latter substance, if the chlorine atom is assumed to be univalent, only the one structure III can be drawn to satisfy

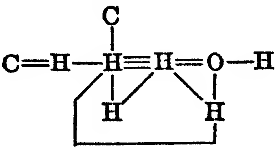


$$\begin{array}{ccccccc} & & H & & H & & \\ & & | & & | & & \\ H & — & C & — & C & — & Cl \\ & & | & & | & & \\ & & H & & H & & \end{array}$$

III

the molecular formula. Consequently, since ethyl chloride must therefore have structure III, ethyl alcohol must have structure I, inasmuch as this structure is much more closely related to III than is II.

The foregoing arguments are elementary and should be familiar. A more careful examination of their various features, however, will prove illuminating. First of all, it may be asked why the only structures that are considered are the ones in which carbon, oxygen, hydrogen, and chlorine are quadrivalent, bivalent, univalent, and univalent, respectively, and why, in particular, such structures as IV are immediately



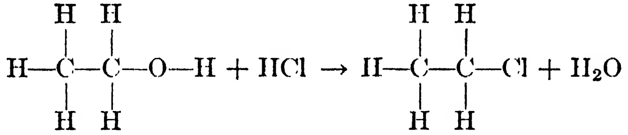
IV

dismissed. Indeed, the more fundamental question may be asked why it is supposed that the molecule can be adequately represented by any structure whatever. No simple and conclusive answer can be given to either of these questions. That is to say, no single experiment, or combination of a small number of experiments, can prove that the valences of the atoms must be those supposed, or even that the concept of structure itself is valid. The justification of these aspects of the structural theory is rather that they permit a self-consistent, logical, and extremely useful interpretation of an enormous number of independent experiments of many different kinds. They do not permit an interpretation of *all* the experiments that can be performed. As has already been noted (see the preceding section), numerous examples of variable valence are known. Moreover, as has also already been noted (see Chapter 1), the electrostatic interactions of the sort in tetramethylammonium nitrate, and the still weaker dipole-dipole and van der Waals forces, do not lend themselves at all readily to treatment in this manner. Nevertheless, if valences are assumed to be constant, and if the simple concept of structure is assumed to be valid, a large part of organic chemistry can be interpreted. Consequently, one can, with considerable reason, feel justified in employing these assumptions as working hypotheses within the field in which they have proved valuable until experience has shown them to fail.

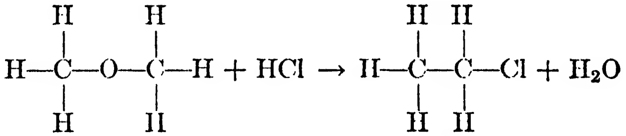
The second part of the argument leading to the assignment of structure I to ethyl alcohol (and hence of structure II to methyl ether) was concerned with the reactions between the alcohol and active metals. The fact that only one hydrogen atom is replaceable by such metals does indeed suggest, but it by no means proves, that one hydrogen atom is structurally different from the others. For example, the same reasoning would lead to the certainly fallacious conclusion that the two hydrogen atoms in *water* are nonequivalent, since here too only one is replaceable by a metal like sodium. To be sure, sodium oxide Na_2O, in which both hydrogen atoms have been replaced, is known. However, this substance is not made by the direct action of the metal upon water at ordinary temperatures; and there is no assurance that a substance with a formula like $C_2H_4ONa_2$ might not also be capable of preparation by some indirect method, or even by a direct one if only the organic substance could withstand sufficiently high temperatures. The point involved here is that, after one hydrogen atom (or, rather, ion) has been replaced, the resulting ethoxide or hydroxide ion, $C_2H_5O^-$ or HO^-, respectively, is not the same substance as the original alcohol or water. Even if alcohol had two equivalent hydrogen atoms, as water doubtless does, the fact that one of them can be replaced by sodium would not require that one of those remaining in the resulting ethoxide ion must react similarly. The situation is very roughly analogous to that in a dibasic acid like oxalic acid, V. The fact that the first and second ionization constants of this substance are rather widely different (approximately 6×10^{-2} and 7×10^{-5}, respectively) is no proof whatever that the two carboxyl groups are not equivalent; the first ionization constant refers to the neutral oxalic acid, V, whereas the second refers to the different substance, the acid oxalate ion, VI.

$$\underset{\text{V}}{\mathrm{HO_2C{-}CO_2H}} \qquad\qquad \underset{\text{VI}}{\mathrm{HO_2C{-}CO_2^-}}$$

If, then, the reaction with sodium does not provide conclusive proof of the structure of ethyl alcohol, what about the one with hydrogen chloride? Although the argument based upon this latter reaction is probably less objectionable than the previous one, it is still not entirely conclusive. The reaction of equation 4·1 certainly looks much more reasonable than does the one of equation 4·2; there is, however, no rigorous proof that the latter reaction is impossible or that the former must be the one which takes place.



$$\mathrm{H{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}O{-}H + HCl \rightarrow H{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}Cl + H_2O} \qquad (4{\cdot}1)$$



$$\mathrm{H{-}\overset{H}{\underset{H}{C}}{-}O{-}\overset{H}{\underset{H}{C}}{-}H + HCl \rightarrow H{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}Cl + H_2O} \qquad (4{\cdot}2)$$

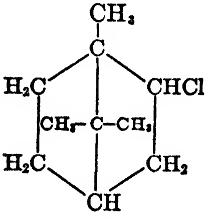
The justification for the belief that equation 4·1 is correct and that equation 4·2 is incorrect is merely that reaction 4·1 requires much the less drastic structural change. Indeed, the validity of what may be called the *principle of minimum structural change* must be assumed before any conclusion regarding the structure of ethyl alcohol can be drawn from its reaction with hydrogen chloride (or, for that matter, with any other reagent). This principle seems so obvious, *a priori*, that the essential role which it plays in proofs of structure is usually not even realized. Nevertheless, in spite of its apparent obviousness, it is not always valid. The frequent occurrence of *molecular rearrangements*, in fact, shows that the actual courses of reactions cannot be safely predicted on the basis of relative inherent reasonableness. Numerous examples of such rearrangements will be given later, especially in Chapters 12 and 13; it will be sufficient here to mention, as two specific examples, that the action of hydrogen chloride upon diisopropylcarbinol, VII, does not give the expected 3-chloro-2,4-dimethyl-

$(CH_3)_2CH{-}CHOH{-}CH(CH_3)_2$
VII

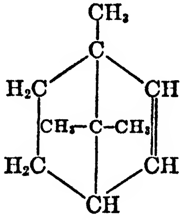
$(CH_3)_2CH{-}CHCl{-}CH(CH_3)_2$
VIII

$(CH_3)_2CCl{-}CH_2{-}CH(CH_3)_2$
IX

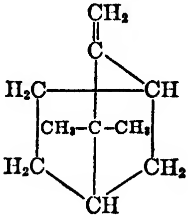
pentane, VIII, but instead 2-chloro-2,4-dimethylpentane, IX;[6] and that the dehydrohalogenation of isobornyl chloride, X, does not give the expected bornylene, XI, but instead camphene, XII. In view of the



X



XI



XII

more or less drastic structural changes which occur in these, and in numerous other, reactions, the fact that ethyl alcohol gives ethyl chloride, of definite structure, cannot be considered conclusive proof of the structure of the alcohol.

In spite of the occurrence of molecular rearrangements, however, the study of the chemical reactions which substances undergo has in practice provided a convenient method for the determination of their structures. Although, as in the reaction between ethyl alcohol and hydrogen chloride, the possibility of a molecular rearrangement prevents the assignment of a definite structure to any substance on the basis of a single reaction, reliable conclusions can usually be reached, nevertheless, from a study of a number of related reactions. The aim of such a study is to obtain a self-consistent picture of the whole series of reactions and, in particular, to determine in which ones the rearrangements, if any, occur. For example, as was noted above, the dehydrohalogenation of isobornyl

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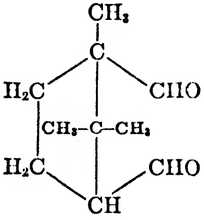
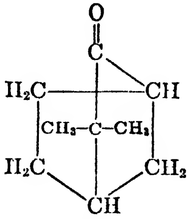
[6] F. C. Whitmore and F. Johnston, *J. Am. Chem. Soc.* 60, 2265 (1938).

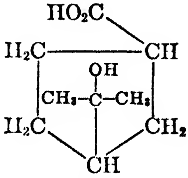
chloride, X, might be expected to give bornylene, XI. If the reaction followed that course, the ozonolysis of the resulting hydrocarbon would be expected to give a mixture of camphoric dialdehyde, XIII, and its various oxidation products. Actually, however, the ozonolysis gives instead formaldehyde, camphenilone, XIV, its oxidation product δ-hydroxycamphenilonic acid, XV, and the lactone of this hydroxy acid.



XIII



XIV



XV

These products are the ones to be expected from camphene, XII. Clearly, therefore, a rearrangement must have occurred either in the dehydrohalogenation or in the ozonolysis (or in both). Experience with a large number of similar reactions has shown that the best self-consistent interpretation of the field as a whole is obtained if the assumption is made that rearrangements occur often in dehydrohalogenations like that of isobornyl chloride, but seldom, if ever, in ozonolyses. Consequently, the inference is drawn that here the rearrangement occurs in the dehydrohalogenation.

Similarly, in the original problem of the structure of ethyl alcohol, experience has shown that the simplest interpretation of all the pertinent facts is obtained if rearrangements of the particular sort depicted in equation 4·2 are considered to be impossible or, at any rate, extremely rare. Consequently, the inference may be drawn that equation 4·1 is correct and hence that ethyl alcohol has the structure I. The more detailed analysis of the problem therefore suggests that, at any rate in this one instance, the simple intuitive approach is justified.

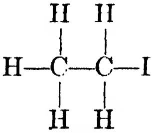
A further general method of employing chemical reactions in the determination of structure can be based upon a study of the reactions by which the substance in question is formed, rather than upon a study of the ones which it can be induced to undergo. This method, like the preceding one, involves the rule of minimum structural change, and so it also is subject to the limitations just discussed. Ethyl alcohol and methyl ether can again be used as examples. Thus, ethyl alcohol results from the action of dilute aqueous bases upon ethyl iodide (equation 4·3), whereas methyl ether results from the action of concentrated

$$\underset{\text{ethyl iodide}}{C_2H_5I} + NaOH \rightarrow \underset{\text{ethyl alcohol}}{C_2H_6O} + NaI \qquad (4\cdot3)$$

sulfuric acid upon methyl alcohol (equation 4·4). Since the structure

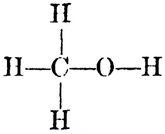
$$\underset{\text{methyl alcohol}}{2CH_4O} + H_2SO_4 \rightarrow \underset{\text{methyl ether}}{C_2H_6O} + H_2SO_4\cdot H_2O \qquad (4\cdot4)$$

of ethyl iodide is definitely known to be XVI, and since the molecular formula of methyl alcohol CH_4O permits only the single structure XVII, the principle of minimum structural change again leads to the conclusion that ethyl alcohol must have structure I and methyl ether must have structure II.



$$\begin{array}{ccccccc} & & H & & H & & \\ & & | & & | & & \\ H & - & C & - & C & - & I \\ & & | & & | & & \\ & & H & & H & & \end{array}$$

XVI



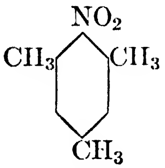
$$\begin{array}{ccccccc} & & H & & & & \\ & & | & & & & \\ H & - & C & - & O & - & H \\ & & | & & & & \\ & & H & & & & \end{array}$$

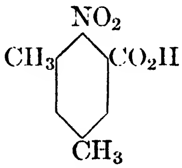
XVII

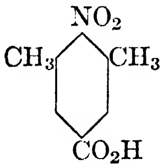
A final method of determining structure with the aid of chemical reactions makes no explicit use of the principle of minimum structural change; it is based upon a comparison of the reactions of the substances of unknown structure with those of other substances of known structure. Thus, ethyl alcohol and methyl alcohol resemble each other closely in their chemical properties, whereas methyl ether behaves quite differently toward most reagents. In particular, the two alcohols react with metallic sodium to give alkoxides, and with acid chlorides to give esters, whereas methyl ether is inert toward each of these reagents. Consequently, the structures of ethyl alcohol and of methyl alcohol may be presumed to be similar to each other. Since that of methyl alcohol is necessarily XVII, that of ethyl alcohol must therefore be I. Moreover, the remaining structure II must belong to the remaining substance, methyl ether. The assignment of structures is thus the same as by the preceding methods.

In the ways illustrated above with simple examples, chemical reactions can be used for the determination of structure. From the emphasis placed upon the difficulties caused by molecular rearrangements, in which the principle of minimum structural change is violated, the impression may have been given that these difficulties present greater obstacles than they actually do. In practice, the field of rearrangements has now been so carefully explored that one can usually be fairly sure in advance when a rearrangement is likely to occur, and when the possible occurrence of a rearrangement can be safely ignored. Fortunately, most reactions belong to the latter category. This question will be dealt with later in much greater detail. (See Chapters 12 and 13.)

In addition to the danger of rearrangements, a further complication which sometimes makes more difficult the use of chemical reactions for the determination of structure is that it may be impossible to predict which of two or more competing reactions will actually take place. For example, it would take a brave man, or else one well acquainted with the field, to predict with assurance whether the oxidation of nitromesitylene, XVIII, would give the monocarboxylic acid XIX or its isomer XX.


XVIII


XIX


XX

Consequently this reaction would hardly be a suitable one for the determination of the structure of the acid which is formed. (The acid that is obtained in larger amount is the one with structure XX.)

In extreme cases, reactions may follow entirely unexpected courses, without violating the principle of minimum structure change, even when it seems as if they ought to be straightforward and unambiguous. For example, the action of concentrated aqueous sodium hydroxide upon chloral, XXI, might be expected to lead, through hydrolysis of the carbon-chlorine bonds, to sodium glyoxylate, XXII, or else to some transformation product of this salt. Actually, however, the reaction results in cleavage of the carbon-carbon bond with production of chloroform, XXIII, and sodium formate, XXIV. This reaction is most unexpected, since ordinarily carbon-carbon bonds are completely unaffected by aqueous sodium hydroxide, whereas carbon-chlorine bonds are relatively susceptible to hydrolysis by that reagent. Complications of this sort, although they could make the determination of structure very difficult, are fortunately rather rare and, in any event, can usually be easily detected, when they do occur. Thus, in the hydrolysis of chloral, the occurrence of an unexpected reaction could be shown simply by the fact that neither of the products obtained has the correct analysis or molec-

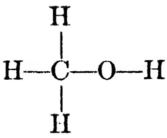
$CCl_3—CHO$	$NaO_2C—CHO$	$HCCl_3$	NaO_2CH
XXI	XXII	XXIII	XXIV

ular weight for glyoxylic acid, or by the further fact that the products obtained are familiar and easily identifiable substances. However, if one knew only the fact that chloroform and sodium formate are formed in the reaction, he might have considerable difficulty in correctly deducing the structure of the original chloral.

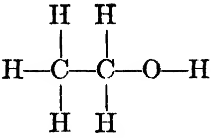
4·4 Use of Isomer Numbers in the Determination of Structure. Of the three main groups of methods employed in the determination of structure, the second requires a knowledge of the total numbers of isomers possessed by the substances under investigation, or of the total numbers of isomeric derivatives that can be made from the substances. Often it requires also a knowledge of the methods of preparation of these substances, or of their chemical and physical properties. Usually the methods of this group, if they are carried through with sufficient care, are considered more reliable than are those based merely upon chemical reactions; in practice, however, they are usually much too tedious to be convenient. As a matter of fact, they are hardly ever used at the present time, although, in the early days of structural organic chemistry, they were sometimes found to provide the only possible method of making a reliable assignment of structure. Now that the structures of a number of reference compounds have been definitely established, however, the determination of the structure of any new substance usually involves only its relation, by a series of chemical reactions, to one or more of the reference compounds. Consequently, the methods here being considered, although of historical interest and of great fundamental importance, are now seldom of much value to the practicing organic chemist.

As a simple example of the use of isomer numbers, the structure of ethyl alcohol may again be considered. Corresponding to the molecular formula CH_4O, only a single substance, methyl alcohol, is known; corresponding to the formula C_2H_6O, two substances, ethyl alcohol and methyl ether, are known; and corresponding to the formula C_3H_8O, three substances, *n*-propyl alcohol, isopropyl alcohol, and methyl ethyl ether, are known. Of these six substances, the four designated as alcohols resemble each other closely in methods of preparation and in physical and chemical properties; similarly, the two designated as ethers also resemble each other but are quite different from the four alcohols. The inference is therefore drawn that the four alcohols must have closely analogous structures, and that the two ethers must likewise have closely analogous structures, but that the alcohols and ethers, as groups, must have structures which are not so closely analogous.

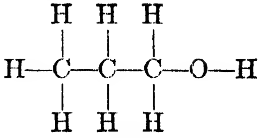
For the formulas CH_4O, C_2H_6O, and C_3H_8O, the six structures I–VI


$H-C-O-H$

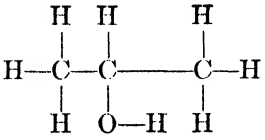
I


$H-C-C-O-H$

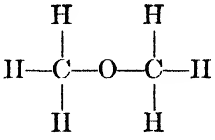
II


$H-C-C-C-O-H$

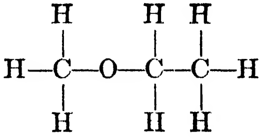
III


$H-C-C(OH)-C-H$

IV


$H-C-O-C-H$

V

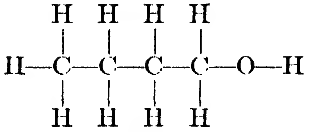

$H-C-O-C-C-H$

VI

can be drawn. The first four of these resemble each other in having hydroxyl groups, and the last two resemble each other in having C—O—C linkages instead. Consequently, the first four structures must belong to the four alcohols, and the last two structures must belong to the two ethers. Ethyl alcohol, therefore, has structure II. The reasoning here is obviously equivalent to that employed earlier on page 98, the difference between the two treatments being one only of emphasis and of generality.

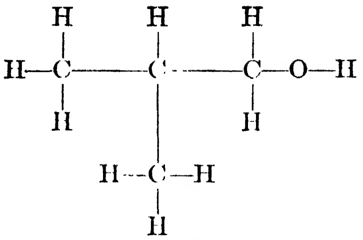
That this method of approach is self-consistent is shown by a more detailed discussion. The single substance CH_4O must have a hydroxyl group since no structure without one can be drawn for this molecular formula; as expected, this substance does indeed have the properties classified as those of an alcohol. Of the two structures for C_2H_6O, one has a hydroxyl group, whereas the other does not; as expected, one of the known isomers has the properties of an alcohol, whereas the other has the properties of an ether. Finally, of the three structures for C_3H_8O, two have hydroxyl groups, whereas the third does not; again, as expected, two of the known isomers have the properties of alcohols, whereas the third has the properties of an ether.

Arguments analogous to the above can now be used to decide which of the two propyl alcohols has structure III and which has structure IV. For this purpose it must be recognized as an experimental fact that marked and characteristic differences in chemical properties exist among primary, secondary, and tertiary alcohols. Empirically, it is found that the one known alcohol with the formula CH_4O is primary; that the one known alcohol with the formula C_2H_6O is also primary; that, of the two alcohols with the formula C_3H_8O, one is primary and one is secondary; and that, of the four *structurally* isomeric alcohols with the formula $C_4H_{10}O$, two are primary, one is secondary, and one is tertiary. Comparison of structures I–IV with the further ones VII–X, for the four

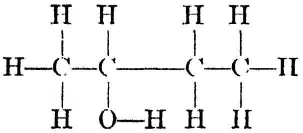


$$\begin{array}{ccccccccccc} & & H & & H & & H & & H & & \\ & & | & & | & & | & & | & & \\ H & — & C & — & C & — & C & — & C & — & O — H \\ & & | & & | & & | & & | & & \\ & & H & & H & & H & & H & & \end{array}$$

VII

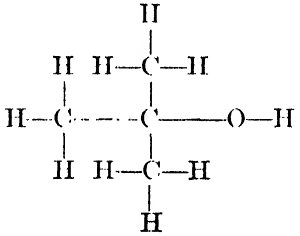


VIII



$$\begin{array}{ccccccccccc} & & H & & H & & H & & H & & \\ & & | & & | & & | & & | & & \\ H & — & C & — & C & — & C & — & C & — & H \\ & & | & & | & & | & & | & & \\ & & H & & O—H & & H & & H & & \end{array}$$

IX



X

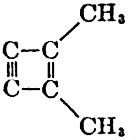
possible alcohols with formula $C_4H_{10}O$, shows that these isomer numbers require that a primary alcohol be one in which at least two hydrogen atoms are joined to the carbon atom which carries the hydroxyl group, that a secondary alcohol be one in which only one hydrogen atom is joined to the carbon atom in question, and that a tertiary alcohol be one in which no hydrogen atom is joined to the carbon atom. Consequently, *n*-propyl alcohol, being primary, must have structure III; and isopropyl alcohol, being secondary, must have structure IV. Similarly, the primary *n*-butyl alcohol must be either VII or VIII, whereas the also primary isobutyl alcohol must be the other; and the *sec*-butyl and *tert*-butyl alcohols must be IX and X, respectively.

As a further example of a somewhat different type, the structure of benzene will now be discussed. From its analysis and molecular weight, this substance is known to have the molecular formula C_6H_6. The large number of structures which can be drawn in agreement with this formula is materially reduced when account is taken of the fact that, for a given substituent R, such as chlorine, methyl, carboxyl, or the like, only a single monosubstituted derivative C_6H_5R exists. For example, there is only one chlorobenzene C_6H_5Cl, only one toluene $C_6H_5—CH_3$, only one benzoic acid $C_6H_5—CO_2H$, and so on. This fact shows that all the hydrogen atoms are equivalent, so that, no matter which one is replaced by the substituent R, the same derivative is obtained. As a corollary, therefore, it follows that the structure of benzene must be representable as $C_4(CH_3)_2$, as $C_3(CH_2)_3$, or as $(CH)_6$, where the various CH_3, CH_2, or CH groups, respectively, are equivalent to each other. This conclusion follows because any other possibility, such as $C_3(CH_3)(CH_2)(CH)$, for example, or even such as $C_3(CH_2)_3$ with nonequivalent CH_2 groups, would have nonequivalent hydrogen atoms, so that more than one isomeric substance C_6H_5R ought to exist.

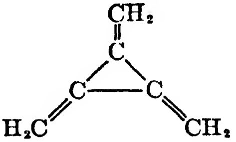
For definiteness, the rather vague expression $C_4(CH_3)_2$ can be thought of as representing the structure of, say, either the actually known dimethylbiacetylene, XI, or the unknown and highly improbable dimethylcyclobutenyne, XII. Similarly, the expression $C_3(CH_2)_3$ can be considered to represent some such structure as XIII or XIV; and the expression $(CH)_6$ can be considered to represent a structure like XV,

$CH_3—C≡C—C≡C—CH_3$

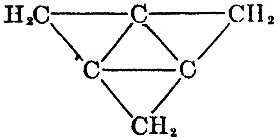
XI



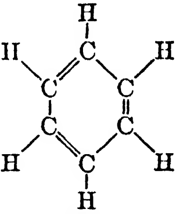
XII



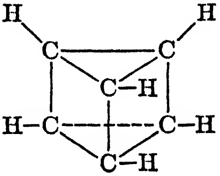
XIII



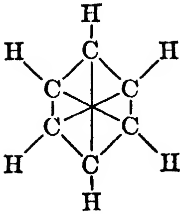
XIV



XV



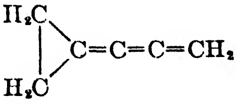
XVI



XVII

$H—C≡C—CH_2—C≡C—CH_3$

XVIII



XIX

XVI, or XVII. (In structure XVI, the broken line represents an edge of the prism which is behind the figure.) Moreover, the expression $C_3(CH_3)(CH_2)(CH)$ can be considered to represent a structure like XVIII; and the expression $C_3(CH_2)_3$ with nonequivalent CH_2 groups can be considered to represent a structure like XIX.

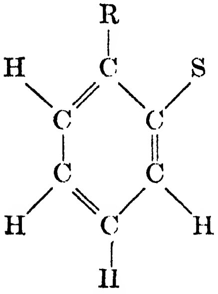
A further important fact in regard to the structure of benzene is that, for any two given substituents R and S, which may be either the same or different, there exist exactly three disubstituted derivatives C_6H_4RS.

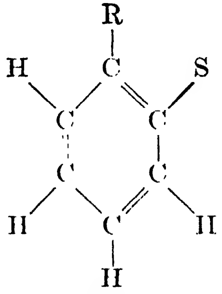
For example, there are three dichlorobenzenes $C_6H_4Cl_2$, three xylenes, $C_6H_4(CH_3)_2$, three nitrobenzoic acids $C_6H_4(NO_2)(CO_2H)$, and so on. This fact cannot be reconciled with the arrangement $C_4(CH_3)_2$, which permits only the two isomers $C_4(CH_3)(CHRS)$ and $C_4(CH_2R)(CH_2S)$. It should be noted that $C_4(CHRS)(CH_3)$ cannot be different from the first of these, and that $C_4(CH_2S)(CH_2R)$ cannot be different from the second; if such differences did exist, then the two CH_3 groups would be nonequivalent, and hence two monosubstituted derivatives C_6H_5R should exist, contrary to experiment. Consequently, the structure of benzene cannot be expressed as $C_4(CH_3)_2$.

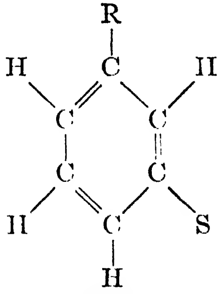
The arrangement $C_3(CH_2)_3$ also permits only two isomeric disubstituted derivatives, namely, $C_3(CH_2)_2(CRS)$ and $C_3(CH_2)(CHR)(CHS)$. Here again it is to be noted that any further arrangements, such as $C_3(CRS)(CH_2)_2$ and $C_3(CHS)(CH_2)(CHR)$, add nothing new. If the arrangement $C_3(CRS)(CH_2)_2$ were not identical with $C_3(CH_2)_2(CRS)$, then $C_3(CHR)(CH_2)_2$ would also not be identical with $C_3(CH_2)_2(CHR)$; consequently two isomeric *mono*substituted derivatives would then have to be possible. Moreover, $C_3(CHS)(CH_2)(CHR)$ must be identical with $C_3(CH_2)(CHR)(CHS)$, as can be seen most easily from consideration of the special case in which R and S represent the same substituent atom or group, and in which the observed number of isomers is still three. Here, the two arrangements become $C_3(CHR)(CH_2)(CHR)$ and $C_3(CH_2)(CHR)_2$, respectively; these differ only in the choice of the CH_2 group which remains unmodified; therefore, since all three CH_2 groups are equivalent, the two arrangements must actually be the same. Reference to the specific structures XIII and XIV will make clearer the significance of these arguments. It therefore follows that the structure of benzene cannot be expressed as $C_3(CH_2)_3$.

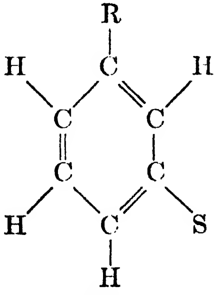
The arguments advanced in the two preceding paragraphs are not entirely conclusive since they ignore the possibility that *stereo*isomerism, as well as *structural* isomerism, might occur. Thus, the fact that neither of the two atomic arrangements $C_4(CH_3)_2$ and $C_3(CH_2)_3$ permits more than two structurally isomeric disubstituted derivatives C_6H_4RS is not necessarily inconsistent with the observation that three different substances with this molecular formula can be obtained; for, since two of these substances might be stereoisomers of each other and hence might share a single structure (cf. page 90), two structures altogether could conceivably be sufficient for the description of the three known compounds. Although the stereochemical principles that are necessary for a complete analysis of the problem have not yet been discussed (and, in fact, will not be discussed until Chapter 6), some of the conclusions which can easily be derived from these principles may nevertheless be stated here without proof. If the structure of benzene were describable as $C_4(CH_3)_2$, stereoisomeric derivatives C_6H_4RS would not be possible when R and S are identical substituents; such derivatives would, however, be possible when R and S are different substituents. In the former event, there could exist only the two structural isomers that were originally considered; in the latter event, there would be altogether three isomers, of which two would be optically active stereoisomers and, in fact, enantiomorphs (see Sections 5·9 and 6·2) of each other, with the same structure, $C_4(CH_3)(CHRS)$. On the other hand, if the structure of benzene were describable as $C_3(CH_2)_3$, stereoisomeric derivatives with formula C_6H_4RS would always exist; the total number of structural isomers plus stereoisomers would always be at least four. These predicted isomer numbers are in definite disagreement with the observed values. Thus, exactly three dichlorobenzenes $C_6H_4Cl_2$, with two identical substituents, and exactly three nitrobenzoic acids, $C_6H_4(NO_2)(CO_2H)$, with two nonidentical substituents, can be obtained; moreover, in each instance all three forms are optically inactive. Since entirely similar situations are encountered with all other sets of isomeric benzene derivatives of formula C_6H_4RS, it is evident that, even when the possibility of stereoisomerism is taken into account, the observed isomer numbers (and isomer types) are sufficient to show that benzene cannot have any structure describable as either $C_4(CH_3)_2$ or $C_3(CH_2)_3$.

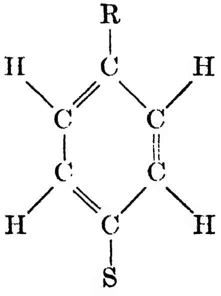
Since both the arrangements $C_4(CH_3)_2$ and $C_3(CH_2)_3$ can therefore be excluded, the remaining one, $(CH)_6$, must be correct. Before any predictions regarding the number of isomeric disubstituted derivatives C_6H_4RS can be based upon this arrangement, however, the complete structure of the benzene molecule must be specified more precisely. The three structures XV, XVI, and XVII, above, are the only ones which satisfy the usual valence rules. Of these, the Kekulé structure, XV,[7] permits the five different disubstituted derivatives XX–XXIV, of which


XX


XXI


XXII


XXIII


XXIV

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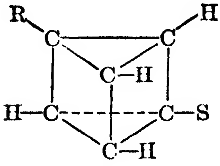
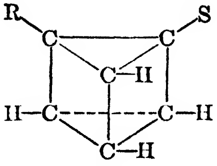
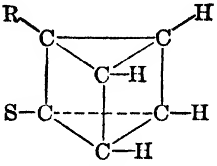
[7] A. Kekulé, *Bull. soc. chim.* [2] **3**, 98 (1865); *Ann.* **137**, 129 (1866); **162**, 77 (1872).

XXII and XXIII become identical if R and S represent the same substituent. Since, therefore, at least four of the structures XX–XXIV must always be different, the Kekulé structure can apparently be excluded.

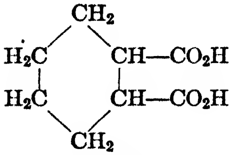
The Ladenburg prism structure, XVI,[8] permits only the three structurally isomeric disubstituted derivatives XXV, XXVI, and XXVII. Although this structure might therefore appear to be in agreement with the observed numbers of isomers, it can nevertheless be excluded on stereochemical grounds. (Cf. the above paragraph in fine print.) Thus, structure XXV ought to correspond to two optically active stereoisomers if R and S are either the same or different; and structure XXVI ought similarly to correspond to two optically active stereoisomers if R and S are different. (Cf. Chapter 6.) The prediction of altogether five isomers when R and S are different, and of altogether four isomers when R and S are the same, is, however, contrary to the experimental facts. Moreover, no optically active disubstituted benzenes C_6H_4RS have ever been observed, unless, of course, at least one of the substituents R and S is itself an optically active group. Finally, the physical methods mentioned in Section 4·7 have shown conclusively that the molecule of benzene does not have the shape of a trigonal prism, but instead has that of a regular plane hexagon. Consequently, the Ladenburg structure must also be excluded.

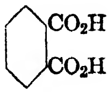

XXV

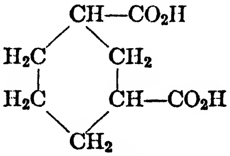

XXVI

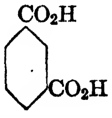

XXVII

It is of historical interest that the Ladenburg structure had been given up before these stereochemical ideas and physical methods were applied to the problem. The reasons for the abandonment of this structure were derived from considerations of the chemical reactions of benzene and its derivatives. Their nature can be seen from the following examples. In the first place,[9] cyclohexane-1,2-dicarboxylic acid, XXVIII, obtained by the reduction of the *ortho* compound, phthalic acid, XXIX,


XXVIII


XXIX


XXX


XXXI

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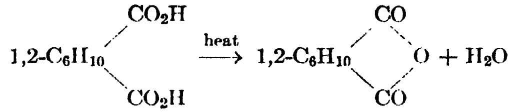
[8] A. Ladenburg, *Ber.* **2**, 140 (1869).

[9] A. Baeyer, *Ber.* **23**, 1272 (1890); *Ann.* **258**, 145 (1890).

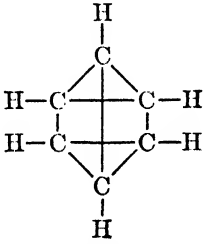
forms an intramolecular anhydride when it is heated (equation 4·5), whereas the



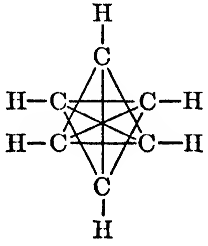
$$\text{1,2-C}_6\text{H}_{10}\begin{matrix}\diagup\,\text{CO}_2\text{H}\\ \diagdown\,\text{CO}_2\text{H}\end{matrix} \xrightarrow{\text{heat}} \text{1,2-C}_6\text{H}_{10}\begin{matrix}\diagup\,\text{CO}\,\diagdown\\ \qquad\text{O}\\ \diagdown\,\text{CO}\,\diagup\end{matrix} + \text{H}_2\text{O} \qquad (4\cdot5)$$

1,3-isomer, XXX, obtained by the reduction of the *meta* compound, isophthalic acid, XXXI, does not. (For the sake of convenience, structures XXVIII-XXXI are given here in their now accepted forms.) It appears, therefore, that the two carboxyl groups are closer to one another in the 1,2- than in the 1,3-diacid, and hence that the *ortho* positions in the benzene ring are closer to one another than are the *meta* positions. However, as will be shown in the last paragraph of Section 4·5, the *ortho* positions in the Ladenburg structure are the ones which are substituted in structure XXV, whereas the *meta* positions are the much closer ones which are substituted in structure XXVI. (The argument would have been both simpler and more conclusive if it had been based upon the original unreduced phthalic acid, XXIX, and isophthalic acid, XXXI; the substances actually studied by Baeyer were, however, the hydrogenated derivatives stated.) In the second place, Baeyer was able to show [10] that, when an *ortho* disubstituted benzene is reduced, the resulting derivative of cyclohexane has its two substituents upon adjacent carbon atoms of the ring. This fact would be extremely difficult to explain on the basis of the Ladenburg structure.

In the foregoing discussion, the Ladenburg structure is regarded not merely as a structure, but also as a configuration, since its prismatic form is considered to be significant. The reason for thus anticipating some of the concepts which are not to be elaborated until the following chapters is that, in this way, the equivalence of the six hydrogen atoms can most easily be brought out. If the structure XVI had instead been written in the *structurally* equivalent way, XVI*a*, the hydrogen atoms would appear to be of two different types; if it had been written in the more symmetrical, but still structurally equivalent way, XVI*b*, all the hydrogen atoms would



XVI*a*



XVI*b*

obviously be alike, but the lack of bonds between adjacent carbon atoms would have given the structure a most unusual and unreasonable appearance. In any event, of course, the stereochemical and other arguments advanced against the structure in the two preceding paragraphs are directed primarily against the geometrical characteristics of the prism form XVI, except for the second one of Baeyer's, which applies to all three forms XVI, XVI*a*, and XVI*b*.

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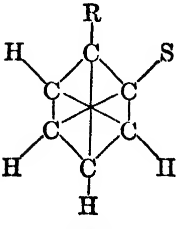
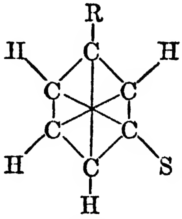
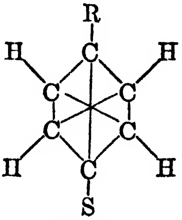
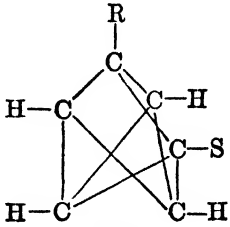
[10] A. Baeyer, *Ber.* **19**, 1797 (1886).

If, then, both the Kekulé and the Ladenburg structures are ruled out, only the Claus diagonal structure, XVII,[11] remains. One of the original arguments in favor of this structure was that it appears to predict the existence of three, and of only three, structurally isomeric disubstituted derivatives, XXXII, XXXIII, and XXXIV. As was pointed out by Ladenburg[12] and by Meyer,[13] however, this argument is not valid; diagrams XXXII and XXXIV are not isomeric with each other but are actually identical, if they are regarded merely as structures, and if they are accordingly considered to have no geometrical significance. (Cf. Section 4·1.) The fact that the atoms are indeed bonded to one another in structure XXXII exactly as they are in structure XXXIV can be proved in the following manner. If the CH group that is diametrically opposite the CR group in diagram XXXII is moved up beside the CS group, and if, in the process, no changes are made in the ways in which the atoms are bonded to one another, diagram XXXII is transformed into the superficially different, but structurally identical one, XXXV.


XXXII


XXXIII


XXXIV


XXXV

If, now, the CS group in diagram XXXV is moved to the position diametrically opposite the CR group, and if again no changes are made in the ways in which the atoms are bonded to one another, diagram XXXIV

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[11] A. Claus, *Ber.* **15,** 1405 (1882); *J. prakt. Chem.* [2] **37,** 455 (1888).
[12] A. Ladenburg, *Ann.* **172,** 331 (1874).
[13] R. Meyer, *Ber.* **15,** 1823 (1882).

is obtained. It follows, therefore, that diagrams XXXII and XXXIV differ only geometrically (just as do, for example, diagrams II and V of Section 4·1), and hence that they represent the same structure. Consequently, the Claus structure of benzene predicts only two structurally isomeric derivatives with formula C_6H_4RS, namely, XXXII (which is identical with XXXIV) and XXXIII. This defect, however, is not sufficient by itself to make the Claus structure untenable, since diagrams XXXII and XXXIV might still correspond to two different substances that are *stereo*isomers of each other. (Cf. the above paragraph in fine print.) Indeed, if the three diagrams XXXII, XXXIII, and XXXIV are considered to have not only structural but also geometrical significance and if, in particular, the six carbon atoms in the molecule of benzene are considered to lie at the corners of a regular plane hexagon (see page 106), then diagrams XXXII, XXXIII, and XXXIV are clearly different, so that the observed total number of isomers is satisfactorily explained. Moreover, this partly structural and partly geometrical interpretation agrees also with the further observation that the three isomeric benzene derivatives with formula C_6H_4RS are never optically active unless, of course, at least one of the substituents R and S is itself optically active. Consequently, the Claus structure cannot be proved incorrect by considerations of isomer number alone. (For a more detailed discussion of the stereochemical principles that are presupposed here, see, for example, Chapter 6.)

The Claus structure has, however, several further defects which are not concerned with isomer numbers, and which are not so easily discounted. These defects, which will be described on page 388, are in fact so serious that this final structure, like the previously considered Kekulé and Ladenburg structures, must also be discarded.

The discussion up to this point has led to the completely baffling conclusion that no one of the several structures of benzene, which are permitted by the existence of only a single monosubstituted derivative C_6H_5R, can be correct. Until comparatively recently, however, the Kekulé structure, XV, in spite of its failure to predict the correct number of isomeric disubstituted derivatives, has been accepted (or, at any rate, used) by doubtless the great majority of all organic chemists. The difficulty introduced by the nonoccurrence of certain predicted isomers [8] has been evaded in several different ways. Kekulé himself suggested [14] that an "oscillation," or, in present-day terminology, a rapid tautomerism (see Chapter 14), exists between the two forms of his structure, as in equation 4·6. He thus assumed that any given *ortho* isomer actually

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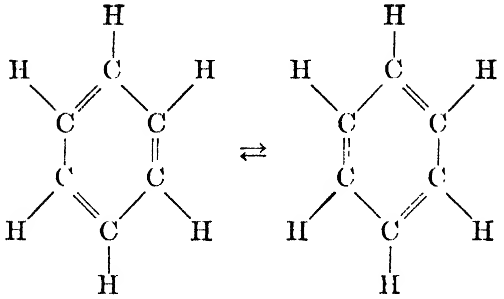
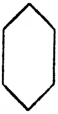
[14] A. Kekulé, *Ann.* **162**, 77 (1872).

 (4·6)

consists of an inseparable mixture of two different substances with structures XX and XXI (page 105), and that any given *meta* isomer, in which the two substituents are different, consists of a similar mixture of different substances with structures XXII and XXIII. Victor Meyer,[15] on the other hand, considered the assumption of oscillation unnecessary, since substances with structures XX and XXI, or with structures XXII and XXIII, would probably be so similar in all chemical and physical properties that they would be inseparable and practically indistinguishable. If this view is correct, then there might really exist the predicted four or five isomeric disubstituted derivatives after all, even though only three of them are recognizably different.

No attempt will be made in this chapter to pursue any further the finer details of the structure of benzene. The Kekulé structure, when interpreted either in the manner suggested by Kekulé or in the one suggested by Meyer, and the Claus structure, when given the geometrical significance proposed above, agree with each other and with the modern view, which will be discussed later (see Chapter 10), in assigning to the benzene ring the symmetry of a regular plane hexagon. That is to say, all three interpretations assume that the six carbon atoms are joined to each other in a plane ring, that the six hydrogen atoms are equivalent to each other, and that the six carbon-carbon bonds which form the ring are experimentally indistinguishable. These characteristics, which are all that can be established by a study of isomer numbers, are reproduced by the simple hexagonal figure XXXVI, which is now used for the representation of benzene, and which will be employed hereafter.



XXXVI

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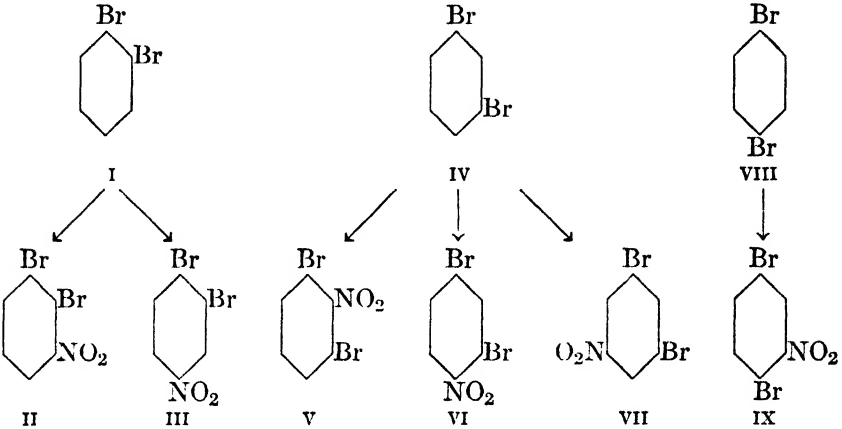
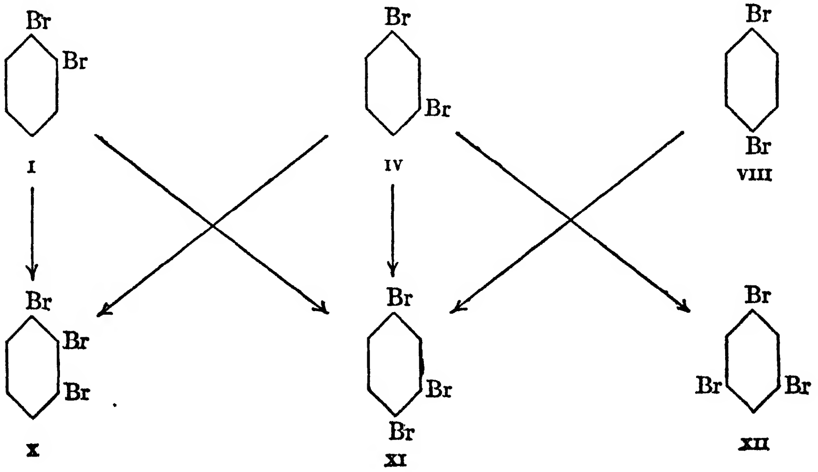
[15] V. Meyer, *Ann.* **156**, 265, 293 (1870).

4·5 The Körner Absolute Method. The most familiar use of isomer numbers in the determination of structure is doubtless the one involved in the so-called Körner absolute method for the establishment of the orientation of the substituents in derivatives of benzene. In principle, this method is simple and straightforward. For example, the nitration of *o*-dibromobenzene, I, could lead to the two isomeric mononitro derivatives II and III; that of *m*-dibromobenzene, IV, could lead to the three mononitro derivatives V, VI, and VII; and that of *p*-dibromobenzene, VIII, could lead to only the one mononitro derivative IX. Similarly, *vic*-tribromobenzene, X, could be obtained by the further bromination of either of the two dibromo compounds I and IV; *unsym*-tribromobenzene, XI, could be obtained from any one of the three dibromo compounds I, IV, and VIII; and *sym*-tribromobenzene, XII,





could be obtained from only the one dibromo compound IV. Consequently, the structures of the three dibromobenzenes could be established by a determination of the number of isomeric mononitro derivatives which each gives, and the structures of the three tribromobenzenes could be established by a determination of the number of isomeric dibromo compounds from which each can be made.

In practice, however, the actual application of the Körner method is by no means as simple as the foregoing discussion would make it appear to be. The difficulty arises from the fact that only seldom can all the conceivable isomeric products of a given reaction be obtained in the laboratory. For example, from the nitration of *o*-dibromobenzene, I, Körner obtained [16] only the mononitro derivative III, but not II; and, from the nitration of *m*-dibromobenzene, IV, he obtained only the mononitro derivatives V and VI, but not VII. Moreover, he did not study the direct *bromination* of the dibromobenzenes at all. Obviously, no definite conclusions regarding the structures of the di- and tribromobenzenes can be drawn from such incomplete data.

The procedure actually employed by Körner was a very complicated one, of which only the steps shown in Figure 4·1 need be mentioned here. For definiteness, the various substances are designated in this figure by the structures which are now known to be correct; and, throughout the following discussion, they will be called by the corresponding names. It is easily seen that no circular reasoning will be introduced thereby, since no direct use will be made of the precise structure of any substance until it has been proved.

As was mentioned before, Körner obtained the two nitrodibromobenzenes V and VI by the direct nitration of *m*-dibromobenzene, IV. The third nitrodibromobenzene, VII, which is in principle obtainable from the *meta* compound, was prepared in an indirect way. *p*-Nitroaniline, XIII, on bromination, gave the dibromonitroaniline, XIV. This compound, through its diazonium salt, was deaminated to give the nitrodibromobenzene, VII, in question. Comparison of physical properties showed that this substance was different from any of the four nitrodibromobenzenes, III, V, VI, and IX, obtained by direct nitration of the dibromobenzenes. Moreover, the fact that it was the missing nitro derivative of the *meta* dibromo compound was shown by the fact that it could be reduced to the amine, XV, which could then be deaminated to the dibromobenzene, IV. As a result of all these reactions, this dibromobenzene was shown to have three mononitro derivatives, namely, V, VI, and VII, even though only the first two of these could be obtained directly. Consequently, IV could only be the *meta* isomer.

The proof of the structures of *o*- and *p*-dibromobenzene was more difficult and required previous information in regard to the structures of the three tribromobenzenes. The *unsym*-tribromo compound, XI, was relatively easy to identify, since it was made indirectly from each of the three dibromobenzenes, I, IV, and VIII.

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[16] W. Körner, *Gazz. chim. ital.* **4**, 305 (1874); *Jahresbericht* **1875**, 299 ff.

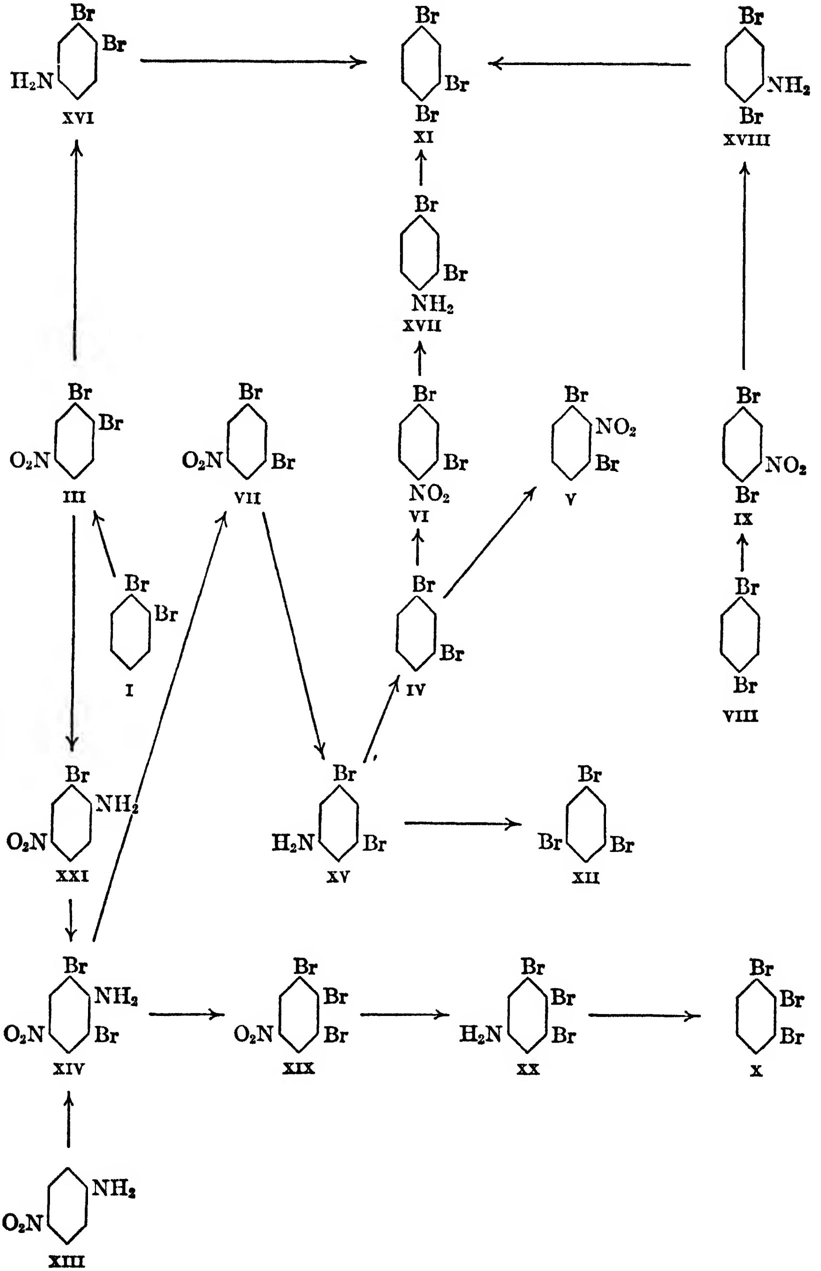

Figure 4·1. Körner's proof of the orientation in the di- and tribromobenzenes.[16]

As has already been noted, these substances, on nitration, gave the mononitro compounds III, VI, and IX respectively. The three nitro compounds, in turn, were reduced to the corresponding amines, XVI, XVII, and XVIII, respectively, each of which, by a diazo reaction, was transformed into the same tribromobenzene. This tribromo compound must therefore be the unsymmetrical one, XI.

vic-Tribromobenzene was next identified. In the dibromonitroaniline, XIV, the two bromine atoms must be *meta* with respect to each other on account of the already described relationship of this substance to *m*-dibromobenzene. Consequently, XIV itself, as well as any substance which can be derived from it, could in principle be obtained from *m*-dibromobenzene. A diazo reaction was used for the transformation of XIV into the nitrotribromobenzene, XIX, which, by reduction to the amine, XX, and then by a diazo reaction, was changed to a tribromobenzene, X, that was different from the already identified unsymmetrical one, XI. This new tribromo compound must therefore be either the vicinal or the symmetrical isomer. That it was actually the vicinal compound, X, was shown by the fact that it could also be derived from a second of the dibromobenzenes by the following sequence of reactions. *o*-Dibromobenzene, I, on nitration, gave the nitrodibromobenzene, III, which, on treatment with concentrated aqueous ammonia, gave the bromonitroaniline, XXI. In XXI the amino group must occupy the same position in the ring that was formerly occupied by one of the two bromine atoms. For future reference, this position will be designated as position *p*, and the one occupied by the second bromine atom will be designated as position *q*. Clearly, *p* and *q* are not *meta* with respect to each other, since, if they were, the original dibromobenzene, I, would have had to be the *meta* isomer, which has already been identified as IV. Now, XXI was found to give the same dibromonitroaniline, XIV, from which the second tribromobenzene had previously been obtained. Since the two bromine atoms in XIV were known to be *meta* with respect to each other, and since the amino group and one of the bromine atoms were known to be in positions *p* and *q*, respectively, which were not *meta* with respect to each other, it followed that in the nitrotribromobenzene, XIX, and also in the tribromobenzene, X, itself, at least one pair of bromine atoms were not *meta* with respect to each other. This condition is satisfied by the vicinal and unsymmetrical tribromobenzenes, but not by the symmetrical one, XII. Since the unsymmetrical compound had already been identified as XI, the tribromo compound under discussion must therefore be the vicinal one, X. Moreover, since *vic*-tribromobenzene could not have been derived from *p*-dibromobenzene, the further conclusion could be drawn that I must be the *ortho* compound, so that VIII must be the *para* compound. And finally, the remaining tribromo compound, XII, must be the symmetrical isomer. In this way the structures of all three dibromo- and of all three tribromobenzenes were established.

Almost simultaneously with Körner, and apparently quite independently, Griess[17] carried through a much simpler proof of the structures of the three phenylenediamines, by a method which was based upon the same principles as was Körner's more tedious proof of structure of the di- and tribromobenzenes. Griess managed in indirect ways to obtain a sample of each of the six theoretically possible diaminobenzoic acids. XXII–XXVII. Each substance, on being strongly heated, lost a mole-

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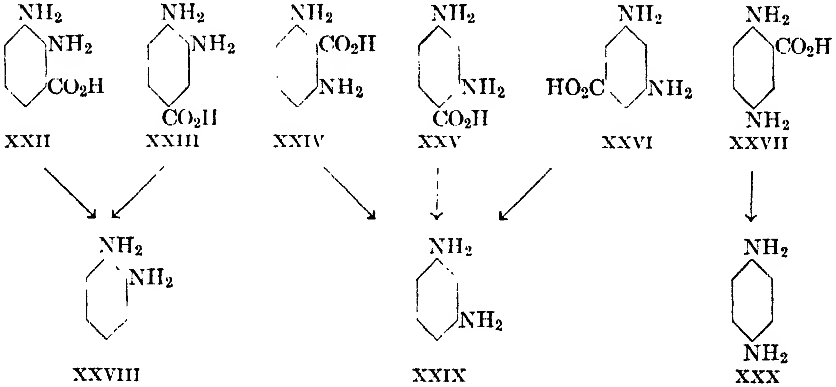
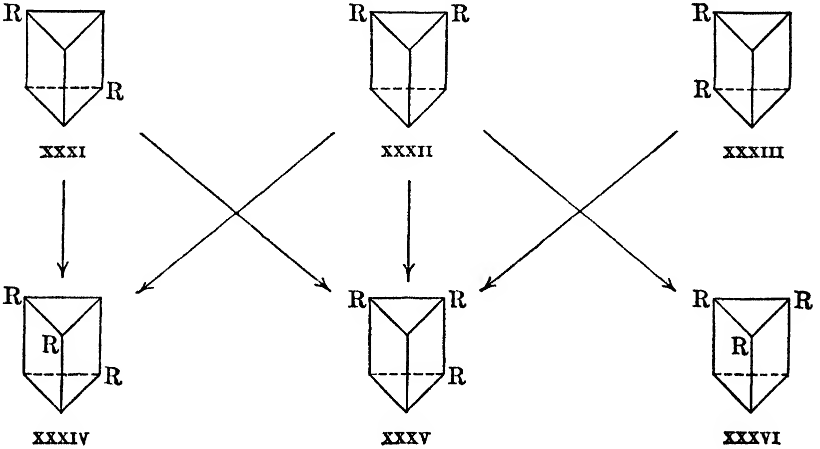
[17] P. Griess, *Ber.* **7**, 1223 (1874).

cule of carbon dioxide and was transformed into one of the phenylenediamines, XXVIII–XXX. Obviously, the *ortho*, *meta*, and *para* diamines were identified as the ones obtained, respectively, from two, three, and one different diamino acid.



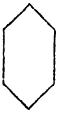
The remaining discussion of the Körner absolute method will be restricted to a proof of a statement, made earlier on page 107, in regard to the identification of the *ortho*, *meta*, and *para* isomers in the Ladenburg structure. From the number of different trisubstituted derivatives obtainable in principle from each disubstituted derivative, it is evident that, as was stated before, XXXI is the *ortho*, and XXXII is the *meta* isomer, since the former leads to two, and the latter to three, different trisubstituted derivatives. Moreover, it is evident also that XXXIII is the *para* isomer; and that, among the trisubstituted benzenes, XXXIV,



XXXV, and XXXVI are the vicinal, unsymmetrical, and symmetrical isomers, respectively. (In this discussion, of course, the possibility of *stereo*isomers must be ignored.)

4·6 Limitations upon the Use of Isomer Numbers for the Determination of Structure. As has already been observed in the discussion of the Körner absolute method, arguments based upon the numbers of known isomers may be rendered unreliable, or even quite impossible, by the fact that some of the isomers predicted by the structural theory are not known. At best, this difficulty ordinarily makes such a procedure very tedious; at worst, it may lead to the reaching of erroneous conclusions. Obviously, great pains must be taken to ensure that the isomer numbers used in such treatments are correct.

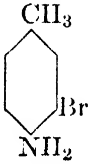
In any application of the Körner absolute method, this source of uncertainty is of relatively little importance since, as soon as structure I of



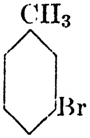
I

benzene has been accepted, the total number of isomers of any given type can be immediately calculated. Consequently, it is possible to be entirely sure either that all the isomers are known, or else that a certain definite number of further ones remain to be found. Before this conclusion can be reached, however, structure I of benzene must first be shown to be correct. The proof of this structure, which was given in Section 4·4, was based upon the fact that, for a given substituent R, only a single substance C_6H_5R exists, and that, for a given pair of substituents R and S, exactly three isomeric substances C_6H_4RS exist. Here, there is no *a priori* way of demonstrating that the one known monosubstituted derivative and the three known disubstituted derivatives are the only ones possible. The fact that no chemist has as yet discovered any additional isomers is a strong suggestion that no such isomers can exist, but it is by no means a rigorous proof. As far as anything that has been said so far is concerned, it is not impossible that some day a second chlorobenzene, for example, or a fourth dibromobenzene may be discovered. In such an event, structure I for benzene would have to be given up, and the significance of the whole assignment of structures to the *ortho*, *meta*, and *para* and to the vicinal, unsymmetrical, and symmetrical isomers would require extensive revision.

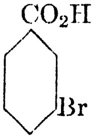
Probably the most nearly conclusive argument that can be advanced against the possibility of additional isomers which are at present unknown is simply that, in spite of the tremendous amount of time and effort which has been expended in the study of aromatic compounds, no single example of such an anomalous isomer has as yet been found. However, in the early days of the theory, before such an enormous store of knowledge had been accumulated, this sort of argument carried considerably less weight than it now does. Consequently, a great deal of work was carried out with the express purpose of proving that the isomer numbers under discussion were correct. The sequence of reactions[18] shown in Figure 4·2, for example, was considered to provide conclusive proof that no more than three bromotoluenes, in which the bromine atom is not joined to the methyl carbon atom, or more than three bromobenzoic acids can exist. It was felt that, if further isomers were possible, then the two paths leading to the *meta* compounds, III and IV, or else the two paths leading to the *ortho* compounds, V and VI, or both, would surely have to give nonidentical products. The argument is conclusive, however, only if it is known in advance that, in the toluene from which the starting compound (the bromotoluidine, II) was made, the position occupied by the methyl group is immaterial. In other words, the argument presupposes that only one toluene is possible, or, in more general terms, that all six positions in benzene are equivalent.



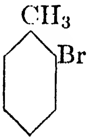
II



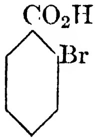
III



IV



V



VI

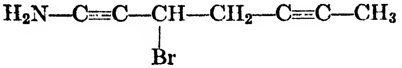
It can be easily shown that the foregoing argument does indeed require the assumption that all the hydrogen atoms in benzene are equivalent. The experimental facts contained in the reaction map of Figure 4·2 would be completely consistent with the supposition that the structure of benzene is VII, that that of the original toluene

$H—C\equiv C—CH_2—CH_2—C\equiv C—H$

VII

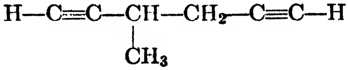
$H—C\equiv C—CH_2—CH_2—C\equiv C—CH_3$

VIII



$H_2N—C\equiv C—\underset{\mathrm{Br}}{\underset{|}{CH}}—CH_2—C\equiv C—CH_3$

IX



$H—C\equiv C—\underset{\mathrm{CH_3}}{\underset{|}{CH}}—CH_2—C\equiv C—H$

X

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[18] E. Wroblewsky, *Ann.* **192**, 196 (1878). Cf. also A. Lachman, *The Spirit of Organic Chemistry*, The Macmillan Company, New York, 1899, pages 29 ff.

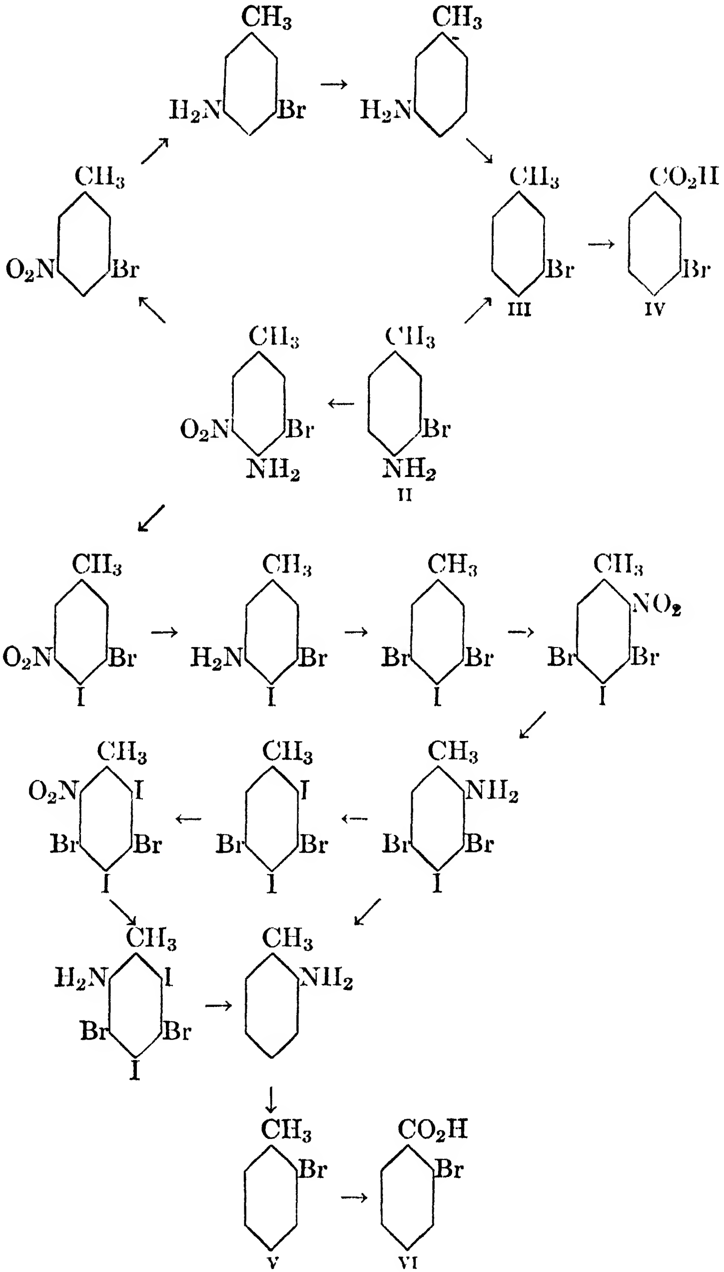

FIGURE 4·2. Wroblewsky's proof that, with given substituents R and S, no more than three disubstituted derivatives C_6H_4RS can exist.[18]

was VIII, and that that of the bromotoluidine which was represented in the figure as II was actually IX. If structures VII–IX were correct, however, there should exist a second "toluene," X, from which could be derived altogether four bromotoluenes (in no one of which is the bromine atom joined to the methyl carbon atom), in addition to the three bromotoluenes derived from the "toluene" VIII. Consequently, the reactions under discussion, by themselves, are insufficient to prove conclusively that there may not be as many as seven isomeric disubstituted derivatives of benzene with the molecular formula C_6H_4RS.

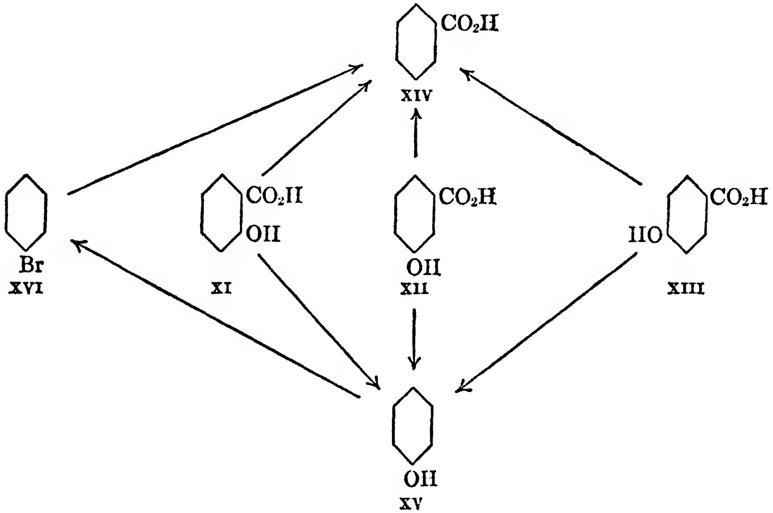

FIGURE 4·3. Ladenburg's proof of the equivalence of the six hydrogen atoms in the molecule of benzene.[19]

The required equivalence of the six positions in benzene was considered to be proved by the further sequence of reactions[19] given in Figure 4·3. In the three hydroxybenzoic acids, XI, XII, and XIII, of this figure, the carboxyl groups must occupy equivalent positions, since, with each compound, elimination of the hydroxyl group (by treatment first with phosphorus pentachloride and then with sodium amalgam) was shown to lead to the same benzoic acid, XIV. Since this benzoic acid was identical with the one obtained by oxidation of the toluene used in the preceding series of experiments (Figure 4·2), it follows that, even if a second benzoic acid could exist, the two positions *ortho* to the carboxyl group of, at any rate, this particular benzoic acid are equivalent to each other. Similarly, the two positions which are *meta* to the carboxyl group must also be equivalent to each other. Moreover, the three hydroxy-

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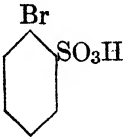
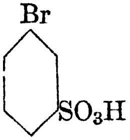
[19] A. Ladenburg, *Ber.* **7**, 1684 (1874). Cf. also A. Lachman, *The Spirit of Organic Chemistry*, The Macmillan Company, New York, 1899, pages 32 f.

benzoic acids, when heated with lime, were decarboxylated to give the same phenol, XV. Consequently, the positions occupied by the hydroxyl groups in these hydroxybenzoic acids must be equivalent to each other, except with respect to their relationship to the carboxyl group. Since, as was shown above, the two positions that are *ortho*, and also the two that are *meta*, to the carboxyl group are respectively equivalent, the further conclusion follows that all the positions in benzene, aside possibly from the one occupied by the carboxyl group in the various acids, are equivalent to each other. That this sixth position too is equivalent to the other five was shown by the transformation of phenol, XV, first into bromobenzene, XVI, by the action of phosphorus pentabromide, and then into benzoic acid, XIV, by the action of sodium and carbon dioxide. Consequently, the proof of the equivalence of all six positions in benzene is complete, as is also that of the existence of only three isomeric disubstituted derivatives C_6H_4RS.

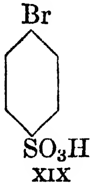
In spite of the apparent rigor of the above arguments, objections can still be raised to them, since they implicitly involve the assumption that the principle of minimum structural change was valid, or, in other words, that molecular rearrangements did not occur. On the basis of what is now known about the reactions in question, it does indeed seem highly probable that no rearrangements did occur in them; at the time the work was done, however, there could have been no assurance that such was the case. That rearrangements can occur in analogous reactions is shown by the fact that the sodium salts of the three different bromobenzenesulfonic acids XVII, XVIII, and XIX, on fusion with sodium hydroxide,



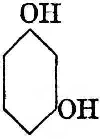
XVII



XVIII



XIX



XX

give the same disodium salt of resorcinol, XX. If only this fact were known, the completely erroneous conclusion might be drawn that, corresponding to the molecular formula C_6H_4RS, there are three isomers if R and S are different, but only one if R and S are the same. Obviously, such a conclusion would require that benzene be assigned a structure which is entirely different from the one now accepted.

The phenomenon of tautomerism, by introducing the possibility of a particularly easy molecular rearrangement, may also cause difficulties in the determination of isomer numbers. (Cf. Chapter 14.) For example, acetaldehyde has four hydrogen atoms which can be (indirectly) replaced by methyl groups. Structure XXI allows only the two isomeric

$CH_3{-}CH{=}O$
XXI

$CH_3{-}CH_2{-}CH{=}O$
XXII

$CH_3{-}C(CH_3){=}O$
XXIII

$CH_2{=}CH{-}OH$
XXIV

$CH_3{-}CH{=}CH{-}OH$
XXV

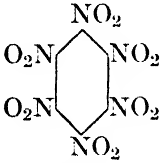
$CH_2{=}C(CH_3){-}OH$
XXVI

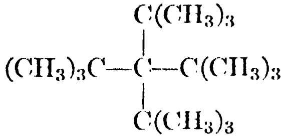
$CH_2{=}CH{-}O{-}CH_3$
XXVII

monomethyl derivatives XXII and XXIII, whereas the structure, XXIV, allows the three derivatives XXV, XXVI, and XXVII. Since three monomethyl derivatives are known, structure XXIV appears to be favored. Nevertheless, structure XXI is instead commonly assumed correct, and structures XXII, XXIII, and XXVII are assigned to the three "derivatives." The fact that the compound XXVII is really a derivative of the tautomeric form, XXIV, and not of ordinary acetaldehyde, XXI, is not immediately obvious experimentally but can be established only by a careful study of preparative methods and of chemical and physical properties. In general, great care must be exercised in the counting of the known isomeric derivatives of a given substance lest compounds be included which are not actually derivatives of the substance of interest.

Still a further difficulty which has not infrequently led to erroneous reports in the chemical literature with respect to isomer numbers results from the fact that experimenters are humanly fallible. Many reported isomers have been found on more careful study not to be isomers at all, but to differ in composition or in molecular weight or in both. Still others have been found to be identical with other, already counted isomers, or to be mixtures of known isomers either with each other or with extraneous impurities. The existence of some substances in different crystalline forms, and the occurrence of stereoisomerism in addition to structural isomerism, have also led to errors. All these various factors must be kept constantly in mind when structural conclusions are drawn from isomer numbers.

In addition to these complications, which can lead to the apparent existence of too great a number of isomers, there are further factors which can lead to the apparent existence of too small a number. Frequently, there is no known experimental method by which certain substances, which are predicted by the structural theory, can be prepared. As examples of such substances, hexanitrobenzene, XXVIII, and tetra-


XXVIII



$$\begin{array}{c} C(CH_3)_3 \\ | \\ (CH_3)_3C\text{—}C\text{—}C(CH_3)_3 \\ | \\ C(CH_3)_3 \end{array}$$

XXIX

tert-butylmethane, XXIX, may be mentioned. Moreover, certain other substances may even be incapable of existence or, at any rate, of isolation. For example, structure XXX of propylene appears to require the

$CH_3\text{—}CH\text{=}CH_2$
XXX

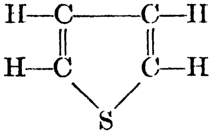
$CH_2R\text{—}CH\text{=}CH_2$
XXXI

$CH_3\text{—}CR\text{=}CH_2$
XXXII

$CH_3\text{—}CH\text{=}CHR$
XXXIII

existence of the three isomeric monosubstituted derivatives XXXI, XXXII, and XXXIII. However, if the substituent R happens to be hydroxyl, only one of these substances can be made, namely, allyl alcohol, XXXI. The two remaining structures, XXXII and XXXIII (which are identical, respectively, with XXVI and XXV), are those of the enol forms of acetone, XXIII, and of propionaldehyde, XXII, respectively; hence they do not correspond to substances that can be isolated. (See also above.) On the other hand, if the substituent R is instead chlorine, all three isomers can be obtained. As in this example, it is not infrequently true that the apparent number of isomers depends upon the identity of some of the atoms or groups present. In such an event, the maximum number of isomers obtained with any choice of atoms or groups is presumably most significant. Thus, in the above example of propylene, the three isomers obtained when the substituent is chlorine are significant, whereas the single isomer obtained when the substituent is hydroxyl is not significant. (For further discussion of the nonexistence of predicted isomers, see pages 89 f.)

Finally, even if all the foregoing difficulties are avoided, the observed numbers of isomers may in some instances still not provide sufficient information to determine the structures uniquely; in fact, it is sometimes found that two or more structures lead to exactly the same set of isomer numbers. Such a situation is encountered, for example, with the various substitution products of thiophene, XXXIV; indeed, for no one of these



XXXIV

compounds can a unique structure be assigned by any method which makes use of only isomer numbers, even if the structure of the parent

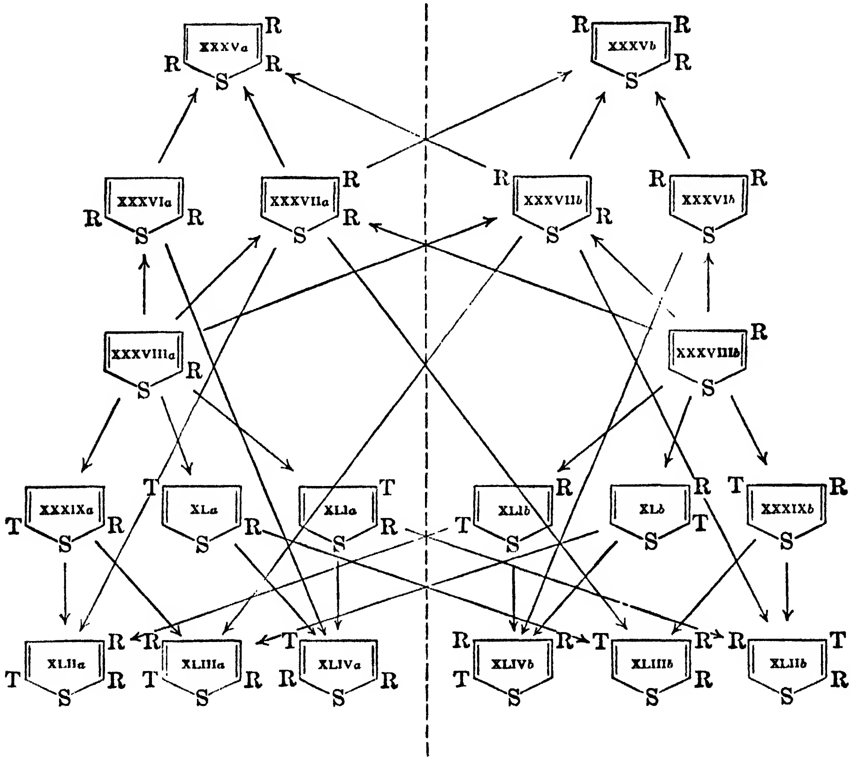


Figure 4·4. A partial proof that the structures of the substituted thiophenes cannot be uniquely determined by the method of isomer numbers.

compound, XXXIV, is given at the outset. A partial proof of this statement is contained in Figure 4·4, where R and T represent any two substituents which are different both from each other and from hydrogen atoms. The pattern which is here formed by the arrows is seen to remain unaltered if it is reflected in a plane mirror that is perpendicular to the paper and that passes through the vertical broken line; clearly, therefore, no two structures which occupy mirror-image positions in this figure can be distinguished from one another by the method of isomer numbers and with the use of only those transformations that are explicitly represented. Thus, it is impossible in this manner to distinguish structure XXXV*a* from structure XXXV*b*, structure XL*a* from structure XL*b*, and so on for all ten pairs of structures. Moreover, nothing is gained if the reaction map is completed by the inclusion in it of the trisubstituted derivatives C_4HSRTV, in which altogether four different atoms or groups H, R, T, and V are joined to the ring; in fact, the resulting figure, although it is too complicated to be profitably given here, retains the symmetry of the simpler one. The structures therefore still occur in indistinguishable pairs. (For another example, in which configuration as well as structure is involved, see Section 6·4.)

4·7 Physical Methods for Determining Structure. The third and final method for the determination of structure, which will be discussed here, involves a study of the physical properties of the substances of interest. An adequate description of even a few of these methods would, however, lie outside the scope of this book; hence the following remarks will be restricted to the listing of the most important methods of this type, with a minimum of illustrative examples, and to a brief discussion of some features which all such methods have in common.

Spectroscopic methods have often been found useful for the identification of certain groups, such as carbonyl and ethylenic. For this purpose, infrared, Raman, visible, and ultraviolet spectra have all found their use.[20] A further optical method consists in the measurement and interpretation of the molecular refraction.[21] The study of optical activity, although it has been found most useful in the investigation of *stereo*isomerism, has also sometimes been of value in the determination of structure, since the knowledge that a given substance is, or is not, capable of optical activity may shed considerable light upon its structure. For example, the fact that a certain substance (*sec*-butyl alcohol) with the molecular formula $C_4H_{10}O$ is optically active is sufficient to show that this substance has structure I, since no other structure cor-

$$CH_3—CHOH—CH_2—CH_3$$

I

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[20] G. Herzberg, *Molecular Spectra and Molecular Structure*, I, *Diatomic Molecules* (translated by J. W. T. Spinks), Prentice-Hall, New York, 1939; *Infrared and Raman Spectra of Polyatomic Molecules*, D. Van Nostrand, New York, 1945; W. West in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume II, 1946, Chapter XVII. K. W. F. Kohlrausch, *Der Smekal-Raman-Effekt*, J. Springer, Berlin, 1931, Erg.-Band, 1938; J. H. Hibben, *The Raman Effect and Its Chemical Applications*, Reinhold Publishing Corporation, New York, 1939.

[21] N. Bauer and K. Fajans in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume I, 1945, Chapter XVI.

responding to formula $C_4H_{10}O$ and permitting optical activity can be written. (Cf. Chapter 6.)

Among the nonoptical methods, the use of the parachor[22] has been especially important. This property may be described qualitatively as a molecular volume that has been corrected to a standard surface tension in order that the effect of the intermolecular forces may be equalized to the greatest possible extent. The molecular volumes themselves,[23] measured either at the boiling points of the substances or at some specified constant temperature, have also been employed.

Such physical properties as boiling point, melting point, and solubility have occasionally been used in the determination of structure.[24] The fact that the boiling point always increases, that the melting point often increases, and that the solubility in water always decreases as the number of CH_2 groups increases in a homologous series is too familiar to require comment. It has already been mentioned (see page 25) that, among isomers of closely similar structure, the boiling point decreases as the symmetry increases. A further, and often even more striking, effect of symmetry is shown by the fact that in general the melting point increases markedly with increasing symmetry. These last two rules can be illustrated by a comparison of *n*-octane, II, with its much more symmetrical isomer hexamethylethane, III. The former of these two substances melts at −56.6°C and boils at 125.5°C; the latter melts at 100.6°C and boils at 106.3°C. Among less closely similar isomers, several useful rules are well known. Alcohols boil at higher temperatures and are more soluble in water than their isomeric ethers; tertiary alcohols or halides boil at lower temperatures and are more soluble than their primary isomers. Numerous further rules of this type have been established. Such rules have occasionally been of value in determining the structures of substances which undergo rearrangement so easily that the usual chemical methods are indecisive. For example,[25] when

$$CH_3—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3$$

II

$$(CH_3)_3C—C(CH_3)_3$$

III

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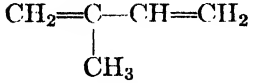
[22] S. Sugden, *The Parachor and Valency*, G. Routledge and Sons, London, 1930.

[23] S. Smiles, *The Relations between Chemical Constitution and Some Physical Properties*, Longmans, Green and Co., London, 1910, Chapter IV; W. Hückel, *Theoretische Grundlagen der Organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, 2nd ed., 1935, Volume 2, Chapter 11.

[24] For a discussion of such methods, see W. Hückel, *Theoretische Grundlagen der Organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, 2nd ed., 1935, Volume 2, "3 Buch."

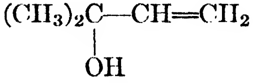
[25] L. Claisen, F. Kremers, F. Roth, and E. Tietze, *J. prakt. Chem.* [2] **105**, 65 (1922).

1 mole of hydrogen bromide is added to 1 mole of isoprene, IV, the resulting organic bromide can be hydrolyzed to the alcohol V of definitely known structure. On the other hand, this same bromide reacts with sodium ethoxide to give the ether VI, also of definitely known structure. (Cf. Section 13·2.) The hydrolysis suggests that the bromide has structure VII, whereas the formation of the ether suggests that it has instead structure VIII. Here, then, is an example in which the principle of minimum structural change is obviously violated and in which, therefore, the structure of the bromide cannot be determined by the reactions mentioned. A consideration of the boiling points of the various substances, however, permits a solution of the problem. The bromide in question boils at 129°–133°C, whereas the alcohol V boils about 30° lower at 98°–99°C. In cases in which the structures are not in doubt, an alcohol usually boils at least 10° higher than does its corresponding bromide. Consequently, this bromide can hardly have structure VII, but must have structure VIII. Its relatively high boiling point is therefore in agreement with the fact that it is primary rather than tertiary.



$CH_2{=}C(CH_3){-}CH{=}CH_2$

IV

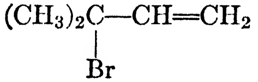


$(CH_3)_2C(OH){-}CH{=}CH_2$

V

$(CH_3)_2C{=}CH{-}CH_2OC_2H_5$

VI



$(CH_3)_2C(Br){-}CH{=}CH_2$

VII

$(CH_3)_2C{=}CH{-}CH_2Br$

VIII

Two final physical methods exist by which, in principle, the complete structure of a molecule can be determined. These methods are based, respectively, upon a study of the diffraction of electrons by the gaseous substance [26] and upon the determination of the crystal structure of the solid.[27] In practice, these methods are usually limited to relatively simple molecules, and they have found their greatest use in providing more or less precise information regarding the exact sizes and shapes of molecules, the gross structures of which are already known from chemical evidence. However, in a few instances in which the chemical evi-

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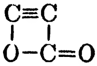
[26] L. O. Brockway, *Rev. Modern Phys.* 8, 231 (1936); L. O. Brockway in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume I, 1945, Chapter XV.

[27] R. W. G. Wyckoff, *The Structure of Crystals*, Chemical Catalog Company, New York, 2nd ed., 1931; W. H. Zachariasen, *The Theory of X-Ray Diffraction in Crystals*, John Wiley and Sons, New York, 1945; I. Fankuchen in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume I, 1945, Chapter XIV.

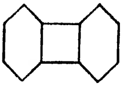
dence is inconclusive, such methods have led to more fundamental results. For example, the structure of carbon suboxide was shown by electron diffraction [28] to be IX and not X, and that of biphenylene was shown by both electron diffraction [29] and crystal-structure analysis [30] to be XI and not XII.

$O{=}C{=}C{=}C{=}O$

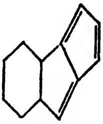
IX



X



XI



XII

With the exception of the electron-diffraction and crystal-structure methods, none of these physical methods is able to lead to a complete structure for any but a few especially simple molecules. Instead, they merely provide evidence which, when taken in conjunction with the available chemical evidence, may permit a decision to be made among a limited number of alternatives. Partially to counterbalance this limitation, however, they have the great advantage of dealing with single molecules and not with the much more complex interaction between two or more molecules. In fact, all the chemical methods discussed above require that deductions be drawn from chemical reactions, or, in other words, that the structure of a given molecule be inferred from the way it is derived from, or transformed into, a different molecule. Thus, even the methods based upon isomer number require the assumption of the principle of minimum structural change. The physical methods, on the other hand, involve much less drastic changes in the molecule being examined, and they leave the molecule in the same state after the experiment that it was in before. As a very rough analogy, which *greatly* exaggerates the advantages of the physical methods, the chemical methods of establishing structure might be compared to the determination of the shape of an egg by examining either the hen that laid it or its fragments after it had been hit by a hammer, whereas the physical methods might be compared to the determination of the shape by looking at the egg itself. Nevertheless, in spite of this apparently great advantage of the physical methods, the limitations mentioned above are in practice so great that ordinarily such methods are, at best, useful only as guides for, or as checks upon, the more familiar chemical methods.

4·8 Classification of Structural Isomers. Efforts have been made by various chemists to subdivide the field of structural isomerism

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[28] L. O. Brockway and L. Pauling, *Proc. Natl. Acad. Sci. U. S.* **19**, 860 (1933).

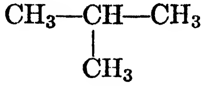
[29] J. Waser and V. Schomaker, *J. Am. Chem. Soc.* **65**, 1451 (1943).

[30] J. Waser and C.-S. Lu, *J. Am. Chem. Soc.* **66**, 2035 (1944).

into smaller fields. Thus, those structurally isomeric organic compounds which have different arrangements of the carbon atoms (e.g., *n*-butane, I, and isobutane, II) are sometimes said [31] to be *nucleus* or *chain isomers;*

$CH_3—CH_2—CH_2—CH_3$

I



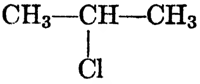
$$\begin{array}{l} CH_3—CH—CH_3 \\ \quad\quad\ | \\ \quad\quad CH_3 \end{array}$$

II

$CH_3—CH_2—CH_2—Cl$

III

those which have the same carbon skeleton but differ with respect to the positions of one or more substituent atoms or groups (e.g., *n*-propyl chloride, III, and isopropyl chloride, IV) are said to be *position isomers;*



$$\begin{array}{l} CH_3—CH—CH_3 \\ \quad\quad\ | \\ \quad\quad Cl \end{array}$$

IV

$CH_3—CH_2—OH$

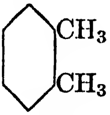
V

$CH_3—O—CH_3$

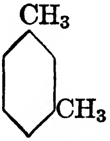
VI

and those which have different functional groups (e.g., ethyl alcohol, V, and methyl ether, VI) are said to be *functional-group isomers.*

In an alternative, but partially overlapping, system of classification,[32] every structure is considered to consist of a *skeleton* (which may or may not contain atoms of elements other than carbon), plus a number of *univalent substituents* that are attached to the skeleton; *univalent substitution isomers* are then structural isomers which differ only by some permutation of the univalent substituents, whereas *skeletal isomers* are isomers which differ in the structure of the skeleton. Although these latter definitions are logical and mutually consistent, they do not always lead to a unique separation of structural isomers into the two subdivisions. For example, *o*-xylene, VII, and *m*-xylene, VIII, are univalent



VII



VIII

substitution isomers if the skeleton is considered to consist of only the six carbon atoms of the benzene ring, but they are skeletal isomers if the skeleton of each substance is considered to consist of all eight carbon atoms.

All the schemes which have been proposed for the subdivision of structural isomerism suffer from the fact that they are rather cumbersome;

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[31] See, for example, R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, 1st ed., 1938, Volume I, pages 154 f., 2nd ed., 1943, Volume I, pages 218 f.

[32] A. C. Lunn and J. K. Senior, *J. Phys. Chem.* **33**, 1027 (1929).

moreover, the distinctions upon which they are based are often not very important. Consequently, they are seldom found in practice to be very helpful. Possibly for these reasons, no one scheme has as yet been generally accepted by all chemists. Throughout the remainder of this book, therefore, the field of structural isomerism will not be further divided, unless the subject of tautomerism, discussed in Chapter 14, be considered to constitute a subdivision.

5.

Stereoisomerism

5·1 The Meaning of Configuration. On the basis of the definitions introduced in the preceding chapters, any two structures must be considered identical if they can be specified, in the manners discussed above in Section 4·1, by the same verbal description and by the same table. When the structural theory was first developed, the natural assumption was made that two substances which in this sense correspond to identical structures must themselves be identical too. There were soon found, however, examples of isomeric substances which differed unmistakably in chemical or physical properties, or in both, but which nevertheless had to be assigned the same structure. (See paragraph 2 of Section 4·2.) As this phenomenon was more carefully studied and as it became better understood, a special terminology was in time developed for its convenient description. Thus, such isomers are at present distinguished from the longer-known structural isomers by being called *stereoisomers;* moreover, stereoisomers, although identical in structure, are at present said to differ in *configuration.*

In Section 1·18, a distinction was drawn between isomers and stoichiomers; it is now desirable to consider how this distinction affects the above definition of stereoisomers. Thus, two (un-ionized) acids which are stereoisomers of each other are also isomers of each other; however, their (ionized) salts, which are formed by reaction with the same base (or with isomeric bases), are not isomers, but are instead stoichiomers, of each other. In the same manner, stereoisomeric bases are likewise transformed into stoichiomeric salts. It is, therefore, somewhat illogical to call such salts "stereoisomers" of one another, since they are not isomers at all; consistency in nomenclature, in fact, requires that these substances be called "stereostoichiomers." Throughout this book, however, compounds of the type described will be referred to as "stereoisomers." This conventional, but inexact, terminology can cause no confusion, because the only stereostoichiomers which will hereafter be considered are ones in which each component molecule (or ion) of each substance either is identical with, or else is a stereoisomer of, the corresponding component molecule (or ion) of the other substance. (See, however, the paragraph in fine print on page 160.)

Still another feature of the definition of the word "isomer" (Section 1·18) also requires comment here. Two substances are isomers of each other only if they retain their differences in the fluid states. Since stereoisomers satisfy this condition, they are isomers (or stoichiomers, see above) and are not merely different crystalline modifications or polymorphic forms.

The exact physical significance of what is now known as configuration was in dispute for some time. In 1873, Wislicenus,[1] adopting a still earlier idea of Pasteur's,[2] suggested that this property might be related to the geometrical arrangements of the various atoms, or, in other words, to the sizes and shapes of the molecules in ordinary Euclidean three-dimensional space. In the following year, van't Hoff[3] and Le Bel[4] independently carried the suggestion much further by making fairly definite proposals in regard to the most probable arrangements of the atoms in a number of organic molecules. Their proposals were soon widely accepted, and they now form the basis of nearly all present-day discussions of stereoisomerism. Indeed, the prefix "stereo" is derived[5] from such considerations (Greek στερεός, solid). Consequently, although it is not inconceivable that some entirely different meaning could be assigned instead to the concept of configuration, and that some entirely different explanation could be found instead for the phenomenon of stereoisomerism, the assumption will be made explicitly throughout this book that configuration does actually refer to ordinary three-dimensional geometry, and that stereoisomers do actually differ in the arrangements of their atoms in Euclidean space. More precisely, it will be assumed that the configuration of a molecule can be defined as that representation of it which not only states the number of covalent bonds by which each atom is joined to each other atom, but also specifies the actual geometrical arrangement of all the atoms. This assumption receives a partial justification in the fact that it is consistent with all the extremely numerous known facts of science.

5·2 Historical Interlude. Before the discussion of stereoisomerism is begun, a brief historical interlude may be not only amusing but also instructive. At the present time, the stereochemical ideas introduced by van't Hoff and Le Bel seem so simple and so obvious that one is likely to forget that they were new and revolutionary when they were first published. Actually, they by no means met with instantaneous and unanimous acceptance; indeed, they gave rise to much heated argument

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[1] J. Wislicenus, *Ann.* **167**, 302 (1873).

[2] L. Pasteur, two lectures delivered before the Société Chimique de Paris, January 20 and February 3, 1860. See L. Pasteur, *Researches on the Molecular Asymmetry of Natural Organic Products*, Alembic Club reprint, University of Chicago Press, Chicago, 1902; *Œuvres de Pasteur*, Masson et Cie., Paris, 1922, Volume 1, pages 315 ff., 329 ff.

[3] J. H. van't Hoff, *Bull. soc. chim.* [2] **23**, 295 (1875); *The Arrangement of Atoms in Space*, 2nd ed. (translated by A. Eiloart), Longmans, Green, and Company, London, 1898.

[4] J. A. Le Bel, *Bull. soc. chim.* [2] **22**, 337 (1874).

[5] K. Auwers and V. Meyer, *Ber.* **21**, 784 (1888); V. Meyer, *ibid.* **23**, 567 (1890).

in the chemical literature. The following excerpts from an article by Kolbe[6] will serve to indicate the attitude of at least one highly respected, but very conservative, older organic chemist.

> In a recently published paper with the same title [*Signs of the Times*], I pointed out that one of the causes of the present-day retrogression of chemical research in Germany is the lack of general and, at the same time, fundamental chemical knowledge; under this lack no small number of our professors of chemistry are laboring, with great harm to the science. A consequence of this is the spread of the weed of the apparently scholarly and clever; but actually trivial and stupid natural philosophy, which was displaced fifty years ago by exact natural science, but which is now brought forth again, out of the store-room harboring the errors of the human mind, by pseudoscientists who try to smuggle it, like a fashionably dressed and freshly rouged prostitute, into good society, where it does not belong.
>
> Anyone to whom this concern seems exaggerated may read, if he is able to, the book by Messrs. van't Hoff and Herrmann on *The Arrangement of Atoms in Space*, which has recently appeared and which overflows with fantastic foolishness. I would ignore this book, as [I have] many others, if a reputable chemist had not taken it under his protection and warmly recommended it as an excellent accomplishment.
>
> A Dr. J. H. van't Hoff, of the Veterinary School at Utrecht, has no liking, it seems, for exact chemical investigation. He has considered it more convenient to mount Pegasus (apparently borrowed from the Veterinary School) and to proclaim in his *La chimie dans l'espace* how the atoms appear to him to be arranged in space, when he is on the chemical Mt. Parnassus which he has reached by bold flight.
>
> The prosaic chemical world had little liking for these hallucinations. Therefore, Dr. F. Herrmann, Assistant at the Agricultural Institute at Heidelberg, undertook to give them wider vogue by means of a German edition. This carries the title "*The Arrangement of Atoms in Space*, by Dr. J. H. van't Hoff; translated into German from the author's monograph *La chimie dans l'espace* by Dr. F. Herrmann, Assistant at the Agricultural Institute in Heidelberg; with a foreword by Dr. Johannes Wislicenus, Professor of Chemistry at the University of Würzburg. . . ."
>
> It is not possible to criticize this work even half-way thoroughly because the play of phantasy therein dispenses completely and entirely with factual basis and is absolutely unintelligible to the sober scientist. . . .
>
> It is indicative of the present day, in which critics are few and hated, that two practically unknown chemists, one from a veterinary school and the other from an agricultural institute, judge with such assurance the most important problems of chemistry, which may well never be solved—in particular, the question of the spatial arrangement of atoms—and undertake their answer with such courage as to astonish the real scientists.
>
> As I have said, I would have taken no notice of that work if Wislicenus had not inconceivably written a foreword for it and, not jokingly but in complete seriousness, warmly recommended it as a worthwhile contribution—whereby many young inexperienced chemists might be misled into assigning some value to these shallow speculations. . . .
>
> It is a sign of the times that the modern chemists feel themselves qualified and able to give an explanation for everything, and, when the results of experience are not sufficient, they seize upon supernatural explanations. Such treatment of scien-

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[6] H. Kolbe, *J. prakt. Chem.* [2] **15**, 473 (1877).

tific questions, which is not far removed from the belief in witches and from ghost-rapping, even Wislicenus considers to be admissible. . . .

Wislicenus makes it clear thereby that he has left the ranks of exact scientists and has gone over to the camp of the natural philosophers of ominous memory, who are only by a narrow "medium" separated from the spiritualists.

5·3 Polarized Light. Since stereoisomers often, although not always, differ most markedly in their effects upon polarized light, a brief digression into the nature of light will be necessary here. It is now recognized [7] that any beam of light is composed of (or perhaps merely accompanied by) two different kinds of field: first, a varying electric field in a direction perpendicular to that of propagation of the light; and, second, a varying magnetic field in a direction perpendicular to both that of propagation and that of the electric field. Since the magnetic field is not necessary to the following discussion, it will here be ignored. In the detailed mathematical treatment of the theory of optical activity,[8] however, the magnetic field is found to be of equal importance with the electric one. The significance of the electric field can be explained with reference to a hypothetical experiment. In Figure 5·1, a beam of light may be considered to pass through the point O; the direction of propagation may be taken as that perpendicular to the plane of the paper. A unit positive charge placed at O would be subjected to a force due to the electric component of the beam of light. At any given instant, this force would have a definite magnitude and direction that can be represented graphically by the length and direction, respectively, of the arrow OP, which of course lies in the plane of the paper. Over even a very short period of time, the position of the point P, which marks the head of the arrow, varies widely as the electric field, to which it corresponds, varies widely. As a result, over this period of time, P can be considered to move and hence to follow some sort of path. The nature of the path depends upon the kind of light. With ordinary light, such as is emitted by the sun or by any other incandescent source, the path is extremely irregular and might look like that shown in Figure 5·2. On the other hand, the various types of *polarized* light correspond to more regular patterns. With *plane* polarized light (discovered by Malus [9]

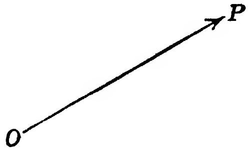

FIGURE 5·1. A representation of the magnitude and direction of a force, acting at point O, by the length and direction, respectively, of an arrow OP.

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[7] See any textbook of physics or any treatise on light.

[8] L. Rosenfeld, *Z. Physik* **52,** 161 (1928).

[9] Malus, *Mém. de la soc. d'Arcueil* **2,** 143 (1809); cf. E. Mascart, *Traité d'optique,* Gauthier-Villars et Fils, Paris, Volume I, 1889, page 521.

in 1809), for example, the direction of the electric field remains constant and only its magnitude varies; consequently, the point marking the head of the arrow is restricted to a back-and-forth movement, with a frequency equal to that of the light, along a single straight line, such as PP' of Figure 5·3. This line necessarily, of course, passes through the point O, which, as before, designates the place at which the beam of light strikes the plane of the paper and hence also the place at which the force acts. The plane which is defined by this line PP' and by the direction of propagation is then said to be the *plane of polarization* of the light. This plane is, of course, perpendicular to the paper. When one speaks of polarized light, he ordinarily has in mind the plane polarized light of this type; still other kinds are, however, well known. Of these further types, *circularly* polarized light (discovered by Fresnel[10] in 1817) is of most interest with respect to stereoisomerism. With circularly polarized light, the magnitude of the electric field remains constant, and only its direction varies; consequently, the point marking the head of the arrow is restricted to motion, again with a frequency equal to that of the light, about a circle with O as center, as in Figure 5·4. Since the point may

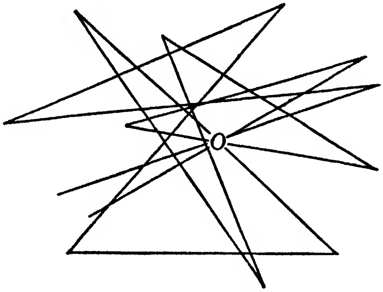

FIGURE 5·2. A schematic representation of the way in which the electric field in ordinary light might vary with the time in both magnitude and direction.

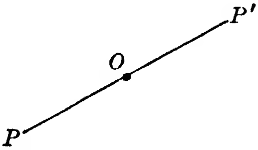

FIGURE 5·3. A schematic representation of the way in which the electric field in plane polarized light varies with the time.

FIGURE 5·4. A schematic representation of the two types of circularly polarized light.

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[10] A. Fresnel, *Ann. chim.* [2] **28**, 147 (1825).

move round the circle in either the clockwise or the counterclockwise direction, as in Figures 5·4*a* and 5·4*b*, respectively, two distinct types of circularly polarized light are possible. These are known, respectively, as *right* and *left* circularly polarized light if the direction of propagation of the light is from below the plane of the paper to above it, or vice versa if the direction of propagation is from above the paper to below it.

The experimental methods by which the various types of polarized light can be produced in the laboratory need not be discussed here.[7,11] It will be sufficient, rather, merely to point out that ordinary light may be polarized in any desired way by being passed through suitable optical instruments known as *polarizers*.

5·4 Optical Activity. If plane polarized light is allowed to pass through any transparent medium, it will ordinarily be found afterwards to be still plane polarized. However, its plane of polarization may have changed in the process.[12] In such an event, the medium is said to be *optically active* and to have *rotated* the plane of polarization of the light. The magnitude of the rotation is given by that of the angle between the initial and the final planes of polarization; the direction of the rotation is specified as *positive* or *negative*, if it appears to be clockwise or counterclockwise, respectively, to an observer who is looking directly toward, rather than away from, the source. Positive and negative rotations are also frequently designated as being to the *right* and to the *left*, respectively. For example, in Figure 5·5, if the light is considered to be coming from below the paper in a direction perpendicular to it, and if the line PP' marks its original plane of polarization, then, the lines RR' and LL' represent, respectively, the planes of polarization which would result from rotations by $+\phi°$ (or by $\phi°$ to the right) and by $-\theta°$ (or by $\theta°$ to the left). Substances which rotate the plane to the right are called *dextrorotatory;* those which rotate it to the left are called *levorotatory.* The fact that a substance is dextro- or levorotatory is conveniently specified explicitly in its name by the prefix (+) or (−), respectively. The older prefixes *d* and *l*, respectively, which were originally used for the same purpose, have been assigned other meanings, as will be dis-

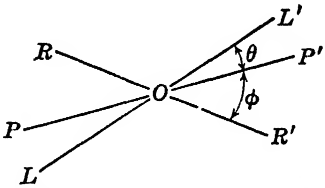

FIGURE 5·5. Possible changes in the plane of polarization of plane polarized light on passage through an optically active medium.

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[11] Cf. R. L. Shriner, R. Adams, and C. S. Marvel, in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 200 ff., 2nd ed., 1943, Volume I, pages 281 ff.

[12] Arago, *Mém. classe sciences math. phys. de l'Institut Imp. France* **12**, 93, 115 (1811); cf. E. Mascart, *Traité d'optique*, Gauthier-Villars et Fils, Paris, Volume II, 1891, page 247.

cussed in the next chapter (see Section 6·15); since they have now therefore become ambiguous, they will not be employed in this book, although they are still often encountered in the current chemical literature.

In Figure 5·5, it might not be clear that the rotation represented by the line *RR′*, for example, corresponds to one of $+\phi°$, as stated, rather than to one of $+(\phi° + n \cdot 180°)$, where n is any integer. Indeed, it might not be clear even that the rotation is to the right at all, since a rotation by $-(n \cdot 180° - \phi°)$, where n is again any integer, would likewise bring the plane of polarization to the position marked by *RR′*. Ambiguities of this sort are, however, easily resolved. In general, the magnitude of the rotation produced by any substance is proportional to its concentration and to the length of the path which the light follows through it. (However, see Section 5·5.) Consequently, by varying either the concentration or the length of path or both, one can always decide empirically among the various possibilities. For example, if the apparent rotations of a given substance at a given concentration are +20° and +10°, when the path lengths are 20 cm and 10 cm, respectively, the possibility that the actual rotation is negative is excluded; an actual rotation of, say, −160° with the 20-cm path would require a rotation of −80° with a 10-cm path, so that the apparent positive rotations would be not +20° and +10°, as observed, but +20° and +100°, respectively. In analogous ways the choice among the various possible *positive* rotations can also be made.

It should be noted further at this time that an optically active substance can appear to be inactive if the concentration and path length happen to be such that the rotation is an exact multiple of ±180°. For this reason, a substance should be reported as inactive only if it produces no detectable rotation at several different concentrations or with several different path lengths. And finally, attention should be called to the fact that an optically active substance may have a truly zero rotation under certain specified experimental conditions, although naturally not under all experimental conditions. (For examples, see Section 5·5.)

5·5 The Specific Rotation. For the characterization of an optically active substance, the so-called *specific rotation* has proved useful.[13] This quantity is defined by equation 5·1, where $[\alpha]_\lambda^t$ is the specific rota-

$$[\alpha]_\lambda^t = \frac{\alpha}{ld} \qquad (5\cdot1)$$

tion for light of wave length λ at the temperature t°C; and α is equal to the rotation produced after the light has passed through a tube which is l decimeters in length, and which is filled with the optically active substance (either pure or in solution in an optically inactive solvent) at a concentration of d grams per cubic centimeter. As has already been

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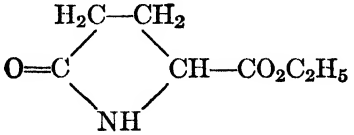
[13] (*a*) Biot, *Mém. de l'Acad. Roy. Sciences de l'Institut France* **13**, 39, 116 (1835); cf. W. Kuhn in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, page 318. (*b*) R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 209 ff., 2nd ed., 1943, Volume I, pages 290 ff.

mentioned, the rotation is taken with the positive sign if it is to the right, and with the negative sign if it is to the left.

Ideally, the specific rotation (as so defined) should be a characteristic property of the substance to which it applies, and its value should be independent of the experimental conditions. In practice, however, extensive investigation has shown that it varies somewhat in magnitude with the wave length of the light, with the temperature, with the solvent (if any), and with the concentration.[13b] In a few instances, even the *sign* of rotation is found to change with conditions. Thus, ethyl pyroglutamate, I, has a positive rotation if light of wave length less than about 4990 A is used, but a negative rotation if light of wave length greater than about 5165 A is used instead; aspartic acid, II, has a positive rotation at temperatures below about 75°C, but a negative one at higher temperatures; the particular form of tartaric acid, III, which has a positive rotation in aqueous solution has a negative one in the crystalline form and also in solution in a solvent consisting of a mixture of benzene and ethyl alcohol; and, at room temperature, the particular form of malic acid, IV, which has a negative rotation in dilute aqueous solution has a positive one when the concentration is greater than about 35 per cent. In such instances as these, there must exist intermediate wave lengths, temperatures, solvents, or concentrations, respectively, such that the observed rotations are exactly zero.



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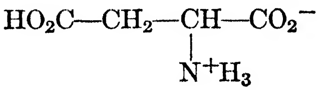

$$HO_2C—CH_2—\underset{N^+H_3}{\underset{|}{CH}}—CO_2^-$$

II

$HO_2C—CHOH—CHOH—CO_2H$

III

$HO_2C—CH_2—CHOH—CO_2H$

IV

With *colorless* compounds, the variation in specific rotation with the wave length of the light that is used is ordinarily small, but nevertheless great enough to make necessary the precise statement of the wave length. The remaining variations are usually minimized by standardization of the experimental procedure to as great an extent as possible. Thus, unless statements are made to the contrary, specific rotations are considered to apply to room temperature and to dilute solutions in stated solvents. Within these limitations, specific rotations may be employed for the characterization, identification, and even quantitative analysis of optically active substances.

Of somewhat greater theoretical significance than the specific rotation is the so-called *molecular rotation* $[M]_\lambda^t$. This quantity is defined by equation 5·2, in which W is the molecular weight of the substance

$$[M]_\lambda^t = W \cdot [\alpha]_\lambda^t \tag{5·2}$$

in question. Since the molecular rotations are usually rather large in magnitude, the values are often given as $\frac{1}{100}$ of the ones defined in equation 5·2. Clearly, the molecular rotation of any substance must exhibit the same sorts of variation in magnitude (and occasionally also in sign) that are characteristic of the specific rotation, to which it is proportional.

5·6 Nature of the Substances Exhibiting Optical Activity. The substances capable of optical activity are found to be of several different types. Some substances, of which quartz, sodium chlorate, and magnesium sulfate may be mentioned as typical examples, are active only in the solid state. If these substances are melted, dissolved in any liquid solvent, or vaporized, they become inactive. The observed activities of such substances appear therefore to be properties of the crystals and not of the individual molecules. Consequently, they are of little organic chemical interest, and will hereafter be ignored. It is of historical interest, however, that quartz was the first optically active substance to be recognized as such.[12] A more important type of optical activity is revealed by the fact that any substance, even if it is ordinarily inactive, possesses an optical rotatory power in the liquid and gaseous states, as well as in the solid state, when it is subjected to an intense magnetic field. This phenomenon, which is called the *Faraday effect* after its discoverer,[14] has been of some practical use, since the magnetic rotation has proved to be an additive and constitutive property like the molecular volume and molecular refraction.[15] However, since it has usually been found in practice to be a less convenient tool than the other analogous physical properties, it will seldom be mentioned in the remainder of this book. (See, however, pages 248 and 350.) In any event the rotatory power which a substance exhibits only in the presence of a powerful external field is hardly an intrinsic property of its molecules alone; hence, such a rotatory power is of relatively little fundamental importance in stereochemistry.

A third group of optically active substances consists of those which retain their activity not only in the liquid and gaseous states, but also in the absence of external fields. The existence of substances of this type was discovered by Biot, who found that oil of turpentine, alcoholic solutions of camphor, and aqueous solutions of cane, beet, and milk sugar

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[14] M. Faraday, *Faraday's Diary*, G. Bell and Sons, London, 1933, Volume IV, pages 263 ff. (13 Septr., 1845).

[15] See S. Smiles, *The Relations between Chemical Constitution and Some Physical Properties*, Longmans, Green, and Company, London, 1910, Chapter XIII.

are optically active;[16] and, slightly later, that even *gaseous* turpentine is also active.[17] With such substances, the observed activities must be intrinsic properties of the respective individual molecules, and therefore must be of fundamental theoretical significance. Only substances belonging to this final class will be spoken of hereafter as optically active.

5·7 The Cause of Optical Activity. The theoretical problem presented by the occurrence of substances which are, in the sense just defined, optically active has been attacked with the aid of both the classical electromagnetic theory[18] and the modern quantum mechanics.[8,18] As a result, the broad outlines of the subject are at present fairly well understood, even though no actual applications of the mathematical treatments to specific substances have ever been carried through rigorously. The following purely classical and greatly oversimplified discussion bears little superficial resemblance to these more elaborate analyses of the problem; it should, however, be sufficient to bring out some of the essential features.

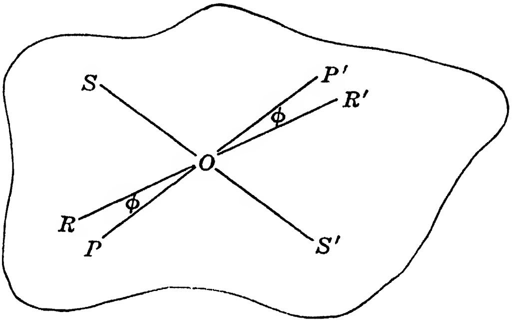

FIGURE 5·6. A schematic representation of a molecule through which plane polarized light is passing.

In Figure 5·6, the irregular closed curve is intended to be a schematic representation of a molecule through which plane polarized light is passing. For definiteness, the beam of light may be considered perpendicular to the plane of the paper. At the point O, the direction of the varying electric field that is due to the incident light is along the line PP', which therefore indicates also the original plane of polarization of the light. The electric forces (due to the light) acting upon the charged particles within the molecule at the point O are consequently along this same line

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[16] Biot, *Bull. soc. philom. Paris* **1815,** 190; **1816,** 125; cf. W. Kuhn in K. Freudenberg, *Stereochemie,* Franz Deuticke, Leipzig and Vienna, 1933, page 317.

[17] Biot, *Mém. de l'Acad. Roy. Sciences de l'Institut France* **2,** 41, 114 (1817); cf. W. Kuhn in K. Freudenberg, *Stereochemie,* Franz Deuticke, Leipzig and Vienna, 1933, page 317; H. Landolt, *Das Optische Drehungsvermögen organischer Substanzen,* Friedrich Vieweg und Sohn, Braunschweig, 1898, page 36.

[18] Cf. J. G. Kirkwood, *J. Chem. Phys.* **5,** 479 (1937), and further references given there.

PP′. As a result of these forces, the electrons and, to a much smaller extent, the heavier atomic nuclei are given a periodic motion with the same frequency as that of the light which produces it. Although, as has just been mentioned, the forces which cause the motion act along the line *PP′*, the motion itself, if the molecule is sufficiently unsymmetrical, may lie along some different line, such as *SS′*. (See the following paragraph.) Now, the charged particles moving periodically along the line *SS′* must, according to classical electromagnetic theory, emit radiation which is plane polarized, and which has as its plane of polarization the one represented by the line *SS′*. Consequently, after the light has passed through the molecule, it consists of two components, namely, the original radiation polarized along *PP′* and the induced radiation polarized along *SS′*. The intensity of the original radiation has, of course, been slightly reduced; for, as the light passes through the molecule, a fraction of its energy is used up in producing the periodic polarization. Since these two components of the emergent beam are of the same frequency, and since they are also coherent, they combine to form a resultant beam of light which is polarized in a new plane such as that represented by *RR′*, intermediate between *PP′* and *SS′*. Consequently, the plane of polarization has been rotated, during its passage through the molecule, by the angle ϕ between the original and resultant directions *PP′* and *RR′*, respectively. In practice, the rotation ϕ due to a single molecule is, of course, infinitesimal, but that due to a succession of a great many different molecules in the path of the light may be quite appreciable.

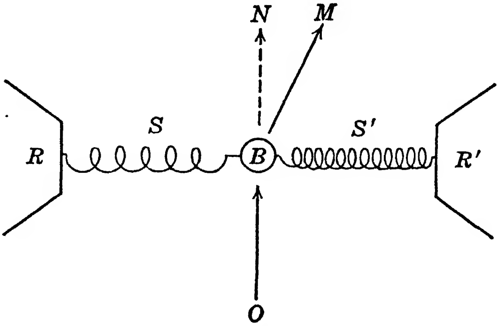

FIGURE 5·7. A mechanical system in which an object *B* moves in a direction *BM* which is different from that of the force *OB* acting upon it.

Some explanation of the reason why the charged particles in a molecule do not have to move in the directions of the external forces acting upon them is necessary if the above interpretation of the cause of optical activity is to seem convincing. The situation can be made clear with the aid of a simple mechanical analogy. Figure 5·7 shows a ball *B*, which is joined by two springs *S* and *S′*, of different stiffness, to the rigid supports *R* and *R′*. A force acting upon the ball in the direction shown by the arrow OB will cause the ball to move so that the two springs are stretched. However, the motion of the ball will not be along BN (i.e., it will not be in the direction of the force acting), but rather along BM, since the weaker spring S is stretched by a greater amount than is the stronger one S'. In a similar way, an electron in a molecule need not move in the direction of the external force acting upon it if the internal "restoring forces" are unsymmetrical.

Still a further feature of the above explanation of optical activity requires discussion. Molecules in the liquid and gaseous states are not held rigidly in fixed positions, but instead are distributed at random over all possible positions and over all possible orientations with respect to the beam of light. Moreover, the magnitudes and even the signs of the individual rotations that are produced by the tremendously large number of individual molecules encountered by the light in its passage through the material must be presumed to depend upon the orientations of these molecules with respect to the plane of polarization of the light. Under what circumstances, then, must the observed resultant rotation be equal to zero, and under what other circumstances may it differ from zero?

It will be shown below in this section that the answer to the above question is as follows: Any single substance, each molecule of which is identical (or, more precisely, congruent) with its own mirror image, must be optically inactive; on the other hand, any other single substance, each molecule of which is not identical with its own mirror image, must instead be optically active. Moreover, two different optically active substances, so related that each molecule of either one is identical with the mirror image of each molecule of the other one, must have specific (and also molecular) rotations of exactly the same magnitude but of opposite sign; the two members of a pair of *enantiomorphs* are presumed to be related in this manner. (See Section 5·9.) Finally, a mixture of two or more substances is inactive if each of its optically active components, if any, is matched by an exactly equal amount of its enantiomorph; *racemic modifications* (see Section 5·12) are the only important examples of such inactive mixtures.

It is, of course, possible to imagine a mixture of two or more nonenantiomorphic dextro- and levorotatory substances in such proportions that the rotations of the different components exactly cancel one another. However, on account of the variations of rotatory power produced by changes in the temperature, in the wave length of the light used, and in the nature of the solvent (Section 5·5), such a cancellation could hardly persist at all temperatures, with all wave lengths, and in all solvents. Consequently, such a mixture would not in a strict sense be optically inactive.

Before the theoretical derivation of the above general conclusions is outlined, the significance of the rather abstract geometrical relationships just discussed can profitably be made more concrete with the aid of a few familiar examples. Common objects which are identical with their own mirror images include spheres, cubes, right circular or elliptical cylinders or cones, and regular tetrahedra. Thus, the mirror image of a sphere (reflected in a plane mirror) is another sphere of the same size as the original one; hence (in thought, although of course not in actuality), the sphere and its image can be exactly superposed. Consequently, in accordance with the above rule, a substance composed of spherical molecules would necessarily be optically inactive. Other common objects which are *not* identical with their own mirror images include gloves, shoes, hands, feet, spiral staircases, and screws. Thus, the mirror image of a right-hand glove, for example, is not another right-hand glove, but is instead a left-hand glove; even in thought, therefore, the glove and its image cannot be superposed. Consequently, a purely hypothetical substance composed of molecules with the shape of right-hand gloves should be optically active. Its equally hypothetical enantiomorph would be composed of molecules with the shape of left-hand gloves of the same size as before, and the racemic modification would consist of equal numbers of molecules of the two kinds.

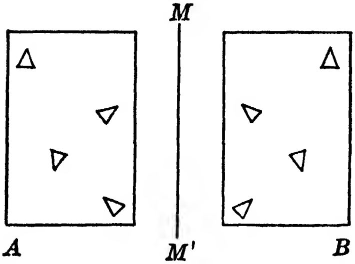

FIGURE 5·8. A container *A*, with four "molecules" arranged at random, and its reflection *B* in the plane mirror *MM'*.

The problem of the extent to which the infinitesimal rotations produced by the individual molecules cancel each other can now be considered. At the outset, it will be assumed that each molecule of the substance under discussion is identical with its own mirror image. Even under such circumstances, a macroscopic sample of the substance can hardly be identical with its mirror image at any given instant of time, since the sample and its image must almost certainly differ in the positions and orientations of individual molecules.

The reason for this possibly unexpected conclusion can be made clear with the aid of a simple example. In Figure 5·8, the rectangle *A* represents a container with four triangular "molecules" arranged at random, and the rectangle *B* represents its image in the plane mirror *MM'*. The three lower triangles in each container lie in the plane of the paper; the upper triangle in each container lies in front of the plane of the paper. It should be evident that, even though each triangle individually is identical with its mirror image, nevertheless no conceivable translation or rotation, or combination of translations and rotations, can bring the containers *A* and *B* (including their contents) into superposition.

Now, although a macroscopic sample of material may not be identical with its mirror image at a single instant, as has just been stated, a measurement of optical activity requires a finite time. If the positions and orientations of the molecules are averaged over even an extremely short time, the resulting average will be identical with its mirror image if, as is here assumed, the molecules are individually symmetrical; this conclusion follows because the positions and orientations of the molecules are completely random. Consequently, in the only sense which is of experimental significance, the sample of material under consideration may be said to be identical with its mirror image, even if the positions and orientations of the individual molecules are taken into account. Obviously, these considerations are restricted to substances in the fluid states. The optical activities of solids, which are therefore ignored, are of little interest, however, in the discussion of organic stereochemistry.

The foregoing argument might more logically have been based upon an averaging over the volume of the container instead of over the time required for the measurement; if this alternative viewpoint had been adopted, the reasoning would have been made more complicated, but the same conclusion would have been reached. Consequently, the foregoing discussion will be left without further elaboration.

The following proposition can now be demonstrated: If plane polarized light passes through a sample of material which, in the above sense, is identical with its mirror image, the rotations due to the individual molecules must exactly cancel each other so that no resultant rotation occurs. For the demonstration of this proposition, two experimenters may be considered to observe an experiment in which plane polarized light passes through a sample of the substance under investigation; the first experimenter observes the experiment directly, whereas the second observes it by watching its reflection in a mirror which lies in a plane parallel to that of polarization of the incident light. Even if the positions and orientations of the individual molecules could be distinguished, the sample itself would have the same appearance to the two experimenters, as has already been explained; moreover, the incident light also must have the same appearance to them, since its plane of polarization is parallel to that of the mirror. On the other hand, any resultant rotation of the plane of polarization that might occur would necessarily appear to them to be in opposite directions. Now, the laws of physics are such that the apparent behavior of any system which is observed by reflection in a plane mirror is not distinguishable from a possible actual behavior of an equivalent system which is viewed directly. (Cf. the following paragraph in fine print.) Consequently, if the first of the two above experimenters observed a real dextrorotation (or levorotation), the second should observe an apparent dextrorotation (or levorotation), since the system composed of sample plus incident light has the same appearance to him that it has to the first. Nevertheless, as has just been pointed out, the fact that the first experimenter observes a real dextrorotation (or levorotation) requires that the second observe instead an apparent levorotation (or dextrorotation). Consequently, the only way in which a contradiction can be avoided is for the rotation observed by each experimenter to be exactly zero. Moreover, if the resultant rotation is thus zero, the rotations due to the individual molecules must either have been themselves zero or else have exactly canceled one another. In a way which is modeled closely after the discussion on page 146, but which need not be described further here, the first of these two alternatives can be shown to be improbable except with molecules of exceptionally high symmetry. The second alternative must therefore be the one which ordinarily obtains. The demonstration of the proposition stated at the beginning of this paragraph is accordingly complete.

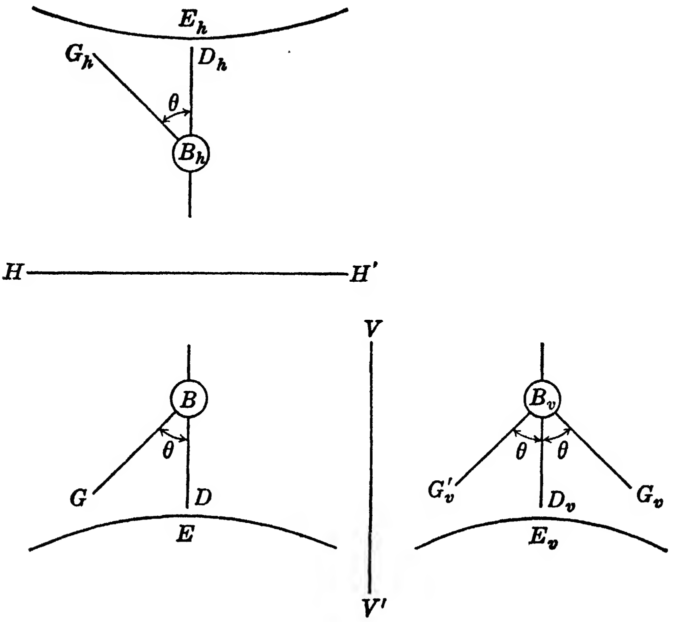

FIGURE 5·9. A system composed of a ball B and the earth E, together with the reflections of this system in the vertical plane mirror VV' and in the horizontal plane mirror HH'.

A simple mechanical analogy may help to clarify the principles which are here involved. In Figure 5·9, the circle B represents a ball which is subject to no restraints and is initially at rest; the arc E represents the surface of the earth. The further circles B_v and B_h represent, respectively, the reflections of the ball B in the vertical plane mirror VV' and in the horizontal plane mirror HH'; the arcs E_v and E_h represent the reflections of the earth E in the two respective mirrors. The ball B may be assumed to move in the direction of the line BG, which forms an angle θ with the vertical line BD; the images B_v and B_h therefore move in the directions of the lines B_vG_v and B_hG_h, respectively, which likewise form angles θ with the reflections B_vD_v and B_hD_h of the vertical line BD. (As will be shown immediately, the angle θ must, of course, be equal to either 0° or 180°.) The actual system, consisting of the ball B and the earth E, may first be compared with its reflection in the vertical mirror VV'. To any observer, the system and its image have exactly the same appearance; in fact, the observer might not be sure whether he is seeing one system and its reflection, or two different, but completely equivalent, systems. Since the laws of physics have the characteristic mentioned in the preceding paragraph, it therefore follows that the apparent behavior of the reflected system (B_v plus E_v) must be exactly the same as the real behavior of the real system (B plus E). Consequently, if the ball B moves in the direction of the line BG, its image B_v must move in the direction of the line B_vG_v'. A contradiction can be avoided therefore only if the angle θ is equal to either 0° or 180°, so that the two lines B_vG_v and B_vG_v' are coincident both with each other and with the reflection B_vD_v of the vertical line BD. Hence, the ball itself must move along the vertical line BD as, of course, it actually does. The answer to the question whether θ is equal to 0°, so that the ball moves downward (i.e., toward the earth), or instead is equal to 180°, so that the ball moves upward (i.e., away from the earth), cannot be obtained with the use of only such general considerations; the answer, in fact, requires fairly precise information regarding the exact forms of the pertinent physical laws and regarding also the relative densities of the ball and of its surrounding medium.

The following objection may be raised to the foregoing discussion. The line B_vG_v' was drawn to the left of the vertical line B_vD_v because it was meant to represent the same direction as that represented by the line BG, which was similarly drawn to the left of the vertical line BD. However, the lines B_vG_v' and BG are related to two different systems, the first of which is the reflection of the second in the mirror VV'; when a system is thus reflected, the meanings of the words "right" and "left" are reversed. Is it then correct to say that the line B_vG_v' lies to the left of the vertical line B_vD_v? Is not, instead, the line B_vG_v the one which really lies to the left? If this objection were valid, the proof that the ball must move along the line BD would then be fallacious. The objection is, however, not valid. The words "right" and "left" have definite meanings with respect to the observer. Since the observer is here not part of the system that is being observed, he is not to be reflected in the mirror; hence there is no uncertainty regarding the meanings of the words "right" and "left."

A different sort of objection can be raised if the real system (B plus E) is compared with its reflection (B_h plus E_h) in the *horizontal* mirror HH'. If, for definiteness, the density of the ball is considered to be greater than that of the surrounding medium, the ball B then falls toward the earth E, and hence the image B_h moves toward the image E_h; in other words, the angle θ is equal to 0°. It might therefore be considered that the real experiment and its reflection are not equivalent, since the real ball B falls *down* whereas its image B_h appears to fall *up*. This objection also, however, is not valid. An observer viewing the experiment through the mirror HH' would not see the real earth E, which would therefore not be included in the complete system which he was studying; in his system, which contains only the images B_h and E_h, the "ball" moves toward the "earth" or, in other words, falls down since, by definition, "down" means "toward the earth." It may, however, be asked why the words "up" and "down" must be defined with reference to the earth, and why they cannot, like the words "right" and "left," be defined instead with reference to the observer. The answer to this question is most clearly seen if the observer is imagined to be somewhere in interstellar space and to be watching the experiment through a powerful telescope. With respect to such an observer, the words "right" and "left" have the same meanings as before, but the words "up" and "down" are now undefined. The real and the apparent motions of the ball may therefore be described as in the same direction; furthermore, they must at all times have the same velocities and the same accelerations. These two motions are, in fact, entirely equivalent in all significant respects.

The further fact that, under the same conditions, two enantiomorphs rotate the plane of polarization by exactly equal amounts in opposite directions can be derived in a similar manner. A macroscopic sample of one enantiomorph is easily seen to be identical, in the same sense as before, with the mirror image of an equivalent sample of the other enantiomorph. Consequently, if one experimenter, observing directly the passage of plane polarized light through a sample of the first enantiomorph, finds a rotation of $N°$ (where N may be either positive or negative), another experimenter, observing by reflection in a mirror the passage of the same light through an equivalent sample of the second enantiomorph, must find an apparent rotation of exactly the same $N°$. In the latter case, however, the apparent rotation of $N°$ corresponds to a true rotation of $-N°$. Consequently, if now each experimenter (and not only the first one), views his experiment directly, the two must find that, as was stated originally, the enantiomorphs cause rotations of exactly the same amount but in opposite directions. Moreover, only as a result of a most extraordinary coincidence, which doubtless never occurs in practice, could the observed rotations of the enantiomorphs ($N°$ and $-N°$, respectively) be zero under all experimental conditions. There is, in fact, no more reason for N to be exactly 0 than there is for it to be, say, exactly 10 or exactly $93.672\sqrt{\pi}$. Consequently, the further conclusion can be drawn that, as was also stated earlier, any substance must be optically active if it consists of molecules that are not identical with their own mirror images.

The principles which have just been employed can be illustrated by an extension of the mechanical analogy discussed in the above paragraphs in fine print. It would be possible to construct an "inverted" clock, every individual part of which is equivalent to the mirror image of the corresponding part of an ordinary clock. The original real ordinary clock then looks exactly like the mirror image of the corresponding inverted clock. Consequently, since the hands of the real ordinary clock go round in the clockwise direction, the images of the hands in the reflection of the inverted clock must appear likewise to go round in the clockwise direction. The real hands of the real inverted clock must therefore go round in the counterclockwise direction. This conclusion is, of course, obviously correct; for, in an inverted clock, constructed in the way specified, the hands must indeed move in the direction stated.

Finally, the optical inactivity of racemic modifications, and of all other similar mixtures in which each optically active component is matched by an exactly equal quantity of its enantiomorph, is a necessary consequence of the foregoing theoretical considerations. Any such mixture, just like a sample of a single inactive substance, can be considered identical with its mirror image; consequently, the same reasoning used above can be applied here too. As before, therefore, the sample can have no effect upon the plane of polarization of the light.

More direct evidence that molecules which are not identical with their own mirror images can indeed rotate the plane of polarization of plane polarized light has been obtained by Lindman [19] in a series of ingenious experiments on the effects of macroscopic molecular models upon short radio waves. Each model was made from four equivalent copper or brass balls, which were placed at the corners of an irregular tetrahedron. In some experiments, the radii of the balls were 3.5 cm; in other experiments, the radii were 0.9 cm. The wave lengths of the radio waves ranged from 12 to 36 cm. Lindman found that, when a beam of plane polarized radio waves passes through one or more such models, the plane of polarization is rotated. The angle of rotation depends upon the orientation of the model with respect to the plane of polarization and also upon the wave length; moreover, it is proportional to the number of models through which the beam passes. (Cf. Equation 5·1, page 136.) Finally, models which are identical with each other's mirror images produce rotations of equal magnitudes, but in opposite directions. In all respects, therefore, the effects which the models were observed to exert upon the plane polarized radio waves were the same as those which actual molecules are considered to exert upon plane polarized light. In fact, the most significant difference between the two types of experiment is merely one of size.

5·8 The Symmetry Properties of Molecules.[20] In view of the conclusions reached in the preceding section, a simple rule by which it can easily be decided whether a given object is identical with, or different from, its mirror image should be of great value in the discussion of stereoisomerism. Such a rule can indeed be stated, as will be seen later in this section; first, however, a brief discussion of symmetry in general is desirable.

The symmetry of any rigid body can be described with the aid of its so-called *symmetry elements.* These elements are of several different kinds. (1) An object is said to possess a *plane of symmetry* if a plane

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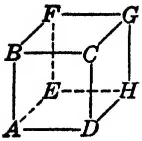
[19] K. F. Lindman, *Ann. Physik* [4] **74,** 541 (1924); 77, 337 (1925); *Acta Acad. Åboensis Math. et Phys.* **4,** No. 1 (1927); *C.A.* **23,** 1789 (1929).

[20] F. M. Jaeger, *Lectures on the Principle of Symmetry,* Publishing Company "Elsevier," Amsterdam, 1917.

mirror can be imagined passing through it so that one half of the object coincides with the reflection in the mirror of the other half. The plane of the mirror is then the plane of symmetry. (2) An object is said to possess an *n-fold axis* (or an *axis of order n*) if it possesses an axis, about which rotation by 360°/*n* brings the object into a position indistinguishable from its original one. The order *n* can have any positive integral value, or it may be infinite if the object has the complete symmetry of, for example, a right circular cylinder or cone. In general, *n* rotations by 360°/*n* bring the object into a position identical with, and not merely indistinguishable from, the original one. Any straight line passing through any object is clearly a 1-fold axis; such 1-fold axes, however, may usually be ignored in discussions of symmetry since an infinite number of them are always present. For the purpose of distinction from the *alternating* axes discussed below, the symmetry axes of this first type may be called *simple* axes. (3) An object is said to possess an *n-fold alternating* (or *mirror*) *axis* if a rotation of 360°/*n* about some axis, followed by a reflection in a plane perpendicular to that axis, brings the object into a position indistinguishable from its original one. A 1-fold alternating axis, in which the rotation is by 360°, is equivalent to a simple plane of symmetry. On the other hand, a 2-fold alternating axis, in which the rotation is by 180°, is equivalent to what is frequently called a *center of inversion* (or *of symmetry*). Without explicit reference to axes or to planes of reflection, an object may be said to have a center of inversion if it contains a point within it, such that any straight line through that point encounters exactly the same environment in each of its two directions. Alternating axes of order higher than 2 are also possible but require no special comment here. (However, see below.)

A few examples will serve to make the above concepts more concrete. Diagram I represents a cube, the corners of which are lettered from *A* to



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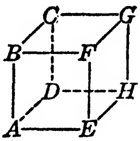
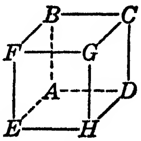
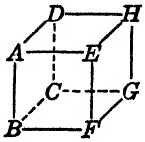


II



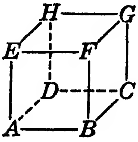
III



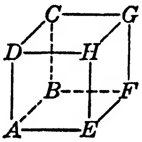
IV

H for the sake of future identification. It is easily verified that such a cube possesses several planes of symmetry. Of these planes, one contains the edges *AB* and *GH*; reflection in this plane leaves the corners *A*, *B*, *G*, and *H* unchanged, and it transforms the corners *C* and *D* into *F* and *E*, respectively; hence, the original diagram, I, is transformed into the completely equivalent one, II. Altogether six planes of symmetry of this type, containing opposite edges of the cube, are present. Moreover, three planes of symmetry of a different type are also present; these are the planes which are parallel to, and halfway between, two parallel faces of the cube. For example, reflection in the plane lying between the faces *ABCD* and *EFGH* transforms I into the equivalent III.

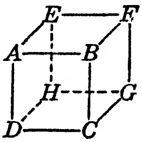
A cube possesses also several *axes* of symmetry. The common bisector of any of the six pairs of opposite edges is a 2-fold axis. For example, rotation by 360°/2, or 180°, about the bisector of the edges *AB* and *GH* transforms I into IV; a second rotation by the same angle about the same axis brings IV back to I. Each of the four body-diagonals of the cube is a 3-fold axis. For example, rotation by 360°/3, or 120°, about the diagonal *AG* transforms I into V; a second rotation of the same kind transforms V into VI; and a third transforms VI back into I. Finally, the line perpendicular to, and passing through the center of, any one of the three pairs of opposite faces is a 4-fold axis. For example, rotation by 360°/4, or 90°, about the line passing through the centers of the faces *ABCD* and *EFGH* transforms I into VII; a second such rotation transforms VII into VIII; a third transforms VIII into IX; and a fourth transforms IX back into I.



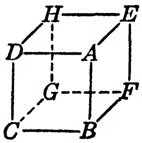
V



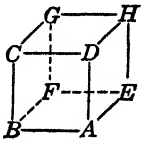
VI



VII

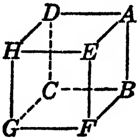


VIII

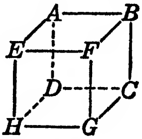


IX

In addition to all the foregoing symmetry elements, a cube possesses also several *alternating* axes. Each of the planes of symmetry noted above can be considered equivalent to a 1-fold alternating axis, as has already been mentioned. Moreover, each 2-fold and 4-fold simple axis is also a 2-fold alternating axis. For example, if the rotations by 180° which transform I into either IV or VIII is followed by reflection in a plane perpendicular to the respective axis of rotation, diagram X results. The equivalence of the 2-fold alternating axis to a center of symmetry may be seen from the fact that X can be obtained from I directly by inversion through the center (i.e., by an interchange of each



X



XI

pair of corners joined by a straight line through the center). Finally, each of the 4-fold simple axes of the preceding paragraph is also a 4-fold alternating axis. For example, if the rotation by 90° which transforms I into VII is followed by a reflection in a plane perpendicular to the axis, diagram XI results.

As should be apparent from the foregoing example, an object may possess several different symmetry elements of several different kinds. The complete symmetry is defined by a statement of the elements that are present and of the angles between the various axes and planes of symmetry. Frequently, certain of the symmetry elements are merely combinations of others or are implied by others; in such instances, only the independent elements need be stated. For example, it is ordinarily unnecessary to call attention to the fact that any 4-fold simple axis is always also a 2-fold simple axis. Moreover, the above-mentioned 4-fold alternating axis of the cube is merely a result of the presence of a 4-fold simple axis plus a plane of symmetry perpendicular to it; consequently, the alternating axes in this instance need not have been mentioned explicitly. Finally, as can easily be verified, any alternating axis of odd order is always equivalent to a simple axis of the same order plus a plane of symmetry perpendicular to it; and any alternating axis of order $4p + 2$, where p is either an integer or zero, is always equivalent to a simple axis of order $2p + 1$ plus a center of inversion. Consequently, since alternating axes of these two latter types may always be ignored, only those of order $4p$ need be explicitly considered.

The original problem stated at the beginning of this section may now be further considered. Mathematical analysis has shown that an object is identical with its own mirror image if, and only if, it possesses an alternating axis of some order. In stereochemistry, this rule finds its only important applications in those instances in which the molecules have planes of symmetry (alternating axes of order 1) or centers of inversion (alternating axes of order 2). There is at present no known example of an optically inactive substance, the molecules of which are made identical with their mirror images *only* by the existence of alternating axes of order greater than 2. There is no theoretical reason, however, why such substances could not be obtained; it just happens that no chemist has as yet taken the trouble to prepare one. (For the reason stated in the preceding paragraph, only the alternating axes of order 4, 8, 12, and so on need be considered.) The statement is often made that a compound must be optically active unless either it is a racemic modification or else its molecules possess either *planes* or *centers* of symmetry. In practice, this simpler, but incomplete, form of the rule, which ignores the possibility of inactivity due to the presence of alternating axes of order $4p$, is adequate for most purposes. It is especially to be noted, however, that the presence of *simple* axes of symmetry is not sufficient to ensure optical inactivity.

From a purely logical point of view, the expression "alternating (or mirror) axis of order n" should not be used when n is an *odd* integer. The reason for this limitation is that, if n is odd, the composite operation consisting of rotation by $360°/n$ about the axis, and of subsequent reflection in a plane perpendicular to the axis, must be carried out altogether $2n$ times, and not merely n times, before the object is brought back to its original position. Moreover, the "alternating axis" under discussion, although it is thus in one sense really of order $2n$, is not at all the same thing as a true alternating axis of order $2n$, since the rotation involved in its definition is one of $360°/n$, rather than one of $360°/2n$. For this reason, alternating axes of odd order are not ordinarily considered to exist; instead, the types of symmetry described above in terms of such axes are most commonly defined by means of their components, namely, the respective n-fold simple axes and the planes of symmetry. Clearly, therefore, the terminology employed in the preceding paragraphs is neither entirely correct nor completely in agreement with conventional usage; it has nevertheless been deliberately adopted here, since it makes possible a particularly simple and compact statement of the necessary and sufficient condition that an object be identical with its mirror image, and hence of the necessary and sufficient condition that a substance be optically inactive.

According to the most generally accepted terminology, an object is said to be *dissymmetric* if it is not superposable on its mirror image (i.e., if it contains no alternating axis of any order), and to be *asymmetric* if it possesses no element of symmetry whatever, except, of course, for the always-present 1-fold simple axes. An asymmetric object is necessarily also dissymmetric, but a dissymmetric object need not be also asymmetric, since it may possess a simple axis of rotation. For example, a flat square board with an ordinary right-handed screw driven into each corner may have a simple 4-fold axis if the screws are properly placed and aligned; it cannot, however, be identical with its mirror image under any circumstances, since its image would contain left-handed screws. It is, therefore, dissymmetric but not asymmetric. In discussions of stereoisomerism, the word "asymmetric" is often used loosely in places where "dissymmetric" is intended; in this book, however, the distinction will be observed.

5·9 Enantiomorphs. Among a group of stereoisomers, there may occur one or more pairs of substances with very closely similar properties. The two members of any such pair have the same melting point and boiling point; they exhibit the same chemical properties in all optically inactive environments; they rotate the plane of polarization, under identical conditions, by equal amounts in opposite directions; and they resemble each other in the various other ways that will be discussed below in greater detail. Two substances related in this manner are said to be *enantiomorphs* (or *antimers* or *optical antipodes*) of one another. As was stated in Section 5·7, the individual molecules of either member of a pair of enantiomorphs are assumed to be identical with the mirror images of the molecules of the other member. In this section, the assumption thus made will be shown to lead to a simple interpretation of many of the characteristic properties of pairs of enantiomorphs.

In the first place, it may be noted that the relationship of an object to its mirror image is a perfectly definite and precise one, so that two objects either are, or else are not, identical with each other's mirror image. No further possibility exists; two objects cannot be both identical with and different from each other's mirror image at the same time, and they cannot be neither identical with nor different from each other's mirror image. Correspondingly, the relationship of a substance to its enantiomorph is also a perfectly definite and precise one, so that two substances either are, or else are not, enantiomorphs of each other. Again, no further possibility exists; two substances cannot be both enantiomorphs and nonenantiomorphs of each other at the same time, and they cannot be neither enantiomorphs nor nonenantiomorphs of each other. This point may perhaps seem too obvious to deserve mention here; it will be of interest later, however, when attention is called to the lack of a similarly definite and precise distinction between *optical* and *geometrical* isomerism. (Cf. Section 6·14.)

A further feature of the relationship between an object and its mirror image is that every object must always have exactly one mirror image. This image is often, of course, identical with the original object, so that the two correspond to only one distinct geometrical form. It is impossible, however, to imagine an object which has no mirror image at all (whether identical with itself or not), or one which has two or more nonequivalent mirror images. Correspondingly, every substance may be associated with exactly one enantiomorph. This enantiomorph is often, of course, identical with the original substance, so that the two correspond to only one distinct, optically inactive compound; there is, however, no substance which can be shown to be incapable of having any enantiomorph at all (whether identical with itself or not), or which has two or more distinguishable enantiomorphs.

Although the relationship between an object and its mirror image is thus completely analogous to that between a substance and its enantiomorph, two features of the correspondence deserve special comment. The first of these is that an optically inactive substance, described above as identical with its own enantiomorph, is more commonly described instead as having no enantiomorph at all. It is readily seen, however, that the contradiction between these two manners of speaking is only apparent, since the statement that a certain optically inactive substance has no enantiomorph really means merely that it has no enantiomorph other than itself. The second point to be discussed here is that very frequently only one of a pair of nonidentical enantiomorphs is actually known. A large number of optically active substances are found in nature (for example, proteins, carbohydrates, terpenes, alkaloids); in many instances, the enantiomorphs of the naturally occurring forms have never been obtained. However, there is every reason to suppose that, although the production of certain ones of these missing enantiomorphs might be extremely difficult, or even impossible, in practice, nevertheless the substances should in principle be able to exist. In any event, experience has shown (cf. pages 230 f.) that, whenever a substance capable of optical activity is prepared from exclusively inactive reagents, and in the absence of any optically active catalysts, the product obtained is always completely racemic (i.e., it always consists of exactly equal amounts of the two active enantiomorphs). Consequently, it may be inferred that both enantiomorphs of even a protein or polysaccharide could be obtained if there could be found a method of preparation which employs only optically inactive reagents, and which does not require the catalytic effect of the optically active enzymes present in all living matter. (Cf. Section 7·3.)

The various respects in which two enantiomorphs may differ, and the various other respects in which they must be identical, can be understood readily with the aid of the assumed mirror-image relationship between such pairs of substances. In fact, the equal but opposite rotatory powers of enantiomorphs have already been explained in this way. (See Section 5·7, and also the following paragraph.) Moreover, by a continuation of the line of reasoning developed in Section 5·7, the general conclusion can be drawn that every property of any optically active substance must be (in the rather special sense discussed below) the mirror image of the corresponding property of its enantiomorph; or, in other words, that two enantiomorphs must be identical with respect to all those properties which are themselves identical (in this same sense) with their own mirror images, and can differ with respect to only those other properties which are different from their mirror images. For example, the melting point of any substance may be considered identical with its own mirror image, since the temperature at which the pure solid and pure liquid are in equilibrium must be the same whether the experiment is viewed directly or by reflection in a mirror. Consequently, two enantiomorphs must have the same melting point. In a similar way, it can be shown that two enantiomorphs must have also the same vapor tension at any specified temperature, the same boiling point at any specified pressure, the same density under the same conditions, the same solubility in any specified *optically inactive* solvent, the same rate of reaction with any specified *optically inactive* reagent (or reagents), the same equilibrium in their reactions with any specified *optically inactive* reagent (or reagents), and so on.

On the other hand, as was pointed out in Section 5·7, the mirror image of a rotation of the plane of polarization by any specified number of degrees to the right (or left) may be considered to be a rotation by exactly the same number of degrees to the left (or right). Consequently, under identical conditions, two enantiomorphs must rotate the plane of polarization by equal amounts but in opposite directions. Similarly, the mirror image of right (or left) circularly polarized light is identical, not with itself, but instead with left (or right) circularly polarized light. Consequently, two enantiomorphs may be expected to possess different optical properties (e.g., absorption spectra, indexes of refraction) when examined with circularly polarized light, but not when examined with ordinary light or even, except for the optical rotation, when examined with plane polarized light; conversely, the optical properties of a single optically active substance may be expected to be different with right and left circularly polarized light. The expected differences in spectrum have been observed experimentally (*circular dichroism, Cotton effect*[21]); the differences in index of refraction, although so small that their direct observation is difficult,[22] are known always to exist since the observed angle of rotation by an optically active substance can be shown to be proportional to the difference in the indexes of refraction for right and left circularly polarized light. Moreover, since an optically active solvent is not identical with its mirror image, the solubilities of two enantiomorphs in such a solvent need not be the same; differences of this sort are found in practice, however, to be too small to be observed. On the other hand, measurable differences have been found in the extents of adsorption of enantiomorphs upon optically active solid adsorbents,[23] and in the rates and equilibria of their reactions with optically active reagents. (See Sections 7·2 and 7·3.) Finally, the crystals of two enantiomorphs may be nonsuperposable mirror images of each other, although often they are symmetrical and have identical form.

Whenever two enantiomorphs exhibit different physical or chemical properties of the foregoing types, the two corresponding experimental situations, as a whole, are neither identical with, nor mirror images of,

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[21] A. Cotton, *Ann. chim.* [7] **8**, 347 (1896).

[22] Cf. W. Kuhn in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 327 f.

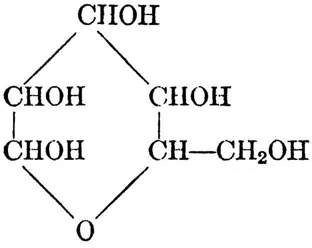
[23] G. M. Henderson and H. G. Rule, *Nature* **141**, 917 (1938).

each other. Thus, a sample of a dextrorotatory substance through which right circularly polarized light is passing is neither identical with, nor the mirror image of, a sample of the levorotatory enantiomorph through which the same right circularly polarized light is passing. This fact may be considered to provide the reason why (as stated above) the absorption spectra and indexes of refraction are different. On the other hand, the sample of dextrorotatory substance through which the right circularly polarized light is passing *is* the mirror image of a sample of the levorotatory enantiomorph through which *left* circularly polarized light is passing; consequently, the same spectrum and index of refraction must be observed. Similarly, the spectrum and index of refraction of the dextrorotatory substance for left circularly polarized light must be the same, respectively, as those of the levorotatory enantiomorph for right circularly polarized light. The same sorts of relationship hold also among all the other properties (discussed above) in which enantiomorphs may differ.

5·10 Diastereomers. Examples of stereoisomers which are not enantiomorphs of each other are well known. For example, the three stereoisomeric tartaric acids with structure I consist of a pair of enantiomorphs, known as (+)- and (−)-tartaric acid, and an optically inactive form, known as *meso*-tartaric acid, which differs from the active forms in physical and chemical properties. Moreover, the stereoisomeric maleic and fumaric acids with structure II are both inactive, and no active isomer is known. Finally, the pyranose structure, III, of the aldohexoses permits altogether thirty-two stereoisomeric forms, divisible into sixteen pairs of enantiomorphs; all are known. As is shown by these examples, a group of stereoisomers may consist of some inactive and some active forms, or of only inactive forms, or of only active forms.

$HO_2C—CHOH—CHOH—CO_2H$
I

$HO_2C—CH{=}CH—CO_2H$
II



III

No general term has been universally adopted for the description of the relationship between two stereoisomers which are not enantiomorphs of each other. The word *diastereomer* (or *diastereoisomer* or *diamer*) is often applied to certain, but usually not to all, such pairs of substances. Thus, (+)-tartaric acid and *meso*-tartaric acid are considered diastereomers of each other, as are also any nonenantiomorphic two of the thirty-two aldohexoses; on the other hand, maleic and fumaric acids are not usually considered diastereomeric. The reason for this distinction is that the isomerism of the tartaric acids and of the aldohexoses is of the type known as *optical*, whereas that of maleic and fumaric acids is of the type known as *geometrical* (or *cis-trans*); most commonly, two nonenantiomorphic stereoisomers are said to be diastereomers of each other only if they are optical isomers, and not if they are geometrical isomers. The distinction between these two kinds of stereoisomerism cannot be discussed here; it will, however, be taken up later. (See Section 6·14.) For the present, it may be mentioned only that this distinction is not at all sharp, since many pairs of substances are both optical and geometrical isomers at the same time. For this reason, and also for purposes of brevity and convenience, the word "diastereomer" will be used throughout the remainder of this book to designate any nonenantiomorphic stereoisomer. Thus, even fumaric and maleic acids will be described as diastereomers of each other. It is to be noted, however, that this terminology departs somewhat from the most common usage.

Unlike enantiomorphs, diastereomers (in the broad sense just defined) need not have closely similar physical and chemical properties. Indeed, they may differ as greatly as do structural isomers. The explanation of this fact is that two systems formed from diastereomeric substances cannot be either identical with, or mirror images of, each other under any conceivable circumstances. Thus, each of the optically active tartaric acids melts at 187°C, whereas *meso*-tartaric acid melts at 143°C; maleic acid melts at 130.5°C and loses water at 160°C to form an anhydride, whereas fumaric acid melts at 287°C and forms no anhydride, except under such vigorous conditions that it is transformed into the anhydride of *maleic* acid; the two diastereomeric bromomalic acids with structure IV are hydrolyzed in basic solution at rates which differ by a

$$\mathrm{HO_2C{-}CHOH{-}CHBr{-}CO_2H}$$

IV

factor of more than a thousand; and at 18°C the first ionization constant of either (+)- or (−)-tartaric acid is approximately 1.2×10^{-3}, whereas that of *meso*-tartaric acid is approximately 0.78×10^{-3}. Further similar examples could be given almost without limit.

5·11 *Meso* Forms. As with the tartaric acids, it frequently happens that a set of stereoisomers contains both optically active and optically inactive members. The inactive members of such sets are frequently distinguished from their active isomers by being called *meso forms.* This is, of course, the significance of the name "*meso*-tartaric acid." *Meso* forms are often referred to as *internally compensated,* since their individual molecules can (in thought) be divided into two halves, each of which is dissymmetric and the mirror image of the other half; the rotatory powers of these two halves therefore exactly cancel each other, so that the entire molecule is inactive. (However, see pages 191 f.) Like any other optically inactive substance, a *meso* form must consist of molecules which are identical with their own mirror images, and which therefore contain alternating axes of some order.

5·12 Racemic Modifications. An equimolecular mixture of two enantiomorphs is, of course, optically inactive; such a mixture is known as a *racemic modification.* A racemic modification is sometimes said to be *externally compensated.* (Cf. the internally compensated *meso* forms.) Any process by which an optically active substance is transformed into the corresponding racemic modification is known as a *racemization;* conversely, any process by which a racemic modification is separated into the two enantiomorphs is known as a *resolution.* (Further discussion, with examples, of both racemization and resolution is given in the following chapters.)

A solid racemic modification, like any other similar mixture of different substances, may belong to any one of three distinct types. In the first place, it may be a *conglomerate* or *racemic mixture,* consisting of separate, although usually indistinguishable, crystals of the two enantiomorphs; in the second place, it may be a *solid solution* (sometimes called a *pseudoracemic mixed crystal*), consisting of a single homogeneous phase in which the molecules of the two enantiomorphs are distributed more or less at random; and finally, it may be a *compound* or *racemate,* formed between the two enantiomorphs.

The three possibilities may be experimentally distinguished in several different ways. One of the theoretically simplest of these ways requires the use of melting-point-composition curves in the usual manner.[24] The procedure consists in plotting the melting points of mixtures of the two enantiomorphs against the composition. In this way, curves of the types shown in Figures 5·10, 5·11, 5·12, and 5·13 could be obtained. Figure 5·10 shows the nature of the results to be expected if the racemic modification is a conglomerate or mixture. The composition at which the melting point is lowest must then correspond to the racemic mixture itself, containing exactly equal amounts of the two enantiomorphs; as in any such diagram, this composition is that of the *eutectic* mixture. Figure 5·11 shows the relation between melting point and composition

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[24] H. W. B. Roozeboom, *Z. physik. Chem.* **28**, 494 (1899).

which obtains if the racemic form is a solid solution. The curve need not, however, be perfectly horizontal, as in this figure, since it could either rise to a low maximum or descend to a shallow minimum at the midpoint; there can, however, be no *sharp* minimum (as in Figure 5·10) which would correspond to a eutectic. Figures 5·12 and 5·13 show two different possibilities that could arise if a compound, or racemate, were formed between the enantiomorphs. In Figure 5·12, the compound melts at a higher temperature, and in Figure 5·13 it melts at a lower temperature than does either optically pure enantiomorph; in each of these last two curves, there are two sharp minima, which correspond, respectively, to the eutectics between the compound and the two enantiomorphs.

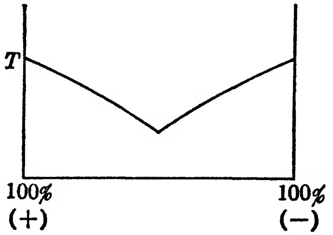

FIGURE 5·10. Melting-point–composition curve for a pair of enantiomorphs which form a conglomerate or mixture.

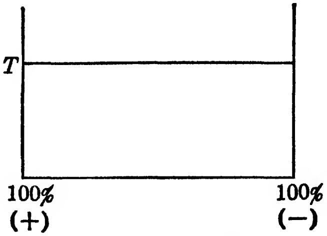

FIGURE 5·11. Melting-point–composition curve for a pair of enantiomorphs which form a solid solution or mixed crystal.

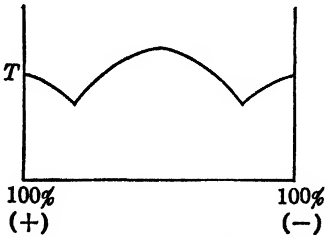

FIGURE 5·12. Melting-point–composition curve for a pair of enantiomorphs which form a *higher*-melting compound or racemate.

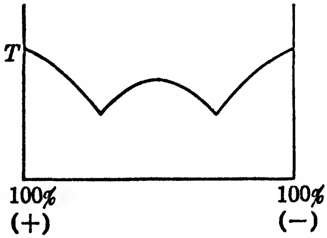

FIGURE 5·13. Melting-point–composition curve for a pair of enantiomorphs which form a *lower*-melting compound or racemate.

Another important method by which racemic mixtures, solid solutions, and compounds can be distinguished, but which need not be described further here, is based upon the study of solubility relationships.[24,25]

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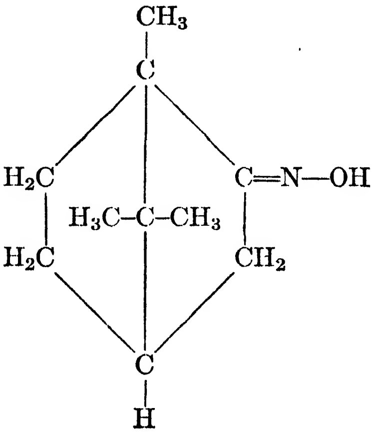
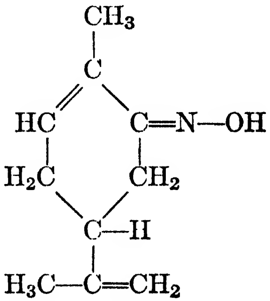
[25] G. Bruni, *Gazz. chim. ital.* **30**, 35 (1900).

In one way or another, examples of all possible types of racemic modifications have been discovered. Sodium ammonium tartrate forms a conglomerate at temperatures below about 27°C, and a compound at higher temperatures. On the other hand, with rubidium tartrate, the compound is stable below about 40°C, and the mixture is stable above that temperature. The two enantiomorphic forms of camphor oxime, I, form a continuous series of solid solutions which, regardless of the composition, melt at a constant temperature of 118°C, as in Figure 5·11; at temperatures below 103°C, however, the solution changes to a compound. Carvone oxime, II, likewise forms a series of solid solutions, which, however, have a maximum melting point when equal amounts of the dextro- and levorotatory forms are present. Racemic dimethyl tartrate, III, and mandelic acid, IV, are compounds which melt at higher and at lower temperatures, respectively, than do the optically pure enantiomorphs (as in Figures 5·12 and 5·13, respectively); whereas racemic N-benzoyltetrahydroquinaldine, V, is a compound which melts at almost exactly the same temperature as do the enantiomorphs. In



I



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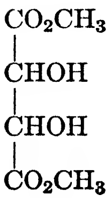
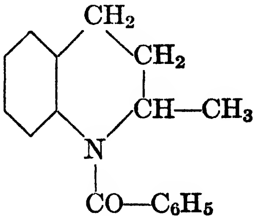


$$\begin{array}{l} CO_2CH_3 \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CO_2CH_3 \end{array}$$

III

$C_6H_5—CHOH—CO_2H$

IV



V

general, racemic compounds appear to be more common than either conglomerates or solid solutions.

Evidence regarding the existence of racemic compounds in the *liquid* state is not completely conclusive. Probably the most reliable way of studying this question involves the examination of the extent to which the maximum in the melting-point-composition curve is rounded. In general, the more rounded this maximum is, the greater is the dissociation of the compound into its components in the liquid phase at the melting point. In this way, the dissociation has been estimated in several instances to be appreciable, but not complete.[26] Such a method, however, can provide no information regarding the degree of dissociation at temperatures much above the melting point. Determinations of the apparent molecular weights of racemic forms in solution have been consistent with the assumption of complete dissociation under such circumstances [27] (except in so far as substances containing free hydroxyl or amino groups, or the like, are associated as a result of the presence of intermolecular hydrogen bonds. Cf. Section 2·6.) On the other hand, the fact that the color of Fehling's solution that is made from racemic tartaric acid is appreciably different from the color of an equivalent solution which is made from dextrorotatory tartaric acid [21,28] strongly suggests that, in racemic Fehling's solution, the enantiomorphic forms are in some way combined with each other. There is, however, no evidence which supports the existence of *gaseous* racemic compounds.[29]

Occasionally, a racemic modification is spoken of as a definite substance, as if it were distinguishable from the enantiomorphs of which it is composed. Such a mode of description is, however, not really correct. If the racemic modification is a compound, it has a greater molecular weight than does either enantiomorph, and so it is not strictly an isomer of the enantiomorphs; on the other hand, if it is not a compound, then it is not a single pure substance, but a (stoichiometric) mixture of the two enantiomorphs. Although, in the latter event, the racemic modification might be described as a stereostoichiomer, and hence also as a stereoisomer (see page 130), of the enantiomorphs, such a description would be both inconvenient and confusing. Consequently, in this book, racemic modifications will not be treated as additional stereoisomeric forms.

A racemic modification can conveniently be designated by any one of the prefixes *r*-, *dl*-, DL-, or (±)-. Thus, racemic tartaric acid is, respectively, *r*-tartaric acid, *dl*-tartaric acid, DL-tartaric acid, or (±)-tartaric acid. All four representations are encountered in the current chemical literature.

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[26] J. D. M. Ross and I. C. Somerville, *J. Chem. Soc.* **1926**, 2770.

[27] See, for example, R. Anschütz, *Ann.* **247**, 111 (1888); P. Frankland and R. H. Pickard, *J. Chem. Soc.* **69**, 123 (1896).

[28] A. Byk, *Z. physik. Chem.* **49**, 641 (1904); *Ber.* **37**, 4696 (1904).

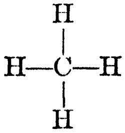
[29] See, for example, R. Anschütz, *Ber.* **18**, 1397 (1885).

6.

The Configurations of Carbon Compounds

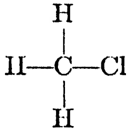
6·1 The Tetrahedral Carbon Atom. The above extremely general considerations require no assumptions in regard to the exact geometrical forms of the molecules under discussion. Such assumptions become necessary, however, when the attempt is made to account for the observed numbers of stereoisomers corresponding to each structural formula. The first successful theory based upon explicit geometrical assumptions was brought forth simultaneously and independently in 1874 by van't Hoff [1] and by Le Bel.[2] (Cf. Section 5·1.) The ideas of van't Hoff were somewhat more definite than were those of Le Bel, but they differed in no respect important to this discussion. The following development does not follow very closely either van't Hoff's or Le Bel's treatment; its purpose is instead to present the fundamental principles in logical, and not necessarily in historical, order.

For the molecular formula CH_4, only the single structure I can be



$$\begin{array}{ccc} & H & \\ & | & \\ H- & C & -H \\ & | & \\ & H & \end{array}$$

I



$$\begin{array}{ccc} & H & \\ & | & \\ H- & C & -Cl \\ & | & \\ & H & \end{array}$$

II

drawn if, as usual, carbon and hydrogen are considered to be, respectively, quadrivalent and univalent; and only the single substance, methane, is known. Similarly, for the formula CH_3Cl, only the single structure II can be drawn, and only the single substance, methyl chloride, is known. Now, if one hydrogen atom in methane were in any respect different from any one of the others, the substance produced by the replacement of the first hydrogen atom by a chlorine atom should be different from the one produced by the replacement of the second hydrogen atom. Consequently, at least two distinct substances CH_3Cl should exist. The fact that only one such substance is known strongly

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[1] J. H. van't Hoff, *Bull. soc. chim.* [2] **23**, 295 (1875); *The Arrangement of Atoms in Space*, 2nd ed. (translated by A. Eiloart), Longmans, Green, and Company, London, 1898.

[2] J. A. Le Bel, *Bull. soc. chim.* [2] **22**, 337 (1874).

suggests, therefore, that all four hydrogen atoms of methane are completely equivalent to each other, not only structurally (cf. Section 4·1), but also geometrically.

Alternative interpretations of the existence of only one substance with the formula CH_3Cl can be imagined. Thus, it might be that several different substances with this formula are theoretically possible, but that only one is stable enough to be isolated; or it might be that the various substances are too closely similar in all their properties to be separated or distinguished from one another; or it might be that additional isomers could be obtained if only suitable methods of preparation could be discovered; and so on. At one time, chemists made serious efforts to establish beyond question the complete equivalence of the four hydrogen atoms of methane. Thus, in various series of reactions, they replaced these atoms systematically and one at a time; they hoped to prove in this way that, no matter which hydrogen atom is replaced by a given substituent atom or group, the same product results. It is now recognized, however, that this work was of no significance, because it involved the implicit assumption that, in a chemical reaction, the principle of minimum *configurational*, as well as structural, change is valid. As will be discussed later in much greater detail (see Section 7·8), the phenomenon known as the *Walden inversion* shows conclusively that such an assumption is absolutely inadmissible. However, as a matter of historical interest, the reaction map of Figure 6·1 is given here in order to show the reactions employed in the "proof" that only a single nitromethane CH_3NO_2 can exist.[3] In this map, the positions in space of the four substituents joined to the central carbon atom are designated schematically in the plane figures as to the right of, to the left of, above, and below the carbon atom, respectively. The true geometrical significance of the four positions thus represented is not involved in the argument.

As a matter of fact, even if the principle of minimum configurational change were valid, the above proof would still be incomplete, since there would then be no assurance that, in the reaction which gives tricarboethoxymethane, at the lower left-hand corner of the map, the hydrogen atom replaced by the carboethoxyl group is the one stated; or, in other words, that it is the same one which is replaced in the reaction which gives chloromalonic ester, at the lower right-hand corner of the map.

The most satisfactory evidence supporting the belief that all the hydrogen atoms of methane are equivalent is doubtless the fact that, in spite of the tremendously large number of known organic compounds, there has never been encountered more than one substance CH_3R, where R is any specified atom or group unless, of course, R is sufficiently com-

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[3] L. Henry, *Compt. rend.* **104**, 1106 (1887).

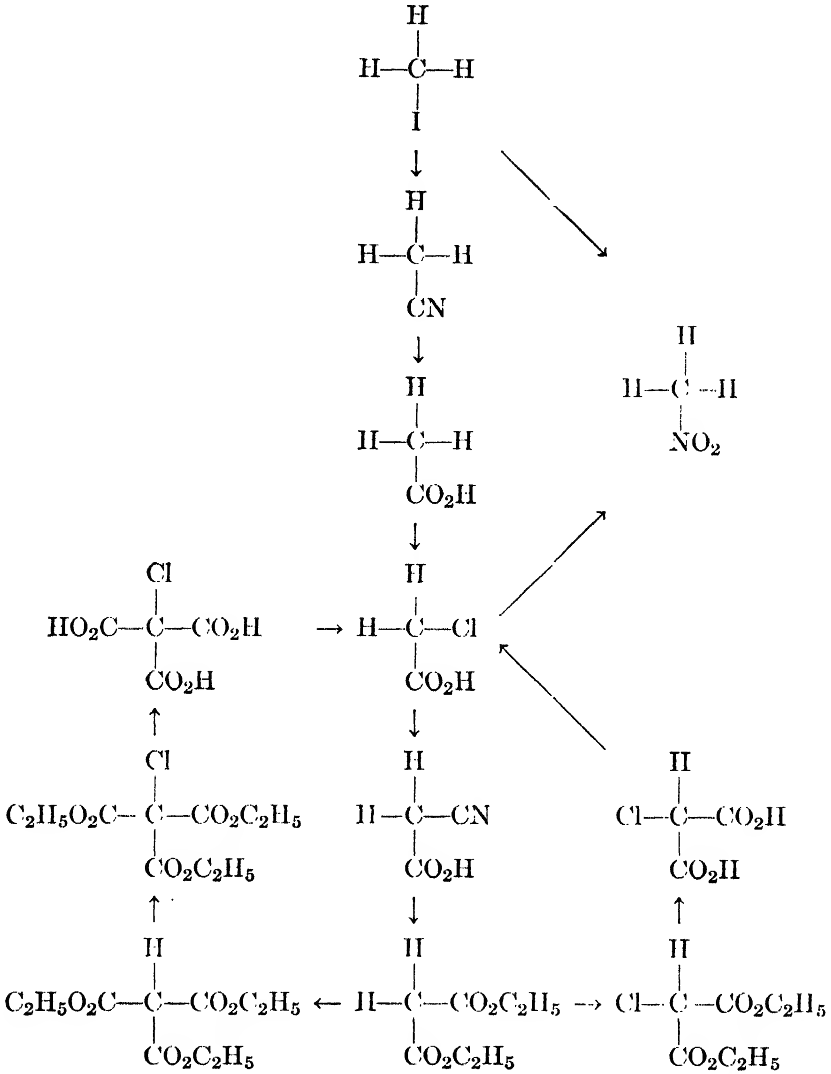
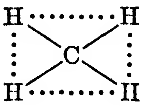


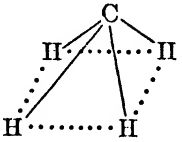
FIGURE 6·1. Reactions carried out in the attempt[3] to prove the equivalence of the four hydrogen atoms in methane.

plex to permit isomerism within itself. Thus, there is only one CH_3Cl or CH_3NO_2 (as has already been mentioned), only one CH_3F, only one CH_3Br, only one CH_3I, only one CH_3CO_2H, only one $CH_3—CH_3$, and so on almost without limit. For this reason, no chemist now seriously considers the possibility of nonequivalent hydrogen atoms in methane.

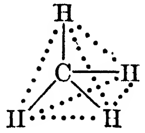
The requirement that all four hydrogen atoms of methane be geometrically equivalent restricts the atomic arrangements to the following: (1) The hydrogen atoms might lie at the corners of a rectangle, with the carbon atom at the center, as in diagram III. The dotted lines outlining the rectangle are given only for the sake of clarity; they do not represent valence bonds of any kind. This model is known as the *planar* model. (2) The hydrogen atoms might lie at the corners of the base of a square pyramid, with the carbon atom at the apex, as in diagram IV. It should be noted that, if the base of the pyramid were rectangular rather than square, two enantiomorphic forms of each monosubstituted derivative CH_3R would be possible. Such a configuration can therefore be excluded. The dotted lines are again given only for the sake of clarity.



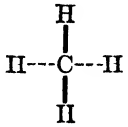
III



IV



V



$$\begin{array}{c} H \\ | \\ H{-}{-}{-}C{-}{-}{-}H \\ | \\ H \end{array}$$

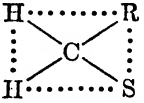
VI

This model is known as the *pyramidal* model. (3) The hydrogen atoms might lie at the corners of a tetrahedron, with the carbon atom in the center, as in diagram V. The dotted lines which outline the imaginary tetrahedron are given, as before, only for the sake of clarity. A more convenient, but equivalent, representation of this so-called *tetrahedral* model, which is employed throughout the remainder of this book, is shown in diagram VI. The two broken lines here represent valence bonds to hydrogen atoms lying behind the plane of the paper; the two heavy lines represent bonds to hydrogen atoms lying in front of the plane of the paper. The equivalence of the hydrogen atoms does not require that the tetrahedron be a regular one, just as, in the planar model, it does not require that the rectangle be a square; only certain, rather symmetrical, types of tetrahedron, however, are satisfactory.

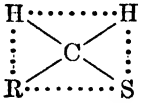
It is perhaps not entirely logical to distinguish the configurations IV and V (or VI) by the respective designations "pyramidal" and "tetrahedral," since a tetrahedron is merely one special kind of pyramid (i.e., a triangular pyramid). Consequently, both the configurations IV and V (or VI) are really pyramidal. Throughout this book, however, a configuration will be described as pyramidal only if the multivalent atom is to be regarded as lying at an *apex* of the pyramid, and never if this atom is to be regarded as located instead at the *center* of the pyramid. This arbitrary distinction is here made in order that conventional terminology may be followed to the greatest possible extent.

The decision among the planar, pyramidal, and tetrahedral models is made possible by a consideration of the numbers of isomeric substances

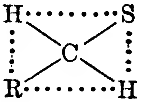
CH_2RS, where R and S represent any two specified, but not necessarily different, atoms or groups. Only one known substance, methylene chloride, corresponds to the formula CH_2Cl_2; only one, chloroacetic acid, corresponds to the formula CH_2Cl—CO_2H; and so on. For no formula of this type is more than a single substance known unless, as before, the groups R and S permit isomerism within themselves. Now, the planar model would lead to the three distinct spatial arrangements, or *configurations*, VII, VIII, and IX, of which VII and VIII are identical if the rectangle is a square. Since, however, the configuration IX cannot be identical with VII or VIII under any circumstances, this model requires the existence of at least two stereoisomeric forms and so can be excluded from further consideration.



VII



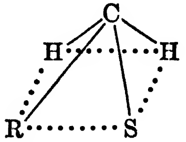
VIII



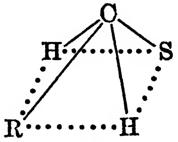
IX

It might be suggested that methane does indeed have the planar configuration, but that, in the derivative CH_2RS, transition among the configurations VII, VIII, and IX is easy. The existence of only a single isolable substance CH_2RS would then be explained, but the existence of stereoisomers in those other instances in which they do occur could not be explained. Consequently, this alternative interpretation can here be ruled out, although one analogous to it will be invoked later in connection with the stereochemistry of trivalent nitrogen. (See Section 8·2.)

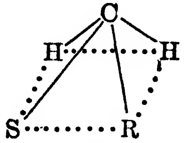
The pyramidal model, like the square planar one, might be expected to permit two stereoisomeric substances CH_2RS since, corresponding to this molecular model, the two configurations X and XI are possible. If R and S are not identical, however, the configuration X is dissymmetric, and so its nonsuperposable mirror image (enantiomorph), XII, represents still a third stereoisomer. Since isomerism has never been observed with structures of this type and, since, moreover, optical activity has never been encountered, the inference can be drawn that the pyramidal model also is incorrect. Again, the assumption of an easy transition



X



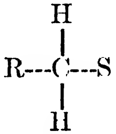
XI



XII

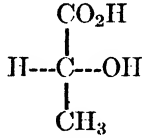
among the configurations X, XI, and XII cannot be reconciled with the occurrence of stereoisomerism in other instances.

Only the tetrahedral model remains. If the tetrahedron is regular, this model permits only a single substance CH_2RS, whether R and S are identical or different. (Once more, R and S must be assumed not to allow isomerism within themselves.) In particular, the configuration XIII is symmetrical, since it has a plane of symmetry passing through R, S, and C; hence no optical activity is possible, and no enantiomorphs can exist. The regular tetrahedral model is therefore consistent with the experimentally observed numbers of isomers. The irregular tetrahedral model, on the other hand, permits too many isomers and so can be excluded.



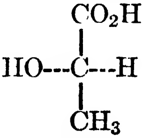
$$\begin{array}{c} H \\ | \\ R\text{---}C\text{---}S \\ | \\ H \end{array}$$

XIII



$$\begin{array}{c} CO_2H \\ | \\ H\text{---}C\text{---}OH \\ | \\ CH_3 \end{array}$$

XIV



$$\begin{array}{c} CO_2H \\ | \\ HO\text{---}C\text{---}H \\ | \\ CH_3 \end{array}$$

XV

The regular tetrahedral model is therefore the only one that is in agreement with the observed numbers of isomers; consequently, it must be considered correct. Confirmation of this model is provided by the fact that it correctly predicts the occurrence of optical activity, and hence also the existence of enantiomorphs, with substances of formula CPRST, where no two of the atoms or groups P, R, S, and T are identical. Lactic acid CH_3—CHOH—CO_2H, for example, occurs in enantiomorphic dextro- and levorotatory forms (and also, of course, as an optically inactive racemic modification). For the molecules of these substances, the nonsuperposable, mirror-image configurations XIV and XV are possible. One of these configurations must therefore represent the molecule of the dextrotatory lactic acid, whereas the other must represent that of the levorotatory form; however, there is at present no way of deciding with complete certainty which configuration belongs to which isomer. (Cf., however, Section 7·13.) The existence of the two stereoisomeric lactic acids shows that the spatial configuration about a carbon atom is stable, and that the above suggestion of an easy interconversion among the configurations can be ruled out.

The conclusions reached above have recently been confirmed by various kinds of physical evidence. Studies of spectra[4] and of x-ray[5] and

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[4] See, for example, G. Herzberg, *Infrared and Raman Spectra of Polyatomic Molecules*, D. Van Nostrand Company, New York, 1945.

[5] See, for example, W. H. Bragg and W. L. Bragg, *Proc. Roy. Soc.* (London), **A89**, 277 (1913); F. J. Llewellyn, E. G. Cox, and T. H. Goodwin, *J. Chem. Soc.* **1937**, 883.

electron [6] diffraction have shown that a saturated carbon atom is indeed tetrahedral, in the sense that the four single bonds which it forms are directed toward the corners of a tetrahedron, of which it occupies the center. The tetrahedron itself, of course, is only an intellectual construction without physical reality. Moreover, the tetrahedron has been found [4, 5, 6] to be regular (or very nearly regular), so that the angle between any two of the single bonds that are formed by the central carbon atom has the so-called *tetrahedral value* of 109° 28′ (or very nearly that value). When the four atoms or groups joined to the carbon atom are of the same kind, as in methane CH_4 or carbon tetrachloride CCl_4, the tetrahedron seems always to be strictly regular; but, when the atoms or groups are not of the same kind, as in methylene chloride CH_2Cl_2, small distortions may occur. Thus, in methane [4] and carbon tetrachloride,[6] each H—C—H and Cl—C—Cl bond angle, respectively, is exactly 109° 28′; but in methylene chloride,[6b] the Cl—C—Cl angle is found instead to be about 112°. The spreading of the angle here can be explained on the assumption that the repulsion between the relatively large chlorine atoms is greater than either that between the chlorine atoms and the much smaller hydrogen atoms or that between the two hydrogen atoms.

As mentioned above, an irregular tetrahedral model would apparently allow the existence of a greater number of stereoisomers than is observed; nevertheless, it may be presumed that no small distortion of the type found in methylene chloride can give rise to a greater number of isomers than could be accounted for by the perfectly regular model. This conclusion follows because all the various configurations which appear to be permitted by the irregular model are so nearly identical that, at every instant, an appreciable fraction of the molecules must have enough energy to undergo the transition from any one form to any other. (Cf. Section 6·6 for a more detailed discussion of the rather analogous situation which arises in connection with free rotation.) Moreover, since the distortion of the tetrahedron in methylene chloride is presumably due primarily, as was just noted, to the mutual repulsions of the two chlorine atoms, the one observed configuration (in which the chlorine-chlorine distance is greater than it would have been if the tetrahedron were not distorted) must be considerably more stable than is any other configuration (in which that distance is smaller than it would have been if the tetrahedron were not distorted).

It is not strictly correct to speak of the atoms in a molecule as if they occupy definitely fixed positions; for, as is now known,[4] the atoms are constantly vibrating with respect to one another about their positions of minimum potential energy.

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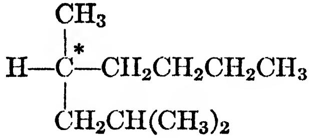
[6] See, for example, L. O. Brockway, (*a*) *Rev. Modern Phys.* **8**, 231 (1936); (*b*) *J. Phys. Chem.* **41**, 747 (1937).

The bond angles and interatomic distances, which are mentioned both here and below, therefore oscillate slightly, but very rapidly, about their respective average values. The molecular shapes and sizes, whether they are derived by studies of isomer numbers or by physical methods, refer of course to these average bond angles and interatomic distances.

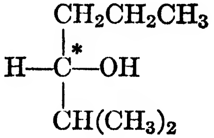
6·2 Asymmetric Carbon Atoms. A carbon atom is said to be *asymmetric* if it is joined to four nonequivalent atoms or groups. Thus, of the three carbon atoms in the above-mentioned lactic acid (configurations XIV and XV on page 166), the central one is seen to be asymmetric. (The terminology here is correct since an "asymmetric" carbon atom possesses no element of symmetry and so is actually asymmetric, and not merely dissymmetric.) The majority of all known optically active substances consist of molecules which contain one or more asymmetric carbon atoms. However, the presence of such atoms is neither necessary nor sufficient for optical activity. As will be discussed later in this chapter, many substances which contain no asymmetric atoms are active; and, conversely, many others which do contain asymmetric atoms are inactive. Optical activity is caused by the dissymmetry of each individual molecule as a whole; the presence or absence of asymmetric atoms is important only in so far as it determines the symmetry or dissymmetry of the molecules.

It is of interest to consider the question how similar two atoms or groups may be without destruction of the asymmetry of a carbon atom to which they are attached. *Structurally isomeric* groups are found to be sufficiently different to permit asymmetry, as is shown, for example, by the observed optical activities of the hydrocarbon, I,[7] and alcohol,



$$\begin{array}{l} \mathrm{CH_3} \\ \ | \\ \mathrm{H{-}\overset{*}{C}{-}CH_2CH_2CH_2CH_3} \\ \ | \\ \mathrm{CH_2CH(CH_3)_2} \end{array}$$

I



$$\begin{array}{l} \mathrm{CH_2CH_2CH_3} \\ \ | \\ \mathrm{H{-}\overset{*}{C}{-}OH} \\ \ | \\ \mathrm{CH(CH_3)_2} \end{array}$$

II

II.[8] In the former substance, the asymmetric carbon atom, designated by the asterisk, carries both a *n*-butyl and an isobutyl group; in the latter, it carries both a *n*-propyl and an isopropyl group. Structurally identical but *configurationally isomeric* groups are likewise sufficiently different to permit the occurrence of stereoisomerism, although not always of optical activity. Further discussion of such situations must, however, be postponed until later. (See Section 6·10.)

Two atoms of *different elements* are clearly nonequivalent in the sense

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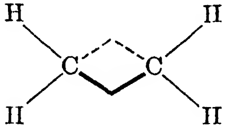
[7] P. A. Levene and R. E. Marker, *J. Biol. Chem.* **92**, 455 (1931).

[8] P. D. Bartlett, M. Kuna, and P. A. Levene, *J. Biol. Chem.* **118**, 503 (1937).

now under discussion. However, two atoms of different *isotopes* of the same element are much more similar, and it is not certain whether they are sufficiently different to permit retention of the asymmetry of an atom to which they are attached. A number of attempts have been made [9] to prepare an optically active substance, the molecules of which owe their dissymmetry to the difference between hydrogen and deuterium. All such attempts have failed.[9a] On theoretical grounds, however, it may be presumed that substances of this type should nevertheless be active, even though their optical rotations might be too small to be observable by present methods.

6·3 The Configurations of Olefinic Compounds. van't Hoff assumed that the carbon atoms in unsaturated compounds have the same tetrahedral form as do those in the saturated substances. The configuration of ethylene thus becomes I. If this configuration is correct,



I

the six atoms in the molecule lie in the same plane (the plane of the paper in diagram I), the H—C—H bond angles have the tetrahedral value of 109° 28′, the C—C—H angles (or, more precisely, the angles between the carbon-hydrogen bonds and the straight line passing through the carbon atoms) is 125° 16′, and the carbon-carbon distance is 0.58 times that in ethane CH_3—CH_3.

Although erroneous in some respects (see below), van't Hoff's configuration of ethylene is correct in all essential stereochemical details. In particular, it leads to correct predictions of the numbers of stereoisomeric forms of suitably substituted ethylenes. Indeed, its stereochemically significant features can be deduced directly, but not quite rigorously (see Section 6·4), from considerations of isomer number alone, and without reference to the tetrahedral carbon atom. As in the above discussion of the saturated compounds, the assumption must be made here also that, for each structural formula considered, all the theoretically possible stereoisomers are known. The fact that ethylene is the only known substance with the molecular formula C_2H_4 shows that the lines bisecting the two H—C—H angles must lie along continuations of the line joining the carbon atoms; otherwise, at least two stereoisomeric

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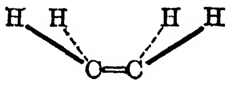
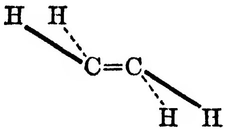
[9] See H. C. Brown and C. Groot, *J. Am. Chem. Soc.* **64**, 2563 (1942), and further references given there.

[9a] However, see E. R. Alexander and A. G. Pinkus, *J. Am. Chem. Soc.* **71**, 1786 (1949).

substances, with configurations like II and III, should be possible. (For



II



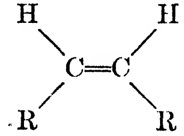
III

the sake of both simplicity and generality, the geometrical arrangement of the two bonds constituting the double bond is here not indicated explicitly.) Moreover, the planes defined by the two CH_2 groups must be either identical with, or at right angles to, each other, since otherwise the molecule would be dissymmetric and the substance would be optically active. Finally, the decision between the planar and perpendicular models can be made by a consideration of the nature of the isomeric substances with structure IV, in which, as before, R is any spec-

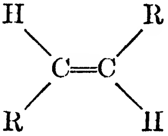
$$RCH{=}CHR$$

IV

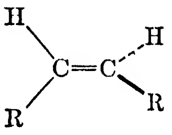
ified atom or group which does not permit isomerism within itself. The planar model permits the two configurations V and VI, whereas the perpendicular model permits the configurations VII and VIII. Now, the configurations V and VI must represent optically inactive diastereomers



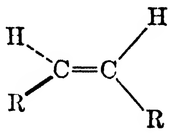
V



VI



VII

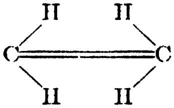


VIII

since, with each, the plane of the molecule is a plane of symmetry; on the other hand, the configurations VII and VIII must represent a pair of enantiomorphs since they are nonsuperposable mirror images of each other. In the particular case in which R is the carboxyl group CO_2H, two substances, fumaric and maleic acids, are known; as was stated above (Section 5·10), each of these acids is optically inactive, and the two differ markedly in nearly all their properties. Consequently, they must be diastereomers and cannot be enantiomorphs. Since numerous further examples of similar type are known, and since optical activity has never been encountered in substances with structure IV, unless R represents a dissymmetric group, the planar model must be correct, as was assumed by van't Hoff.

From considerations of isomer numbers alone, no information can be obtained regarding the values of the bond angles or of the interatomic distances in ethylene and its derivatives (see the following paragraph); consequently, the angles and distances derived from van't Hoff's configuration, with the tetrahedral carbon atoms, cannot be verified by purely chemical procedures. Recent physical investigations[4] have shown, however, that it is precisely in such respects that van't Hoff's model is incorrect. Thus, in ethylene, the H—C—H and C—C—H angles are more nearly equal to 120° than to 109° 28′ and 125° 16′, respectively, and the carbon-carbon distance is more nearly 0.87 than 0.58 times that in ethane. Moreover, the modern quantum-mechanical picture of the double bond[10] is rather different from that provided by the tetrahedral model, I. Nevertheless, these defects in no way limit the usefulness of the simple model for the prediction and interpretation of the observed numbers of stereoisomers.

The impossibility of determining, by the classical stereochemical methods, the exact values of either the bond angles or the bond lengths in ethylene becomes especially apparent if it is realized that the further planar configuration, IX, is also entirely consistent with the observed isomer numbers. This configuration is superficially very different from van't Hoff's original configuration, I, and also from the slightly modified one derived by the physical methods just mentioned. Nevertheless, all three configurations are stereochemically equivalent, since they all lead to the same predicted isomer numbers.



IX

6·4 An Alternative Model of Ethylene.[11] An interesting alternative model of ethylene is one where the four hydrogen atoms lie at the corners of a rectangle (which is *not* a square); and where the two carbon atoms lie at equal distances from, but on opposite sides of, the plane defined by the hydrogen atoms. The line joining the carbon atoms passes through the center of the rectangle and is perpendicular to its plane. The assumed shape of the molecule can then be described as a somewhat irregular octahedron; it can be represented by the figure obtained when two equal rectangular pyramids are placed base to base. The hydrogen atoms are located at the four corners of the rectangular "girdle" of this figure, whereas the carbon atoms are located at the two remaining corners. If this model were correct, the molecule could have any one of the four apparently nonequivalent configurations

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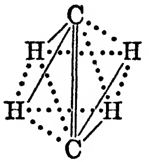
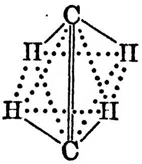
[10] E. Hückel, *Z. Physik* **60,** 423 (1930); W. G. Penney, *Proc. Roy. Soc.* (London) **A144,** 166 (1934); **A146,** 223 (1934).

[11] The author is indebted to Professor J. K. Senior for calling his attention to this interesting model.

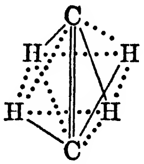
I, II, III, and IV, in which the dotted lines serve merely to outline the figures, and



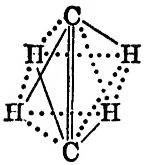
I



II



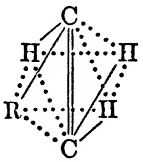
III



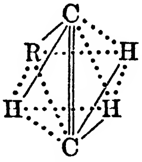
IV

in which only the full lines represent valence bonds. (It is somewhat ambiguous whether these diagrams should be called "configurations" or "structures.") In diagram I, each carbon atom is bonded to two hydrogen atoms at the ends of a short side of the rectangular girdle; in II, each carbon atom is bonded to two hydrogen atoms at the ends of a long side of the girdle; and in III and IV, each carbon atom is bonded to two diagonally opposite hydrogen atoms. These last two diagrams are dissymmetric, and are mirror images of one another.

Clearly, this alternative model is not in agreement with the facts, since only a single, optically inactive form of ethylene is known. Moreover, even though this objection could be answered by the assumption that all forms except, say, the symmetrical one, I, are unstable and hence cannot exist, several further difficulties still remain. Thus, if ethylene were really describable by diagram I, then every monosubstituted ethylene $CH_2{=}CHR$ should be separable into the two enantiomorphic forms V and VI. Moreover, if ethylene were describable by the likewise symmetrical



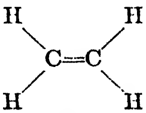
V



VI

diagram II, rather than by I, the situation would be completely analogous. Since no compounds of this type have ever been resolved, unless the substituent R is itself dissymmetric, the unavoidable conclusion is that no one of the diagrams I–IV can represent ethylene.

The reader may have wondered why such an unlikely and generally unsatisfactory model of ethylene has been mentioned here at all. The reason is that, if the valence bonds are considered (in the sense defined below) to be *not real*, then the model under consideration turns out to be indistinguishable, by any method making use only of isomer numbers, from the planar one, VII, which was proposed by van't Hoff

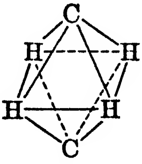


VII

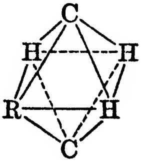
(cf. Section 6·3), and which is now considered to be correct. (However, see the next-to-last paragraph of this section.) Now, diagrams I–IV differ from one another only in the positions of the valence bonds, and not at all in those of the individual atoms; in other words, the hypothetical molecules to which they refer are made nonsuperposable, and hence nonequivalent, only by their differences in the positions of the bonds. Consequently, if these differences were considered not to be significant, the four diagrams would be equivalent and therefore capable of representing the one known, and optically inactive, form of ethylene. Moreover, the two enantiomorphic diagrams, V and VI, would then likewise be equivalent, and therefore similarly capable of representing the one known, and optically inactive, monosubstituted ethylene $CH_2{=\!=}CHR$. Thus, by the assumption that the bonds are not real (i.e., by the assumption that it is immaterial which pair of atoms is linked by each bond), the alternative model of ethylene is brought into agreement with the observed numbers of isomeric unsubstituted and monosubstituted ethylenes.

It may, of course, be argued that the positions of the valence bonds cannot legitimately be ignored, since they represent positions of relatively high average electronic density (see Section 1·8), and since they therefore have definite physical significance. This objection is, however, not valid. Although, for example, the four diagrams I–IV must represent four different distributions of electronic charge, they are so closely similar that they can hardly correspond to four separable and distinguishable isomeric substances. (See Section 4·4 for a discussion of the analogous problem presented by the nonoccurrence of all the isomeric disubstituted benzenes C_6H_4RS, which are apparently required by the Kekulé structure.) From an elementary viewpoint, which is now somewhat out of date, the four substances I–IV would be expected to exist in an extremely mobile tautomeric equilibrium with one another (cf. Chapter 14); from a more recent, and presumably better, viewpoint, only a single substance with a charge distribution intermediate among those represented by the diagrams I–IV could exist. (See Chapter 10.) In either event, each of the two carbon atoms would necessarily (at least, on the average) be related in exactly the same way to each of the four hydrogen atoms; consequently, the differences which distinguish the diagrams I–IV from one another, and which make III and IV dissymmetric, cannot be significant. Similarly, the differences which distinguish the further diagrams V and VI from one another, and which make each of these dissymmetric, likewise cannot be significant. It therefore follows that, in the special sense defined above, the bonds cannot be real, and hence also that only the relative positions of the various atoms need be considered when the isomers are counted.

A corollary of the above considerations is that the four diagrams I–IV can be replaced by the single one VIII, in which only the figure is outlined, and no valence bonds are represented explicitly. The broken lines here represent the edges of the octahedron which are behind the figure. A molecule with this geometrical form is clearly not dissymmetric since it has several planes and one center of symmetry. Similarly, the one known monosubstituted derivative $CH_2{=\!=}CHR$, with given substituent R, can be represented by the corresponding symbol IX; again the molecule cannot be dissymmetric since it has a plane of symmetry passing through the three hydrogen atoms and through the substituent R. This diagram would, then, of

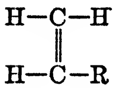


VIII



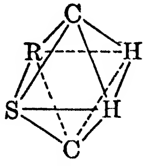
IX

course, replace the conventional one, X. Moreover, for a disubstituted derivative, the three isomeric forms, XI, XII, and XIII, are possible; since each of these has a

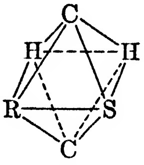


$$\begin{array}{c} H-C-H \\ \| \\ H-C-R \end{array}$$

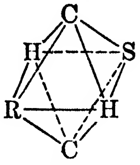
X



XI

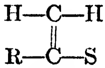


XII



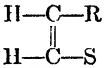
XIII

plane of symmetry passing through the two hydrogen atoms and through the two substituents R and S, none of them is dissymmetric. This conclusion is in complete accord with the observation that, for any given substituents R and S, exactly three optically inactive disubstituted derivatives are indeed obtained; these isomers are, of course, the ones ordinarily represented by the different diagrams XIV, XV, and



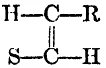
$$\begin{array}{c} H-C-H \\ \| \\ R-C-S \end{array}$$

XIV



$$\begin{array}{c} H-C-R \\ \| \\ H-C-S \end{array}$$

XV

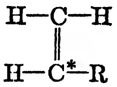


$$\begin{array}{c} H-C-R \\ \| \\ S-C-H \end{array}$$

XVI

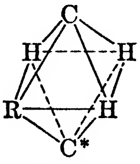
XVI. (Cf. Section 6·9.) As can easily be verified by an extension and continuation of such considerations, the model VIII of ethylene leads always to the same numbers of isomeric derivatives as does the conventional model, VII; even the nonoccurrence of optical activity is accounted for by the plane of symmetry which always passes through the four atoms or groups that are joined to the ethylenic carbon atoms.

Although the classical methods of using isomer numbers are therefore insufficient to distinguish between the models VII and VIII of ethylene, these methods can at the present time be extended in such a way that they become able in principle, although probably not in practice, to permit a definite decision between the two possibilities. Thus, if the model VII is correct, a molecule of a monosubstituted ethylene, in which the two carbon atoms are isotopically different, must have the symmetrical planar configuration XVII; consequently, the substance must be optically inactive. (The asterisk here indicates that the carbon atoms are experimentally

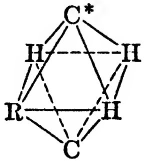


$$\begin{array}{c} H-C-H \\ \| \\ H-C^{*}-R \end{array}$$

XVII



XVIII

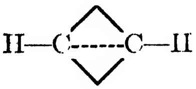


XIX

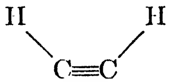
distinguishable.) On the other hand, if the alternative model, VIII, is correct, such a molecule must have one of the two dissymmetric and enantiomorphic configurations XVIII and XIX; consequently, the substance should be capable of optical activity. This conclusion follows because the plane defined by the three hydrogen atoms and by the substituent is now no longer a plane of symmetry since the two carbon atoms are no longer equivalent. There is, however, considerable reason to doubt that, under such circumstances, the racemic modification could be resolved by any method that is now known (cf. Section 7·2), and to doubt also that the optically pure enantiomorphs, even if they could be obtained, would have specific and molecular rotations which are large enough to be observed. (See Section 6·2 for a discussion of the analogous problem which arises in connection with the relatively much greater difference between hydrogen and deuterium.) It is, therefore, extremely improbable that any conclusive evidence either for or against the alternative model, VIII, could be obtained in the way just outlined.

An interesting situation has therefore been found to exist. For partly theoretical and partly practical reasons, the models VII and VIII of ethylene are at present indistinguishable by any method which makes use only of isomer numbers; consequently, the decision between these two models cannot be made without recourse to additional and entirely independent data. Following van't Hoff, all chemists have accepted the model VII, because it can be derived by the more logical extension of the concept of the tetrahedral carbon atom. Conclusive evidence that this model is the correct one was not obtainable, however, until the shape of the ethylene molecule was determined by the physical methods mentioned in the next-to-last paragraph of Section 6·3; in fact, on the basis of all the purely chemical evidence which is now available, or which seems likely to become available in the foreseeable future, van't Hoff's choice may well have been the wrong one. The existence of molecules like that of ethylene, for which unambiguous models cannot be derived from considerations of isomer numbers alone, introduces still a further limitation, of course, upon the use of such data for the determination of structures and configurations. (Cf. also the last paragraph of Section 4·6.)

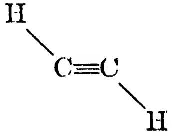
6·5 The Configurations of Acetylenic Compounds. van't Hoff[1] assumed that the carbon atoms in acetylene, like those in ethylene, are tetrahedral. He accordingly wrote the configuration of the former substance as I. In agreement with this linear model, no stereoisomers,



I



II



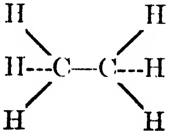
III

to which configurations like II and III must be assigned, have ever been encountered. (In diagrams II and III, as in the corresponding ones of the two preceding sections, the geometrical arrangement of the bonds constituting the multiple bond is not indicated explicitly.) Moreover, recent physical evidence[4] supports the linear arrangement of the atoms. Consequently, although van't Hoff's model of acetylene is inaccurate in several respects that are analogous to those in which his model of ethylene is inaccurate (see Section 6·3), it always leads to correct predictions of the numbers of isomers.

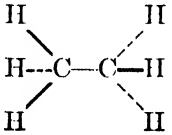
6·6 Free Rotation. Certain limitations must be imposed upon the general statement that two molecules always correspond to different substances unless they are exactly alike with respect to the relative positions in space of all their atoms. For structure I, for example, an infinite number of geometrical arrangements (or *conformations*) are consistent with the assumption of tetrahedral carbon atoms; these include the two represented by diagrams II and III, as well as all the further intermediate ones obtainable from either II or III by rotation of one CH_3 group with respect to the other about the carbon-carbon bond. If each of these conformations represented a distinct substance, then an infinite number of stereoisomers with the structure in question should exist; nevertheless, only a single substance, ethane, is known. Similar considerations apply to all further structures in which multivalent atoms are joined by single bonds. It is therefore evident that, if the geometrical interpretation of stereoisomerism is to be maintained, some further assumption, which restricts the predicted numbers of isomers, is required.

$$H_3C{-}CH_3$$

I



II



III

The assumption generally adopted for this purpose is contained in the rule that any two conformations (such as II and III, or any other two of the infinite number of possible ones) are to be considered equivalent if they differ only by the rotation of one or more parts of the molecule about one or more single bonds. Thus, the conformations II, III, etc., are equivalent; all these correspond to the same substance, ethane, and all are said to represent the same configuration. Although this rule has a number of exceptions (see Sections 6·12 and 6·13), it is sufficiently general to find application throughout stereochemistry. It has indeed already been assumed implicitly at several points in the preceding discussion, and it will be assumed throughout the following discussion without further comment, except, of course, in those instances in which it is not valid.

The equivalence of conformations which differ only by a rotation about a single bond is often described by the statement that the rotation is *free,* or that *free rotation* exists, about such a bond. Since the significance of the expression "free rotation" is often misunderstood, a brief discussion of the principles involved is here desirable.

In Figure 6·2 are represented four conceivable ways in which the energy E of a molecule might vary as part of the molecule is rotated, with respect to the rest of it, about some specified bond. The abscissa ϕ is the angle of rotation, as measured from some arbitrary starting point; obviously, ϕ goes only from 0° to 360°, and these two extreme values correspond to the same relative orientation of the two parts of the molecule (i.e., to the same conformation). In Figure 6·2*a*, the energy is independent of the angle; hence, no value of ϕ is preferred over any other, no forces operate to prevent rotation from occurring, and all values of ϕ are equally probable. Under such circumstances, stereoisomers differing in extent of rotation about the bond in question would obviously be impossible. Such a situation, which might be designated as "absolutely free rotation," is the one visualized by many people when they speak of "free rotation." However, it seldom if ever occurs in nature.

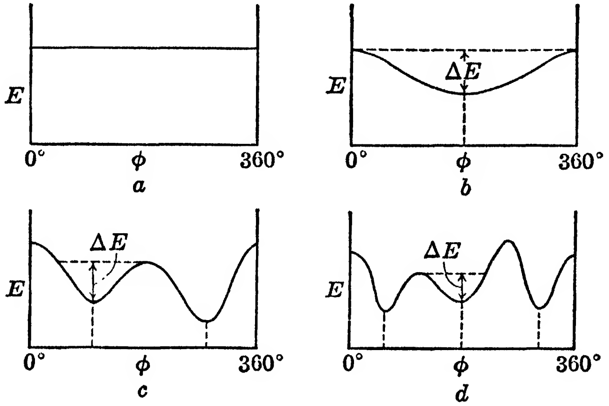


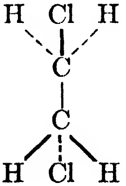
FIGURE 6·2. Four possible ways in which the energy E of a molecule might depend upon the angle ϕ by which a part of the molecule has been rotated with respect to the rest of it about some particular bond.

Figure 6·2*b* represents a molecule which has one preferred value of ϕ (shown by the vertical broken line) at which its energy is lowest. Most of the molecules would then be so oriented that their ϕ's are equal to, or at any rate near, this favored value; moreover, any given molecule would correspond most of the time to a ϕ that is equal to, or near, this same value. Two extreme cases require consideration; the energy ΔE that the molecule needs in order to be able to reach the top of the "energy hill" (the so-called *activation energy* for the rotation) may be very small, or it may be very large. If this activation energy is very small, the rotation is almost absolutely free; the tendency of the molecules to congregate near the favored value of ϕ is relatively unimportant, and a large number of molecules at any time have sufficient energy to pass completely over the hill. On the other hand, if ΔE is very large, the rotation is "frozen out"; the concentration of molecules near the favored value is practically complete, and only a very few molecules at any time have sufficient energy to pass over the hill. There is, of course, no sharp dividing line between these two extreme situations, which, instead, shade imperceptibly into each other. If ΔE is no greater in order of magnitude than RT, or about 600 cal per mole at room temperature, the rotation is practically free; if ΔE is greater than about 20 kcal per mole, then, at room temperature, the rotation is practically frozen out; and, if ΔE has some intermediate value, the rotation is neither completely free nor completely frozen out. Under no circumstances, however, can stereoisomers exist: for, if ΔE is small, the different geometrical arrangements are so readily interconvertible that the corresponding substances cannot be separated; if ΔE is large, only the single arrangement, corresponding to the favored value of ϕ, exists; and if ΔE is of intermediate magnitude, the situation is intermediate between these two extremes.

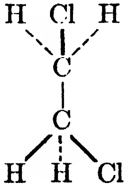
In Figure 6·2*c*, there are two angles, represented by the two vertical broken lines, at which the energy is at a minimum, and which are therefore favored over all others. If the hills between the two valleys are not of equal height, or if the valleys are not of equal depth, the activation energy ΔE may here be taken as the height of the lower hill above the higher valley. As before, if ΔE is small, the rotation is practically free, whereas, if ΔE is large, the rotation is practically frozen out. In the former event, stereoisomerism is again impossible on account of the easy interconversion of the steroisomeric forms. In the latter event, however, stereoisomerism may occur. Since ΔE is large, each molecule must be near one or the other of the two favored values of ϕ; at any time, very few molecules are able to pass from one position to the other. If these two positions are not equivalent to each other (i.e., if they correspond to nonsuperimposable conformations), two different isomeric forms, which can be separated from each other, are therefore possible. The existence of stereoisomeric substances that differ in configuration by a rotation of 180° about a double bond (such as maleic and fumaric acids mentioned on page 170) can clearly be interpreted on this basis. The situation is commonly described by the statement that rotation about a double bond is *not free*. On the other hand, if the two valleys are completely equivalent so that they correspond to indistinguishable configurations, no stereoisomerism is possible, regardless of the magnitude of ΔE. This is doubtless the situation with ethylene itself, for example. Finally, if ΔE has an intermediate value, stereoisomers may be separable at some sufficiently low temperature, at which the average molecular energy is small, but not at some higher temperature, at which the average energy is greater. Under such circumstances, either isomer, after separation at the lower temperature, would be more or less rapidly converted into the equilibrium mixture of the two forms at the higher temperature. Examples of this phenomenon will be given later in Section 6·12 and 7·7.

Figure 6·2*d* represents a molecule with three favored positions, which are, as before, indicated by the vertical broken lines. Ethane, for example, undoubtedly can be assigned a curve of this sort, with all three valleys completely equivalent, and with all three hills likewise equivalent. The valleys and the hills presumably correspond to the "staggered" and "eclipsed" conformations, III and II, respectively. For this substance, the activation energy ΔE has been estimated,[12] from a combination of spectroscopic and thermochemical data, to be about 3 kcal per mole. Since this value is appreciably greater than RT at ordinary temperatures, but nevertheless considerably smaller than 20 kcal per mole, the rotation is somewhat restricted, but far from frozen out. There could be imagined a substituted ethane, for which the three valleys correspond to nonequivalent conformations separated by hills more than 20 kcal per mole in height. Under such circumstances, separable stereoisomeric forms should exist. No example of this type of stereoisomerism, however, has ever been reported; consequently, the inference may be drawn that, for rotation about a single bond between two saturated carbon atoms, the activation energy ΔE is always less than 20 kcal per mole.

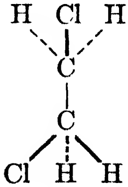
Although, as has just been stated, no substituted ethane has yet been obtained in stereoisomeric forms differing by a rotation about the ethane carbon-carbon bond, there can nevertheless be no doubt that the expected isomers are always actually present. Indeed, fairly direct evidence for the existence of inseparable isomers of this type has been derived from several kinds of physical data; for example, a study of Raman spectra and of dipole moments has led to the conclusion [13] that, in the fluid states, some molecules of ethylene chloride have the particular staggered conformation IV, in which the distance between the two chlo-



IV



V



VI

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[12] J. D. Kemp and K. S. Pitzer, *J. Am. Chem. Soc.* **59**, 276 (1937).

[13] Cf. K. W. F. Kohlrausch and G. P. Ypsilanti, *Z. physik. Chem.* **B29**, 274 (1935); J. Cabannes, *J. chim. phys.* **35**, 1 (1938); S. Mizushima and Y. Morino, *Z. Physik* **119**, 188 (1942).

rine atoms is as great as possible, whereas the other molecules have the two remaining (enantiomorphic) staggered conformations V and VI. Moreover, there is a distinct possibility that an at least partial separation of such isomeric forms could be effected at an extremely low temperature. One experimental procedure[14] that has been used with this end in view deserves mention here, even though the results reported by the original investigators were not confirmed by subsequent workers.[15] The heat capacity of isopentane, VII, was measured as a function of tem-

$$(CH_3)_2CH{-}CH_2{-}CH_3$$

VII

perature over the range −93° to −33°C. It was originally reported[14] that the measured value of this quantity at any given, low temperature depends upon whether the substance has or has not recently been kept for some time at −93°C. The interpretation of this result was that, at the higher temperatures, the rotation about all bonds is practically free, whereas, at much lower temperatures, it is more nearly frozen out. If the substance investigated has just been cooled from the higher temperature, therefore, it consists of a mixture of stereoisomeric forms, the interconversion of which is slow at the low temperature; these forms are present in the proportions corresponding to equilibrium at the higher temperature. On the other hand, if the substance has just been warmed from −93°C, at which temperature it has previously been kept for a sufficient time so that the low-temperature equilibrium has been established, then it again consists of a mixture of stereoisomeric forms, but of one in which the various forms are present in different proportions from before. Since each form presumably has its own characteristic heat capacity, the reported facts are therefore explained. Although unfortunately, as has already been noted, later investigators have been unable to confirm these experiments,[15] the foregoing discussion is nevertheless of interest in illustrating an apparently completely valid way in which the problem can be attacked. Clearly, much further work would be desirable.

6·7 Plane Projection Diagrams for Noncyclic Molecules. The use of three-dimensional models of the sort considered in the preceding sections becomes extremely cumbersome if the molecule to be represented is even moderately complicated. Moreover, such models cannot be depicted very conveniently on a plane surface, such as a printed page; even the relatively simple diagrams given above in this chapter, for example,

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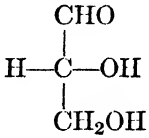
[14] J. G. Aston and S. C. Schumann, *J. Am. Chem. Soc.* **64**, 1034 (1942); S. C. Schumann, J. G. Aston, and M. Sagenkahn, *ibid.* **64**, 1039 (1942); J. G. Aston, *ibid.* **65**, 2041 (1943).

[15] G. B. Guthrie, Jr., and H. M. Huffman, *J. Am. Chem. Soc.* **65**, 1139 (1943). See also J. G. Aston, D. H. Rank, N. Sheppard, and G. J. Szasz, *ibid.* **70**, 3525 (1948).

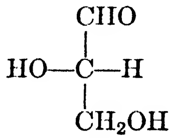
are not too easily intelligible, and the situation rapidly becomes worse as the complexity of the molecule increases. Consequently, some simpler method of representation is highly desirable.

The convention which has been most generally adopted consists in representing the three-dimensional models by what are called *plane projection diagrams* or, more simply, *plane configurations*. Thus, by definition, diagrams I and II represent, respectively, the dextro- and levorotatory forms of glyceraldehyde.[16,17] It is to be noted that these diagrams do not completely specify the *absolute* configurations (i.e., the true three-dimensional forms of the actual molecules). Diagram I, for example, can be considered the projection either of the absolute configuration, III, or of its enantiomorph, IV; similarly, diagram II can be considered the projection either of the absolute configuration, V (identical with IV) or of its enantiomorph, VI (identical with III).



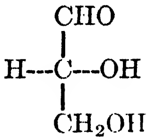
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

I



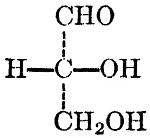
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{CH_2OH} \end{array}$$

II



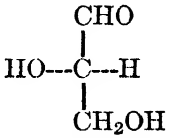
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H}\cdots\mathrm{C}\cdots\mathrm{OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

III



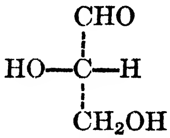
$$\begin{array}{c} \mathrm{CHO} \\ \vdots \\ \mathrm{H{-}C{-}OH} \\ \vdots \\ \mathrm{CH_2OH} \end{array}$$

IV



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HO}\cdots\mathrm{C}\cdots\mathrm{H} \\ | \\ \mathrm{CH_2OH} \end{array}$$

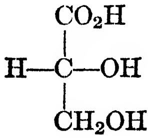
V



$$\begin{array}{c} \mathrm{CHO} \\ \vdots \\ \mathrm{HO{-}C{-}H} \\ \vdots \\ \mathrm{CH_2OH} \end{array}$$

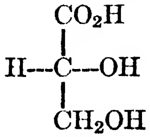
VI

The usefulness of the plane configurations like I and II lies in the fact that they make possible the representation of *relative* configurations. Thus, the oxidation of (+)-glyceraldehyde, I, gives (−)-glyceric acid which (since the reaction does not directly affect the asymmetric carbon atom, and hence cannot alter its configuration) can be described by the plane projection diagram VII. The assignment of this plane configuration to (−)-glyceric acid does not, of course, uniquely define the correct three-dimensional configuration of the substance, just as the assignment



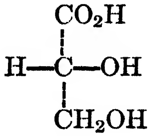
$$\begin{array}{c} \mathrm{CO_2H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

VII



$$\begin{array}{c} \mathrm{CO_2H} \\ | \\ \mathrm{H}\cdots\mathrm{C}\cdots\mathrm{OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

VIII



$$\begin{array}{c} \mathrm{CO_2H} \\ \vdots \\ \mathrm{H{-}C{-}OH} \\ \vdots \\ \mathrm{CH_2OH} \end{array}$$

IX

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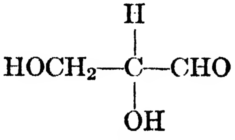
[16] Cf. M. A. Rosanoff, *J. Am. Chem. Soc.* **28**, 114 (1906).

[17] K. Freudenberg in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 662 ff.

of the corresponding plane configuration I to (+)-glyceraldehyde does not uniquely define the three-dimensional configuration of this substance. The meaning of the statement that (−)-glyceric acid has the plane configuration VII is instead merely that, if the absolute configuration of (+)-glyceraldehyde is III, then that of (−)-glyceric acid is VIII; but that, if the absolute configuration of (+)-glyceraldehyde is IV, then that of (−)-glyceric acid is IX. Further examples of the methods by which relative configurations are assigned to specific isomers will be described later in Sections 6·15, 7·12, and 7·13. (For a discussion of certain complications which arise when the plane projection diagrams are correlated with the corresponding three-dimensional configurations, see the paragraph in fine print near the end of this section.)

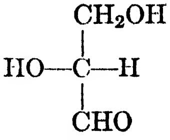
Considerable care must be exercised in the use of the plane configurations since errors and inconsistencies can easily be introduced. It might appear, for example, that diagrams I and II are identical since a rotation by 180° about a vertical axis lying in the plane of the paper would transform either into the other. Consequently, if the plane configurations I and II are to represent enantiomorphs, the convention must be adopted that a rotation which takes the figure out of the plane in which it is drawn *inverts* the configuration (i.e., changes it into that of the enantiomorph). Further similar conventions also must be adopted if further similar discrepancies are to be avoided. Unfortunately, however, no unanimity exists at present among chemists as to exactly what all these further conventions are. As a matter of fact, at least three different, and mutually inconsistent, sets of conventions are possible; moreover, each of these three sets is used to at least some extent in books and articles. Any one of the sets is self-consistent and generally satisfactory, if it is used alone and is not combined with any of the others. (However, see the last two paragraphs of this section.)

1. The convention which seems to be most widely adopted and which was used implicitly in the preceding paragraph may be called the "rigid-body convention," since it assigns meanings to only those operations upon the plane configurations which could be performed upon rigid bodies. When this convention is employed, a rotation by 180° out of the plane of the paper is considered to invert the configuration (as was stated above), but any rotation within the plane of the paper is considered to leave the configuration unchanged. Thus, diagrams X, XI, and XII are



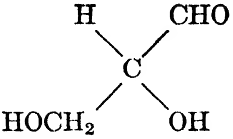
$$\begin{array}{ccccc} & & \mathrm{H} & & \\ & & | & & \\ \mathrm{HOCH_2} & — & \mathrm{C} & — & \mathrm{CHO} \\ & & | & & \\ & & \mathrm{OH} & & \end{array}$$

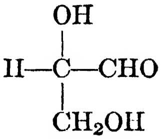
X



$$\begin{array}{ccccc} & & \mathrm{CH_2OH} & & \\ & & | & & \\ \mathrm{HO} & — & \mathrm{C} & — & \mathrm{H} \\ & & | & & \\ & & \mathrm{CHO} & & \end{array}$$

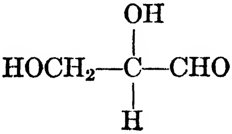
XI


XII


$$\begin{array}{c}\mathrm{OH}\\ | \\ \mathrm{H{-}C{-}CHO}\\ | \\ \mathrm{CH_2OH}\end{array}$$
XIII

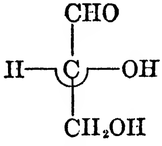
equivalent to I and, like it, represent dextrorotatory glyceraldehyde. On the other hand, diagram XIII is configurationally undefined since it cannot be obtained from either I or II by any sort of rotation, whether within, or out of, the plane of the paper; in other words, it does not represent specifically either the dextro- or the levorotatory enantiomorph.

2. A second, somewhat less commonly adopted, convention may be called the "permutation convention," since it assigns meanings to only those operations upon the plane configurations which are equivalent to permutations of the atoms or groups that are joined to the asymmetric atom (or atoms). When this convention is employed, any operation which is equivalent to an odd number of single interchanges of atoms or groups that are joined to the same asymmetric atom is considered to invert the configuration of that atom, but any operation which is equivalent to an even number of such interchanges at the same atom is considered to leave the configuration unchanged. Thus, diagram II can be derived from I not only by a rotation of 180° out of the plane of the paper but also by an interchange of the hydrogen atom and the hydroxyl group. Consequently, if diagram I represents the dextrorotatory glyceraldehyde, diagram II represents the levorotatory enantiomorph, just as it does by the rigid-body convention. That agreement between the two conventions is not general, however, is shown by the fact that diagram X, which represents (+)-glyceraldehyde by the rigid-body convention, represents (−)-glyceraldehyde instead by the permutation convention, since it can be obtained from I by an odd number of single interchanges. Thus, one interchange transforms I into XIII; a second transforms XIII into XIV; and a third transforms XIV into X. More-


$$\begin{array}{c}\mathrm{OH}\\ | \\ \mathrm{HOCH_2{-}C{-}CHO}\\ | \\ \mathrm{H}\end{array}$$
XIV

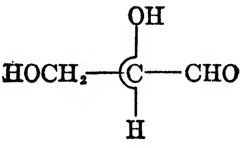
over, diagram XII no longer represents the dextrorotatory form, as before, but is instead configurationally undefined since it cannot be obtained from I by any sort of permutation; and XIII is no longer undefined but represents the levorotatory form since it can be obtained from I by a single interchange. It may be noted that in general the permutation convention leads to the rule that a rotation by 90° in the plane inverts the configuration, one by 180° in the plane leaves it unchanged, and one by any other angle in the plane is undefined.

3. A final convention, which in practice is very seldom employed,[17] may be called the "quasi-three-dimensional convention," since, at the expense of additional complexity, it retains many of the advantages of the three-dimensional models. When this convention is employed, the appearance of the projection diagrams is somewhat modified; thus, (+)-glyceraldehyde, for example, is represented as XV instead of as I. Since the absolute configuration of the substance is not known, no assumption is to be made whether the atoms or groups at the ends of the line with the bend in it (in this diagram, the hydrogen atom and the hydroxyl group) lie in front of or behind the plane of the paper. Similarly, no assumption is to be made regarding the exact relative positions of the atoms or groups joined by the straight line. However, the use of the two kinds of line does serve to distinguish between the positions in space occupied by the two pairs of atoms or groups. The complete convention can now be stated as follows: An operation performed upon the diagram inverts the configuration about an asymmetric atom if it involves (*a*) a single interchange of atoms or groups joined to the asymmetric atom, (*b*) an interchange of the bent line and the straight line, or (*c*) any odd number of the "inverting" operations *a* and *b*; on the other hand, an operation leaves the configuration unchanged if it involves (*d*) a rotation by any angle within the plane of the paper, or (*e*) any even number of the "inverting" operations. A few examples will suffice to show the application of these rules; diagrams XVI, XVII, and XVIII represent (−)-glyceraldehyde, whereas XIX, XX, and XXI represent (+)-glyceraldehyde.



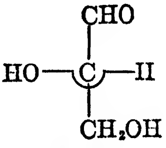
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H}\text{—}\mathrm{C}\text{—}\mathrm{OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

XV



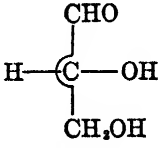
$$\begin{array}{c} \mathrm{OH} \\ | \\ \mathrm{HOCH_2}\text{—}\mathrm{C}\text{—}\mathrm{CHO} \\ | \\ \mathrm{H} \end{array}$$

XVI



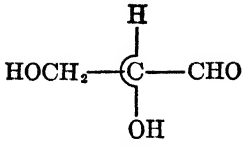
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HO}\text{—}\mathrm{C}\text{—}\mathrm{H} \\ | \\ \mathrm{CH_2OH} \end{array}$$

XVII



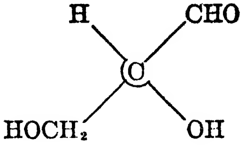
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H}\text{—}\mathrm{C}\text{—}\mathrm{OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

XVIII

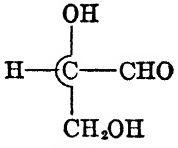


$$\begin{array}{ccc} & \mathrm{H} & \\ & | & \\ \mathrm{HOCH_2}- & \mathrm{C} & -\mathrm{CHO} \\ & | & \\ & \mathrm{OH} & \end{array}$$

XIX



XX



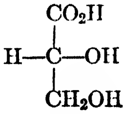
$$\begin{array}{ccc} & \mathrm{OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{CHO} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

XXI

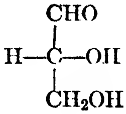
It is to be noted that, regardless of which convention is adopted, freedom of rotation does not in general exist about the single bonds in plane projection diagrams. This limitation is due to the fact that a rotation about any bond in such a diagram requires that that part of the diagram which is rotated leave the plane of the paper, or else that a single interchange of atoms or groups within it be performed. If this part is dissymmetric, then, according to any one of the above conventions, it is inverted in the process, so that the resulting configuration is not equivalent to the original one. For example, a rotation (by 180°) of the lower part of the plane configuration I about the upper carbon-carbon bond changes this configuration into the enantiomorphic one, II. (The CH_2OH group is not affected by the rotation, since it is symmetric and therefore identical with its own mirror image.) These remarks, of course, do not imply any corresponding lack of freedom of rotation about the single bonds in the actual molecules or in the three-dimensional models; they have reference instead only to the conventions which must be adopted if the plane configurations are not to lead to inconsistencies.

Of the three conventions, the permutation convention is the most generally satisfactory, since, for the reasons given in the following paragraph, it is theoretically superior to the rigid-body convention, and since it obviously is less cumbersome than the quasi-three-dimensional convention. The rigid-body and permutation conventions can, however, be made equivalent to one another if each is arbitrarily restricted in a certain definite manner. Thus, if (with the rigid-body convention) no rotation by an angle other than 180° is ever permitted, and if also (with the permutation convention) no permutation which is not equivalent to such a rotation is ever permitted, then no inconsistencies of the types described above can ever occur. Although these restrictions may in some instances make impossible the assignment of specific plane configurations to certain isomers, such a difficulty will not arise with any of the substances considered in this book. Consequently, the restrictions in question will hereafter be imposed (except in the following paragraph and in the paragraph in fine print near the end of Section 6·8), and the resulting "rigid-body-and-permutation" convention will be adopted. In general, however, the *language* of the rigid-body convention will be used, since it is both wide-spread and convenient.

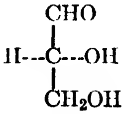
As was mentioned earlier in this section (page 182), the statement that (−)-glyceric acid has the plane configuration VII means that, if (+)-glyceraldehyde (with the plane configuration I) has the particular three-dimensional configuration III, then


$\begin{array}{c}\text{CO}_2\text{H}\\ |\\ \text{H—C—OH}\\ |\\ \text{CH}_2\text{OH}\end{array}$

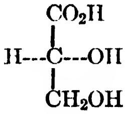
VII


$\begin{array}{c}\text{CHO}\\ |\\ \text{H—C—OH}\\ |\\ \text{CH}_2\text{OH}\end{array}$

I

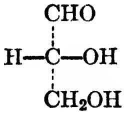

$\begin{array}{c}\text{CHO}\\ |\\ \text{H}\cdots\text{C}\cdots\text{OH}\\ |\\ \text{CH}_2\text{OH}\end{array}$

III

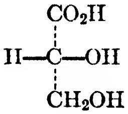

$\begin{array}{c}\text{CO}_2\text{H}\\ |\\ \text{H}\cdots\text{C}\cdots\text{OH}\\ |\\ \text{CH}_2\text{OH}\end{array}$

VIII

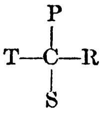
the acid, VII, has the three-dimensional configuration VIII; but that, if (+)-glyceraldehyde has instead the enantiomorphic three-dimensional configuration IV, then the acid has instead the likewise enantiomorphic three-dimensional configuration IX. The reader may have therefore assumed that any arbitrary plane configuration


$\begin{array}{c}\text{CHO}\\ \vdots\\ \text{H—C—OH}\\ \vdots\\ \text{CH}_2\text{OH}\end{array}$

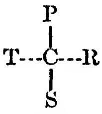
IV


$\begin{array}{c}\text{CO}_2\text{H}\\ \vdots\\ \text{H—C—OH}\\ \vdots\\ \text{CH}_2\text{OH}\end{array}$

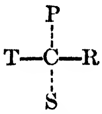
IX


$\begin{array}{c}\text{P}\\ |\\ \text{T—C—R}\\ |\\ \text{S}\end{array}$

XXII

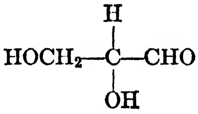

$\begin{array}{c}\text{P}\\ |\\ \text{T}\cdots\text{C}\cdots\text{R}\\ |\\ \text{S}\end{array}$

XXIII

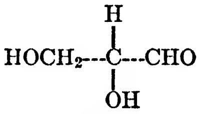

$\begin{array}{c}\text{P}\\ \vdots\\ \text{T—C—R}\\ \vdots\\ \text{S}\end{array}$

XXIV

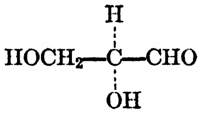
XXII must similarly always imply the corresponding three-dimensional configuration XXIII (or XXIV), if diagram I for (+)-glyceraldehyde implies, respectively, the configuration III (or IV). This assumption is, however, correct only if the permutation convention is adopted; in general, it is incorrect if instead the rigid-body convention is adopted. For example, if the letters P, R, S, and T in the generalized plane configuration XXII are identified, respectively, as the atoms or groups H, CHO, OH, and CH_2OH, this diagram then assumes the specific form X. If the assumption under discussion is valid in this instance, the plane configuration X must represent the three-dimensional configuration XXV (or XXVI), if diagram I repre-


$\begin{array}{c}\text{H}\\ |\\ \text{HOCH}_2\text{—C—CHO}\\ |\\ \text{OH}\end{array}$

X


$\begin{array}{c}\text{H}\\ |\\ \text{HOCH}_2\cdots\text{C}\cdots\text{CHO}\\ |\\ \text{OH}\end{array}$

XXV

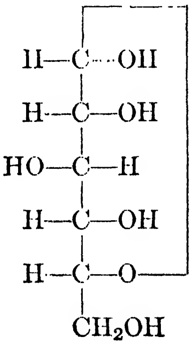

$\begin{array}{c}\text{H}\\ \vdots\\ \text{HOCH}_2\text{—C—CHO}\\ \vdots\\ \text{OH}\end{array}$

XXVI

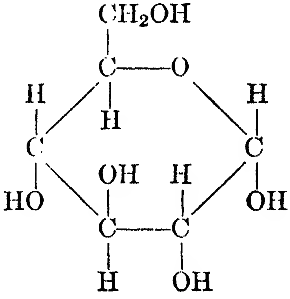
sents, respectively, the configuration III (or IV). The configurations XXV and III are, however, enantiomorphs, as are also the other configurations XXVI and IV. In either event, therefore, the plane configuration X must represent (−)-glyceraldehyde; hence, the plane configuration I is inverted when it is rotated by 90° in the plane in which it is written. Thus, it follows that, as was stated above, the assumption now being considered is consistent with the permutation convention, but is inconsistent with the rigid-body convention, if a rotation by an angle other than 180° is permitted. From the theoretical point of view, therefore, the permutation convention is superior to the rigid-body convention. No analogous difficulties arise when the quasi-three-dimensional convention is adopted.

In order that possible misunderstandings may be avoided, it should here be emphasized that the rigid-body convention discussed above has no application to the actual molecules, to the three-dimensional models, or to the diagrams (like II and III of Section 6·6 or like III–VI, VIII, IX, etc., of this section) which are designed to represent three-dimensional models. It has meaning, in fact, only with reference to the conventional plane projection diagrams. On the other hand, the permutation convention is less restricted, since an interchange of two atoms or groups linked to the same asymmetric atom inverts the configuration of that atom not only in the corresponding plane configuration, but also in the molecule itself, in the three-dimensional model, and in any diagram designed to represent the three-dimensional model. (Cf. also pages 228 f.)

6·8 Plane Projection Diagrams for Cyclic Molecules. If a molecule contains a ring of atoms, its configuration may be expressed on a plane surface in either of two ways. When the first of these methods is used, the diagram is written as if no ring were present (cf. the preceding section), and then the fact that a ring is present is indicated, more or less as an afterthought, by the drawing in of the necessary bonds as long, and frequently curved or bent, lines. Thus, the configuration of α-(+)-glucose is often written as I. When the second method of representation is employed instead, the ring is drawn as if it were a plane polygon approximately at right angles to the plane of the paper, and the substituents that are attached to the ring atoms are represented by the appropriate symbols above and below the plane of the ring. Thus, the configuration of α-(+)-glucose can be written as II; this diagram is to be considered equivalent to I. Plane projection diagrams like II do not imply knowledge of the corresponding absolute configurations. A molecule of glucose in which the upper horizontal line (of II) is in front of the plane of the paper, and the lower line is behind it, would be the enantiomorph of a molecule in which the upper line is behind the plane of the paper, and the lower line is in front of it; since the diagram does not explicitly signify which line is in front, and which is behind, it can be con-



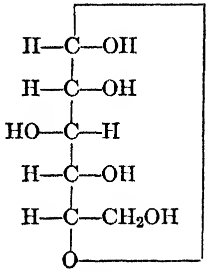
I



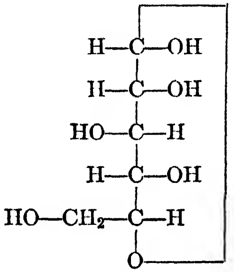
II

sidered the projection of either absolute configuration. Neither do these diagrams imply that at any instant the rings are completely planar (see Section 9·3); they imply rather that the *average* positions of the atoms of the ring lie within a single plane.

The equivalence of the configurations I and II can be shown in the following way. Since the rigid-body convention that was discussed in the preceding section is here clearly inapplicable, the permutation convention must be adopted. On this basis, then, one single interchange of substituents joined to the bottom asymmetric carbon atom transforms configuration I into III; and a second such interchange transforms III into IV. Since each of these two interchanges inverts the configuration of the bottom asymmetric atom, and since no other asymmetric atom is affected, configurations I and IV must be equivalent to each other. Now, although the permutation convention can carry the argument no further, the identity of configurations II and IV is almost obvious; for, in each of these two configurations, the atoms or groups H, H, OH, H, and CH_2OH occur in sequence on the same side of the ring. It should perhaps also be noted at this point that such diagrams as III and IV do not imply the *absolute* configurations of the corresponding molecules any more than do such ones as I and II. Thus, configuration IV, for example, can be considered to be a projection either of a three-dimensional model in which the carbon and oxygen atoms that are linked by the "long bond" lie in front of the plane of the paper, or of the enantiomorphic model in which the atoms in question lie behind the plane of the paper.



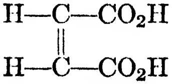
III



IV

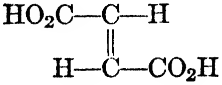
The fact that the plane projection diagrams of the types described in both this and the preceding section do not give the absolute configurations is not a defect, but instead a desirable feature. Since the absolute configurations are not known with certainty, any diagram which implies the absolute configuration might be incorrect; the conventional plane configurations, however, do not suffer from this defect of implying more knowledge than is actually possessed. (Cf. Section 7·13).

6·9 The Representation of Ethylenic Compounds. The representation of the configuration of an ethylenic compound is relatively easy since the two carbon atoms that are joined to one another by the double bond, and the four other atoms that are joined by single bonds to these two, lie in the same plane. Consequently, the conventional diagrams like I and II for maleic acid and fumaric acid, respectively, can



$$\begin{array}{c} H-C-CO_2H \\ \| \\ H-C-CO_2H \end{array}$$

I



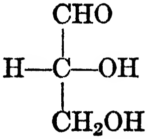
$$\begin{array}{c} HO_2C-C-H \\ \| \\ H-C-CO_2H \end{array}$$

II

be taken to represent the absolute configurations, even though they do not correspond to exactly the correct bond angles. In accordance with accepted nomenclature, the first of these two substances is said to be the *cis* isomer (from the Latin *cis*, on this side), whereas the second is said to be the *trans* isomer (from the Latin *trans*, across). These terms imply, of course, that the like substituents that are joined to the unsaturated carbon atoms are, respectively, on the same side and on opposite sides of the double bond. Diagrams like I and II are sufficiently simple, and their interpretation is sufficiently obvious, that no further discussion of them is necessary here.

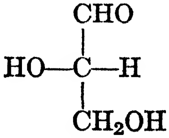
If a molecule contains several double bonds or both double bonds and rings or several rings, the representation of its configuration may be rather difficult. In such instances, the conventional scheme just outlined in this and in the preceding sections must often be supplemented by the use of heavy and broken lines to represent bonds to atoms in front of and behind the paper, respectively, or by other devices analogous to those employed earlier. Examples of such molecules are given in the following sections.

6·10 Use of Plane Projection Diagrams in Predicting the Number of Stereoisomers. The foregoing rather general considerations can be made more definite by a discussion of some specific examples of stereoisomerism. As has already been mentioned, the dextro- and levorotatory glyceraldehydes are represented by diagrams I and II, re-



$$\begin{array}{c} CHO \\ | \\ H-C-OH \\ | \\ CH_2OH \end{array}$$

I

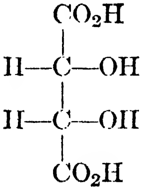


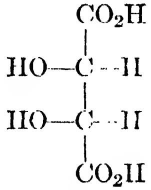
$$\begin{array}{c} CHO \\ | \\ HO-C-H \\ | \\ CH_2OH \end{array}$$

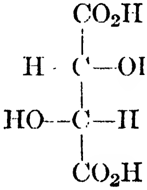
II

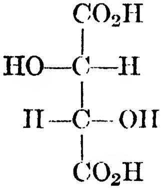
spectively.[16,17] That these two diagrams correspond to enantiomorphs (according to the conventions adopted) is shown by the facts: first, that they are not identical with each other (cf. the discussion of the tartaric acids, III–VI, below); and, second, that each is identical with the reflection of the other in a plane mirror which is halfway between them and perpendicular to the plane of the paper. Since there is only one asymmetric atom in the molecule, and no other sources of molecular dissymmetry, these two enantiomorphs are the only possible stereoisomeric forms. (As usual, the racemic modification is not considered a distinct substance but only a mixture of the two enantiomorphs. See Section 5·12.)

A molecule of tartaric acid, $HO_2C—C^*HOH—C^*HOH—CO_2H$, has the two asymmetric carbon atoms that are here designated by the asterisks. Since there are two possible configurations about each such atom, there might be anticipated altogether 2 × 2, or 4, distinct stereoisomers, which could be represented by diagrams III–VI. Of these diagrams, however, the first two are equivalent inasmuch as either is transformed into the other by a rotation of 180° in the plane of the paper. Since these two equivalent diagrams are mirror images of each other, they must represent a substance which is identical with its own mirror image and hence optically inactive; they are therefore equivalent forms of the plane configuration of *meso*-tartaric acid. The optical inactivity of this substance follows also from the presence of a plane of symmetry in either of the two diagrams; indeed, the upper half of either diagram is identical with the reflection of the lower half in a mirror perpendicular to both the plane of the paper and the central carbon-carbon bond. *meso*-Tartaric acid is therefore an example of a substance which is optically inactive even though its molecule contains two asymmetric carbon atoms. In contrast, the last two configurations, V and VI, are not equivalent since neither can be transformed into the other by any rotation in the plane. Since they are mirror images of each other, they must correspond to enantiomorphs, and so one must represent the dextrorotatory, and the other must represent the levorotatory, tartaric acid. Alternatively, the enantiomorphism of the tartaric acids, V and VI, can be shown by the fact that each is transformed into the other by a rotation of 180° out of the plane of the paper; such a rotation, of course, inverts the configuration about each of the two asymmetric atoms. In a way discussed in Section 7·12, the configuration V has been shown to belong to the dextrorotatory enantiomorph, and the configuration VI has been shown to belong to the levorotatory one. Thus, the existence of the three known tartaric acids can be explained; moreover, the prediction that no further stereoisomers are possible can be made.


III

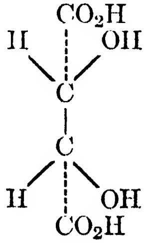

IV


V

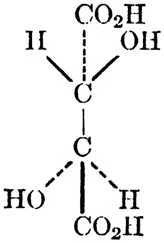

VI

Diagrams V and VI have centers of symmetry, but neither the molecules which they represent nor the three-dimensional models of which they are projections do; conclusions regarding the presence or absence of centers of symmetry cannot easily be drawn from the plane projection diagrams of this type. (However, see the discussion of the cyclic compounds below.)

As was pointed out above, the plane projection diagram of *meso*-tartaric acid (III or IV) has a plane of symmetry. It will be of interest now to consider what elements of symmetry are possessed by the three-dimensional model, and so presumably also by the actual molecule. If the relative orientation of the two halves of the molecule with respect to rotation about the central carbon-carbon bond is the exactly "eclipsed" one shown in diagram VII, then the molecule does indeed possess a plane of symmetry perpendicular to, and bisecting, the central carbon-carbon bond. On the other hand, if the orientation is instead the exactly "staggered" one, VIII, then the molecule possesses a *center* of symmetry. None of the infinitely many remaining possible conformations, however, possesses either a plane or a center of symmetry. Since the rotation is almost certainly not frozen out in either the eclipsed or staggered conformation, the observed inactivity of the substance, therefore, requires explanation.



VII



VIII

The statement is often made that *meso*-tartaric acid is inactive on account of "internal compensation."[18] (Cf. Section 5·11.) This statement implies that, since the two halves of the molecule have opposite configuration, the optical rotation due to each half is exactly canceled by the equal but opposite rotation due to the other. However, as has just been noted, this assumed cancellation occurs only in the exactly eclipsed and exactly staggered conformations. Consequently, the term "internal compensation" would be strictly correct only if each molecule were in one of these two symmetrical conformations. A more precise description of the situation can be reached in the following way. Two molecules of *meso*-tartaric acid may be imagined initially to be held fixed in either one of the inactive conformations, say, the exactly stag-

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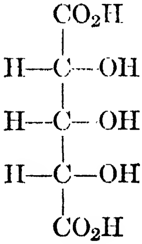
[18] The following discussion is based upon one by C. R. Noller, *Science* **102**, 508 (1945).

gered one, VIII. If now the top half of one of these molecules is twisted by any angle about the central carbon-carbon bond, and if the top half of the other molecule is twisted by the same angle but in the opposite direction about the same bond, then in general each molecule will no longer have either a plane or a center of symmetry. The two will, however, be mirror images, and hence enantiomorphs, of each other. Since any actual molecule of *meso*-tartaric acid may be considered to have fairly free rotation, it is evident that at any given time there will be just as many molecules in any given dissymmetric conformation as there are in its enantiomorphic conformation, and consequently that the substance must be optically inactive. In a sense, therefore, *meso*-tartaric acid is really a racemic modification, in which the two enantiomorphs are interconverted so easily that they cannot be separated. Nothing seems to be gained, however, by the adoption of this extreme, though logically unassailable, point of view. The situation can indeed be most easily described by the statement that, on the time-average, as a result of the freedom of rotation, each molecule of *meso*-tartaric acid (or of any other substance of the same type) possesses both a plane and a center of symmetry, even though, at any given instant, very few of the molecules actually possess either type of symmetry element, and none of them can possess both.

If the rotation about the central carbon-carbon bond were completely frozen out, so that each molecule were required to remain in one or another of the three valleys of a curve like that of Figure 6·2*d*, then the configuration III, or its equivalent IV, would correspond to three separable stereoisomeric forms; these would consist of an inactive form, in the staggered conformation VIII, and a pair of enantiomorphs in the two remaining staggered conformations.

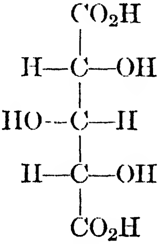
Although only three tartaric acids are possible (as long as there is sufficient freedom of rotation), four monomethyl esters should exist; for, when one, and only one, of the carboxyl groups is modified, the two asymmetric atoms are no longer equivalent, and therefore no *meso* form is then possible. Indeed the two expected enantiomorphic monomethyl esters of *meso*-tartaric acid have been reported. The dimethyl esters, like the parent acids, however, exist only in dextrorotatory, levorotatory, and *meso* forms.

The trihydroxyglutaric acids, $HO_2C—C^*HOH—C^*HOH—C^*HOH—CO_2H$, have the three asymmetric carbon atoms marked by asterisks. The central carbon atom may appear not to be asymmetric since two of the groups attached to it are structurally identical in all the possible stereoisomeric forms and indeed are configurationally identical as well in some of the forms. It is common practice, however, to regard such atoms as asymmetric; the expression *pseudo-asymmetric*[19] is also occasionally used for their description. (See the following paragraph.) One might expect 2^3, or 8, stereoisomeric forms, but, as with the tartaric acids, the number is somewhat reduced by the occurrence of *meso* forms. Only the four nonequivalent configurations IX–XII can be drawn, and,



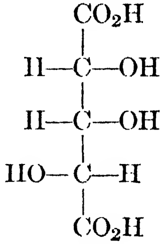
$$\begin{array}{c} \mathrm{CO_2H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CO_2H} \end{array}$$

IX



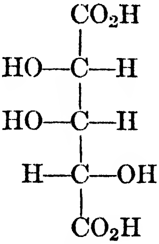
$$\begin{array}{c} \mathrm{CO_2H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CO_2H} \end{array}$$

X



$$\begin{array}{c} \mathrm{CO_2H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{CO_2H} \end{array}$$

XI



$$\begin{array}{c} \mathrm{CO_2H} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CO_2H} \end{array}$$

XII

in agreement with prediction, only four stereoisomeric substances with this structure are known. It is easily seen that diagrams IX and X represent two different *meso* forms since each has a plane of symmetry passing through the central CHOH group and perpendicular to the paper, and that diagrams XI and XII represent a pair of enantiomorphs. With the monomethyl esters of these acids, no *meso* forms are possible and so altogether eight stereoisomers should exist; none of these are, however, now known.

Further consideration of the pseudo-asymmetric carbon atom of the trihydroxyglutaric acids leads to some possibly unexpected results. In either of the forms IX and X, the two CHOH—CO_2H groups have opposite configurations, as can be seen if the diagram is rotated by 180° in the plane of the paper; although the central carbon atom can therefore with some reason be considered asymmetric, the substance is nevertheless optically inactive. On the other hand, in either of the forms XI and XII, the two CHOH—CO_2H groups have identical configuration as well as structure; although the central carbon atom can therefore not be considered really asymmetric, the substance is nevertheless optically active. These examples serve to illustrate the fact that the presence or absence of asymmetric atoms is not of primary significance in the interpretation of optical activity. (Each of the configurations IX–XII, of course, contains two carbon atoms that are asymmetric in the most usual sense.)

The aldohexoses have five asymmetric atoms in the pyranose structure. (Cf. configurations I and II of Section 6·8.) Since no *meso* forms are possible 2^5, or 32, different optically active stereoisomers should exist. As has already been mentioned (Section 5·10), all these forms are known.

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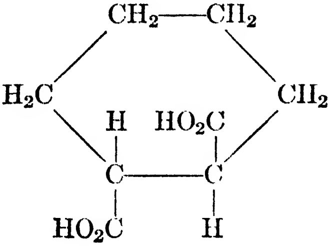
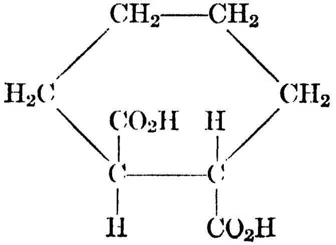
[19] Cf. A. W. Stewart, *Stereochemistry*, Longmans, Green and Company, London, 1907, page 21.

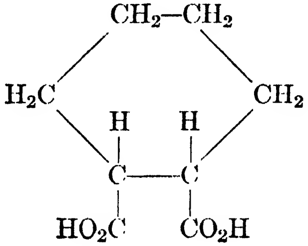
The cyclohexane-1,2-dicarboxylic acids, like the tartaric acids, contain two equivalent asymmetric carbon atoms per molecule; consequently, these substances also exist in two enantiomorphic forms, XIII and XIV, and one *meso* form, XV. It is readily verified that the configurations XIII and XIV are mirror images of each other, and that neither possesses a plane or center of symmetry. On the other hand, the configuration XV has a plane of symmetry which is the perpendicular bisector of the bond that joins the two asymmetric atoms; the corresponding molecule is therefore identical with its mirror image.



XIII



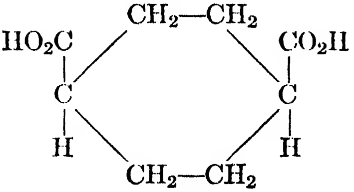
XIV

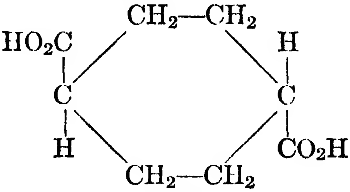


XV

The isomerism of the cyclohexane-1,2-dicarboxylic acids, as well as that of other analogous cyclic compounds, is frequently described by the statement that the optically active forms, XIII and XIV, are *trans*, whereas the *meso* form, XV, is *cis*. This nomenclature is convenient since it clearly and concisely expresses the relative positions of the substituent groups with respect to the plane of the ring. However, it has given rise to much confusion since it suggests a false analogy with the *cis-trans* isomerism in such ethylenic compounds as maleic and fumaric acids. (See Section 6·9.) Indeed, the statement is often encountered that the isomerism of the cyclic compounds is due to a restriction of rotation by the more or less rigid ring, just as that of maleic and fumaric acids is due to a restriction of rotation about the double bond which, in a formal sense, can be regarded as a two-membered ring. In the former substances, however, the rigidity of the ring is not significant; the isomerism, being due to the presence of two asymmetric atoms, would persist if the ring were perfectly flexible, or even if it were broken to form a noncyclic compound, so long as the asymmetry of the carbon atoms is not destroyed.

In cyclohexane-1,4-dicarboxylic acid, *cis* and *trans* forms again exist. Here, however, both the *cis* form, XVI, and the *trans* form, XVII, are


XVI


XVII

optically inactive; the former has two planes of symmetry, whereas the latter has one plane of symmetry and a center of symmetry. In the past, there has been some discussion whether or not the two carbon atoms to which the carboxyl groups are attached are asymmetric. Baeyer[20] maintained that they are asymmetric because the sides of the ring, although structurally identical, differ in a rather subtle geometrical way. The reasoning which led him to this conclusion was the following. An observer may be imagined to be swimming on his side inside the six-membered ring of, say, diagram XVI, with his face toward the center, and with his back initially toward the carbon atom at the extreme left of the diagram. Then, if he swims in the clockwise direction, he will find, when he reaches the carbon atom at the extreme right of the figure, that the carboxyl group attached to this atom lies to his right and the hydrogen atom lies to his left. (For definiteness, the upper horizontal carbon-carbon bond of the configuration XVI is here considered to be behind the plane of the paper, and the lower such bond is considered to be in front of that plane.) On the other hand, if the observer had instead turned round and swum in the counterclockwise direction, with his face still toward the center, he would have found that the carboxyl group and hydrogen atom lie instead to his left and right, respectively. Consequently, the two sides of the ring, considered as substituents attached to the carbon atom at the left of the ring, are not geometrically identical. The carbon atom in question may therefore be considered asymmetric in a certain sense. Similarly, the carbon atom at the right of the ring in diagram XVI, and also the two corresponding carbon atoms of diagram XVII, are also asymmetric in the same sense. For this type of asymmetry, Baeyer coined the term *relative asymmetry*. At the present time, the discussion seems rather pointless, since the pres-

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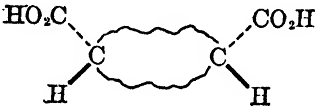
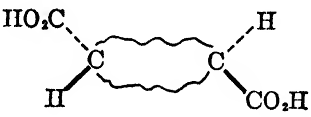
[20] A. Baeyer, *Ann.* **245**, 103, 128 (1888).

ence or absence of asymmetric atoms is no longer considered of primary significance in stereochemistry.

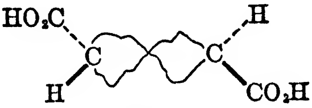
The isomerism of these two cyclohexane-1,4-dicarboxylic acids, XVI and XVII (like that of the 1,2-dicarboxylic acids, XIII–XV), is not due to the rigidity of the ring; no conceivable rotation about any bond or bonds in the ring could transform either isomer into the other, even if the ring were perfectly flexible. To be sure, if the ring were extremely flexible, the two carboxyl groups in a molecule of, for example, the *cis* acid, XVI, might be forced onto opposite sides of the plane defined by the ring; nevertheless, the molecule, even when distorted in this way, would still not be identical with the molecule of the *trans* acid, XVII. Thus, the conventional "ball-and-stick" models of the *cis* and *trans* acids may be modified (for the sake of maximum flexibility in the ring) by the use of moderately long strings to represent the two chains of methylene groups that link the H—C—CO_2H groups to each other; the models of these acids can then be represented by diagrams XVIII and XIX, respectively, instead of by XVI and XVII, respectively. It is easily verified that this use of strings in the models affects neither the nature of the isomerism nor the total number of nonequivalent geometrical forms. Now, the model XVIII of the *cis* acid may be distorted, in any one of several different ways, so that the carboxyl groups appear to be *trans* with respect to one another; two such distortions are shown by diagrams XX and XXI. Obviously, however, neither of these resulting models XX and XXI is superposable on the model XIX of the *trans* acid; moreover, there can exist no other type of distortion which does permit the *cis* and *trans* models to be superposed. It is therefore evident that the *cis* and *trans* acids cannot be interconverted by any sort of rotation about the bonds within the ring, and hence also that the isomerism under discussion is in no way related to the assumed rigidity of the ring. There are, in fact, only two ways in which the *cis* model, XVIII, can be made equivalent to the *trans* model, XIX: in the first place, one of the carboxyl groups of XVIII may be interchanged with the hydrogen atom which is joined to the same carbon atom; in the second place, the ring carbon atom of the H—C—CO_2H group at the right of model XXI may be forced still farther to the right and simultaneously "turned wrong side out," so that it assumes the configuration of the corresponding carbon atom of the *trans* model, XIX. (Cf. Werner's mechanism of racemization, discussed in Section 7·6.) The same result would, of course, be achieved if the carbon atom at the left of diagram XVIII, rather than the one at the right of diagram XXI, were thus "turned wrong side out." In neither event, however, can



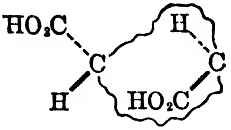
XVIII



XIX

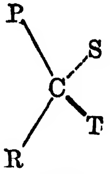


XX

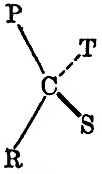


XXI

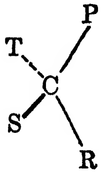
the operation employed be called a "rotation." In fact, the relation between models XVIII and XIX is exactly the same as that between models XXII and XXIII of two optically active enantiomorphs; moreover, the relation between models XXI



XXII



XXIII

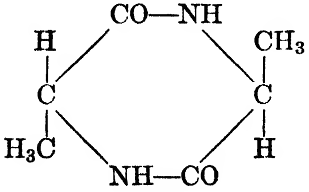


XXIV

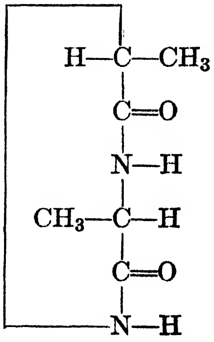
and XIX is exactly the same as that between models XXIV and XXIII of the same two optically active enantiomorphs. (Models XXII and XXIV are, of course, identical.) Consequently, if either the operation by which XVIII is transformed into XIX, or the one by which XXI is transformed into XIX, is called a "rotation," then *any* operation by which the configuration about an asymmetric atom is inverted must likewise be called a "rotation."

It should perhaps be noted here explicitly that neither of the two operations considered in the preceding paragraph can correspond to a process that takes place readily in any actual molecule; for, if two atoms or groups joined to the same atom could easily exchange places, or if a carbon atom could be easily "turned wrong side out," then no asymmetric carbon atom would be able to maintain its configuration, and the existence of stereoisomerism due to the presence of such atoms would be impossible. (Cf. also Section 7·6.) Even in a ball-and-stick model, no carbon atom can be "turned wrong side out" without breaking the model.

Alanine anhydride (dimethyldiketopiperazine), with a six-membered ring, exists in *cis* and *trans* forms. Here, the *trans* form, XXV, has a

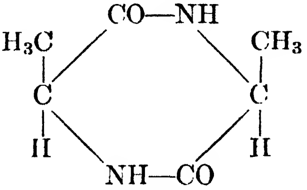


XXV

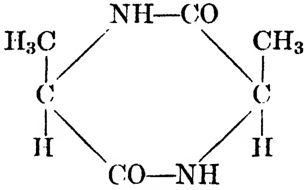


XXVI

center of symmetry (at the center of the ring) and so it is optically inactive. The presence of this center of symmetry is apparent if the ring in diagram XXV is visualized as lying in a plane perpendicular to that of the paper; on the other hand, if the configuration is written instead in the equivalent manner as XXVI, the presence of the center of symmetry cannot be so easily seen. The *cis* form has neither plane nor center of symmetry, and so it exists in the two enantiomorphic forms, XXVII and XXVIII.

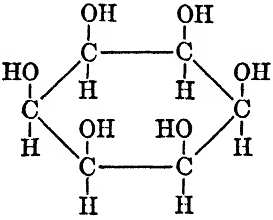


XXVII

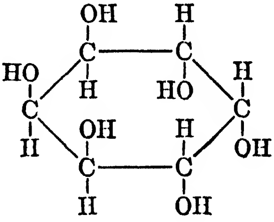


XXVIII

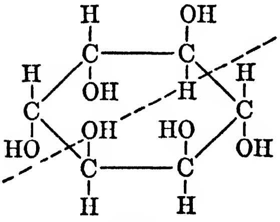
Inositol (hexahydroxycyclohexane) should exist, theoretically, in seven optically inactive forms, of which XXIX and XXX are typical examples, and also in the two enantiomorphic forms, XXXI and XXXII.



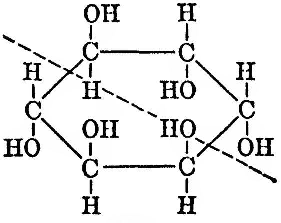
XXIX



XXX



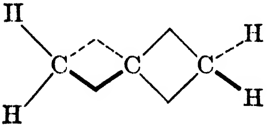
XXXI

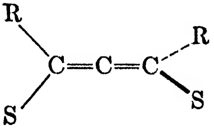


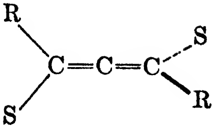
XXXII

Not all the predicted inactive forms are known, but the two active ones have been obtained. It is of interest that neither of the enantiomorphs, XXXI and XXXII, has an asymmetric atom in the usual sense, although both have "relatively asymmetric" carbon atoms. (Cf. page 195.) It is of interest also that the molecules represented by diagrams XXXI and XXXII, although dissymmetric, have the two-fold axes shown by the broken lines.

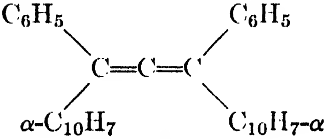
6·11 Optically Active Allenes and Their Analogs. van't Hoff[1] pointed out that, if his tetrahedral model of the double bond (see Section 6·3) is correct, the two CH_2 groups in allene $H_2C{=}C{=}CH_2$ should lie in planes which are at right angles to each other, as in diagram I; and

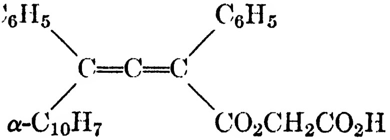

I


II

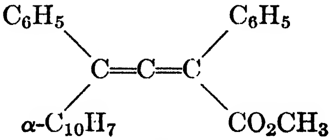

III

that a substance with the structure RSC=C=CRS, where R and S are any two different atoms or groups, should exist in the enantiomorphic forms II and III. It was not until 1935, however, that this prediction was verified by Maitland and Mills,[21] who obtained the optically active diphenyldi-α-naphthylallene, IV. In the same year, Kohler, Walker,


IV


V

and Tischler[22] reported the preparation of the similar optically active allene, V. It is of interest that neither of these substances contains an asymmetric atom. No further optically active allenes have been prepared subsequently, although the acid, V, has been changed into the simpler, but still active, ester VI.[23]


VI

Although the existence of optically active allenes was not confirmed until comparatively recently, several analogous substances have been known for a longer time. These substances may be considered related to the allenes proper by the replacement of one or both of the "two-membered rings" (i.e., double bonds) by larger rings. A typical pair of enantiomorphs, in which only one of the allenic double bonds has been thus replaced, is represented by the substances VII and VIII. In these

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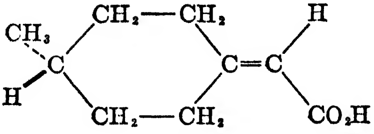
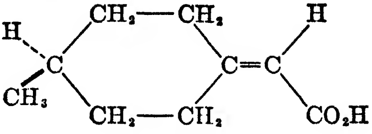
[21] P. Maitland and W. H. Mills, *Nature* **135**, 994 (1935).

[22] E. P. Kohler, J. T. Walker, and M. Tischler, *J. Am. Chem. Soc.* **57**, 1743 (1935).

[23] E. P. Kohler and W. J. Whitcher, *J. Am. Chem. Soc.* **62**, 1489 (1940).

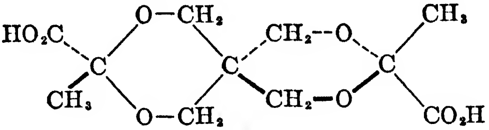


VII

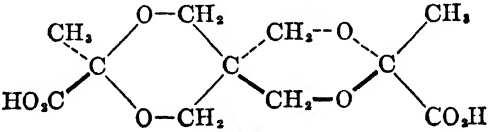


VIII

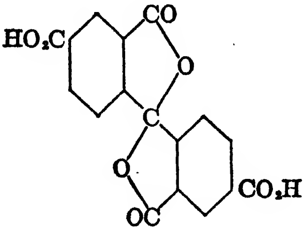
figures, the six-membered rings and the H—C—CO$_2$H groups are to be considered lying in the plane of the paper, and the H—C—CH$_3$ groups are to be considered lying in a plane perpendicular to that of the paper. A further pair of enantiomorphs, in which now both double bonds have been replaced by six-membered rings, is given by the "spiranes," IX and X.[24] (A spirane is a compound in which a single atom is a common member of two rings with three or more members. The central carbon atom of the compounds IX and X, which is a member of the two six-membered rings, is called the "spiro atom.") Like the allenes, to which they are analogous, the substances VII–X contain no asymmetric atom in the usual sense, although the spiro atoms might perhaps be considered relatively asymmetric (see above). Two further spirane systems, which similarly lead to optical activity, can be illustrated by the structures (not configurations here) XI [25] and XII.[26] The first of these structures



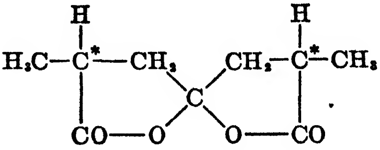
IX



X



XI



XII

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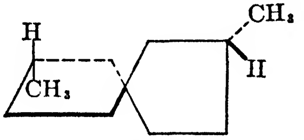
[24] J. Böeseken and B. B. C. Felix, *Ber.* **61**, 1855 (1928).

[25] W. H. Mills and C. R. Nodder, *J. Chem. Soc.* **117**, 1407 (1920).

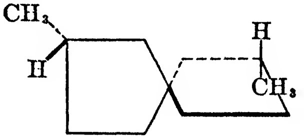
[26] H. Sutter and N. Wijkman, *Ann.* **519**, 97 (1935).

permits the existence of a pair of enantiomorphs, which are analogous to the spiranes, IX and X; the second structure is more complicated, however, as a result of the presence of the two equivalent asymmetric carbon atoms marked by the asterisks. In fact, structure XII permits altogether three pairs of enantiomorphs; the three racemic modifications have been obtained, but not resolved.

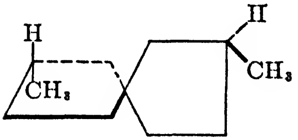
The configurations of the six optically active forms of the spirane, XII, can be expressed symbolically as XIII–XVIII. It might appear that a fourth pair of enantiomorphs, XIX and XX, should also exist, but it is easily shown that XIX is identical with XIII and that XX is identical with XIV. Thus, rotation by 90° about a horizontal axis lying in the plane of the paper transforms XIII into XXI, and rotation of XXI by 180° about a vertical axis lying in the plane of the paper transforms it into XIX. In a completely analogous manner, XIV (the enantiomorph of XIII) can be shown to be identical with XX (the enantiomorph of XIX).



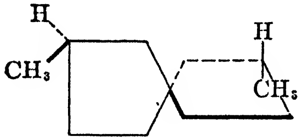
XIII



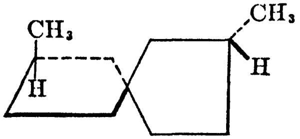
XIV



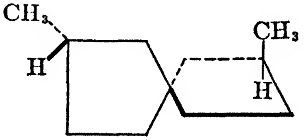
XV



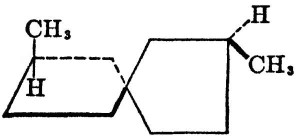
XVI



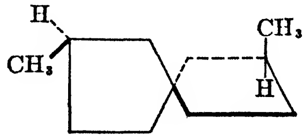
XVII



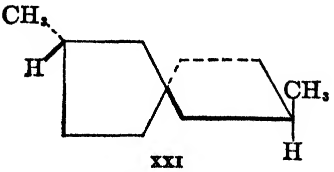
XVIII



XIX

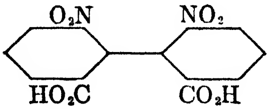


XX



XXI

6·12 Optically Active Biphenyls.[27] In 1922, Christie and Kenner[28] found that *o,o′*-dinitrodiphenic acid, I, can be separated into a pair of enantiomorphs. At one time, the possibility was seriously considered that these two substances might be representable as II and III. Although the so-called *Kaufler*[29] *configuration* here assigned to the biphenyl system seems most improbable from general stereochemical considerations, it was nevertheless supported by a certain amount of independent experimental evidence. This configuration had been proposed originally by Kaufler[29] in 1907 as a necessary corollary of his conclusion that the product of the reaction between phthalic anhydride and benzidine possesses the structure IV and therefore a configuration like V. Still further evidence supporting the Kaufler configuration was provided by the fact that, in addition to the two enantiomorphic *o,o′*-dinitrodiphenic acids of Christie and Kenner, a third substance with apparently the same structure I had previously been reported by Schultz;[30] a logical interpretation of this additional isomer was accordingly that it had the sym-



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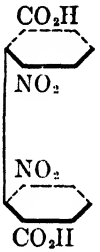
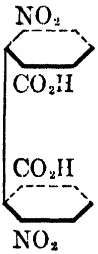
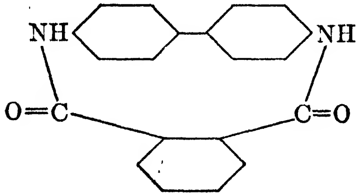


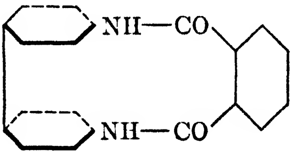
II



III



IV



V

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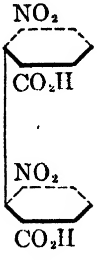
[27] For a summary, see R. Adams and H. C. Yuan, *Chem. Revs.* **12,** 261 (1933); R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 259 ff., 2nd ed., 1943, Volume I, pages 343 ff.

[28] G. H. Christie and J. Kenner, *J. Chem. Soc.* **121,** 614 (1922).

[29] F. Kaufler, *Ann.* **351,** 151 (1907).

[30] G. Schultz, *Ann.* **203,** 95 (1880); J. Schmidt and A. Kämpf, *Ber.* **36,** 3745 (1903).

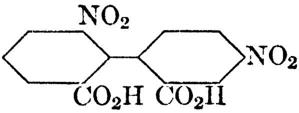
metrical "*cis*" configuration, VI, with a plane of symmetry parallel to,



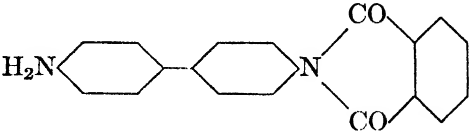
VI

and halfway between, the benzene rings.

In spite of the experimental support which it had thus received, the Kaufler configuration of biphenyl was never very widely accepted, and it soon was completely discarded. In 1926, Christie, Holderness, and Kenner[31] found that Schultz's dinitrodiphenic acid was not a stereoisomeric *o,o'*-compound with structure I after all, but was instead a structurally isomeric *o,p'*-compound with structure VII. They found also that it, like the true *o,o'*-isomer, could be resolved. This fact alone, of course, was sufficient to exclude the symmetrical configuration VI. Moreover, Le Fèvre and Turner[32] and Kuhn, Jacob, and Furter[33] showed that Kaufler's original evidence for his configuration was incorrect since the product of the reaction between phthalic anhydride and benzidine has structure VIII instead of IV. Still more recently, studies of dipole moments[34] and of crystal structure[35] have shown that the two benzene rings in biphenyl and in several of its derivatives are *coaxial;* or, in other words, that, in the molecule of any compound of this type, a straight line drawn along the central carbon-carbon bond and continued in each direction passes through the two *para* carbon atoms. The experimental evidence supporting the Kaufler configuration was accordingly found to be incorrect, and the configuration was shown to be untenable.



VII



VIII

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[31] G. H. Christie, A. Holderness, and J. Kenner, *J. Chem. Soc.* **1926,** 671.

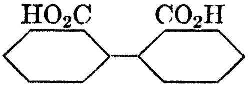
[32] R. J. W. Le Fèvre and E. E. Turner, *J. Chem. Soc.* **1926,** 2476.

[33] R. Kuhn, P. Jacob, and M. Furter, *Ann.* **455,** 254 (1927).

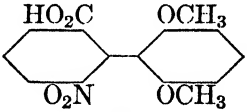
[34] A. Weissberger and J. W. Williams, *Z. physik. Chem.* **B3,** 367 (1929).

[35] J. Dhar, *Indian J. Physics* **7,** 43 (1932); *C.A.* **26,** 4517 (1932).

There still remained, however, the fact that various derivatives of biphenyl are optically active. Some other interpretation of the molecular dissymmetry of these substances had therefore to be provided. A hint as to the direction in which this interpretation was to be sought was provided by the regularities observed in both the occurrence and the nonoccurrence of optical activity. As the problem was studied more carefully, and as the number of known optically active biphenyls greatly increased, two conditions that are necessary for optical activity became apparent. In the first place, it was found that every optically active biphenyl possesses several bulky substituents in the positions *ortho* to the central carbon-carbon bond (the so-called *pivot bond*); and, in the second place, it was found that every optically active biphenyl is so substituted that neither of its two benzene rings possesses a plane of symmetry that is perpendicular to the plane of the ring and that contains the pivot bond. Thus, of the two above resolvable dinitrodiphenic acids, the *o,o'*-isomer, I, has four large *ortho* substituents, and the *o,p'*-isomer, VII, has three. Moreover, neither ring of either of these two substances has a plane of symmetry in the required position, although, of course, each ring, when considered by itself alone, has a plane of symmetry in its own plane. On the other hand, all attempts to resolve the unsubstituted diphenic acid, IX, have failed, presumably because the number of *ortho* substituents is insufficient; similarly, all attempts to resolve the substance with structure X have also failed, presumably because the ring with the two methoxyl groups has a plane of symmetry of the required type. Additional examples of both active and inactive biphenyls are given below in this section.



IX



X

On the basis of the foregoing empirical generalizations, a satisfactory interpretation of the optically active biphenyls was soon discovered. The accepted view, which was closely approached by Christie and Kenner[28] as early as 1922, was expressed in its present form almost simultaneously in 1926 by Turner and Le Fèvre,[36] by Bell and Kenyon,[37] and by Mills.[38] This view is that, in all the biphenyl derivatives, the

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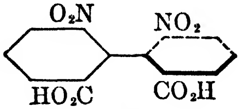
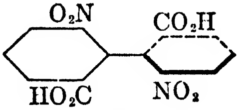
[36] E. E. Turner and R. J. W. Le Fèvre, *Chemistry & Industry* **45**, 831, 883 (1926).
[37] F. Bell and J. Kenyon, *Chemistry & Industry* **45**, 864 (1926).
[38] W. H. Mills, *Chemistry & Industry* **45**, 884 (1926).

two benzene rings are coaxial, but that, in the optically active ones, the rings are held in approximately perpendicular planes by the repulsions of the *ortho* substituents. (Cf. Sections 1·15 and 9·6.) Thus, the configurations of the enantiomorphic *o,o'*-dinitrodiphenic acids are considered to be XI and XII. It is easily verified that these configurations are indeed nonsuperposable mirror images of one another.

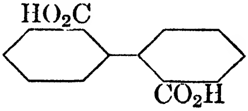


XI



XII

On the other hand, the parent diphenic acid, which cannot be resolved, must be able to achieve a completely planar conformation, in which the plane of the molecule is a plane of symmetry; this planar conformation is presumably the one represented by diagram XIII rather than the one



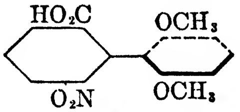
XIII

represented by IX (these two diagrams now being considered to represent not merely structures but also geometrical forms), since the interference of the two carboxyl groups in IX would doubtless prevent the coplanarity of the rings, whereas the much smaller interference of the carboxyl groups and hydrogen atoms in XIII would be insufficient to do so. The reason why every optically active biphenyl must have bulky *ortho* substituents should now be apparent; for, without such substituents, the molecule can always become planar so that it possesses a plane of symmetry.

If one or more *dissymmetric* substituents are attached to a biphenyl system, the substance may of course be optically active even when the two rings can achieve the coplanar conformation. This conclusion follows because the plane of the two rings might then no longer be a plane of symmetry for the entire molecule, including the dissymmetric substituents. Such a substance would not, however, be an "optically active biphenyl," in the sense in which the term is used here. It would instead be merely an optically active substance of a type that depends on the nature of the dissymmetric substituents; the presence of the biphenyl system would then be purely incidental.

Moreover, the further inactive substance X must also possess a plane of symmetry, even though the two rings probably cannot be coplanar.

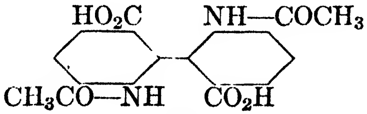
As can be seen from the configuration XIV, this plane of symmetry is the plane of the ring at the left of the figure (i.e., the plane of the paper). The reason why every optically active biphenyl must be so substituted that neither benzene ring has a plane of symmetry which is perpendicular to it and which contains the pivot bond should now be apparent; for, if either ring has such a plane of symmetry, then the plane of the *other* ring is a plane of symmetry for the entire molecule when the two rings are mutually perpendicular. (As before, the possibility that dissymmetric substituents may be attached to the biphenyl system can be ignored as irrelevant.)



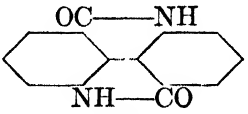
XIV

It should be noted here that the above discussion does not imply either that diphenic acid, IX (or XIII), is held rigidly in the planar conformation, or that the substance X (or XIV) is held rigidly in the conformation in which the two rings are perpendicular to one another. As a matter of fact, it is improbable that the molecules of either substance spend more than small fractions of their time in the conformations in question. Nevertheless, even though all remaining conformations are dissymmetric, each substance must be optically inactive. The justification for this statement is that the molecules are *able* to assume symmetric conformations; when they depart from these conformations, the probabilities that they will assume any given dissymmetric ones are exactly equal to the probabilities that they will instead assume the enantiomorphic ones. Consequently, each substance may be described, in a certain sense, as a nonresolvable racemic modification. The situation here is thus analogous to that with *meso*-tartaric acid. (See pages 191 f.)

The above interpretation of the optically active biphenyls receives considerable support from several further kinds of experimental evidence. If the activity is due to a lack of coplanarity of the two benzene rings, it should disappear if the rings were enabled in some way to become coplanar. Thus, if the two acetyl groups of the optically active substance XV are removed by hydrolysis, an inactive dilactam, XVI, results.[39]



XV



XVI

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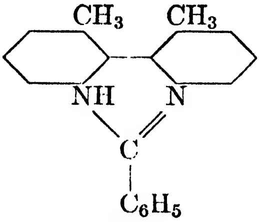
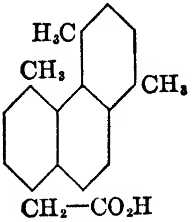
[39] J. Meisenheimer and M. Höring, *Ber.* **60**, 1425 (1927).

The two six-membered lactam rings do not require coplanarity of the benzene rings, but they do permit it. (Cf. Section 9·3.) It is doubtless important here that there are no large interatomic repulsions hindering coplanarity. In the substance XVII, on the other hand, the two methyl groups interfere strongly, and the seven-membered ring has sufficient flexibility to permit some rotation about the pivot bond; the substance can accordingly be obtained in active form.[40] Moreover, the phenanthrene derivative, XVIII, also has been resolved.[41] Possibly, therefore, even the six-membered aromatic ring in the center of this molecule can be puckered enough to permit a small rotation about the pivot bond; on the other hand, the observed optical activity could be explained equally well on the assumption that the two interfering methyl groups are displaced by their mutual repulsion in opposite directions away from the plane of the phenanthrene ring system. Probably both some puckering and some displacement of the methyl groups occur.



XVII



XVIII

The repulsions preventing coplanarity can be altered by changes in either the number or the sizes of the blocking *ortho* substituents. A great many optically active biphenyls, like the *o,o'*-dinitrodiphenic acid, I, have the maximum number of such substituents, i.e., four. In numerous other substances, however, a smaller number of substituents are sufficient for optical activity. In many of these compounds three groups

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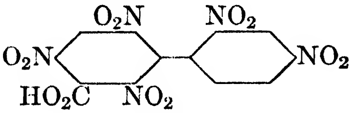
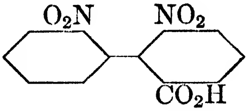
[40] S. Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.* **6**, 263 (1932); *C.A.* **26**, 3246 (1932).

[41] M. S. Newman and A. S. Hussey, *J. Am. Chem. Soc.* **69**, 978, 3023 (1947); M. S. Newman and W. B. Wheatley, *ibid.* **70**, 1913 (1948).

are still present, as in the above-mentioned *o,p'*-dinitrodiphenic acid, VII, and also in the further substances XIX [42] and XX.[43] Moreover,

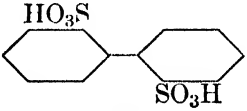


XIX

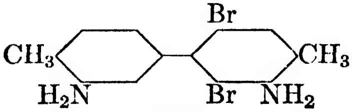


XX

in some substances, such as the ones with structures XXI [44] and XXII,[45]

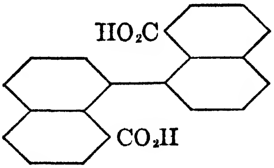


XXI

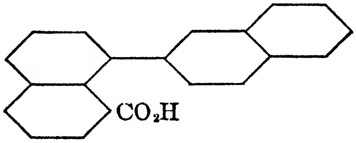


XXII

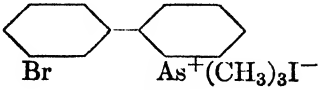
two very large *ortho* substituents permit optical activity; since these substances are easily racemized, however, they can evidently achieve the coplanar conformations without particularly great difficulty. The α,α'-binaphthyl derivative, XXIII,[46,47] also can be resolved, although racemization is again easy; apparently, therefore, the benzene rings with the carboxyl groups act as *ortho* substituents upon the biphenyl system to which they are fused. On the other hand, the similar α,β'-binaphthyl derivative, XXIV,[47] cannot be resolved; here only a single *ortho* substituent is present. In the arsonium salt, XXV,[48] some fairly conclusive



XXIII



XXIV



XXV

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[42] H. A. Stearns and R. Adams, *J. Am. Chem. Soc.* **52**, 2070 (1930).

[43] R. Adams and J. B. Hale, J. *Am. Chem. Soc.* **61**, 2825 (1939).

[44] M. S. Lesslie and E. E. Turner, *J. Chem. Soc.* **1932**, 2394.

[45] W. I. Patterson and R. Adams, *J. Am. Chem. Soc.* **57**, 762 (1935).

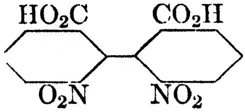
[46] A. Corbellini, *Atti accad. Lincei* **13**, 702 (1931); *C.A.* **26**, 1277 (1932). W. M. Stanley, . *Am. Chem. Soc.* **53**, 3104 (1931).

[47] J. Meisenheimer and O. Beisswenger, *Ber.* **65**, 32 (1932).

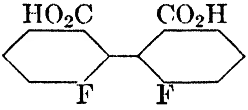
[48] M. S. Lesslie and E. E. Turner, *J. Chem. Soc.* **1933**, 1588; see also R. Adams and T. L. Cairns, *J. Am. Chem. Soc.* **61**, 2179 (1939).

evidence of optical activity has been reported; if this substance is indeed active, then a single substituent, provided that it be sufficiently large, can prevent coplanarity.

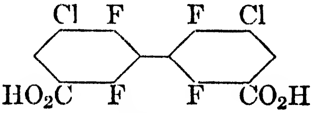
As has already been suggested, the *size* of the *ortho* substituents is also an important factor governing the occurrence of optical activity. Even in those molecules which have fewer than four substituents, hydrogen atoms are present at the otherwise unoccupied *ortho* positions. If these hydrogen atoms are considered to fill up appreciable volumes, as they must certainly do (cf. Section 9·6), then every biphenyl, regardless of the number of *ortho* substituents, has four blocking atoms or groups. It is evident from the above data, however, that hydrogen atoms are too small to interfere successfully with any but the largest groups. That other small atoms can have similar limitations is shown by the sequence of compounds I, XXVI,[49] and XXVII.[50] As has been mentioned several times already, the first of these three substances can readily be resolved; since, moreover, the optically active forms cannot be racemized, the resistance to the achievement of coplanarity must be very great. If the two nitro groups are replaced by the much smaller fluorine atoms, as in the compound XXVI, the substance can still be resolved, but racemization is now easy. Finally, if the carboxyl groups also are replaced by fluorine atoms, as in the compound XXVII, the substance can no longer be resolved. (The presence of additional substituents in XXVII is required in order that neither benzene ring have a plane of symmetry perpendicular to itself.) In a similar manner, the substance XIX, above, cannot be racemized,[42] whereas XX, with smaller substituents, can be.[43]



I



XXVI



XXVII

Considerable success has been achieved in the attempt to treat in a more quantitative manner the relation between the sizes of the *ortho* substituents and the resolvabilities of the corresponding biphenyls. From x-ray and other similar data, the atomic and group radii given in Table 6·1 have been derived. These radii imply that each substituent atom or group is to be regarded as a sphere with the radius stated. Two groups in the *ortho* positions of different benzene rings may be assumed just to touch in the planar conformation if the sum of their radii is equal to 2.90 A. Consequently, if this sum is appreciably less than 2.90 A, the groups do not interfere significantly; if it is appreciably greater than

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[49] W. M. Stanley, E. McMahon, and R. Adams, *J. Am. Chem. Soc.* **55**, 706 (1933).

[50] E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.* **55**, 4219 (1933).

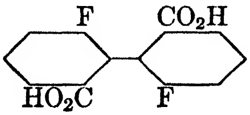
TABLE 6·1

ATOMIC AND GROUP RADII USED IN ESTIMATING THE AMOUNTS OF INTERFERENCE BETWEEN *Ortho* SUBSTITUENTS IN BIPHENYLS[a]

Atom or Group	*Radius (in A)*
H	0.94
F	1.39
OH	1.45
CO_2H	1.56
NH_2	1.56
CH_3	1.73
Cl	1.89
NO_2	1.92
Br	2.11
I	2.20

[a] R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 268 f.

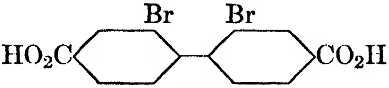
2.90 A, they interfere strongly; and if it is approximately equal to 2.90 A, they interfere slightly. There is, of course, no sharp dividing line between the pairs of groups which do, and those which do not, interfere; nevertheless the table has proved useful in the interpretation of the occurrence and nonoccurrence of optical activity. For example, in the nonracemizable *o,o′*-dinitrodiphenic acid, I, the sums of the group radii are 3.84 A for two nitro groups, 3.12 A for two carboxyl groups, and 3.48 A for one nitro and one carboxyl group. No matter which pairs of groups interfere, therefore, great interference cannot be avoided. With the substance XXVI, similarly, the sums of the radii are 2.78 A for two fluorine atoms, 3.12 A for two carboxyl groups, as before, and 2.95 A for one fluorine atom and one carboxyl group. Although the fluorine-fluorine interaction is therefore so small that it probably would not greatly hinder coplanarity, the conformation in which the two fluorine atoms interfere with one another requires that at the same time the two carboxyl groups also interfere with one another (as in diagram XXVI). Consequently, the easy racemization of the substance probably proceeds through the planar conformation shown in diagram XXVIII, in which



XXVIII

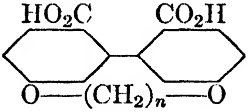
each fluorine atom interferes with a carboxyl group. Finally in the tetrafluoro compound, XXVII, only fluorine-fluorine interactions are possible; accordingly, the substance cannot be resolved.

The foregoing rather qualitative considerations have been made much more precise in recent semiquantitative treatments,[51, 52] in which use is made of empirical values for the energies required to overcome interatomic repulsions and to stretch, shorten, and bend valence bonds. Although the details of these elaborate computations are too complex to be given here, mention may nevertheless be made of the fact that the calculated activation energy for the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl, XXIX (18 kcal per mole), is of a quite reasonable magnitude and can hardly be seriously in error.[52]



XXIX

As was mentioned above, diphenic acid cannot be obtained in optically active form. This fact is reasonable since the molecule can achieve the planar conformation XIII, in which the carboxyl groups interfere only with hydrogen atoms; the sum of radii is then equal to 2.50 A, which is appreciably less than 2.90 A. On the other hand, the substance should be resolvable if the only permissible planar conformation were IX, in which the two carboxyl groups interfere strongly with each other; the sum of the radii would then be 3.12 A, which is appreciably greater than 2.90 A. That this conjecture is correct receives support from the fact that the two substances XXX,[53] with n equal to 8 and to 10, have been resolved. Here, a conformation analogous to XIII is rendered impossible by the chain of methylene groups joining the *meta* carbon atoms; consequently, the slow racemization which occurs must proceed through a conformation analogous to IX. As has just been shown, however, such a conformation is made unstable by the interference of the carboxyl groups. The resolvability of the substance is therefore explained.



XXX

Although a satisfactory explanation of the optical activity of the biphenyls can be obtained with the assumption that rotations about the pivot bonds are restricted by the atoms or groups in the *ortho* positions

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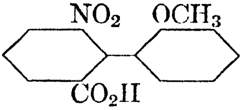
[51] F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.* **14**, 733 (1946). See also T. L. Hill, *ibid.* **14**, 465 (1946); I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.* **1946**, 173.

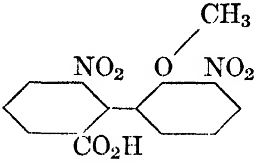
[52] F. H. Westheimer, *J. Chem. Phys.* **15**, 252 (1947).

[53] R. Adams and N. Kornblum, *J. Am. Chem. Soc.* **63**, 188 (1941).

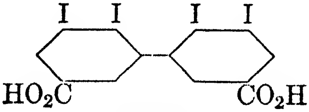
(cf., however, the preceding paragraph), some evidence can be brought forward to support the belief that still other factors must also be involved. Thus, at 25°C the optical rotatory power of an ethyl alcoholic solution of the substance XXXI decreases to half its original value in 9.4 minutes.[54] However, if a nitro group is introduced in the *meta* position that is *ortho* to the methoxyl group, the "half-life" of the resulting substance, XXXII, under identical conditions is increased to 1905 minutes.[55] The nitro group here can hardly interfere directly with the *ortho* substituents on the other ring, but it may do so indirectly by repelling the methoxyl group and by thus forcing *it* to interfere more strongly in the compound XXXII than in XXXI. Many of the variations in optical stability produced by substituents in positions other than *ortho* may be attributed to a "buttressing effect" of this type. An extreme example is provided by 2,3,2′,3′-tetraiodo-5,5′-dicarboxybiphenyl, XXXIII, which is racemized only about 3.3 × 10^{-5} times as fast as is the analogous 2,2′-diiodo-5,5′-dicarboxybiphenyl, XXXIV.[56] The idea of buttressing is, however, not sufficient to explain all effects of substituents in positions other than *ortho* upon the rate of racemization; for example, it cannot account for the fact that, with the substance XXXV, the nitro group in the *para* position increases the half-life (in acetone) to 115 minutes.[57] Its effect is therefore similar to, although smaller than,



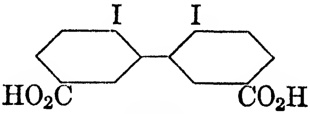
XXXI



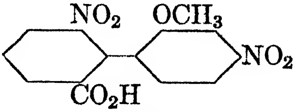
XXXII



XXXIII



XXXIV



XXXV

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[54] R. W. Stoughton and R. Adams, *J. Am. Chem. Soc.* **54**, 4426 (1932).

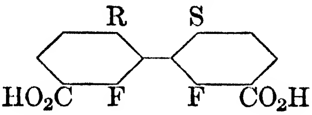
[55] S. L. Chien and R. Adams, *J. Am. Chem. Soc.* **56**, 1787 (1934).

[56] F. H. Westheimer and M. Rieger, personal communication.

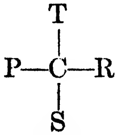
[57] W. E. Hanford and R. Adams, *J. Am. Chem. Soc.* **57**, 1592 (1935).

that of the *meta* nitro group in the compound XXXII. Numerous further examples of such variations have been reported. Obviously, certain additional effects of not completely understood nature are responsible for these smaller variations in optical stability; possibly, electrostatic interactions of some kind are involved.

A very striking, and theoretically important, characteristic of the optically active biphenyls is that they, unlike the optically active substances of all the classes considered heretofore, cannot be unambiguously classified by means of type formulas. For example, in discussing the structure XXXVI, one cannot make a general statement either that the corresponding substance must be resolvable or that it must be nonresolvable. Moreover, the situation is unaltered if the condition is imposed that the symbols R and S must represent the same substituent, or that they must represent different substituents, or that they must or must not represent fluorine. Indeed, the resolvability or nonresolvability of the substance XXXVI cannot be predicted unless it is known precisely what atoms or groups are represented by the symbols R and S. Thus, a substance of structure XXXVI should be resolvable if R and S are both nitro groups or if one is a nitro group and the other is a carboxyl group; on the other hand, it should be nonresolvable if R and S are both hydrogen atoms or if one is a hydrogen atom and the other is a hydroxyl group. The situation here is therefore entirely different from that encountered with the other classes of optically active compound. Thus, any substance with structure XXXVII should be resolvable if no two of the atoms or groups P, R, S, and T are identical, but it should be nonresolvable if at least one pair of them is identical; similarly, any substance with structure XXXVIII should be resolvable if R and S are different, but nonresolvable if they are identical; and so on. With such substances, one can make the desired predictions without knowing exactly what the atoms or groups are, provided only that the required identity or nonidentity of pairs of them be satisfied. (In the foregoing

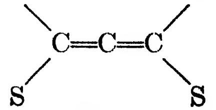


XXXVI



$$\begin{array}{c} T \\ | \\ P\text{—}C\text{—}R \\ | \\ S \end{array}$$

XXXVII

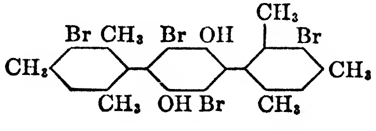


XXXVIII

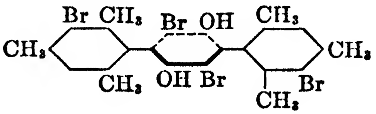
discussion, the assumption must, of course, be made that no substituent in XXXVI, XXXVII, or XXXVIII is itself dissymmetric.)

As with the allenes and their analogs, none of these optically active biphenyls contain asymmetric atoms.

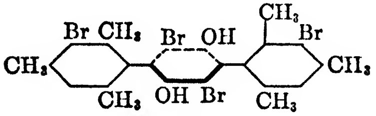
6·13 Analogs of the Optically Active Biphenyls. An obvious way in which the principles discussed in the preceding section can be generalized is by the introduction of additional benzene rings and of additional pivot bonds into the molecules considered. Thus, a substituted terphenyl of structure I [58] can exist in altogether three stereoisomeric forms. The *trans* form, II, is optically inactive because it has a center of symmetry; the two *cis* forms, III and IV, however, are enantiomorphs of each other, with neither center nor plane of symmetry. All three of these tetrabromo compounds, on further bromination, are transformed into the same inactive hexabromo derivative, V; [58] this fact strongly supports the generally accepted interpretation of the isomerism.



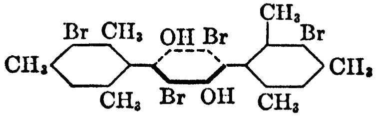
I



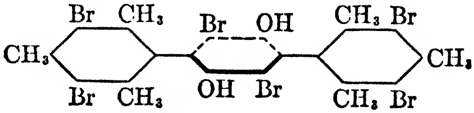
II



III

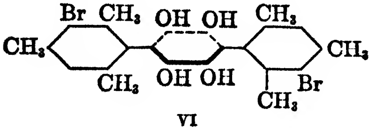


IV

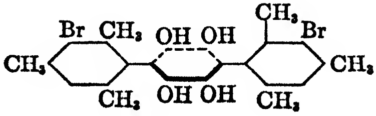


V

Of the two further stereoisomeric terphenyls, VI and VII, the *trans* form, VI, again possesses a center of symmetry, but the *cis* form, VII,



VI



VII

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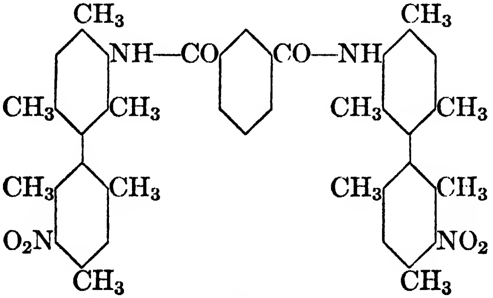
[58] P. R. Shildneck and R. Adams, *J. Am. Chem. Soc.* **53,** 343, 2203 (1931).

now has a plane of symmetry in the plane of the two external rings. Both forms are therefore optically inactive.[58]

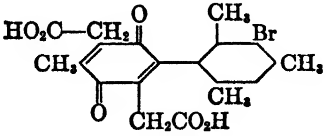
A different type of structure with two pivot bonds is shown by VIII.



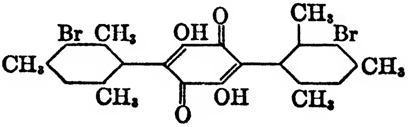
VIII

Since the two biphenyl systems here are equivalent, a *meso* form and a pair of enantiomorphs should exist. Two inactive forms have been prepared; these are presumed to be *meso* and racemic, but no attempt has been made to resolve either form.[59]

A second obvious generalization of the optically active biphenyls consists in the replacement of one or more benzene rings with rings of other types. In the substance IX, in which one of the two rings is quinoid instead of aromatic, rotation about the central carbon-carbon bond must be restricted, just as it is in a true optically active biphenyl, since the compound has been resolved into enantiomorphic forms.[60] Moreover, the further structure, X, is analogous to I and, like it, has been found to correspond to both a *meso* form and a pair of enantiomorphs.[58]



IX



X

Heterocyclic rings also can be introduced without essential alteration of the situation. Each of the structures XI,[61] XII,[62] XIII,[63] and XIV,[64] for example, belongs to a separable pair of enantiomorphs; and the further structure, XV,[65] with two equivalent pivot bonds, corresponds to

[59] R. Adams and R. M. Joyce, Jr., *J. Am. Chem. Soc.* **60**, 1489 (1938).

[60] D. W. Hill and R. Adams, *J. Am. Chem. Soc.* **53**, 3453 (1931).

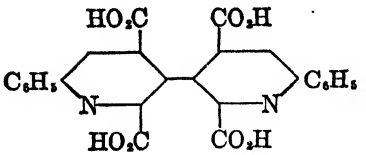
[61] E. H. Woodruff and R. Adams, *J. Am. Chem. Soc.* **54**, 1977 (1932).

[62] L. H. Bock and R. Adams, *J. Am. Chem. Soc.* **53**, 374 (1931).

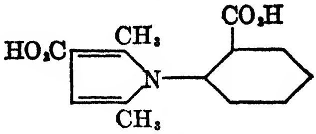
[63] C. Chang and R. Adams, *J. Am. Chem. Soc.* **53**, 2353 (1931).

[64] W. I. Patterson and R. Adams, *J. Am. Chem. Soc.* **55**, 1069 (1933).

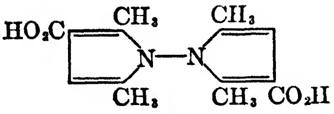
[65] C. Chang and R. Adams, *J. Am. Chem. Soc.* **56**, 2089 (1934).



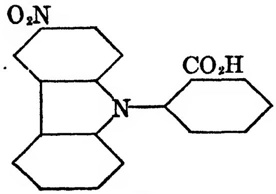
XI



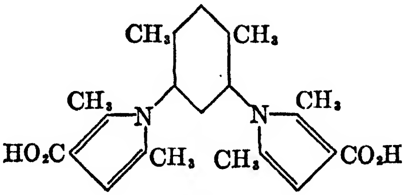
XII



XIII



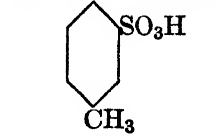
XIV



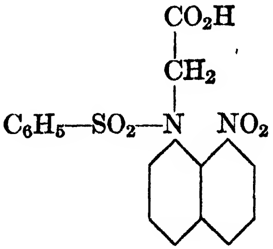
XV

both a *meso* form and a pair of enantiomorphs.

Among the analogs of the optically active biphenyls are included several substances which owe their activities to the restriction of rotation about pivot bonds that do not join two distinct rings of any kind. Typical examples are represented by the structures XVI [66] and XVII,[67] in



XVI



XVII

which the pivot bonds are between the carbon atoms of the remaining rings and the nitrogen atoms of the noncyclic substituents; and also by

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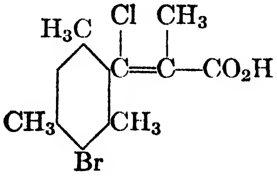
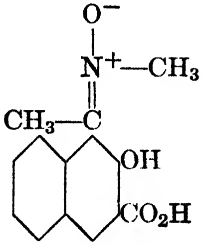
[66] W. H. Mills and R. M. Kelham, *J. Chem. Soc.* **1937**, 274.

[67] W. H. Mills and K. A. C. Elliott, *J. Chem. Soc.* **1928**, 1291.

the structures XVIII [68] and XIX,[69] in which the pivot bonds are between pairs of carbon atoms. (For further discussion of compound XVII, see pages 235 f.)

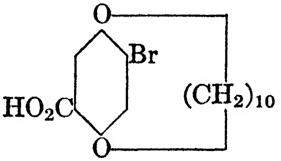


XVIII



XIX

Finally, a substituted benzoic acid with structure XX has been found to be resolvable.[70] Here, the chain of ten CH_2 groups is in front of the plane of the ring in one enantiomorph, and behind that plane in the other enantiomorph. Racemization of the optically active forms would therefore require that the chain pass round the ring from a position behind it to one in front of it, or vice versa. The situation is accordingly analogous to that with the enantiomorphs possessing the structure XXX of the preceding section. (See page 211.)



XX

As with the optically active biphenyls proper, none of the above substances contain asymmetric atoms.

6·14 Optical and Geometrical Isomerism. Although stereoisomerism is commonly divided into the smaller fields of *optical* and *geometrical* (or *cis-trans*) isomerism, the distinction between these two subdivisions is rarely, if ever, stated explicitly. Often, indeed, optical isomerism is described merely as that kind of stereoisomerism displayed by the tartaric acids, and geometrical isomerism is described as that kind displayed by maleic and fumaric acids. Such descriptions are clearly not definitions, however, since the significant point of difference between

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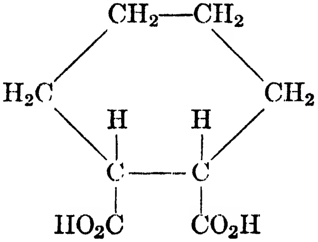
[68] R. Adams and M. W. Miller, *J. Am. Chem. Soc.* **62**, 53 (1940).

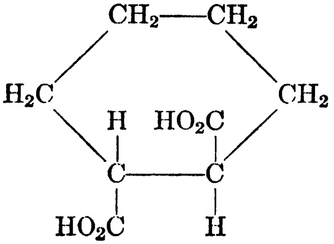
[69] J. Meisenheimer, W. Theilacker, and O. Beisswenger, *Ann.* **495**, 249 (1932).

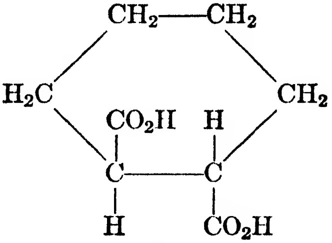
[70] A. Lüttringhaus and H. Gralheer, *Naturwissenschaften* **28**, 255 (1940); *Ann.* **557**, 108 (1947); *C.A.* **42**, 879 (1948).

the two kinds of isomerism is not specified. On the basis of merely these examples, one might, in fact, draw the completely erroneous (and rather ridiculous) conclusion that stereoisomers are optical isomers of each other if the number of oxygen atoms in the molecule of each is greater than that of carbon atoms, and are geometrical isomers otherwise.

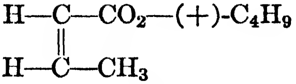
In view of the vagueness which thus generally attends the terms "optical" and "geometrical" isomerism, a consideration of the meanings of these terms is desirable here. Such a consideration is made rather difficult, however, by the fact that no complete agreement exists among chemists as to exactly where the dividing line between the two types of stereoisomerism is to be drawn. Thus, many chemists consider *cis*-cyclohexane-1,2-dicarboxylic acid, I, to be a geometrical isomer of the two enantiomorphic *trans* forms, II and III, as is indeed suggested by the prefixes *cis* and *trans*, respectively; other chemists, however, consider all three stereoisomeric forms to be optical isomers of one another, as is suggested by the close analogy with the three corresponding tartaric acids. (Cf. page 190.) The two enantiomorphic *trans* forms, of course, are always regarded as optical isomers of each other. It is therefore clearly impossible for any definition of optical and geometrical isomerism to lead to a classification of stereoisomers in complete agreement with the usage of all chemists.


I


II

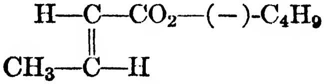

III

Another difficulty encountered in the attempt to state precisely the distinction between geometrical and optical isomerism is that some substances must be regarded as both optical and geometrical isomers of one another at the same time. For example, the ester IV, formed from *cis*-



$$\begin{array}{l} H\text{—}C\text{—}CO_2\text{—}(+)\text{-}C_4H_9 \\ \quad \| \\ H\text{—}C\text{—}CH_3 \end{array}$$

IV



$$\begin{array}{l} \quad\;\; H\text{—}C\text{—}CO_2\text{—}(-)\text{-}C_4H_9 \\ \qquad\quad \| \\ CH_3\text{—}C\text{—}H \end{array}$$

V

crotonic acid and (+)-*sec*-butyl alcohol, and the ester V, formed from *trans*-crotonic acid and (−)-*sec*-butyl alcohol, must be so regarded. As a result of this unavoidable overlapping, the distinction between the two kinds of stereoisomerism is neither so clean cut nor so useful as is that, for example, between structural isomerism and stereoisomerism. (The above-mentioned *cis*- and *trans*-cyclohexane-1,2-dicarboxylic acids may be considered similarly to be both optical and geometrical isomers, but they do not need to be. When the definitions given below are employed, in fact, they are found to be purely optical isomers.)

The formulation of satisfactory definitions of optical and geometrical isomerism can now be attempted. Since, as was pointed out above, there exist borderline cases which are classified differently by different chemists, it is evident that the desired definitions can be stated in several equally satisfactory, but nonequivalent (and indeed mutually inconsistent), ways. The definitions adopted below are therefore not unique; moreover, they are not necessarily the best ones that could be devised.

Before the distinction between optical and geometrical isomerism can be stated, the concept of a *dissymmetric grouping* must be introduced. Such a grouping may be defined as a set of interconnected atoms, which represents a part or the whole of a neutral molecule or ion, and which satisfies all three of the following conditions.

1. The grouping must be dissymmetric in at least one of its possible configurations.

2. The addition of any further atoms to the grouping (whether these are contained in the molecule under consideration or not) cannot produce a larger grouping violating condition 1.

3. The removal of *any one* of the external atoms of the grouping (i.e., the removal of any single atom which is bonded to only one other atom of the grouping) must produce a smaller grouping violating either condition 1 or 2 (or both).

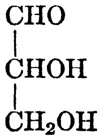
A few examples will make the situation clearer. With chlorobromoiodomethane, VI, the entire molecule is a dissymmetric grouping since

$CHClBrI$
VI

$-CHClBr$
VII

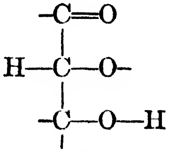
(1) it is dissymmetric in at least one (actually in both) of its possible configurations; (2) it cannot be expanded, by the addition of further atoms,

to a larger group of any sort, and so it obviously cannot be expanded to one violating condition 1; and (3) the removal of any external atom from it, such as the iodine atom, leaves a residue like VII, which would be made symmetric by the addition of a second hydrogen atom, and which therefore violates condition 2. Obviously there is no further dissymmetric grouping in chlorobromoiodomethane. In a similar way, the two glyceraldehydes of structure VIII contain the dissymmetric grouping



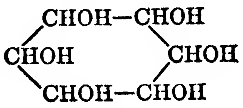
$CHO{-}CHOH{-}CH_2OH$

VIII

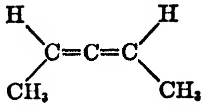


IX

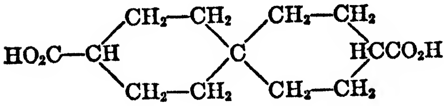
IX; here, the entire molecule is not a dissymmetric grouping since it violates condition 3. Moreover, the inositols, allenes, spiranes, and biphenyls of structures X–XIII, respectively, contain the dissymmetric groupings XIV–XVII, respectively.



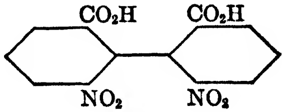
X



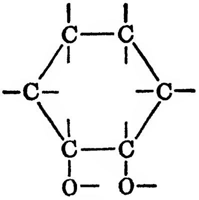
XI



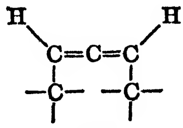
XII



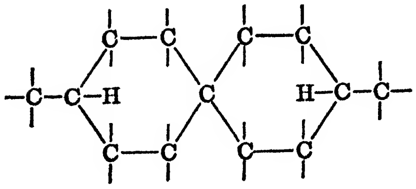
XIII



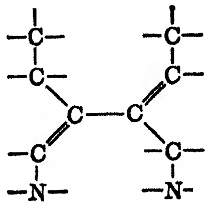
XIV



XV

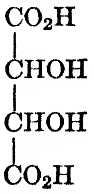


XVI



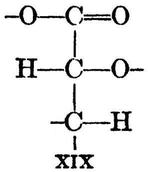
XVII

A molecule may contain two or more dissymmetric groupings. The tartaric acids of structure XVIII, for example, contain the two equivalent ones represented by diagram XIX, whereas the analogous cyclohexane-1,2-dicarboxylic acids, I–III, contain the two equivalent ones represented by diagram XX. As in these last two examples, different dissymmetric groupings within the same molecule may have atoms in common, although they do not need to do so.

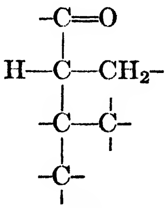


$$\begin{array}{l} CO_2H \\ | \\ CHOH \\ | \\ CHOH \\ | \\ CO_2H \end{array}$$

XVIII

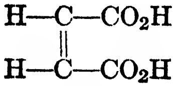


XIX



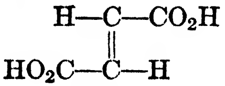
XX

Stereoisomerism can exist in the complete absence of dissymmetric groupings, as, for example, with maleic acid, XXI, and fumaric acid,



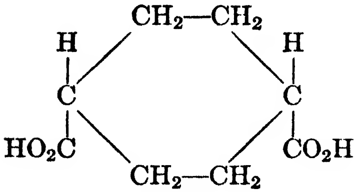
$$\begin{array}{c} H-C-CO_2H \\ \| \\ H-C-CO_2H \end{array}$$

XXI

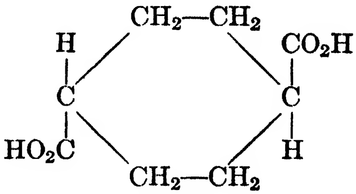


$$\begin{array}{c} H-C-CO_2H \\ \| \\ HO_2C-C-H \end{array}$$

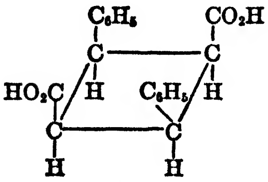
XXII



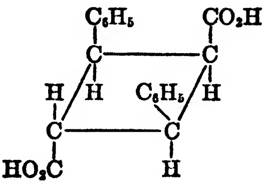
XXIII



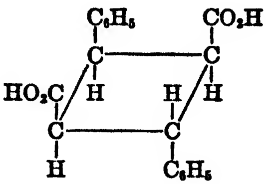
XXIV



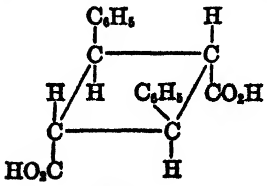
XXV



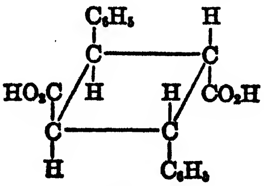
XXVI



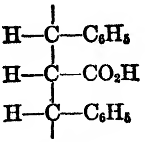
XXVII



XXVIII

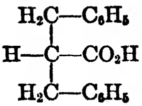


XXIX



$$\begin{array}{rcl} & | & \\ H- & C & -C_6H_5 \\ & | & \\ H- & C & -CO_2H \\ & | & \\ H- & C & -C_6H_5 \\ & | & \end{array}$$

XXX



$$\begin{array}{rcl} H_2 & C & -C_6H_5 \\ & | & \\ H- & C & -CO_2H \\ & | & \\ H_2 & C & -C_6H_5 \end{array}$$

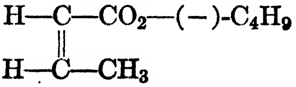
XXXI

XXII, with the two cyclohexane-1,4-dicarboxylic acids, XXIII and XXIV, and with the five truxillic acids, XXV–XXIX. (The grouping XXX of the truxillic acids satisfies the first of the above conditions for a dissymmetric grouping, but it violates the second since it is transformed into the symmetrical grouping XXXI by the addition of two hydrogen atoms.)

Geometrical isomers can now be defined as stereoisomers which do not differ in the configuration of any dissymmetric grouping. Thus, maleic and fumaric acids, the two cyclohexane-1,4-dicarboxylic acids, and the five truxillic acids exhibit only geometrical isomerism. As with these examples, any set of stereoisomers without a dissymmetric grouping must consist of purely geometrical isomers, and can contain no optically active member.

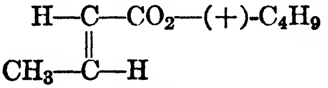
In an analogous manner, *optical* isomers can be defined as stereoisomers which differ only in the configuration or configurations of one or more dissymmetric groupings. Thus, the two glyceraldehydes, the three tartaric acids, and the three cyclohexane-1,2-dicarboxylic acids (cf. structures VIII, XVIII, and I, II, and III, respectively) exhibit only optical isomerism. As with these examples, a set of purely optical isomers always contains at least one pair of enantiomorphs; it may or may not contain in addition one or more optically inactive *meso* forms.

In more complicated cases, geometrical and optical isomerism may occur simultaneously. For example, the four *sec*-butyl crotonates, IV, V, XXXII, and XXXIII, contain only the one dissymmetric grouping,



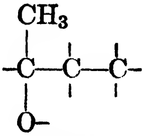
$$\begin{array}{rcl} H- & C & -CO_2-(-)\text{-}C_4H_9 \\ & \| & \\ H- & C & -CH_3 \end{array}$$

XXXII



$$\begin{array}{rcl} H- & C & -CO_2-(+)\text{-}C_4H_9 \\ & \| & \\ CH_3- & C & -H \end{array}$$

XXXIII



$$\begin{array}{ccccccc} & CH_3 & & & & & \\ & | & & | & & | & \\ - & C & - & C & - & C & - \\ & | & & | & & | & \\ & O- & & & & & \end{array}$$

XXXIV

XXXIV, which forms part of the *sec*-butyl group. The two *cis*-crotonates, IV and XXXII, are purely optical isomers of each other since they differ only in the configuration of this dissymmetric grouping; similarly, the two *trans*-crotonates, V and XXXIII, are also purely optical isomers of each other. On the other hand, the two esters of (+)-*sec*-butyl alcohol, IV and XXXIII, are purely geometrical isomers of each other since they do not differ in the configuration of the dissymmetric grouping; similarly, the two esters of (−)-*sec*-butyl alcohol, V and XXXII, are also purely geometrical isomers. Finally, the esters, IV and V, are both geometrical and optical isomers, as was stated above (page 219); and the esters, XXXII and XXXIII, also are related in this same way.

In many, but unfortunately not in all, instances, the foregoing rather formidable definitions of optical and geometrical isomerism can be replaced by simpler ones. In maleic and fumaric acids, XXI and XXII, respectively, the two carboxyl groups, the two remaining hydrogen atoms, and the two remaining carbon atoms form a set of six atoms or groups which are held rigidly in a single plane. On account of the freedom of rotation about the oxygen-hydrogen and carbon-carbon single bonds, all the atoms of the carboxyl groups do not have to lie in the same plane as the rest of the molecule. However, since these groups are not dissymmetric, they are stereochemically equivalent to single atoms, which can be assumed to lie in the plane of the molecule. In many other *simple* examples of purely geometrical isomerism, a similar set of six coplanar atoms or groups is present, and the isomers differ only in the arrangement of these atoms or groups in the plane. With certain stereoisomeric nitrogen compounds, however, either one or two of these six atoms or groups may be missing. (See Sections 8·3 and 8·6.) Even with the cyclohexane-1,4-dicarboxylic acids, XXIII and XXIV, in which at any single instant the flexibility of the ring permits the atoms in question to depart appreciably from coplanarity, the *average* conformation, which alone is stereochemically significant, is doubtless planar. With the truxillic acids, inositol, and numerous other substances, however, this simplified definition of geometrical isomerism is not completely unambiguous, and so it cannot be generally used.

Whenever stereoisomers differ otherwise than in the arrangement of a set of six coplanar atoms or groups, the isomerism may be considered to be optical. As with the corresponding definition of geometrical isomerism, however, this further definition of optical isomerism also is restricted to simple cases and is not generally applicable.

In view of the complexity of any precise statement of the distinction between geometrical and optical isomerism, and in view also of the inadequacy of any less elaborate version, this distinction will be employed very little throughout the remainder of the book.

6·15 Optically Active Series. The sign of the rotation produced by an optically active substance can occasionally be reversed by a change in the experimental conditions. (See Section 5·5.) A further factor which similarly introduces confusion into stereochemical classification is that a parent substance often gives rise to derivatives with identical configuration but with opposite sign of rotation. For example, the salts and esters of the levorotatory lactic acid, I, are dextrorotatory. For

$$CH_3—CHOH—CO_2H$$

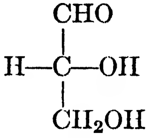
I

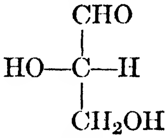
these reasons, it would be desirable to include in the complete name of an optically active substance a symbol which refers directly to the configuration of the substance and is independent of the sign of rotation. This symbol would then remain unchanged when the substance, under different conditions, exhibits different signs of rotation, or when it forms derivatives with opposite rotation.

It may be doubted whether any completely general and completely unambiguous classification of configurations, of the type desired, is possible; certainly, no such classification has as yet been devised. Nevertheless, there has been developed a scheme which permits the classification of configurations (but not without some ambiguity) within certain narrowly defined groups of compounds. This scheme consists in dividing configurations into those of the so-called D-series and those of the L-series on the basis of the genetic relationships among them. A substance is then said to belong to the D-series (or to the L-series) if it is, respectively, a derivative of a different substance belonging to the D-series (or L-series).

Originally, the two optically active series were designated by the lower-case prefixes *d*- and *l*-; more recently, however, the corresponding small capitals D- and L-, just mentioned, have instead become rather widely adopted. At the present time, there is no single convention that is uniformly and consistently used throughout the chemical literature. Thus, many authors retain the older symbols *d*- and *l*- to represent the two series, and then employ the different symbols (+)- and (−)- to represent the two possible signs of rotation; other authors have adopted the newer symbols D- and L- to represent the series, and then employ the older ones *d*- and *l*-, or the expressions (dextro)- and (levo)-, to represent the signs of rotation; still others, unfortunately, use the same prefixes *d*- and *l*- to represent both the series and the signs of rotation, and then ignore the resulting confusion. Throughout this book, the optically active series are designated only by the prefixes D- and L-, and the signs of rotation are designated only by the prefixes (+)- and (−)-; the now quite ambiguous symbols *d*- and *l*- are therefore not used at all. (Cf. pages 135 f.)

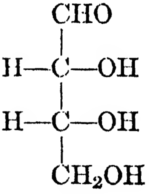
In order that an optically active series may be set up, some particular substance must be defined as belonging to the D- or L-series, so that the remaining substances may be related to it. Originally, Emil Fischer chose the natural dextrorotatory glucose as the prototype of the D-series, and, accordingly, he named this substance D-glucose. More recently, dextrorotatory glyceraldehyde, II,[16] has been chosen instead; since these

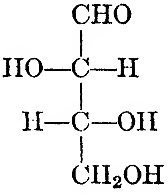

$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$
II

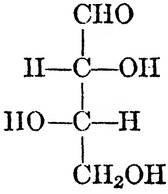

$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CH_2OH}\end{array}$$
III

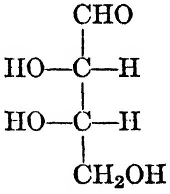
two conventions lead to the same assignment of series, no ambiguity results.

The way in which the optically active series are built up can be illustrated by a few examples. As has been mentioned before (see Section 6·7), (+)- and (−)-glyceraldehyde are by definition assigned the plane configurations II and III, respectively. Also by definition, they are said to belong to the D- and L-series, so that their complete names are, respectively, D-(+)- and L-(−)-glyceraldehyde. By the well-known methods of carbohydrate chemistry,[71] the aldehyde group in each of these substances can be changed into a CHOH—CHO group. (However, see below.) Since this larger group contains an asymmetric carbon atom that is not present in the original one, each of the glyceraldehydes can give rise to two products which, not being enantiomorphs, need not be formed in equal amounts. Thus, D-(+)-glyceraldehyde, II, gives rise to the tetroses IV and V, which are therefore said to belong to the D-series. Similarly, L-(−)-glyceraldehyde, III, gives rise to the tetroses VI and VII, which are said to belong to the L-series. It is particularly important here to observe that the assignment of the several tetroses IV–VII to the D- and L-series is based entirely on the preparation of the substances from D- and L-glyceraldehyde; it is completely independent of the signs of rotation. Actually, each of the D-sugars, IV and V, is levorotatory in aqueous solution, whereas each of the L-sugars, VI and VII, is dextrorotatory.[72]


$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$
IV


$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$
V


$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CH_2OH}\end{array}$$
VI


$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CH_2OH}\end{array}$$
VII

The procedure can be continued further. Each of the tetroses IV–VII can be transformed into two pentoses, each of which can in turn be

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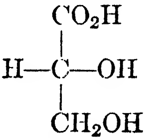
[71] See any elementary textbook of organic chemistry.

[72] Cf. M. L. Wolfrom in H. Gilman, *Organic Chemistry*, Johy Wiley and Sons, Inc., New York, 1st ed., 1938, Volume II, page 1411, 2nd ed., 1943, Volume II, page 1544.

transformed into two hexoses, and so on. In each reaction, the two products, regardless of their signs of rotation, belong to the same optically active series as does the substance from which they are derived. Three of the four D-aldopentoses and two of the eight D-aldohexoses are levorotatory in aqueous solution after the equilibria between the α and β forms have been attained; necessarily, therefore, three of the four L-aldopentoses and two of the eight L-aldohexoses are dextrorotatory.[72] In general, and without explicit reference to the sequence of reactions starting with the glyceraldehydes, the optically active series to which any monosaccharide belongs is determined by the configuration about the asymmetric carbon atom that is farthest removed from the carbonyl group; when the chain of carbon atoms is written vertically and with the carbonyl group at the top, the hydroxyl group upon the atom in question is to the right of the chain in the D-series, and to the left in the L-series.

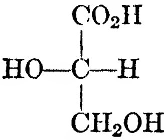
Several of the reactions mentioned in the two preceding paragraphs have not as yet been carried out in the laboratory. However, the configurational relationships, which were explained above with reference to these hypothetical reactions, have been experimentally established in indirect ways which need not be described here.

If the glyceraldehydes are oxidized, they give the glyceric acids VIII



$$\begin{array}{c} CO_2H \\ | \\ H—C—OH \\ | \\ CH_2OH \end{array}$$

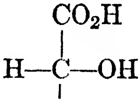
VIII



$$\begin{array}{c} CO_2H \\ | \\ HO—C—H \\ | \\ CH_2OH \end{array}$$

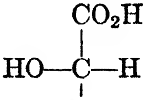
IX

and IX. The first of these products, VIII, even though it is levorotatory, is said to belong to the D-series on account of its genetic relationship to D-glyceraldehyde; it is accordingly called D-(−)-glyceric acid. Similarly, its enantiomorph, IX, is called L-(+)-glyceric acid. In accordance with the most widely accepted convention, an α-hydroxy acid is said to belong to the D-series if it contains the grouping X, and to belong



$$\begin{array}{c} CO_2H \\ | \\ H—C—OH \\ | \end{array}$$

X

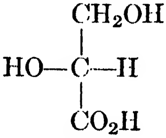


$$\begin{array}{c} CO_2H \\ | \\ HO—C—H \\ | \end{array}$$

XI

to the L-series if it instead contains the grouping XI. If more than one -CHOH—CO_2H group is present in the molecule, this definition of D- and L-series may become ambiguous; consequently, the series are not often employed with such substances, except with the tartaric acids, with which there is no ambiguity.

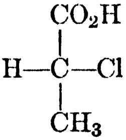
The arbitrariness of the now generally accepted definitions of the optically active series can be made apparent by a more detailed consideration of the glyceric acids. The acid VIII was said to belong to the D-series because of its formation from the D-aldehyde, II. In principle, however, it could instead be formed equally well from the L-aldehyde, III; for if, in the compound III, the primary alcohol group at the bottom is oxidized to a carboxyl group, and if the aldehyde group at the top is then reduced to a primary alcohol group, the resulting configuration is XII, which is easily seen to be identical with VIII. Of course, this second transformation is more complicated than is the first, but logically the two are on the same basis. Only considerations of convenience have led to the adoption of the first as the significant one.



$$\begin{array}{ccc} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CO_2H} & \end{array}$$

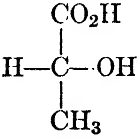
XII

Aside from the monosaccharides and the α-hydroxy acids, no other important independent optically active series have as yet been defined. These two series have been extended somewhat, however, in the following way. The α-chloropropionic acid, XIII, may be said to have the same configuration as does D-(−)-lactic acid, XIV, because the two molecules differ only in the replacement of the chlorine atom by the analogous hydroxyl group. Consequently, the substance of configuration XIII, like the one of configuration XIV, is considered to belong to the D-series; hence, the former compound is called D-α-chloropropionic acid. Similarly, the alanine represented by configuration XV is called L-alanine on account of its similarity in configuration to L-(+)-lactic acid, XVI. In all such instances, the prefixes D- and L- refer only to configuration and not to the sign of rotation. The problem of deciding which enantiomorphs possess which configurations is made difficult by the possibility of Walden inversions (see Section 7·8), and it cannot always be solved with complete finality. For example, all the α-amino acids (such as alanine) which are obtained by the hydrolysis of proteins are *known* to belong to the same series; this series is *thought* to be L.



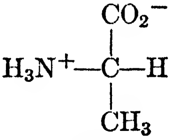
$$\begin{array}{ccc} & \mathrm{CO_2H} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{Cl} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

XIII



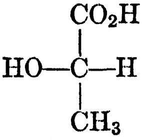
$$\begin{array}{ccc} & \mathrm{CO_2H} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

XIV



$$\begin{array}{ccc} & \mathrm{CO_2^-} & \\ & | & \\ \mathrm{H_3N^+}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

XV



$$\begin{array}{ccc} & \mathrm{CO_2H} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

XVI

The simple method of classification outlined above has proved to be very useful within the narrowly restricted field to which it applies. The attempt to devise a similar method that can be extended to significantly broader fields, however, encounters serious difficulties. The nature of some of these difficulties should be apparent from what has already been said; that of another one is illustrated by the sequence of reactions shown in Figure 6·3.[73] The net result of these reactions is the interchange of a carboxamide group $CONH_2$ and a carboxyl group CO_2H, without destruction of the asymmetry of the central carbon atom at any stage. (The plane projection diagrams in this figure serve only to show the relative configurations of the substances in question with respect to one another, and they may not be correct with respect to the glyceraldehydes. Cf. Section 6·7.) Now, the final product, (−)-isopropylmalonamic acid, is the enantiomorph of the original substance, (+)-isopropylmalonamic acid; these two compounds must therefore belong to different series. Consequently, a sudden transition from one series to the other must be considered to have occurred in some single reaction

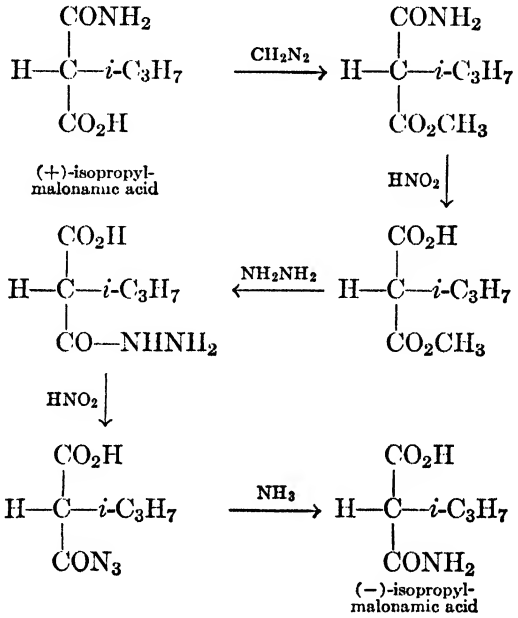


FIGURE 6·3. The conversion of an optically active substance into its own enantiomorph by a sequence of reactions[73] that do not directly involve the asymmetric carbon atom.

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[73] E. Fischer and F. Brauns, *Ber.* **47**, 3181 (1914).

of the sequence. There is, however, no logical and unambiguous way to decide in which particular reaction the change takes place, since all the reactions seem clearly to be of the same general type. It should therefore be evident that, with respect to the various compounds participating in the reactions of Figure 6·3, the concept of optically active series would have little theoretical significance or practical utility.

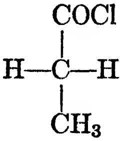
The reaction map of Figure 6·3 is of considerable theoretical interest from still another point of view. It was pointed out on page 187 that, if the tetrahedral model of the carbon atom is correct, then the configuration of any asymmetric carbon atom must be inverted if two of the atoms or groups joined to it are interchanged. The reactions by which (+)-isopropylmalonamic acid is transformed into its enantiomorph provide experimental evidence which confirms this theoretical conclusion.

7.

The Stereochemistry of Carbon

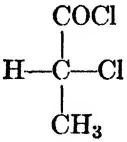
7·1 Stereochemistry. In Chapter 6, stereoisomeric substances were treated as merely so many aggregates of nonequivalent geometrical figures. The emphasis was accordingly placed upon the different types of configuration, upon the numbers of possible or actual stereoisomeric forms, and upon the conventional systems of graphical representation and of nomenclature. In this chapter, on the other hand, stereoisomeric substances are instead treated as chemical compounds in the full meaning of the term. The emphasis will accordingly now be placed upon the chemical properties of the substances, upon their chemical relationships, and upon the chemical effects of their geometrical differences.

7·2 Resolution.[1] Whenever a substance that can be optically active is prepared under the usual experimental conditions from exclusively inactive reagents (whether these be symmetrical or racemic), the product is always the inactive racemic modification. (However, see Section 7·4.) For, in view of the complete symmetry of the experimental situation, the probability that a molecule of the dextrorotatory enantiomorph will be formed is exactly equal to the probability that one of the levorotatory enantiomorph will be formed. For example, in the preparation of α-chloropropionyl chloride by the chlorination of propionyl chloride, I, the α-hydrogen atom that is replaced in the reaction



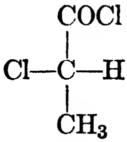
$$\begin{array}{c} \mathrm{COCl} \\ | \\ \mathrm{H{-}C{-}H} \\ | \\ \mathrm{CH_3} \end{array}$$

I



$$\begin{array}{c} \mathrm{COCl} \\ | \\ \mathrm{H{-}C{-}Cl} \\ | \\ \mathrm{CH_3} \end{array}$$

II



$$\begin{array}{c} \mathrm{COCl} \\ | \\ \mathrm{Cl{-}C{-}H} \\ | \\ \mathrm{CH_3} \end{array}$$

III

may be either the one at the right of the figure or the one at the left. In the former event, D-α-chloropropionyl chloride, II, results; in the latter, the enantiomorph, L-α-chloropropionyl chloride, III, is formed instead. Since the two hydrogen atoms in question are equivalent, the probability

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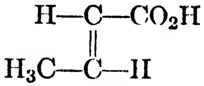
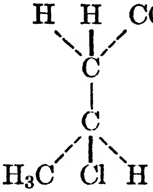
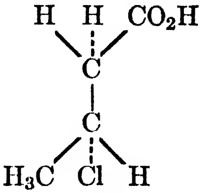
[1] For general discussions of methods of resolution, see F. Ebel in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 564 ff.; R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 187 ff., 2nd ed., 1943, Volume I, pages 254 ff.

that either will be replaced must be exactly equal to the probability that the other will be replaced. Consequently, the product must be racemic. Similarly, in the preparation of β-chlorobutyric acid by the addition of hydrogen chloride to crotonic acid, IV, the hydrogen chloride has equal


IV

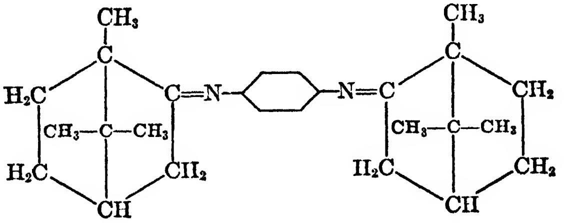

V

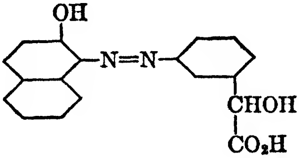

VI

probabilities of approaching from the front of the paper to give the product V, and from the rear to give the enantiomorph VI. Consequently, the product must again be racemic. Any other type of reaction in which dissymmetric molecules are made from symmetric ones can be shown in a completely analogous way to be incapable of leading to an optically active product. Moreover, since enantiomorphs must have identical rates of reaction with all optically inactive reagents, it is evident that no active products can result from reactions between racemic modifications and any such reagents.

The two examples of the production of racemic modifications from symmetrical reagents (given above) involved the assumption that any entering substituent necessarily occupies the same position in space as did the one which it replaces, and also the further assumption that any two new substituents introduced by the addition of a reagent molecule to a double bond necessarily approach from the same side of the original unsaturated molecule. These assumptions, which were made here only for the sake of simplicity, are frequently incorrect, as will be discussed later (cf., for example, Sections 7·8 and 7·9); the conclusions reached with their aid are nevertheless correct. In fact, the same conclusions are obtained no matter what assumptions are adopted in regard to the detailed mechanisms of the reactions; for, in general, any reaction by which one enantiomorph is formed from inactive reagents is the mirror image of a second reaction in which the other enantiomorph is formed from the same reagents; the two reactions must therefore always proceed at the same rate. (Cf. pages 153 f.)

If it is desired to obtain an optically active product, instead of the inactive one that is formed in the reaction employed, a resolution must be performed. Such a separation of a racemic modification into its two active components is made rather difficult, however, by the close similarity of enantiomorphs in nearly all their properties. A separation by crystallization, for example, is impossible because enantiomorphs have identical solubilities in all optically inactive solvents and also (within the limits of measurement) in all active solvents as well. A separation by fractional distillation is likewise impossible because enantiomorphs have identical boiling points at all pressures, and identical vapor tensions at all temperatures. In a small number of instances, however, partial separations have been effected by fractional adsorption on an optically active adsorbent. Thus, the camphor derivative, VII, is partially resolved when a dilute solution of the racemic modification in a hydrocarbon solvent is allowed to trickle down through a tube packed with lactose.[2] The dextrorotatory form is adsorbed more strongly by this optically active sugar than is its enantiomorph; hence samples of the substance recovered from the top and bottom of the tube are, respectively, dextro- and levorotatory after they have been separated from the lactose. Moreover, it has been claimed that, in an analogous way, the dextrorotatory form of the azo compound, VIII, dyes wool appreciably faster than does its enantiomorph,[3] so that a solution of the racemic modification becomes slightly levorotatory after having been in contact with wool for some time. This claim was, however, disputed by Brode and Adams.[3]


VII


VIII

Two important methods of resolution were developed by Pasteur. The first of these, known as the method of *spontaneous separation*, was discovered by Pasteur[4, 5] in 1848, while he was engaged in a crystallo-

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[2] G. M. Henderson and H. G. Rule, *Nature* **141**, 917 (1938).

[3] C. W. Porter and H. K. Ihrig, *J. Am. Chem. Soc.* **45**, 1990 (1923); see, however, W. R. Brode and R. Adams, *ibid.* **48**, 2193, 2202 (1926).

[4] L. Pasteur, *Ann. chim.* [3] **24**, 442 (1848); **28**, 56 (1850).

[5] L. Pasteur, two lectures delivered before the Société Chimique de Paris, January 20 and February 3, 1860. See L. Pasteur, *Researches on the Molecular Asymmetry of Natural Organic Products*, Alembic Club reprint, University of Chicago Press, Chicago, 1902; *Œuvres de Pasteur*, Masson et Cie., Paris, 1922, Volume 1, pages 315 ff., 329 ff.

graphic study of (+)-tartaric acid (the only optically active tartaric acid that was known at the time when he commenced his investigations), and of racemic tartaric acid (called racemic acid), and of numerous salts of each. It had previously been found that these two acids have identical compositions and structures, but that they differ in numerous physical and chemical properties and, in particular, in their effects upon plane polarized light. It had also been found previously that the crystals of (+)-tartaric acid and of all its salts which had been examined are dissymmetric, but that those of racemic acid and of all its salts which had been examined (with the single exception of sodium ammonium racemate) are instead symmetric. In order to gain experience in a, to him, new field of scientific investigation, Pasteur repeated the older very precise microscopic examination of these various crystals. In doing so, he discovered a remarkable fact which had been missed by the earlier workers. This fact was that the crystals of sodium ammonium racemate are of two different kinds, provided that they have been obtained by crystallization from water at a temperature below about 27°C. The crystals of one type have exactly the same dissymmetric form as do those of the sodium ammonium salt of (+)-tartaric acid, whereas the crystals of the second type are the nonsuperposable mirror images of the former. Pasteur separated the two kinds of crystal under magnification and examined them independently. The crystals of the first type proved to be identical in all respects with those of sodium ammonium (+)-tartrate, and from them he was able to obtain ordinary (+)-tartaric acid. The crystals of the second kind, however, were found to give a levorotatory aqueous solution, and from them Pasteur was able to obtain a hitherto unknown levorotatory tartaric acid. The specific rotation of this new acid is equal in magnitude to that of (+)-tartaric acid, but it is opposite in sign; and its crystals are the nonsuperposable mirror images of those of (+)-tartaric acid. It is therefore evident that Pasteur had separated sodium ammonium racemate into its two enantiomorphic components, and that his new levorotatory tartaric acid was the substance now known as (−)-tartaric acid. He had accordingly effected the first resolution of a racemic modification.

In principle, this method of resolution can be applied generally in all instances in which the solid racemic modification is a conglomerate (cf. Section 5·12) composed of observably different crystals. In practice, however, only about a dozen instances in which this condition is satisfied have been reported in the organic chemical literature.[6] Consequently,

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[6] F. Ebel, in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, page 565.

the method, although of great historical and theoretical importance, is seldom applicable.

Pasteur's second method of resolution [5,7] is of much greater generality than is his first; it is the only one which is now commonly used. It is based upon the transformation of the mixture of enantiomorphs into a mixture of diastereomers, which, since they may differ in physical properties, can often be separated relatively easily. This transformation requires the use of some previously obtained optically active substance. For example, Pasteur showed in 1853 that, when racemic acid is treated with any one of the optically active bases (alkaloids), quinine, cinchonine, quinicine, brucine, or cinchonicine, the resulting salt is a mixture of diastereomers and is no longer one of enantiomorphs. Thus (if, for definiteness, the base is assumed to be dextrorotatory), the salt formed from the (+)-acid and (+)-base is not the mirror image of the one formed from the (−)-acid and the same (+)-base; the mirror image would instead be the salt formed from the (−)-acid and (−)-base. The two salts that are present in the mixture may therefore be expected to have different solubilities and so to be separable by crystallization. After the separation has been carried out, the salt from the (+)-acid and (+)-base gives the optically pure (+)-acid when treated with a strong mineral acid, and the other salt gives the optically pure (−)-acid when similarly treated. The optically active base can, of course, be recovered and used for further resolutions. (In regard to the legitimacy of describing *salts* as diastereomers or as enantiomorphs of one another, see page 130.)

Since a large number of optically active alkaloids, in addition to those mentioned above, occur in nature, this method for the resolution of a racemic acid can be widely varied. It is not, however, completely general since, with any given racemic acid, there may arise certain complications which make the procedure inapplicable. The mixture of diastereomeric salts may, for example, be an uncrystallizable syrup or oil; or it may be an inseparable solid solution or compound. Even if these difficulties do not occur, the solubilities of the two salts may be so similar in all solvents that the desired separation is extremely difficult. Finally, although the less soluble diastereomer can often be precipitated from the solution in a satisfactorily pure state, the more soluble one, when recovered from the mother liquor, is nearly always contaminated with its isomer (or, more precisely, stoichiomer). Consequently, the method, in its simplest form, seldom permits the isolation of both optically pure enantiomorphic acids. These difficulties, of varying types, can frequently be avoided by the employment of several different optically

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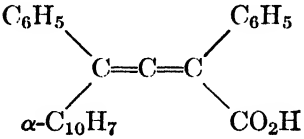
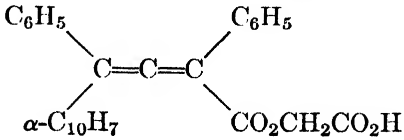
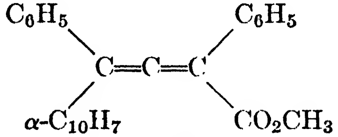
[7] **L. Pasteur,** ***Ann. chim.*** **[3] 38, 437 (1853);** ***Compt. rend.*** **37, 162 (1853).**

active bases, or of several different solvents, or of both. In this way, there may perhaps be found some particular combination of base and solvent which permits a satisfactory separation of the diastereomeric salts. If no such combination can be found, however, a resolution is still sometimes possible if the racemic acid is transformed into a (still racemic) derivative which can be resolved, and from which the original substance can be regenerated. For example, the allenic acid, IX (cf. page 199),


IX

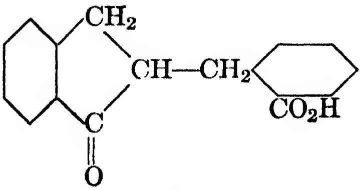

X

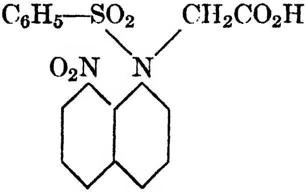
could not be resolved since its salts did not crystallize; its derivative, X, however, was easily resolved through its brucine salt.[8] Although regeneration of the original acid, IX, was here not attempted, the optically active methyl ester, XI, was obtained.[9] Clearly, in these difficult


XI

instances, the problem can be attacked only by trial and error, and no assurance can be given that any satisfactory method of resolution will ultimately be discovered at all.

Different sorts of complication can arise if the enantiomorphs which it is desired to separate are optically unstable or, in other words, are easily racemized. Under such circumstances, it may happen that the diastereomeric salts are obtainable, but that decomposition of either salt leads to the same racemic acid from which both were made. On the other hand, under similar circumstances, it may happen instead that nearly the entire racemic acid is transformed into only one of the two theoretically possible diastereomeric salts. For example, if the acid XII


XII


XIII

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[8] E. P. Kohler, J. T. Walker, and M. Tischler, *J. Am. Chem. Soc.* **57**, 1743 (1935).

[9] E. P. Kohler and W. J. Whitcher, *J. Am. Chem. Soc.* **62**, 1489 (1940).

is dissolved in acetone and treated with one equivalent of brucine, a 94 per cent yield of a *single* salt is precipitated. (A 50 per cent yield would be the maximum expected here since the remaining 50 per cent should be in the form of a different diastereomeric salt.) If this salt is decomposed with sulfuric acid, there is obtained a brucine-free solution of the organic acid, which is initially dextrorotatory, but which rapidly loses its optical activity. No active acid can be isolated from the solution. Apparently, in this instance, the salt formed from the dextrorotatory acid is much less soluble in acetone than is its diastereomer formed from the levorotatory acid. Consequently, the less soluble salt precipitates alone and almost completely. On account of the optical instability of the acid, however, the material remaining in solution is rapidly racemized, and the additional dextrorotatory acid thereby produced is also precipitated as its insoluble brucine salt. The process continues until, as stated above, 94 per cent of the original racemic acid is obtained as the salt of the dextrorotatory enantiomorph. This example is by no means exceptional, since a number of other ones are also known. With at least the one compound XIII, in fact, the racemic acid can be changed almost completely into whichever one of the two diastereomeric brucine salts may be desired, since the salts of the dextro- and levorotatory acids are precipitated from solutions in methyl alcohol and acetone, respectively.[10] As before, brucine-free solutions of the acids lose their activities rapidly, and the optically active acids cannot be isolated. (The acid XIII, of course, owes its optical activity to a restriction of rotation about the carbon-nitrogen bond at the right of the figure. Cf. Section 6·13.) In examples of the two preceding types, the fact that the acids in question are actually active is shown, even though the enantiomorphic forms cannot be isolated, by the observed activities of the alkaloid-free solutions. In other instances, however, optically active alkaloid-free solutions cannot be obtained; unstable activities of the original acids can then sometimes be inferred with some assurance, however, if the solutions of the alkaloid salts show rotations which vary with the time and which approach as limits the rotations observed with equivalent solutions of the salts formed between the same alkaloids and optically inactive acids.

From the discussion so far, it may appear that Pasteur's second method of resolution is restricted to racemic *acids*. No such limitation actually exists, however, since the method can be extended to include nearly all, if not all, other types of compound. A racemic base, for example, can in an obvious manner be resolved by separation of the dia-

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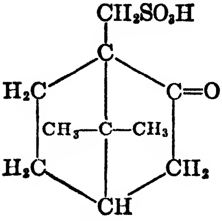
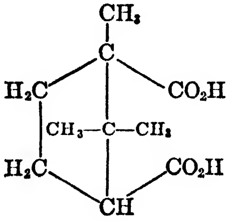
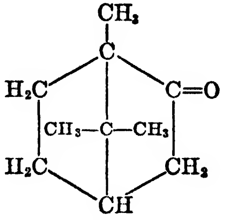
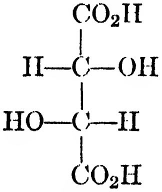
[10] W. H. Mills and K. A. C. Elliott, *J. Chem. Soc.* **1928**, 1291.

stereomeric salts formed between it and an optically active acid. Numerous acids are readily available for this purpose, just as numerous bases (alkaloids) are available for the resolution of acids. Thus, (+)-camphor-10-sulfonic acid, XIV, and (+)-camphoric acid, XV, can be easily obtained by sulfonation and oxidation, respectively, of the naturally occurring (+)-camphor, XVI; D-(+)-tartaric acid, XVII, and


XIV

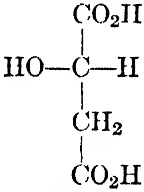

XV


XVI



$$\begin{array}{c} CO_2H \\ | \\ H—C—OH \\ | \\ HO—C—H \\ | \\ CO_2H \end{array}$$

XVII

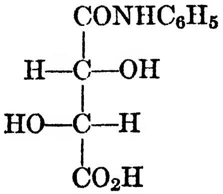


$$\begin{array}{c} CO_2H \\ | \\ HO—C—H \\ | \\ CH_2 \\ | \\ CO_2H \end{array}$$

XVIII

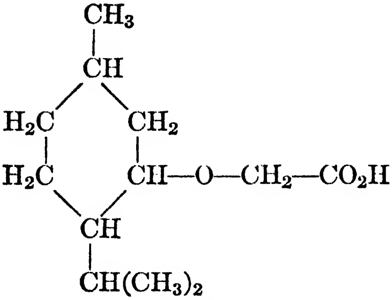
L-(−)-malic acid, XVIII, occur naturally; and so on. (For the assignment of configurations to these last two acids, see Section 7·12.)

Several methods have been devised for the resolution of a racemic alcohol or phenol. One of these methods involves the formation of the half-ester of a dibasic acid like phthalic or succinic acid; the product, being acidic, can then be resolved in the manner already described and finally hydrolyzed to the enantiomorphic forms of the original alcohol or phenol. Further methods are based upon the formation of diastereomeric esters of D-(+)-tartranilic acid, XIX, or of (−)-menthoxyacetic

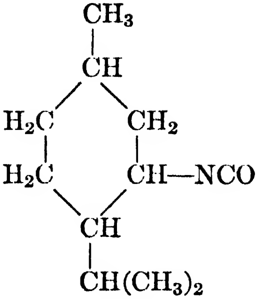


$$\begin{array}{c} CONHC_6H_5 \\ | \\ H—C—OH \\ | \\ HO—C—H \\ | \\ CO_2H \end{array}$$

XIX



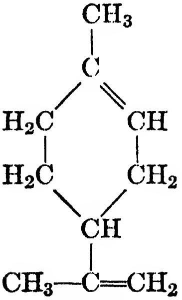
XX



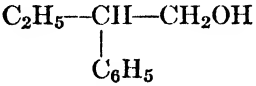
XXI

acid, XX; and upon the formation of diasteromeric urethans by the action of (−)-menthyl isocyanate, XXI.

Aldehydes and ketones have been resolved through their diastereomeric hydrazones or semicarbazones, which are themselves formed from optically active hydrazines or semicarbazides, respectively; and similar schemes of greater or less complexity have been worked out for most remaining types of compound. Even some racemic hydrocarbons, such as dipentene, XXII, have been resolved by means of their diastereomeric choleic acids.[11] (Cf. Section 2·11.) This last method is of course not restricted to hydrocarbons but is very generally applicable, since a great many different kinds of substance form such addition compounds with desoxycholic and apocholic acids; for example, 2-phenyl-1-butanol, XXIII, camphor, XVI, and methylethylacetic acid, XXIV, have been thus resolved.[11]

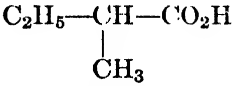


XXII



$$C_2H_5-\underset{\displaystyle C_6H_5}{\underset{|}{CH}}-CH_2OH$$

XXIII



$$C_2H_5-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CO_2H$$

XXIV

All these closely related methods of resolution, in which the racemic modification is first transformed into a mixture of diastereomers, are of course subject to the various types of limitation discussed more fully

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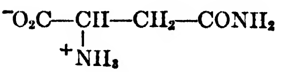
[11] H. Sobotka and A. Goldberg, *Biochem. J.* **26**, 905 (1932).

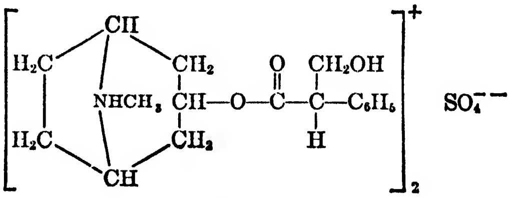
above in connection with the resolution of racemic acids. It is of interest, therefore, that some success has been achieved in the separation of diastereomers by procedures not involving fractional crystallization. Partial separations have been effected in a few instances, for example, by fractional distillation[12] and by fractional adsorption on optically inactive adsorbents.[13] Such methods have not as yet, however, been so widely applied or proved so generally effective as have the more familiar ones based on crystallization.

The two methods of resolution discovered by Pasteur are not the only ones now known. Another method, reminiscent of the earliest one (i.e., that of spontaneous separation), but of somewhat greater generality, makes use of an induced selective precipitation of one enantiomorph from a supersaturated solution of the racemic modification. Such a separation occurs in certain instances when the solution is inoculated with a crystal of the desired enantiomorph; the solution itself, of course, remains supersaturated with respect to the other enantiomorph. Zinc ammonium lactate, for example, has been resolved in this way. Occasionally, the inoculating crystal may be merely isomorphous, and not identical, with the enantiomorph which precipitates; thus, a crystal of (−)-asparagine, XXV, causes the precipitation of pure sodium ammonium (+)-tartrate from a supersaturated solution of the corresponding racemate. An apparently spontaneous separation of atropine sulfate, XXVI, is reported[14] to have occurred when the racemic modification was crystallized from absolute alcohol; presumably here the solution was inoculated by microscopic crystals that were suspended in the air of the laboratory in which the experiment was performed.



$^{-}O_2C{-}\underset{+NH_3}{CH}{-}CH_2{-}CONH_2$

XXV



XXVI

A further method of resolving a racemic modification makes use of the difference between the rates at which two enantiomorphs react with an optically active substance. For example, (+)-mandelic acid, with structure XXVII, is esterified appreciably more rapidly by (−)-menthol,

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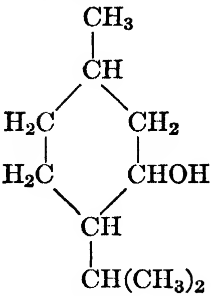
[12] M. E. Bailey and H. B. Hass, *J. Am. Chem. Soc.* **63**, 1969 (1941).

[13] A. Stoll and A. Hofmann, *Z. physiol. Chem.* **251**, 155 (1938).

[14] L. Anderson and D. W. Hill, *J. Chem. Soc.* **1928**, 993.



$C_6H_5—CHOH—CO_2H$

XXVII

XXVIII

XXVIII, than is its enantiomorph. Consequently, if, with the racemic acid, the reaction is stopped before it has gone to completion, the unchanged mandelic acid is slightly levorotatory. The small amount of (−)-mandelic acid that is thus present can be separated from the much larger amount of racemic mandelic acid by fractional crystallization. A corresponding amount of (+)-mandelic acid should be obtainable by hydrolysis of the ester formed, unless of course racemization occurs too rapidly.

7·3 Asymmetric Syntheses and Decompositions.[15] As was stated above (pages 230 f.), an optically active product cannot be formed in any reaction in which all reagents are inactive and all other experimental conditions are also symmetrical. However, an optically active product can be formed in a reaction which employs active reagents or dissymmetric conditions, or both. An obvious (and rather trivial) example of such a reaction is one in which an optically active substance is transformed into some derivative that also is active, as when an active acid is transformed into its ester or salt, or the like. Much more interesting examples, however, are also known; in these reactions the required optically active reagents play a less obviously fundamental role, and they do not form an essential part of the final product. Such reactions are commonly called *asymmetric syntheses* or *asymmetric decompositions*, as the case may be (although the word "dissymmetric" would here seem more appropriate than does "asymmetric").

A typical example of an asymmetric synthesis is the reduction of benzoylformic acid, I, to mandelic acid, II. The molecule of the former

$C_6H_5—CO—CO_2H$

I

$C_6H_5—CHOH—CO_2H$

II

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[15] For further discussions of asymmetric syntheses and decompositions, see F. Ebel in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 580 ff.; R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 224 ff., 2nd ed., 1943, Volume I, pages 308 ff.

substance is symmetric, and so, under the ordinary experimental conditions, the resulting mandelic acid must be completely racemic. However, if the benzoylformic acid is first transformed into its ester with (−)-menthol, and if this menthyl benzoylformate is reduced with aluminum amalgam in moist ether, the two diastereomeric menthyl mandelates are not formed in exactly equal amount. Hydrolysis of the resulting ester gives a mandelic acid which is slightly levorotatory and which therefore must contain a slight excess of the levorotatory enantiomorph. This excess can, if desired, be separated from the racemic modification by crystallization. The (−)-menthol used in the reactions is, of course, recovered unchanged.

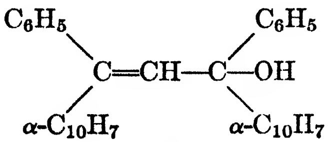
A second asymmetric synthesis of a somewhat different type involves the base-catalyzed addition of hydrogen cyanide to benzaldehyde.[16] Since both these reagents are necessarily optically inactive, the product of the reaction, mandelonitrile, III, must be racemic if the reaction is

$$C_6H_5—CHOH—CN$$

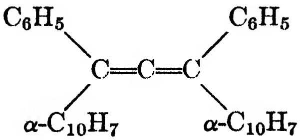
III

carried out in the usual way with an optically inactive catalyst. However, a slightly levorotatory nitrile is obtained if (+)-quinidine is used as catalyst, whereas a slightly dextrorotatory nitrile is obtained instead if (−)-quinine is used. The mandelic acids obtained by hydrolysis of these nitriles are slightly dextro- and levorotatory, respectively. Even though the signs of rotation of the acids are thus the opposite of those of the nitriles from which they are obtained, no changes in configuration are presumed to have occurred in the hydrolyses; these reactions merely provide further examples of the fact that a change in the sign of rotation does not necessarily imply a change in configuration. The optically active catalysts used in these reactions can of course be recovered unaltered.

The asymmetric decompositions are completely analogous to the asymmetric syntheses; the distinction between the two types of reaction is, in fact, more or less arbitrary. If the racemic unsaturated alcohol, IV, is dehydrated by the action of (+)-camphor-10-sulfonic acid, VI, the



IV



V

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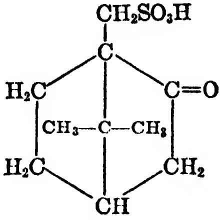
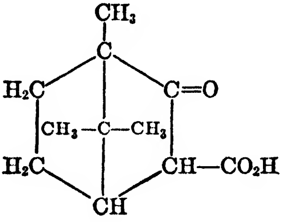
[16] G. Bredig and P. S. Fiske, *Biochem. Z.* **46**, 7 (1912); G. Bredig and M. Minaeff, *ibid* **249**, 241 (1932).

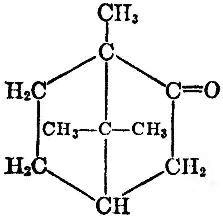
resulting allene, V, is dextrorotatory (cf. Section 6·11); the pure dextrorotatory enantiomorph can be obtained from the original product by fractional crystallization.[17] On the other hand, if the same alcohol, IV, is dehydrated by the action of (−)-camphor-10-sulfonic acid instead, the levorotatory allene, V, is similarly obtained. The opposite effects of the enantiomorphic sulfonic acids are in agreement with expectation. An optically inactive acid catalyst, of course, leads to a completely racemic allene. A second asymmetric decomposition is illustrated by the base-catalyzed decarboxylation of racemic camphor carboxylic acid, VII. If the reaction is stopped before completion, the camphor, VIII, that has been formed is found to be completely racemic, or slightly dextrorotatory, or slightly levorotatory when the catalyst that is used is, respectively, an inactive base, or (+)-quinidine, or (−)-quinine. If, however, the reaction is allowed to go to completion, the product is always, of course, racemic.



VI



VII



VIII

Asymmetric syntheses and decompositions are of especially great importance in *biological* reactions, since the reactions which occur in living systems are so frequently brought about by optically active reagents or are catalyzed by optically active catalysts (enzymes). For example, photosynthesis, by which green plants transform optically inactive water and carbon dioxide into active carbohydrates, must involve asymmetric syntheses. Similarly, the fact that the natural D-(+)-glucose is easily digested by animals and is fermented by yeast, whereas

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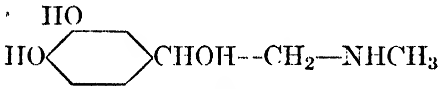
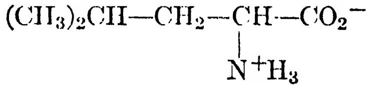
[17] P. Maitland and W. H. Mills, *Nature* **135**, 994 (1935).

its enantiomorph undergoes neither reaction, must be attributed to the occurrence of asymmetric decompositions. An important application of such biological reactions was discovered by Pasteur,[5,18] who found that the mold *Penicillium glaucum,* when allowed to grow in the presence of racemic tartaric acid, preferentially destroys the dextrorotatory enantiomorph, so that the acid which remains becomes levorotatory. This method of obtaining optically active substances is fairly general, since other microorganisms have been found to have similar effects, and since other racemic compounds have been found to be made active in similar ways; it has, however, serious limitations, since many substances are not attacked by any known organisms, since sometimes the organisms attack both enantiomorphs with equal speed, and since often the organism destroys just the enantiomorph which is desired. It should be noted also that the method cannot be called a *resolution* (i.e., a separation) since one of the two enantiomorphs is always destroyed.

Mention may be made here of a few further biological differences between enantiomorphs.[19] These differences also must be related to the occurrence of asymmetric syntheses or decompositions, and hence to the presence of optically active reagents or catalysts. The physiological effect of the natural (−)-adrenaline, IX, is about twelve to fifteen times as great as is that of its enantiomorph; L-(−)-tartaric acid is appreciably more poisonous than is its enantiomorph; (−)-leucine, of structure X, has an insipid and slightly bitter taste, whereas its enantiomorph is sweet; and so on.



IX



$$(CH_3)_2CH{-}CH_2{-}\underset{\displaystyle N^+H_3}{\underset{|}{C}H}{-}CO_2^-$$

X

A number of other asymmetric syntheses and decompositions are intermediate between these last, purely biological, reactions and the more typically chemical ones described earlier in this section. Thus, the addition of hydrogen cyanide to benzaldehyde gives nearly, but not quite, pure (+)-mandelonitrile, III, when the enzyme emulsin is used as catalyst; benzoylformic acid, I, when treated with raw milk, is reduced (presumably as a result of bacterial action) to (−)-mandelic acid, II, containing a relatively small amount of the racemic modification; emulsin catalyzes the hydrolysis of (+)-, but not that of (−)-mandelo-

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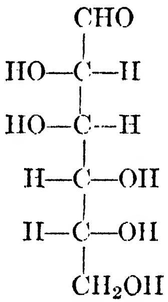
[18] L. Pasteur, *Compt. rend.* **46,** 615 (1858); **51,** 298 (1860).

[19] G. Wittig, *Stereochemie,* Akademische Verlagsgesellschaft, Leipzig, 1930, pages 20, 71; H. Brockmann in K. Freudenberg, *Stereochemie,* Franz Deuticke, Leipzig and Vienna 1933, pages 921 ff. Cf. also G. M. Badger, *Nature* **159,** 194 (1947).

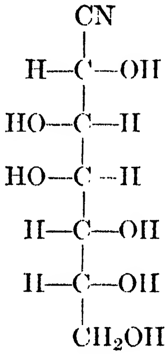
nitrile, III, so that the racemic modification becomes levorotatory when treated with this enzyme; and so on.

In the various examples given above, the biological catalysts are more effective in promoting asymmetric reactions than are the other types of optically active substance. The reason for this difference is possibly that the molecules of enzymes and the like contain very large numbers of asymmetric atoms, whereas the simpler chemical reagents contain only a few. An analogy is provided by the addition of hydrogen cyanide, in the presence of a little ammonia, to D-mannose, XI; of the two theoretically possible products, XII and XIII, the former is obtained in much the greater amount. In this reaction, altogether four asymmetric atoms (in the aldehyde form, XI) are present, and these are able to direct the addition almost exclusively into only one of its two conceivable courses. This reaction is not, however, an "asymmetric synthesis" in the sense in which the term is used in this section, since the D-mannose is not recoverable but forms an essential part of the product. The distinction, however, is slight and possibly not very significant.



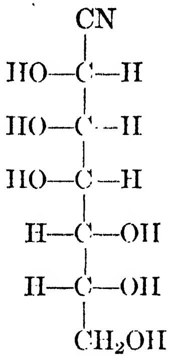
$$\begin{array}{c} \text{CHO} \\ | \\ \text{HO—C—H} \\ | \\ \text{HO—C—H} \\ | \\ \text{H—C—OH} \\ | \\ \text{H—C—OH} \\ | \\ \text{CH}_2\text{OH} \end{array}$$

XI



$$\begin{array}{c} \text{CN} \\ | \\ \text{H—C—OH} \\ | \\ \text{HO—C—H} \\ | \\ \text{HO—C—H} \\ | \\ \text{H—C—OH} \\ | \\ \text{H—C—OH} \\ | \\ \text{CH}_2\text{OH} \end{array}$$

XII



$$\begin{array}{c} \text{CN} \\ | \\ \text{HO—C—H} \\ | \\ \text{HO—C—H} \\ | \\ \text{HO—C—H} \\ | \\ \text{H—C—OH} \\ | \\ \text{H—C—OH} \\ | \\ \text{CH}_2\text{OH} \end{array}$$

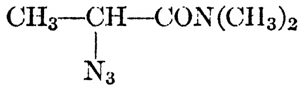
XIII

7·4 Absolute Asymmetric Syntheses and Decompositions.

All the asymmetric reactions of the preceding section require the presence of a previously obtained optically active substance. Even though this substance is in principle recoverable, and hence is available for subsequent reactions, the necessity that it be employed at all imposes a rather serious theoretical limitation upon the reactions in question. If nature had not happened to be so kind as to provide a large number of optically active substances, asymmetric reactions of the foregoing types could hardly have been discovered. It is of great theoretical interest, therefore (although of little practical value), that several *absolute* asymmetric syntheses and decompositions, which are not subject to this limitation, have been carried out. These reactions, of course, depend upon the production of dissymmetric experimental conditions by methods that do not require the use of any optically active substance or substances.

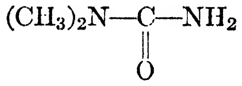
The most logical, and only successful, approach to the problem of providing such dissymmetric conditions makes use of the fact that circularly polarized light is not identical with its own mirror image and that, accordingly, two enantiomorphs may have different spectra when examined with circularly polarized light. (Cf. page 154.) Since the rate of a *photochemical* reaction is determined by the amount of light that is absorbed by the molecules undergoing the reaction (and not by the total amount of light available), it therefore follows that two enantiomorphs can react at different rates in a photochemical reaction which is brought about by the action of circularly polarized light. Since, moreover, this required kind of light can be provided without the use of any optically active substances (for example, by reflection), it follows also that any optical activity produced in such a way must be attributed to an absolute asymmetric reaction of some sort.

The most conclusive absolute asymmetric reaction that has been reported in the chemical literature is doubtless the photochemical decomposition of the dimethylamide, I, of racemic α-azidopropionic acid.[20]



$$CH_3\text{—}\underset{\displaystyle N_3}{\underset{|}{CH}}\text{—}CON(CH_3)_2$$

I



$$(CH_3)_2N\text{—}\underset{\displaystyle O}{\underset{\|}{C}}\text{—}NH_2$$

II

(For the structure of the azido group $-N_3$, see page 461.) When right circularly polarized light with wave length about 3000 A was used, the levorotatory enantiomorph was found to be destroyed more rapidly than was the dextrorotatory one, so that the unchanged amide, which remained, became dextrorotatory. The only decomposition product identified was unsymmetrical dimethylurea, II. In this way there was obtained α-azidopropionic acid dimethylamide, I, with a rotation of 0.78° in a 1-dm tube. Since the rotation of the optically pure substance under the same conditions would have been 198°, the excess of the dextro- over the levorotatory form in this sample was therefore small. When left circularly polarized light of the same wave length was employed, the undecomposed amide became slightly levorotatory, as ex-

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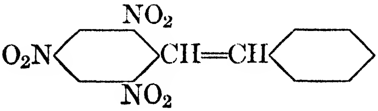
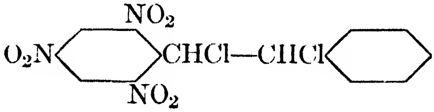
[20] W. Kuhn and E. Knopf, *Naturwissenschaften* **18**, 183 (1930); *Z. physik. Chem.* **B7**, 292 (1930). For an earlier successful, but less conclusive, experiment of the same type, see also W. Kuhn and E. Braun, *Naturwissenschaften* **17**, 227 (1929). For some still earlier. unsuccessful attempts, see A. Byk, *Z. physik. Chem.* **49**, 641 (1904); *Ber.* **37**, 4696 (1904); F. Ebel in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 584 ff.

pected; and material with a rotation of −1.04° was obtained. The difference between the magnitudes of the dextro- and levorotations obtained is doubtless due to unavoidable deviations of the experimental conditions.

A few analogous, but even less nearly complete, absolute asymmetric syntheses have also been reported.[21] For example, when the trinitrostilbene, III, is dissolved in nitrobenzene and treated with chlorine in the presence of right circularly polarized light with wave length 3600–4500 A, a small optical activity can be observed. The rotation first increases to a maximum value, with $[\alpha]_{5461}$ equal to 0.050° and $[\alpha]_{5890}$ equal to 0.034°; it then decreases and finally disappears by the completion of the reaction. No optical activity results from the action of the circularly polarized light upon either the original compound, III, or the racemic product, IV. Similar results have been obtained also in the addition of bromine to the same stilbene, III.[21] On the other hand, circularly polarized light with wave length 5890 A, which is not absorbed by the stilbene, produces no measurable activity. The observed rotations in these syntheses, although small, are definitely greater than the probable experimental errors.



III



IV

The method of resolution by spontaneous separation may perhaps be classified as a further type of absolute asymmetric transformation, since it apparently does not require the use of any previously obtained optically active substance. However, at the risk of quibbling over trivial matters, one could argue that the essential feature of the method in question is the selection *by the experimenter* of the two different types of crystal, and that the power to make such a selection might be due to the presence of optically active substances within the experimenter's body. In other words, the amusing but unanswerable question might be raised whether a completely racemic person could distinguish a dissymmetric object from its mirror image.

7·5 The Origin of Optically Active Substances in Nature.[20,22] The frequent occurrence of optically active (i.e., not completely racemized) substances in animal and vegetable sources can be explained only as the result of asymmetric syntheses or decompositions. These reactions are made possible by the presence (in the organism) of preexisting optically active substances, which must themselves have been

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[21] T. L. Davis and R. Heggie, *J. Am. Chem. Soc.* **57**, 377, 1622 (1935). For still another reaction of this type see T. L. Davis and J. Ackerman, Jr., *ibid.* **67**, 486 (1945).

[22] Cf. G. Wittig, *Stereochemie*, Akademische Verlagsgesellschaft, Leipzig, 1930, pages 42 f.

made by asymmetric syntheses or decompositions; and so on. If life started on this earth many millions of years ago by the coming together of simple inorganic, and optically inactive, materials, there must have been a time at which the optical activity began. The question therefore arises how, in the absence of any pre-existing optically active substances, this activity could have begun. If life is assumed not to have started on this earth but to have come from some other body, the difficulty is merely pushed back in time and is not avoided. Naturally, the answer to this question is unknown, and possibly unknowable. Scientists have nevertheless speculated about it for many years.

Two types of theory have been advanced. The first of these is based upon the fact of spontaneous separation. It is not inconceivable that an optically active substance that was produced in small amount in this way may have been involved somehow in the origin of life. Thus, some early and very simple organism may have happened to consume D-(+)-sodium ammonium tartrate, or to have lived on the surface of a crystal of (−)-quartz, or the like. An objection raised against this explanation is that it depends too much upon chance. Thus, there should on the average be just as much L-(−) as D-(+)-sodium ammonium tartrate for the organism to consume, and just as many crystals of (+)- as of (−)-quartz for it to live on; the suggestion that the universal and uniform occurrence of optical activity could have arisen in such a manner seems *a priori* to be unlikely. (However, see below.)

The second kind of theory is based upon the existence of absolute asymmetric syntheses and decompositions. The earth's magnetic field, for example, provides a constant dissymmetric environment; hence, since all chemical reactions take place under the influence of this field, there is a possibility that every reaction is, to at least some extent, asymmetric. In the laboratory, however, all attempts to carry out asymmetric reactions in the presence of magnetic fields have so far failed. In other words, the optical activities which have been thus produced by relatively intense magnetic fields are too small to be observed (if, indeed, they are not actually zero); hence, it follows that any optical activities which are due to the relatively very weak magnetic field of the earth can at most be infinitesimal. In order to overcome this objection, Byk[20] suggested that the effect of the earth's magnetic field may have been an indirect one. His argument was as follows. Ordinary daylight is, to an appreciable extent, plane polarized because, first, the diffused light that comes in at right angles to the direct rays of the sun has an easily detectable plane polarized component; and, second, even the direct rays become more or less plane polarized when they are reflected from plane surfaces. Moreover, plane polarized light becomes partially circularly polarized when it is, itself, reflected from a plane surface. Consequently, there must be at least a trace of circularly polarized light in ordinary daylight. As a first approximation, to be sure, the amounts of the thus produced right and left circularly polarized lights must, on the average, be equal. The earth's magnetic field, however, introduces a dissymmetric factor which may make one form of circularly polarized light predominate over the other form; for, while the light is still plane polarized, and before it has become circularly polarized, the earth's field must slightly rotate its plane of polarization. (Cf. the Faraday effect, discussed on page 138.) Consequently, since the finally resulting daylight has therefore been affected by a dissymmetric influence, it need not, even on the average, contain exactly equal amounts of the right and left circularly polarized components. Since daylight is therefore slightly dissymmetric, the products of photochemical reactions that are induced by daylight may have small optical activities. Although the direct experimental proof that circularly polarized light can in fact lead to an absolute asymmetric reaction was not obtained until several years after Byk's paper was published, this author nevertheless considered that his theory completely explains natural optical activity. It may be questioned, however, whether this more elaborate interpretation is significantly superior to the earlier and simpler view that the earth's magnetic field directly causes the required asymmetric reactions. For, although the maximum optical activity which has as yet been produced by the action of a magnetic field in any reaction between optically inactive reagents is unobservably small, there is no reason to expect that an appreciably greater optical activity could result from the action of ordinary daylight upon the same inactive reagents. Indeed, since only small optical activities are produced by light that is completely circularly polarized, only infinitesimal activities could be produced by daylight, in which the predominance of one type of circularly polarized light is extremely slight.

The objections which have been raised above to the several proposed explanations of natural optical activity may not be insuperable. Thus, the suggestion that the first optically active compound was produced by spontaneous separation becomes less unreasonable if life is assumed to have started only once, and if, therefore, all living organisms are considered to be the direct descendants of some single, extremely simple organism. Moreover, the alternative suggestion that optical activity was produced, either directly or indirectly, by the dissymmetry of the earth's magnetic field becomes less unreasonable if the effects of successive asymmetric reactions are assumed to be cumulative. Thus, the ratio of the amounts of the two enantiomorphs which are produced in any particular asymmetric reaction may be set equal to $1 + x$, where x is some extremely small positive number. Now, this slightly optically active product is one of the raw materials from which the same substance will at some later time be resynthesized by either the same or a different organism; consequently, the ratio in question may be as large as $(1 + x)^2$ when the material is produced for the second time, and as large as $(1 + x)^n$ when it is produced for the nth time. No matter how small x may be (provided, of course, that it is not exactly equal to zero), the quantity $(1 + x)^n$ can have any desired large value, if only n is sufficiently large. Moreover, since the formation and re-formation of the substance of interest must have occurred an enormous number of times since life began, n can legitimately be considered to be enormous. Hence, the occurrence of optically pure substances in nature is not inconsistent with the belief that x must be extremely small.

If natural optical activity is supposed to be the result of an original spontaneous separation, there still remains the problem of explaining why *racemization* has not occurred in the millions of years which have elapsed since the first optically active compound was produced. This difficulty is a serious one since many, although not all, of the naturally occurring optically active substances can, in the laboratory, be racemized without great difficulty. Moreover, if natural optical activity is instead supposed to be the result of the cumulative effect of absolute asymmetric reactions, there remains the similar problem of explaining why the spontaneous racemization is not much faster than is the extremely slow approach to optical purity. In either event, therefore, it appears necessary to assume that optical activity has "survival value," in the Darwinian sense. There is, in fact, some reason to believe than an organism is aided by its optical activity. Thus, as a very simple example, a given organism may be assumed to have a certain dextrorotatory enzyme, which acts upon a certain dextrorotatory substrate, but which has no effect upon the enantiomorphic, and hence levorotatory, substrate. If this organism is "optically pure" (i.e., if it contains none of the levorotatory enzyme), and if the substrate is likewise optically pure, then all of the enzyme can act upon all of the substrate. On the other hand, if a second organism and its substrate are both "racemic," then only half the enzyme can act upon each enantiomorph in the substrate, and only half the substrate can be acted upon by each of the enantiomorphic enzymes. The former organism is then clearly the better adjusted to its environment; hence it is doubtless the more efficient of the two, and has the better chance to survive and to reproduce. Whether the failure of racemization to occur is satisfactorily explained in the manner just outlined cannot at present, however, be definitely decided, since there is not as yet sufficient information regarding the mechanisms and kinetics of all the essential biological reactions.

Many of the known enzymes have the complete stereochemical specificity that was postulated in the preceding paragraph. (Cf. pages 242 f.) Moreover, it is highly improbable that any enzyme without at least some stereochemical specificity could be developed in the evolutionary process. For, since there is no reason why, say, a dextrorotatory enzyme must have exactly the same effects upon enantiomorphic substrates, a complete lack of specificity of the type that is here being considered could result only from a most extraordinary accident. Consequently, it can legitimately be assumed that one of the enantiomorphic enzymes must always act upon one of the enantiomorphic forms of the substrate more rapidly than it acts upon the other form. If the thus assumed specificity is not complete, the advantage which optical activity gives to the organism is, of course, somewhat reduced, but it is not thereby destroyed.

Actually, the situation is much more complicated than was suggested above, since diastereomers as well as enantiomorphs must be considered in any complete examination of the problem. For example, each individual structure of a hypothetical (rather simple) protein molecule that contains only 300 (dissymmetric) amino acid residues corresponds to altogether 2^{300}, or to about 10^{90}, stereoisomeric forms. The significance of this enormous number becomes apparent when it is realized that a sample which is composed of just one molecule of each of these forms would have a mass that is greater than 10^{60} tons. For comparison, the mass of the earth is only about 6×10^{21} tons, and that of the entire solar system is only about 2×10^{27} tons. Clearly, therefore, the efficiency of any organism would be expected to be greatly reduced if it contained both enantiomorphic forms of every amino acid that was represented in its structure.

7·6 Racemization.[23] The ease with which an optically active substance can be transformed into the corresponding racemic modification varies between wide limits. Some substances are configurationally so unstable that they cannot be obtained in optically active form; others are so stable that the active forms, when obtained, cannot be racemized by any known method (except, of course, by being mechanically mixed with exactly equal amounts of their respective enantiomorphs); and still others are of intermediate stability, so that the racemic modifications can be separated into enantiomorphs, which can then be racemized more or less easily. The experimental conditions under which racemization occurs also vary widely. In many instances, the loss of optical activity occurs spontaneously at a rate which increases with temperature; in others, catalysts are necessary. Examples of these various possibilities

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[23] For further discussion of racemization, see W. Hückel, *Theoretische Grundlagen der Organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, Volume I, pages 54 ff., 254 ff., 2nd ed., 1934, Volume I, pages 56 ff., 281 ff.; R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 176 ff., 2nd ed., 1943, Volume I, pages 240 ff.; T. Wagner-Jauregg in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 852 ff.

are given below in this and subsequent sections and in the following chapter.

An early suggestion regarding the mechanism of racemization was made by Werner.[24] Although this proposed mechanism is at present considered to be incorrect, at any rate when it is applied to the carbon compounds now under discussion, it nevertheless deserves brief mention here since it, or analogs of it, may be correct in other situations considered later. In Figure 7·1*a*, the curved lines may be considered to outline a sphere and to indicate two mutually perpendicular great circles on its surface; they are drawn here merely as aids in the visualization of the figure. An asymmetric carbon atom C is located at the center of the sphere, and its four different substituents R, T, Y, and Z are located on the two great circles. As a result of the thermal motion, these substituents are not at rest with respect to each other and to the carbon atom, but are instead executing vibrations of small amplitude about their positions of minimum energy; these vibrations are symbolized by the double-headed arrows attached to each of the corresponding letters. The statistical fluctuations in the vibrational energy ensure that, at any given time, some molecules are vibrating with much greater than average amplitude. It is consequently possible to suppose that a few molecules may have sufficient energy to reach the planar arrangement shown in Figure 7·1*b*. Since this arrangement has a plane of symmetry, it is no longer dissymmetric like that of Figure 7·1*a*. Consequently, when the carbon atom returns to its stable tetrahedral configuration, as it must do immediately, the probability that it will return to the original configuration of Figure 7·1*a* is exactly equal to the probability that it will instead assume the enantiomorphic configuration of Figure 7·1*c*. The optically active substance, therefore, must more or less rapidly become racemic.

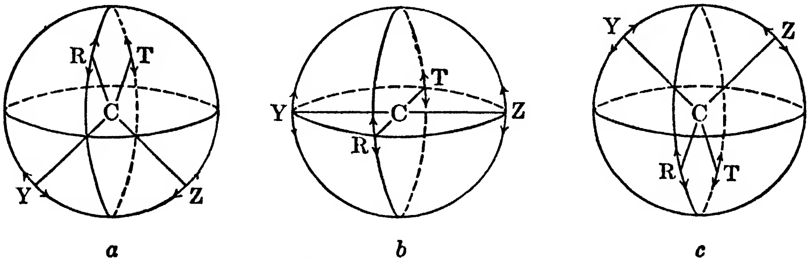

FIGURE 7·1. Werner's mechanism of racemization.[24]

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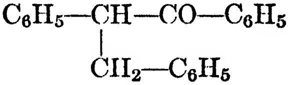
[24] A. Werner, *Lehrbuch der Stereochemie*, Gustav Fischer, Jena, 1904, pages 48 ff.

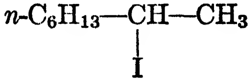
The evidence against the belief that Werner's mechanism of racemization is generally valid comes from various sources. In the first place, this mechanism (at least, in the specific form outlined above) is obviously restricted to those instances in which the racemization involves a change of configuration about an asymmetric atom; it is therefore inapplicable to the allenes and their analogs or to the biphenyls and their analogs. In the second place, in those instances in which asymmetric carbon atoms are present, there is considerable reason to doubt that any molecules have sufficient energy at ordinary temperatures to achieve the necessary planar configuration. Moreover, it seems probable that, as the temperature is raised, and as the thermal energies of the molecules accordingly increase, decomposition resulting from the rupture of valence bonds will occur before an appreciable fraction of the molecules can become planar. Some of the evidence supporting this conclusion comes from spectroscopic studies, which provide information regarding the energies required to distort molecules out of their preferred shapes. Further evidence is provided by the empirical fact that, in those instances in which Werner's mechanism is the only reasonable one that can be devised, racemization simply does not occur. For example, an optically active saturated hydrocarbon is always extremely resistant to racemization. Such hydrocarbons occur to some extent in petroleum; during the millions of years which must have elapsed since their original formation, these substances should have had ample opportunity to undergo a spontaneous racemization if Werner's mechanism were valid. The fact that they have not done so casts considerable doubt therefore upon the mechanism.

More specific arguments against Werner's mechanism of racemization can also be advanced. One of these arguments is that the mechanism does not account for the striking, and often very specific, effects of catalysts upon the rates of racemization. For example, the racemization of phenylbenzylacetophenone, I, is catalyzed by either acids or bases,



$C_6H_5\text{—}CH(CH_2\text{—}C_6H_5)\text{—}CO\text{—}C_6H_5$

I



$n\text{-}C_6H_{13}\text{—}CH(I)\text{—}CH_3$

II

the latter being much the more effective;[25] that of 2-iodoöctane, II, is catalyzed by iodide ion;[26] and so on. It is difficult to see how these cat-

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[25] J. B. Conant and G. H. Carlson, *J. Am. Chem. Soc.* **54,** 4048 (1932).

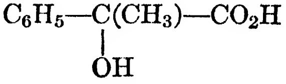
[26] E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.* **1935,** 1525. Cf. also E. D. Hughes, F. Juliusburger, A. D. Scott, B. Topley, and J. Weiss, *ibid.* **1936,** 1173; W. A. Coudrey, E. D. Hughes, T. P. Nevell, and C. L. Wilson, *ibid.* **1938,** 209.

alysts could affect the ease with which the corresponding planar arrangements postulated by Werner can be assumed.

A further way in which the mechanism now under discussion is inadequate is that it is unable to account for the great differences in the ease with which, under identical conditions, certain apparently similar substances are racemized. For example, mandelic acid, III, is readily

$C_6H_5—CHOH—CO_2H$

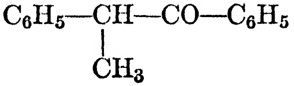
III



$$\underset{\displaystyle OH}{C_6H_5—C(CH_3)—CO_2H}$$

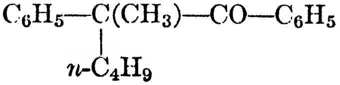
IV

racemized in alkaline solution, but the methylmandelic acid (atrolactic acid), IV, is not racemized at all under the same conditions;[27] phenylmethylacetophenone, V, is readily racemized in n-butyl alcoholic sodium



$$\underset{\displaystyle CH_3}{C_6H_5—CH—CO—C_6H_5}$$

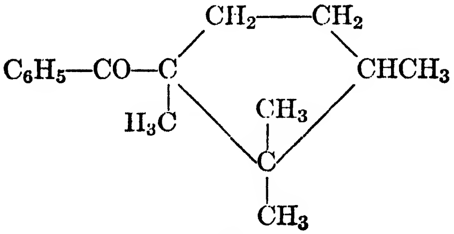
V



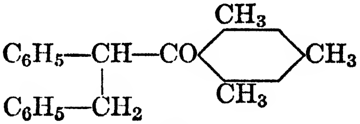
$$\underset{\displaystyle n\text{-}C_4H_9}{C_6H_5—C(CH_3)—CO—C_6H_5}$$

VI

n-butoxide,[25] but neither phenylmethyl-n-butylacetophenone,[25] VI, nor campholyl phenyl ketone,[25] VII, is racemized at all under even more



VII



VIII

vigorous conditions; and so on. That the failure of the compounds IV, VI, and VII to be racemized is not due to steric hindrance (cf. Section 9·7), or to the sizes of the substituent groups, is suggested by the fact that phenylbenzylacetomesitylene, VIII, is readily racemized by bases.[25] There is no obvious reason, therefore, why the above nonracemizable substances should be unable to reach the planar configuration of Figure 7·1*b*, if the other racemizable ones are able relatively easily to do so.

If, for the foregoing reasons, Werner's mechanism of racemization must be given up, it is desirable to devise another one (or several other ones, if necessary) in better agreement with the facts. At the present time, the view is commonly held that no single mechanism can account for all the known examples of racemization, but that several different mechanisms, each with its own field of application, are required. In the

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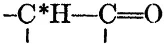
[27] A. McKenzie, *J. Chem. Soc.* **85**, 1249 (1904); **89**, 365 (1906).

remainder of this section, some of the most important types of racemization will be considered.

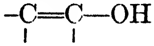
One of the now-accepted mechanisms of racemization has already been discussed in connection with the optically active biphenyls and their analogs. (See Sections 6·12 and 6·13.) With these substances, racemization is considered to result from rotations (about pivot bonds) which bring each molecule into a single plane. Since this mechanism therefore refers the racemization to the geometrical distortions produced by the thermal motions of the molecules, and hence does not require the assumption of any purely chemical reactions, it differs from the ones described below. It may, in fact, be considered a rather close analog of the mechanism proposed by Werner.

A quite different mechanism of racemization is suggested by the fact that the racemizable ketones and acids I, III, V, and VIII possess the characteristic grouping IX (in which C* represents an asymmetric carbon atom), whereas the otherwise similar but nonracemizable substances IV, VI, and VII lack the hydrogen atom alpha to the carbonyl group.



$$-\underset{|}{C}^{*}H-\underset{|}{C}=O$$

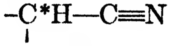
IX



$$-\underset{|}{C}=\underset{|}{C}-OH$$

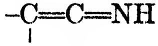
X

Since the keto grouping, IX, can be expected to exist in tautomeric equilibrium (cf. Chapter 14) with the corresponding enol grouping, X, which no longer has an asymmetric atom, the racemization of any substance containing such a grouping could conceivably depend upon a preliminary enolization. In other words, the optically active keto form could undergo a transition to the inactive enol form which, on returning to the stable keto form, would be exactly as likely to give one enantiomorph as to give the other. Consequently, even though only a minute trace of the enol might be present at any one time, the optically active substance must sooner or later be completely racemized. Further evidence supporting this mechanism of racemization is provided by the fact that the grouping XI, in which the cyano group replaces the carbonyl group of IX, and which can be assumed to exhibit an analogous tautomerism with the unstable structure XII, similarly permits a relatively easy racemization.



$$-\underset{|}{C}^{*}H-C\equiv N$$

XI



$$-\underset{|}{C}=C=NH$$

XII

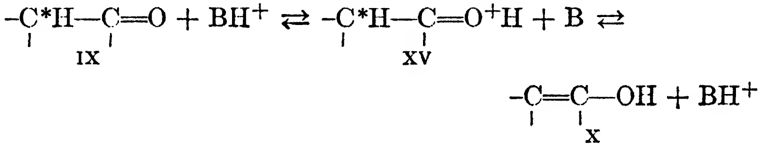
For example, mandelonitrile, XIII, is rapidly racemized in the presence of water, and α-cyanopropionic acid, XIV, with

C_6H_5—CHOH—CN XIII

CH_3—CH(CN)—CO_2H XIV

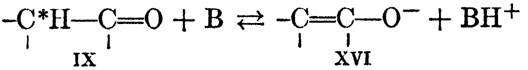
both a cyano and carbonyl group,[28] is exceptionally easily racemized. Moreover, the mechanism permits a simple interpretation of the observed catalytic effects of acids and bases, since these substances have been found generally to catalyze keto-enol transformations and the like, as, for example, in acetoacetic ester and similar compounds with which the composition of the tautomeric mixture and the rate of interconversion can be directly measured. (See Section 14·2.)

Within recent years, the belief has grown that the above tautomeric mechanism of racemization, although essentially correct, is somewhat oversimplified since it does not show just how acids and bases produce their catalytic effects. At present, the acid-catalyzed and base-catalyzed racemizations are considered to proceed by independent mechanisms.[29] That of the acid-catalyzed reaction, for example, is supposed to involve the equilibrium shown in equation 7·1, where the Brønsted base B is



$$\underset{\mathrm{IX}}{-\underset{|}{C}{}^*H-\underset{|}{C}=O} + BH^+ \rightleftarrows \underset{\mathrm{XV}}{-\underset{|}{C}{}^*H-\underset{|}{C}=O^+H} + B \rightleftarrows \underset{\mathrm{X}}{-\underset{|}{C}=\underset{|}{C}-OH} + BH^+ \qquad (7\cdot1)$$

frequently the solvent. (Cf. Section 3·2.) The function of the acid catalyst BH^+ is thus to produce the oxonium cation, XV, which, by the loss of a different proton to the base B, gives the optically inactive enol X. The ionization of the C*-H bond is, of course, much easier in the cation XV (on account of the positive ionic charge) than it is in the neutral molecule IX. (Cf. Chapter 11.) The mechanism of the base-catalyzed racemization, on the other hand, is considered to involve the equilibrium of equation 7·2, where the base B may be hydroxide ion,



$$\underset{\mathrm{IX}}{-\underset{|}{C}{}^*H-\underset{|}{C}=O} + B \rightleftarrows \underset{\mathrm{XVI}}{-\underset{|}{C}=\underset{|}{C}-O^-} + BH^+ \qquad (7\cdot2)$$

alkoxide ion, acetate ion, an amine, or any other similar proton acceptor. The function of the catalyst is here to remove the proton from the asymmetric carbon atom of the molecule IX, and thus to produce the optically inactive anion XVI. If these two mechanisms are correct, the acid-catalyzed racemization does indeed involve a preliminary enolization, as was originally assumed, but the base-catalyzed one involves instead an ionization. However, the considerations (see the preceding paragraph) which suggested that enolization is necessary for racemization, are not thereby shown to be without significance; in fact, the enolization and the

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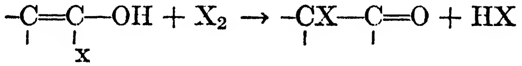
[28] K. Freudenberg, W. Kuhn, and I. Bumann, *Ber.* **63**, 2380 (1930).

[29] See, for example, L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, New York, 1940, pages 97 ff., 109 ff., 230 ff.

ionization are so closely related that any carbonyl compound which can undergo either reaction can also undergo the other.

Very satisfactory experimental support for the above mechanisms of racemization has been obtained from kinetic studies.[29] Equation 7·1 requires that the rate of the acid-catalyzed racemization be equal to the rate of enolization under the conditions of the experiment; and equation 7·2 similarly requires that the rate of the base-catalyzed racemization be equal to the rate of ionization under the now, of course, different conditions. This equality of rates is confirmed in the following way. The rate of halogenation of a ketone has been found, with a given ketone, to be independent of the concentration of the halogen and to be the same (under identical conditions) for all the halogens.[29] This rather surprising fact finds a logical explanation in the assumption that the reaction goes in two steps. Under the conditions of acid catalysis, the first step is the one shown in equation 7·1. This initial reaction is considered to occur relatively slowly, whereas the subsequent reaction (equation 7·3) is considered to occur much more rapidly. With acetoacetic ester and other similar substances with which the enol form can be isolated, the reaction of equation 7·3 is indeed almost instantaneous. (See Section 14·2.) Consequently, the enol, X, reacts as fast as it is formed, so that the measured rate of halogenation is equal to the rate of the enolization (equation 7·1). This rate is, of course, independent of the concentration of the halogen, or even of its identity, since the halogen is not involved in the reaction in any way. It therefore follows that the rates of the acid-catalyzed halogenation and racemization of a ketone under the same conditions should be identical. This prediction has been confirmed,[30] for example, with the racemization and iodination of phenyl *sec*-butyl ketone, XVII.

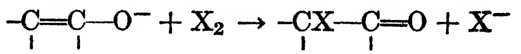


$$-\underset{|}{C}=\underset{\underset{\textstyle X}{|}}{C}-OH + X_2 \rightarrow -\underset{|}{C}X-\underset{|}{C}=O + HX \qquad (7\cdot3)$$

$$C_6H_5-CO-CH(CH_3)-C_2H_5$$

XVII

Under the conditions of base catalysis, the first step in the halogenation of a ketone is considered to be the one shown in reaction 7·2. This step is presumably a slow one followed by the rapid reaction of equation 7·4. Like reaction 7·3, reaction 7·4 also has been found to be very fast



$$-\underset{|}{C}=\underset{|}{C}-O^- + X_2 \rightarrow -\underset{|}{C}X-\underset{|}{C}=O + X^- \qquad (7\cdot4)$$

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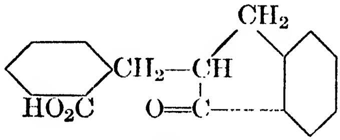
[30] P. D. Bartlett and C. H. Stauffer, *J. Am. Chem. Soc.* **57**, 2580 (1935).

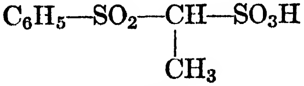
with the stable anions derived from acetoacetic ester and its analogs. (See Section 14·6.) Consequently, the measured rate of halogenation is equal to the rate of ionization; as before, the halogen is not involved in the step which determines the rate of the reaction. The rates of halogenation and of racemization under the same conditions should therefore again be identical. This prediction has been confirmed, for example, with the bromination and racemization of the ketone, XVIII, with catalysis by acetate ion.[31]



XVIII

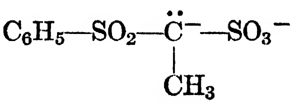
Another reaction of a ketone which is likewise considered to involve the equilibria of reactions 7·1 and 7·2 under the conditions, respectively, of acid and base catalysis is the replacement of the enolizable hydrogen atom by a deuterium atom. As with the halogenations and racemizations, the measured rates of such exchange reactions should be simply the rates of enolization (equation 7·1) or of ionization (equation 7·2), since the introduction of the deuterium atom into either the enol, X, or the anion, XVI, should be very rapid. Consequently, the rates of deuterium exchange, of halogenation, and of racemization should all, under the same conditions, be identical. No direct comparison of the acid-catalyzed exchange and racemization seems to have been made as yet, but the rates of the exchange and of bromination have been found to be equal with acetone.[32] On the other hand, the base-catalyzed exchange reaction and racemization of, for example, phenyl *sec*-butyl ketone, XVII, have been shown to have the same rate.[33] (The catalyst here was deuteroxide ion OD^-.)

The base-catalyzed racemization of a sulfonyl compound, like that of a carbonyl compound, presumably goes through a preliminary ionization. Thus, the very rapid racemization of α-phenylsulfonylethane sulfonic acid, XIX,[34] may be considered to involve the formation of an



$$C_6H_5\text{—}SO_2\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}SO_3H$$

XIX



$$C_6H_5\text{—}SO_2\text{—}\underset{\displaystyle CH_3}{\underset{|}{\overset{\bullet\bullet}{C}{}^-}}\text{—}SO_3^-$$

XX

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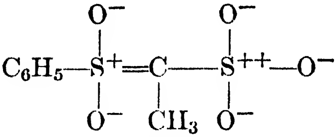
[31] S. K. Hsü and C. L. Wilson, *J. Chem. Soc.* **1936,** 623.

[32] O. Reitz, *Z. physik. Chem.* **179,** 119 (1937).

[33] S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.* **1938,** 78.

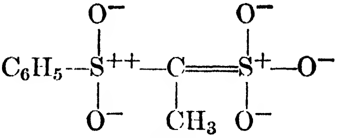
[34] I. Hedlund, *Arkiv Kemi, Mineral. Geol.* **13A,** No. 12 (1939); *C.A.* **33,** 6277 (1939).

ion for which the three structures XX, XXI, and XXII can be written.



$$C_6H_5-\overset{O^-}{\underset{O^-}{S^+}}=\underset{CH_3}{C}-\overset{O^-}{\underset{O^-}{S^{++}}}-O^-$$

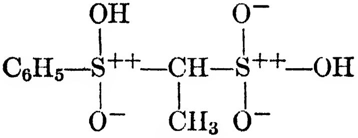
XXI



$$C_6H_5-\overset{O^-}{\underset{O^-}{S^{++}}}-\underset{CH_3}{C}=\overset{O^-}{\underset{O^-}{S^+}}-O^-$$

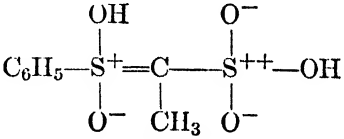
XXII

In the first of these structures, the carbon atom that is joined to the two sulfonyl groups forms only three bonds and has an unshared pair of electrons; in the second and third structures, this carbon atom is joined by a double bond to one of the sulfur atoms, which has 10 electrons in its valence shell. It is not certain which type of structure is correct, since the octet rule does not necessarily apply rigorously to sulfur. Possibly *resonance* occurs among all three structures. (See page 425.) In any event, it appears that the ion is unable to maintain the dissymmetric configuration of the original acid, XIX, either because it undergoes an easy racemization by a mechanical deformation analogous to that postulated by Werner (as would be anticipated if structure XX is correct) or because its formerly asymmetric carbon atom has become planar (as in structures XXI and XXII). Unlike bases, acids do not catalyze the racemization of the substance XIX; apparently, therefore, an ion such as XXIII (cf. structure XV), if it is formed at all, does not readily lose a



$$C_6H_5-\overset{OH}{\underset{O^-}{S^{++}}}-\underset{CH_3}{CH}-\overset{O^-}{\underset{O^-}{S^{++}}}-OH$$

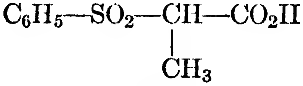
XXIII



$$C_6H_5-\overset{OH}{\underset{O^-}{S^+}}=\underset{CH_3}{C}-\overset{O^-}{\underset{O^-}{S^{++}}}-OH$$

XXIV

proton to give an inactive substance like XXIV. (Cf. equation 7·1.) On the other hand, α-phenylsulfonylpropionic acid, XXV, is racemized



$$C_6H_5-SO_2-\underset{CH_3}{CH}-CO_2H$$

XXV

by either acids or bases;[35] for, since the asymmetric carbon atom is here adjacent to a carbonyl group as well as to a sulfonyl group, enolic intermediates of the previously considered types can again be formed.

A different group of substances which have been considered to be racemized by ionization is represented by α-chloroethylbenzene, XXVI.

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[35] L. Ramberg and I. Hedlund, *Arkiv Kemi, Mineral. Geol.* **12A**, No. 24; **13A**, No. 1 (1938); *C.A.* **32**, 4550, 9080 (1938).

$$\underset{\text{XXVI}}{C_6H_5\text{—}CHCl\text{-}CH_3} \qquad \underset{\text{XXVII}}{C_6H_5\text{—}C^+H\text{-}CH_3}$$

When either enantiomorphic form of this compound is dissolved in liquid sulfur dioxide or formic acid, a more or less rapid racemization occurs spontaneously. The half-life in sulfur dioxide at 0°C is 18 hours.[36] Since analogous halides have been found to give conducting solutions in these solvents, a natural inference is that the cation XXVII is formed. Since, moreover, the central carbon atom in this ion forms only three bonds and has only six electrons in its valence shell, it may be assumed to be planar; or else to be capable of achieving planarity relatively easily, and hence of being racemized by a mechanism analogous to Werner's. More recent work has suggested, however, that racemization of the substance XXVI is due to a reversible loss of a molecule of hydrogen chloride,[36] as in equation 7·5. The styrene XXVIII that is formed in the

$$\underset{\text{XXVI}}{C_6H_5\text{—}CHCl\text{—}CH_3} \rightleftarrows \underset{\text{XXVIII}}{C_6H_5\text{—}CH{=}CH_2} + HCl \qquad (7{\cdot}5)$$

dissociation must be optically inactive; hence, the reassociation gives the racemic modification of the original halide. This second explanation of the racemization is supported by the fact that the rates of racemization and of formation of free hydrogen chloride have been found to be approximately equal. It may be noted, however, that the ion XXVII is commonly considered to be an intermediate in the dehydrohalogenation, so that the original theory of racemization by ionization is not at present completely discarded.

The racemization of 2-iodoöctane, XXIX, is catalyzed by iodide ion;

$$\underset{\text{XXIX}}{CH_3\text{—}CHI\text{—}n\text{-}C_6H_{13}}$$

this reaction, therefore, cannot be analogous to the above spontaneous racemization of α-chloroethylbenzene, XXVI, the rate of which is independent of the concentration of chloride ion. Consequently a different mechanism must be found for it. The mechanism which has been established [26] cannot be discussed in this section, since it involves the Walden inversion; it will, however, be taken up in a later section of this chapter. (See pages 274 ff.)

The final mechanism of racemization to be described here is exhibited by alkali-metal alkoxides (but not by the corresponding alcohols) at high temperatures. The first reaction of this type was discovered in 1878 by Le Bel, who found that the sodium alkoxide, XXX, is racemized at

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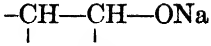
[36] E. Bergmann and M. Polanyi, *Naturwissenschaften* **21**, 378 (1933); E. D. Hughes, C. K. Ingold, and A. D. Scott, *Nature* **138**, 120 (1936).

$C_2H_5-CH(CH_3)-CH_2ONa$

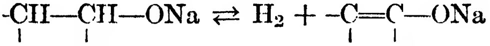
XXX



$-\underset{|}{C}H-\underset{|}{C}H-ONa$

XXXI

200°C. Subsequent investigation has shown that racemization is fairly general, provided that the asymmetric carbon atom either is joined directly to the ONa group or else (as in the alkoxide, XXX) is separated from that group by a single other carbon atom, and provided also that the grouping of atoms XXXI is present. (Cf. pages 263 f.) A reasonable

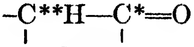


$$-\underset{|}{C}H-\underset{|}{C}H-ONa \rightleftarrows H_2 + -\underset{|}{C}=\underset{|}{C}-ONa \qquad (7\cdot6)$$

XXXI XXXII

mechanism for the racemization is suggested both by these regularities and also by the fact that a certain amount of ketone (or aldehyde) seems always to be formed simultaneously by dehydrogenation of the alkoxide. It is in fact conceivable that, at the high temperature employed, the equilibrium of equation 7·6 is established.[37] Since the enolate salt, XXXII, is of course optically inactive, the reaction from right to left must lead to the racemic alkoxide, XXXI. The configuration about any atom that is more distant from the ONa group than are the two explicitly represented in structures XXXI and XXXII cannot, however, be affected.

A more likely explanation of the racemization is that, as has been suggested by Doering, Cortes, and Knox,[37] there is a mobile equilibrium between the alkoxide, XXXI, and the corresponding aldehyde or ketone, XXXIII. Such an equilibrium would, in fact, merely illustrate the



$-\underset{|}{C}^{**}H-\underset{|}{C}^{*}=O$

XXXIII

well-known Meerwein-Ponndorf reduction. In the carbonyl structure, XXXIII, the carbon atom that is designated by the single asterisk can no longer be asymmetric, whereas the one that is designated by the double asterisk is adjacent to a carbonyl group and also is linked to a hydrogen atom. It is therefore clear that, when the alkoxide, XXXI, is first transformed into the carbonyl compound, XXXIII, and then regenerated, the configurations about both of the two carbon atoms can

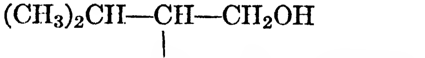
[37] W. Hückel, *Theoretische Grundlagen der organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, Volume 1, pages 260 ff., 2nd ed., 1934, Volume 1, pages 286 ff. However, see also W. E. Doering, G. Cortes, and L. H. Knox, *J. Am. Chem. Soc* **69**, 1700 (1947).

easily be altered. As in the theory of Hückel, the configurations about any asymmetric atoms that are still more distant from the ONa group of the original alkoxide cannot be affected.

Further evidence supporting the above mechanism of racemization is provided by a second type of reaction which is commonly observed under the same experimental conditions, with either optically active or optically inactive alkoxides. Thus, isoamyl alcohol, XXXIV, undergoes

$$(CH_3)_2CH{-}CH_2{-}CH_2{-}OH$$

XXXIV



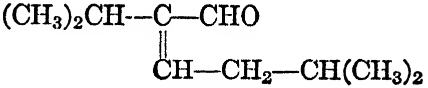
$$\begin{array}{l}(CH_3)_2CH{-}CH{-}CH_2OH\\ \qquad\qquad\quad\ |\\ \qquad\qquad\quad CH_2{-}CH_2{-}CH(CH_3)_2\end{array}$$

XXXV

a self-condensation to the decyl alcohol, XXXV. A reasonable interpretation of this reaction is that, first, oxidation to the aldehyde, XXXVI, occurs; that, next, two molecules of this aldehyde react by an

$$(CH_3)_2CH{-}CH_2{-}CHO$$

XXXVI



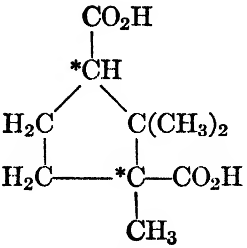
$$\begin{array}{l}(CH_3)_2CH{-}C{-}CHO\\ \qquad\qquad\quad\ \|\\ \qquad\qquad\quad CH{-}CH_2{-}CH(CH_3)_2\end{array}$$

XXXVII

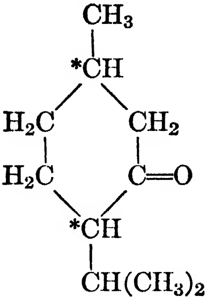
aldol condensation to give the substance XXXVII; and that, finally, this unsaturated aldehyde is reduced to the saturated alcohol, XXXV.[37] (For the sake of clarity, the structures of the initial alcohol, of the postulated intermediates, and of the final product are written here in their usual forms XXXIV–XXXVII, even though at least some of the respective substances presumably participate in the series of reactions as their sodium salts.)

7·7 Interconversion of Diastereomers. When two diastereomers differ only in their configurations about one or more pivot bonds or about one or more asymmetric carbon atoms, the transformation of either substance into the other is governed by the same factors that are involved in the interconversion of enantiomorphs—i.e., in racemization. (Cf. the preceding section.) The only important difference between the two types of reaction, in fact, is that, although the final equilibrium mixture in a racemization must always contain exactly equal quantities of the two enantiomorphs, that in an interconversion of diastereomers need not, and ordinarily does not, contain exactly equal quantities of the two diastereomers. Since, therefore, no new principles are involved, the discussion of this further type of reaction can be restricted to a few examples, chosen on the basis of their relation to the previously considered mechanisms of racemization.

In camphoric acid, I, the configuration about the asymmetric carbon

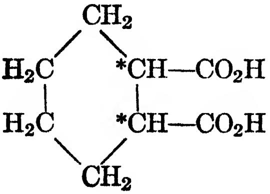


I

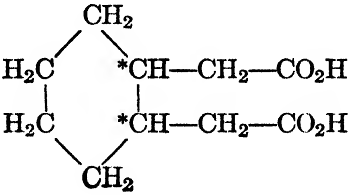


II

atom that is joined to a hydrogen atom can be readily changed under the influence of acidic or basic catalysts, with the production of the diastereomeric isocamphoric acid. (Here and below, asymmetric atoms are designated by asterisks.) On the other hand, the configuration about the second asymmetric carbon atom, which is joined to no hydrogen atom, cannot be changed under any comparable experimental conditions. This difference between the stabilities of the configurations about the two atoms could have been predicted on the basis of the mechanisms of racemization by enolization (or ionization) discussed in the preceding section; thus, only the carbon atom joined to a hydrogen atom is able to form part of a tautomeric keto-enol system. That the presence of a hydrogen atom is, however, not sufficient to permit a change in configuration is shown by the example of menthone, II. Here again there are two asymmetric atoms. The configuration of only the one adjacent to the carbonyl group can be reversed by the action of acidic or basic catalysts; the other asymmetric carbon atom, with completely stable configuration, cannot be part of an enol system, even though it is linked to a hydrogen atom, because it is too far from the carbonyl group. A further example, which illustrates the same principle, is provided by the fact that, although *cis*-hexahydrophthalic acid, III, is readily converted



III



IV

into its more stable *trans* isomer by basic catalysts,[38] the analogous *cis*-

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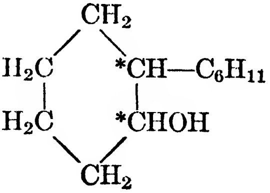
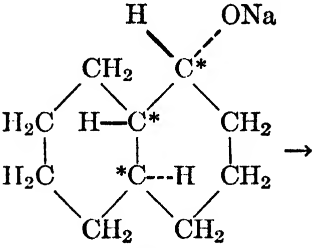
[38] W. Hückel and E. Goth, *Ber.* **58**, 447 (1925).

cyclohexane-1,2-diacetic acid, IV, cannot be made to undergo a similar reaction.[39]

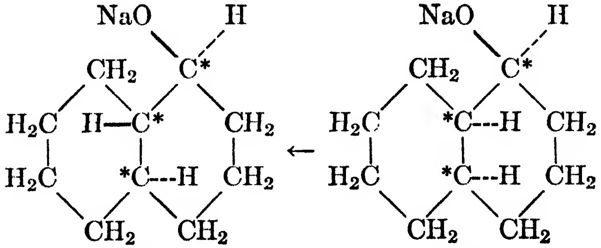
The sodium derivative of *cis*-2-cyclohexylcyclohexanol, V, is transformed at high temperature into the more stable *trans* isomer. Since this reaction could have involved a change of configuration about either one of the two asymmetric atoms, it is not clear which atom was the one affected. If, however, a third asymmetric carbon atom is present in the molecule, and if this atom is farther removed from the ONa group, so that it must retain its original configuration, the details of the transformation can then be demonstrated. Thus, with the α-decalols,[37] the sodium salt, VI, is changed at the temperature of boiling xylene into its



V



VI



VII VIII

diastereomer, VII, which can be obtained also from the further diastereomer, VIII, under the same conditions. In the first reaction, the carbon atom affected is the one to which the ONa group is attached; in the second, it is the atom adjacent to this one. In no instance is the remain-

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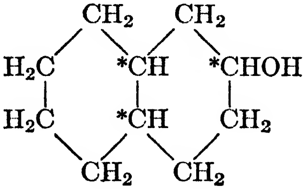
[39] W. Hückel, *Z. angew. Chem.* **39**, 842 (1926).

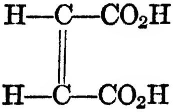
ing, and still more distant, asymmetric atom altered. With the β-decalols of structure IX, the configuration of the carbon atom which



IX

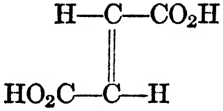
carries the ONa group in the salts can be changed, but the configurations of the two remaining asymmetric atoms cannot be affected.

The interconversion of diastereomers that differ in their configuration, not about either pivot bonds or asymmetric carbon atoms, but rather about double bonds, can be brought about in a variety of ways. Frequently the change occurs spontaneously at a rate which increases with temperature. Thus, although maleic acid, X, and fumaric acid, XI, are



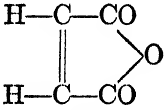
$$\begin{array}{c} H—C—CO_2H \\ \| \\ H—C—CO_2H \end{array}$$

X



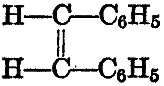
$$\begin{array}{c} H—C—CO_2H \\ \| \\ HO_2C—C—H \end{array}$$

XI



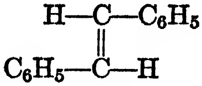
XII

stable at room temperature, the former substance is changed into the latter when it is kept in the melted state at a temperature above 130°C. On the other hand, fumaric acid is transformed into maleic anhydride, XII, either when heated alone to 230°C or when warmed with phosphorus pentoxide. Moreover, the dimethyl ester of maleic acid in the gas phase is converted at a high temperature into the corresponding ester of fumaric acid. From a study of the temperature coefficient of the rate of this interconversion over the range 279°–380°C, the conclusion has been drawn that the activation energy for the transition is about 26.5 kcal per mole; or, in other words, that only molecules with an energy that is at least 26.5 kcal per mole greater than the average are able to undergo the transition.[40] A similar study of the conversion of *cis*-stilbene (isostilbene), XIII, into its *trans* isomer, XIV, has led to a



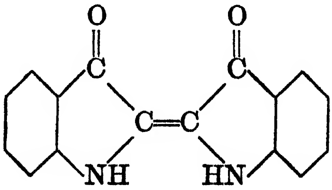
$$\begin{array}{c} H—C—C_6H_5 \\ \| \\ H—C—C_6H_5 \end{array}$$

XIII



$$\begin{array}{c} H—C—C_6H_5 \\ \| \\ C_6H_5—C—H \end{array}$$

XIV



XV

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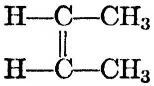
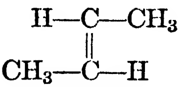
[40] M. Nelles and G. B. Kistiakowsky, *J. Am. Chem. Soc.* **54**, 2208 (1932).

larger value of about 43 kcal per mole for the activation energy.[41] On the other hand, *cis*-indigo, XV, changes rapidly even at room temperature into the stable *trans* form,[42] so that, with this substance, the activation energy must be relatively small. In all these instances, the equilibrium between the two stereoisomers is such that the less stable form is changed almost completely into the second, more stable, one. In other instances, however, the difference in stability is less, so that either form is converted into a mixture that contains comparable amounts of the two. This situation is encountered, for example, with the 2-butenes, XVI and XVII.[43]



$$\begin{array}{c} H\text{—}C\text{—}CH_3 \\ \| \\ H\text{—}C\text{—}CH_3 \end{array}$$

XVI



$$\begin{array}{c} H\text{—}C\text{—}CH_3 \\ \| \\ CH_3\text{—}C\text{—}H \end{array}$$

XVII

A reasonable interpretation of the above thermal reactions can be derived from a consideration of Figure 6·2*c* on page 177. The more shallow minimum of the curve in this figure corresponds to the configuration of the less stable isomer, whereas the deeper minimum corresponds to that of the more stable isomer. The conversion of either form into the other then results when the molecule passes over the "hill" from one "valley" to the other. In the figure, the activation energy (i.e., the amount of excess energy required for the change) is then represented by the height ΔE. The situation here is therefore closely analogous to that encountered in the racemizations of the optically active biphenyls and their analogs; the most significant difference, in fact, is that, in the two types of molecule, the forces restricting the freedom of rotation arise from entirely different causes.

There is another interesting difference between the restricted rotation in a biphenyl and that in an ethylenic compound. With a biphenyl, the two "valleys" of Figure 6·2*c* correspond to enantiomorphic configurations, and hence must lie at the same value of the energy E; whereas the two "hills" correspond to nonenantiomorphic configurations, and hence in general lie at different values of the energy. On the other hand, with an ethylenic compound, the two "valleys" now correspond to nonenantiomorphic configurations, and hence in general lie at different values of the energy, whereas the two "hills" correspond to enantiomorphic configurations (cf. Section 6·3), and hence must lie at the same energy.

It seems probable that the above mechanism is correct in many, if not in all, purely thermal interconversions. There is, however, a second mechanism which may also operate in some instances.[44] As a result of

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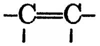
[41] G. B. Kistiakowsky and W. R. Smith, *J. Am. Chem. Soc.* **56**, 638 (1934).

[42] G. Heller, *Ber.* **72**, 1858 (1939).

[43] H. H. Voge and N. C. May, *J. Am. Chem. Soc.* **68**, 550 (1946).

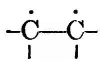
[44] J. L. Magee, W. Shand, Jr., and H. Eyring, *J. Am. Chem. Soc.* **63**, 677 (1941).

collisions, the molecules of an ethylenic compound with the grouping XVIII may undergo so-called *electronic transitions* to an unstable state



$$-\underset{|}{C}=\underset{|}{C}-$$

XVIII

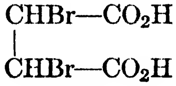


$$-\overset{\cdot}{\underset{|}{C}}-\overset{\cdot}{\underset{|}{C}}-$$

XIX

representable by some such structure as XIX. The two isolated dots here show the presence of two unpaired electrons (cf. pages 416ff.) in the molecule. Since, in structure XIX, there is only a single bond between the carbon atoms, rotation may be presumed to occur readily. Indeed, there is some theoretical reason to believe that the most stable configuration of a molecule with the grouping XIX would be the perpendicular one. (Cf. configurations VII and VIII on page 170.) Consequently, when the molecule returns to its stable electronic structure with the grouping XVIII, it may readily assume the configuration opposite to the one which it originally possessed. Although only a small fraction of the molecules could at any one time be in the state represented by structure XIX, all the molecules could sooner or later pass through this state to the isomeric configuration. When this mechanism is the correct one, the activation energy of the isomerization is approximately equal to the difference in energy between structures XVIII and XIX. (Cf. also the discussion, below, of the photochemical isomerization.)

Cis-trans interconversions with ethylenic compounds can be brought about by the action of various catalysts, of which the halogens, strong acids, nitrous acid, alkali metals, and substances with unpaired electrons are characteristic examples. Since most of these substances can (at any rate, in some instances) add to carbon-carbon double bonds, the suggestion was at one time made that their catalytic effects are due to their abilities to add. Thus, the bromine-catalyzed conversion of maleic acid, X, to fumaric acid, XI, was presumed to proceed through the preliminary formation of α,α'-dibromosuccinic acid, XX. Since the double



$$\begin{array}{l}\mathrm{CHBr{-}CO_2H}\\ |\\ \mathrm{CHBr{-}CO_2H}\end{array}$$

XX

bond of the original substance, X, has been decreased in the assumed intermediate XX to a single bond, the rotation can now easily occur; therefore, when bromine splits off again, fumaric acid, XI, could be formed. The evidence against this mechanism, however, seems to be conclusive. The addition product, XX, is a stable substance which does not lose bromine again under the conditions of the experiment; hence it cannot possibly be an intermediate in the reaction. Moreover, similar objections can be raised against the assumption that analogous mechanisms apply to the isomeric changes induced by the other catalysts named; consequently, such mechanisms are no longer considered to be generally valid. (For a more precise discussion of the stereochemical principles involved in the addition reactions of ethylenic compounds, see Section 7·9.)

Recent studies of the catalyzed *cis-trans* interconversions have shown that no single mechanism can account for all the varied phenomena which have been observed. Evidently, therefore, there must be several different mechanisms, each of which operates only within some more or less narrowly restricted field. Many isomerizations may, of course, proceed by two or more independent paths at the same time. Discussion of the proposed mechanisms that now seem most likely to be valid will, however, be postponed until Section 7·11, since these mechanisms can be most easily described after those of the closely related additions (Sections 7·9 and 7·10) have first been considered.

Like the purely thermal isomerizations, the catalyzed reactions result in the transformation of the less stable isomer into the more stable one, or else in the transformation of either form into the equilibrium mixture of the two. There exists, however, still a different method, by which the more stable form can often be transformed, at least partially, into the less stable one. This *photochemical* method consists in subjecting the substance to the action of light which has such a wave length (usually in the ultraviolet) that it is absorbed by the unsaturated substance. The energy thereby acquired by the substance from the light may change a certain amount of the more stable isomer into the less stable one. The latter substance can then be separated from the unchanged starting material by fractional crystallization or by other analogous methods. *cis*-Stilbene, XIII, for example, has been made from *trans*-stilbene, XIV, in this way.

Light also induces the reverse transformation of the less stable form into the more stable one; hence, the same mixture of isomers is finally obtained by the irradiation of either form. The success of the photochemical method for the production of the less stable isomer is due to the fact that the proportion of this isomer is frequently higher in the "steady-state" mixture produced by irradiation than it is in the mixture corresponding to thermal equilibrium. Since the light is not strictly a *catalyst* for the reaction, but is instead a constant source of energy, the displacement of the equilibrium by the light is not contrary to the general principle, rigorously derived from the second law of thermodynamics, that no catalyst can ever affect the position of a chemical equilibrium. (See also the paragraphs in fine print, below.)

The mechanism of the photochemical *cis-trans* isomerization has not been definitely established. Possibly, both the mechanisms suggested above for the corresponding thermal reactions operate here also. That is, by the absorption of light, just as by molecular collisions, the molecules of the ethylenic compound may gain enough energy to "go over the hill" of Figure 6·2*c*, or (more probably) they may be raised to excited electronic states of the type represented by structure XIX. Possibly also, of course, there may be still further mechanisms in addition to these.

The distinction between the photochemical steady state and the ordinary chemical equilibrium becomes apparent when the kinetics of the photochemical transformation is considered. As the light passes through, and is partly absorbed by, the ethylenic compound, its intensity of course decreases along its path; within any sufficiently small region, however, the intensity can be assumed to have the constant value I. The rate at which the *cis* form in this region is raised by the light to some excited state is proportional both to the intensity I and to the amount of the *cis* isomer that is present in the region of interest. Similarly, the rate at which the *trans* form in this same region is raised to the excited state is proportional both to the intensity I and to the amount of the *trans* isomer that is present in the region of interest. Moreover, the rates at which the excited form returns to the *cis* and *trans* forms are proportional to the amount of excited form. Hence, if the concentrations of the *cis*, *trans*, and excited forms are designated, respectively, as C, T, and E, the rates of the several reactions are given by the kinetic equations 7·7 and 7·8, where

$$\frac{dC}{dt} = -k_1IC + k_3E \tag{7·7}$$

$$\frac{dT}{dt} = -k_2IT + k_4E \tag{7·8}$$

k_1, k_2, k_3, and k_4 are the proportionality constants (i.e., the *rate constants*). When the steady state has been reached, the concentrations C and T of the *cis* and *trans* forms, respectively, are constant, and each of the derivatives $\frac{dC}{dt}$ and $\frac{dT}{dt}$ is therefore equal to zero. Since equations 7·9 and 7·10 must then be satisfied, the ratio C/T

$$-k_1IC + k_3E = 0 \tag{7·9}$$

$$-k_2IT + k_4E = 0 \tag{7·10}$$

must have the value shown in equation 7·11. Moreover, since this ratio is independent of the intensity I, it must have the same value in every irradiated region within the sample of material; hence equation 7·11 applies not merely to the infinitesimal volume originally considered, but to the entire sample.

$$\frac{C}{T} = \frac{k_2k_3}{k_1k_4} \tag{7·11}$$

There is, of course, no necessary relation between, on the one hand, the rate constants k_1, k_2, k_3, and k_4 which apply to the photochemical transformation and, on the other hand, the rate constants for the nonphotochemical interconversion. It therefore follows that the relative concentrations of the *cis* and *trans* isomers in the photochemical steady state are in general different from those in the mixture at thermal equilibrium. Moreover, since the values of the rate constants k_1 and k_2 may be expected to depend upon the wave length of the light used, the ratio C/T in the steady state may also be expected to depend upon the wave length; such variations have indeed been observed. Thus, with cinnamic acid, XXI, in dilute

$$C_6H_5—CH{=}CH—CO_2H$$

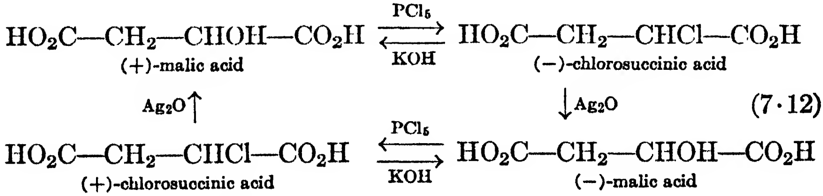
XXI

aqueous solution at 15°C, this ratio has the value 3.55 when the light has previously passed through a potassium chromate filter, but the value 1.18 when the light has previously passed through a chlorine filter.[45] Variations with the temperature have also been observed; for example, when the chlorine filter is used, the ratio with cinnamic acid varies from 1.18 at 15°C (as was just stated) to 1.77 at 90°C.[45]

It was concluded above that the relative concentrations of stereoisomers in their photochemical steady states are independent of the intensity of the light used; this conclusion may, however, seem to be inconsistent with the fact that this steady state is usually achieved only with the aid of *intense* illumination. Indeed, most thermal (or catalyzed) interconversions are carried out in the presence of diffused natural or artificial light; yet they lead to the ordinary chemical equilibrium and not to the photochemical steady state. The point at issue here is, of course, one of relative rates. In the preceding paragraphs, it was implicitly assumed that all reactions except the photochemical ones under discussion could be ignored. Now, the rate at which the photochemical steady state is reached decreases as the intensity of the light decreases; evidently, therefore, this rate must be very small if the light is very weak. Hence, under such circumstances, the thermal (or catalyzed) reactions may proceed so much faster than the photochemical ones that the latter can only slightly affect the equilibrium. Finally, if the light is of intermediate intensity, the rates of the photochemical and thermal (or catalyzed) reactions may be comparable; then the system may reach a steady state which is different from the ordinary equilibrium, but which depends upon the intensity of the light.

7·8 The Walden Inversion.

In 1893, Walden discovered[46] the cycle of reactions 7·12. Thus, by treating either of the optically active



$$\begin{tikzcd} \underset{(+)\text{-malic acid}}{HO_2C—CH_2—CHOH—CO_2H} \arrow[r, shift left, "PCl_5"] & \underset{(-)\text{-chlorosuccinic acid}}{HO_2C—CH_2—CHCl—CO_2H} \arrow[l, shift left, "KOH"] \arrow[d, "Ag_2O"] \\ \underset{(+)\text{-chlorosuccinic acid}}{HO_2C—CH_2—CHCl—CO_2H} \arrow[u, "Ag_2O"] \arrow[r, shift right, "KOH"'] & \underset{(-)\text{-malic acid}}{HO_2C—CH_2—CHOH—CO_2H} \arrow[l, shift right, "PCl_5"'] \end{tikzcd} \quad (7·12)$$

malic acids, first with phosphorus pentachloride (in chloroform solution) and then with silver oxide (in aqueous solution), he was able to transform it into its own enantiomorph; conversely, by treating either of the chlorosuccinic acids first with silver oxide and then with phosphorus

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[45] A. R. Olson and F. L. Hudson, *J. Am. Chem. Soc.* **55**, 1410 (1933).

[46] P. Walden, *Ber.* **26**, 210 (1893); **29**, 133 (1896).

pentachloride, he was able to transform it also into its enantiomorph. In each sequence of reactions, considerable racemization occurs, so that the optical activities of the final products are not very great. Other similar sequences have been discovered subsequently, however; in some of these, relatively little racemization occurs.

It is evident that, in one (and only one) of the two reactions in each of these sequences (i.e., in either the reaction with phosphorus pentachloride or the one with silver oxide, but not in both), the entering substituent at the asymmetric carbon atom does not take up the same relative position in space that was formerly occupied by the substituent which it replaces. The change in configuration which thus results is called an *inversion* or, more precisely, a *Walden inversion.*

The expression "Walden inversion" was introduced in 1906 by Emil Fischer.[47] Originally, it referred to the complete sequence of reactions by which the optically active substance is converted into its enantiomorph, and not to the single reaction in which the inversion of configuration occurs. At the present time, however, the expression seems more commonly to refer to the single reaction; it is so used throughout this book.

The problem of identifying the particular reaction in which the inversion takes place is a difficult one since, almost always, the occurrence of the inversion becomes apparent only after at least two reactions have been performed. This inconvenient situation arises because the relative configurations of two substances with different structures cannot be decided merely on the basis of their properties. For example, the fact that the action of phosphorus pentachloride on dextrorotatory malic acid gives levorotatory chlorosuccinic acid does not imply that the reaction is necessarily accompanied by inversion. Very frequently, in fact, the sign of rotation changes in a reaction in which the asymmetric atom is not affected, and in which therefore no inversion can have taken place. Thus, the salts and esters of either enantiomorphic form of lactic acid have rotations of opposite sign from the parent acid, although their configurations must surely be the same. (Cf. page 224.) In an analogous manner, the fact that the action of silver oxide on levorotatory chlorosuccinic acid gives levorotatory malic acid does not imply that no inversion of configuration can have taken place. Consequently, the occurrence of an inversion can usually be demonstrated only after one or more further reactions have been carried out, and after a final product which has the *same structure* as does the original substance has been obtained. When this rather elaborate procedure has been completed, there is then no longer any uncertainty whether or not a net inversion has taken place, since there can be no uncertainty whether the initial

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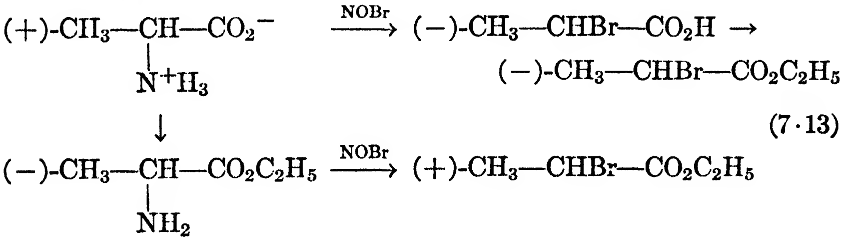
[47] E. Fischer, *Ber.* **39**, 2893 (1906).

and final substances are, respectively, enantiomorphic or identical. There is, however, uncertainty regarding the identity of the particular reaction in which the change in configuration occurred.

If the substance under investigation has one or more further dissymmetric groupings that are not affected by the reactions performed, an inversion will of course lead to a diastereomer, and not to an enantiomorph, of the original compound. In such an event, however, the interpretation of the data is neither more nor less difficult than it is in the simpler example.

It has just been remarked that, even after a substance with the same structure as the original one has been obtained, there still remains the problem of identifying the particular reaction, or reactions, in which inversion occurs. The situation is usually made more difficult by the fact that there is no way of knowing how many inversions have taken place. If no *net* inversion is observed, there may really have been no inversion at all, or there may instead have been two, or any other even number, of them. Thus, in the transformation of (+)-malic acid into (−)-chlorosuccinic acid, and the transformation of the latter substance back into the original (+)-malic acid, there is no net inversion since the final product is identical (aside from the partial racemization) with the original substance. The maximum conclusion that can be drawn is, however, that either an inversion has occurred in neither reaction or else that one has occurred in each reaction. Similarly, when a net inversion is observed, there may really have been one, three, or any other odd number of single inversions. (See, however, pages 286 f., 316 f.)

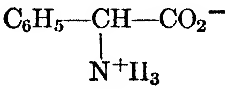
A further feature of the Walden inversion which makes its study difficult is the extremely erratic way in which it occurs. For example, a given reagent in a given type of reaction might be expected either always to invert, or else always to retain, the configuration. That this expectation is not justified, however, is shown by the sequence or reactions 7·13.



$$\begin{array}{lll} (+)\text{-CH}_3\text{—}\underset{\displaystyle \text{N}^+\text{H}_3}{\text{CH}}\text{—CO}_2^- & \xrightarrow{\text{NOBr}} & (-)\text{-CH}_3\text{—CHBr—CO}_2\text{H} \rightarrow \\ & & \qquad (-)\text{-CH}_3\text{—CHBr—CO}_2\text{C}_2\text{H}_5 \\ \downarrow & & \\ (-)\text{-CH}_3\text{—}\underset{\displaystyle \text{NH}_2}{\text{CH}}\text{—CO}_2\text{C}_2\text{H}_5 & \xrightarrow{\text{NOBr}} & (+)\text{-CH}_3\text{—CHBr—CO}_2\text{C}_2\text{H}_5 \end{array} \qquad (7\cdot13)$$

Since the esterification of the original amino acid (alanine) does not affect the asymmetric carbon atom, it cannot be accompanied by inversion, even though it changes the sign of rotation. Consequently, the reaction with nitrosyl bromide, which does affect the asymmetric atom, must either lead to retention of configuration with the amino acid and to inversion with the ester, or vice versa. It is not possible, from the reactions cited, to decide which of these two alternatives is correct. A closely related anomaly in the occurrence of the Walden inversion is that two reagents which behave differently in one reaction may behave similarly in an apparently analogous reaction. Thus, an alkali-metal hydroxide and silver oxide lead to enantiomorphic products with either of the optically active chlorosuccinic acids (see above); hence, in these reactions, one of the bases must invert the configuration, and the other must retain it. On the other hand, with (+)-α-chloroethylbenzene, I, both reagents lead to the same (−)-methylphenylcarbinol, II, so that

$C_6H_5—CHCl—CH_3$ I $C_6H_5—CHOH—CH_3$ II $C_6H_5—CHCl—CO_2H$ III

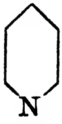


$$C_6H_5—\underset{N^+H_3}{\underset{|}{CH}}—CO_2^-$$

IV

here either both must invert or else both must retain the configuration. As before, the data given do not permit a decision to be made between the alternatives. Even with exactly the same pair of reagents, the steric course of a reaction may be varied by a change of solvent. Thus, the action of ammonia upon (−)-α-chlorophenylacetic acid, III, gives (+)-phenylglycine, IV, in aqueous or alcoholic solution, but it gives the enantiomorphic (−)-phenylglycine in solution in methyl cyanide or liquid ammonia. Clearly, the reaction must be accompanied by inversion in one of these groups of solvents and by retention in the other, even though the solvent does not play any immediately obvious role. Moreover, the action of thionyl chloride $SOCl_2$ on levorotatory ethyl mandelate, V, gives levorotatory α-chlorophenylacetate, VI, in the

$C_6H_5—CHOH—CO_2C_2H_5$ V $C_6H_5—CHCl—CO_2C_2H_5$ VI



VII

absence of pyridine, VII, but the enantiomorphic dextrorotatory ester in the presence of pyridine.[48] Finally, when levorotatory phenylethylcarbinol, VIII, is treated with dry hydrogen bromide in the absence of a

$C_6H_5—CHOH—C_2H_5$ VIII $C_6H_5—CHBr—C_2H_5$ IX

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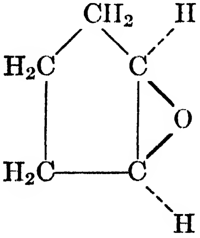
[48] J. Kenyon, A. G. Lipscomb, and H. Phillips, *J. Chem. Soc.* **1930,** 415; **1931,** 2275; W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *ibid.* **1937**, 1252; E. D. Hughes, *Trans. Faraday Soc.* **34,** 202 (1938).

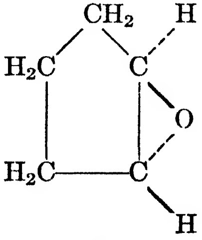
solvent, the resulting bromide, IX, is levorotatory if the reaction is carried out at a temperature below about −36°C, but is dextrorotatory if the reaction is carried out at any higher temperature.[49] (Cf. also page 289.)

Anomalies of the various foregoing types are now fairly well understood. Kinetic studies have shown that very frequently two reactions, which appear to be completely analogous, actually proceed by entirely different mechanisms. A simple example, which is, however, not directly related to the Walden inversion, is given by the hydrolysis of *n*-butyl chloride and by that of *tert*-butyl chloride. The first of these reactions has been found to take place at a rate which is proportional to the concentration of hydroxide ion, whereas the second has been found to be unaffected by hydroxide ion and hence to occur as rapidly in acidic solution as in basic solution.[50] Clearly, therefore, these two reactions are not at all comparable, even though they are described by very similar stoichiometric equations. Analogous differences in mechanism have been found to exist also among the reactions in which substitutions occur at asymmetric atoms. Consequently, it would not be surprising if such reactions were found to follow different steric courses. Since the mechanism of a reaction depends in general upon the natures of all the reagents taking part in it, and also upon that of the solvent, it would accordingly be rather extraordinary if some irregularities in the occurrence of the Walden inversion were not observed.

In spite of the above-described difficulties, however, it has been found possible in a number of instances to determine the particular reactions in which inversions occur. The first examples to be worked out conclusively were of the following type. In cyclopentene oxide, the three-membered ring must be fused onto the five-membered one so that the configuration is *cis*, as in diagram X, since the alternative *trans* configuration, XI, is geometrically impossible. (Cf. Section 9·5.) Hydrolysis of the oxide, however, gives the *trans* glycol, which is separable



X



XI

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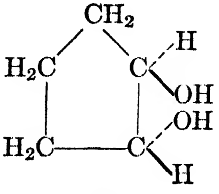
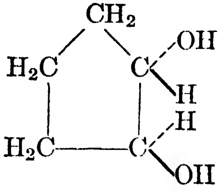
[49] P. A. Levene and A. Rothen, *J. Biol. Chem.* **127**, 237 (1939). Cf. also C. L. Arcus, *J. Chem. Soc.* **1944**, 236.

[50] Cf. E. D. Hughes and C. K. Ingold, *J. Chem. Soc.* **1935**, 244.

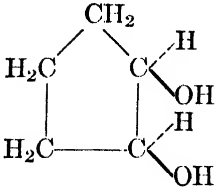
into the two enantiomorphic forms, XII and XIII, and it does not give



XII



XIII



XIV

the nonresolvable *cis* compound, XIV.[51] Since the configurations of the original substance and of the product are therefore definitely known to be different, a Walden inversion must have occurred in the single reaction performed.

A further reaction which has been shown definitely to involve a Walden inversion is the one responsible for the racemization of an optically active chloride, bromide, or iodide by chloride ion, bromide ion, or iodide ion, respectively. (Cf. pages 252, 259.) For example, the racemization of 2-iodoöctane, XV, by iodide ion in acetone solution has been found [26] to

$$n\text{-}C_6H_{13}\text{—}CHI\text{—}CH_3$$

XV

proceed by way of the reaction 7·14, in which the iodide ion attacks the

$$I^- + (+)\text{-}C_8H_{17}I \rightleftarrows (-)\text{-}IC_8H_{17} + I^- \qquad (7\cdot 14)$$

molecule of octyl iodide and replaces, with inversion, the iodine atom contained in it. Since the reaction must proceed with equal ease in each of the two opposed directions, complete racemization is more or less rapidly achieved. That this mechanism is correct is suggested, but not proved, by the fact that similar reactions can be observed directly when two different halogens are employed. Thus, under the same experimental conditions as those under which iodide ion leads to racemization of an organic iodide, an iodide ion can replace either the chlorine atom in an organic chloride (equation 7·15) or the bromine atom in an organic

$$I^- + RCl \rightarrow IR + Cl^- \qquad (7\cdot 15)$$

bromide (equation 7·16). It would therefore be strange if reaction 7·14

$$I^- + RBr \rightarrow IR + Br^- \qquad (7\cdot 16)$$

did not take place, as well as reactions 7·15 and 7·16.

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[51] C. van Loon (1919), quoted by J. Böeseken, *Ber.* **58**, 1470 (1925); see also R. Kuhn and F. Ebel, *Ber.* **58**, 919 (1925); C. E. Wilson and H. J. Lucas, *J. Am. Chem. Soc.* **58**, 2396 (1936).

There still remains, however, a possibility that the exchange of iodine atoms is an unimportant side-reaction not accompanied by inversion, and that the racemization is due to some entirely different cause. Equation 7·14 would than have to be replaced by the pair of equations 7·17

$$I^- + (+)\text{-}C_8H_{17}I \rightleftarrows (+)\text{-}IC_8H_{17} + I^- \qquad (7{\cdot}17)$$

and 7·18. Moreover, there also remains the further possibility that,

$$I^- + (-)\text{-}C_8H_{17}I \rightleftarrows (-)\text{-}IC_8H_{17} + I^- \qquad (7{\cdot}18)$$

even if racemization does occur by the mechanism proposed, an inversion of configuration may not take place in every reaction; or, in other words, that the exchange does not always, or even most commonly, follow equation 7·14 but can also to some extent follow equations 7·17 and 7·18 instead. These possibilities have been eliminated, however, by means of experiments carried out with artificially radioactive halogens. Thus, if nonradioactive 2-iodoöctane, XV, is treated with radioactive sodium iodide, the rate at which the organic compound acquires radioactivity can be measured and compared with the rate of racemization in the same experiment. If equation 7·14 represents the only way in which either iodine exchange or racemization can occur, then the rate of racemization should be exactly twice that of exchange. The reason why the rates differ by this factor of 2 can be seen most easily if the original sample of optically active octyl iodide is at first considered to consist of only two molecules. When one of these molecules has reacted with, and been inverted by, a radioactive iodide ion, the exchange has gone only halfway to completion, but the racemization has gone all the way. Consequently, the rate of racemization is twice that of exchange in this simple example. Moreover, as should be obvious, the situation would not be essentially altered if the original sample contained a larger number of molecules; consequently, the same ratio of rates should obtain also with macroscopic quantities of material. This predicted ratio has been confirmed within the limits of accuracy of the experimental methods.[26] Moreover, the same ratio has been found also for the racemization and *bromine* exchange with both α-bromopropionic acid, XVI,[26] and α-bromoethylbenzene, XVII.[26] Consequently, unless the unlikely assumption is made that the observations are the results of an extraordinary set of fortuitous coincidences, it must be concluded that equation 7·14 is correct, and that an inversion occurs in every substitution of the type under consideration. On account of the close similarity of the reactions of equa-

$$CH_3\text{—}CHBr\text{—}CO_2H$$

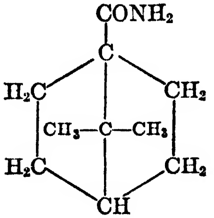
XVI

$$C_6H_5\text{—}CHBr\text{—}CH_3$$

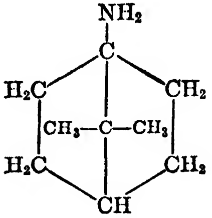
XVII

tions 7·15 and 7·16 to that of equation 7·14, the further inference may be drawn that these reactions also are always accompanied by inversions; the correctness of this inference has not, however, been established with complete rigor.

In certain reactions, a Walden inversion is geometrically impossible. Consequently, if these reactions take place at all, they must do so without inversion. For example,[52] the amide XVIII readily undergoes the Hofmann rearrangement (cf. pages 459, 520) with production of the amine XIX. The reaction may be regarded as a replacement of the carboxamide group $CONH_2$ in the original compound XVIII by the amino group NH_2. Although the carbon atom at which the substitution occurs is not asymmetric, the question may still be raised whether the amino group in the product XIX occupies the same relative position in space as did the carboxamide group in the reagent XVIII. If it does, then the reaction may be said to have proceeded without inversion; if it does not, the reaction may be said instead to have proceeded with inversion. The carbon atom in question could of course be made asymmetric by the introduction of one or more substituents in suitable positions; the situation would not be altered thereby, however, in any of its features that are pertinent to this discussion. Now, it may be easily shown with the aid of molecular models that the ring-system in the molecules XVIII and XIX is completely rigid, and that there is only one possible position in space for either the carboxamide or the amino group, respectively. Consequently, no inversion can have occurred in the reaction by which the latter substance is prepared from the former. The conclusion cannot be drawn that the configuration is always, or even usually, retained in the Hofmann rearrangement, since the reaction of the amide XVIII may not be typical. The demonstration that the configuration may be retained is, nevertheless, of considerable interest. (See also Section 12·9.)



XVIII



XIX

When the amine XIX is treated with nitrous acid,[52] it is transformed into the alcohol XX; when it is treated with nitrosyl chloride NOCl,[52]

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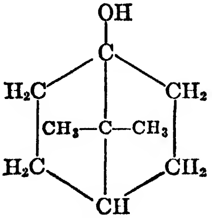
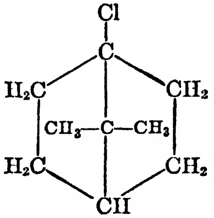
[52] P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.* **61**, 3184 (1939).

it is transformed into the corresponding chloride XXI. The two reactions must therefore in these instances occur without inversion. As



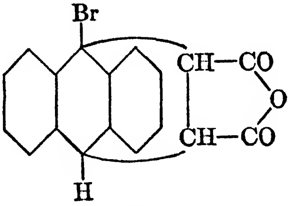
XX



XXI

before, however, the generality of retention in the reactions of nitrous acid and of nitrosyl chloride with primary amines is not certain. There exists a possibility that an inversion might have occurred if it could have done so.

Since the alcohol XX and the chloride XXI are tertiary, the transformation of either substance into the other might be expected to be easy. It has been found, however, that no such transformations can be forced to occur. Phosphorus pentachloride, hydrogen chloride, and thionyl chloride are without effect upon the alcohol, and sodium hydroxide does not bring about hydrolysis of the chloride.[52] The natural inference, therefore, is that these reactions are unable to proceed except with inversions; hence, since the inversions are geometrically impossible, the reactions cannot take place. Similarly, the tertiary bromide XXII cannot be hydrolyzed to the corresponding alcohol.[53] As with the pre-



XXII

vious examples in which the expected reactions do occur, the data are insufficient here also to show how general are the conclusions reached.

A method developed principally by Freudenberg[54] for deciding whether a Walden inversion does or does not occur in a single reaction is of somewhat greater generality than are the foregoing methods; since,

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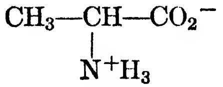
[53] P. D. Bartlett and S. G. Cohen, *J. Am. Chem. Soc.* **62**, 1183 (1940).

[54] For a discussion of this method, see K. Freudenberg in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 699 ff.

however, this method is also less rigorous, the conclusions to which it leads are less certain. The action of nitrous acid upon (+)-alanine of structure XXIII, for example, gives (+)-lactic acid of structure XXIV.



$$CH_3—\underset{\substack{|\\ N^{+}H_3}}{CH}—CO_2^{-}$$

XXIII

$CH_3—CHOH—CO_2H$

XXIV

Although the sign of rotation does not change in the reaction, a Walden inversion may, or may not, have occurred. The problem is therefore to determine whether the configurations of the alanine and lactic acid are opposite or identical. Evidence permitting a very reasonable conclusion to be drawn is shown in Table 7·1, in which are listed the molecular rotations of several corresponding derivatives of the two substances. It will be observed that the various derivatives (both those of alanine and those of lactic acid) are arranged in the table so that the rotation becomes progressively less positive, or more negative, as one reads from the top to the bottom of the appropriate column. Since, therefore, similar substitutions in the two series produce changes of rotation in the same direction, the inference may be drawn that the original alanine and the lactic acid produced from it have identical configurations. If this inference is correct, the conclusion then follows that no Walden inversion can have occurred in the reaction between the alanine and nitrous acid.

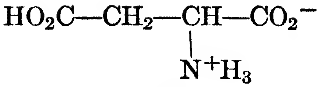
TABLE 7·1

FREUDENBERG'S DETERMINATION OF THE RELATIVE CONFIGURATIONS OF (+)-ALANINE AND (+)-LACTIC ACID [54]

Molecular Rotation [a] *of*	(+)-*Alanine*	(+)-*Lactic acid*
Amide of benzoyl derivative	70°–80°	120°
Ethyl ester of benzoyl derivative	12°	49°
Methyl ester of benzoyl derivative	4° to −4°	35°
Ethyl ester of acetyl derivative	−74°	−76°
Ethyl ester of toluenesulfonyl derivative	−78°	−129°

[a] The molecular rotations listed in this table are equal to 1/100 of the respective values defined in equation 5·2. See page 138.

In the above example of alanine and lactic acid, there are no inconsistencies in the directions in which the rotations change from derivative to derivative. A possibly more typical example is provided by the comparison of (+)-aspartic acid, XXV, with the (−)-malic acid, XXVI



$$HO_2C—CH_2—\underset{N^+H_3}{\underset{|}{CH}}—CO_2^-$$

XXV

$$HO_2C—CH_2—CHOH—CO_2H$$

XXVI

that is obtained from it by the action of nitrous acid. From the data of Table 7·2, it can be seen that, with the derivatives of these two sub-

TABLE 7·2

FREUDENBERG'S DETERMINATION OF THE RELATIVE CONFIGURATIONS OF (+)-ASPARTIC ACID AND (−)-MALIC ACID [54]

Molecular Rotation [a] *of Diethyl Ester of*	*(+)-Aspartic Acid*		*(−)-Malic Acid*	
	20°C	100°C	20°C	100°C
Cinnamyl derivative	25°	20°	7°	−13°
Benzoyl derivative	About 5°	12°	−12°	−28°
Formyl derivative	−0.3°	−13°	−56°	−58°
Hydrocinnamyl derivative	−18°	−9°	−56°	−68°
Acetyl derivative	−21°	−18°	−53°	−68°
n-Heptoyl derivative	−46°	−20°	−60°	−70°
Ethanesulfonyl derivative	−29°	−31°	−105°	−101°

[a] The molecular rotations listed in this table are equal to 1/100 of the respective values defined in equation 5·2. See page 138.

stances, a few inconsistencies occur, but that, on the whole, the variations in rotatory power are parallel. The conclusion is therefore that (+)-aspartic acid and (−)-malic acid have the same configuration, and that, as before, the reaction with nitrous acid is not accompanied by inversion, even though it does lead here to a change in the sign of rotation.

Although this method of establishing relative configuration has not been shown rigorously to be necessarily correct in all instances, it seems reasonable on theoretical, as well as on *a priori*, grounds. There are several precautions, however, which must be observed in its application to specific problems. Thus, the compounds compared with each other must be very similar in structure. In particular, they must differ only with respect to substituents of approximately the same degree of electropositiveness or electronegativeness, and their absorption spectra must not be too different. Moreover, the compounds must be in as nearly the same condition as possible; hence, free hydroxyl or amino groups, for example, are undesirable on account of the association which they cause This is, of course, the reason why the parent substances were not included in the above Tables 7·1 and 7·2. Within these limitations, however, the method has proved to be useful and apparently reliable. At any rate, it has led to no inconsistencies in the assignments of configuration, and to no disagreements with assignments made in different ways.

Considerable information is now available regarding the occurrence of Walden inversions in the reactions of alcohols and of their derivatives. In the esterification of an alcohol by a carboxylic acid, and in the hydrolysis of the resulting ester, the reaction might possibly take place either at the carbon atom of the alcohol or at the oxygen atom that is joined to it. In other words, the reactions might follow either of the two courses represented schematically by the equations 7·19 and 7·20.

$$\text{R—}\boxed{\text{O—H} + \text{H}}\text{—O—CO—R}' \rightleftarrows \text{R—O—CO—R}' + \text{H}_2\text{O} \qquad (7\cdot 19)$$

$$\text{R—O—}\boxed{\text{H} + \text{H—O}}\text{—CO—R}' \rightleftarrows \text{R—O—CO—R}' + \text{H}_2\text{O} \qquad (7\cdot 20)$$

(These equations are, of course, not intended to represent the mechanisms of the reactions but only to indicate the points at which bonds are broken and new ones are formed.) If the reactions follow the first of these two courses, Walden inversions may perhaps occur, but, if they follow the second, inversions cannot take place, since the asymmetric atoms are not affected.

It is at present generally agreed that, *in most instances*, the esterification of an alcohol by a carboxylic acid proceeds in accordance with equation 7·20. The evidence supporting this belief is of several types.[55] It has been found, for example, that any sequence of reactions, in which substitution occurs directly at an asymmetric atom, is nearly always accompanied by an appreciable racemization, whether inversion of configuration predominates over retention or vice versa. On the other hand, an optically active alcohol in which the hydroxyl group is attached to the asymmetric atom can usually be esterified with a carboxylic acid and regenerated from the resulting ester with no significant change in rotation.[56] (For exceptions to this general rule, however, see below.) The fact that no net inversion is observed shows that inversion occurs either in both the esterification and the hydrolysis or else in neither; the fact that no loss of activity is observed suggests that the reactions do not take place at the asymmetric atom. It therefore follows that there has been no inversion at all.

Further evidence pointing to the same conclusion has been obtained from studies of such pairs of isomeric alcohols as the ones with structures XXVII and XXVIII. If either of these two alcohols is treated

$$\underset{\text{XXVII}}{\text{CH}_3\text{—CH═CH—CH}_2\text{OH}} \qquad \underset{\text{XXVIII}}{\text{CH}_3\text{—CHOH—CH═CH}_2}$$

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[55] For a discussion and summary of the evidence, see J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.* **37**, 686 (1941).

[56] See, for example, B. Holmberg, *Ber.* **45**, 2997 (1912).

with hydrogen bromide, a mixture of the two corresponding bromides, XXIX and XXX, results.[57] In these reactions, the carbon-oxygen bonds

$$\underset{\text{XXIX}}{CH_3{-}CH{=}CH{-}CH_2Br} \qquad \underset{\text{XXX}}{CH_3{-}CHBr{-}CH{=}CH_2}$$

of the alcohols are necessarily broken. The partial rearrangements which occur may be considered to be dependent upon the rupture of these bonds; in fact, similar rearrangements occur fairly generally with compounds of this type in any reaction which takes place directly at the carbon atom to which the halogen atom, hydroxyl group, alkoxyl group, or the like is attached. (Cf. Section 13·2.) On the other hand, in the esterification of the two alcohols with acetic acid, and in the hydrolysis of the esters thus formed, no analogous rearrangements are observed. Each alcohol gives its own acetate, and each may be regenerated unchanged from its acetate.[58] Consequently, the inference may again be drawn that the reactions here proceed in accordance with equation 7·20 above, and not in accordance with equation 7·19. (For mention of some analogous systems which behave differently, however, see below.)

When a mercaptan is esterified with a carboxylic acid, the carbon-sulfur bond of the former reagent is not broken; this conclusion follows from the fact that the products are the thioester and water, as in equation 7·21. Conversely, when an alcohol is esterified with a thioacid,

$$C_2H_5SH + C_6H_5CO_2H \rightarrow C_6H_5COSC_2H_5 + H_2O \qquad (7{\cdot}21)$$

the carbon-oxygen bond of the former reagent is not broken; this further conclusion follows similarly from the fact that the products are the sulfur-free ester and hydrogen sulfide, as in equation 7·22. In each in-

$$CH_3OH + C_6H_5COSH \rightarrow C_6H_5CO_2CH_3 + H_2S \qquad (7{\cdot}22)$$

stance, the reaction proceeds in a manner which is analogous to that of equation 7·20 and is not analogous to that of equation 7·19. If the replacement of oxygen by sulfur has not altered the mechanisms of these reactions, the conclusion can again be drawn, therefore, that equation 7·20 is correct for the esterification of an alcohol by a carboxylic acid. The argument here is not conclusive, however, since there can be no assurance that the sulfur-containing compounds must behave exactly like their oxygen-containing analogs. It is fortunate, therefore, that similar, but completely unambiguous, experiments have been carried out with the use of isotopic indicators, and that these experiments have led

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[57] W. G. Young and J. F. Lane, *J. Am. Chem. Soc.* **60,** 847 (1938).

[58] See, for example, C. Prévost, *Ann. chim.* [10] **10,** 147 (1928); E. H. Ingold and C. K Ingold, *J. Chem. Soc.* **1932,** 756.

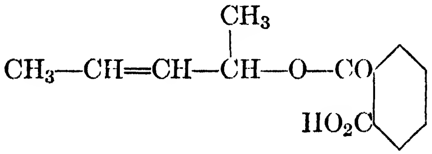
to the same conclusions. Thus, the reactions 7·23 and 7·24 show that

$$\mathrm{CH_3O^{18}{-}H + C_6H_5CO^{16}{}_2H \rightarrow C_6H_5CO^{16}{-}O^{18}{-}CH_3 + H_2O^{16}} \qquad (7\cdot23)$$

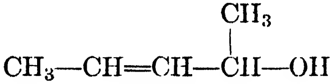
$$\mathrm{CH_3CO^{16}{}_2{-}C_5H_{11} + [O^{18}H]^- \rightarrow [CH_3CO^{16}O^{18}]^- + C_5H_{11}O^{16}{-}H} \qquad (7\cdot24)$$

the carbon-oxygen bond of the alcohol is not broken in either the esterification or the saponification.[59]

In view of the experimental evidence cited above, it may be considered that *ordinarily* the esterification of a carboxylic acid and the hydrolysis of a carboxylic ester follow the courses shown in equation 7·20, rather than the ones shown in equation 7·19. A few reactions are known, however, in which the opposite is apparently true. For example, hydrolysis of the optically active ester XXXI leads to the expected active alcohol



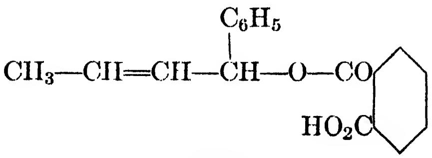
XXXI



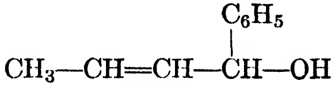
$$\mathrm{CH_3{-}CH{=}CH{-}\overset{\overset{\displaystyle CH_3}{|}}{C}H{-}OH}$$

XXXII

XXXII if the reaction is effected with 5 *N* aqueous sodium hydroxide, but to a racemic alcohol if the reaction is effected with aqueous sodium acetate.[60] Moreover, the hydrolysis of the ester XXXIII by hot alco-

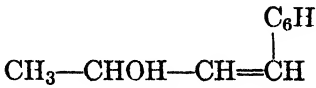


XXXIII



$$\mathrm{CH_3{-}CH{=}CH{-}\overset{\overset{\displaystyle C_6H_5}{|}}{C}H{-}OH}$$

XXXIV



$$\mathrm{CH_3{-}CHOH{-}CH{=}\overset{\overset{\displaystyle C_6H_5}{|}}{C}H}$$

XXXV

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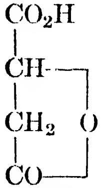
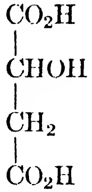
[59] I. Roberts and H. C. Urey, *J. Am. Chem. Soc.* **60,** 2391 (1938); **61,** 2584 (1939); M. Polanyi and A. L. Szabo, *Trans. Faraday Soc.* **30,** 508 (1934).

[60] H. W. J. Hills, J. Kenyon, and H. Phillips, *J. Chem. Soc.* **1936,** 576; see also J. Kenyon, S. M. Partridge, and H. Phillips, *ibid.* **1936,** 85.

holic sodium hydroxide leads only to the unrearranged alcohol XXXIV; but the action of aqueous alcoholic sodium carbonate leads instead to a mixture containing the rearranged alcohol XXXV.[61] Finally, in either basic or strongly acidic solution, the hydrolysis of (+)-malolactonic acid, XXXVI, gives (+)-malic acid, XXXVII, probably



XXXVI



$$\begin{array}{l} CO_2H \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ CO_2H \end{array}$$

XXXVII

with retention of configuration; but in weakly acidic solution it gives instead the enantiomorphic (−)-malic acid, probably with inversion of configuration.[62] Whether the configuration is retained under the first conditions and inverted under the last, as stated, or vice versa, it is evident that an inversion must have occurred in at least one of the reactions. The hydrolysis of the esters XXXI, XXXIII, and XXXVI, therefore, can apparently proceed in accordance with either equation 7·19 or equation 7·20. It is interesting to observe that in the first two instances, and probably also in the last, the anomalous reaction occurs under the *more mild* experimental conditions.

The exceptional hydrolyses just mentioned are not completely typical because, in the first two, the esters contain the easily rearranged allylic system C═C—C (cf. Section 13·2) and, in the last one, the four-membered ring is highly strained. (Cf. Chapter 9.) When complications of these two types are avoided, however, the ordinary carboxylic esters under the ordinary experimental conditions seem always to be formed and hydrolyzed in accordance with equation 7·20; in fact, even when the complications mentioned are not avoided, the reactions usually still proceed normally. If this conclusion is accepted as experimentally established, then the particular reaction in which a Walden inversion occurs in a sequence of reactions can sometimes be identified. For example,[63] in the transformation of the ester XL into its enantiomorph XLI (equations 7·25), the hydrolysis of the original carboxylic ester

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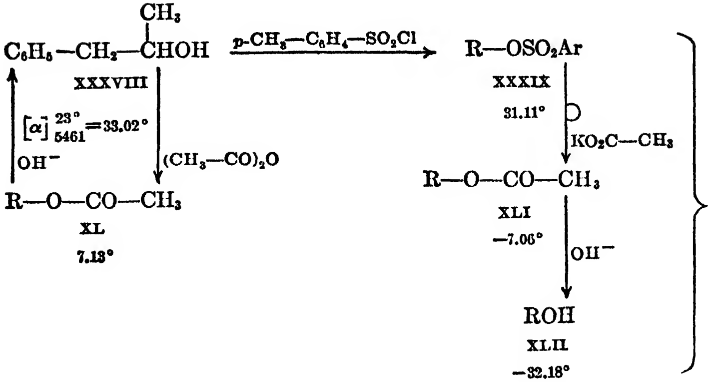
[61] J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.* **1937,** 207.

[62] Cf. A. R. Olson and R. J. Miller, *J. Am. Chem. Soc.* **60,** 2687 (1938), and further references given there.

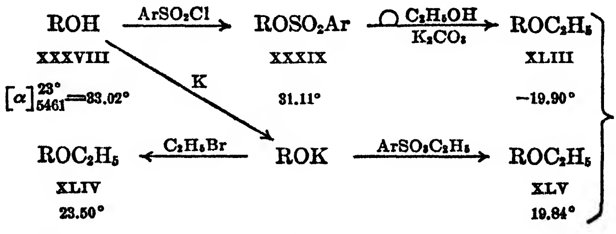
[63] H. Phillips, *J. Chem. Soc.* **123,** 44 (1923).



(7·25)

cannot (for the reasons just outlined) have involved inversion; moreover, the esterification of the alcohol by means of the sulfonyl chloride cannot have involved inversion either, since, in this reaction, the asymmetric carbon atom is not directly affected. Consequently, the only step in which an inversion is possible is the one in which the sulfonic ester XXXIX reacts with acetate ion. The necessary conclusion is therefore that the inversion occurs in this last-mentioned reaction. In order that this conclusion may be included in the equation for the reaction, the customary arrow → is here replaced by the more elaborate symbol $\xrightarrow{\bigcirc}$. (It may be noted further that the acetylation of the alcohol XXXVIII with acetic anhydride clearly proceeds with retention of configuration.) Analogous results have been obtained in the study of the corresponding reaction of valerate ion.[63]

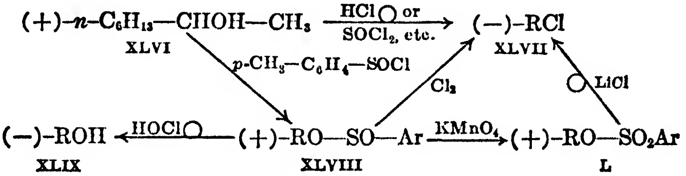
Since carboxylate ions react with sulfonic esters of the type XXXIX with inversion, it is of interest to determine whether other negative ions behave similarly. That ethoxide ion does so is shown by a sequence of reactions [63] (equations 7·26), in which the same optically active alcohol XXXVIII as before is transformed into either of its two enantiomorphic



(7·26)

ethyl ethers, XLIII or XLIV (XLV). In this sequence, the only reaction in which the asymmetric atom is directly affected is the one between the *p*-toluene sulfonic ester, XXXIX, and ethoxide ion (ethyl alcohol plus potassium carbonate); hence, the inversion must have occurred in this step. Other alkyl sulfonates besides the one derived from methylbenzylcarbinol, XXXVIII, have been found [64] to behave similarly toward both carboxylate and alkoxide ions.

Since inversion occurs when a sulfonic ester of an optically active alcohol reacts with either a carboxylate ion or an alkoxide ion, the reasonable assumption may be made that inversion occurs generally whenever an ester of this type reacts with *any* negative ion. To the extent that this assumption is justified, still other classes of reaction can then be studied. An example [65] is shown in the sequence of reactions 7·27. The



(7·27)

dextrorotatory 2-octanol, XLVI, is converted by *p*-toluenesulfinyl chloride into a dextrorotatory sulfinic ester, XLVIII, which is converted by potassium permanganate into a dextrorotatory sulfonic ester, L. Since no inversion could have occurred in either reaction, the esters, XLVIII and L, must have the same configuration as does the original alcohol, XLVI. If an inversion occurs in the reaction between the sulfonic ester, L, and chloride ion, the levorotatory chloride, XLVII, must therefore have a configuration opposite to that of the dextrorotatory alcohol. That this interpretation of the reaction is correct is to some extent supported by the further reactions of the sulfinic ester, XLVIII. With hypochlorous acid, this ester gives the levorotatory alcohol, XLIX. Since an inversion must necessarily have occurred in this reaction, it seems reasonable to assume that one occurs also in the apparently similar reaction between the same sulfinic ester and chlorine. If this assumption is correct, then the configuration of the levorotatory chloride is again seen to be opposite to that of the dextrorotatory alcohol. On the basis of all this converging evidence, therefore, the conclusion can be drawn that the reaction between the alcohol and hydrogen chloride, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, or phosphorus oxychloride is accompanied by inversion.

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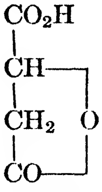
[64] Cf. J. Kenyon, H. Phillips, and H. G. Turley, *J. Chem. Soc.* **127**, 399 (1925); H. Phillips, *ibid.* **127**, 2552 (1925); G. A. C. Gough, H. Hunter, and J. Kenyon, *ibid.* **1926**, 2052; J. Kenyon, H. Phillips, and V. P. Pittman, *ibid.* **1935**, 1072; C. M. Bean, J. Kenyon, and H. Phillips, *ibid.* **1936**, 303.

[65] A. J. H. Houssa, J. Kenyon, and H. Phillips, *J. Chem. Soc.* **1929**, 1700.

By application of the various methods described above, sufficient information has been obtained to justify the conclusion that a Walden inversion occurs in almost every replacement at an asymmetric carbon atom, provided that the reaction proceeds in a single step, and in such a manner that the entering substituent is becoming attached to the asymmetric carbon atom while the displaced substituent is still breaking away. (Cf. the last paragraph of this section.) To some extent, of course, this rule involves circular reasoning, since the decision whether a given reaction does or does not proceed by a mechanism of the type described is often based upon prior knowledge (or belief) that an inversion does or does not occur. Nevertheless, since the rule permits a logical and self-consistent interpretation of all the reactions concerned, considerable confidence in its essential correctness appears to be justified. (However, see below.)

A few examples will be sufficient to illustrate the significance of the above conclusion regarding the occurrence of Walden inversions. In the cycle of reactions discovered originally by Walden (see page 269), the reaction between chlorosuccinic acid and potassium hydroxide has been shown by kinetic studies to involve a direct attack by hydroxide ion upon the asymmetric atom.[66] Since the reaction therefore presumably requires only one step, and since the chloride ion presumably departs as the hydroxide ion approaches, an inversion may be considered to occur. On the other hand, the reaction of the same chlorosuccinic acid with silver oxide is considered to require two steps.[66] In the first of these steps, silver oxide, or possibly silver ion, attacks the chlorine atom, removing it from the molecule and leaving the β-lactone, XXXVI.



XXXVI

This reaction is presumably accompanied by inversion. In the second step, the lactone, which can indeed be shown to be present in the reaction mixture, is hydrolyzed to malic acid; since the solution is ap-

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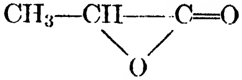
[66] Cf. E. D. Hughes, *Trans. Faraday Soc.* **34,** 202 (1938); L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, New York, 1940, pages 175 ff.; and further references given in the places cited. For further reactions which, like the hydrolysis of chlorosuccinic acid by silver oxide, are considered to proceed in two steps with an inversion in each, and with the formation of a cyclic intermediate, see S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.* **61,** 1576, 1581 (1939); S. Winstein, H. V. Hess, and R. E. Buckles, *ibid.* **64,** 2796 (1942); E. Grunwald and S. Winstein, *ibid.* **70,** 841 (1948); and other references cited in the last one of these.

proximately neutral, this reaction is presumably also accompanied by inversion (see above). The net result of the two steps, with an inversion in each, is then hydrolysis of the chlorosuccinic acid with retention of configuration. Other α-halogen-substituted acids behave like chlorosuccinic acid in that their reactions with potassium hydroxide and with silver oxide transform them into enantiomorphic α-hydroxyacids, presumably with inversion and with retention of configuration, respectively. In general, with such substances, however, a β-lactone cannot be formed, since no second carboxyl group, to which the hydroxyl group is beta, may be present. In such instances, an α-lactone is postulated as an intermediate. Thus, in the hydrolysis of α-bromopropionic acid, LI, with

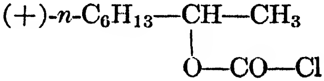
$CH_3—CHBr—CO_2H$
LI


LII

silver oxide, the lactone, LII, is assumed to be formed in the first step. Unlike the β-lactones, however, such α-lactones cannot be shown to be formed in these reactions; in fact, they cannot be made by any known method. Nevertheless, the analogy with the hydrolysis of chlorosuccinic acid seems so close that there is little reason to doubt the proposed mechanism.

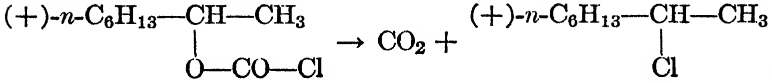
The rule which has been discussed in the two preceding paragraphs is not always valid. Although the most important and most clearly established group of exceptions cannot be considered until later (see Section 12·9), a few probable exceptions may nevertheless be mentioned here. Thus, when dextrorotatory 2-octanol, XLVI, is treated

$(+)\text{-}n\text{-}C_6H_{13}—CHOH—CH_3$
XLVI



$$(+)\text{-}n\text{-}C_6H_{13}—\underset{\displaystyle O—CO—Cl}{\underset{|}{CH}}—CH_3$$
LIII

with phosgene, it is converted into the dextrorotatory octyl chloroformate, LIII, which must have the same configuration as did the

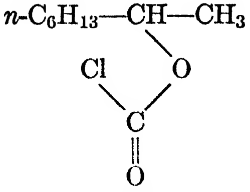


$$(+)\text{-}n\text{-}C_6H_{13}—\underset{\displaystyle O—CO—Cl}{\underset{|}{CH}}—CH_3 \rightarrow CO_2 + (+)\text{-}n\text{-}C_6H_{13}—\underset{\displaystyle Cl}{\underset{|}{CH}}—CH_3 \qquad (7\cdot28)$$
LIII LIV

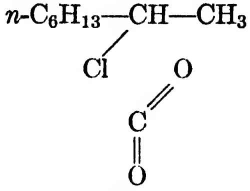
original alcohol; when this ester is heated, it is transformed (with loss of a molecule of carbon dioxide) into the still dextrorotatory 2-chlorooctane, LIV. The latter reaction (equation 7·28) is apparently, therefore (cf. equation 7·27), a substitution without a Walden inversion.[67]

[67] A. H. J. Houssa and H. Phillips, *J. Chem. Soc.* **1932**, 108, 1232; M. B. Harford, J. Kenyon, and H. Phillips, *ibid.* **1933**, 179.

Although the mechanism of this reaction is not definitely known, there is no obvious way in which the substitution could proceed by an even number of steps, with an inversion in each. An alternative suggestion is that the ester molecule, in the course of its thermal motions, assumes the cyclic conformation, LV, which is then transformed, by merely a redistribution of the electrons, into structure LVI; as soon as this second structure is achieved, the molecule of carbon dioxide breaks away. No conclusive evidence in support of this mechanism has as yet, however, been advanced.

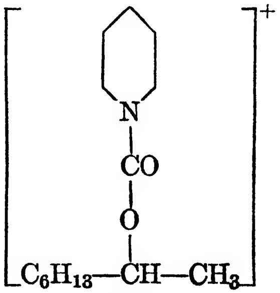


LV



LVI

When the dextrorotatory octyl chloroformate, LIII, is treated with pyridine, the resulting 2-chlorooöctane is found to be not dextrorotatory, but instead levorotatory.[67] Apparently, therefore, this reaction is accompanied by a Walden inversion. The most reasonable mechanism for the transformation here involves the formation of the intermediate pyridinium cation, LVII, which is then attacked, with inversion, by chloride ion. The reaction of thionyl chloride, $SOCl_2$, like that of phosgene, with an optically active alcohol has been found to be similarly affected by the presence of pyridine when the asymmetric atom is directly joined to a phenyl group.[68] (Cf. page 272.) On the other hand, the corresponding reactions of phosphorus trichloride and pentachloride seem always to be accompanied by inversion.[69]



LVII

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[68] J. Kenyon, A. G. Lipscomb, and H. Phillips, *J. Chem. Soc.* **1930**, 415.

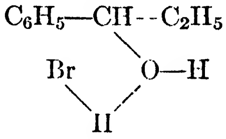
[69] J. Kenyon, A. G. Lipscomb, and H. Phillips, *J. Chem. Soc.* **1931**, 2275.

Moreover, as was mentioned on pages 272f., the reaction between the levorotatory phenylethylcarbinol, VIII, and hydrogen bromide gives

$$C_6H_5\text{—}CHOH\text{—}C_2H_5 \qquad\qquad C_6H_5\text{—}CHBr\text{—}C_2H_5$$

VIII IX

the levorotatory bromide, IX, at temperatures below about −36°C, but the dextrorotatory bromide at higher temperatures. Clearly, therefore, the substitution proceeds with predominant inversion at certain temperatures, but with predominant retention at other temperatures. Since the levorotatory bromide is considered to have the same configuration as the original levorotatory alcohol, the low-temperature reaction is here presumably the one without inversion. For this reaction, there has been proposed a one-step mechanism in which the intermediate LVIII, with



LVIII

a hydrogen bond between the bromine and oxygen atoms, replaces the corresponding intermediate LV, considered above.[70] Such an intermediate as LVIII, to be sure, seems somewhat unlikely, since the hydrogen bond to the bromine atom would doubtless be weak, and since the strain in the four-membered ring must be great. (Cf. Section 2·6.) Even so, however, this postulated intermediate may be sufficiently stable to permit a substitution reaction which, at low temperatures, is faster than the more usual reaction with inversion.

So far, nothing has been said about the detailed mechanism of the Walden inversion. The problem is of course to devise a way in which an entering substituent can take a position in space which is different from the one formerly occupied by the atom or group which it replaces. The most reasonable interpretation of the reaction is the one illustrated in Figure 7·2.[71] In Figure 7·2*a*, which represents an early stage of the

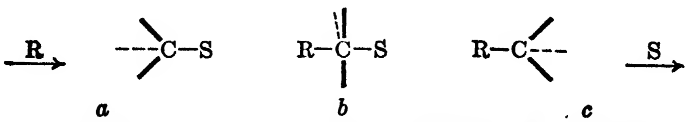


FIGURE 7·2. A reasonable mechanism of the Walden inversion.

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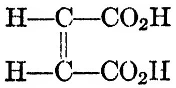
[70] W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.* **1937**, 1252.

[71] Cf. L. P. Hammett, pages 157 ff. of reference 66; G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 216 ff.

reaction, the reagent R approaches the carbon atom from the side opposite the substituent S; in Figure 7·2*b*, which represents the midpoint of the reaction, the atoms or groups R and S are equidistant (or nearly equidistant) from the carbon atom, which is no longer tetrahedral; and in Figure 7·2*c*, which represents the conclusion of the reaction, the displaced substituent S is departing, and the entering one R is attached to the carbon atom. In the process, the molecule has been "turned inside out" like an umbrella in a high wind. It is indeed readily seen that the configuration of the product (Figure 7·2*c*) is opposite to that of the original substance (Figure 7·2*a*), and, hence, that an inversion has occurred during the reaction.

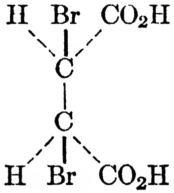
7·9 The Stereochemistry of Additions to Carbon-carbon Double Bonds. The preceding sections have contained brief references to the addition reactions of ethylenic compounds. It is now desirable to examine these reactions more carefully, and to consider their stereochemical features more precisely.

When bromine adds to maleic acid, I, for example, the two bromine atoms might naturally be expected to approach the organic molecule from the same side. If this expectation should prove to be correct, the single molecule formed in any individual reaction must have either the configuration II (if the approach is from the front of the paper) or the configuration III (if the approach is instead from the rear). Since, however, these two configurations are symmetrical and identical, the product isolated must be *meso*-α,α′-dibromosuccinic acid, of which the conventional plane projection diagram is IV. Moreover, when bromine adds to fumaric acid, V, the single molecule formed in any individual reaction might similarly be expected to have one of the two dissymmetric

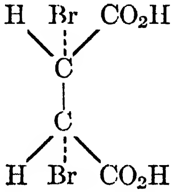


$$\begin{array}{c} \text{H—C—CO}_2\text{H} \\ \| \\ \text{H—C—CO}_2\text{H} \end{array}$$

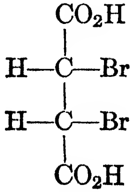
I



II

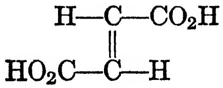


III



$$\begin{array}{c} \text{CO}_2\text{H} \\ | \\ \text{H—C—Br} \\ | \\ \text{H—C—Br} \\ | \\ \text{CO}_2\text{H} \end{array}$$

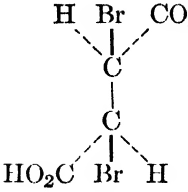
IV



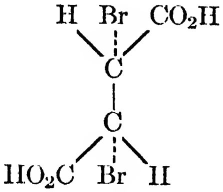
$$\begin{array}{c} \text{H—C—CO}_2\text{H} \\ \| \\ \text{HO}_2\text{C—C—H} \end{array}$$

V

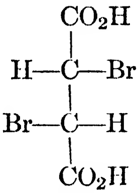
and enantiomorphic configurations VI and VII. Since the molecule of



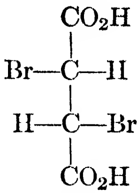
VI



VII



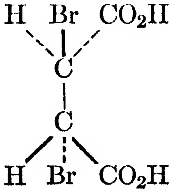
VIII



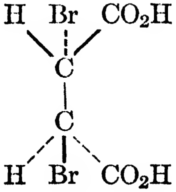
IX

bromine is exactly as likely to approach the one of fumaric acid from the front as from the rear, the two enantiomorphs (VI and VII, respectively) must be produced at equal rates; hence, the product formed in the reaction between macroscopic amounts of the two reagents must be racemic α,α'-dibromosuccinic acid, the two components of which are represented (not necessarily respectively) by the conventional plane projection diagrams VIII and IX. Additions of the stereochemical type here postulated can conveniently be described as *cis* additions. (Cf. pages 230 f.)

It seems entirely logical to suppose that all additions to double bonds must be *cis;* in fact, on the basis of the three-dimensional models depicted in the diagrams I–III and V–VII, no other mode of addition appears reasonable. Nevertheless, the occurrence of Walden inversions (Section 7·8) shows that the steric courses of reactions are not always the ones which are most easily interpreted with the aid of such models. Consequently, it is necessary to consider the remaining possibility that, in the addition of bromine to either maleic or fumaric acid, the two bromine atoms approach the molecule of the organic reagent from opposite sides. If the reactions should proceed in this manner, maleic acid, I, must give the racemic α,α'-dibromosuccinic acid (and not the *meso* isomer, as before), since the two dissymmetric and enantiomorphic configurations, X and XI, are equally probable. As is easily verified, the

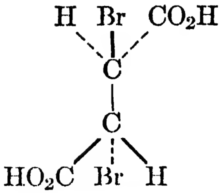


X

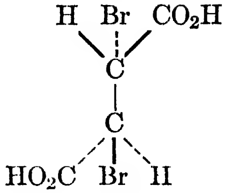


XI

configuration X is identical with VI, and the configuration XI is identical with VII. Moreover, fumaric acid, V, must give *meso*-α,α'-dibromosuccinic acid (and not the racemic modification, as before), since the two symmetric configurations, XII and XIII, are identical both with each



XII

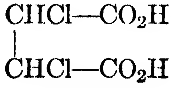


XIII

other and with II and III. Additions of the stereochemical type here postulated can conveniently be described as *trans* additions.

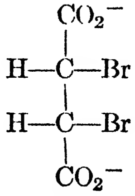
The question whether the additions of bromine to maleic and fumaric acids are *cis* or *trans* is answered unambiguously as soon as the products of the respective reactions are identified; for, as has just been shown, *cis* additions would lead to the formation of a *meso* product from maleic acid and of a racemic product from fumaric acid, whereas *trans* additions would lead instead to the formation of a racemic product from maleic acid and of a *meso* product from fumaric acid. Experimentally, the α,α'-dibromosuccinic acid formed in larger amount (not less than 80 per cent) from maleic acid is found to be resolvable, and hence racemic; whereas that formed in larger amount from fumaric acid is found to be nonresolvable, and hence *meso*. In each instance, therefore, the addition is predominantly *trans*; hence, just as with the Walden inversion, the reaction is more complex than the simple molecular models would lead one to expect.

In most other reactions in which a halogen adds to a carbon-carbon double bond, the additions are considered similarly to be predominantly *trans*. For example, the major products formed in the addition of chlorine to maleic and fumaric acids are, respectively, the racemic and *meso* α,α'-dichlorosuccinic acids of structure XIV. *Trans* additions are



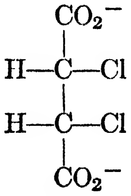
$$\begin{array}{l}\mathrm{CHCl{-}CO_2H}\\ |\\ \mathrm{CHCl{-}CO_2H}\end{array}$$

XIV



$$\begin{array}{c}\mathrm{CO_2^-}\\ |\\ \mathrm{H{-}C{-}Br}\\ |\\ \mathrm{H{-}C{-}Br}\\ |\\ \mathrm{CO_2^-}\end{array}$$

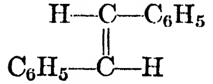
XV



$$\begin{array}{c}\mathrm{CO_2^-}\\ |\\ \mathrm{H{-}C{-}Cl}\\ |\\ \mathrm{H{-}C{-}Cl}\\ |\\ \mathrm{CO_2^-}\end{array}$$

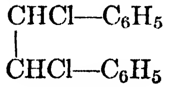
XVI

not, however, observed in all instances. Thus, maleate ion and fumarate ion (i.e., maleic acid, I, and fumaric acid, V, respectively, in basic solution) give mostly the same *meso*-α,α'-dibromosuccinate ion, XV, and *meso*-α,α'-dichlorosuccinate ion, XVI; although the additions of both halogens to fumarate ion are therefore still *trans*, those to maleate ion are instead *cis*. Moreover, the addition of chlorine to *trans*-stilbene, XVII, leads to not widely different amounts of the *meso* and racemic



$$\begin{array}{c}\mathrm{H{-}C{-}C_6H_5}\\ \|\\ \mathrm{C_6H_5{-}C{-}H}\end{array}$$

XVII

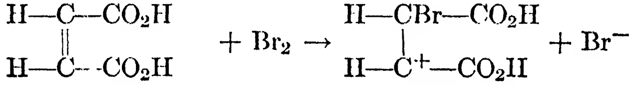


$$\begin{array}{l}\mathrm{CHCl{-}C_6H_5}\\ |\\ \mathrm{CHCl{-}C_6H_5}\end{array}$$

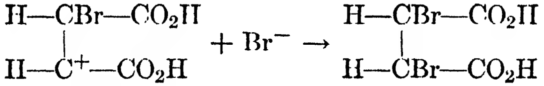
XVIII

α,α'-dichlorobibenzyls of structure XVIII; with this unsaturated hydrocarbon, therefore, *cis* and *trans* additions occur at not widely different rates.

The mechanism of the addition of a halogen to a carbon-carbon double bond is now fairly well understood; and the preponderant *trans* addition can be satisfactorily explained. On the basis of evidence derived from many sources,[72, 73] it is now generally agreed that any such reaction proceeds in two steps which, for the addition of bromine to maleic acid, may be provisionally represented (however, see below) by the equations 7·29 and 7·30. The belief that some such organic cation as XIX is involved as an intermediate is strongly supported by the fact that, in this and other analogous reactions, the product often contains atoms or groups which must have been provided (in the form of anions) by the solvent or by other components of the reaction mixture. For example, the addition of chlorine to fumaric acid in basic aqueous solution gives a chloromalic acid of structure XX; the addition of bromine to *trans*-stilbene in methyl alcoholic solution gives mostly the methoxybromide, XXI (plus a little α,α'-dibromobibenzyl, XXII, the amount of which increases with the concentration of bromide ion in the reaction mixture);[73] the addition of bromine to ethylene in a saturated solution of



$$\begin{array}{c}\mathrm{H{-}C{-}CO_2H}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\\ \mathrm{I}\end{array} + \mathrm{Br_2} \rightarrow \begin{array}{c}\mathrm{H{-}CBr{-}CO_2H}\\ |\\ \mathrm{H{-}C^{+}{-}CO_2H}\\ \mathrm{XIX}\end{array} + \mathrm{Br^-} \qquad (7\cdot29)$$



$$\begin{array}{c}\mathrm{H{-}CBr{-}CO_2H}\\ |\\ \mathrm{H{-}C^{+}{-}CO_2H}\\ \mathrm{XIX}\end{array} + \mathrm{Br^-} \rightarrow \begin{array}{c}\mathrm{H{-}CBr{-}CO_2H}\\ |\\ \mathrm{H{-}CBr{-}CO_2H}\end{array} \qquad (7\cdot30)$$

$\mathrm{HO_2C{-}CHOH{-}CHCl{-}CO_2H}$
XX

$\mathrm{C_6H_5{-}CH(OCH_3){-}CHBr{-}C_6H_5}$
XXI

$\mathrm{C_6H_5{-}CHBr{-}CHBr{-}C_6H_5}$
XXII

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[72] See, for example, R. Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions*, Institute of Chemistry of Great Britain and Ireland, London, 1932; C. K. Ingold, *Chem. Revs.* **15**, 225 (1934).

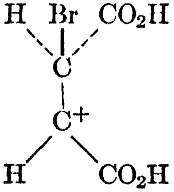
[73] P. D. Bartlett and D. S. Tarbell, *J. Am. Chem. Soc.* **58**, 466 (1936).

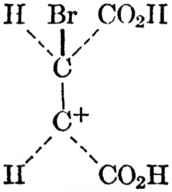
sodium chloride or sodium nitrate gives, respectively, 1-bromo-2-chloroethane, XXIII, or β-bromoethyl nitrate, XXIV. A kinetic study [73] has

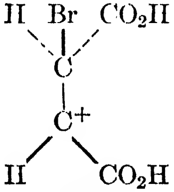
$$\underset{\text{XXIII}}{CH_2Br\text{—}CH_2Cl} \qquad \underset{\text{XXIV}}{CH_2Br\text{—}CH_2\text{—}O\text{—}NO_2} \qquad \underset{\text{XXV}}{CH_3\text{—}OBr}$$

shown that the formation of the methoxybromide, XXI, cannot be due to an addition of methyl hypobromite, XXV, to the stilbene, since the rate of the reaction is proportional to the concentration of uncombined bromine Br_2, but is independent of that of methyl hypobromite; moreover, the formation of the bromochloroethane, XXIII, cannot be due to an addition of bromine chloride, BrCl; for, although this interhalogen compound is known, no appreciable quantity of it could be present in the solution.

Although it is, therefore, practically certain that an unstable organic cation is frequently an intermediate in the reaction, there is good reason to doubt that this cation is adequately represented by structure XIX (equations 7·29 and 7·30); for, if the intermediate did have such a structure, maleic and fumaric acids would be expected to give the same intermediate and, hence, in the concluding step (equation 7·30) the same α,α′-dibromosuccinic acid, or the same mixture of α,α′-dibromosuccinic acids. In fact, if structure XIX were correct, the only essentially different configurations of the cation would then be XXVI, in which the trivalent carbon atom is planar, and XXVII and XXVIII, in which this atom is pyramidal. (Since these diastereomeric configurations are dissymmetric, their enantiomorphs are also possible, but need not be separately considered.) It is extremely unlikely, however, that the atom in question could maintain the pyramidal form which it has in the configurations XXVII and XXVIII, since either of these configurations should be easily transformed into the other by passing through the configuration XXVI. (Cf. Werner's mechanism of racemization, pages 251 f.) Indeed, the configuration XXVI is probably the most stable of the three, and hence the one which the cation would actually assume. Moreover, the rotation about the single bond between the two central carbon atoms in each of the configurations XXVI–XXVIII should be essentially free. In any event, therefore, the intermediate cations


XXVI

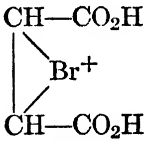

XXVII


XXVIII

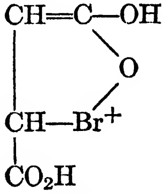
formed from maleic and fumaric acids should (as was noted above) be configurationally, as well as structurally, identical.

It is important that the freedom of rotation about the carbon-carbon single bonds in the structure XIX is not by itself sufficient to ensure that the intermediate cations derived from maleic and fumaric acids must be identical. If, for example, the cation derived from maleic acid had, say, the configuration XXVIII, whereas the one derived from fumaric acid had instead the diastereomeric configuration XXVII, then the two intermediates would be different, and no rotation about the bond in question could transform either cation into the other. Consequently, if the configurations XXVII and XXVIII are assumed to be sufficiently stable that they can persist until the concluding step of the addition (equation 7·30) has taken place, the predominant *trans* addition can be explained. Consequently, the statement that structure XIX cannot be reconciled with the observed formation of stereoisomeric addition products from maleic and fumaric acids is based primarily upon the belief that the trivalent carbon atom in this structure cannot long maintain either of the configurations XXVII and XXVIII; on the other hand, the correctness of this statement is almost, if not entirely, independent of the freedom of rotation about the central bond. The emphasis which (in discussions of the problem) has often been placed upon the freedom of rotation is, therefore, misleading.

If, for the reasons just described, the intermediate cation is considered not to have structure XIX, a more satisfactory representation is clearly required. At the present time, the best supported and most widely held interpretation of the reaction is that the intermediate has a *bromonium* structure (cf. Section 2·3) like XXIX or XXX.[74]



XXIX



XXX

Obviously, an analog of the first of these structures can be written for the intermediate similarly postulated in any other reaction in which a halogen adds to an olefin; an analog of the second, however, cannot be written unless the molecule of the original olefin contains a carbonyl group conjugated with the ethylenic linkage. For the sake of both simplicity and generality, therefore, only structure XXIX will hereafter be employed. Although this structure may be incorrect with an unsaturated carbonyl compound, the treatment is not thereby invalidated since, as can easily be verified, neither the following argument nor the conclusions to which it leads would be significantly altered if the second structure, XXX, were instead employed.

For obvious geometrical reasons, the formation of the three-membered ring in structure XXIX can hardly have involved a configurational

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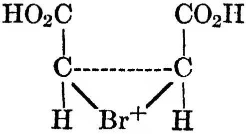
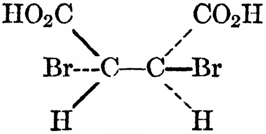
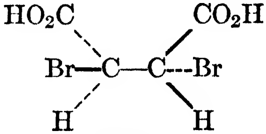
[74] I. Roberts and G. E. Kimball, *J. Am. Chem. Soc.* **59**, 947 (1937).

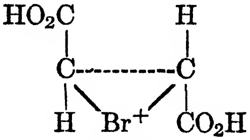
change analogous to a Walden inversion about either of the two carbon atoms concerned. Consequently, in the intermediate formed from maleic acid, the two carboxyl groups must be *cis* with respect to each other, just as they are in the original reagent. The intermediate must therefore have the symmetric (*meso*) configuration, XXXI. In the concluding step of the reaction, a bromide ion attacks one of the carbon atoms in the ring and breaks the corresponding carbon-bromine bond. As in the rather analogous substitution reactions considered in Section 7·8, the bromide ion may be presumed to approach the carbon atom from the side opposite the carbon-bromine bond. A Walden inversion therefore occurs at the atom attacked. Consequently, the molecule of α,α'-dibromosuccinic acid that is formed when the bromide ion attacks the carbon atom at the left of the ring must have the dissymmetric configuration XXXII, whereas the molecule that is formed when the bromide ion attacks the carbon atom at the right of the ring must have the enantiomorphic configuration XXXIII. Since the two carbon atoms are equally likely to be thus attacked, equal quantities of the two enantiomorphs must be formed. The product is therefore the racemic modification; hence, the addition is *trans*.

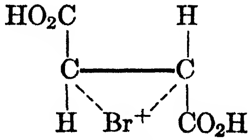

XXXI

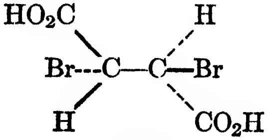

XXXII

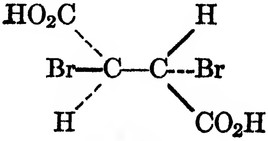

XXXIII

Similarly, in the addition of bromine to fumaric acid, the postulated intermediate must have the *trans* configuration, and hence must be a racemic modification containing equal amounts of the two enantiomorphs XXXIV and XXXV. The molecule of α,α'-dibromosuccinic acid formed (again with a Walden inversion) from the intermediate XXXIV has the configuration XXXVI if the bromide ion attacks the


XXXIV


XXXV

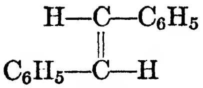

XXXVI


XXXVII

carbon atom at the left of the ring, or the configuration XXXVII if the bromide ion attacks the carbon atom at the right of the ring; on the other hand, the molecule formed from the enantiomorphic intermediate XXXV has the configuration XXXVII if the bromide ion attacks the carbon atom at the left of the ring, or the configuration XXXVI if the bromide ion attacks the carbon atom at the right of the ring. Since the configurations XXXVI and XXXVII are symmetric and identical, the product is the *meso* form. Again, therefore, the addition is *trans*.

The *cis* additions of chlorine and of bromine to maleate ion remain to be considered. The explanation of these exceptional reactions is probably that, on account of the powerful repulsions between the two negatively charged carboxylate groups —CO_2^- in the cyclic intermediates, the *trans* configurations, in which these groups are as far apart as possible (cf. configurations XXXIV and XXXV), are much more stable than is the *cis* configuration, in which the groups are much closer (cf. configuration XXXI). Consequently, the molecules of the *cis* intermediate must have a great tendency to go over into the *trans* configurations, if they can possibly do so. Moreover, the transformation of the *cis* form into either *trans* form should be relatively easy since it requires only the rupture of a carbon-halogen bond to give a noncyclic product (cf. structure XIX and configurations XXVI–XXVIII, above); then a rotation about the central carbon-carbon bond and an inversion of the configuration about the trivalent carbon atom; and finally the formation of a new carbon-halogen bond. No one of the individual steps in this sequence should be difficult: the carbon-halogen bond that must be broken is doubtless very weak, since stable chloronium and bromonium compounds with structures analogous to the ones here considered are rare, if not actually unknown (cf., however, page 46); the assumed rotation about the single bond in the noncyclic molecule should be essentially free; the inversion of configuration is almost certainly rapid (see above); and, finally, the formation of the new carbon-halogen bond should occur spontaneously. If the transformation of the *cis* intermediate XXXI into the racemic mixture of the *trans* forms XXXIV and XXXV occurs sufficiently fast, it can be practically complete before the intermediate has had time to react appreciably with the halide ions. Consequently, the fact that the final product is the *meso* ion XV, or XVI (i.e., the fact that the addition of the halogen to maleate ion is *cis*), is satisfactorily explained. The further fact that fumarate ion undergoes normal *trans* additions, and therefore gives the same products as does maleate ion, clearly requires no special explanation.

In the addition of chlorine to *trans*-stilbene, XVII, comparable



$$\begin{array}{c} H—C—C_6H_5 \\ \| \\ C_6H_5—C—H \end{array}$$

XVII

$$C_6H_5—CHCl—CHCl—C_6H_5$$

XVIII

amounts of the *meso* and racemic α,α'-dichlorobibenzyls, XVIII, are formed (see pages 292 f.); this fact also is rather unexpected. The reaction here, however, can hardly proceed by the mechanism outlined above, since the rate of the addition is greatly increased by the influence of light.[75] A reasonable interpretation of the therefore clearly photochemical addition is shown in equations 7·31–7·33. The assumed function of the light is thus to produce chlorine atoms by dissociating the corresponding molecules (equation 7·31). These atoms are considered then to react with the *trans*-stilbene (equation 7·32) to produce the intermediate free radicals XXXVIII. (Cf. Chapter 15.) Since the chlorine atoms which are consumed in reaction 7·32 are replaced in reaction 7·33, and since the radicals which are consumed in reaction 7·33 can then be replaced by a repetition of reaction 7·32 (and so on), the process can continue more or less indefinitely. (However, see below.) A reaction occurring in such a way is called a *chain* reaction; whenever, as is true here, the *chain-carriers* (i.e., the chlorine atoms Cl and the intermediate radicals XXXVIII) are free radicals with unpaired electrons, such a reaction is more precisely called a *radical-chain* reaction. Each individual chain (i.e., each individual sequence of reactions initiated by one chlorine atom and proceeding by an alternation of reactions 7·32 and 7·33) must sooner or later be broken by some *chain-terminating* step, like that of equation 7·34, in which at least one of the chain car-

$$Cl_2 + \text{light} \rightarrow 2Cl \qquad (7\cdot31)$$

$$\underset{\text{XVII}}{\textit{trans}\text{-}C_6H_5—CH{=}CH—C_6H_5} + Cl \rightarrow \underset{\text{XXXVIII}}{C_6H_5—CHCl—\dot{C}H—C_6H_5} \qquad (7\cdot32)$$

$$\underset{\text{XXXVIII}}{C_6H_5—CHCl—\dot{C}H—C_6H_5} + Cl_2 \rightarrow \underset{\text{XVIII}}{C_6H_5—CHCl—CHCl—C_6H_5} + Cl \qquad (7\cdot33)$$

$$C_6H_5—CHCl—\dot{C}H—C_6H_5 + Cl \rightarrow C_6H_5—CHCl—CHCl—C_6H_5 \qquad (7\cdot34)$$

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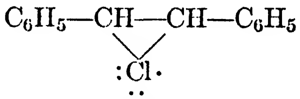
[75] Cf. for example, S. Winstein and D. Seymour, *J. Am. Chem. Soc.* **68**, 119 (1946).

riers is irreplaceably consumed. Nevertheless, the production of a single pair of chlorine atoms by the absorption of a single quantum of light by a single chlorine molecule can lead ultimately to the formation of a great many molecules of α,α'-dichlorobibenzyl, XVIII. The *quantum yield* (i.e., the ratio of the number of the original stilbene molecules that are chemically transformed to the number of light quanta that are absorbed) is therefore much larger than one. If the quantum yield were not very high, the photochemical addition would be an extremely slow reaction (and not a fast one, as is observed) since, with light sources of reasonable intensity, the number of quanta absorbed by any substance in even, say, an hour, is, at most, only a minute fraction of the number of molecules present.

The fact that the rates of the photochemical *cis* and *trans* additions of chlorine to *trans*-stilbene are comparable suggests that, if these reactions occur by the mechanism just outlined (equations 7·31–7·33), the trivalent carbon atom in the assumed intermediate XXXVIII is unable to maintain a pyramidal configuration. (Cf. configurations XXVII and XXVIII on page 294.) Moreover, the further conclusion can be drawn that, if a cyclic intermediate radical XXXIX (cf. structure XXIX, above) is formed at all, it must contain a particularly unstable ring, since the observed easy inversion of the configuration about one of the carbon atoms can occur only in the noncyclic radical XXXVIII. (Cf. the above discussion of the nonphotochemical addition of bromine to maleate ion. For further and more detailed discussions of photochemical and radical-chain reactions, see pages 307 f. and Sections 15·4 and 15·5.)



$$\begin{array}{c} C_6H_5\text{—}CH\text{—}CH\text{—}C_6H_5 \\ \diagdown\!\diagup \\ :\underset{\cdot\cdot}{Cl}\cdot \end{array}$$

XXXIX

The additions of *hydrogen* to olefins are much too numerous and too varied to be discussed here in detail.[76, 77, 78] It will, accordingly, be sufficient to mention merely that hydrogenations over platinum, palladium, or nickel catalysts are likely to be predominantly *cis*,[76, 77, 78] whereas those brought about by such reducing agents as metal-acid combinations (e.g., sodium and an alcohol) or as hydrogen iodide are likely to be more nearly *trans*. For example, the major products formed in the hydro-

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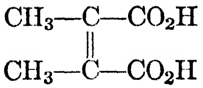
[76] Cf., however, K. N. Campbell and B. K. Campbell, *Chem. Revs.* **31,** 77 (1942); H. Adkins and R. L. Shriner in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 2nd ed., 1943, Volume I, Chapter 9.

[77] See R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.* **64,** 1985 (1942), and other literature quoted there.

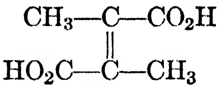
[78] A. Farkas and L. Farkas, *Trans. Faraday Soc.* **33,** 837 (1937).

genations of dimethylmaleic acid, XL, and of dimethylfumaric acid,



$$CH_3-C(CO_2H)=C(CO_2H)-CH_3$$

XL



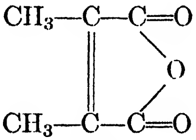
$$CH_3-C(CO_2H)=C(CH_3)-CO_2H$$

XLI

$$HO_2C-CH(CH_3)-CH(CH_3)-CO_2H$$

XLII

XLI, over a nickel catalyst are, respectively, the *meso* and the racemic α,α'-dimethylsuccinic acids with structure XLII. On the other hand, reduction of the anhydride, XLIII, of dimethylmaleic acid, XL, with



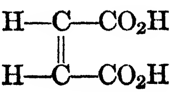
XLIII

sodium and alcohol, or with zinc and sulfuric acid, or with hydrogen iodide, gives a mixture containing comparable amounts of the *meso* and racemic α,α'-dimethylsuccinic acids, XLII; moreover, reduction of dimethylfumaric acid, XLI, with sodium amalgam and alcohol, or with zinc and acetic acid, gives a similar mixture of products. In all these reactions, however, the relative proportions of the products vary considerably with the experimental conditions (e.g., the activity of the metallic catalyst, the acidity or basicity of the medium).

A reasonable explanation of these regularities is the following. In a catalytic hydrogenation, the organic molecule possibly is adsorbed on, and lies flat against, the metallic surface, so that the hydrogen atoms (which are dissolved in the metal) must approach from the same side; hence the addition is *cis*.[77,78] On the other hand, some entirely different mechanism is doubtless involved in a reduction by a metal-acid combination, or by hydrogen iodide, or by any other analogous reagent; possibly, a reaction belonging to one of these latter types proceeds in steps, so that only one hydrogen atom, or its equivalent, is added at a time. If the thus postulated intermediate is unable to maintain a definite stereochemical configuration, two stereoisomeric olefins must give rise to the same intermediate, and hence also to the same final product, or to the same mixture of final products. Under such circumstances, therefore, both *cis* and *trans* additions should be observed. (Cf. the analogous additions of the halogens to maleate and fumarate ions, and of chlorine to *trans*-stilbene, discussed above.) Moreover, both in the catalytic hydrogenations and in the reductions by metal-acid combinations and the like, the original olefin may rearrange more or less completely to its stereoisomer before the addition of the hydrogen occurs; similarly, the product initially formed in the reaction may likewise rearrange more or less completely to its stereoisomer after the addition is complete. If rearrangements of either or both kinds take place, the identities of the products isolated are determined not only by the relative rates of the *cis* and *trans* additions, but also by the positions of the stereochemical equilibria involved. Such rearrangements should be especially common when the addition of the hydrogen is slow and when the experimental conditions are particularly vigorous. Hence, it is not surprising that *trans* addition is observed more frequently with nickel catalysts (which often permit only slow reactions except at high temperatures and pressures) than with platinum or palladium catalysts (which ordinarily permit fairly rapid reactions even at low temperatures and pressures).

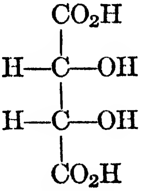
In the several ways just outlined, it is often possible to explain the stereochemical details of the various reactions in which carbon-carbon double bonds are saturated by the addition of hydrogen atoms. The phenomena are, however, so complex and (not infrequently) so discordant that no such simple interpretation can be completely satisfactory. Consequently, numerous exceptions to the generalizations stated above must be expected. (For further details, the reader is referred to the comprehensive reviews of the subject that are now available.[76, 77])

Comparatively little is known about the steric courses of those reactions in which reagents other than the halogens or hydrogen add to double bonds. The most carefully investigated reactions of these further classes are the ones where hydroxyl groups become attached to the formerly unsaturated carbon atoms; such additions may be brought about by the action of dilute alkaline aqueous potassium permanganate or by that of sodium chlorate in the presence of a little osmium tetroxide OsO_4. By either reaction, maleic acid, I, is transformed into *meso*-tartaric acid, XLIV, and fumaric acid, V, is transformed into racemic



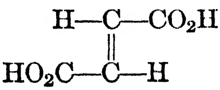
$$\begin{array}{rcl} \mathrm{H}- & \mathrm{C} & -\mathrm{CO_2H} \\ & \| & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{CO_2H} \end{array}$$

I



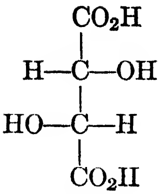
$$\begin{array}{rcl} & \mathrm{CO_2H} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CO_2H} & \end{array}$$

XLIV



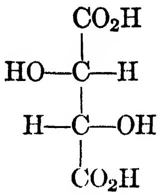
$$\begin{array}{rcl} \mathrm{H}- & \mathrm{C} & -\mathrm{CO_2H} \\ & \| & \\ \mathrm{HO_2C}- & \mathrm{C} & -\mathrm{H} \end{array}$$

V



$$\begin{array}{c} \text{CO}_2\text{H} \\ | \\ \text{H—C—OH} \\ | \\ \text{HO—C—H} \\ | \\ \text{CO}_2\text{H} \end{array}$$

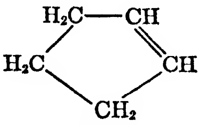
XLV



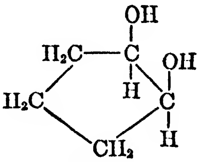
$$\begin{array}{c} \text{CO}_2\text{H} \\ | \\ \text{HO—C—H} \\ | \\ \text{H—C—OH} \\ | \\ \text{CO}_2\text{H} \end{array}$$

XLVI

tartaric acid, XLV and XLVI; each addition is therefore *cis*. Similarly, cyclopentene, which necessarily has the *cis* configuration XLVII (see Section 9·5), is oxidized by permanganate to the nonresolvable, and hence *cis*, cyclopentane-1,2-diol, XLVIII; here also, therefore, the addition is *cis*.



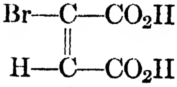
XLVII



XLVIII

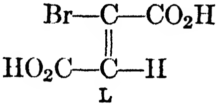
To the extent that any generalization is permitted by the limited number of reactions for which all the required data have as yet been reported, the addition of two hydroxyl groups seems always (as in the examples cited) to be *cis*. Nothing is now known, however, about the detailed mechanisms of the reactions; consequently, no explanation for their stereochemical features can be given.

The reactions of hydrogen halides with olefins have been so little studied from the stereochemical viewpoint that no general statement regarding the occurrence of *cis* or *trans* addition can at present be made. The most carefully investigated reactions of this type are probably the additions of hydrogen bromide to bromomaleic acid, XLIX, and to bromofumaric acid, L.



$$\begin{array}{c} \text{Br—C—CO}_2\text{H} \\ \| \\ \text{H—C—CO}_2\text{H} \end{array}$$

XLIX



$$\begin{array}{c} \text{Br—C—CO}_2\text{H} \\ \| \\ \text{HO}_2\text{C—C—H} \end{array}$$

L

$\text{HO}_2\text{C—CHBr—CHBr—CO}_2\text{H}$

LI

In the older literature, each of these acids is reported to be transformed into a mixture of the *meso* and racemic α,α'-dibromosuccinic acids, LI. In a more recent study,[79] however, it has been found that bromomaleic acid, XLIX, gives only the *meso* product, whereas bromofumaric acid, L, gives mostly, but not exclusively, this same *meso* product. In the former reaction, therefore, the addition is

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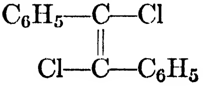
[79] M. S. Kharasch, J. V. Mansfield, and F. R. Mayo, unpublished results. See J. V. Mansfield, Ph.D. Thesis, University of Chicago, 1942.

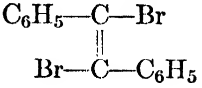
entirely *trans;* in the latter, it is mostly, but not exclusively, *cis*. Clearly, no significant generalization can be based upon such meager data.

7·10 The Stereochemistry of Additions to Carbon-carbon Triple Bonds. The stereochemical features of the additions of halogens to carbon-carbon triple bonds have been relatively little studied. It has been established, however, that *trans*-dichlorostilbene, I, and *trans*-dibromostilbene, II, are the major ethylenic products formed in the additions of the respective halogens to tolane (diphenylacetylene), III.[80] Similarly, the reaction between bromine and acetylene dicarboxylic acid, IV, gives largely dibromofumaric acid, V. In each of these three reactions, the addition of the halogen to the triple bond is, therefore, predominantly *trans*. Since, however, only a comparatively few such additions have thus been definitely classified, there can be no assurance that *trans* addition of a halogen to a triple bond is entirely general, nor even that it is more common than *cis* addition.



$$\begin{array}{c} C_6H_5—C—Cl \\ \| \\ Cl—C—C_6H_5 \end{array}$$

I



$$\begin{array}{c} C_6H_5—C—Br \\ \| \\ Br—C—C_6H_5 \end{array}$$

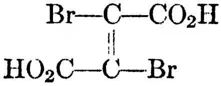
II

$C_6H_5—C{\equiv}C—C_6H_5$

III

$HO_2C—C{\equiv}C—CO_2H$

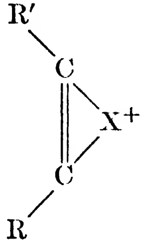
IV



$$\begin{array}{c} Br—C—CO_2H \\ \| \\ HO_2C—C—Br \end{array}$$

V

If, however, on the basis of the incomplete evidence now available, the addition of one mole of a halogen X_2 to an acetylene $R—C{\equiv}C—R'$ is assumed always to be *trans*, the possibility that an unstable intermediate like VI (cf. the intermediate XXIX on page 295) may participate in the reaction is immediately suggested. There is, however, no necessity that the addition of a halogen to an acetylene be so closely analogous to the addition of the same reagent to an olefin. In fact, the



VI

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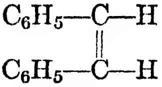
[80] For the assignment of configurations to the *cis* and *trans* isomers of these halogen compounds, see E. Bergmann, *J. Chem. Soc.* **1936,** 402.

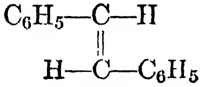
two reactions could conceivably proceed by entirely different mechanisms, and through entirely dissimilar intermediates. Thus, it is not impossible that, in any reaction in which an acetylene could give rise to either of two stereoisomeric addition products, the material isolated may be merely the equilibrium mixture of the two; under such circumstances, *trans* addition should predominate, since *trans* compounds are usually more stable than are their *cis* isomers. (Cf. pages 319 and 323.)

The addition of hydrogen to acetylenes has been rather more extensively studied than has that of the halogens to the same substances.[76, 78] When elementary hydrogen in the presence of a platinum, palladium, or nickel catalyst is used as the reducing agent, the addition of the first molecule of hydrogen to the triple bond is usually *cis*. For example, the hydrogenation of tolane, III, over a palladium or nickel catalyst gives mostly *cis*-stilbene, VII, and only a little *trans*-stilbene, VIII. Similarly, the hydrogenation of 5-decyne (di-*n*-butylacetylene), IX, over nickel gives *cis*-5-decene, X, and little if any of the *trans* isomer, XI.[81] The occurrence here of *cis* addition is most easily explained with the aid of two assumptions: first, that the organic molecule is adsorbed on the surface of the catalyst; and second, that the two hydrogen atoms which add to the triple bond approach simultaneously and together (presumably as a hydrogen molecule).[78] The second of these assumptions was not required above for the interpretation of the corresponding reactions of olefins (cf. page 300); it is, however, essential here since, if the two hydrogen atoms were only required to pass directly from the metal to the adsorbed unsaturated molecule, the addition to an acetylene (unlike that to an olefin) could be *trans* as easily as it could be *cis*.



$$\begin{array}{c} C_6H_5-C-H \\ \| \\ C_6H_5-C-H \end{array}$$

VII

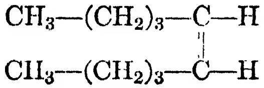


$$\begin{array}{c} C_6H_5-C-H \\ \| \\ H-C-C_6H_5 \end{array}$$

VIII

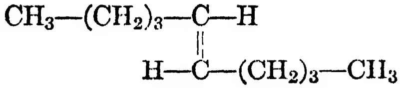
$CH_3-(CH_2)_3-C\equiv C-(CH_2)_3-CH_3$

IX



$$\begin{array}{c} CH_3-(CH_2)_3-C-H \\ \| \\ CH_3-(CH_2)_3-C-H \end{array}$$

X



$$\begin{array}{c} CH_3-(CH_2)_3-C-H \\ \| \\ H-C-(CH_2)_3-CH_3 \end{array}$$

XI

When the addition of one molecule of hydrogen to a carbon-carbon triple bond is brought about by a metal-acid combination, or the like, the addition is most commonly *trans*.[76, 78] For example, the reduction of tolane, III, by sodium and methyl alcohol, or by zinc and acetic acid, gives mostly *trans*-stilbene, VIII; and that of 5-decyne, IX, by sodium

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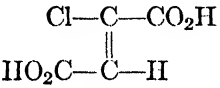
[81] K. N. Campbell and L. T. Eby, *J. Am. Chem. Soc.* **63**, 216, 2683 (1941).

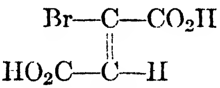
in liquid ammonia gives mostly *trans*-5-decene, XI.[81] As in the addition of a halogen to an acetylene, the predominance of *trans* over *cis* addition may here be merely a direct consequence of the fact that, of the two possible stereoisomeric olefins, the *trans* form is usually the most stable. (See pages 319 and 323.) On the other hand, it has been reported that, by the action of the zinc-copper couple in alcohol, tolane is reduced to *cis*-stilbene, VII.

The addition of hydrogen chloride and of hydrogen bromide to acetylenedicarboxylic acid, IV, gives, respectively, chlorofumaric acid, XII, and bromofumaric acid, XIII. In each reaction, therefore, the



$$\begin{array}{c} \mathrm{Cl{-}C{-}CO_2H} \\ \| \\ \mathrm{HO_2C{-}C{-}H} \end{array}$$

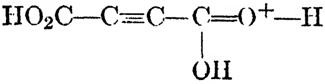
XII



$$\begin{array}{c} \mathrm{Br{-}C{-}CO_2H} \\ \| \\ \mathrm{HO_2C{-}C{-}H} \end{array}$$

XIII

addition to the triple bond is *trans*. The participation here of an intermediate analogous to the one with structure VI seems rather less likely than does that of the intermediate XIV. The justification of this

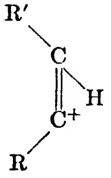


$$\begin{array}{l} \mathrm{HO_2C{-}C{\equiv}C{-}C{=}O^{+}{-}H} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\;\mathrm{OH} \end{array}$$

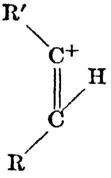
XIV

statement is twofold. In the first place, a hydrogen atom cannot form two covalent bonds, as does the halogen X in structure VI. (Cf. Section 1·8 and also page 423.) In the second place, the proton would be expected to attach itself to an oxygen atom rather than to a carbon atom since, if the proton becomes bonded to the oxygen atom (as in structure XIV), no covalent bond of the original organic molecule need be broken; whereas, if it instead becomes bonded to one of the carbon atoms, the triple bond is necessarily decreased to a double bond. (Cf. structure VI.) Moreover, the assumed intermediate XIV is merely an oxonium cation of the type discussed in Section 2·3; consequently, at least a trace of such a cation must certainly be present, whether or not it be an intermediate in the addition of the hydrogen halide to the acetylenedicarboxylic acid.

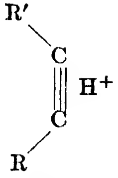
When a molecule of a strong acid adds to a carbon-carbon triple bond which is not conjugated with a carbonyl group, the second of the objections just stated no longer applies. Moreover, the first objection also may not be completely valid, since, in the reaction of an acetylenic molecule without a conjugated carbonyl group, the hypothetical intermediate might have a charge distribution that is some sort of average of the distributions corresponding to the three different structures XV, XVI,



XV



XVI

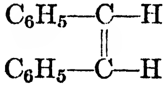


XVII

and XVII. (Cf. Chapter 10.) Such a cation would, of course, have a close geometrical, if not structural, analogy to the above intermediate VI. (Similar considerations have been applied also in the discussion of the additions of strong acids to unconjugated double bonds.[82] Cf. page 310.)

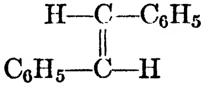
In view of the present lack of information regarding the mechanisms of the respective reactions, further speculation regarding the cause of the observed *trans* additions to acetylenic compounds would here be unprofitable. Indeed, as has already been noted in connection with other reactions, the fact that any given addition reaction leads to a *trans* product may mean only that the *trans* compound, since it is more stable than its *cis* isomer, predominates in the equilibrium mixture of the two.

7·11 Mechanisms for the Catalyzed *Cis-trans* Interconversions of Ethylenic Compounds. Although many of the substances that add to carbon-carbon double bonds can frequently also catalyze the interconversion of ethylenic *cis-trans* isomers, the addition of the catalyst to the double bond cannot in general be a step in such isomerizations. (Cf. Section 7·7.) Nevertheless, the various additions and the corresponding isomerizations may still be closely related, and they may still involve common intermediates. Thus, it is not unreasonable to suppose that the bromine-catalyzed reaction, by which *cis*-stilbene (isostilbene), I, is converted into the more stable *trans*-stilbene, II, may



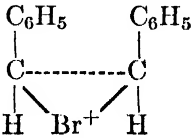
$$\begin{array}{c} C_6H_5-C-H \\ \| \\ C_6H_5-C-H \end{array}$$

I



$$\begin{array}{c} H-C-C_6H_5 \\ \| \\ C_6H_5-C-H \end{array}$$

II



III

proceed by way of the same cation III that is postulated as an intermediate in the (nonphotochemical) addition of bromine to the original hydrocarbon I. (Cf. configuration XXXI on page 296.) If the concentration of bromine is small, the subsequent reaction, in which racemic α,α'-dibromobibenzyl, IV, is produced from this cation (cf. equation

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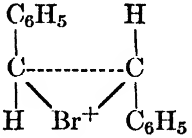
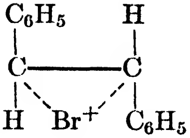
[82] Cf. C. C. Price, *Mechanisms of Reactions at Carbon-carbon Double Bonds*, Interscience Publishers, New York, 1946, page 40.

$C_6H_5—CHBr—CHBr—C_6H_5$

IV



V



VI

7·30 on page 293), must be slow; in fact, the reaction may be so slow that, before it has occurred, the *cis* cation, III, has had sufficient time to rearrange to one of its more stable *trans* isomers, V and VI. The mechanism of the rearrangement would presumably, of course, be the one postulated on page 297 for the analogous rearrangement in the addition of a halogen to maleate ion. If, now, the reactions by which the cations III and V (or VI) are formed from *cis*- and *trans*-stilbene, respectively, are readily reversible, the two stilbenes not only are constantly transformed into their corresponding cations, but also are constantly produced from these cations. Evidently, therefore, a relatively large amount of the *cis* compound could be changed into the equilibrium mixture (which is almost the pure *trans* form) by merely a trace of bromine.

Although the mechanism just outlined seems quite reasonable, and although it may well be involved in many *cis-trans* interconversions, it is probably not correct for the particular reaction considered above; at any rate, it can probably account for no more than a small fraction of the observed isomerization of *cis*-stilbene. This conclusion follows from the fact that, *in the dark*, bromine has little, if any, effect upon the rate of the reaction.[83] The interconversion is therefore photochemical (cf. pages 298 f.); hence it cannot proceed by the obviously nonphotochemical mechanism just described. Moreover, the reaction (although photochemical) is also clearly not one of the *uncatalyzed* photochemical transformations mentioned in a previous section (cf. pages 267 ff.); for, if it were one of these, the bromine could then have no effect upon the rate. An uncatalyzed photochemical isomerization of *cis*-stilbene occurs also, but can easily be distinguished from the much faster catalyzed one.

The isomerization of *cis*-stilbene in the presence of bromine is induced by visible light, as well as by ultraviolet light. Since visible light is absorbed only by the bromine, and not by the (colorless) hydrocarbon, the primary photochemical process clearly involves only the former substance, and not the latter. Moreover, since bromine molecules are known to be dissociated by light into bromine atoms,[84] it is logical to as-

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[83] M. S. Kharasch, J. V. Mansfield, and F. R. Mayo, *J. Am. Chem. Soc.* **59**, 1155 (1937).

[84] Cf., for example, O. Darbyshire, *Proc. Roy. Soc.* (London) **A159**, 93 (1937).

sume that these atoms are the active agents responsible for the isomerization. A reasonable mechanism for the reaction is therefore the one indicated in equations 7·35–7·37. (Cf. also equations 7·31–7·33 on

$$\mathrm{Br_2} + \text{light} \rightarrow 2\mathrm{Br} \tag{7·35}$$

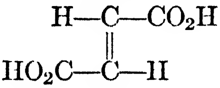
$$\underset{\text{I}}{cis\text{-}\mathrm{C_6H_5{-}CH{=}CH{-}C_6H_5}} + \mathrm{Br} \rightarrow \underset{\text{VII}}{\mathrm{C_6H_5{-}CHBr{-}\dot{C}H{-}C_6H_5}} \tag{7·36}$$

$$\underset{\text{VII}}{\mathrm{C_6H_5\text{-}CHBr{-}\dot{C}H{-}C_6H_5}} + \underset{\text{I}a}{cis\text{-}\mathrm{C_6H_5{-}CH{=}CH{-}C_6H_5}} \rightleftarrows \underset{\text{II}}{trans\text{-}\mathrm{C_6H_5{-}CH{=}CH{-}C_6H_5}} + \underset{\text{VII}a}{\mathrm{C_6H_5{-}CHBr{-}\dot{C}H{-}C_6H_5}} \tag{7·37}$$

page 298.) The intermediate VII, like the bromine atom, is a free radical with the single unpaired electron that is represented by the isolated dot. (Cf. Chapter 15.) Since, in the intermediate VII, the trivalent carbon atom could hardly be expected to maintain a pyramidal configuration, and since there should now be free rotation about the central carbon-carbon bond, the intermediate derived from *cis*-stilbene must presumably be in all respects identical with the one derived (in a reaction analogous to 7·36) from *trans*-stilbene. (See pages 294f. for a discussion of a similar situation that arises in connection with a cationic intermediate.) Consequently, when this intermediate loses its bromine atom (reaction 7·37), it need not become a molecule of the original *cis*-stilbene, I, since it can instead become one of *trans*-stilbene, II. In this reaction 7·37, the bromine atom is transferred from the free radical VII to a second molecule (I*a*) of *cis*-stilbene; the original molecule (VII) of the intermediate, by thus losing its bromine atom, is transformed into one of *trans*-stilbene, II, while the second molecule (I*a*) of *cis*-stilbene is transformed into a second molecule (VII*a*) of the intermediate, equivalent to the one (VII) which it replaces. (Cf. also the following paragraph.) This chain of reactions can then obviously continue until, with the aid of only a single bromine atom, a great many molecules of *cis*-stilbene have been isomerized. (For further discussions of chain reactions see below in this section, and also pages 298f. and Sections 15·4 and 15·5.)

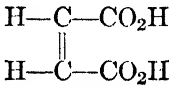
It is not necessary here to assume that, in each individual reaction of the type 7·37, a molecule of the *cis* isomer must be used up and that one of the *trans* isomer must be formed in its place. Undoubtedly, in such reactions, many molecules of the *trans* isomer must, in fact, be used up, and many of the *cis* isomer must be formed. The destruction of a molecule of *trans*-stilbene, with the simultaneous production of one of *cis*-stilbene, is represented by the reverse arrow of equation 7·37; the replacement of a molecule of *cis*- (or *trans*-) stilbene by a second molecule of the same isomer can be represented by an obvious slight modification of equation 7·37. In order that a macroscopic sample of *cis*-stilbene be ultimately converted into the equilibrium mixture, in which the *trans* isomer greatly predominates, all that is required is that there be some path by which the isomerization can take place; for, once such a path is provided, the direction in which the net reaction proceeds (from *cis* to *trans*, or vice versa) is determined by the position of the equilibrium under the experimental conditions employed. Consequently, although the discussion in the preceding paragraph is incomplete, since it does not consider all the reactions which can and do occur, it is nevertheless sufficient to explain the observed bromine-catalyzed photochemical *cis-trans* interconversion.

The formation of *trans*-stilbene from its *cis* isomer is catalyzed not only by bromine but also by chlorine and by iodine. Similarly, the formation of fumaric acid, VIII, from maleic acid, IX, is catalyzed, in



$$\begin{array}{c} \text{H—C—CO}_2\text{H} \\ \| \\ \text{HO}_2\text{C—C—H} \end{array}$$

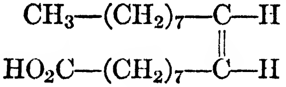
VIII



$$\begin{array}{c} \text{H—C—CO}_2\text{H} \\ \| \\ \text{H—C—CO}_2\text{H} \end{array}$$

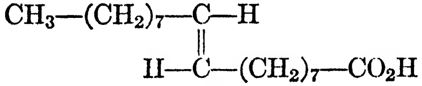
IX

the presence of light, by each of the three halogens named. Presumably, the mechanisms of all these further reactions are analogous to that of the one just discussed. Moreover, *cis-trans* interconversions in general can frequently be catalyzed by other substances which, like the several halogen atoms, are free radicals with unpaired electrons. For example, nitrogen dioxide NO_2 (cf. Section 15·7) brings about the transformation of oleic acid, X, to elaidic acid, XI. In most, if not in all such reactions,



$$\begin{array}{r} \text{CH}_3\text{—(CH}_2)_7\text{—C—H} \\ \| \\ \text{HO}_2\text{C—(CH}_2)_7\text{—C—H} \end{array}$$

X



$$\begin{array}{l} \text{CH}_3\text{—(CH}_2)_7\text{—C—H} \\ \qquad\qquad\qquad\quad \| \\ \qquad\qquad\qquad \text{H—C—(CH}_2)_7\text{—CO}_2\text{H} \end{array}$$

XI

radical-chain mechanisms, which are completely analogous to the one described in equations 7·36 and 7·37, are probably involved.[85, 86]

Hydrogen bromide is also an effective catalyst for the isomerization of *cis*-stilbene, I. Of the various possible explanations of this reaction, one of the first to be proposed was that the hydrogen bromide donates a proton to the stilbene molecule (equation 7·38); since, in the resulting

$$\left.\begin{array}{c} cis\text{-C}_6\text{H}_5\text{—CH=CH—C}_6\text{H}_5 \\ \text{I} \\ trans\text{-C}_6\text{H}_5\text{—CH=CH—C}_6\text{H}_5 \\ \text{II} \end{array}\right] + \text{HBr} \rightleftarrows \underset{\text{XII}}{\text{C}_6\text{H}_5\text{—CH}_2\text{—C}^+\text{H—C}_6\text{H}_5} + \text{Br}^- \qquad (7\cdot38)$$

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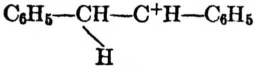
[85] For further examples and further discussions of those *cis-trans* interconversions which presumably go by radical-chain mechanisms, see F. R. Mayo and C. Walling, *Chem. Revs.* **27**, 351 (1940).

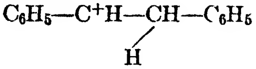
[86] Cf. C. C. Price, *Mechanisms of Reactions at Carbon-carbon Double Bonds*, Interscience Publishers, New York, 1946, pages 56 ff.; R. Kuhn in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 913 ff.

organic cation XII, the trivalent carbon atom should not be able to maintain a pyramidal configuration, and since, moreover, the rotation about the central carbon-carbon bond should be essentially free, the stilbene regenerated from the cation XII could be either the *cis* isomer, I, or the *trans* isomer, II. (Cf. the above paragraph in fine print.) Consequently, the mechanism appears able to account for the observed isomerization. (However, see below.)

It has been suggested[82] that the intermediate cation of reaction 7·38 cannot be adequately represented by structure XII, or by any other single structure of the classical type; but that instead it has a charge distribution which is some sort of average of the distributions corresponding to structures XIII, XIV, and XV. (Cf. structures XV, XVI, and XVII on page 306.) In this way, the mechanism is made more closely analogous to the one considered above (and then discarded) for the bromine-catalyzed reaction. However, the assumption here of such a cyclic intermediate merely complicates the mechanism without adding to it anything that is both significantly new and relevant to the subject now under discussion; consequently, the simpler representation, XII, will hereafter be used.



XIII



XIV

XV

Although the reaction 7·38 seems entirely reasonable, and although the formation of an intermediate like XII is commonly assumed to be an essential step in most additions of strong acids to ethylenic hydrocarbons,[72, 82, 87] the mechanism here outlined is probably not the most important one involved in the isomerization of *cis*-stilbene by hydrogen bromide, although, as will be discussed below, it probably is the most important one in certain other isomerizations of similar type. Since, in this proposed mechanism, the catalyst (hydrogen bromide) acts merely as a proton donor, any other equally strong acid would be expected to be equally effective. This prediction, however, is not in agreement with the facts when it is applied to the isomerization of *cis*-stilbene;[83] hydrogen chloride, for example, produces only an extremely slow isomerization of this substance. It might be suggested that, since the reaction is usually carried out in a nonionizing solvent like benzene, the enormous difference between the catalytic effects of hydrogen bromide and hydrogen chloride is due merely to the difference in acid strengths of the two substances; for, since hydrogen bromide is a stronger acid than is hydrogen chloride (cf. page 77), it should be the more effective proton donor, and hence the more effective catalyst for the isomerization. This suggestion, however, is not sufficient to explain all

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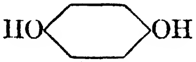
[87] G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 232 ff.

the pertinent data. Thus, even hydrogen bromide, in the absence of air, cannot produce a rapid isomerization of *cis*-stilbene if the reaction is carried out in the dark, and if, moreover, all reagents are highly purified. In fact, the above-mentioned rapid isomerization by hydrogen bromide is observed only if the reaction mixture is subjected to the action of ultraviolet light, or if it contains at least traces of certain impurities like oxygen, peroxides (e.g., benzoyl peroxide, XVI), or reduced iron. (The effect of air is possibly due, at least in part, to the formation of a peroxide by the reaction of oxygen with the unsaturated hydrocarbon.) Moreover, even in the presence of ultraviolet light or of a peroxide, the rate of the isomerization can be greatly decreased, and it may become practically zero, if there is added a small amount of a substance (a so-called *antioxidant*) like hydroquinone, XVII, or ethyl mercaptan, XVIII. These various effects of light, of peroxides, and of antioxidants are observed only when the reaction is catalyzed by hydrogen bromide; if hydrogen chloride is used instead, the reaction is always extremely slow, and its rate is not appreciably changed by any of the factors mentioned.

$C_6H_5—CO—O—O—CO—C_6H_5$

XVI



XVII

$C_2H_5—SH$

XVIII

Clearly, if the cation XII is an intermediate in any isomerization of *cis*-stilbene, it can be involved only in such slow reactions as the ones induced by hydrogen chloride and, in the absence of air, light, peroxides, etc., by hydrogen bromide. The mechanism of the *fast* isomerization by hydrogen bromide must, therefore, be entirely different. The most likely suggestion[83,85] regarding this latter mechanism is that it is essentially the same as the one proposed above (equations 7·36 and 7·37) for the bromine-catalyzed reaction; or, in other words, that the isomerization is a chain reaction initiated by bromine atoms. These bromine atoms are, of course, assumed to be produced from the hydrogen bromide by the light, by the oxygen, by the peroxide, or by hydrogen atoms (which are themselves formed in a reaction between reduced iron, or the like, and the acid). Moreover, the effect of the antioxidants is explained by the assumption that these substances react with, and destroy, either the bromine atoms or the intermediate free radicals (or both). By thus "breaking" the chains, the antioxidants increase the number of individual chains that must be initiated before any given amount of isomerization can occur; hence, they decrease the rate of the overall reaction. Finally, the reason why hydrogen chloride does not behave in the same way as does hydrogen bromide is presumably that, since the hydrogen-chlorine bond is stronger than the hydrogen-bromine bond, the chlorine atoms required to initiate the chains cannot be easily produced; and perhaps also that, for an analogous reason, the reaction corresponding to the one of equation 7·37 (when the bromine atoms are replaced by chlorine atoms) may be rather slow.

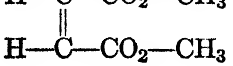
The above radical-chain mechanism for the isomerization of *cis*-stilbene by hydrogen bromide receives some support from the fact that, in the presence of oxygen, a trace of α,α′-dibromobibenzyl, IV, has been

$$C_6H_5—CHBr—CHBr—C_6H_5$$

IV

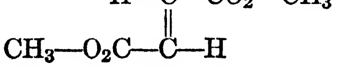
found among the reaction products,[79,88] along with a much greater amount of *trans*-stilbene; this dibromide could, of course, arise from a reaction either between a molecule of the intermediate radical VII and a bromine atom, or between two molecules of the intermediate. The evidence is, however, not conclusive, since the formation of the dibromide IV might instead be due to the oxidation of the hydrogen bromide (by oxygen or by a peroxide) to molecular bromine Br_2, which then adds in the usual manner to the hydrocarbon. More satisfactory evidence for the proposed mechanism of isomerization is provided, however, by the fact that, under the influence of air, light, peroxides, etc., hydrogen bromide (but not hydrogen chloride) takes part in other reactions besides the isomerization of *cis*-stilbene, and that these further reactions can also be most easily explained in terms of analogous free-radical chains.[85] (Cf. Section 15·5.) Consequently, the mechanism in question does not stand by itself; rather, it is merely a single example taken from a fairly extensive group of closely related mechanisms.

The discussion in this section has so far been largely restricted to the isomerization of *cis*-stilbene, I. There is, however, no justification for the belief that the *cis-trans* interconversions of all ethylenic compounds must be analogous to that of this particular hydrocarbon. Indeed, there is conclusive evidence that important differences do exist.[85] Thus, for the conversion of methyl maleate, XIX, into methyl fumarate, XX,



$$\begin{array}{l} H—C—CO_2—CH_3 \\ \quad \| \\ H—C—CO_2—CH_3 \end{array}$$

XIX



$$\begin{array}{r} H—C—CO_2—CH_3 \\ \| \quad\quad\quad\quad\quad \\ CH_3—O_2C—C—H \quad\quad\quad\quad\quad \end{array}$$

XX

hydrogen chloride is nearly as effective as is hydrogen bromide;[89] moreover, neither oxygen nor antioxidants here affect the rate of the reaction catalyzed by hydrogen bromide. For the conversion of maleic acid, IX, itself into fumaric acid, VIII, in the presence of air, hydro-

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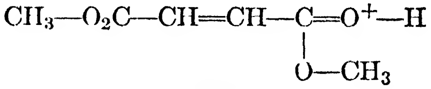
[88] Y. Urushibara and O. Simamura, *Bull. Chem. Soc. Japan* **13**, 566 (1938).

[89] O. Simamura, *Bull. Chem. Soc. Japan* **14**, 22 (1939).

chloric acid and hydrobromic acid have been found to be approximately equally effective.[79] In these several reactions, therefore, the catalyst presumably acts principally as a proton donor (as in the original mechanism discussed on pages 309 f.), and not as a source of halogen atoms, although the opposite is true in the isomerization of *cis*-stilbene. With methyl maleate, for example, the intermediate organic cation, which undergoes the actual *cis-trans* interconversion, probably does not have structure XXI (cf. structure XII) since, for the reasons given on page 305, the proton would be more likely to become linked to an oxygen atom, as in structure XXII, than to a carbon atom. This greater tendency of the proton to attack an oxygen atom than to attack a carbon atom possibly explains why hydrogen chloride, for example, is so much more effective as a catalyst for the isomerization of methyl maleate and of maleic acid than it is for that of *cis*-stilbene.

$$CH_3—O_2C—CH_2—C^+H—CO_2—CH_3$$

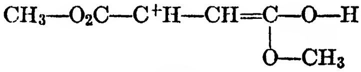
XXI



$$CH_3—O_2C—CH{=}CH—\underset{\substack{|\\ O—CH_3}}{C}{=}O^+—H$$

XXII

An alternative, and possibly better, description of the postulated intermediate cation which is represented above by structure XXII is that it has a charge distribution which is an average of the distributions corresponding to structures XXII and XXIII. (Cf. Chapter 10.) The catalysis by the acid is thus considered to be due to the tendency of the proton to attract electrons toward itself by pulling them out of the carbon-carbon double bond at the center of the original molecule. To the extent that electrons are thus removed from the double bond, this bond becomes more similar to a single one; consequently, the rotation about the bond is made more nearly free, and the carbon atom which is trivalent in structure XXIII becomes less able to maintain any specified configuration. The catalytic effect of the acid can therefore be explained without recourse to the rather improbable structure XXI.



$$CH_3—O_2C—C^+H—CH{=}\underset{\substack{|\\ O—CH_3}}{C}—O—H$$

XXIII

Other Lewis acids (cf. Section 3·3) besides the proton can catalyze *cis-trans* interconversions. Thus, methyl maleate, XIX, is isomerized to methyl fumarate, XX, by aluminum chloride, ferric chloride, and zinc chloride.[90] Presumably, these reactions involve intermediates with charge distributions that are intermediate between the extremes repre-

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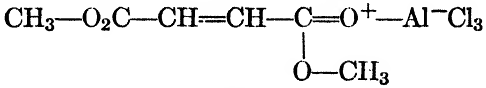
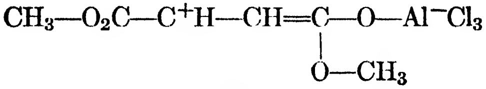
[90] W. I. Gilbert, J. Turkevitch, and E. S. Wallis, *J. Org. Chem.* **3**, 611 (1939).

sented by structures like XXIV and XXV. (Cf. structures XXII and



$$CH_3{-}O_2C{-}CH{=}CH{-}\underset{\overset{|}{O{-}CH_3}}{C}{=}O^+{-}Al^-Cl_3$$

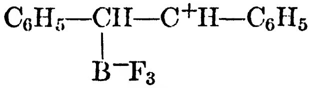
XXIV



$$CH_3{-}O_2C{-}C^+H{-}CH{=}\underset{\overset{|}{O{-}CH_3}}{C}{-}O{-}Al^-Cl_3$$

XXV

XXIII.) Not all strong Lewis acids, however, are effective; boron trifluoride BF_3, for example, does not catalyze the isomerization of methyl maleate; perhaps surprisingly, however, it does catalyze that of *cis*-stilbene,[91] possibly through such an intermediate as XXVI.



$$C_6H_5{-}\underset{\overset{|}{B^-F_3}}{CH}{-}C^+H{-}C_6H_5$$

XXVI

The reason why hydrogen bromide, which acts mostly as a source of bromine atoms in the isomerization of *cis*-stilbene, acts instead mostly as a proton donor in that of methyl maleate is rather obscure. The explanation cannot be that methyl maleate is unable to be isomerized by the radical-chain mechanism; for, since the bromine-catalyzed isomerization of this substance is fast only under the influence of light, the reaction then doubtless involves chains in which bromine atoms participate. Perhaps, a larger number of bromine atoms can be formed in a given time, and hence a larger number of chains can be initiated, if molecular bromine is present than if only hydrogen bromide is present; consequently, the radical-chain mechanism permits a fast reaction when the catalyst is bromine, but only a slow one when the catalyst is hydrogen bromide. There is not at present, however, sufficient evidence to show whether this suggested explanation is satisfactory.

Numerous other aspects of the catalyzed *cis-trans* interconversions are likewise obscure. Thus, boron trifluoride is a much more effective catalyst than is hydrogen chloride for the isomerization of *cis*-stilbene, but a much less effective one for the isomerization of methyl maleate. (See above.) Nevertheless, the respective mechanisms of the several reactions are considered to be analogous, since each isomerization is supposed to be made possible by the addition of a strong Lewis acid

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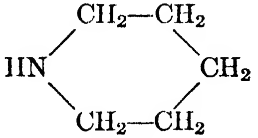
[91] C. C. Price and M. Meister, *J. Am. Chem. Soc.* **61**, 1595 (1939).

(either boron trifluoride or the proton) to the organic molecule. If only the isomerization of *cis*-stilbene is considered, boron trifluoride appears to be a stronger acid than the proton (as provided by the hydrogen chloride molecule); on the other hand, if only the isomerization of methyl maleate is considered, boron trifluoride appears to be a weaker acid than the proton. Clearly, therefore, the acidity (in the Lewis sense) of the catalyst is not its only significant property; hence, other characteristics of the catalysts, which are more specific than are their acidities, and which have not been considered in the preceding discussion, must also be important. It is not possible at the present time, however, to see clearly what these other characteristics are; perhaps they are related, in some way that it is not immediately obvious, to the phenomenon known as *steric hindrance*. (See Section 9·7.)

Finally, many substances, which have little apparent resemblance to the catalysts mentioned earlier in this section, have been observed to exert similar effects upon the rates of *cis-trans* interconversions.[85] For example, ammonia and primary and secondary amines (e.g., methyl amine, XXVII, aniline, XXVIII, dimethylamine, XXIX, and piperidine,

$CH_3—NH_2$ XXVII $C_6H_5—NH_2$ XXVIII $(CH_3)_2NH$ XXIX

XXX) are reported to catalyze the isomerization of methyl maleate,



XXX

$(C_2H_5)_3N$

XXXI

XIX;[92] a tertiary amine like triethylamine, XXXI, is, however, ineffective. Moreover, platinum black and palladium black bring about a number of isomerizations,[85, 93] as does also colloidal sulfur.[85] Such transformations as these have not yet been satisfactorily explained.

7·12 The Determination of Relative Configuration. A few examples of the methods by which the configurations of optically active substances are determined (relative to those of the glyceraldehydes) have already been given on pages 181 f., 225 f., and 277 ff. A more extensive,

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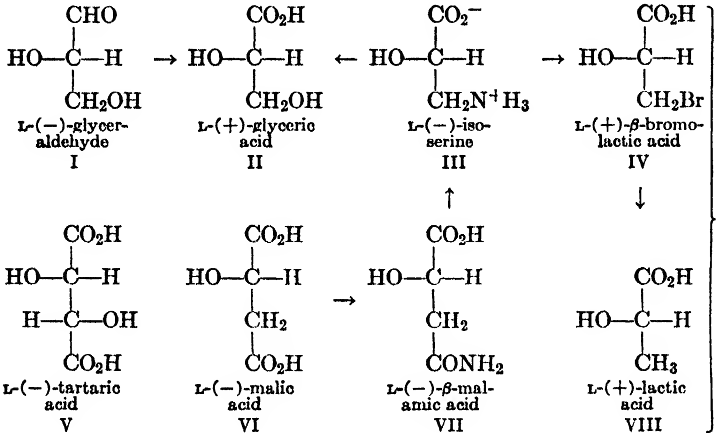
[92] G. R. Clemo and S. B. Graham, *J. Chem. Soc.* **1930,** 213.

[93] B. Tamamushi and H. Akiyama, *Bull. Chem. Soc. Japan* **12,** 382 (1937).

and possibly more typical, set of examples[94] is given by the sequence of reactions 7·39. (Cf. also equations 7·40 on page 320.) The preparation



(7·39)

of (+)-glyceric acid, II, from L-(−)-glyceraldehyde, I, shows that the former substance, like the latter, belongs to the L-series and has the configuration shown. Similarly, the preparation of the same L-(+)-glyceric acid from (−)-isoserine (by the action of nitrous acid) shows that (−)-isoserine also belongs to the L-series and has the configuration III. In the same way, the remaining reactions of the sequence show that (−)-β-malamic acid, VII, (−)-malic acid, VI, (−)-tartaric acid, V, (+)-β-bromolactic acid, IV, and (+)-lactic acid, VIII, likewise belong to the L-series and have the respective configurations shown. Similar, but frequently more complicated, schemes have been employed for the determination of the configurations of many other optically active substances.

It is important to observe that, in any rigorous determination of configuration, reactions in which asymmetric atoms are directly involved must be avoided; for, if this precaution is not observed, the number of Walden inversions which have taken place cannot then be known with complete certainty. Although, to be sure, considerable information regarding the occurrence of inversions can be obtained in the ways described in Section 7·8, the conclusions based upon such information may perhaps in some instances be incorrect. Thus, from the fact that, as was shown above, (−)-malic acid belongs to the L-series and has the configuration VI, and from the belief that the reaction between this malic acid and phosphorus pentachloride is accompanied by inversion, it can be concluded that the resulting (+)-chlorosuccinic acid belongs to the

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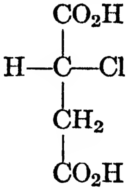
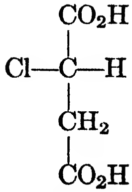
[94] K. Freudenberg, *Ber.* **47**, 2027 (1914).

D-series and has the configuration IX. (Cf. equation 7·12 on page 269.)



$$\begin{array}{c} CO_2H \\ | \\ H-C-Cl \\ | \\ CH_2 \\ | \\ CO_2H \end{array}$$

IX

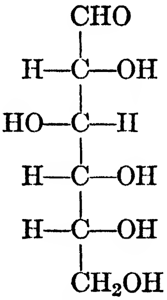


$$\begin{array}{c} CO_2H \\ | \\ Cl-C-H \\ | \\ CH_2 \\ | \\ CO_2H \end{array}$$

X

However, the occurrence of an inversion in this reaction has not been rigorously proved; it is instead only inferred from the analogy between the reaction in question and other reactions that are assumed to be of similar type. If the analogy should happen to be false, so that an inversion does not occur here after all, then (+)-chlorosuccinic acid must belong to the L-, instead of to the D-series, and its configuration must be X instead of IX. Similar uncertainties exist in most, if not in all, other determinations of configuration that are based upon reactions occurring at asymmetric atoms.

An entirely different method of determining relative configuration can be taken from the sugar series. In most elementary textbooks of organic chemistry, the configuration of the aldehyde form of D-(+)-glucose is shown, by methods not essentially different from the above, to be XI.

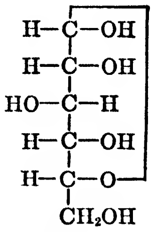


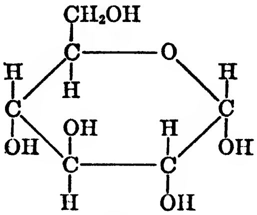
$$\begin{array}{c} CHO \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ CH_2OH \end{array}$$

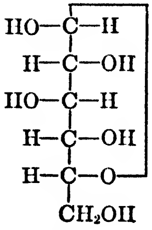
XI

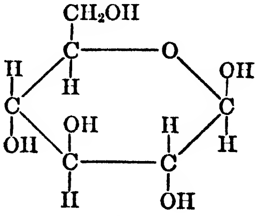
The cyclic α and β forms of this monosaccharide, however, possess an additional asymmetric carbon atom that is not contained in the aldehyde form, and they differ from each other in the configuration about this atom. The classical methods of Emil Fischer, by which the configurations about the four asymmetric atoms of the aldehyde form were established, have proved to be inapplicable to the problem of determining the configurations about this fifth asymmetric atom which is present in only the α and β forms. The conclusion has nevertheless been reached that the α form has the configuration XII (equivalent to XIII, cf. pages 187 f.).

whereas the β form has the other possible configuration XIV (equivalent to XV). The evidence supporting this conclusion is as follows.[95] Since

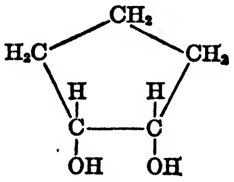

XII

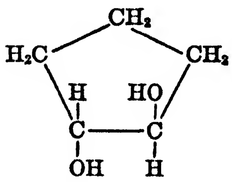

XIII

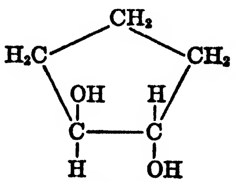

XIV


XV

boric acid is a very weak acid, its aqueous solution is a poor conductor of the electric current. The conductivity of such a solution is often increased, however, by the addition of an organic substance that contains hydroxyl groups in its molecules. This increase in conductivity, which is presumably due to the formation of complex ions, is found to be particularly great if the molecules of the added hydroxylic compound contain two or more hydroxyl groups that are attached to adjacent carbon atoms and are *cis* with respect to one another. For example, the nonresolvable, and therefore *cis*, 1,2-cyclopentanediol, XVI, greatly increases the conductivity, whereas its optically active, and therefore *trans*, isomers, XVII and XVIII, produce small *decreases* in conductivity.


XVI


XVII


XVIII

Now, α-D-(+)-glucose is found to lead to a higher conductivity than does the β form; consequently, the α and β forms presumably have, respectively, the larger and the smaller numbers of adjacent *cis*-hydroxy

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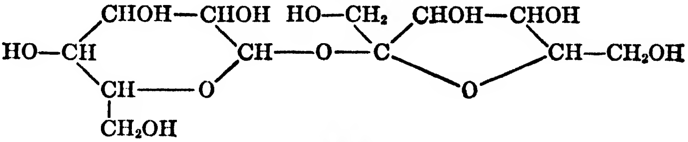
[95] J. Böeseken, *Ber.* **46**, 2612 (1913); *Rev. trav. chim.* **40**, 553 (1921).

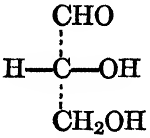
groups; hence, they may be represented, respectively, by the configurations XIII and XV. This conclusion is supported also by the further fact that with D-(+)-glucose the equilibrium mixture contains approximately twice as much of the β as of the α form; since *trans* forms are usually more stable than their *cis* isomers (see the following section), the form with the configuration XV would be expected to predominate over the one with the configuration XIII. Finally, an analysis of the crystal structure of sucrose, XIX, which is considered to be an α glucoside but a β fructoside, has shown that the oxygen atom which links the two halves



XIX

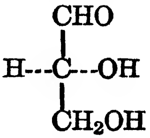
of the molecule is *cis* with respect to the adjacent hydroxyl group of the glucose component, but is *trans* with respect to the adjacent hydroxyl group of the fructose component.[96]

7·13 The Determination of Absolute Configuration. If a substance is optically active, its absolute configuration cannot be uniquely determined by any purely experimental methods. Thus, although it is clear that D-(+)-glyceraldehyde, for example, must have the configuration shown in either I or II, there is no known experiment, or combina-



$$\begin{array}{c} CHO \\ H-C-OH \\ CH_2OH \end{array}$$

I



$$\begin{array}{c} CHO \\ H-C-OH \\ CH_2OH \end{array}$$

II

tion of experiments, which permits the decision between these two absolute configurations to be made.[96a] In principle, the problem of assigning absolute configurations could be solved by theoretical calculations; in practice, however, mathematical difficulties have so far made impossible the rigorous treatment of any single substance. Consequently, the only calculations which have as yet been made [97, 98, 99, 100] have employed

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[96] C. A. Beevers and W. Cochran, *Proc. Roy. Soc.* (London) **A190,** 257 (1947).

[96a] However, see J. Waser, *J. Chem. Phys.* 17, 498 (1949).

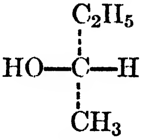
[97] Cf. J. G. Kirkwood, *J. Chem. Phys.* **5,** 479 (1937), and further references given there. In a personal communication, Professor Kirkwood has informed the author that there is an error of sign in his paper. The discussion of Kirkwood's treatment, given above and also later in this section, is based upon his *corrected* calculations.

[98] Cf. W J. Kauzmann, J. E. Walter, and H. Eyring, *Chem. Revs.* **26,** 339 (1940), and further references given there.

[99] S. F. Boys, *Proc. Roy. Soc.* (London) **A144,** 655, 675 (1934).

[100] W. Kuhn, *Z. physik. Chem.* **B31,** 23 (1936).

various sorts of simplifying assumption, and hence have been of somewhat uncertain reliability. One calculation of this type [97] has led to the conclusion that (+)-*sec*-butyl alcohol has the absolute configuration III;

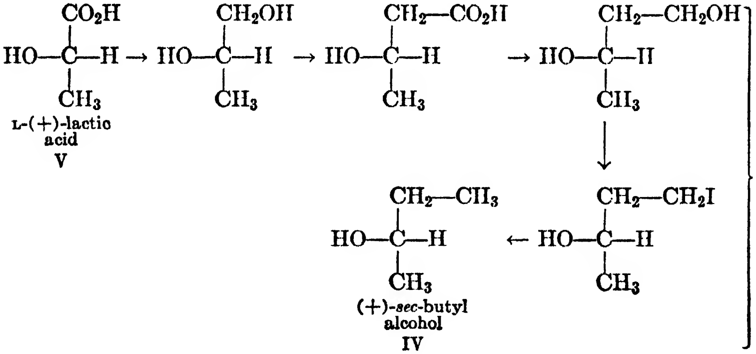


$$\begin{array}{c} C_2H_5 \\ \vdots \\ HO\text{—}C\text{—}H \\ \vdots \\ CH_3 \end{array}$$

III

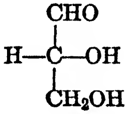
however, a second calculation,[99] based upon a different set of assumptions, has led to the opposite conclusion that the absolute configuration III belongs to the *levo*-rotatory enantiomorph. Moreover, still a third calculation [100] for D-(−)-lactic acid is consistent with the first, but inconsistent with the second, of these two for the *sec*-butyl alcohols. (See below.) Hence, it is evident that, in at least some instances, at least one of the methods is unreliable. Clearly, therefore, the problem of the absolute configurations of optically active compounds must at the present time be regarded as unsolved.[96a]

The sequence of reactions [101] 7·40 shows that (+)-*sec*-butyl alcohol must be repre-



(7·40)

sented by the conventional plane configuration IV, since the dextrorotatory lactic acid is known (cf. reactions 7·39) to have the configuration V. If now, for the sake of definiteness, this alcohol is assumed to have the absolute configuration III, it follows that the symbol VI for D-(+)-glyceraldehyde is really a projection of the



$$\begin{array}{c} CHO \\ | \\ H\text{—}C\text{—}OH \\ | \\ CH_2OH \end{array}$$

VI

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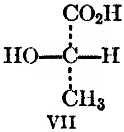
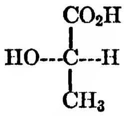
[101] P. A. Levene, A. Walti, and H. L. Haller, *Science* **64**, 558 (1926); *J. Biol. Chem.* **71**, 465 (1927).

three dimensional figure I, rather than of the figure II. Similarly, the diagram V for L-(+)-lactic acid is a projection of the figure VII, rather than of the figure VIII; as noted above, this conclusion is in agreement with the calculation of Kuhn,[100] although inconsistent with that of Boys.[99]



$$\begin{array}{c} CO_2H \\ \vdots \\ HO—C—H \\ \vdots \\ CH_3 \end{array}$$

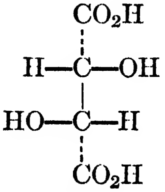
VII



$$\begin{array}{c} CO_2H \\ | \\ HO\text{---}C\text{---}H \\ | \\ CH_3 \end{array}$$

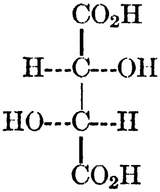
VIII

Since an optically inactive substance may be considered its own enantiomorph, its absolute configuration can be determined uniquely. Thus, although there is some doubt whether D-(+)-tartaric acid is IX or X,



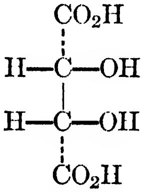
$$\begin{array}{c} CO_2H \\ \vdots \\ H—C—OH \\ | \\ HO—C—H \\ \vdots \\ CO_2H \end{array}$$

IX



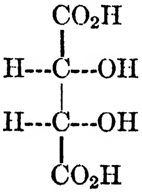
$$\begin{array}{c} CO_2H \\ | \\ H\text{---}C\text{---}OH \\ | \\ HO\text{---}C\text{---}H \\ | \\ CO_2H \end{array}$$

X



$$\begin{array}{c} CO_2H \\ \vdots \\ H—C—OH \\ | \\ H—C—OH \\ \vdots \\ CO_2H \end{array}$$

XI



$$\begin{array}{c} CO_2H \\ | \\ H\text{---}C\text{---}OH \\ | \\ H\text{---}C\text{---}OH \\ | \\ CO_2H \end{array}$$

XII

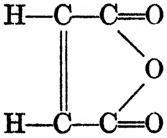
there is no doubt that *meso*-tartaric acid is XI. This statement is justified because the configuration XII, which bears the same enantiomorphic relation to XI that the configuration X bears to IX, is actually identical with XI; consequently, although one of the two possible configurations IX and X for D-(+)-tartaric acid must be correct, and the other must be incorrect, each of the corresponding configurations XI and XII of *meso*-tartaric acid is correct, and neither is incorrect.

An important group of optically inactive compounds, to which absolute configurations can be assigned, consists of the ethylenic substances of the type represented by maleic and fumaric acids of structure XIII.

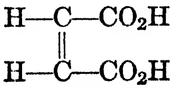
$$HO_2C—CH{=}CH—CO_2H$$

XIII

With this pair of stereoisomers, the configurations can be determined relatively easily and with almost complete certainty. Thus, maleic acid is transformed at a temperature slightly above its melting point into an anhydride, for which only the configuration XIV is possible. (Cf.

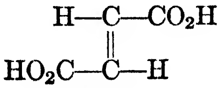


XIV



$$\begin{array}{c} H—C—CO_2H \\ \| \\ H—C—CO_2H \end{array}$$

XV

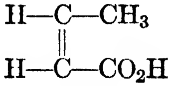


$$\begin{array}{c} H—C—CO_2H \\ \| \\ HO_2C—C—H \end{array}$$

XVI

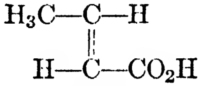
Section 9·5.) On the other hand, fumaric acid forms no anhydride except under more vigorous conditions, and even then it gives the anhydride of *maleic* acid. (See pages 156 and 264.) It may be concluded therefore that maleic acid has the *cis* configuration, XV, whereas fumaric acid has instead the *trans* configuration, XVI.

With a number of other stereoisomers, the relative ease of ring closure permits a similarly unambiguous assignment of configuration. Very frequently, however, the compounds of interest are of such nature that no one of the isomeric forms can be transformed directly into a cyclic substance. This situation is encountered, for example, with the *cis* and *trans*-crotonic acids, XVII and XVIII, respectively. Occasionally, under such circumstances, the configurations can still be determined, in an indirect manner, by a method based upon the ease of ring closure. Thus, of the two trichlorocrotonic acids, XIX and XX, the one melting at 113°–114°C can be hydrolyzed to fumaric acid, XVI; this trichlorocrotonic acid must therefore have the *trans* configuration, XX. Moreover, this same trichlorocrotonic acid can be reduced to the crotonic acid melting at 72°C, which must accordingly have the *trans* configuration, XVIII. The remaining crotonic acid, melting at 15·5°C, must therefore have the *cis* configuration, XVII.



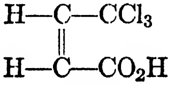
$$\begin{array}{c}\mathrm{H{-}C{-}CH_3}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\end{array}$$

XVII



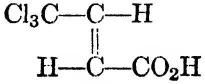
$$\begin{array}{c}\mathrm{H_3C{-}C{-}H}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\end{array}$$

XVIII



$$\begin{array}{c}\mathrm{H{-}C{-}CCl_3}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\end{array}$$

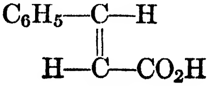
XIX



$$\begin{array}{c}\mathrm{Cl_3C{-}C{-}H}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\end{array}$$

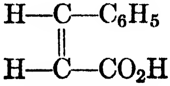
XX

In probably the majority of instances, the configurations of *cis-trans* isomers cannot be established either directly or indirectly by ring closure. For such substances, then, other methods of (usually) more dubious reliability must be employed. Thus, of the two cinnamic acids, the form which is esterified the more rapidly under given conditions may be considered to have the *trans* configuration, XXI, whereas the other form may be considered to have the *cis* configuration, XXII; the not entirely conclusive reason for this assumption is that, in the *cis* form, the pres-



$$\begin{array}{c}\mathrm{C_6H_5{-}C{-}H}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\end{array}$$

XXI



$$\begin{array}{c}\mathrm{H{-}C{-}C_6H_5}\\ \|\\ \mathrm{H{-}C{-}CO_2H}\end{array}$$

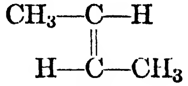
XXII

ence of the phenyl group near the carboxyl group can be expected to make more difficult the approach of the alcohol molecule to the latter group.[102] Since, however, the phenomenon of steric hindrance is at present not completely understood (see Section 9·7), the most that can be said for such a method is probably that (at any rate with the cinnamic acids) it leads to the same assignment of configuration as do the other methods discussed below.

The method which is most commonly used, and which is most generally applicable for the assignment of configurations to *cis-trans* isomers of the type now under discussion, is based upon a comparison of the physical properties of the substances.[103] It has been found that, with those pairs of isomers to which the method of ring closure is applicable, the *trans* form usually has the higher melting point, the lower boiling point, the lower solubility in any specified solvent, and the lower heat of combustion. Moreover, the *trans* form is usually the more stable form, in the sense that it is the one present in larger amount in the mixture resulting from thermal or catalyzed equilibrium. (See pages 264 ff., 306 ff.) The properties of every pair of *cis-trans* isomers are not necessarily in agreement with all these rules; *trans*-crotonic acid, XVIII, for example, boils at a higher temperature than does the *cis* form, XVII. Nevertheless, the properties of most such pairs are in agreement with most of the rules; thus, *trans*-crotonic acid has a higher melting point, a lower solubility in water, and a greater stability than the *cis* form. These same rules are commonly assumed to apply also to those pairs of *cis-trans* isomers with which the method of ring closure cannot be used; and the rules are employed in the establishment of the configurations of such substances. Thus, of the two stereoisomeric 2-butenes, with structure XXIII, the one with the higher melting point, the lower boiling point,

$$\mathrm{CH_3{-}CH{=}CH{-}CH_3}$$

XXIII



$$\begin{array}{c}\mathrm{CH_3{-}C{-}H}\\ \|\\ \mathrm{H{-}C{-}CH_3}\end{array}$$

XXIV

the lower heat of combustion, and the greater stability is considered to be the *trans* form, XXIV. This method is obviously restricted to those isomeric pairs with which the terms "*cis*" and "*trans*" have unambiguous significance. Although there can be no uncertainty as to which of the two configurations of the ethylene dicarboxylic acids, XV and XVI, of the crotonic acids, XVII and XVIII, of the trichlorocrotonic acids, XIX

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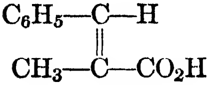
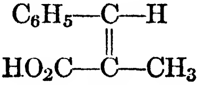
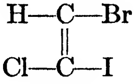
[102] J. J. Sudborough and L. L. Lloyd, *J. Chem. Soc.* 73, 81 (1898).

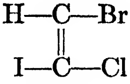
[103] For further discussion of these methods see R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 370 ff., 2nd ed., 1943, Volume I, pages 447 ff.

and XX, or of the cinnamic acids, XXI and XXII, is *cis*, and which is *trans*, there is complete uncertainty in many instances. For example, it is somewhat arbitrary to describe either of the two methylcinnamic acids, XXV and XXVI, as *cis* or *trans;* it would be extremely arbitrary


XXV

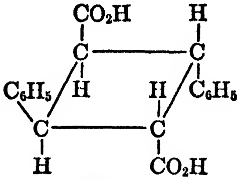

XXVI

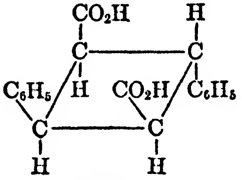

XXVII

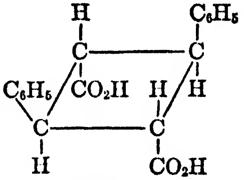

XXVIII

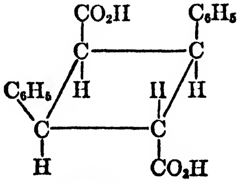
to describe similarly either of the chlorobromoiodoethylenes, XXVII and XXVIII. Consequently, even if one of the isomers in such a case should be found to satisfy all the conditions for a *trans* form, there would still be no unambiguous way of deciding which of the two configurations is *trans*.

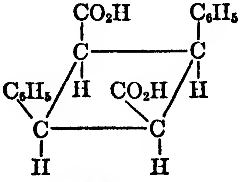
With optically inactive stereoisomers of greater complexity than the foregoing ethylenic *cis-trans* isomers, a variety of methods must sometimes be employed. An example, which brings out several points of interest, is provided by the truxillic acids.[104] There are five of these stereoisomeric acids, with the configurations XXIX–XXXIII. All


XXIX


XXX


XXXI


XXXII


XXXIII

forms are optically inactive, since the isomer XXIX has a center of symmetry, and since each of the four others has at least one plane of symmetry. The five acids are known, for historical reasons, and not necessarily respectively, as α, γ, ϵ, *epi*, and *peri* truxillic acids; the problem of establishing their configurations is of course that of determining which of the diagrams XXIX–XXXIII corresponds to each substance.

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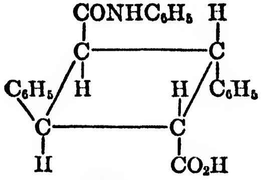
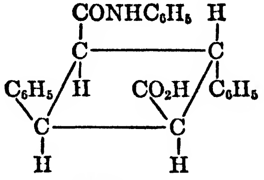
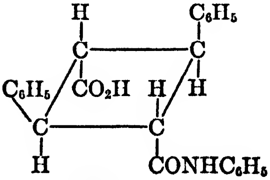
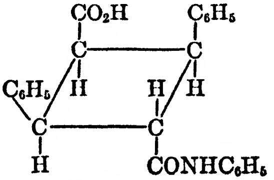
[104] See G. Wittig, *Stereochemie*, Akademische Verlagsgesellschaft, Leipzig, 1930, pages 92 f., and further references given there.

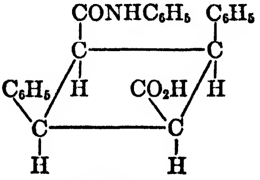
Now, the half-anilides of the α and γ acids have been found to be resolvable. It is easily seen that the acids XXIX and XXX lead, respectively, to the dissymmetric half-anilides XXXIV and XXXV, whereas the remaining three configurations, XXXI–XXXIII, lead instead to the symmetrical half-anilides XXXVI–XXXVIII, with planes of symmetry.


XXXIV

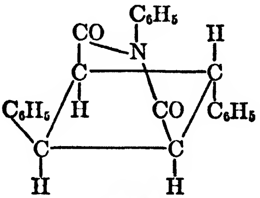

XXXV


XXXVI


XXXVII


XXXVIII

Consequently, α-truxillic acid must be either XXIX or XXX, and γ-truxillic acid must be the other. For the decision whether the α form is XXIX and the γ form is XXX, or vice versa, use is made of the fact that the γ form gives a phenylimide, which can possess only the configuration XXXIX. The γ form is accordingly XXX, whereas the α form is XXIX. Of the remaining ϵ, *peri*, and *epi* forms, the first gives a phenylimide, the second gives an anhydride, and the last gives neither. It is evident therefore that, in the ϵ and *peri* forms, the two carboxyl groups must be on the same side of the four-membered ring, whereas, in the *epi* form, they presumably lie on opposite sides. The ϵ and *peri* forms are therefore XXXI and XXXIII (not necessarily respectively), and the *epi* form is XXXII. Since *peri*-truxillic acid is transformed, when strongly heated, into the ϵ isomer, the latter is the more stable form and


XXXIX

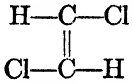
presumably therefore the "more *trans*." Consequently, the *peri* form is considered to be XXXIII, and the ε form is considered to be XXXI. In this way, configurations are assigned to all five inactive stereoisomers.

In recent years, there have been devised several still further methods which permit the most nearly conclusive assignments of configuration that are now possible. One such method involves the measurement of dipole moments. Of the two 1,2-dichloroethylenes, XL, for example,

$$CHCl{=}CHCl$$

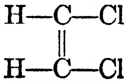
XL

the one with the lower boiling point has zero dipole moment, whereas the other has a fairly large moment.[105] The former isomer must therefore be the *trans* form, XLI, which clearly can have no positive or negative end (see Section 1·6), whereas the latter must be the *cis* form, XLII, which doubtless does have a positive and a negative end (at the left and right, respectively, of the molecule as represented in configuration XLII).



$$\begin{array}{c} H-C-Cl \\ \| \\ Cl-C-H \end{array}$$

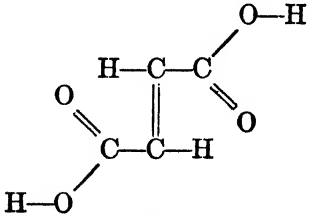
XLI



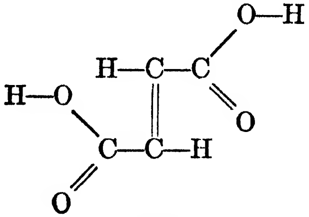
$$\begin{array}{c} H-C-Cl \\ \| \\ H-C-Cl \end{array}$$

XLII

This method, although very convincing in those instances in which it can be employed, is restricted to fairly simple substances. Even with maleic and fumaric acids, XV and XVI, for example, it would be inapplicable because, on account of the freedom of rotation about the carbon-carbon single bonds, the moment of even the *trans* form need not be zero. Thus, although the conformation XLIII corresponds to zero moment, the further one, XLIV, corresponds instead to a finite moment, probably with its positive end at the top of the figure as drawn. Since the magnitude of the measured moment is an average of the magnitudes of those of the various conformations, it cannot be zero.



XLIII



XLIV

In principle, completely unambiguous assignments of configuration can be made by methods based upon the diffraction of electrons by

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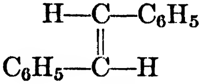
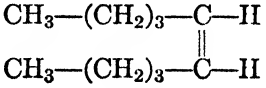
[105] J. Errera, *Physik. Z.* **27**, 764 (1926).

gases[106] or of x-rays by crystals.[107] In the first of these ways, for example, the configurations of the 2-butenes, XXIII,[108] and of the 1,2-dichloroethylenes, XL[109] (derived in the ways mentioned above) have been confirmed. By the x-ray method, moreover, the configuration of *trans*-stilbene, XLV, has likewise been confirmed.[110] (See also pages 319, 348.) In practice, however, these two methods are usually restricted to fairly simple molecules.


$$\begin{array}{c} \mathrm{H{-}C{-}C_6H_5} \\ \| \\ \mathrm{C_6H_5{-}C{-}H} \end{array}$$

XLV

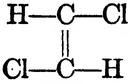
In some instances, the assignments of configurations to olefinic *cis-trans* isomers have been made with the aid of spectroscopic data. Thus, the Raman spectrum of a *cis* olefinic hydrocarbon usually contains a line (attributed to a vibration which is largely a stretching and contracting of the carbon-carbon double bond) at about 1658 cm^{-1}; whereas that of the corresponding *trans* isomer usually contains instead a line at about 1674 cm^{-1}. *cis*-5-Decene, XLVI, and *trans*-5-decene, XLVII, have, for example, been distinguished in this manner.[81] A different spectroscopic procedure is based upon a comparison of infrared and Raman spectra. Thus, with the two 1,2-dichloroethylenes, XLI and XLII, the infrared and Raman spectra of one isomer contain lines with the same frequency, whereas the corresponding spectra of the other


$$\begin{array}{c} \mathrm{CH_3{-}(CH_2)_3{-}C{-}H} \\ \| \\ \mathrm{CH_3{-}(CH_2)_3{-}C{-}H} \end{array}$$

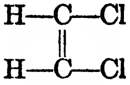
XLVI


$$\begin{array}{c} \mathrm{H{-}C{-}(CH_2)_3{-}CH_3} \\ \| \\ \mathrm{CH_3{-}(CH_2)_3{-}C{-}H} \end{array}$$

XLVII


$$\begin{array}{c} \mathrm{H{-}C{-}Cl} \\ \| \\ \mathrm{Cl{-}C{-}H} \end{array}$$

XLI


$$\begin{array}{c} \mathrm{H{-}C{-}Cl} \\ \| \\ \mathrm{H{-}C{-}Cl} \end{array}$$

XLII

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[106] See, for example, L. O. Brockway, *Rev. Modern Phys.* **8**, 231 (1936); L. O. Brockway in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume I, 1945, Chapter XV.

[107] See, for example, R. W. G. Wyckoff, *The Structure of Crystals*, Chemical Catalog Company, New York, 1931; W. H. Zachariasen, *The Theory of X-Ray Diffraction in Crystals*, John Wiley and Sons, New York, 1945; I. Fankuchen in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume I, 1945, Chapter XIV.

[108] L. O. Brockway and P. C. Cross, *J. Am. Chem. Soc.* **58**, 2407 (1936).

[109] L. O. Brockway, J. Y. Beach, and L. Pauling, *J. Am. Chem. Soc.* **57**, 2693 (1935).

[110] J. M. Robertson and I. Woodward, *Proc. Roy. Soc.* (London) **A162**, 568 (1937).

isomer contain no such coincidences.[111] Since (for theoretical reasons which cannot be explained here) such coincidences are impossible with molecules which have centers of symmetry (see Section 5·8), it follows that the isomer which shows the coincidences must have the *cis* configuration, XLII, whereas the other isomer must have the *trans* configuration, XLI. This assignment of configurations is supported by still further spectroscopic evidence,[111] the nature of which need not here be further discussed; moreover, it is in agreement with the assignments made by the nonspectroscopic methods described above.

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[111] Cf. G. Herzberg, *Infrared and Raman Spectra of Polyatomic Molecules*, D. Van Nostrand Company, New York, 1945, page 330.

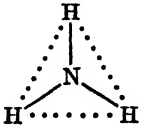
8.

The Configuration and the Stereochemistry of Elements Other Than Carbon

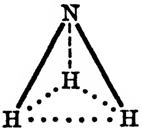
8·1 Introduction. The fundamental principles that are essential to the understanding of the stereochemistry of the elements other than carbon differ in no significant respect from those that are essential to the understanding of the stereochemistry of carbon itself. Since these principles have been described in considerable detail in the preceding chapters, they need not here be discussed further.

8·2 Amines. From the stereochemical point of view, nitrogen is second in importance only to carbon. Of the numerous compounds, of various types, which this element forms, those in which the nitrogen is trivalent are of most interest on account of their great number, and also on account of the relatively large amount of information available concerning them. The compounds of nitrogen in which each nitrogen atom forms three single bonds will be discussed in this section; the further compounds in which each nitrogen atom forms one single bond and one double bond will be discussed in following sections.

Ammonia NH_3 may be considered the simplest amine. In a molecule of this substance, the three hydrogen atoms are thought to be completely equivalent to one another since, with a given substituent atom or group R, no more than one derivative, NH_2R, has ever been encountered. (See the analogous discussion of the equivalence of the four hydrogen atoms in methane, pages 161 ff.) Only two geometrical arrangements of the atoms are therefore possible. These are the *planar* arrangement, I, in which the hydrogen and nitrogen atoms are, respectively, at the corners and at the center of an equilateral triangle; and the *pyramidal* arrangement, II, in which the hydrogen and nitrogen atoms are, respectively, at the corners of the base and at the apex of a triangular pyramid. In diagrams I and II, the dotted, heavy, and broken lines have the same meanings as in the preceding chapters.

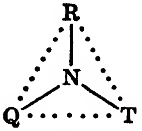


I

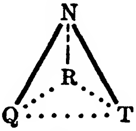


II

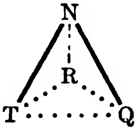
It is natural to suppose that a decision between the planar and pyramidal models of ammonia could be reached from a study of the isomerism and of the properties of suitably substituted derivatives. If the planar model is correct, a substance with the structure NRQT and the configuration III should be optically inactive, whether the atoms or groups R, Q, and T are identical or different, since the plane of the molecule is a plane of symmetry. On the other hand, if the pyramidal model is correct, a substance with this same structure, but with the configuration IV, should be optically active when no two of the atoms or groups R, Q, and T are identical, since the molecule of such a substance would not be superposable on its mirror image, V. Many independent attempts have been made to find an optically active substance of this type (in which, of course, no one of the substituent groups R, Q, or T is itself dissymmetric). In the compounds which have been prepared and tested, the substituents R, Q, and T have been alkyl groups, aryl groups, acyl groups, or single atoms. Moreover, in these experiments, the groups that are joined to the nitrogen atom have been allowed to be independent of one another, or they have been joined together so as to form rings, or combinations of rings, of various types. In spite of these varied and ingenious attempts, however, no example of an optically active compound NRQT has been found, unless at least one of the substituents R, Q, and T is itself dissymmetric.[1] (However, see "Tröger's base," X, below.)



III



IV



V

In view of the foregoing evidence, the nitrogen atom in ammonia appears to be planar, as in the configuration I. Nevertheless, this molecule is now generally considered instead to be pyramidal, as in the configuration II. The nonexistence of stereoisomeric substances with configurations like IV and V is explained as the result of an extremely easy interconversion. Since the planar configuration, III, probably is somewhat less stable than the pyramidal ones, IV and V, most molecules at any one time are doubtless pyramidal; nevertheless, the difference in stability is probably not so great but that an appreciable fraction of the molecules have enough energy at any one time to achieve the planar configuration. The transition between the enantiomorphic forms IV and V is accord-

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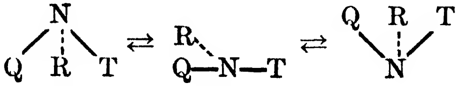
[1] For a survey of these attempts, see R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 328 ff., 2nd ed., 1943, Volume I, pages 402 ff.

ingly interpreted as proceeding through the planar intermediate III, in the manner shown by the equation 8·1. The assumed intermediate III



IV III V

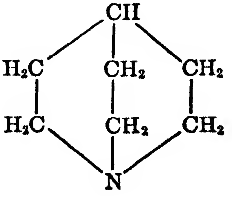
(8·1)

is clearly symmetrical; hence it has equal probabilities of returning to either of the two enantiomorphic forms IV and V. The racemization is therefore rapid and complete. The close analogy between this mechanism for the racemization of amines and the one proposed by Werner (see pages 251 ff.) for the racemization of carbon compounds should be too obvious to require comment. (For ease of visualization, the configurations III and V are represented in equation 8·1 in a form that is different from the one originally employed on page 330. It is readily verified, however, that in each instance the two superficially different representations are actually equivalent.)

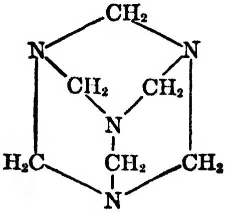
The evidence leading to the above interpretation of the data comes from several sources. In the first place, the belief that the normal states of ammonia and of its derivatives are pyramidal rather than planar is supported by the fact that these substances have dipole moments. The pyramidal configuration of ammonia, II, for example, has a positive and a negative end (presumably at the bottom and top, respectively, of the diagram as drawn), whereas the planar configuration, I, has neither. Consequently, only the former configuration is in agreement with the observed nonvanishing moment of the substance.[2] (Cf. page 10.) The situations with all other substances with the general formula NQRT, for which data are available,[3] are similar and can be interpreted in the same way. Moreover, with trimethylamine, VI, the pyramidal configuration has been confirmed by an electron-diffraction investigation of the gaseous substance.[4] Finally, there exist numerous substances, such as quinuclidine, VII, and hexamethylenetetramine, VIII, in which the nitrogen atoms must be rigidly held, by the respective complex ring systems, in

$(CH_3)_3N$

VI



VII



VIII

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[2] H. E. Watson, *Proc. Roy. Soc.* (London) **A117**, 43 (1927).

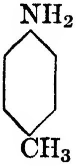
[3] Cf. the table of dipole moments given in an appendix in *Trans. Faraday Soc.* **30** (1934)

[4] L. O. Brockway and H. O. Jenkins, *J. Am. Chem. Soc.* **58**, 2036 (1936).

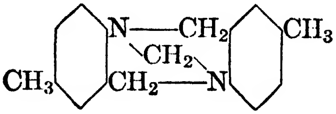
the pyramidal configurations; with hexamethylenetetramine, in fact, the pyramidal configuration has been confirmed by x-ray analyses of the crystal structure of the solid [5] and also by electron-diffraction investigations of the gaseous substance.[6]

The most conclusive evidence regarding the configuration of ammonia itself has been obtained from a spectroscopic study. In this way, it has been shown that the nitrogen atom in this substance is indeed pyramidal.[7] The value of the three equal H—N—H angles in the normal molecule is about 107° (as compared with the value of 120° characteristic of the planar model); the planar configuration is less stable than the pyramidal one by about 6 kcal per mole. Although the extent to which these numerical values are applicable also to *derivatives* of ammonia is not known with certainty in all instances, there is no reason to doubt that these other substances are at least qualitatively analogous to ammonia. In trimethylamine, for example, the C—N—C angle is reported [4] to be 108° ± 4°.

Before the discussion of the stereochemistry of the amines is concluded, mention should be made of the fact that one *di*amine has been obtained in optically active form.[8] The substance in question is the one known as Tröger's base. It is prepared by the action of formaldehyde upon *p*-toluidine, IX, and its structure is believed to be X. In this structure, each of the two nitrogen atoms is held more or less rigidly by the ring system in a pyramidal configuration (cf. quinuclidine, VII, and hexamethylenetetramine, VIII, above); moreover, each nitrogen atom is joined to three different substituents. It is easily verified that the molecule X is dissymmetric, and that racemization by the method outlined above is geometrically impossible. In accordance with expectation, the substance has been resolved (by adsorption on (+)-lactose from chloroform solution). It may nevertheless be observed that the original statement (see above) that no substance with structure NQRT has ever been obtained in optically active form is still correct, since Tröger's base, with



IX



X

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[5] R. W. G. Wyckoff and R. B. Corey, *Z. Krist.* **89**, 462 (1934).

[6] G. C. Hampson and A. J. Stosick, *J. Am. Chem. Soc.* **60**, 1814 (1938); V. Schomaker and P. A. Schaffer, Jr., *ibid.* **69**, 1555 (1947); P. A. Schaffer, Jr., *ibid.* **69**, 1557 (1947).

[7] D. M. Dennison, *Rev. Modern Phys.* **12**, 175 (1940).

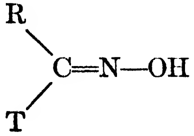
[8] V. Prelog and P. Wieland, *Helv. Chim. Acta* **27**, 1127 (1944).

its *two* equivalent nitrogen atoms, does not have exactly the type of structure specified. To be sure, if one of the nitrogen atoms were replaced by, for example, a CH group, the resulting (actually unknown) substance would then contain only one nitrogen atom, and it should still be optically active (or, at any rate, resolvable); it would not, however, satisfy the stated conditions, since it would contain an asymmetric carbon atom. The question whether its activity is due to the nitrogen atom or to the carbon atom would be meaningless.

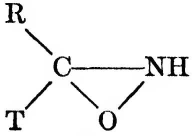
The nitrogen atom in the ammonia molecule (or in any other molecule of similar type) is frequently described as *tetrahedral* rather than as *pyramidal.* This alternative description can be justified in either of two independent ways. In the first place, the word "tetrahedron" is merely another name for a triangular pyramid (cf. the paragraph in fine print on page 164); in the second place, the nitrogen atom under discussion has an unshared pair of electrons which, in at least a formal sense, can be regarded as a substituent occupying the fourth corner of a tetrahedron about the nitrogen atom as center. Nevertheless, the terminology introduced in the preceding paragraphs of this section is employed throughout this book, since, as has already been noted (page 164), it is desirable to distinguish the pyramidal configuration, with the multivalent atom at an apex, from the tetrahedral configuration, with the multivalent atom at the center; and since, moreover, it is desirable also to distinguish a real substituent, such as a hydrogen atom or an alkyl group, from merely a pair of electrons.

8·3 The Isomerism of the Oximes. An aldehyde or ketone with structure RTC=O, when treated with hydroxylamine NH_2OH, gives only a single oxime RTC=NOH if the atoms or groups R and T are identical, but frequently it gives two isomeric oximes if R and T are different.[9] In the past, a number of attempts[10] have been made to explain this isomerism with the assumption that the two isomers derived from any given aldehyde or ketone differ in *structure.* As will be shown below, however, all these attempts have been unsuccessful.

One such attempt was based upon the postulate that the two isomers have the structures I and II. Two arguments can however be advanced



I



II

against this explanation. In the first place, there is no obvious reason why, if this interpretation is correct, the isomerism should be limited to

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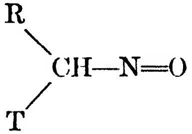
[9] H. Goldschmidt, *Ber.* **16,** 2176 (1883); K. Auwers and V. Meyer, *ibid.* **22,** 705 (1889); E. Beckmann, *ibid.* **22,** 1531 (1889).

[10] Cf. N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen,* Oxford University Press, Oxford, 1937, pages 175 ff.

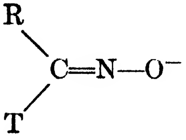
those oximes in which R and T represent different atoms or groups, since the structures I and II are not equivalent to each other even if R and T are identical. In the second place, a substance with the structure II should be capable of optical activity whenever R and T are different, even though neither of these substituents may itself be dissymmetric. However, no examples of such optical activity have ever been encountered.

A second attempted explanation of the isomerism of the oximes is that one form has the structure I, whereas the other is instead a nitroso compound with structure III. This assumption, like the preceding one,

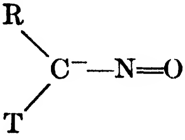


III

fails, however, to account for the necessity that the atoms or groups R and T be different, and it leads to the incorrect prediction that one of the two forms, III, should be optically active when the substituents R and T are different (and neither is a hydrogen atom). Moreover, it is not in agreement with the observed properties of the substances. Compounds in which nitroso groups (—N═O) are joined directly to carbon atoms, as in structure III, have a bluish green color, and they undergo spontaneous transformations into colorless dimeric forms. Neither of the two isomeric oximes of any ordinary aldehyde or ketone, however, shows such behavior; oximes are usually colorless and monomeric, and they do not dimerize. A further difficulty with this suggested interpretation arises from the fact that the oximes are weakly acidic. The anions IV and V, which are derived, respectively, from structures I and

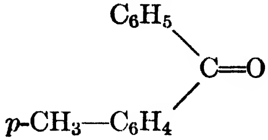


IV



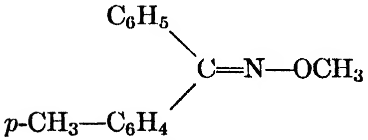
V

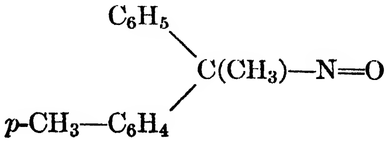
III, differ only in the positions of the electrons, and not in the position of any atom. There are theoretical reasons to believe (see Chapter 10) that distinguishable ions differing in this manner cannot exist; but that, under such circumstances, there is possible only a single ion with an average electronic distribution intermediate between the two extremes. Consequently, if the isomeric oximes have structures I and III, their salts should be identical. The fact that, contrary to this prediction, the isomerism of the oximes is retained in the salts shows therefore that this second interpretation of the isomerism is also unsatisfactory. Moreover, the same conclusion follows in still another way. The O-methyl derivatives of the oximes exhibit an isomerism which appears to be completely analogous to that of the oximes themselves. Since each form of the O-methyl oxime of, for example, phenyl *p*-tolyl ketone, VI, gives on hydrolysis the parent ketone, VI, and O-methylhydroxylamine, VII, the methyl group in each of the original molecules must be linked to an oxygen atom. Consequently, the isomerism of the O-methyl oximes cannot be explained by the assumption that the two substances have structures VIII and IX (analogous to I and III, respectively, for the unsubstituted oxime). In fact, the conclusion seems unavoidable that each form of the O-methyl oxime must have structure VIII, since no other reasonable structure can be drawn for either form. If it is admitted that the two O-methyl oximes therefore have the same structure, it is practically necessary to suppose that the situation is similar with the oximes themselves, and that, therefore, all of these must be describable by the single structure I.


VI

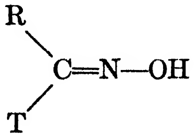
$H_2N—O—CH_3$

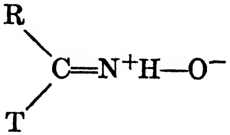
VII


VIII

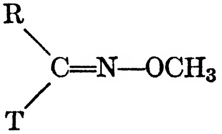

IX

One further unsatisfactory explanation of the isomerism of the oximes deserves brief mention before the now-accepted views are described. The assumption might be made that one of the isomeric forms has the structure I whereas the other has instead structure X. This assumption has almost all the defects of the preceding ones (except that it does not predict optical activity). Thus, it fails to account for the requirement that the two atoms or groups R and T be different whenever isomerism

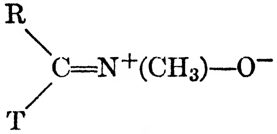

I


X

occurs; it is inconsistent with the existence of isomeric salts; and it cannot explain the existence of two isomeric O-methyl derivatives. Although, for these reasons, the structure X cannot be accepted as correct for either of the two forms of the oxime, there is nevertheless evidence that *tautomerism* occurs between structures I and X. (Cf. Section 14·9.) Thus, when an oxime RTC═NOH is treated with methyl sulfate and sodium hydroxide, a mixture of the O-methyl derivative, XI, and the N-methyl derivative, XII, results. That the methyl group is attached to the nitrogen atom in the latter compound is shown by the fact that hydrolysis leads to the original aldehyde or ketone RTC═O plus N-methylhydroxylamine, XIII. Since each form of the oxime gives its own N-methyl, as well as its own O-methyl, derivative, it follows that altogether four methyl derivatives (two N-methyl and two O-methyl) should be obtainable from any oxime RTC═NOH in which R and T are different. In a few instances, all four forms are known; this is true, for example, with the methyl derivatives derived from phenyl *p*-tolyl ketone,[11] VI, and from phenyl *p*-nitrophenyl ketone,[12] XIV. It should be noted that it is as impossible to obtain a structural interpretation of these isomeric N-methyl oximes as it is to obtain one of the corresponding O-methyl derivatives discussed above. (For further discussion of the topics considered in this paragraph, see Sections 8·6 and 14·9.)



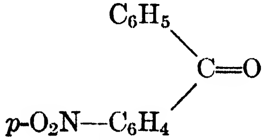
XI



XII

$CH_3\text{—}NH\text{—}OH$

XIII



XIV

Since, on the basis of the above evidence, the isomeric oximes appear to have identical structures, the only reasonable explanation of the isomerism is that the substances in question are *stereo*isomers of one another. This interpretation was first suggested in 1890 by Hantzsch and Werner,[13] who postulated that the two isomers have the configurations XV

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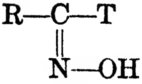
[11] L. Semper and L. Lichtenstadt, *Ber.* **51**, 928 (1918).

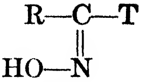
[12] O. L. Brady and R. P. Mehta, *J. Chem. Soc.* **125**, 2297 (1924); L. E. Sutton and T. W. J. Taylor, *ibid.* **1931**, 2190.

[13] A. Hantzsch and A. Werner, *Ber.* **23**, 11 (1890); A. Hantzsch, *ibid.* **24**, 13 (1891).



$$\begin{array}{l} R-\underset{\|}{C}-T \\ \;\;\; N-OH \end{array}$$

XV

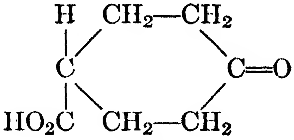


$$\begin{array}{r} R-\underset{\|}{C}-T \\ HO-N\;\;\; \end{array}$$

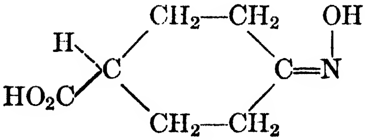
XVI

and XVI. The situation envisaged by these authors, and now generally accepted by all chemists, is therefore analogous to the one discussed previously in connection with the ethylenic stereoisomers like maleic and fumaric acids. The only significant difference between the two classes of compound is that the nitrogen atom of an oxime is trivalent and so forms only one single bond in addition to the double bond, whereas the corresponding carbon atom of an ethylenic compound is quadrivalent and so forms two such single bonds. Frequently, however, the statement is made that the unshared pair of electrons on the nitrogen atom in an oxime can be regarded as equivalent to a fourth valence bond or to an additional substituent. (Cf. the paragraph in fine print at the end of Section 8·2.)

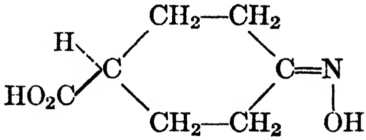
The most conclusive evidence that can be brought forward in support of Hantzsch and Werner's stereochemical interpretation of the isomerism of the oximes is derived from a study of the oximes of certain cyclic ketones. Cyclohexanone-4-carboxylic acid, XVII, for example,



XVII



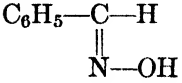
XVIII



XIX

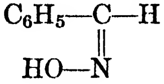
has been found to form two oximes, which are enantiomorphs of each other, and which can accordingly be represented only as XVIII and XIX. (Cf. Section 6·11.) There is in fact no reasonable alternative way of explaining the optical activities of these substances; at any rate, no one of the varieties of structural isomerism considered above is consistent with the observed activities. It appears necessary, therefore, to consider that the isomerism of the enantiomorphic oximes of cyclohexanone-4-carboxylic acid, XVII, is due to a steric difference of exactly the sort postulated by Hantzsch and Werner. It would accordingly be most extraordinary if the isomerism of the remaining oximes as well were not due to a similar cause.

8·4 Methods for Determining the Configurations of the Oximes. In the naming of the stereoisomeric oximes, the prefixes *cis* and *trans*, employed with the ethylenic compounds, are usually replaced by *syn* (Greek σύν, with) and *anti* (Greek ἀντί, against), respectively. Thus, the configuration I is that of *syn*-benzaldoxime, whereas the con-



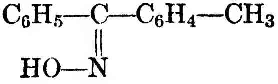
$$\begin{array}{l} C_6H_5\text{—}C\text{—}H \\ \quad\;\; \| \\ \quad\;\; N\text{—}OH \end{array}$$

I



$$\begin{array}{r} C_6H_5\text{—}C\text{—}H \\ \| \quad\;\; \\ HO\text{—}N \quad\;\; \end{array}$$

II



$$\begin{array}{l} C_6H_5\text{—}C\text{—}C_6H_4\text{—}CH_3 \\ \qquad\quad \| \\ HO\text{—}N \end{array}$$

III

figuration II is that of *anti*-benzaldoxime. It is to be observed that a *syn*-aldoxime is one in which the aldehydic hydrogen atom is on the same side of the double bond as the hydroxyl group (i.e., is *syn* with respect to it), and that an *anti*-aldoxime is one in which the hydrogen atom is on the opposite side of the double bond from the hydroxyl group (i.e., is *anti* with respect to it). The nomenclature of the ketoximes can be illustrated by a single example; the oxime with the configuration III may be called either *syn*-phenyltolylketoxime or *anti*-tolylphenylketoxime.

The methods by which the configurations of the isomeric oximes are established depend upon the natures of the oximes. With *aldoximes*, the reactions by which the substances are dehydrated to nitriles (equation 8·2) are most commonly employed. With a reagent like phosphorus

$$RCH\text{=}NOH \rightarrow RCN + H_2O \qquad (8\cdot2)$$

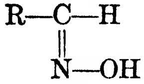
trichloride, phosphorus pentachloride, or warm acetic anhydride, both isomeric forms usually undergo this reaction with ease. Under more mild conditions, however, the two forms may behave differently; this fact can then be used in the determination of configuration.[13] The usual procedure involves, first, the treatment of the oxime with *cold* acetic anhydride, and then the treatment of the resulting acetyl derivative with sodium carbonate. One of the two isomeric oximes derived from a given aldehyde ordinarily follows the sequence of reactions 8·3, whereas

$$RCH\text{=}NOH \xrightarrow{(CH_3\text{—}CO)_2O} RCH\text{=}NO\text{—}CO\text{—}CH_3 \xrightarrow{Na_2CO_3} RCN \qquad (8\cdot3)$$

the second ordinarily follows the different sequence 8·4. The first oxime

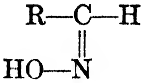
$$\begin{aligned} RCH\text{=}NOH &\xrightarrow{(CH_3\text{—}CO)_2O} RCH\text{=}NO\text{—}CO\text{—}CH_3 \\ &\qquad\qquad\qquad \xrightarrow{Na_2CO_3} RCH\text{=}NOH \qquad (8\cdot4) \end{aligned}$$

is accordingly dehydrated to the nitrile in the process, whereas the other is regenerated unchanged. Originally, it was believed[13] that the oxime which gives the nitrile in this way has the *syn* configuration, IV, in which



$$\begin{array}{l} \mathrm{R{-}C{-}H} \\ \quad \| \\ \quad \mathrm{N{-}OH} \end{array}$$

IV

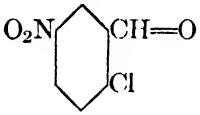


$$\begin{array}{r} \mathrm{R{-}C{-}H} \\ \| \quad \\ \mathrm{HO{-}N} \quad \end{array}$$

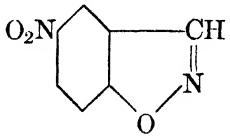
V

the hydrogen atom and hydroxyl group that are lost in the process are as close to one another as possible; and, conversely, that the oxime which is regenerated unchanged has the *anti* configuration, V. Evidently, therefore, if this belief is correct, the configurations of the oximes can easily be determined, since it need only be observed which of the two isomers follows each of the above sequences of reactions.

At the present time, it is considered that the *anti*, and not the *syn*, aldoxime is the one which is dehydrated the more easily, and that, accordingly, all configurations assigned in the manner just outlined are the exact opposites of the correct ones. The evidence supporting this belief is of the following nature.[14] From 2-chloro-5-nitrobenzaldehyde, VI, for



VI



VII

example, the usual pair of isomeric oximes can be obtained. Of these two substances, one reacts readily with sodium hydroxide to lose a hydrogen and a chlorine atom, and to give a product which can possess only the structure and configuration VII. The second oxime, on the other hand, reacts much more sluggishly with sodium hydroxide; apparently, it slowly undergoes a rearrangement into the first isomeric form, which then reacts readily as before. The product is of course again the same substance VII. Now, since the nitrogen atom of the oxime group is not involved in the reaction with the sodium hydroxide, there is no reason to suppose that its configuration is altered in the process. Consequently, the oxime which reacts the more readily must be presumed to have the *anti* configuration, VIII; whereas the second oxime, which reacts sluggishly, must be presumed to have the *syn* configuration, IX. Thus, the configurations can be assigned to the two forms, by an apparently unambiguous method, without reference to the transformation of either into a nitrile. Now, when these oximes are subjected to the above treatment with first acetic anhydride and then sodium carbonate, the *anti* compound, VIII, is found to be the one which is dehydrated, and the *syn* compound, IX, is found to be the one which is regenerated unchanged. All the reactions involved are shown in the equations 8·5. If

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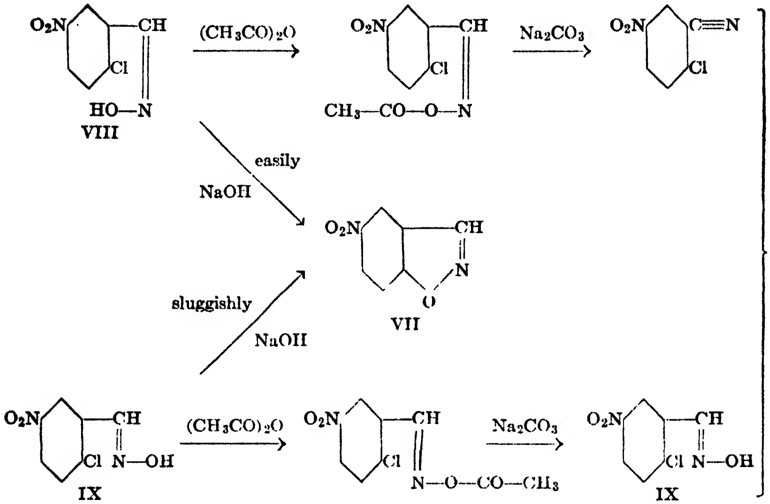
[14] O. L. Brady and G. Bishop, *J. Chem. Soc.* **127**, 1357 (1925).



(8·5)

all remaining pairs of isomeric aldoximes can be considered to behave in this same manner, then the original method employed for the determination of configuration can still be used; the conclusions reached must be, however, the exact opposites of those reached by the earlier investigators.

The configurations of the *ketoximes* cannot be determined by the same method that was described above for the aldoximes, since the former compounds cannot be transformed into nitriles by dehydration. The method originally introduced by Hantzsch[13] (and the one still most generally used) makes use instead of the so-called *Beckmann rearrangement.*[15] When a ketoxime is treated with any one of a variety of reagents (of which only phosphorus pentachloride, acetyl chloride, and sulfuric acid need be mentioned here), it is converted into a substituted amide, as in equation 8·6. If the two radicals attached to the carbon

$$\mathrm{R_2C{=}NOH} \rightarrow \mathrm{R{-}CO{-}NHR} \tag{8·6}$$

atom of the C=NOH group are different, there is a possibility that the reaction might follow either one of the two independent courses shown in equations 8·7 and 8·8, and hence that it might lead to two structurally

$$\mathrm{RTC{=}NOH} \rightarrow \mathrm{R{-}CO{-}NHT} \tag{8·7}$$

$$\mathrm{RTC{=}NOH} \rightarrow \mathrm{T{-}CO{-}NHR} \tag{8·8}$$

isomeric amides. In general, under these circumstances, one of the two stereoisomeric oximes is found to react predominantly in accordance

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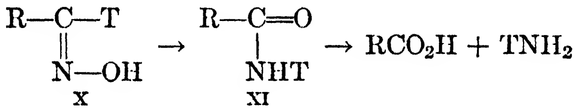
[15] E. Beckmann, *Ber.* **19**, 988 (1886); **20**, 1507, 2580 (1887); **22**, 514 (1889).

with one of these equations, whereas the other oxime reacts predominantly in accordance with the other equation.

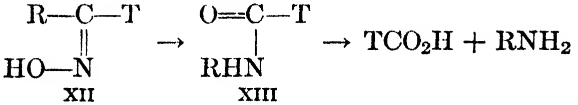
Without attempting to describe the actual mechanism of the reaction (see, however, Chapter 12), one can imagine that the Beckmann rearrangement proceeds in the following steps. First, the hydroxyl group and one of the radicals that are joined to the carbon atom of the C=N—OH group exchange places; and second, the thus resulting *lactim* form of the amide goes over spontaneously into the stable *lactam* form. (Cf. Section 14·9.) The postulated steps are shown in equation 8·9.

$$R_2C{=}NOH \rightarrow R{-}C(OH){=}NR \rightarrow R{-}CO{-}NHR \qquad (8{\cdot}9)$$

Originally, it was assumed[13] that the group which migrates from a carbon to a nitrogen atom is the one which, in the oxime, is *syn* with respect to the hydroxyl group; indeed, it was considered obvious that the groups which exchange places must thus be close to one another in space. If this assumption is correct, the configurations of the two isomeric ketoximes can easily be established in the manner illustrated by equations 8·10 and 8·11. For, as soon as the acid and the amine that are



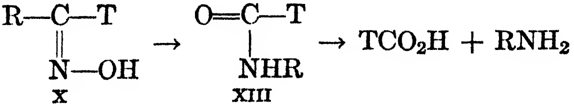
$$\underset{\text{X}}{\begin{array}{l}R{-}C{-}T\\ \quad\ \|\\ \quad\ N{-}OH\end{array}} \rightarrow \underset{\text{XI}}{\begin{array}{l}R{-}C{=}O\\ \quad\ |\\ \quad\ NHT\end{array}} \rightarrow RCO_2H + TNH_2 \qquad (8{\cdot}10)$$



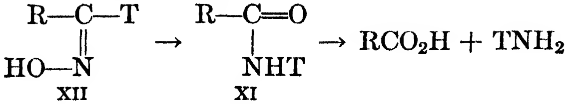
$$\underset{\text{XII}}{\begin{array}{r}R{-}C{-}T\\ \|\quad\ \\ HO{-}N\quad\ \end{array}} \rightarrow \underset{\text{XIII}}{\begin{array}{r}O{=}C{-}T\\ |\quad\ \\ RHN\quad\ \end{array}} \rightarrow TCO_2H + RNH_2 \qquad (8{\cdot}11)$$

obtained by hydrolysis of the amide have been identified, both the structure of the amide and the configuration of the original oxime are uniquely determined.

At the present time, however, it is believed that, in the Beckmann rearrangement, the two groups which exchange places are not *syn*, but *anti*, with respect to each other; and, accordingly, that the original assignments of configuration to the ketoximes are exactly reversed. That is to say, it is now believed that the equations 8·10 and 8·11 are incorrect, and that the rearrangements should instead be written as in equations 8·12 and 8·13. Consequently, the oxime which leads ulti-



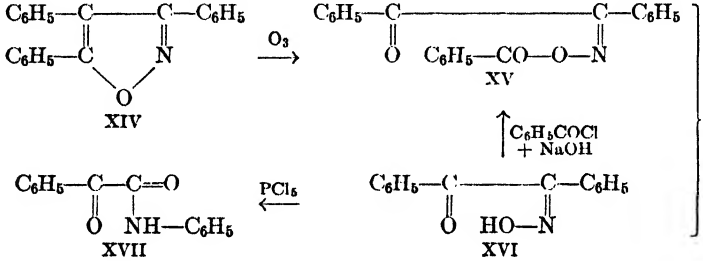
$$\underset{\text{X}}{\begin{array}{l}R{-}C{-}T\\ \quad\ \|\\ \quad\ N{-}OH\end{array}} \rightarrow \underset{\text{XIII}}{\begin{array}{r}O{=}C{-}T\\ |\quad\ \\ NHR\quad\ \end{array}} \rightarrow TCO_2H + RNH_2 \qquad (8{\cdot}12)$$



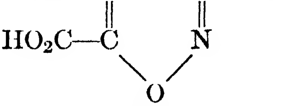
$$\underset{\text{XII}}{\begin{matrix}\text{R—C—T}\\ \|\\ \text{HO—N}\end{matrix}} \rightarrow \underset{\text{XI}}{\begin{matrix}\text{R—C=O}\\ |\\ \text{NHT}\end{matrix}} \rightarrow \text{RCO}_2\text{H} + \text{TNH}_2 \qquad (8\cdot 13)$$

mately to the acid RCO_2H and the amine TNH_2 is the one with the configuration XII and not, as was originally believed, the one with the configuration X.

The first experimental evidence suggesting that the earlier assumption of an interchange of *syn* groups was incorrect was obtained in 1921 by Meisenheimer[16] in an investigation of the ozonization of triphenylisoxazole, XIV. (Equation 8·14.) The product of this reaction is the benzoyl derivative of benzil β-monoxime; its preparation from the cyclic compound XIV shows that its configuration must be XV. The benzil β-monoxime, of which the compound XV is a derivative, and which must therefore have the configuration XVI, is transformed by the action of phosphorus pentachloride into the anilide, XVII, of phenylglyoxylic acid. The groups that exchange places in this rearrangement are accordingly *anti* with respect to each other. A similar conclusion was reached a few years later by Kohler,[17] who found that the ozonization of 3,4-diphenylisoxazole-5-carboxylic acid, XVIII, gives benzil β-monoxime, so that once more this latter substance is found to have the configuration XVI.



(8·14)



XVIII

Additional evidence[18] supporting the belief that, in a Beckmann rearrangement, the hydroxyl group of the oxime interchanges positions

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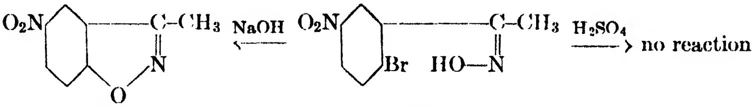
[16] J. Meisenheimer, *Ber.* **54**, 3206 (1921).

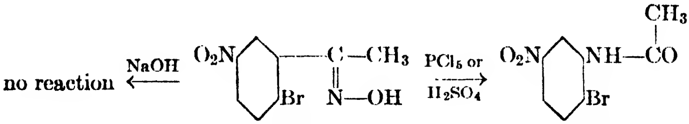
[17] E. P. Kohler, *J. Am. Chem. Soc.* **46**, 1733 (1924).

[18] J. Meisenheimer, P. Zimmermann, and U. v. Kummer, *Ann.* **446**, 205 (1925).

with the radical *anti* to it can be derived from the reactions indicated by the equations 8·15 and 8·16. As with the closely similar aldoximes con-



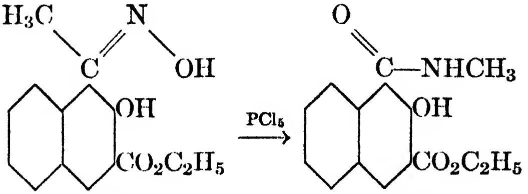
XXI XIX (8·15)



XX XXII (8·16)

sidered above, the configurations of the ketoximes, XIX and XX, are established by the fact that the former substance reacts with sodium hydroxide to give the cyclic product, XXI, whereas the latter does not. Although one of the oximes, XIX, does not undergo the Beckmann rearrangement, the other one, XX, gives the amide XXII by the exchange of *anti* groups.

Still further evidence supporting the *anti* shift in the Beckmann rearrangement makes use of a principle not heretofore employed. Of the two stereoisomeric oximes XXIII and XXIV, one is the ester of an acid which has been found to be resolvable[19] (although its optically active forms are racemized with extreme ease). The only reasonable explanation of the resolvability of this acid is that, in its molecule, there is a restriction of rotation about the single bond which joins the $—C(CH_3)=NOH$ group to the naphthalene ring. (See Section 6·13.) Now, of the two configurations XXIII and XXIV, the former is clearly the one with the greater hindrance to rotation about the bond in question; consequently, this configuration must correspond to that of the resolvable acid, whereas the remaining configuration, XXIV, must correspond to that of the remaining, nonresolvable acid. Since the products of the Beckmann rearrangements (equations 8·17 and 8·18) of the two stereo-



XXIII XXV (8·17)

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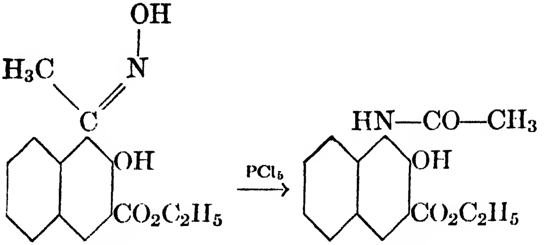
[19] J. Meisenheimer, W. Theilacker, and O. Beisswenger, *Ann.* **495**, 249 (1932).

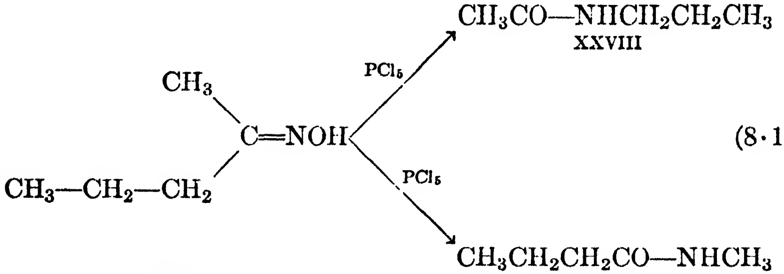


XXIV XXVI

(8·18)

isomeric esters are respectively, the two amides XXV and XXVI, the exchange of radicals is again seen in each instance to be *anti.*

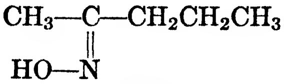
Frequently, it is not possible to isolate the expected isomeric oximes, even though the atoms or groups attached to the carbon atom of the C═NOH group are different. Under such circumstances, one form may be too unstable to exist; more probably, the two forms may be so easily interconvertible that they cannot be separated. Only a single form of methyl-*n*-propylketoxime, XXVII, for example, is known. When this compound is subjected to the Beckmann rearrangement (equation 8·19),



XXVII XXVIII XXIX

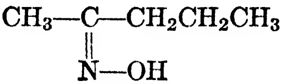
(8·19)

it gives a mixture of the two possible amides, XXVIII and XXIX; it is, therefore, possibly a mixture of the respective stereoisomers, XXX and XXXI.



$$\underset{\displaystyle \mathrm{HO{-}N}}{\mathrm{CH_3{-}\overset{}{C}{-}CH_2CH_2CH_3}}$$

XXX



$$\underset{\displaystyle \mathrm{N{-}OH}}{\mathrm{CH_3{-}C{-}CH_2CH_2CH_3}}$$

XXXI

8·5 Interconversion of Stereoisomeric Oximes. The interconversion of stereoisomeric oximes can be brought about in several different ways.[20] With some substances, the isomerization occurs spon-

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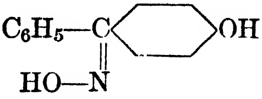
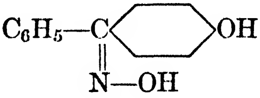
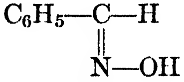
[20] See, for example, G. Wittig, *Stereochemie,* Akademische Verlagsgesellschaft, Leipzig. 1930, pages 195 ff.; J. Meisenheimer and W. Theilacker in K. Freudenberg, *Stereochemie* Franz Deuticke, Leipzig and Vienna, 1933, pages 984 ff., 1030 ff.

taneously; thus, the above-mentioned methyl-*n*-propylketoximes (structures XXX and XXXI of Section 8·4) probably undergo such a reaction. With other substances, however, the transformation occurs only at a high temperature; *syn*-phenyl-*p*-hydroxyphenylketoxime, I, for example, is converted at its melting point of 81°C into its more stable isomer, II. Even when both isomers can be isolated, a partial interconversion frequently occurs during the Beckmann rearrangement, so that the product contains not only the expected amide but also a small amount of the structurally isomeric amide derived from the stereoisomeric oxime; the less stable oxime is especially likely in this way to give the amide related to the more stable form.


I

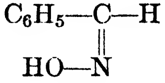

II

A number of reagents have been found to catalyze the transformation of the less stable into the more stable form;[20] these include such substances as hydrogen chloride, lithium chloride, tetramethylammonium chloride, bromine, and charcoal with adsorbed oxygen. For example, *syn*-phenyl-*p*-hydroxyphenylketoxime, I, is changed into its isomer, II, even at room temperature in the presence of hydrogen chloride. Ultraviolet light also often produces an interconversion of the isomeric oximes; this reaction occurs, for example, with the benzaldoximes, with which the *syn* and *anti* forms have, respectively, the configurations III and IV.[20,21] (Cf. Section 7·7.)



$$\begin{array}{l} C_6H_5\text{—}C\text{—}H \\ \qquad\quad \| \\ \qquad\quad N\text{—}OH \end{array}$$

III



$$\begin{array}{r} C_6H_5\text{—}C\text{—}H \\ \| \quad\;\; \\ HO\text{—}N \quad\;\; \end{array}$$

IV

8·6 Analogs of the Oximes. In several other types of compound besides the oximes, a nitrogen atom takes part in a double bond. With such other compounds, as with the oximes themselves, stereoisomerism is frequently encountered.

As has already been mentioned (see pages 335 f.), alkyl derivatives of the oximes may exist in stereoisomeric, as well as in structurally isomeric, forms. The two O-methyl derivatives of, for example, the phenyl-*p*-nitrophenylketoximes, I and II, can be represented by the configura-

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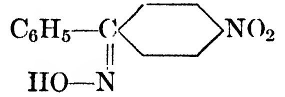
[21] O. L. Brady and G. P. McHugh, *J. Chem. Soc.* **125**, 547 (1924).

tions III and IV, respectively, whereas the two N-methyl derivatives of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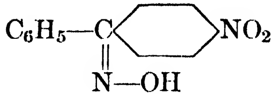
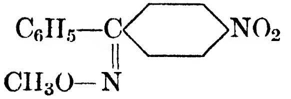
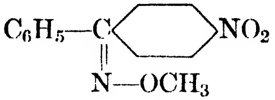
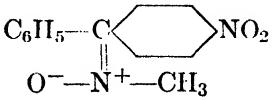
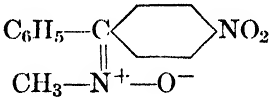

II


III


IV


V


VI

the same oximes can be represented by the configurations V and VI, respectively.[12] The assignment of these last two configurations to the appropriate stereoisomeric substances has been made by means of a measurement of dipole moments.[22] With the isomer V, since the most negative centers (i.e., the oxygen atoms) are approximately at opposite ends of the molecule, the dipole moment should be relatively small; with the isomer VI, on the other hand, since the most negative centers are approximately on the same side of the molecule, the dipole moment should be relatively large. Experimentally, the moment of one isomer is found to be about six times as great as that of the other (6.6 D and 1.09 D, respectively); the former substance must therefore be represented as VI, and the latter as V. It is of interest that methylation of the oxime I (with methyl sulfate and sodium hydroxide) gives the O-methyl derivative, III, and the N-methyl derivative, V. In the formation of the first of these two products, the configuration about the nitrogen atom could hardly have been altered, since the nitrogen atom is not directly attacked; in the formation of the second, however, the observed retention of the original configuration about the nitrogen atom could hardly have been foreseen. In a similar way, methylation of the oxime II gives both the O-methyl derivative, IV, and the N-methyl derivative, VI, with no change of configuration in either reaction.

Further close analogs of the oximes, which also have been obtained in stereoisomeric forms,[23] include the substances with the structures VII–

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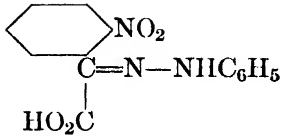
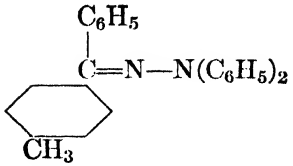
[22] L. E. Sutton and T. W. J. Taylor, *J. Chem. Soc.* **1931,** 2190.

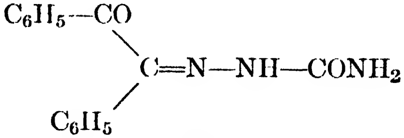
[23] See also R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry,* John Wiley and Sons, New York, 1st ed., 1938, Volume 1, pages 391 f., 2nd ed., 1943, Volume I, page 473; J. Meisenheimer and W. Theilacker in K. Freudenberg, *Stereochemie,* Franz Deuticke, Leipzig and Vienna, 1933, pages 1090 ff.



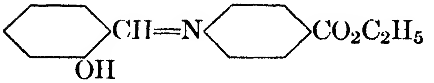
VII



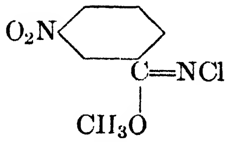
VIII



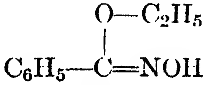
IX [24]



X



XI



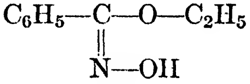
$$\begin{array}{l} \qquad\; O-C_2H_5 \\ \qquad\;\; | \\ C_6H_5-C{=}NOH \end{array}$$

XII

XII. Up to the present time, however, the stereoisomerism of the compounds of these several types has received comparatively little attention. In fact, only with ethylbenzhydroximic acid, XII, and its analogs, is any information available in regard to the configurations of the isomers. Thus, when one of the two compounds corresponding to structure XII is treated with phosphorus pentachloride, it is transformed into N-phenylurethan, XIII; since this reaction appears to be

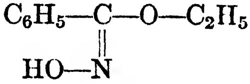
$C_6H_5-NH-CO-OC_2H_5$

XIII



$$\begin{array}{l} C_6H_5-C-O-C_2H_5 \\ \qquad\;\; \| \\ \qquad\;\; N-OH \end{array}$$

XIV



$$\begin{array}{l} C_6H_5-C-O-C_2H_5 \\ \qquad\;\; \| \\ \quad HO-N \end{array}$$

XV

merely a special type of Beckmann rearrangement (Section 8·4), the isomer in question can be presumed to have the configuration XIV. The second isomer, on the other hand, undergoes no comparable reaction, but is instead converted (without rearrangement) into a derivative of phosphoric acid; this isomer must, therefore, have the remaining configuration, XV.

Nitrogen-nitrogen, as well as nitrogen-carbon, double bonds have been found to permit stereoisomerism. The most clearly established

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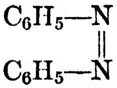
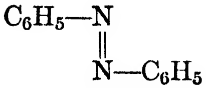
[24] I. V. Hopper, *J. Chem. Soc.* **127**, 1282 (1925).

example of this additional type of stereoisomerism is given by azobenzene, which exists in both *syn* and *anti* forms, XVI and XVII, respectively.[25]



$$\begin{array}{r}C_6H_5\text{—}N\\ \| \\ C_6H_5\text{—}N\end{array}$$

XVI

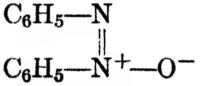


$$\begin{array}{rl}C_6H_5\text{—}N & \\ \| & \\ N & \text{—}C_6H_5\end{array}$$

XVII

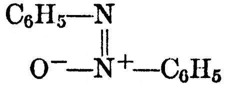
Of these two substances, the *anti* form, XVII, is the more stable, but the *syn* form, XVI, can be made from it by the action of light. From a study of the temperature-dependence of the rate of the thermal interconversion of the *syn* into the *anti* form, the conclusion has been reached that only those molecules which have an energy at least 23 kcal per mole higher than the average are able to make the transition. (Cf. Section 6·6.) The configurations of the two azobenzenes have been definitely established in two different ways. In the first place, the crystal structure of each form has been completely analyzed.[26] In the second place, the *syn* form, XVI, must have a fairly large dipole moment, since it has a positive and a negative end (at the left and right, respectively, of diagram XVI); on the other hand, the *anti* form, XVII, must instead have zero dipole moment since it can have neither a positive nor a negative end. In agreement with expectation, the isomer which has been shown by the study of its crystal structure to be *syn* has a dipole moment of 3.0 D, whereas the one which has been shown in the same way to be *anti* has a vanishingly small dipole moment.[25]

The azoxybenzenes, like the azobenzenes, exist as separable *syn* and *anti* forms. Azoxybenzene itself, for example, has been obtained in the two forms XVIII and XIX. The assignments of configuration to stereoisomers of this type have been based upon the dipole moments of the substances.[27] The *anti* forms, like XIX, have in general smaller moments than do their respective *syn* isomers.



$$\begin{array}{rl}C_6H_5\text{—}N & \\ \| & \\ C_6H_5\text{—}N^+ & \text{—}O^-\end{array}$$

XVIII



$$\begin{array}{rl} & N\text{—}C_6H_5\\ & \| \\ O^-\text{—} & N^+\text{—}C_6H_5\end{array}$$

XIX

The sodium diazotate derived from a given aromatic primary amine can exist in two different forms, both of which can in a few instances[28]

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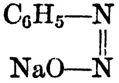
[25] G. S. Hartley, *Nature* **140**, 281 (1937); *J. Chem. Soc.* **1938**, 633.

[26] G. C. Hampson and J. M. Robertson, *J. Chem. Soc.* **1941**, 409, J. J. de Lange, J. M. Robertson, and I. Woodward, *Proc. Roy. Soc.* (London) **A171**, 398 (1939).

[27] E. Müller and W. Kreutzmann, *Ann.* **495**, 132 (1932); K.-A. Gehrkens and E. Müller, *ibid.* **500**, 296 (1933).

[28] Cf. N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, 1937, pages 413 ff.

be isolated. The two forms are known as the *labile* and *stable* forms, or frequently instead as the *normal* and *iso* forms, respectively. Hantzsch proposed[29] that these substances are stereoisomers differing in their configurations about a nitrogen-nitrogen double bond. For the simplest member of the series, sodium benzene diazotate, for example, he accordingly wrote the configurations XX and XXI. He assumed further



$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ NaO\text{—} & N & \end{array}$$

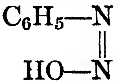
XX

$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ & N & \text{—}ONa \end{array}$$

XXI

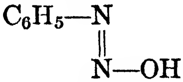
that the labile (or normal) diazotate possesses the *syn* configuration, XX, whereas the stable (or iso) diazotate possesses the *anti* configuration, XXI. In spite of the considerable amount of work which has been done in the study of the problem, however, the nature of the isomerism between these diazotates is still not completely understood. It is in fact conceivable that the isomerism in question is structural rather than steric. Although the majority of organic chemists have accepted Hantzsch's views as probably correct, a number of others[30] have defended alternative views. Even if the isomerism is of the *syn-anti* type assumed by Hantzsch, there is still a possibility that the assignment of the *syn* and *anti* configurations to the labile and stable diazotates, respectively, is reversed; there is, in fact, no completely conclusive experimental evidence either in favor of or opposed to this assignment. (However, see the following paragraph.)

Similar situations have been encountered with several further pairs of substances that are closely related to the above diazotates. For example, Hantzsch wrote the configurations XXII and XXIII for the



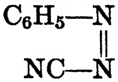
$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ HO\text{—} & N & \end{array}$$

XXII



$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ & N & \text{—}OH \end{array}$$

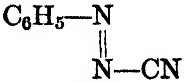
XXIII



$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ NC\text{—} & N & \end{array}$$

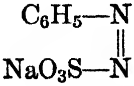
XXIV

benzene diazohydrates (analogous to XX and XXI, respectively, for their salts, the diazotates), XXIV and XXV for the benzene diazo-



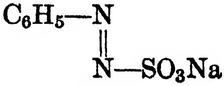
$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ & N & \text{—}CN \end{array}$$

XXV



$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ NaO_3S\text{—} & N & \end{array}$$

XXVI



$$\begin{array}{rcl} C_6H_5\text{—} & N & \\ & \| & \\ & N & \text{—}SO_3Na \end{array}$$

XXVII

cyanides,[31] and XXVI and XXVII for the sodium benzene diazo-

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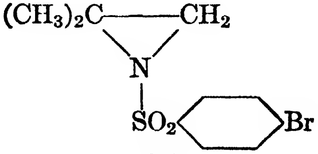
[29] A. Hantzsch, *Ber.* **27**, 1702 (1894).

[30] See, for example, A. Angeli, *Ber.* **62**, 1924 (1929); H. H. Hodgson and E. Marsden, *J. Chem. Soc.* **1945**, 207.

[31] A. Hantzsch and O. W. Schultze, *Ber.* **28**, 2073 (1895).

sulfonates.[32] As before, he considered that the labile and stable forms of each of these further types of compound have, respectively, the *syn* and *anti* configurations. Although again some authors [30,33] have maintained that the two members of each such pair of substances are *structural* isomers of one another, most organic chemists have accepted Hantzsch's stereochemical interpretation. In fact, with the diazocyanides, spectroscopic [34] and dipole-moment [35] studies have almost conclusively shown not only that the isomerism is steric, but also that Hantzsch's assignment of the *syn* and *anti* configurations is correct. Moreover, studies of the magnetic optical rotatory powers [36] (Faraday effect, see page 138) and of the diamagnetic susceptibilities [36] of several diazocyanides have likewise strongly suggested that the isomerism is steric. Although there is no equally satisfactory evidence in regard to the remaining substances considered in this and the preceding paragraphs, the close resemblance of these compounds to the diazocyanides provides strong evidence for Hantzsch's explanation of their isomerism.

In the oximes and their various analogs discussed above, the trivalent nitrogen atoms are found to have sufficient configurational stability to permit the isolation of stereoisomeric forms. These substances are therefore sharply distinguished from the amines, in which the likewise trivalent nitrogen atoms are ordinarily unable to maintain their normal pyramidal configurations. No satisfactory theoretical explanation of this difference has ever been given. If a carbon-nitrogen or nitrogen-nitrogen double bond be considered to constitute a two-membered ring, the strain in this ring (cf. Chapter 9) may be responsible for the stability of the configuration about the nitrogen atom, or atoms. Attempts have accordingly been made to prepare an optically active ethylenimine, such as the one with structure XXVIII,[37] in which the three-membered ring



XXVIII

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[32] A. Hantzsch, *Ber.* **27**, 1726 (1894).

[33] For example, see H. H. Hodgson and E. Marsden, *J. Chem. Soc.* **1943**, 470; **1944**, 395.

[34] D. Anderson, R. J. W. Le Fèvre, and J. Savage, *J. Chem. Soc.* **1947**, 445; N. Sheppard and G. B. B. M. Sutherland, *ibid.* **1947**, 453. Cf. also N. Campbell, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **44**, 134 (1947).

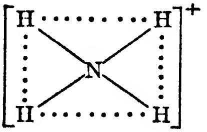
[35] R. J. W. Le Fèvre and H. Vine, *J. Chem. Soc.* **1938**, 431; see also D. Anderson, R. J. W. Le Fèvre, and J. Savage, Reference 34.

[36] D. Anderson, M. E. Bedwell, and R. J. W. Le Fèvre, *J. Chem. Soc.* **1947**, 457.

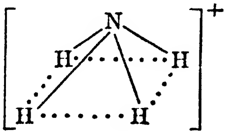
[37] R. Adams and T. L. Cairns, *J. Am. Chem. Soc.* **61**, 2464 (1939); for a list of further unsuccessful attempts, see R. L. Schriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 2nd ed., 1943, Volume I, pages 412 f.

also is highly strained. All such attempts, however, have failed; the substances obtained have always been optically inactive, and they were not successfully resolved by any of the methods used.

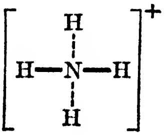
8·7 Ammonium Ions and Their Analogs. The methods used for the determination of the configuration of methane (see Section 6·1) can be applied without essential change to the determination of the configuration of the ammonium ion. From the fact that isomeric ions of structure $[NR_3T]^+$, where R and T are any two specified atoms or groups, have never been encountered, the conclusion can be drawn that all four hydrogen atoms of the ammonium ion are equivalent. The only possible configurations are therefore the planar one, I, the square pyramidal one, II, and the tetrahedral one, III. Moreover, since isomeric ions of structure $[NR_2T_2]^+$ have also never been encountered, the further conclusion can be drawn that the tetrahedral model, III, must be correct.



I

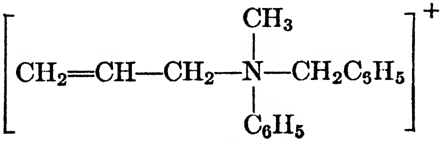


II



III

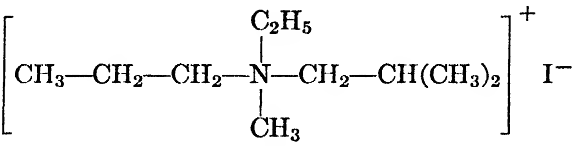
Since the nitrogen atom of an ammonium ion thus has the same tetrahedral configuration as does a saturated carbon atom, the numbers and types of stereoisomeric ammonium ions must be the same as those of stereoisomeric carbon compounds of analogous structure. In particular, an ion in which the nitrogen atom is joined by single bonds to four different radicals should be dissymmetric and hence able to impart optical activity to a salt of which it is a part. In 1899, the optically active ammonium salt, IV, was obtained by Pope and Peachey. This substance is of considerable historical interest since it is not only the first recorded example of an optically active ammonium salt, but also the first recorded example of an optically active compound of *any* sort which owes its activity to the configuration about an atom of an element other



$$\left[\begin{array}{c} \quad\quad\quad\quad\quad\quad\quad\quad CH_3 \\ \quad\quad\quad\quad\quad\quad\quad\quad | \\ CH_2{=}CH{-}CH_2{-}N{-}CH_2C_6H_5 \\ \quad\quad\quad\quad\quad\quad\quad\quad | \\ \quad\quad\quad\quad\quad\quad\quad\quad C_6H_5 \end{array}\right]^+ I^-$$

IV

than carbon. (Somewhat earlier, in 1891, Le Bel claimed that he had obtained the salt V in optically active form; his work was shown sub-

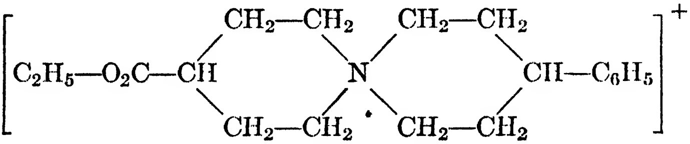


$$\left[CH_3-CH_2-CH_2-\overset{C_2H_5}{\underset{CH_3}{N}}-CH_2-CH(CH_3)_2\right]^+ I^-$$

V

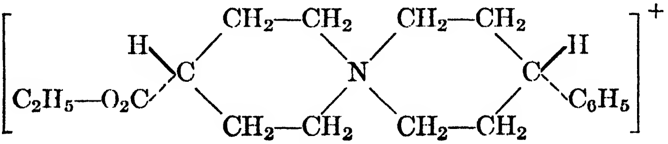
sequently, however, to have been erroneous.) Numerous further optically active ammonium salts, besides methylallylphenylbenzylammonium iodide, IV, have also been prepared.

The most conclusive evidence for the tetrahedral configuration of the nitrogen atom in an ammonium ion is doubtless that illustrated with the ion of structure VI.[38] If the central nitrogen atom in this ion were pla-

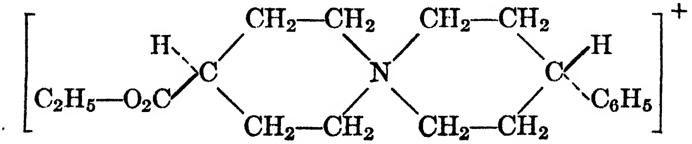


VI

nar (and square), there should exist two optically inactive forms, with the configurations VII and VIII. If the nitrogen atom were pyramidal,



VII



VIII

the four optically inactive forms IX, X, XI, and XII similarly should exist. On the other hand, if the nitrogen atom is tetrahedral, a single

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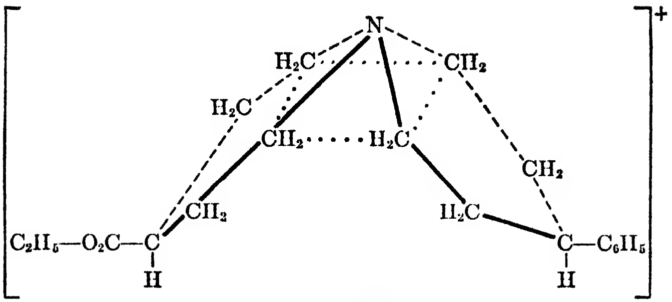
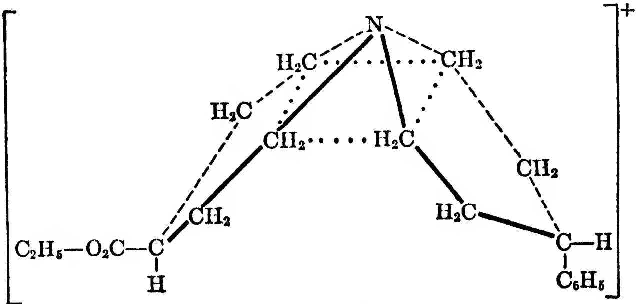
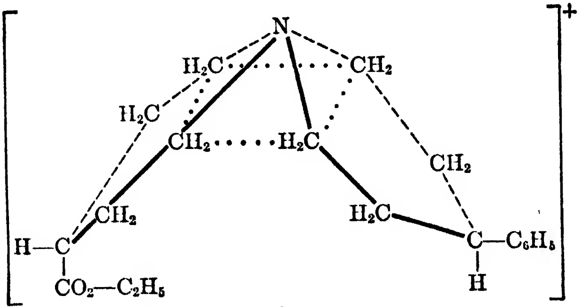
[38] W. H. Mills and E. H. Warren, *J. Chem. Soc.* **127**, 2507 (1925).


N
H₂C
CH₂
H₂C
CH₂
H₂C
CH₂
CH₂
H₂C
C₂H₅—O₂C—C
H
C—C₆H₅
H
+

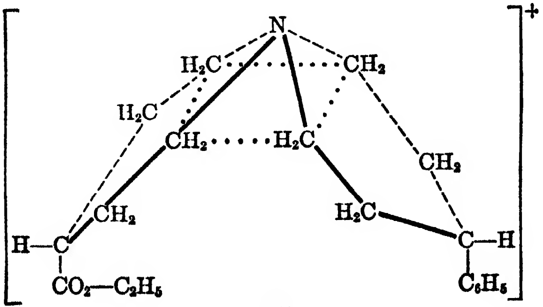
IX


N
H₂C
CH₂
H₂C
CH₂
H₂C
CH₂
CH₂
H₂C
C₂H₅—O₂C—C
H
C—H
C₆H₅
+

X

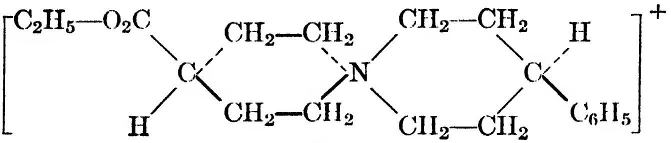

N
H₂C
CH₂
H₂C
CH₂
H₂C
CH₂
CH₂
H₂C
H—C
CO₂—C₂H₅
C—C₆H₅
H
+

XI

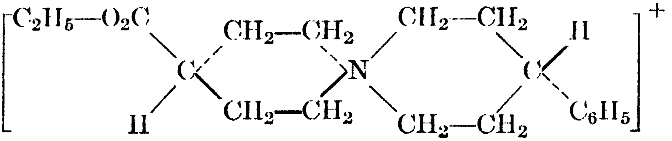

N
H₂C
CH₂
H₂C
CH₂
H₂C
CH₂
CH₂
H₂C
H—C
CO₂—C₂H₅
C—H
C₆H₅
+

XII

pair of enantiomorphic ions with the configurations XIII and XIV is



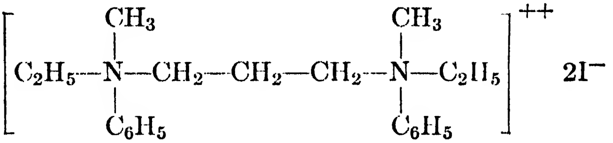
XIII



XIV

possible. (Cf. structures IX and X of Section 6·11.) Although the optically inactive isomers predicted on the basis of the planar and pyramidal models have never been encountered, the bromide salt containing this ammonium ion has been resolved. The proof of the tetrahedral configuration seems therefore to be completely rigorous.

If two or more "asymmetric nitrogen atoms" are present in an ion, diastereomeric and *meso* forms are possible. The salt with structure (not configuration) XV, for example, has been obtained in two different



$$\left[C_2H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{N}}}}-CH_2-CH_2-CH_2-\overset{\displaystyle CH_3}{\underset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{N}}}}-C_2H_5\right]^{++}\quad 2I^-$$

XV

optically inactive forms; although neither of these forms has been resolved, one of them is presumably racemic, whereas the other is *meso*.

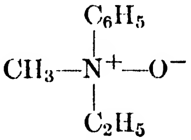
Very much less is known about the stereochemistry of the ammonium ions than about that of the analogous carbon compounds. With respect to such ions, therefore, nothing can be said here about asymmetric syntheses and decompositions, the Walden inversion, or the determination of relative configurations. Moreover, the methods of resolution of the racemic ammonium salts need no discussion at this point since they differ in no significant respect from those which are employed with the carbon compounds, and which have already been discussed in Section 7·2.

In general, the optically active ammonium salts are rather more easily racemized than are the analogous carbon compounds. The mechanism of the racemization is presumed, at least in most instances, to involve a dissociation into a tertiary amine plus an ester, and a subsequent recombination, as in equation 8·20. Since the amine NRQT is unable to

$$[\mathrm{NRQTZ}]^+\mathrm{X}^- \rightleftarrows \mathrm{NRQT} + \mathrm{ZX} \tag{8·20}$$

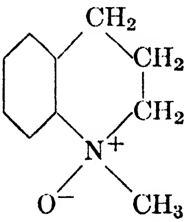
maintain a dissymmetric configuration, a more or less rapid racemization occurs. Support for this mechanism is provided by the fact that ammonium halides are usually racemized with greater ease than are the other types of ammonium salt; the equilibrium depicted above in equation 8·20 would, of course, be expected to be especially mobile when X represents a halogen.

In the amine oxides R_3NO, as in the ammonium ions, the central nitrogen atom is joined to four distinct substituents. That the configuration of the nitrogen atom is again tetrahedral is suggested by the fact that several such compounds, in which the three radicals R are different, have been obtained in optically active form. The pyramidal configuration, as well as the tetrahedral, is of course consistent with such optical activity, but it is made most improbable by the close analogy between the structures of the amine oxides and those of the ammonium ions, which are known to be tetrahedral. Two typical examples of optically active amine oxides are given by structures XVI and XVII.



$$\mathrm{CH_3{-}\overset{C_6H_5}{\underset{C_2H_5}{N^+}}{-}O^-}$$

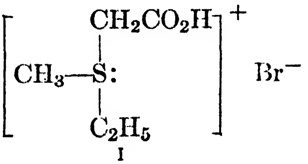
XVI



XVII

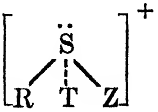
8·8 Compounds of Sulfur.

A sulfonium salt $[\mathrm{RTZS}]^+\mathrm{X}^-$ can be resolved if the three substituents R, T, and Z are different, as in structure I. It is evident, therefore, that a sulfur atom forming three single



$$\left[\mathrm{CH_3{-}\overset{CH_2CO_2H}{\underset{C_2H_5}{S{:}}}}\right]^+\mathrm{Br}^-$$

I

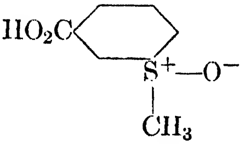


II

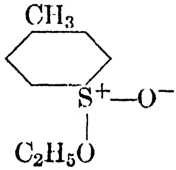
III

bonds must have the pyramidal configuration shown in diagram II. It may seem strange that a sulfonium cation like II is able to maintain its configuration, whereas a tertiary amine, with closely analogous electronic structure III is not able to do so; although the presence of the ionic charge in the former, and its absence in the latter, may perhaps be an important factor, the reason for this great difference in configurational stability is at present not completely understood.

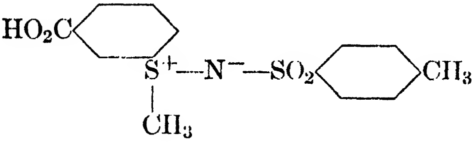
Further optically active sulfur compounds, in which the sulfur atoms are again joined to three dissimilar groups, include the sulfoxides $RTSO$, the sulfinic esters $RSO—OC_2H_5$, and the sulfilimines $RTS^+—N^-Z$. Typical examples of these types of compound are given, respectively, by structures IV,[39] V,[40] and VI.[41] As in the sulfonium salts, the sulfur atoms here also must have the pyramidal configuration II. When the optically active sulfoxides and sulfinic esters are oxidized, inactive sulfones $RTSO_2$ and sulfonic esters $RSO_2—OC_2H_5$, respectively, are formed. In the two latter types of substance, therefore, the sulfur atoms are presumably tetrahedral, so that, with two identical substituents (i.e., two oxygen atoms), they no longer permit molecular dissymmetry.



IV



V



VI

In certain reactions of sulfinic esters, configurational changes which are analogous to Walden inversions occur at the sulfur atoms. For example, the same levorotatory *sec*-octyl ester, VII, of *p*-toluenesulfinic acid can be transformed, as is shown in equations 8·21, into either the dextro- or the levorotatory ethyl ester, VIII or IX, respec-

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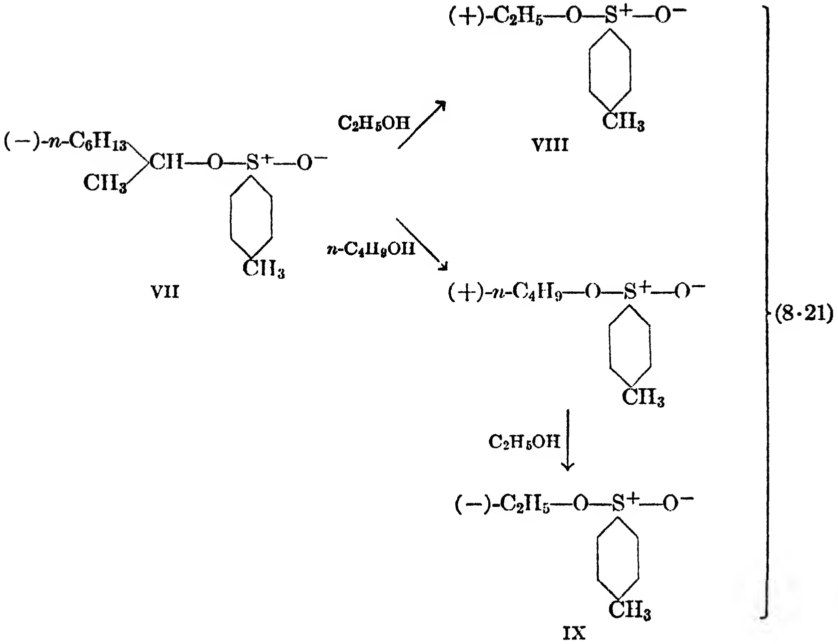
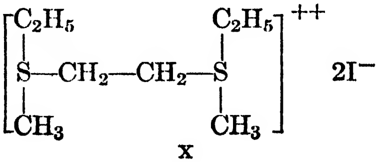
[39] P. W. B. Harrison, J. Kenyon, and H. Phillips, *J. Chem. Soc.* **1926,** 2079.
[40] H. Phillips, *J. Chem. Soc.* **127,** 2552 (1925).
[41] S. G. Clarke, J. Kenyon, and H. Phillips, *J. Chem. Soc.* **1927,** 188.



(8·21)

tively.[40] Clearly, therefore, there must be an inversion of configuration in at least one of the reactions cited; presumably there is an inversion in each reaction. The occurrence here of inversions shows that the sulfur-oxygen bonds of the esters, and not the carbon-oxygen bonds, are broken in the reactions. In this respect, sulfinic esters resemble carboxylic esters rather than sulfonic esters. (Cf. pages 280 ff.)

When two or more "asymmetric sulfur atoms" are present in a molecule or ion, diastereomers and *meso* forms are possible. For example, the salt with structure X has been obtained in two inactive forms, of which



$$\left[\begin{array}{ccc} C_2H_5 & & C_2H_5 \\ | & & | \\ S & -CH_2-CH_2- & S \\ | & & | \\ CH_3 & & CH_3 \end{array}\right]^{++} \quad 2I^-$$

X

one is doubtless racemic, whereas the other is *meso;* neither inactive form, however, has as yet been resolved. Similarly, the two stereoisomeric disulfoxides, XI and XII, are known;[42] both the *cis* form, XI,

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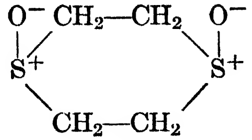
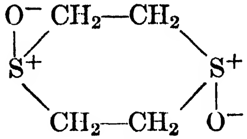
[42] E. V. Bell and G. M. Bennett, *J. Chem. Soc.* **1927,** 1798.

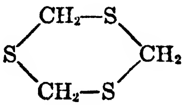


XI

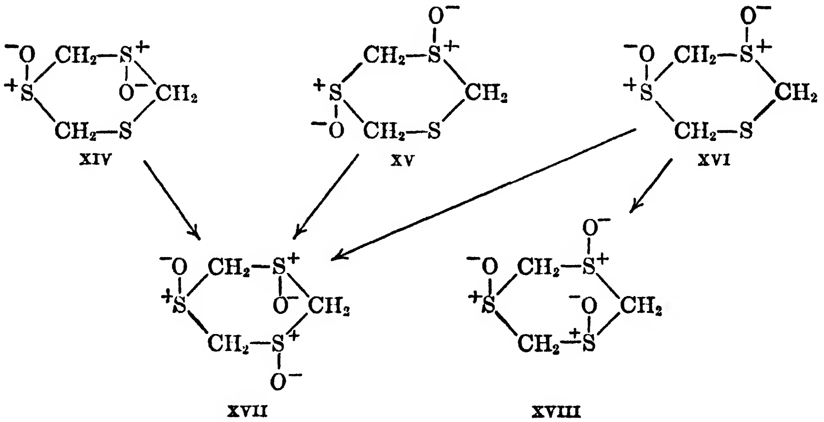


XII

and the *trans* form, XII, have planes of symmetry and so are necessarily optically inactive. Moreover, the disulfoxide formed from trithioformaldehyde, XIII, can exist in the three stereoisomeric forms XIV, XV, and XVI; the first two of these configurations correspond to a pair of enantiomorphs, whereas the last corresponds instead to an inactive diastereomer.[43] Although neither of the two known inactive forms has been resolved, the problem of deciding which is racemic and which is *meso* has been solved by a method reminiscent of the one devised by Körner for the determination of the structures of the isomeric derivatives of benzene. (See Section 4·5.) The action of hydrogen peroxide



XIII



upon the racemic disulfoxide (XIV plus XV) gives a trisulfoxide which necessarily has the configuration XVII, whereas the action of the same reagent upon the *meso* form, XVI, gives a mixture of the same trisulfoxide, XVII, and a different trisulfoxide which can have only the configuration XVIII. Consequently, the racemic disulfoxide is the one which gives a single trisulfoxide, whereas the *meso* disulfoxide is the one

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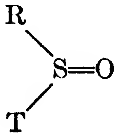
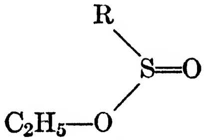
[43] E. V. Bell and G. M. Bennett, *J. Chem. Soc.* **1929**, 15.

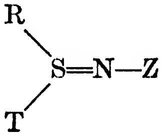
which gives a mixture of two trisulfoxides. Conversely, the trisulfoxide with configuration XVII is the one formed from each disulfoxide, whereas the trisulfoxide with configuration XVIII is the one formed from only a single disulfoxide. In this way, the configurations of both the di- and the trisulfoxides are unambiguously determined.[43] It may be observed that neither of the two trisulfoxides, XVII and XVIII, can be optically active since each possesses a plane of symmetry. When the foregoing di- and trisulfoxides are oxidized to sulfones, the isomerism of course disappears.

The interconversion of stereoisomeric sulfur compounds is often nearly as difficult as is that of carbon compounds. When such an interconversion does occur, its mechanism may possibly be analogous to the one which was proposed originally by Werner (see pages 251 ff.), and which is considered to be involved in the rapid racemization of amines (see pages 330 f.).

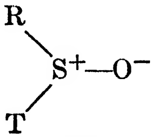
In the older chemical literature, the sulfoxides, sulfinic esters, and sulfilimines were assigned structures XIX, XX, and XXI, respectively,

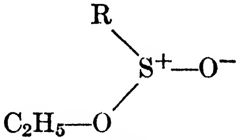

XIX

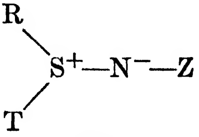

XX


XXI

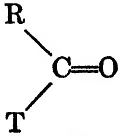
with covalent double bonds between the sulfur atoms and the oxygen or nitrogen atoms. Subsequently, however, these "classical" structures were largely displaced by more "modern" ones like XXII, XXIII, and

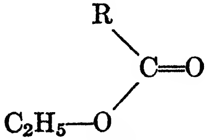

XXII

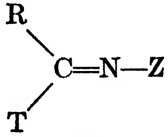

XXIII


XXIV

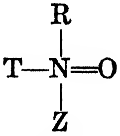
XXIV, respectively (cf. structures IV, V, and VI, above), with semipolar double bonds instead. One of the arguments advanced [40] against the covalent double bonds in these compounds of sulfur is as follows. The classical structures XIX, XX, and XXI are seen to be superficially analogous to those of ketones, XXV, carboxylic esters, XXVI, and Schiff


XXV


XXVI

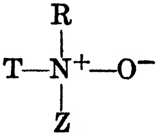

XXVII

bases, XXVII, respectively. Since the sulfur compounds may be optically active, even though the corresponding carbon compounds never are (unless at least one of the radicals R, T, and Z is dissymmetric), the two classes of compound must differ in configuration, and presumably also in structure. Further evidence for the presence of semipolar double bonds in the sulfur compounds was obtained from studies of the parachor.[44] At the present time, however, the natures of the sulfur-oxygen and sulfur-nitrogen bonds in question do not seem entirely clear, although no uncertainty exists regarding the stereochemical relationships. It is now recognized that the presence of *ten* electrons in the valence shells of the sulfur atoms in structures XIX, XX, and XXI, and of only *eight* electrons in the valence shells of the corresponding carbon atoms in structures XXV, XXVI, and XXVII, respectively, makes invalid any argument based upon the superficial analogy between the sulfur and carbon compounds. Moreover, the evidence provided by the parachor is no longer regarded as completely conclusive. The best view at present [45] seems to be that the correct structures are neither XIX, XX, and XXI nor XXII, XXIII, and XXIV, respectively, but are intermediate between the two extremes. That is to say, it is now considered that the actual distributions of charge in the molecules are intermediate between those corresponding to the two types of structures; so that, for example, the net charge on the sulfur atom of a sulfoxide is more positive than it would be if structure XIX were correct, but is less positive than it would be if structure XXII were correct. (Cf. Chapter 10.) It is to be noted, however, that similar considerations do not apply to the azoxy compounds, the N-methyl derivatives of oximes, and the amine oxides considered in the preceding sections; with these substances, the classical structures with quinquivalent nitrogen have been completely replaced by the more modern ones with the semipolar double bonds. Thus, the structure of an amine oxide, which was written at one time as XXVIII, is



$$\mathrm{T{-}\overset{\displaystyle R}{\underset{\displaystyle Z}{N}}{=}O}$$

XXVIII



$$\mathrm{T{-}\overset{\displaystyle R}{\underset{\displaystyle Z}{N^{+}}}{-}O^{-}}$$

XXIX

now written instead as XXIX. The reason for this difference between the nitrogen and the sulfur compounds is that there is a good theoretical

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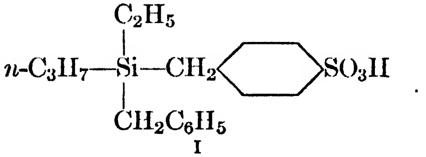
[44] Cf. S. Sugden, *The Parachor and Valency*, George Routledge and Sons, London, 1930, pages 120 ff.

[45] Cf. L. E. Sutton, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **37**, 73 (1940); G. M. Phillips, J. S. Hunter, and L. E. Sutton, *J. Chem. Soc.* **1945**, 146.

reason for believing that an atom as light as one of nitrogen is unable to accommodate more than eight electrons in its valence shell. (Cf. page 423.)

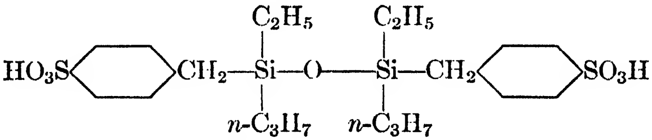
8·9 Configurations of the Remaining Elements.[46] Relatively very little is known about the stereochemistry of those remaining elements that are of importance in organic compounds. Consequently, such elements will here be discussed only very briefly.

That silicon, like carbon, has a tetrahedral configuration is suggested by the optical activity of such a substance as the one with structure I, in



I

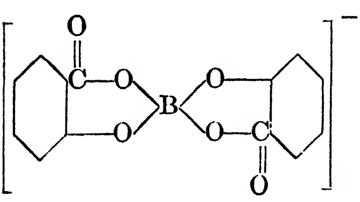
which the silicon atom is linked to four different substituents. Moreover, the substance with structure II has been obtained in two optically



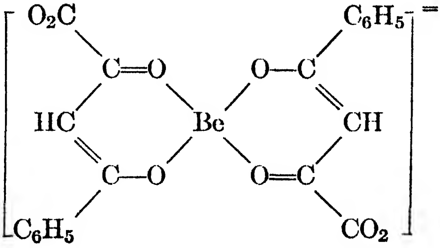
II

inactive forms, of which one is racemic, whereas the other is *meso*.

The tetrahedral configurations of such other quadrivalent elements as boron, beryllium, copper, and zinc are shown by the optical activities of anions like III,[47] IV,[48] V,[48] and VI,[48] respectively. As with the ammo-



III



IV

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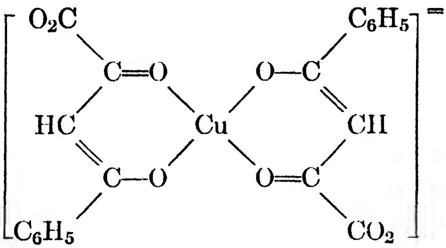
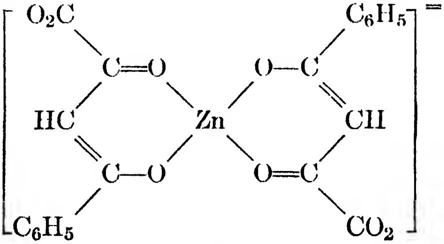
[46] For further details, see, for example, R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 327 f., 348 ff., 2nd ed., 1943, Volume I, pages 401 f., 423 ff.

[47] J. Böeseken and J. Meulenhoff, *Proc. Acad. Sci. Amsterdam* **27**, 174 (1924); *C.A.* **18**, 1998 (1924); A. Rosenheim and H. Vermehren, *Ber.* **57**, 1337 (1924).

[48] W. H. Mills and R. A. Gotts, *J. Chem. Soc.* **1926**, 3121.



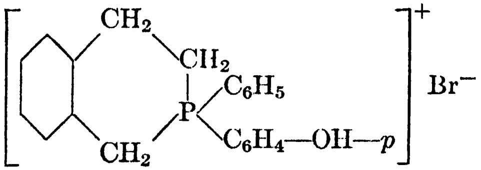
V



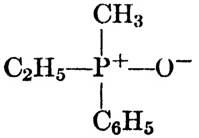
VI

nium ion with structure VI on page 352, the optical activities of these substances exclude the planar configurations for the central atoms.

The phosphonium salt, VII, in which four different groups are attached to the phosphorus atom, has been resolved.[49] Moreover, the phosphine oxide, VIII, has also been resolved,[50] and the more complex

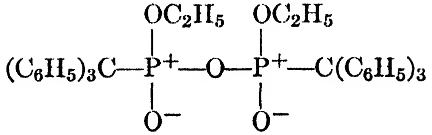


VII



$$\mathrm{C_2H_5{-}\overset{CH_3}{\underset{C_6H_5}{P^+}}{-}O^-}$$

VIII



$$\mathrm{(C_6H_5)_3C{-}\overset{OC_2H_5}{\underset{O^-}{P^+}}{-}O{-}\overset{OC_2H_5}{\underset{O^-}{P^+}}{-}C(C_6H_5)_3}$$

IX

phosphorus compound, IX, has been obtained in two inactive forms, of which one is presumably racemic, whereas the other is *meso*.[51] The configuration of phosphorus in these compounds is therefore considered to be tetrahedral.

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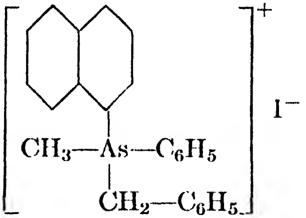
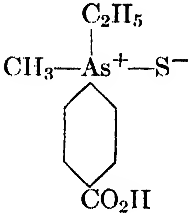
[49] F. G. Holliman and F. G. Mann, *Nature* **159**, 438 (1947).

[50] J. Meisenheimer and L. Lichtenstadt, *Ber.* **44**, 356 (1911).

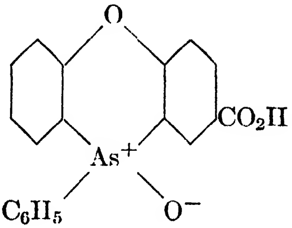
[51] H. H. Hatt, *J. Chem. Soc.* **1933**, 776.



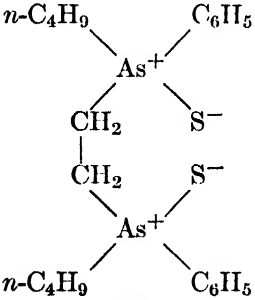
X



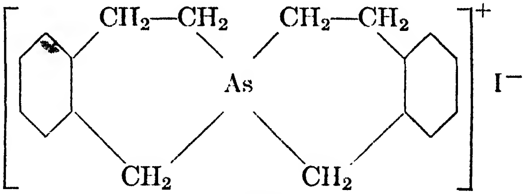
XI



XII



XIII



XIV

A few arsonium salts, of which the compound X is a typical representative, have been resolved.[52] Similarly, the arsine sulfide, XI,[53] and the arsine oxide, XII,[54] have also been resolved; and the more complex compound XIII has been obtained [55] in the expected two inactive forms (*meso* and racemic). Finally, the arsonium salt XIV, with an arsenic spiro atom, has been obtained optically active.[56] In all these compounds, the arsenic atoms which are bonded to four atoms or groups are presumably tetrahedral. The further arsenic compound XV, in which the

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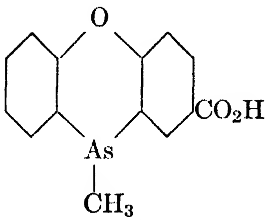
[52] G. J. Burrows and E. E. Turner, *J. Chem. Soc.* **119**, 426 (1921); see also G. Kamai, *Ber.* **66**, 1779 (1933).

[53] W. H. Mills and R. Raper, *J. Chem. Soc.* **127**, 2479 (1925).

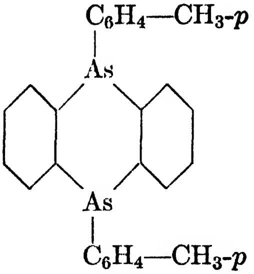
[54] M. S. Lesslie, *J. Chem. Soc.* **1939**, 1050.

[55] J. Chatt and F. G. Mann, *J. Chem. Soc.* **1939**, 610.

[56] F. G. Holliman and F. G. Mann, *J. Chem. Soc.* **1945**, 45.



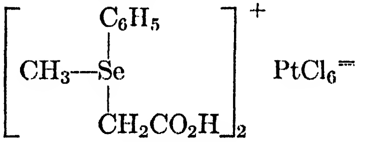
XV



XVI

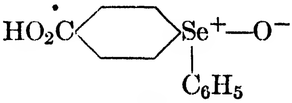
arsenic atom is bonded to only three substituents, however, has also been resolved;[57] apparently here the arsenic atom is pyramidal. The further compound XVI, with two trivalent arsenic atoms, has been obtained in two optically inactive forms,[58] which are presumably *cis* and *trans*.

The selenonium salt XVII has been resolved; hence, a selenium atom



$$\left[CH_3\text{—}\underset{CH_2CO_2H}{\overset{C_6H_5}{Se}}\right]_2^+ PtCl_6^=$$

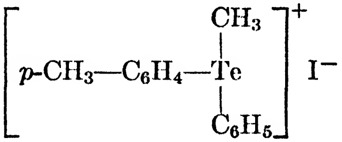
XVII



XVIII

forming bonds to three substituents, like an analogous sulfur atom, must be pyramidal. However, attempts to resolve a selenoxide like XVIII have failed.[59]

The existence of the optically active telluronium salt XIX [60] similarly



$$\left[p\text{-}CH_3\text{—}C_6H_4\text{—}\underset{C_6H_5}{\overset{CH_3}{Te}}\right]^+ I^-$$

XIX

indicates that a tellurium atom joined to three substituents is also pyramidal.

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[57] M. S. Lesslie and E. E. Turner, *J. Chem. Soc.* **1934,** 1170.

[58] J. Chatt and F. G. Mann, *J. Chem. Soc.* **1940,** 1184.

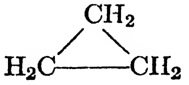
[59] W. R. Gaythwaite, J. Kenyon, and H. Phillips, *J. Chem. Soc.* **1928,** 2280.

[60] T. M. Lowry and F. L. Gilbert, *J. Chem. Soc.* **1929,** 2867.

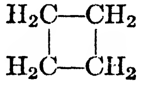
9.

Strain Theory[1] and Steric Hindrance

9·1 The Original Strain Theory of Baeyer. In 1885, Baeyer[2] called attention to the fact that nearly all the then known carbocyclic compounds contained either five- or six-membered rings. To explain this fact, he brought forth a group of ideas now called the *Baeyer strain theory*. The angle between any two single bonds formed by a saturated carbon atom had been postulated by van't Hoff to have the tetrahedral value of 109° 28′. Consequently, Baeyer considered that an angle of this magnitude is most stable; and hence, that, if one or more angles in a molecule are in some way forced to have a widely different value, the molecule is "strained," and therefore unstable. Now in cyclopropane, I, the C—C—C angles of the three-membered ring must be equal to 60°; since this value is much smaller than the preferred 109° 28′, the molecule is strained. Thus, Baeyer considered that the difficulty of preparing such a substance is explained. Similarly in cyclobutane, II, the angles must be equal to 90° if the four-membered ring is planar; again considerable strain is present, and again the difficulty in preparing the substance appears to be explained. The amount of strain in such molecules as these can be expressed in terms of the so-called *valence deviation d*. This quantity is defined by equation 9·1, in which the factor ½ was introduced by Baeyer in order to take account of the fact that the total deviation of the bond angle from the preferred value of 109° 28′ can be



I



II

$$d = \tfrac{1}{2}(109^\circ\ 28' - \text{bond angle}) \qquad (9\cdot 1)$$

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[1] For a general discussion of the strain theory see W. Hückel, *Der Gegenwärtige Stand der Spannungstheorie, Fortschritte der Chemie, Physik und physikalischen Chemie*, Serie A, Band 19, Heft 4, Edited by A. Eucken, Gebrüder Borntraeger, Berlin, 1927; *Theoretische Grundlagen der Organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, Volume 1, pages 56 ff., 2nd ed., 1934, Volume 1, pages 58 ff.

[2] A. Baeyer, *Ber.* **18**, 2269, 2277 (1885).

considered produced by equal deviations of the two corresponding valence bonds from their normal directions.

The values of the valence deviations d in some simple cyclic molecules, calculated on the assumption that the carbon atoms of each molecule lie at the corners of a regular plane polygon, are given in Table 9·1. As is evident from equation 9·1, a positive value of d implies a bond angle that is less than 109° 28′, whereas a negative value implies a bond angle that is greater than 109° 28′. The magnitudes of the deviations are smallest with just those rings which are easiest to prepare and are best known (i.e., with the five- and six-membered rings). Baeyer considered this fact to be evidence both for the correctness of his theory and also for the planarity of the rings.

TABLE 9·1

VALENCE DEVIATIONS IN SOME CYCLOPARAFFINS $(CH_2)_n$

n	3	4	5	6	7	8	∞
d	24° 44′	9° 44′	0° 44′	−5° 16′	−9° 33′	−12° 46′	−35° 16′

9·2 Different Kinds of "Stability." Baeyer's original ideas have undergone extensive revision in subsequent years. However, before the modern views can be discussed, a brief digression must be made into the significance that may be assigned to the word "stable" in any description of the strain theory. As used by chemists, this word has at least four different, and sometimes contradictory, meanings. In order that confusion may be avoided, therefore, it is essential that these meanings now be clearly stated and carefully distinguished.

1. A substance is frequently said to be stable if its internal energy E is low. The significance of this use of the word "stable" can be explained most easily by reference to Figure 9·1. In this figure, the heights of the various horizontal lines above some arbitrary base-line correspond to the internal energies of the system of interest under the conditions stated. The highest line corresponds to the energy of some specified set of isolated gaseous atoms. The next two lines correspond to the energies of two different isomeric molecules R and S, which are composed of the same specified atoms. The distances AB and DF therefore represent the amounts of energy which would have to be supplied in order to dissociate the two molecules into the isolated atoms or, conversely, the amounts of energy which would be liberated if the molecules could be formed from the atoms. In accordance with this first definition, the isomer S represented by the lower of the two horizontal lines under discussion, is the more stable of the two; it is also clearly the one with the greatest energy of formation (from its atoms).

Since the energy of formation of a substance from gaseous atoms is in most instances not directly measurable, the relative stabilities (in this first sense) of the two isomeric substances must usually be determined experimentally in some alternative way. If the substance is burned, heat is liberated; hence the energy of the products of combustion must be less than that of the original substance. Moreover, the two isomeric substances must give the same products of combustion. The lowest line of Figure 9·1 corresponds then to the energy of these products, minus the energy of the oxygen necessary for the combustion. It is seen that the heats (or, more precisely, the energies) of combustion of the two isomers are represented by the distances *BC* and *FG*, and that the more stable isomer S has the smaller heat of combustion. Since heats of combustion are directly measurable, they provide a convenient method for determining relative stabilities.

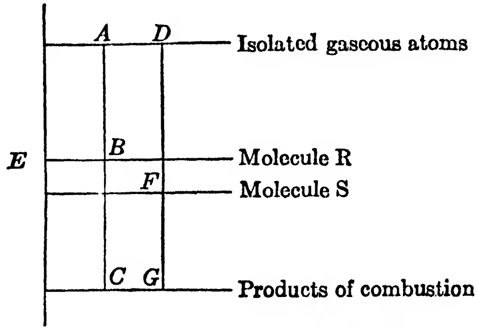

FIGURE 9·1. A diagram illustrating the relation between the thermochemical stabilities of two isomeric molecules R and S and their internal energies *E*.

The foregoing discussion has been limited to the comparison of *isomeric* substances. The reason for this limitation is that two (or more) substances can be represented in a single chart, like that of Figure 9·1, only if they are isomeric. If they are not isomeric, then a different line, corresponding to the energy of the isolated atoms, is needed for each substance; moreover, there would then be no way of locating these various lines with respect to one another, since it is impossible either to calculate theoretically or to measure experimentally the energy liberated or absorbed in a purely imaginary transformation in which there is a change in either the number or the kind of atoms. (Nuclear reactions are of course not under discussion here.)

It follows therefore that, in a strict sense, one can speak of the relative stabilities only of isomeric substances. Nonisomeric substances with the same empirical formula, however, can be treated in a closely analogous way. Thus, in dealing with the cycloparaffins $(CH_2)_n$, one may speak of the energy of formation, or of the heat of combustion, per CH_2 group. The substance with the larger value of the former, or with the smaller value of the latter, may then be said, somewhat loosely, to be the more stable. (See below.)

No name seems at present to have been generally adopted for the type of stability discussed above. For reasons of convenience, however, this type will hereafter be referred to as *thermochemical stability.*

2. A substance is frequently said to be stable if its free energy is low. The significant distinction between this use of the word "stable" and the different use which was considered above is that the energy in question is here the *free* energy, rather than the *internal* energy, of the substance. Stability of this second type will hereafter be called *thermodynamic stability.* Although, in many problems, the free energies of the substances of interest are theoretically more important than are their internal energies, the experimental measurement of the free energies is usually more difficult than is that of the internal energies. For most organic compounds, in fact, the free energies have not yet been determined. Consequently, the discussion in this chapter will be concerned more with thermochemical than with thermodynamic stabilities.

3. A substance is sometimes said to be stable if it is easily prepared. Very frequently, substances which are stable in this sense are also stable thermochemically; a great many exceptions are, however, known. Thermochemical stability is doubtless *one* of the factors influencing the ease of preparation of a substance; it is, however, not the only factor, and often it is not even a very important factor. This question will be discussed later in greater detail. No name seems to have been generally adopted for this third type of stability; for ease of reference, however, the expression *synthetic stability* will hereafter be employed.

4. A substance is very frequently said to be stable if it is unreactive, and especially if it is not readily decomposed. Thermochemical stability is doubtless a factor influencing this fourth type of stability, but it is not the only factor involved, and often it seems to be a relatively unimportant factor. Moreover, there is no necessary relation between the synthetic stability of a compound and its unreactivity. Further discussion of this question will be given below. (See Section 9·4.) In accordance with fairly general usage, stability of this last type will hereafter be referred to as *unreactivity.*

9·3 More Recent Views on the Strain Theory. Puckered Rings. In his original formulation of the strain theory,[2] Baeyer did not distinguish among the four different types of stability described above. Apparently, he considered that the same factors determine all four, so that a single explanation accounts for everything. At present, however, it is realized that the situation is more complicated than Baeyer had assumed, and that the four kinds of stability must be considered separately.

It should be clear that the strain postulated by Baeyer has a direct effect upon the thermochemical stability of any molecule in which it occurs. The reality of the strain can therefore be demonstrated by a comparison of the heats of combustion per CH_2 group (see above) of the various cycloparaffins. The pertinent data are given in Table 9·2. Of all the substances listed in this table, cyclopropane has the highest heat of combustion per CH_2 group. This hydrocarbon, accordingly, has the lowest thermochemical stability and hence is the most strained. Cyclobutane, with a lower heat of combustion per CH_2 group, is less strained; and cyclopentane is still less strained. With these compounds, therefore, the data are in agreement with the expectation based upon Baeyer's original theory. With the six-membered and larger rings, however, the heat of combustion per CH_2 group does not again rise but instead seems asymptotically to approach a low limiting value. From the thermochemical data, therefore, strain appears to exist in the three- and four-membered rings, where the deviation d is positive, but not to any significant extent in the six-membered and still larger rings, where the deviation is negative.

TABLE 9·2

HEATS OF COMBUSTION [a] PER CH_2 GROUP (λ) OF THE CYCLOPARAFFINS $(CH_2)_n$

n	3	4	5	6	7	8	15	17	30
λ	168.5[b]	165.5[b]	158.7[c]	157.4[c]	158.3[c]	158.6[c]	157.1[b]	157.0[b]	156[b]

[a] In kilocalories per formula weight.

[b] Cf. L. Ruzicka, *Chemistry & Industry* **1935**, 2.

[c] R. Spitzer and H. M. Huffman, *J. Am. Chem. Soc.* **69**, 211 (1947).

These observations are now explained by the assumption that the small rings are indeed planar, as was postulated by Baeyer, but that the large rings are instead puckered.[3] Thus, in cyclopropane, the three carbon atoms are necessarily coplanar, since a plane can always be passed through any set of three points. Moreover, with the four-membered and five-membered rings, with which the valence deviations are positive, the least strain results if the rings are planar; consequently, these rings probably are also planar, or nearly so. There is, however, reason [4] to

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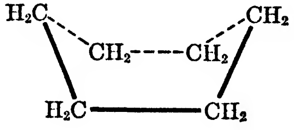
[3] H. Sachse, *Z. physik. Chem.* **10**, 203 (1892); E. Mohr, *J. prakt. Chem.* [2] **98**, 315 (1918)

[4] J. G. Aston, H. L. Fink, and S. C. Schumann, *J. Am. Chem. Soc.* **65**, 341 (1943). K. S. Pitzer, *Science* **101**, 672 (1945); J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.* **69**, 2483 (1947).

believe that, even in cyclopentane, the five carbon atoms are not completely coplanar; for, although the presumed slight puckering must somewhat increase the strain, it nevertheless decreases the internal energy because it allows the hydrogen atoms to be more distant from one another. Finally, with six-membered and larger rings, with which the valence deviations are negative, the strain can be relieved completely if the rings are allowed to be puckered. With cyclohexane, for example, two different strain-free conformations are possible.[3] These are the so-called *boat-form* or *C-form*, I, and the so-called *chair-form* or *Z-form*, II.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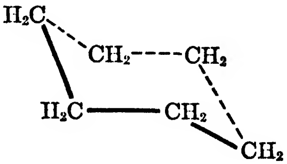
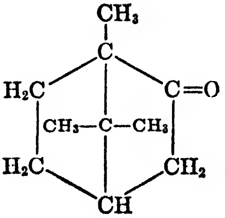
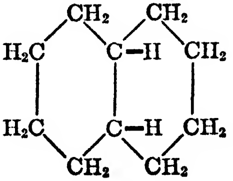
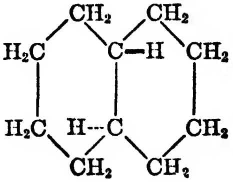

II

With still larger rings, the situations are similar, but more complex. In no instance, however, has it as yet been possible to isolate stereoisomeric substances which differ only in the form of the puckered ring; presumably, therefore, transitions among the various forms must always be relatively easy.

Evidence supporting the belief that six-membered and larger rings are puckered and strain-free can be derived not only (as above) from the heats of combustion, but also in other ways as well. Thus, the existence of such compounds as camphor, III, would be impossible if all rings had to be planar. Moreover, the existence of the stereoisomeric *cis-* and *trans-*decalins, IV and V, respectively, can hardly be explained except


III


IV


V

with the assumption of puckered rings. Finally, the rings in several analogous substances, such as paraldehyde,[5] VI, and metaldehyde, VII,[6] have been found by electron and x-ray diffraction, respectively,

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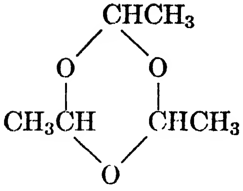
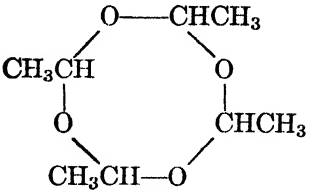
[5] D. C. Carpenter and L. O. Brockway, *J. Am. Chem. Soc.* **58**, 1270 (1936).
[6] L. Pauling and D. C. Carpenter, *J. Am. Chem. Soc.* **58**, 1274 (1936).

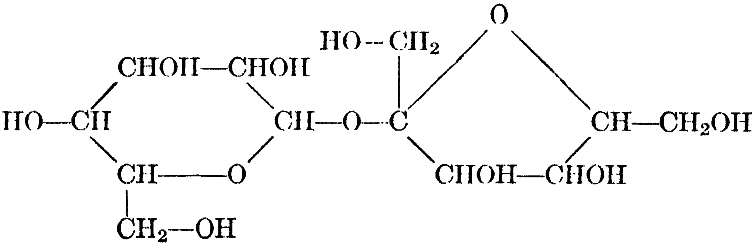


VI



VII

to be puckered. Moreover, an examination of the crystal structure of sucrose, VIII,[7] has shown that, in this substance, both the six-membered



VIII

(glucose) ring and the five-membered (fructose) ring are puckered.

9·4 Factors Influencing the Ease of Forming and Breaking Rings. If only the three- and four-membered rings are appreciably strained, an explanation is needed for the fact that the ease of formation reaches a sharp maximum with the five- and six-membered rings. It might have been anticipated that all the strain-free rings (i.e., all those with five or more members) should be formed with approximately the same ease. Indeed, the fact that this expectation is not borne out by experiment was at least partially responsible for Baeyer's error in believing the large rings to be strained. The problem is clearly, however, not one of the relative *thermochemical* stabilities of the rings, but instead one of their relative *synthetic* stabilities. Consequently, Baeyer's approach was inadequate. It now appears that at least two different factors must be considered in any complete treatment of the problem.[8] The first of these factors is the strain (reflected in the thermochemical stability), which operates against the formation of three- and, to a lesser extent, of four-membered rings. The second is a *probability* factor; this factor is related to the probability that the two ends of a chain of atoms will happen to come so close to one another that they can be joined by a valence bond. It is reasonable to suppose that the likelihood of such an occurrence decreases regularly as the size of the ring increases. The

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[7] C. A. Beevers and W. Cochran, *Proc. Roy. Soc.* (London) **A190**, 257 (1947).

[8] L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz, and M. Stoll, *Helv. Chim. Acta* **9**, 499 (1926); L. Ruzicka, *Chemistry & Industry* **1935**, 2.

relatively great ease of formation of the five- and six-membered rings is then the result of the simultaneous operation of these two independent factors.

Figure 9·2 shows schematically how the probability and strain factors can lead to the observed dependence of synthetic stability upon ring size.[8] Curve *a* represents the probability factor; since all effects of strain are here ignored, this curve drops steadily as the size of the ring increases. Curve *b* represents the thermochemical stabilities of the cyclic compounds; it rises from a low value for cyclopropane to a high constant value for all cycloparaffins from cyclopentane on. Finally, curve *c* represents the observed synthetic stabilities, as measured by the percentage yields of the cyclic products obtained, in closely analogous reactions, from noncyclic reagents. If, as is here assumed, the synthetic stability of a cyclic compound is determined primarily by its thermochemical stability and by the probability factor, curve *c* should then be some sort of combination of curves *a* and *b*. As is immediately apparent, this expectation is indeed correct; although the exact form of curve *c* could not have been predicted in advance, its general shape is nevertheless entirely reasonable. The fact that this last curve reaches a shallow minimum with the eleven-membered ring and then rises to a low maximum with about the fourteen-membered ring is, however, somewhat unexpected. Ruzicka [8] has suggested that this feature of the curve is

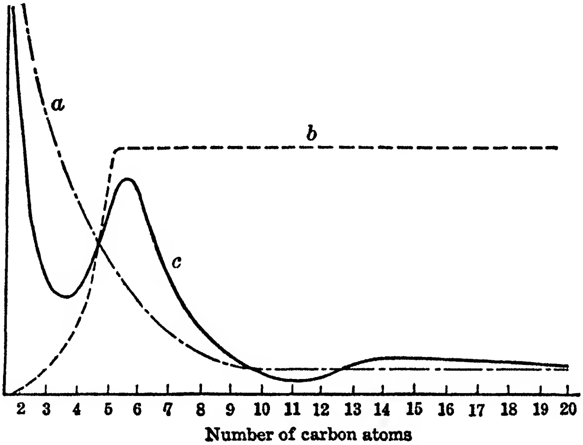
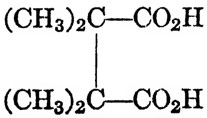


FIGURE 9·2. A schematic plot showing the ways in which the probability factor (curve *a*), the thermochemical stability (curve *b*), and the resultant synthetic stability (curve *c*) of cycloparaffins $(CH_2)_n$ depend upon the number *n* of carbon atoms in the ring. This figure is reproduced by permission of Professor L. Ruzicka and of the Society of Chemical Industry from *Chemistry & Industry* **1935,** 6.

due to a crowding of the hydrogen atoms (cf. Section 9·6), which becomes most serious when n is equal approximately to 11.

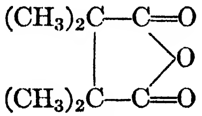
The fourth type of stability (i.e., the unreactivity) of a cyclic compound could be expected to depend upon the thermochemical stability, but hardly upon the probability factor. Consequently, curve b of Figure 9·2 should represent the unreactivities of the cycloparaffins. This expectation is in agreement with the observations. The ring in cyclopropane, for example, is easily broken by such reagents as hydrogen (in the presence of a platinum catalyst), chlorine, or hydrogen chloride; moreover, the slightly larger ring in cyclobutane displays a similar, although reduced, reactivity. On the other hand, the thirty-membered ring of cyclotriacontane $C_{30}H_{60}$ is as unreactive toward these reagents as are the five- and six-membered rings in cyclopentane and cyclohexane.[8] Indeed, it is in general as difficult to break a carbon-carbon single bond in any ring of five or more atoms as it is to break a similar bond in an analogous noncyclic compound. These further facts, like the measured heats of combustion, are therefore in disagreement with Baeyer's view that large rings are planar, and hence strained.

Although a fairly satisfactory explanation of the dependence of both synthetic stability and unreactivity upon ring size can be obtained in the way outlined above, attention should be called here to the fact that still other factors, which have not been considered, appear also to be involved. In general, a consideration of only the strain and probability factors is not sufficient, except within a limited series of closely similar substances, to permit a reliable prediction either of the ease with which a ring of any given size can be formed, or of the resistance which such a ring offers to being ruptured. For example, tetramethylsuccinic acid, I, forms the cyclic anhydride, II, much more readily than unsubstituted succinic acid, III, forms the corresponding anhydride, IV.[9] This difference is not easily explained by the strain theory. Moreover, β,β-dimethylglutaric acid, V, is transformed rapidly and in the cold by



$$\begin{array}{l}(CH_3)_2C\text{—}CO_2H\\ \quad\quad\;\,|\\ (CH_3)_2C\text{—}CO_2H\end{array}$$

I



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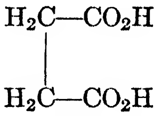
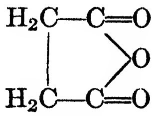


$$\begin{array}{l}H_2C\text{—}CO_2H\\ \quad\;\,|\\ H_2C\text{—}CO_2H\end{array}$$

III



IV

$$HO_2C\text{—}CH_2\text{—}C(CH_3)_2\text{—}CH_2\text{—}CO_2H$$

V

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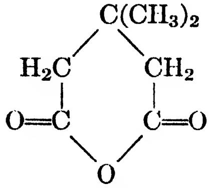
[9] K. Auwers and V. Meyer, *Ber.* **23**, 101 (1890). Cf. also C. K. Ingold, *J. Chem. Soc.* **119**, 305 (1921); E. H. Farmer and J. Kracovski, *ibid.* **1927**, 680.

acetyl chloride into its cyclic anhydride, VI; whereas unsubstituted



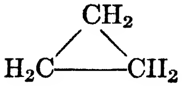
VI

$HO_2C—CH_2—CH_2—CH_2—CO_2H$

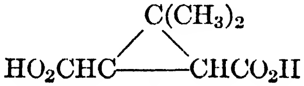
VII

glutaric acid, VII, must be warmed with acetyl chloride to 40°C before the corresponding dehydration proceeds at a satisfactory rate. Again, the reason for the observed difference in ease of ring formation is not immediately obvious.

An example, in which unreactivity rather than synthetic stability is involved, is provided by a comparison of cyclopropane, VIII, with its



VIII



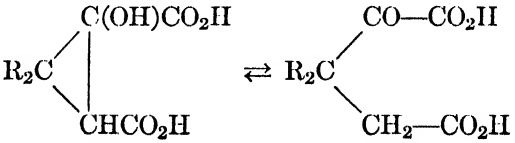
IX

$Br—CH_2—CH_2—CH_2—Br$

X

derivative, *cis*-caronic acid, IX. The first of these substances reacts readily with bromine to give trimethylene bromide, X, but the second is inert toward bromine. If the reactivity of cyclopropane is explained as a result of the strain in the three-membered ring, then the unreactivity of *cis*-caronic acid is anomalous.

Finally, there exist also unexplained variations in thermodynamic stability. Thus, the position of the equilibrium represented by the general equation 9·2 has been found to depend markedly upon the identity



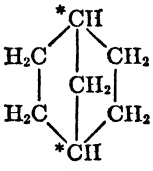
XI XII (9·2)

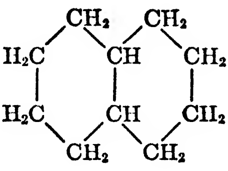
of the radicals R. Thus,[10] when R is hydrogen, the equilibrium mixture consists entirely of keto acid, XII; when R is *n*-propyl, the equilibrium mixture contains about 29 per cent keto acid, XII, and 71 per cent hydroxy acid, XI; and when R_2 represents the bivalent pentamethylene group $—(CH_2)_5—$, the equilibrium mixture consists entirely of the hydroxy acid, XI. Clearly, therefore, the thermodynamic stability of the

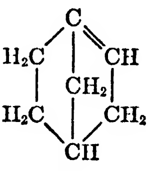
[10] E. W. Lanfear and J. F. Thorpe, *J. Chem. Soc.* **123**, 1683 (1923).

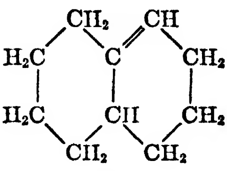
three-membered ring in the compound XI varies widely in a way that is not obviously explainable on the basis of the simple strain theory.

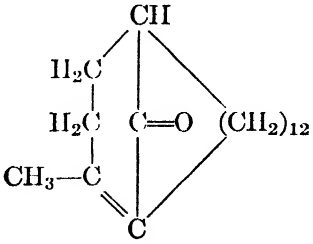
9·5 Nonexistence of Certain Isomers. An important service performed by the strain theory consists in providing a reasonable explanation for the nonexistence of substances with certain structures or with certain configurations. In the field of terpene chemistry especially, for example, there exist a number of so-called *bridge compounds.* These are compounds the molecules of which contain pairs of atoms joined to each other by three different chains of atoms. Two atoms so joined are called *bridge atoms.* For example, in structure I the two bridge atoms are the ones marked with asterisks. It should be noted that decalin, II, is not a bridge compound because, although the two central atoms are joined to each other in three ways, one of these ways is by a single valence bond and not by a chain of atoms. A limitation upon the number of possible bridge compounds is expressed by *Bredt's rule,*[11] which states that no bridge atom can take part in a double bond. Structures like III (but not those like IV) are therefore excluded. The reason for this rule is that structures of the type stated are highly strained; the strain is not enormous, however, and exceptions to the rule are possible if the rings are sufficiently large. Thus, the unsaturated bicyclic ketone, V, which violates the rule, has been prepared.[12]


I


II


III


IV


V

A different type of limitation upon bridge compounds is illustrated with camphor, VI. This substance has the two nonequivalent asym-

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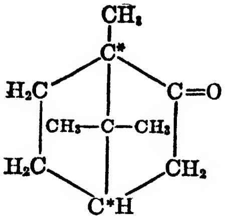
[11] J. Bredt, *Ann.* **395**, 26 (1913).

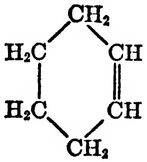
[12] V. Prelog, M. M. Wirth, and L. Ruzicka, *Helv. Chim. Acta.* **29**, 1425 (1946).



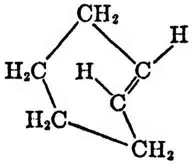
VI

metric atoms marked by asterisks; hence it might be expected to exist in four stereoisomeric forms. Nevertheless, only one pair of enantiomorphs is known. This is the pair in which the union of the —$C(CH_3)_2$— bridge to the outer six-membered ring is *cis;* the second theoretically possible pair of enantiomorphs, in which the union is *trans*, would be too highly strained to exist.

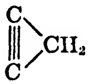
Cyclohexene exists only in the *cis* form, VII; the *trans* form, VIII, would be extremely strained. Similarly, in the unknown cyclopropyne IX, the strain should be tremendous. In such instances as these, the strain would be relieved if the sizes of the rings were greater. Thus, cycloöctyne, X, with a triple bond in an eight-membered ring, has been reported;[13] this substance is probably still somewhat strained since the simplest cycloalkyne that can be constructed with the conventional molecular models is cyclononyne, with a nine-membered ring.



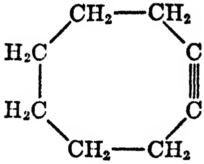
VII



VIII



IX



X

The *para* positions of a benzene ring cannot be joined by a *short* chain of any kind. The situation is different here from that with such bridge compounds as camphor, VI, which have short bridges connecting the 1 and 4 positions of a saturated six-membered ring; this difference exists because the benzene ring is planar rather than puckered, and because the bonds formed by *para* carbon atoms in benzene are directed in exactly opposite directions. Examples of known compounds in which the *para* positions of aromatic rings are joined by *long* chains are given by structure XI, in which *n* has the values 4, 6, and 10.[14] (Cf. also structure XX on page 217.)

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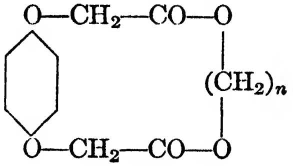
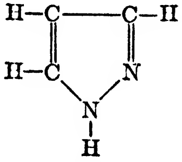
[13] N. A. Domnin, *J. Gen. Chem.* (*U.S.S.R.*) **8**, 851 (1938); *C.A.* **33**, 1282 (1939).

[14] E. W. Spanagel and W. H. Carothers, *J. Am. Chem. Soc.* **57**, 935 (1935).

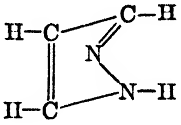


XI

The strain theory is by no means restricted to the carbon compounds of the types considered above, since it applies generally to the compounds of all the other multivalent elements that are important in organic chemistry. Not only with carbon but also with such further elements as nitrogen, oxygen, and sulfur, the most favored angles between single bonds, or between single and double bonds, seem to have magnitudes fairly close to the tetrahedral value. Consequently, heterocyclic as well as carbocyclic compounds exhibit the effects of strain when they contain rings with fewer than five atoms; moreover, the preparation of heterocyclic compounds containing rings with more than about six members is relatively difficult. (Cf. compound XI, above.) The nonexistence of substances with certain configurations can again be explained as the result of strain. Thus, the only known form of pyrazole must certainly have the *syn* configuration, XII; the *anti* isomer, XIII, would doubtless be too strained to exist. (Cf. the configurations VII and VIII.)



XII



XIII

9·6 Impenetrability of Atoms. An idea which is more or less related to the strain theory, but which was not contained in Baeyer's original formulation [2] of this theory, can be expressed by the statement that two atoms cannot be at the same position in space at the same time. To be sure, atoms are not at present considered to be rigid objects (like billiard balls) which occupy definite volumes, and which cannot interpenetrate one another. Nevertheless, considerable resistance is offered to the compression of too many atoms into a limited volume. (Cf. the discussion of repulsive forces, Section 1·15.) For this reason, it is unlikely that a substance such as hexa-*tert*-butylethane, I, can exist. There

$$[(CH_3)_3C]_3C—C[C(CH_3)_3]_3$$

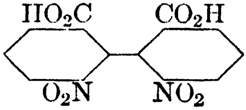
I

are no rings in this structure to require the deformation of one or more bond angles; there is, however, only an extremely small probability that all the atoms could simultaneously crowd into the restricted space available. That such an effect exists is strongly suggested not only, in general, by the low compressibilities of liquids and solids, but also by the fact that, more particularly, the central carbon-carbon bond in hexamethylethane, II, is appreciably longer than normal;[15] apparently, therefore, even the relatively small methyl groups in the molecules of this last substance are large enough to interfere to some extent with one another.

$$(CH_3)_3C{-}C(CH_3)_3$$

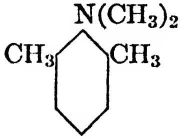
II

The six much larger *tert*-butyl groups in the substance I would undoubtedly interfere to a much greater extent. Moreover, the explanation given in Sections 6·12 and 6·13 for the optical activities of suitably substituted biphenyls and their analogs is based explicitly on the assumption that different atoms cannot come too close to one another. For, if atoms were extremely compressible, there would then be no reason why the two aromatic rings in, for example, the dinitrodiphenic acid, III, could not become coplanar; and hence no reason why the substance can be optically active. (See also Section 9·7.)



III

9·7 Steric Hindrance.[16] It has long been known that the rate of a chemical reaction may be greatly affected by atoms or groups which are close to the reactive centers of the reagent molecules, but which do not appear to be directly involved in the reaction itself. As early as 1872, for example, it had been found that 2,6-N,N-tetramethylaniline, I, forms no quaternary ammonium salt when it is treated with methyl



I

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[15] S. H. Bauer and J. Y. Beach, *J. Am. Chem. Soc.* **64**, 1142 (1942).

[16] For more comprehensive discussions of steric hindrance, see, for example, J. B. Cohen, *Organic Chemistry for Advanced Students*, Edward Arnold, London, 3rd ed., 1920, Volume 1, Chapter V; G. Vavon, *Bull. soc. chim.* [4] **49**, 937 (1931); S. Goldschmidt in K. Freudenberg, *Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, pages 451 ff.

iodide. The reaction is therefore inhibited by the two methyl groups that are *ortho* to the dimethylamino group.

One of the first systematic investigations of this problem was made by Menschutkin,[17] who showed that, when a mixture containing equivalent quantities of an alcohol and a carboxylic acid is heated, the rate of the esterification is markedly decreased by the presence of alkyl groups near either the alcoholic hydroxyl group or the carboxyl group. Thus, in their reactions with acetic acid, II, primary alcohols, III, are, in general, esterified more rapidly than are secondary alcohols, IV, whereas tertiary alcohols, V, are hardly esterified at all; moreover, in their reactions with isobutyl alcohol, VI, formic acid, VII, is esterified most rapidly, the simple primary acids, VIII, are esterified less rapidly, secondary acids, IX, are esterified still less rapidly, and tertiary acids, X, are esterified extremely slowly.

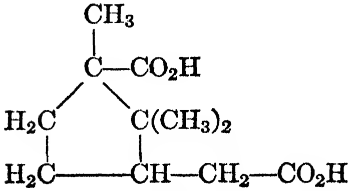
$$\underset{\text{II}}{\mathrm{CH_3\text{—}CO_2H}} \qquad \underset{\text{III}}{\mathrm{RCH_2\text{—}OH}} \qquad \underset{\text{IV}}{\mathrm{R_2CH\text{—}OH}} \qquad \underset{\text{V}}{\mathrm{R_3C\text{—}OH}}$$

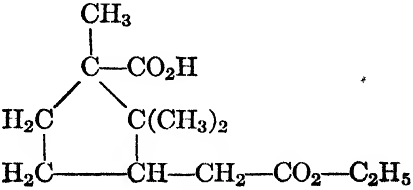
$$\underset{\text{VI}}{\mathrm{(CH_3)_2CH\text{—}CH_2\text{—}OH}} \qquad \underset{\text{VII}}{\mathrm{H\text{—}CO_2H}} \qquad \underset{\text{VIII}}{\mathrm{RCH_2\text{—}CO_2H}} \qquad \underset{\text{IX}}{\mathrm{R_2CH\text{—}CO_2H}}$$

$$\underset{\text{X}}{\mathrm{R_3C\text{—}CO_2H}}$$

In all these structures, the substituent R is an alkyl group, such as methyl and ethyl. The rate of the esterification therefore decreases uniformly as the number of alkyl groups near either the hydroxyl group or the carboxyl group increases. It can, however, be concluded from Menschutkin's work that the positions of the final equilibria are much less dependent upon the structures of the reagents than are the rates at which these equilibria are attained; for, when the reactions were allowed to proceed until no further net changes could be observed, the esterifications were in all instances found to be approximately two-thirds complete. Evidently, therefore, alkyl groups must decrease not only the rate of esterification but also that of hydrolysis.

Somewhat later, in 1889, Haller found that, when homocamphoric acid, XI, is treated with ethyl alcohol and hydrogen chloride, the pri-


XI


XII

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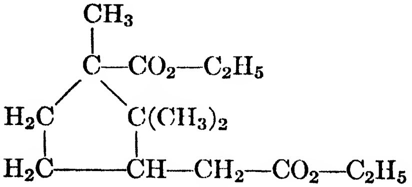
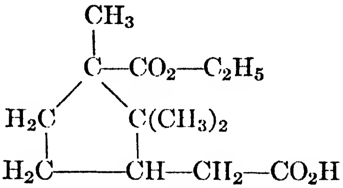
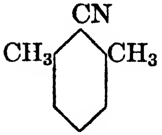
[17] N. Menschutkin, *Ann. chim.* [5] **20**, 289 (1880); [5] **23**, 14 (1881); [5] **30**, 81 (1883).

mary carboxyl group is esterified much more rapidly than is the tertiary carboxyl group. The product obtained is therefore largely the acid ester, XII; unless the reaction is continued for a very long time, only a small amount of the neutral ester, XIII, is formed. On the other hand, when this neutral ester is treated with aqueous alcoholic potassium hydroxide, the primary ester group is hydrolyzed more rapidly than is the tertiary one; the product obtained is therefore largely the isomeric acid ester, XIV. Hence, it is once more seen that alkyl substituents decrease the rates of both the esterification of the acid and the saponification of the ester.


XIII


XIV

At about this same time, several benzonitriles with methyl groups in both the positions *ortho* to the cyano group were found to be not hydrolyzable by any method then known. The compounds of this class include the ones with structures XV and XVI. Moreover, it was shown also that, although benzonitrile itself, XVII, reacts with ethyl alcohol and hydrogen chloride to form the imino ether hydrochloride, XVIII, certain of its *mono*substituted derivates, such as the compounds XIX and XX, do not undergo the analogous reactions.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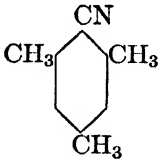
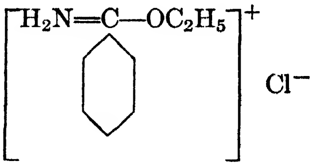
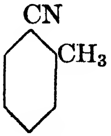
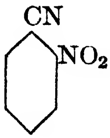

XVI

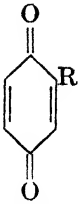

XVII


XVIII

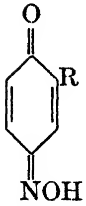

XIX


XX

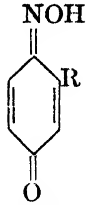
In the formation of an oxime (as well as in the esterification of a carboxylic acid, in the hydrolysis of an ester, and in the reactions of a nitrile), substituents near the reactive centers decrease the rates of the reactions. Thus, Kehrmann found that the action of hydroxylamine upon a monosubstituted *p*-benzoquinone, XXI (where R may be Cl,



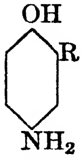
XXI



XXII

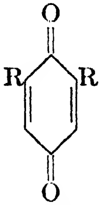


XXIII

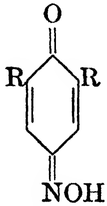


XXIV

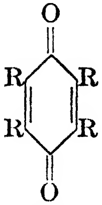
Br, I, CH_3, or $i\text{-}C_3H_7$), leads always first to the monoxime, XXII, rather than to the isomeric one, XXIII.[18] (The structure of the monoxime, XXII, is shown by the fact that, on reduction with tin and hydrochloric acid, this substance is transformed into the *p*-aminophenol, XXIV. See, however, also pages 580 and 626 f.) A disubstituted quinone, XXV, gives only the monoxime, XXVI, and no dioxime, whereas



XXV



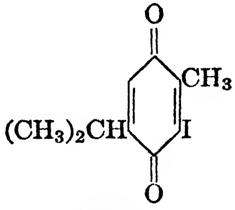
XXVI



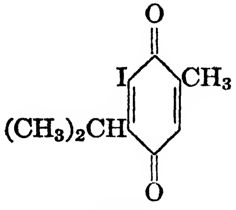
XXVII

the tetrasubstituted quinone, XXVII, gives no oxime at all.

In order to explain these observations (as well as a number of other ones, which involved reactions of several different types, and which had been recorded in the still earlier literature), Kehrmann suggested that the *Raumerfüllung* of the substituents (i.e., the ability of the substituents to "fill up the space" near the reactive centers) is responsible for their effects upon the rates.[18] In other words, he considered that the substituents shield the reactive centers from attack by the molecules of the other reagents. (Cf. Section 9·6.) In order to show the effect of a change in the size of the substituents, he studied the two isomeric quinones, XXVIII and XXIX. The first of these compounds is converted



XXVIII



XXIX

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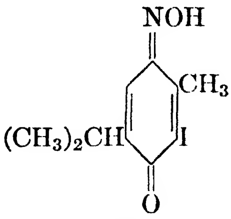
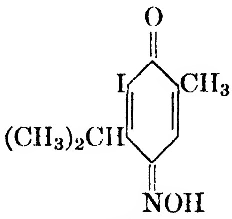
[18] F. Kehrmann, *Ber.* **21**, 3315 (1888); **22**, 3263 (1889); **23**, 130 (1890); *J. prakt. Chem.* [2] **40**, 188, 257 (1889); [2] **42**, 134 (1890).

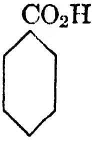
completely into its monoxime, XXX, within 15 minutes; the second is only slightly converted into its monoxime, XXXI, after even 12 hours.

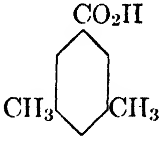

XXX

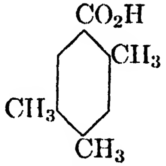

XXXI

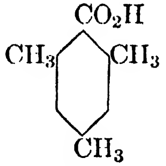
The isopropyl group in the quinone XXIX, therefore, provides more effective shielding than does the smaller methyl group in the quinone XXVIII.

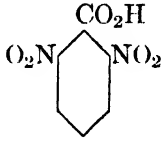
In 1894, Victor Meyer and his coworkers proposed the "law" that no benzoic acid with two *ortho* substituents can be esterified by the combined action of an alcohol and hydrogen chloride.[19] Thus, under identical conditions of esterification, the yields of methyl ester obtained from benzoic acid, XXXII, 3,5-dimethylbenzoic acid, XXXIII, 2,4,5-


XXXII

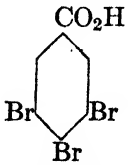

XXXIII

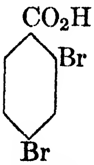

XXXIV

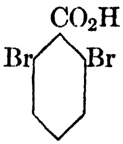

XXXV

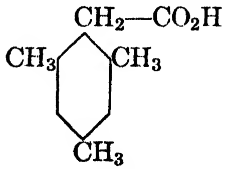

XXXVI

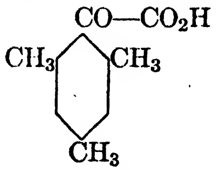
trimethylbenzoic acid, XXXIV, 2,4,6-trimethylbenzoic acid, XXXV, and 2,6-dinitrobenzoic acid, XXXVI, are, respectively, 92–95, 92–93, 83–87, 0, and 0 per cent. (An earlier observation that, with 2,4,6-trimethylbenzoic acid, XXXV, the yield of the methyl ester is about 9 per cent was shown to have been due to the use of an acid containing an esterifiable impurity; the pure acid is not esterified under the conditions employed.) Similarly, the yields of methyl ester obtained from 3,4,5-tribromobenzoic acid, XXXVII, 2,4-dibromobenzoic acid, XXXVIII,


XXXVII


XXXVIII


XXXIX


XL


XLI

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[19] V. Meyer, H. Gümbel, and J. J. Sudborough, *Ber.* **27**, 510 (1894); V. Meyer and J. J. Sudborough, *ibid.* **27**, 1580, 3146 (1894); V. Meyer, *ibid.* **28**, 1254, 2773, 3197 (1895).

and 2,6-dibromobenzoic acid, XXXIX are, respectively, 93–96, 95, and 0 per cent. On the other hand, mesitylacetic acid, XL, and mesitylglyoxylic acid, XLI, are readily esterified; it is therefore evident that the *ortho* substituents do not markedly decrease the rate of the reaction unless they are extremely close to the carboxyl group. Finally, even the acids which cannot be esterified by the action of methyl alcohol and hydrogen chloride are converted smoothly and almost quantitatively into their esters when their silver salts are treated with methyl iodide; the resulting esters, once they are formed, are extremely resistant to hydrolysis by aqueous alcoholic base.

Meyer's explanation [19] of the retarding effect of substituents upon the rates of the reactions studied was the same as the one proposed somewhat earlier by Kehrmann. Thus, he considered that the bulky atoms or groups which are near the reactive centers make it impossible for the molecules of the other reagents to approach these centers closely enough to react with them. To describe this situation, he used both the word "Raumerfüllung," which had been employed by Kehrmann, and also the further expression *steric hindrance,* which has subsequently become rather generally adopted. (However, see below.)

In order to explain the fact that the sterically hindered acids are readily esterified by the action of methyl iodide on their silver salts, Meyer and Sudborough [19] suggested that the silver atom holds the blocking substituents away from the carboxyl group, and hence permits the approach of the methyl iodide molecule. A different explanation which, at the present time, seems more reasonable, is, however, that the reaction of the salt with the alkyl halide takes place at the oxygen atom of the carboxyl group (as it obviously must do), whereas the reaction of the free acid with the alcohol in the presence of hydrogen chloride takes place instead at the corresponding carbon atom. (See pages 280 ff.) Since the oxygen atom is farther from the *ortho* substituents than is the carbon atom, the fact that the former reaction is less subject to steric hindrance than is the latter cannot therefore be considered surprising. (Cf. mesitylacetic acid, XL, and mesitylglyoxylic acid, XLI.)

As has been noted, Kehrmann was the first to suggest that what is now called steric hindrance is due to the purely mechanical interference of bulky and impenetrable atoms. Nevertheless, Meyer's prestige was so great that, in spite of Kehrmann's vigorous defence of his own priority,[20] this latter author's contribution to the field was for many years almost completely forgotten. As a result, most writers on the subject have erroneously attributed the suggestion to Meyer. (However, see Vavon [16] and Goldschmidt.[16])

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[20] F. Kehrmann, *Ber.* **41,** 4357 (1908).

The general concept of steric hindrance can be discussed from two rather different points of view. On the one hand, the phenomenon itself is an experimental *fact* which cannot reasonably be questioned. More precisely, it is a collection of a great many experimental facts, of which only a few typical examples were listed in the preceding paragraphs. On the other hand, the explanation advanced by Kehrmann, and independently by Meyer, is a *theory* which may or may not be entirely satisfactory. The expression "steric hindrance" is, accordingly, somewhat unfortunate, since it suggests the theory (which may conceivably be incorrect) rather than the facts (which are undoubtedly correct). For this reason, some authors have preferred to describe the phenomenon by the different expression "*ortho* effect." This alternative designation, however, is itself not ideal, since it incorrectly implies that the effect in question can be exerted only by *ortho* substituents, and hence can exist only in aromatic substances. The older, but admittedly poor, expression "steric hindrance" is therefore used throughout this book in any instance in which neighboring atoms or groups make a reaction slower.

There is no reason to doubt that Kehrmann's explanation of steric hindrance is in many instances at least partially correct; there is, however, excellent reason to doubt that it provides the complete explanation of all the effects which neighboring groups have been found to exert upon the rates of chemical reactions. A few examples will suffice to show that other factors, besides the impenetrabilities of the atoms, can also greatly influence the rates. Thus, *tert*-butyl alcohol, XLII, is esterified much less rapidly by a carboxylic acid,[17] but much more rapidly by a hydrogen halide, than is *n*-butyl alcohol, XLIII. Although the geometrical interpretation of steric hindrance appears to account nicely for the relative rates in the reactions with the carboxylic acids, it completely fails to account for the ones in the reactions with the hydrogen halides. The four different reactions, which are here compared with one another, are in fact known to proceed by at least two different mechanisms, and therefore to be not strictly comparable.[21] The stereochemical theory does not, however, explain why all the reactions do not follow the same mechanism.

$$\underset{\text{XLII}}{(CH_3)_3C\text{—}OH} \qquad \underset{\text{XLIII}}{CH_3\text{—}CH_2\text{—}CH_2\text{—}CH_2\text{—}OH}$$

Moreover, the hydrolysis of picryl chloride, XLIV, to picric acid, XLV, is much faster than is that, under identical conditions, of chlorobenzene, XLVI, to phenol, XLVII. The nitro groups which are *ortho*

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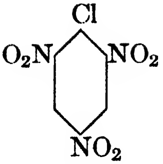
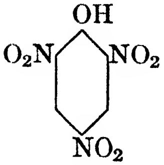
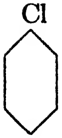
[21] Cf. E. D. Hughes, *Trans. Faraday Soc.* **34**, 202 (1938); **37**, 603 (1941); J. N. E. Day and C. K. Ingold, *ibid.* **37**, 686 (1941).



XLIV



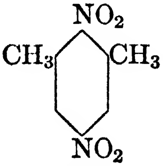
XLV



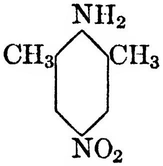
XLVI

XLVII

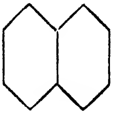
(and *para*) to the chlorine atom in the former chloride therefore do not hinder, but instead greatly facilitate, the reaction. In contrast, the nitro groups which are *ortho* to the carboxyl group in 2,6-dinitrobenzoic acid, XXXVI, completely prevent the esterification by methyl alcohol and hydrogen chloride. (See above.) Here, the hydrolyses of the two chlorides XLIV and XLVI probably occur by the same mechanism. When 1,4-dinitro-2,6-dimethylbenzene, XLVIII, is heated in a sealed tube with aqueous ammonia, the apparently more hindered nitro group in position 1, rather than the less hindered one in position 4, is replaced by an amino group; the product of the reaction is therefore 4-nitro-2,6-dimethylaniline, XLIX.[22] A theoretical explanation of this reaction has been suggested by Spitzer and Wheland.[23] In naphthalene, L, substitution reactions (regardless of their mechanisms) always take place more rapidly at one of the alpha positions than at one of the apparently less hindered beta positions.[24] Finally, 2,4,6-trimethylbenzoic acid, XXXV, which cannot be esterified with methyl alcohol and hydrogen chloride (see above), is smoothly and rapidly converted into its ester, LI, when its solution in 100 per cent sulfuric acid is poured into cold



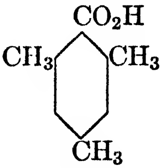
XLVIII



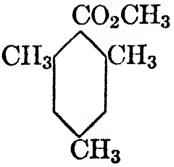
XLIX



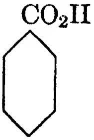
L



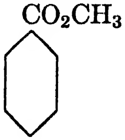
XXXV



LI



XXXII



LII

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[22] K. Ibbotson and J. Kenner, *J. Chem. Soc.* **123**, 1260 (1923).

[23] W. C. Spitzer and G. W. Wheland, *J. Am. Chem. Soc.* **62**, 2995 (1940); see also G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 273 f.

[24] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, Section 8·11.

methyl alcohol;[25] conversely, the resulting ester, LI, which is not affected by hot aqueous alcoholic bases, is hydrolyzed back to the acid when its solution in 100 per cent sulfuric acid is poured onto ice.[25] On the other hand, benzoic acid, XXXII, is not esterified, and its ester, LII, is not hydrolyzed by the procedures described. Here again, the mechanisms of the esterifications and hydrolyses under the different experimental conditions must be entirely different.[25] (Cf. the analogous situation encountered above in the esterification of the sterically hindered benzoic acids by treatment of their silver salts with methyl iodide.)

It is therefore evident that steric factors alone are insufficient to explain all the observed variations in rate that are produced by substituents near the reactive centers. Although any complete theory must, to be sure, include these factors, it must nevertheless also include such other factors as the mechanisms of the respective reactions, the electrostatic interactions between atoms and groups (see Chapter 11), the influence of the solvent (if any), the effects of resonance (see Chapter 10), and possibly many others which are not at present recognized. Further discussion of the problem would, however, lie outside the scope of this book.

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[25] M. S. Newman, *J. Am. Chem. Soc.* **63**, 2431 (1941); M. S. Newman, H. G. Kuivila, and A. B. Garrett, *ibid.* **67**, 704 (1945).

10.

The Theory of Resonance

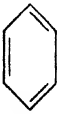
10·1 Intermediate Structures. At several places in the preceding chapters, it has been stated that the true average distributions of electric charge in certain molecules or ions are probably intermediate between the average distributions corresponding to various specified structures. (For examples, see pages 15 f., 20, 46, 52, 91 f., 173, 258, 305 f., 310, 313, 334, and 360.) In such instances, the situations could of course be described equally well by the alternative statements that the true structures of the systems under consideration are probably intermediate between the extreme structures specified.

In order that these rather vague concepts of intermediate charge distributions and of intermediate structures may be made more precise, a discussion of the theoretical principles involved is now desirable.[1]

This discussion can be conveniently initiated by a rather detailed survey of the structure of benzene, since this compound doubtless provides the most important example of a substance with an intermediate structure. (See also pages 102 ff.)

10·2 Early Attempts to Assign a Structure to Benzene. As was stated in a previous chapter (see pages 105 f.), the Kekulé structure, I or II, of benzene[2] is unsatisfactory because it leads to incorrect predictions regarding the numbers of isomeric substitution products. Moreover, it is unsatisfactory also because it is inconsistent with the fact that, in all four of the ways discussed in Section 9·2, benzene is unexpectedly stable; or, in other words, with the facts that benzene has an appreciably


I

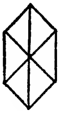

II

[1] For more detailed discussions of the theory of resonance, see L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, 1st ed., 1939, 2nd ed., 1940; L. Pauling in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume II, Chapter 22, 2nd ed., 1943, Volume II, Chapter 26; G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944.

[2] A. Kekulé, *Bull. soc. chim.* [2] **3**, 98 (1865); *Ann.* **137**, 129 (1866); **162**, 77 (1872).

smaller heat of combustion than would be expected of a substance with structure I or II (see pages 427 f.), that it has a lower free energy, that it is formed much more easily, and that it is considerably less reactive. For these reasons, the Kekulé structure must be judged unacceptable.

The Claus diagonal structure, III,[3] leads to correct predictions regarding isomer numbers (cf. pages 108 f.), but it can hardly be reconciled with the observed stability of the substance. Since the bond angles in structure III are very greatly distorted from their most stable values, a molecule with this structure would be extremely strained. Moreover, since the six carbon atoms in the benzene molecule are now known to lie at the corners of a regular plane hexagon, the bonds joining the three pairs of atoms that are *para* with respect to each other are twice as long as are those joining pairs of atoms that are adjacent to each other in the ring. Consequently, the former bonds would have been stretched nearly to their breaking points (if not beyond); hence this structure does not greatly differ from one in which each carbon atom has a free valence. For this reason also, a molecule with the Claus structure, III, could hardly exhibit the unexpectedly high stability that is characteristic of benzene; the structure can therefore be discarded.



III

The Armstrong-Baeyer centric structure, IV,[4] like the Claus structure, III, is in agreement with the observed numbers of isomeric derivatives; it suffers, however, from the difficulty that the meaning of the "centric bonds" which it contains is not clear. These bonds cannot represent free valences since, if such free valences were present in the molecule, the substance should be extremely reactive. Moreover, the centric bonds cannot be left undefined; for, if they were left undefined, the structure would be meaningless. Possibly the least illogical interpretation of these bonds is contained in the statement that the symbol

IV

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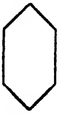
[3] A. Claus, *Ber.* **15**, 1405 (1882); *J. prakt. Chem.* [2] **37**, 455 (1888).

[4] H. E. Armstrong, *Phil. Mag.* [5] **23**, 73 (1887); *J. Chem. Soc.* **51**, 258 (1887); A. Baeyer, *Ann.* **245**, 103 (1888).

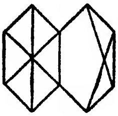
IV, by definition, represents the structure of benzene, whatever that structure may be. Such an interpretation, however, not only begs the entire question but also leads to the result that the centric structure tells no more about the state of the benzene molecule than does the simpler conventional hexagon, V, to which it would then be completely



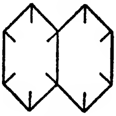
V

equivalent. The centric structure can accordingly also be discarded.

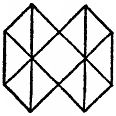
It may be noted in passing that neither the Claus nor the Armstrong-Baeyer structure of benzene can be satisfactorily extended to the condensed aromatic substances like naphthalene, anthracene, and phenanthrene. For naphthalene, for example, the only diagonal and centric structures which can be drawn are either like VI and VII, in which the two rings are not equivalent, or like VIII and IX, in which the two central carbon atoms are not directly joined to each other in any



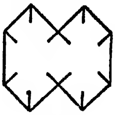
VI



VII



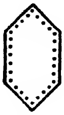
VIII



IX

way. Neither of these possibilities seems reasonable in view of the properties of the substance. Moreover, exactly these same sorts of difficulty are encountered also in the attempt to write either a diagonal or a centric formula for anthracene, or for any other of the more highly condensed aromatic hydrocarbons. Since, however, all these substances (including benzene) have rather similar properties, they may be presumed to have analogous structures. Consequently, the fact that the diagonal and centric structures cannot be satisfactorily generalized to include the more complex systems strongly suggests that, even with benzene, such structures are incorrect.

Thiele's structure, X, of benzene [5] provides a rather closer approach



X

to the modern view than does any of the preceding ones. The dotted lines in this structure represent "partial valences," which may be defined as follows. Each carbon atom of benzene, after it has formed single bonds to the attached hydrogen atom and to each of its neighbors in the ring, is able, since it is quadrivalent, to form one additional

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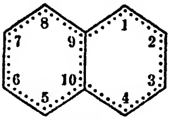
[5] J. Thiele, *Ann.* **306**, 87 (1899).

bond. It can accordingly be said to possess a *residual affinity*. If this affinity of each carbon atom is used up by forming a bond with one of its neighbors, then a Kekulé structure (either I or II) results. If, on the other hand, it is used up by an equal interaction with each of its neighbors, then Thiele's structure, X, results. Since the affinity is therefore divided between two interactions, the partial valences represented by the dotted lines are weaker than ordinary valence bonds; consequently, each of the equivalent carbon-carbon bonds in benzene is weaker than an ordinary carbon-carbon double bond, although it is stronger than a carbon-carbon single bond.

Thiele's structure of benzene has several advantages. In the first place, as is readily seen, it leads to correct predictions of isomer numbers. In the second place, it is not inconsistent with the observed stability of the substance; indeed, Thiele considered that his structure *explained* the stability of benzene, since it shows, he thought, a more nearly complete saturation of the affinities of all the carbon atoms than the Kekulé structure does. Finally, a structure of similar type can be written not only for benzene but also for naphthalene and for the remaining condensed aromatic hydrocarbons. Naphthalene, for example, can be expressed as XI.

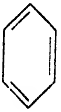


XI

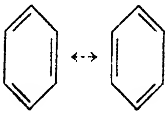
It is to be noted, however, that the various carbon-carbon bonds in structure XI cannot be equivalent to one another even though each is represented by the same symbol, $\overline{\ldots\ldots\ldots\ldots}$. The situation can be described as follows. Each of the two central carbon atoms, C_9 and C_{10}, shares its affinity with *three* neighbors, whereas each of the carbon atoms of benzene shares its affinity with only *two* neighbors. Consequently the C_9—C_{10}, C_9—C_1, C_9—C_8, C_{10}—C_4, and C_{10}—C_5 bonds are presumably somewhat weaker than are any of the ones in benzene. The four alpha carbon atoms, C_1, C_4, C_5, and C_8, accordingly have relatively large amounts of affinity left over; hence the C_1—C_2, C_3—C_4, C_5—C_6, and C_7—C_8 bonds are stronger than are any of those in benzene. Since the beta carbon atoms, C_2, C_3, C_6, and C_7, then have relatively little affinity left over, the C_2—C_3 and C_6—C_7 bonds should again be weak. (Cf. page 429.)

The principal defect of Thiele's structures of benzene and of the other aromatic hydrocarbons consists in the vagueness of the fundamental concept. It may indeed be asked what, precisely, is this "affinity," which every atom is considered to have, but which exists in strictly limited amount; and how, precisely, do the affinities possessed by adjacent atoms saturate each other? The inability of Thiele or of his followers to provide satisfactory answers to such specific questions as these makes the significance of their structures rather uncertain. As a result, it might be maintained that structures of the sort represented by diagrams X and XI, like the centric structure IV, are merely complicated devices for concealing the ignorance of the person who employs them. Although such an extreme criticism of Thiele's views is probably not entirely justified, it nevertheless contains sufficient truth to prevent Thiele's structures from being completely satisfactory representations of the corresponding molecules.

10·3 More Recent Developments. The present view regarding the structure of benzene is that the substance is a so-called *resonance hybrid*,[1, 6] receiving equal contributions from the two Kekulé structures, I and II. That is to say, benzene is now considered to have a structure


I


II


III

which is not identical with either I or II, but is halfway between them. The situation can be described graphically by the symbol III, in which the double-headed arrow[7] ↔, representing resonance, must be carefully distinguished from the pair of arrows ⇄, representing chemical equilibrium. This section and the succeeding ones will be devoted to a discussion of the significance of the above statements.

It is unfortunate that no satisfactory single symbol (analogous, for example, to the symbol IV or V of Section 10·2) has ever been devised for the representation of a structure, like that of benzene, which is presumed to be intermediate between two (or among more than two) extremes. When an organic chemist encounters for the first time such a symbol as III, he is almost certain to draw the entirely erroneous conclusion that the molecule to which it refers is considered to be undergoing transitions between the limiting structures specified. Such a view is, however, not correct. At the present time, it is not supposed that a single molecule of benzene possesses one Kekulé structure part of the time, and the second Kekulé structure the rest of the time; and it is not supposed that, in a sample of the substance at any given time, some of the molecules have one Kekulé structure, while the remaining molecules have the second Kekulé structure. Instead, it is supposed that a given molecule possesses a single structure at all times, and that all molecules have the same structure. The structure possessed by all

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[6] Cf. L. Pauling and G. W. Wheland, *J. Chem. Phys.* **1**, 362 (1933).

[7] C. R. Bury, *J. Am. Chem. Soc.* **57**, 2115 (1935); B. Eistert, *Angew. Chem.* **49**, 33 (1936).

molecules at all times is, however, intermediate between I and II. The situation can be illustrated by a simple analogy. The statement that a mule is a hybrid between a horse and a donkey does not imply that a given mule is a horse part of the time and a donkey the rest of the time; neither does it imply that, at any given time, some mules are horses and the rest are donkeys. Instead, it implies that a mule is neither a horse nor a donkey but is a single kind of animal, intermediate at all times between the two extremes; and that all mules are the same kind of animal. In a similar sense, the structure of benzene, represented by the expression III, is considered to be a *hybrid* of structures I and II.

Since the Kekulé structures differ from each other only by a rotation of 60° about an axis perpendicular to the ring, and since the two are therefore completely equivalent to each other, it may well be asked what a transition between them would mean. The answer to such a question can be given most easily by reference to some specific carbon-carbon bond. In structure I, the bond at the extreme right of the figure is a double one, but, in structure II, the bond between these same two atoms is a single one. If the molecule has structure I part of the time, and structure II the rest of the time, then the individual bond under discussion is double part of the time, and single the rest of the time. On the other hand, if the molecule has a unique structure which all of the time is intermediate between I and II, then the bond is of a unique type, which all of the time is intermediate between double and single.

Such a bond, for lack of a better name, might be called a "one-and-a-half bond" (however, see page 429), or possibly a "benzene bond." Since similar considerations apply also to each of the five remaining carbon-carbon bonds in the molecule, all six of the bonds are equivalent to one another. The interpretation just given for the structure of benzene therefore leads to correct predictions regarding the numbers of isomeric derivatives.

10·4 The Significance of the Hybrid Structure of Benzene.

The concept of a bond which is intermediate between a single and a double bond, but which is not changing back and forth between the two types, is a rather difficult one for many chemists to grasp. The reason for this difficulty is possibly that most chemists unconsciously think of a bond as a more or less static affair, like the lines or pairs of dots in the conventional symbols, or perhaps even like pairs of tiny interlocking hooks which hold the atoms together. With such a mental picture, one can easily visualize a single or a double bond, or a bond which changes back and forth between the two types, but he cannot so easily visualize a bond which is, and remains, intermediate between the two extremes. The picture is, however, not correct, since a bond is actually not a static, but a very dynamic, affair. The electrons that produce the bond are in constant and very rapid motion, in the course of which their paths extend over the entire molecule and even beyond what would ordinarily be considered the boundaries of the molecule. The line, or the pair of dots, by which an individual bond is represented is therefore only a sort of shorthand symbol which implies that, over a period of time, the two electrons are more likely to be in the region between the nuclei of the atoms linked than to be anywhere else; and hence that the average density of electronic charge, again over a period of time, is relatively great in this region between the nuclei. (Cf. Section 1·8.) Indeed, the concept of a bond, or of a structure, at a single instant of time is really meaningless, since *any* set of instantaneous positions of the electrons relative to those of the nuclei is consistent with any structure that can be written for the system under consideration.

The *uncertainty principle* of quantum mechanics [8] permits the theoretical basis of the foregoing statements to be made somewhat clearer. Of the several forms in which this principle can be expressed, the one of interest here is the one shown in the inequality 10·1. Here, $\Delta\epsilon$ is the uncertainty in the knowledge of the energy of a single molecule; Δt

$$\Delta\epsilon \cdot \Delta t \geq h \tag{10·1}$$

represents the uncertainty in the knowledge of the time at which the molecule has the energy that is known within the stated limits; and h is Planck's constant, 6.6×10^{-27} erg sec. The uncertainty principle therefore says that, if a person wishes to consider the state of any atom or molecule during a period of time equal to Δt, he is unable to know the energy of the atom or molecule during that time with a precision greater than $\pm h/\Delta t$; or, conversely, that, if a person knows the energy of a molecule within the limit $\pm\Delta\epsilon$, any information which he may have about the molecule cannot refer to a time interval less than $h/\Delta\epsilon$.

If Planck's constant is transformed into more familiar and more useful units, the statement of the uncertainty principle becomes that shown in inequality 10·2, where ΔE is now the uncertainty in the knowledge of

$$\Delta E \cdot \Delta t \geq 10^{-13} \text{ kcal sec per mole} \tag{10·2}$$

the energy in kilocalories per mole, rather than in ergs per molecule. If it is supposed that a given bond or a given structure corresponds to an energy which is definite to within, say, ±1 kcal per mole (and this is a rather large allowance), then the only properties of the bond or structure which can be known are time averages over intervals of at least 10^{-13} sec. If, on the other hand, it is supposed that the bond or

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[8] See any textbook of quantum mechanics.

structure corresponds to an energy which is definite to within the smaller uncertainty of ±1 cal per mole, then the only properties which can be known are averages over the longer interval of 10^{-10} sec. In general, the more precisely the energy is determined, the less precisely is known the time to which it refers, and vice versa. If the energy were determined with complete precision, so that ΔE is equal to 0, then nothing whatever could be said about the time, since Δt would then be infinite; conversely, if complete information were available about the condition of the system at a definite instant (e.g., if the exact instantaneous relative positions of all the electrons with respect to the nuclei were known), so that Δt is equal to 0, then nothing whatever could be said about the energy, since ΔE would then be infinite. Since *some* information regarding both the time and the energy must always be available, neither Δt nor ΔE can ever be infinite in any problem of physical significance; the values of Δt equal to about 10^{-13} sec and of ΔE equal to about 1 kcal per mole are possibly fair representations of the orders of magnitude of the minimum uncertainties in most chemically interesting situations.

There is of course nothing in the uncertainty principle to prevent one or both of the uncertainties from being larger than these minima, or to prevent their product from being greater than 10^{-13} kcal sec per mole; indeed, it would be difficult to imagine an ordinary chemical experiment in which the product of uncertainties would not be enormously larger than the value stated. As will be shown below, however, the existence of the lower limit is nevertheless of extremely great theoretical importance.

It might be thought that uncertainties Δt of the order of 10^{-10} or 10^{-13} sec are so small that they could cause no trouble. However, since the electrons move with enormous velocities, and since also the intramolecular distances are very small, even such infinitesimal intervals of time as these are important. For example, in the old Bohr theory of the hydrogen atom, an electron in the most stable orbit was considered to make a complete revolution around the proton in about 10^{-15} sec; it would therefore make about 10^5 such revolutions in 10^{-10} sec, or about 10^2 in 10^{-13} sec. Clearly, therefore, if one wishes to talk about the position of the electron in its orbit at any given time, he must consider a time interval that is no longer than 10^{-16} or 10^{-17} sec; the uncertainty in his knowledge of the energy of the atom would then necessarily be at least of the order of 10^3 or 10^4 kcal per gram atom. Clearly also, under such circumstances, the electron under discussion could not be described as being in its most stable orbit or in any other specified orbit, since each orbit is associated, in the Bohr theory, with a definitely known energy; moreover, the hydrogen atom itself could not be described as being in any specified state or as having any specified structure of either chemical or spectroscopic interest. Although the Bohr theory is no longer thought to provide an accurate picture of the hydrogen atom, the order of magnitude of the calculated period is nevertheless significant. In fact, the Bohr theory leads to the same average kinetic energy (and hence also to the same root-mean-square velocity) for the single electron in this atom as does the more modern quantum mechanics;[8] moreover, in the normal hydrogen atom, the radius of the (circular) Bohr orbit has the same value (about 0.53 A) that is found quantum mechanically for the most probable distance between the proton and electron.

The situation in more complicated atoms and molecules is not essentially different from that in the hydrogen atom; consequently, with the former more complicated systems, as with the latter simple one, the interval of, say, 10^{-13} or 10^{-10} sec, required for the establishment of a definite state, representable by a definite structure, is so long that only average properties are significant.

The above discussion is not quite correct since it is based upon *time* averages, and not upon averages of the type that are involved in quantum-mechanical treatments. For example, the average kinetic energy of the electron in a normal hydrogen atom is approximately 4.35×10^{-10} erg. This statement means that, if a single measurement of the kinetic energy is made on each of a large number of different normal hydrogen atoms, the arithmetic average of the results thus obtained will be approximately 4.35×10^{-10} erg. The reason why only one measurement is made on each atom is that, after the first measurement has been made, the atom is in general no longer in its original state. On the other hand, the statement in question does *not* mean that the average kinetic energy of the electron in some individual atom, over an extended period of time, is necessarily equal to 4.35×10^{-10} erg. Such a time average, in fact, cannot be obtained, because, as was just pointed out, only one measurement can be made on each atom. Nevertheless, the two kinds of average, although not necessarily identical, must be of the same order of magnitude; consequently, the above use of the simpler time average can hardly have invalidated the conclusions reached in the preceding paragraphs. Moreover, in the statement of the uncertainty principle, Planck's constant h (on the right side of the inequality 10·1) is frequently replaced by some smaller quantity like $h/2\pi$ or $h/4\pi$. The distinction among these alternative expressions lies in the respective definitions of the uncertainties $\Delta\epsilon$ and Δt which are used. With the particular definitions stated above, it is perhaps not entirely clear whether the inequality 10·1 is exactly correct, or whether, in it, Planck's constant should instead be multiplied by some factor. In any event, however, there can be no question that the product $\Delta\epsilon \cdot \Delta t$ of the two uncertainties must always be equal to, or greater than, some quantity which is of the same order of magnitude as h. Consequently, the foregoing treatment, which makes use of the simplest form of the fundamental inequality, is at least qualitatively correct.

With this brief digression into quantum-mechanical theory out of the way, the problem of the structure of benzene may once more be discussed.

It was stated above that each carbon-carbon bond in this substance is at present considered to be intermediate between a double and a single bond. Since one of the most characteristic properties of any covalent bond is the relatively high average density of electronic charge in the region between the nuclei (cf. Sections 1·8 and 1·9), a bond of intermediate type can be pictured as one in which the average density of charge has an intermediate value. The valence electrons of benzene can therefore be considered to move about the molecule in such a way that the average density of charge between any pair of adjacent carbon atoms is greater than it would have been if the two atoms had been linked by a single bond, as in one of the Kekulé structures, but less than it would have been if the atoms had instead been linked by a double bond, as in the other Kekulé structure.

Further characteristic properties, besides the average charge distribution, can be used for the interpretation of a bond of intermediate type. Thus, the length of each carbon-carbon bond in benzene (1.39 A) is less than that of a typical carbon-carbon single bond (1.54 A), but greater than that of a typical carbon-carbon double bond (1.34 A). Similarly, the energy of each carbon-carbon bond in benzene is intermediate between the energies characteristic of corresponding single and double bonds; the stretching force-constants are likewise intermediate; and so on.

It should be noted, however, that, although the hybrid structure of benzene may be considered exactly halfway between the two Kekulé structures, any given property of the individual carbon-carbon bonds need not be exactly halfway between the corresponding properties of single and double bonds. The length of each carbon-carbon bond in benzene, for example, is considerably nearer to that of a double bond than to that of a single bond; the energy is similarly nearer to that of a double bond, as will be discussed further in Sections 10·10 and 10·11, and so on. Such deviations of the observed properties of a hybrid bond from the arithmetic mean need cause no surprise, since there is no theoretical reason why the arithmetic mean should be of greater significance than any of the numerous other types of mean (e.g., the geometrical mean), which are mathematically possible, but which differ from it. Indeed, the theory of valence has at present been developed to such a point that rough calculations of several properties of such hybrid bonds can now be made; these calculations have led to results in at least qualitative agreement with experiment.[1, 6] The analogy of the mule, introduced on page 392, can again be invoked. The fact that a mule is halfway between a horse and a donkey does not require that, for example, its weight or the length of its tail be the arithmetic mean of the weights or of the lengths of tail of its two parents. (For further discussion of the nature of the mean which is here involved, see Section 10·11.)

10·5 A More General Discussion of the Theory of Resonance.

The modern interpretation of the structure of benzene as a hybrid of the two Kekulé structures may possibly seem just as vague and indefinite as, for example, the interpretation advanced by Thiele. Such a criticism is, however, not valid, since the theory of resonance, upon which are based the views described in this chapter, is a simple corollary of quantum mechanics.[1, 9] To the rather considerable extent, therefore, to which the quantum-mechanical description of any molecule is clear and definite, the concept of a resonance hybrid is also clear and definite.

The general situation can be described in the following way. The most nearly complete description of the state (i.e., of the structure) of any atom or molecule, which is permitted by quantum mechanics, is contained in the so-called *wave function* or *eigenfunction* (or *characteristic function*, or *proper function*) of that atom or molecule.[8] This function is (usually an extremely complicated) one of all the spatial coordinates of all the particles present (i.e., of all the nuclei and electrons); it varies in form, of course, from system to system. Its physical significance can be described partially, but sufficiently well for the purposes of this discussion, by the statement that an eigenfunction is related in a simple way to the average distribution of electric charge within the particular system to which it refers. Indeed, an eigenfunction may conveniently be thought of as merely a detailed mathematical specification of this average distribution.

The situation can be made somewhat more precise, without the introduction of very great mathematical complexities. An atom or molecule consisting of altogether N particles (i.e., electrons and nuclei) can be considered. If the three cartesian coordinates of the jth particle (where j is equal to 1, 2, 3, $\cdots$, N) are called x_j, y_j, and z_j, the wave function is then a function of the $3N$ coordinates x_1, y_1, z_1, x_2, $\cdots$, y_N, z_N, and of the time. It contains also some parameters referring to the states of spin, if any, of all the various particles (for the significance of spin, see page 417); these parameters may be ignored here, however, since they in no way affect the following discussion. Now, if a definite numerical value is assigned to each of the coordinates x_1, $\cdots$, z_N, the wave function reduces to a function of the time alone. Although this function is in general complex (i.e., although it in general involves the imaginary unit i, which is defined as equal to $\sqrt{-1}$), the square of its absolute magnitude is necessarily both real and positive (or zero). The proof of this last statement is as follows. Any complex quantity can be expressed in the form $a + bi$, where a and b are real. The square of the absolute magnitude of this quantity is then given by the product of it and its complex conjugate, i.e., by the product $(a + bi)(a - bi)$, which is equal to $a^2 + b^2$. Since a and b are real, $a^2 + b^2$ is real

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[9] W. Heisenberg, *Z. Physik* **38**, 411 (1926).

and positive, unless both a and b are separately equal to zero, in which case both the original complex quantity $a + bi$ and the square of its magnitude are equal to zero. Moreover, if the wave function of the atom or molecule under discussion corresponds to a state of definite energy, its dependence upon the time is always such that the square of its absolute magnitude is independent of the time. Under such circumstances, the square of the magnitude of the wave function for any set of values of the coordinates $x_1, \cdots, z_N$ is a real constant which cannot have a negative value. It is a fundamental postulate of quantum mechanics that this constant is proportional to the probability (which also, of course, must be real and nonnegative) that an experiment would find that, simultaneously, particle 1 is at the point x_1, y_1, z_1 (or, more precisely, that it is in a region of specified small, but finite, volume centered about the point x_1, y_1, z_1); particle 2 is at the point x_2, y_2, z_2 (in the same sense); $\cdots$ and particle N is at the point x_N, y_N, z_N. If, now, a second set of values of the coordinates $x_1, \cdots, z_N$ is introduced into the wave function under discussion, a corresponding probability, which in general of course has a different numerical value from the first, can be obtained in the same way as before. Indeed, for each of the infinite number of possible sets of values of the $3N$ coordinates, a similar probability can be found. It should now be apparent that, from such detailed information regarding the probabilities of finding the various particles at the various positions in space, the average distribution of electric charge in the atom or molecule can be computed. Although the rather complicated mathematical details of the computation need not here be further discussed, attention should nevertheless be specially called to one important feature of the result: since the square of the absolute magnitude of a wave function corresponding to a state of definitely known energy does not contain the time (see above), the average charge distribution in an atom or molecule of precisely known energy must be independent of the time. (The uncertainty principle in the forms given in the inequalities 10·1 and 10·2, above, states that complete knowledge of the energy precludes any knowledge of the time.)

In principle, the eigenfunction of any atom or molecule can be obtained as the solution of a certain partial differential equation, which is called the *Schrödinger equation* or the *wave equation;* in practice, however, the mathematical difficulties are so great with any system more complicated than the hydrogen atom that some different procedure, leading to only an approximately correct eigenfunction, must be employed. Of the several different approximate methods devised for this purpose, only the one that leads to the concept of resonance need now be discussed. The remaining methods, although they are usually about as satisfactory as the one considered here (and, in certain applications, may even be superior to this one), are not so conveniently describable in ordinary chemical language since they make no explicit use of the idea of structure in its conventional chemical sense.

There has been devised a more or less empirical procedure by which an approximate eigenfunction can be set up for the representation of any specified valence-bond structure of the familiar type.[10] From what

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[10] J. C. Slater, *Phys. Rev.* **38**, 1109 (1931); H. Eyring and G. E. Kimball, *J. Chem. Phys.* **1**, 239 (1933); G. W. Wheland in A. Farkas, *The Physical Chemistry of Hydrocarbons*, Academic Press, New York, Chapter 1 (in press).

was said above regarding the relation between an eigenfunction and the average distribution of charge in the molecule which it represents, it should be evident that *one* of the criteria employed in deciding upon a suitable form of this approximate function is that the function must correspond to relatively high average densities of electronic charge in the regions between pairs of atoms which are joined to one another by covalent bonds, and to relatively low average densities elsewhere. Since the functions thus obtained are not derived by solution of the wave equation, but are instead written down arbitrarily, they could only by the most extraordinary accident be completely correct (i.e., correspond exactly to the true average distributions of charge). There are nevertheless fairly satisfactory reasons for believing that such approximate eigenfunctions are near enough to the correct ones so that they may legitimately be used in a large number of chemical and physical problems.

If, with respect to some particular substance, or in the treatment of some particular problem, the above approximate eigenfunctions are not good enough, there exist certain methods by which these functions can be improved to a greater or less extent. A useful procedure for achieving this end can be illustrated by the example of hydrogen chloride. Two fairly reasonable structures, I and II, can be written for this substance, and the two corresponding approximate wave functions, which may be called ψ_{I} and ψ_{II}, respectively, can be set up. Now, the function ψ_{I} represents a charge distribution such that the two valence electrons are shared equally by the hydrogen and chlorine atoms, whereas ψ_{II} represents one such that these electrons belong entirely to the chlorine atom and not at all to the hydrogen atom. Neither function therefore can be quite satisfactory. In consequence of the relatively great electronegativity of chlorine, the electrons can hardly be shared equally, as in structure I; on the other hand, the transference of the electrons from the hydrogen to the chlorine atom can hardly be complete, as in structure II. It would therefore seem reasonable to suppose[1,11] that the *linear combination* $\psi_{\mathrm{I,II}}$ of equation 10·3, in which a_{I} and a_{II} are

$$\text{H—Cl} \qquad\qquad \text{H}^+\text{Cl}^-$$

I II

$$\psi_{\mathrm{I,II}} = a_{\mathrm{I}}\psi_{\mathrm{I}} + a_{\mathrm{II}}\psi_{\mathrm{II}} \tag{10·3}$$

numerical constants, may be better than either ψ_{I} or ψ_{II} alone (provided, of course, that the values of a_{I} and a_{II} are properly chosen); indeed, such a function necessarily corresponds to a charge distribution that is intermediate between the extremes represented by ψ_{I} and ψ_{II}. (However,

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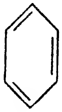
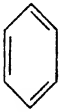
[11] L. Pauling, *J. Am. Chem. Soc.* **54**, 988 (1932).

see Section 10·11.) Quantum mechanics provides a straightforward, but tedious, method by which the best values of a_{I} and a_{II} may be obtained; when these values are employed, then the resulting function $\psi_{\mathrm{I,II}}$ gives the closest approximation to the true distribution of charge that can be obtained by any function of the assumed form. Even without knowledge of the necessary quantum-mechanical theorems, however, it can be inferred that a_{I} must be rather greater in magnitude than a_{II} (or, in other words, that structure I must make a larger contribution to the state of the molecule than does structure II); this conclusion follows because the average net charges on the hydrogen and chlorine atoms, although appreciable, are only about one-sixth as great as would be demanded by structure II.

A further example of greater organic chemical interest is provided by benzene, which was discussed above in some detail, but from a different point of view. For the two Kekulé structures III and IV, the corresponding approximate wave functions ψ_{III} and ψ_{IV}, respectively, may be set up. Neither of these functions can, however, be very satisfactory, since each corresponds to an alternation of bond type within the ring, and since the observed properties of the substance are inconsistent with such an alternation. (See above.) As with hydrogen chloride, an improved, but of course still approximate, wave function can be obtained by means of a linear combination of the two original ones. Thus, the function $\psi_{\mathrm{III,IV}}$ (equation 10·4), with suitable choice of the constant


III


IV

$$\psi_{\mathrm{III,IV}} = a_{\mathrm{III}}\psi_{\mathrm{III}} + a_{\mathrm{IV}}\psi_{\mathrm{IV}} \qquad (10\cdot4)$$

coefficients a_{III} and a_{IV}, should be appreciably better than either ψ_{III} or ψ_{IV} alone. Indeed, without recourse to any quantum-mechanical manipulations, it can be immediately seen that a_{III} and a_{IV} must be exactly equal in magnitude. Since structures III and IV (and hence also the functions ψ_{III} and ψ_{IV}) are equivalent to each other, there can be no reason why the magnitude of a_{III} should be either greater or less than that of a_{IV}. Furthermore, as should be apparent, the undesired alternation in bond type can be completely eliminated in $\psi_{\mathrm{III,IV}}$ only if a_{III} and a_{IV} have exactly the same magnitude.

Whenever an approximate wave function of a molecule is built up, in the manner illustrated above, as a linear combination of two (or more) simpler functions, the molecule in question, or the corresponding substance, is said to *resonate* between (or among) the structures represented by those simpler functions, or to be a *resonance hybrid* of the structures. The structures themselves are said to *contribute* to the state of the molecule and to resonate with one another.

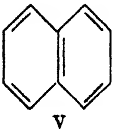
In hydrogen chloride, since the magnitude of the constant coefficient a_{I} is doubtless greater than is that of a_{II} (see above), structure I must make a larger contribution to the state of the molecule than does structure II. In other words, although the true structure of hydrogen chloride (as defined by the average distribution of charge in the actual molecule) is intermediate between I and II, it is nearer to I than it is to II. In benzene, however, since the constants a_{III} and a_{IV} must be equal in magnitude, the two Kekulé structures III and IV must make equal contributions; hence, here, the true structure is exactly halfway between the extremes.

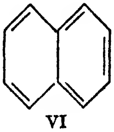
Several further points of interest arise from the quantum-mechanical approach to the theory of resonance. In the first place, it may be noted that the assumption of resonance in any molecule cannot conceivably make the resulting approximate wave function (i.e., the resulting approximate average distribution of charge) any poorer than it was originally. Thus, if an arbitrary molecule is considered to resonate between two specified structures J and K, its wave function ψ_{jk} is to be expressed in the form shown in equation 10·5, where the constants a_j and a_k are

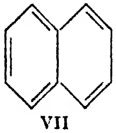
$$\psi_{jk} = a_j\psi_j + a_k\psi_k \qquad (10\cdot 5)$$

to be given the values which make ψ_{jk} *as good as possible*. The very worst that could happen therefore would be that a_j is equal to 1 and a_k is equal to 0, or else that a_j is equal to 0 and a_k is equal to 1. In either event, the result is just the same as if the structure J or K, respectively, had been accepted at the outset and the possibility of resonance had been ignored. If the best values of a_j and a_k are neither 0 nor 1, the assumption of resonance necessarily leads to an improved wave function.

A second point of interest is that, as was suggested above, the resonance in a molecule need not be limited to two structures. In naphthalene, for example, the three structures V, VI, and VII seem about


V


VI


VII

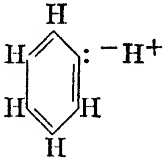
equally reasonable.[6] The charge distribution within the molecule might therefore be expected to be more accurately described by the function

$\psi_{\mathrm{V,VI,VII}}$ of equation 10·6 than by any one of the individual functions

$$\psi_{\mathrm{V,VI,VII}} = a_{\mathrm{V}}\psi_{\mathrm{V}} + a_{\mathrm{VI}}\psi_{\mathrm{VI}} + a_{\mathrm{VII}}\psi_{\mathrm{VII}} \qquad (10\cdot 6)$$

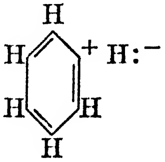
ψ_{V}, ψ_{VI}, or ψ_{VII} alone. Since structures VI and VII are equivalent to each other, they must make equal contributions to the state of the molecule; the magnitudes of a_{VI} and a_{VII} must therefore be equal. Moreover, for reasons which should become apparent later (see Section 10·9), the magnitude of a_{V} should not be extremely different from that of a_{VI} and a_{VII}. Consequently, all three structures should make approximately the same contribution; hence, no one or two of them alone could correspond very closely to the true average distribution of charge.

With other molecules, the number of structures among which resonance must be assumed to occur may become very large. Indeed, it should be apparent from what has already been said that the description of the state of any molecule can only continue to improve as the number of resonating structures is increased. For example, if the carbon and hydrogen atoms of benzene are considered to have small net negative and positive charges, respectively (as in fact seems very likely), then the above function $\psi_{\mathrm{III,IV}}$ (equation 10·4) could be improved by the addition to it of 12 further terms corresponding to resonance with the 12 equivalent structures of the type VIII. The magnitudes of the



VIII

coefficients a_{VIII}, etc., of the 12 functions ψ_{VIII}, etc., would of course be equal to one another, but presumably rather smaller than that of a_{III} and a_{IV}, since the net charges on the carbon and hydrogen atoms are probably rather small. Strangely enough, the inclusion in the resonance of even such structures as the 12 further equivalent ones of the type IX may be expected to result in some further improvement in the



IX

resulting charge distribution, even though the effect of such structures should be to decrease the electron densities about the carbon atoms and to increase those about the hydrogen atoms, instead of vice versa. Certainly (for the reason stated above), resonance with these structures could not at any rate lead to a poorer charge distribution. Moreover, net positive and negative charges on the carbon and hydrogen atoms, respectively, need not result, no matter how great the contributions of these 12 structures like IX may be, if only those of the 12 structures like VIII are still greater.

From what has been said, it should be evident that, the more accurately it is wished to describe the state of any molecule, the greater is the number of structures among which the resonance must be considered to occur. Indeed, it can be shown that a completely accurate eigenfunction can be obtained (in the way just outlined) only by means of a linear combination with an infinite number of terms; most of these terms naturally cannot correspond to structures representable by conventional chemical symbols. Nevertheless, there are reasons for believing that the approximate wave functions consisting of single terms or, at worst, of combinations of fairly small numbers of terms are good enough for all ordinary chemical needs. In other words, there are reasons for believing that most molecules can be described adequately by single structures or, at worst, as resonance hybrids receiving contributions from fairly small numbers of structures. If such a belief were not justified, then the striking success of the structural theory in systematizing and correlating the innumerable facts of chemistry would hardly have been possible.

The factors which determine the number of resonating structures that must be considered in any given instance, and the derivation of these factors from theoretical principles, will be discussed later in greater detail. (See Sections 10·7 and 10·9.) Here, as a convenient working rule (the justification of which may for the present be postponed), it need be mentioned only that, for most chemical purposes, a single structure is ordinarily sufficient if the substance is one like, say, methane, for which a single satisfactory structure can be uniquely assigned by the classical methods of structural organic chemistry; but that resonance among two or more structures must usually be considered if the substance is one like, say, benzene, for which no single satisfactory structure can be so assigned. It is interesting and highly significant that the simple structural concept, developed largely during the second half of the nineteenth century, should thus have proved adequate in just those places where modern theory suggests that it ought to be adequate, but should have proved inadequate in just those places where modern theory suggests that it ought to require a significant extension and generalization.

Some of the concepts introduced above can be made more definite with the aid of an analogy that is essentially equivalent to the previous one of the mule. (See Section 10·3.) The biological facts, however, now require a change in the species of the animals considered. If one parent of a certain dog is a collie, whereas its other parent is a cocker spaniel, then the dog is exactly halfway between a collie and a cocker spaniel, just as a mule is exactly halfway between a horse and a donkey. If now this dog is itself the parent of a second dog, whose other parent is a collie, the offspring is clearly ¾ collie and ¼ cocker spaniel; it is, therefore, intermediate between the two breeds, but it is not exactly halfway between them. Similarly, it is easy to imagine a dog which is, say, $^{11}/_{32}$ collie and $^{21}/_{32}$ cocker spaniel, or one which is ⅞ collie and ⅛ cocker spaniel. In the latter event, the dog would be "mostly collie"; in fact, it might be distinguishable only with considerable difficulty from a pure collie. In an analogous manner, a molecule which resonates between two structures need not receive exactly the same contribution from each structure. If one structure makes a much larger contribution than does the other, the molecule may then be fairly accurately describable by just the single most important structure. Moreover, the analogy can be carried still further, since there is no necessity that a dog be descended from only two breeds. Thus, a given mongrel might be, say, ⅜ collie, ¼ cocker spaniel, ¼ English bulldog, and ⅛ fox terrier. In an analogous manner, a resonating molecule may receive contributions (which may or may not be equal) from three or more different structures.

10·6 A Simple Mathematical Analogy. The above-described procedure for building up a progressively better wave function by the addition of further terms to a linear combination (i.e., the procedure for obtaining a progressively better description of the state of a molecule by the inclusion of further structures in the resonance) can be made somewhat more concrete by the discussion of a simple analogy which (the reader will doubtless be glad to learn) involves neither mules nor dogs. A hypothetical physicist may be supposed to have decided to study the following problem. Two weightless and inextensible cords of equal length, AC and BC, are connected to the respective rigid supports A and B (see Figure 10·1), and also to each other at the point C. A third weightless and inextensible cord CD is connected to AC and BC at the point C. If the cord CD is pulled by a force of fixed magnitude F in a direction perpendicular to that of the straight line between A and B, the cords AC and BC will exert forces of equal magnitude P upon the respective supports A and B. The problem is then to measure P as a function $P(\phi)$ of the angle ϕ between the cords AC and BC.

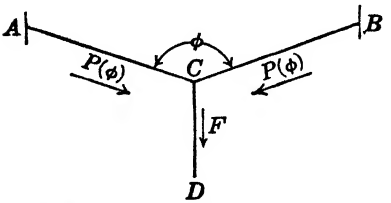


FIGURE 10·1. A simple problem in statics.

This problem is easily solved theoretically by application of the laws of that relatively elementary branch of mathematical physics which is known as statics; its solution is given in equation 10·7. The dependence

$$P(\phi) = \frac{1}{2} F \sec \frac{\phi}{2} \tag{10·7}$$

of $P(\phi)$ upon ϕ is shown by the second column of Table 10·1, in which,

TABLE 10·1

ACCURATE AND APPROXIMATE SOLUTIONS OF A SIMPLE PROBLEM IN STATICS

ϕ/π	$P(\phi)$	$P_1(\phi)$	$P_2(\phi)$	$P_+(\phi)$	$P_-(\phi)$	$P_\pm(\phi)$	$P_2'(\phi)$
−1.0	∞	0.50 F	1.12 F	∞	0.25 F	∞	∞
−0.9	3.20 F	0.50	1.00	5.00 F	0.26	2.63 F	3.16 F
−0.8	1.62	0.50	0.89	2.50	0.28	1.39	1.61
−0.7	1.10	0.50	0.80	1.67	0.29	0.98	1.10
−0.6	0.85	0.50	0.72	1.25	0.31	0.78	0.85
−0.5	0.71	0.50	0.65	1.00	0.33	0.67	0.71
−0.4	0.62	0.50	0.60	0.83	0.36	0.60	0.62
−0.3	0.56	0.50	0.56	0.71	0.38	0.55	0.56
−0.2	0.53	0.50	0.52	0.63	0.42	0.52	0.53
−0.1	0.51	0.50	0.51	0.56	0.45	0.51	0.51
0.0	0.50	0.50	0.50	0.50	0.50	0.50	0.50
+0.1	0.51	0.50	0.51	0.45	0.56	0.51	0.51
+0.2	0.53	0.50	0.52	0.42	0.63	0.52	0.53
+0.3	0.56	0.50	0.56	0.38	0.71	0.55	0.56
+0.4	0.62	0.50	0.60	0.36	0.83	0.60	0.62
+0.5	0.71	0.50	0.65	0.33	1.00	0.67	0.71
+0.6	0.85	0.50	0.72	0.31	1.25	0.78	0.85
+0.7	1.10	0.50	0.80	0.29	1.67	0.98	1.10
+0.8	1.62	0.50	0.89	0.28	2.50	1.39	1.61
+0.9	3.20	0.50	1.00	0.26	5.00	2.63	3.16
+1.0	∞	0.50	1.12	0.25	∞	∞	∞

as throughout this section, the angles are expressed in radians rather than in degrees. It will be noted that $P(\phi)$ approaches infinity as ϕ approaches either $+\pi$ or $-\pi$. A negative value of ϕ refers, of course, to a situation in which the support B is to the left of A, and not to the right of it, as in Figure 10·1. The imaginary physicist, however, may be considered to have no acquaintance with either statics or trigonometry; hence he is not able to derive this theoretical relationship between $P(\phi)$ and F. He can, accordingly, attack the problem which he has set for himself only by means of an experimental investigation. If, at the outset, he restricts his study to those values of the angle ϕ which are fairly close to 0, he will find that $P(\phi)$ has a very nearly constant value. In fact, the quantity $P_1(\phi)$, defined by the simple equation 10·8,

$$P_1(\phi) = \tfrac{1}{2}F \tag{10·8}$$

deviates from the correct function $P(\phi)$ by no more than 2 per cent in the range $-\pi/10 \leq \phi \leq \pi/10$ and by no more than 6 per cent in the range $-\pi/5 \leq \phi \leq \pi/5$. If, however, he extends his observations to angles of still greater magnitude, he finds that $P(\phi)$ is not strictly constant but increases perceptibly with the magnitude of ϕ. In order to obtain a more satisfactory description of the dependence of $P(\phi)$ upon ϕ, he may therefore add to his previous expression $P_1(\phi)$ a second term dependent upon ϕ. The simplest permissible form for this second term is $k\phi^2$, where k is a constant, since only even powers of ϕ can be used; in fact, if a linear term like $k\phi$ were introduced, the resulting function would have different values for $+\phi$ and $-\phi$, contrary to the observations. Thus, the still fairly simple expression 10·9 leads to results

$$P_2(\phi) = \tfrac{1}{2}F(1 + \tfrac{1}{8}\phi^2) \qquad (10 \cdot 9)$$

which are in error by less than 4 per cent in the range $-2\pi/5 \leq \phi \leq +2\pi/5$. (See the fourth column of Table 10·1.) Although $P_2(\phi)$ is clearly therefore a much better approximation to the correct function $P(\phi)$ than is $P_1(\phi)$, it is still far from satisfactory since it does not increase nearly rapidly enough as the magnitude of ϕ increases.

This procedure of building up the function $P(\phi)$ could of course be continued by the addition of terms in ϕ^4, ϕ^6, and so on. However, an investigation of angles in the neighborhood of $\pm\pi$ shows that $P(\phi)$ becomes extremely large, and in fact appears to increase without limit, as ϕ approaches $\pm\pi$. It is therefore evident that the attempt to express $P(\phi)$ as a power series of the form 10·10 cannot be very successful over

$$P(\phi) = \frac{1}{2}F\sum_{s} k_s\phi^{2s} \qquad (10 \cdot 10)$$

the entire range from $-\pi$ to $+\pi$, since a power series in ϕ cannot have a sum which approaches infinity for a finite value of the argument unless it contains an infinite number of terms. Thus, the expansion of the theoretically derived function $P(\phi)$ (equation 10·7) results in an infinite series, the first few terms of which are shown in the expression 10·11.

$$P(\phi) = \frac{1}{2}F\sec\frac{\phi}{2} = \frac{1}{2}F\left(1 + \frac{1}{2^2 \cdot 2!}\phi^2 + \frac{5}{2^4 \cdot 4!}\phi^4 + \frac{61}{2^6 \cdot 6!}\phi^6 + \frac{1385}{2^8 \cdot 8!}\phi^8 + \frac{50{,}521}{2^{10} \cdot 10!}\phi^{10} + \frac{2{,}702{,}765}{2^{12} \cdot 12!}\phi^{12} + \cdots\right) \qquad (10 \cdot 11)$$

Such an expansion would be useful only when the magnitude of ϕ is fairly small, since otherwise the series converges so slowly that a large number of terms would have to be taken before a satisfactory value of the sum could be obtained. When ϕ is equal to $\pm\pi$, the series of course *di*verges.

For the reasons described, the hypothetical physicist would doubtless soon conclude that the expansion of $P(\phi)$ as a power series in ϕ is impractical. He would accordingly try to devise a more suitable type of expression. It would clearly be desirable to employ for this purpose a function of ϕ which is equal to $\frac{1}{2}F$ when ϕ is equal to 0, and to infinity when ϕ is equal to $\pm\pi$. Now, the function $P_+(\phi)$ of equation 10·12

$$P_+(\phi) = \frac{\frac{1}{2}F}{1 - \phi/\pi} \tag{10·12}$$

satisfies these conditions when ϕ is equal to 0 or $+\pi$ since it then acquires, respectively, the value of $\frac{1}{2}F$ or of infinity; it is, however, entirely unsatisfactory when ϕ is negative, since it continues to decrease in value as ϕ decreases, and so it does not rise again toward infinity as ϕ approaches the value $-\pi$. (See the fifth column of Table 10·1.) Similarly, the further function $P_-(\phi)$ of equation 10·13 satisfies the conditions imposed when ϕ is equal to 0 or to $-\pi$, but is unsatisfactory when ϕ is positive. (See the sixth column of Table 10·1.)

$$P_-(\phi) = \frac{\frac{1}{2}F}{1 + \phi/\pi} \tag{10·13}$$

Although neither $P_+(\phi)$ nor $P_-(\phi)$ alone is a good approximation to the correct function $P(\phi)$, the linear combination $P_\pm(\phi)$ of equation 10·14, to which both $P_+(\phi)$ and $P_-(\phi)$ contribute, may be expected to be appreciably better than either one alone, if the constants a_+ and a_- are suitably chosen. Now $P_+(\phi)$ is the same function of ϕ that $P_-(\phi)$ is of $-\phi$; moreover, the experimental (or the correct theoretical) function $P(\phi)$ is an even function of ϕ, so that $P(\phi)$ is identically equal to $P(-\phi)$. (See the second column of Table 10·1.) It follows therefore that, with respect to the problem that is now being considered, the functions $P_+(\phi)$ and $P_-(\phi)$ are completely equivalent to each other, and hence that there is no reason why either one should make a greater contribution to the combination $P_\pm(\phi)$ than does the other. Consequently, a_+ and a_- must be equal in magnitude. The conditions that $P_\pm(0)$ be equal to $\frac{1}{2}F$ and that $P_\pm(\pm\pi)$ be equal to infinity then require that equation 10·15 be satisfied. Equation 10·14 therefore assumes the form

$$P_\pm(\phi) = a_+P_+(\phi) + a_-P_-(\phi) \tag{10·14}$$

$$a_+ = a_- = \tfrac{1}{2} \tag{10·15}$$

10·16. The dependence of this function $P_{\pm}(\phi)$ upon ϕ is shown in the

$$P_{\pm}(\phi) = \tfrac{1}{2}P_{+}(\phi) + \tfrac{1}{2}P_{-}(\phi) = \frac{1}{4}F\left[\frac{1}{1-\phi/\pi} + \frac{1}{1+\phi/\pi}\right] \qquad (10\cdot16)$$

next to last column of Table 10·1. It is seen that, in general, $P_{\pm}(\phi)$ gives a very good approximation to $P(\phi)$, but that the former function does not increase quite as rapidly as does the latter when ϕ approaches $\pm\pi$. The limiting value of the ratio of $P_{\pm}(\phi)$ to $P(\phi)$, when ϕ is equal to $\pm\pi$ is 0.79; the value of $P_{\pm}(\phi)$ is therefore never more than 21 per cent lower than the correct one. Moreover, since the greatest relative deviation of $P_{\pm}(\phi)$ from $P(\phi)$ occurs when the magnitude of ϕ is greatest, and hence when the experimental measurements are least reliable, the approximate function $P_{\pm}(\phi)$ might possibly be good enough to reproduce the empirical data within the experimental error. At worst, this function gives a reasonably satisfactory qualitative representation of the dependence of $P(\phi)$ upon ϕ. In any event, $P_{\pm}(\phi)$ is a much better approximation to $P(\phi)$ than any power series with a practicable number of terms could be.

If a still more accurate function is necessary, $P_{\pm}(\phi)$ could of course be further improved by the use of some such linear combination as $P_{2n}'(\phi)$, which is defined in equation 10·17. The inclusion in this series

$$P_{2n}'(\phi) = P_{\pm}(\phi)[a_0 + a_2\phi^2 + a_4\phi^4 + \cdots a_{2n}\phi^{2n}] \qquad (10\cdot17)$$

of even a small number of terms should lead to a materially better function than $P_{\pm}(\phi)$. Thus, the maximum error remaining in the still relatively simple function $P_2'(\phi)$ of equation 10·18, within the complete

$$P_2'(\phi) = P_{\pm}(\phi)[1 + \tfrac{1}{40}\,\phi^2] \qquad (10\cdot18)$$

range $-\pi \leq \phi \leq +\pi$, is reduced to about 2 per cent. (See the last column of Table 10·1.) The number of terms which must be included in a series of this type is determined by the accuracy of the experimental measurements, and hence by the allowable deviation of $P_{2n}'(\phi)$ from the theoretically correct function $P(\phi)$. As with the simple power series considered above, an infinite number of terms would of course be required before $P_{2n}'(\phi)$ could be made identical with $P(\phi)$.

The foregoing discussion of the problem of finding a mathematical function to fit a set of experimental data has been carried through in possibly boring detail, in order that certain of the essential, but somewhat abstruse, quantum-mechanical principles concerned in the theory of resonance might be illustrated by a simple concrete example. The first point to be brought out here is that, if the hypothetical physicist had been a better physicist and mathematician, he would not have needed to approximate his function $P(\phi)$ by any sort of linear combination of simpler functions, since he could instead have solved the problem in statics and could have written down the rigorous solution shown above in equation 10·7. Similarly, if a person interested in determining the average distribution of charge within a molecule were a sufficiently good mathematician, he would not need to approximate the desired wave function by any sort of linear combination, since he could instead solve the Schrödinger equation, and hence could write down the rigorously correct function. It should possibly be mentioned, however, that no mathematician has as yet been able to perform this feat for even such a simple molecule as that of hydrogen H_2, although several highly skilled ones have tried.

A further point of interest here is that the rigorous solution of the above problem in statics requires a knowledge of the trigonometric function sec $(\phi/2)$—a knowledge which the physicist was assumed not to possess. As far as this imagined person is concerned, therefore, the function sec $(\phi/2)$ can be said never to have been defined. In a similar manner, the rigorous solution of the wave equation for any molecule would doubtless be a function with which even the most skilled mathematicians are not now familiar, and which may accordingly be said to have not yet been defined.

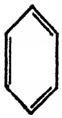
The chemical significance of the considerations up to this point is the following. With the development of the modern quantum-mechanical theory of valence, it has become evident that the chemists of the preceding century based their classical structural theory (quite unwittingly, of course) upon a procedure which consisted in expressing the average charge distributions within molecules as sums of terms. They did not follow this procedure to its logical conclusion, however, since they assumed implicitly and (as is now known) incorrectly that the first term of each such series is sufficient by itself to provide a complete description of the distribution of charge within the corresponding molecule. In other words, they assumed that each molecule could be associated with a single structural formula which would serve as a sort of shorthand symbol representing the distribution of charge; moreover, they assumed that, even though the lines (i.e., the covalent bonds) are interpreted in at least approximately the same way in all such symbols, nevertheless a single symbol suffices for each molecule. (It should of course go without saying that this statement is an interpretation in modern terminology, and in no sense a description, of the mental processes by which the chemists under discussion reached their final conclusions.) Obviously, these assumptions are extremely drastic. Indeed, the surprising feature of the classical structural theory is not that it failed with such substances as benzene, but rather that it worked as well as it did throughout the wide field of aliphatic chemistry for which it was originally devised. It is now realized that the conventional structural formulas can never describe the actual distributions of charge in molecules, except as rough first approximations. Although better descriptions could always be obtained by the inclusion of a few of the remaining terms in each series (i.e., by the consideration of resonance among a few of the additional structures for each molecule), the rigorously correct descriptions would refer to only a single distribution of charge for each molecule, and would not involve the idea of resonance among structures with different distributions of charge. These single distributions are, however, not obtainable by either the mathematical or the chemical methods now available, and, even if they were obtainable, they would not be representable by any kind of structural formula which has as yet been defined. New symbols would in fact be required for the representation of such charge distributions, just as a new function, viz., sec $(\phi/2)$, was required for the representation of the solution of the problem in statics considered above.

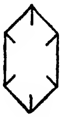
In addition to the foregoing points of interest, several further ones can be brought out with the aid of the above analogy. Thus, it was mentioned that the two functions $P_{+}(\phi)$ and $P_{-}(\phi)$, since they are equivalent to each other, must enter the linear combination with coefficients of the same magnitude. Similarly, the two Kekulé structures, I and II, of benzene, since they also are equivalent to each other, must make identical contributions to the state of the molecule. (Cf. page 400.) Moreover, the function $P_{\pm}(\phi)$, which was expressed above as the linear combination 10·16, can be expressed instead, and more conveniently, by a single term, as in equation 10·19. Similarly, a single

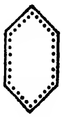
$$P_{\pm}(\phi) = \frac{\frac{1}{2}F}{1 - \phi^2/\pi^2} \qquad (10\cdot19)$$

diagram might possibly be devised for the representation of resonance between the two Kekulé structures of benzene; such a diagram might, for example, take the form of the Armstrong-Baeyer structure, III, or


I

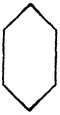

II


III

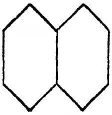

IV

of the Thiele structure, IV. Although a procedure of this type might be convenient for some purposes, it has not as yet, however, been developed into a useful scheme. In view of the extremely great complexity of the chemical problem, in fact, no completely general method of representation has seemed possible.

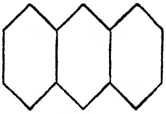
A further interesting analogy arises from the fact that the hypothetical physicist was considered to represent the dependence of the force P upon the angle ϕ by a definite symbol $P(\phi)$. This symbol, by definition, corresponds to the correct functional relationship between P and ϕ, whatever that relationship may prove to be. The experimental, or the theoretical, problem was then to obtain information regarding the actual form of this function $P(\phi)$. Similarly, with benzene, the conventional symbol, V, was established so that it, also by definition, corresponds to the true structure (or charge distribution) of benzene, whatever that structure (or charge distribution) may be. The experimental, or the theoretical, problem of obtaining more detailed information regarding the actual nature of this structure (or charge distribution) then remains to be investigated. In the same manner, the further symbols, VI, VII, etc., represent the correct structures of the further substances, naphthalene, anthracene, etc., respectively, whatever these structures may be. Moreover, with methane, the symbol VIII is ordinarily considered to correspond to the correct structure of the substance, and not to be merely the most important one of the infinite number of resonating structures; this procedure is possible with most of the remaining aliphatic compounds, for which a single structure of conventional type



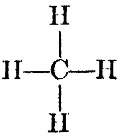
V



VI



VII

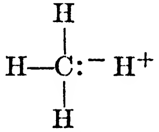


$$\begin{array}{c} \mathrm{H} \\ | \\ \mathrm{H—C—H} \\ | \\ \mathrm{H} \end{array}$$

VIII

has been found to be adequate; it is ordinarily employed implicitly by chemists.

Still other mathematical features of the theory of resonance can be brought out with the aid of the above simple analogy. As was mentioned earlier, the function $P_{\pm}(\phi)$ by itself gives a fairly good approximation to the correct function $P(\phi)$. On the other hand, the function $\phi^2 P_{\pm}(\phi)$ would give an extremely poor approximation, since it assumes the value 0, instead of $\frac{1}{2}F$, when ϕ is equal to 0. Nevertheless, the inclusion of the poor function $\phi^2 P_{\pm}(\phi)$ in the linear combination, in addition to the fairly good one $P_{\pm}(\phi)$, results in a marked improvement. It might perhaps have been anticipated that the opposite would be true. In a similar way, structure VIII of methane is a fairly good one, whereas the further structure IX, when considered by itself, is doubtless a very poor one. Nevertheless, the inclusion of this structure IX (and of the three other ones equivalent to it) in the resonance, in addition to the conventional structure VIII, may result in an appreciably better description of the molecule. Again, it might perhaps have been anticipated that the opposite would be true.



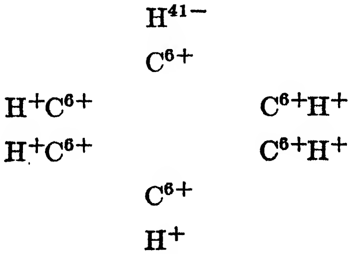
$$\begin{array}{ccc} & H & \\ & | & \\ H- & C & :^{-}\ H^{+} \\ & | & \\ & H & \end{array}$$

IX

The considerable superiority of the function $P_{\pm}(\phi)$ over $\phi^2 P_{\pm}(\phi)$ is reflected in the considerably larger value of the coefficient with which the former function appears in the linear combination $P_2'(\phi)$ of equation 10·18. The situation can be described by the statement that $P_{\pm}(\phi)$ makes a much larger contribution than $\phi^2 P_{\pm}(\phi)$ does; or, in other words, that the correct function $P(\phi)$ is much closer to $P_{\pm}(\phi)$ than it is to $\phi^2 P_{\pm}(\phi)$. Similarly, the superiority of structure VIII over IX is reflected in the greater contribution of the former, than of the latter, structure to the actual state of the methane molecule. In other words, the correct average charge distribution in methane is closer to that represented by structure VIII than it is to that represented by IX.

In certain instances, it can be shown that the expansion of a given function cannot include any terms of certain types. For example, as was pointed out above, the function $P(\phi)$, since it is even in ϕ, can receive no contributions whatever from odd terms like $k\phi$ or $k\phi^3 P_{\pm}(\phi)$. Similarly, in certain other instances, it can be shown that the resonance within a given molecule cannot include any structures of certain types. Examples of this limitation upon the occurrence of resonance will be discussed in the following section.

The final point to be brought out here is that the various functions like $P_+(\phi)$ and $P_-(\phi)$, which were used in the building up of a satisfactory approximate function, are individually without any physical significance whatever. They are, instead, of significance only with respect to the particular method of mathematical approximation employed. They are not involved at all in the rigorous solution $P(\phi)$ of the problem; furthermore, they are not uniquely determined even in the approximate treatment. Indeed, there are an infinite number of superficially independent methods by which an approximate solution can be built up. The choice among these methods is determined merely by considerations of convenience; for example, the power-series expansion of $P(\phi)$ was given up as impractical, and a combination of the functions $P_+(\phi)$ and $P_-(\phi)$ was used instead. Moreover, it would be obviously meaningless to speak of the fraction of the time during which the function $P(\phi)$ is identical with $P_+(\phi)$ and of that during which it is instead identical with $P_-(\phi)$, or of the frequency with which the function $P(\phi)$ changes from $P_+(\phi)$ to $P_-(\phi)$ and back again. Similarly, the structures among which a molecule is considered to resonate are without physical significance. As was discussed above, they do not enter into the rigorous solution of the quantum-mechanical problem; furthermore, they are not uniquely determined even in the approximate treatment. Indeed, there are an infinite number of superficially different sets of structures among which resonance could be considered to occur; the choice among these sets is determined merely by considerations of convenience. Thus, as a rather ridiculous, but theoretically permissible, example, the structure of benzene could be approximated not only in the way discussed previously (see pages 400, 402 f.), but also in terms of resonance among structures in each of which each of the forty-two electrons is in one of the various electronic shells about one predetermined proton. All such structures would of course have to be represented by a single symbol, such as X, although they would differ from one another in the ways in



X

which the electrons are arranged about the proton chosen. Even though this latter extreme procedure offers no advantages over the former, and indeed would be extraordinarily inconvenient, mention should nevertheless be made of the fact that there exists at least one relatively satisfactory method for the quantum-mechanical treatment of molecular structure (the so-called *molecular-orbital* method), which makes no explicit use of the concept either of structure in the familiar chemical sense or of resonance among different structures. This method will be neither employed nor further discussed in this book; the fact of its existence is, however, of considerable theoretical interest, since it makes apparent the arbitrariness of the approach which is based upon the principles of the classical structural theory, and which is here employed. Since, for the reasons given, the structures among which resonance is presumed to occur in any given instance are merely intellectual constructions that have no physical significance, it is apparent that no meaning can be assigned to the relative amounts of time which the molecule spends in each of the structures involved. In other words, it is not legitimate to speak of the molecule as passing back and forth from one resonating structure to another, and no definite frequency can be assigned to such a transition.

10·7 The Conditions for Resonance.[12] Although a completely accurate description of the charge distribution within any molecule would require a consideration of resonance among an infinite number of structures, not every structure which can be written can contribute to the state of any given molecule (see above); of those structures which do contribute, only a few ordinarily are of sufficient importance to deserve explicit mention in any purely chemical discussion. The general rules governing both the occurrence of resonance and the relative contributions of the various structures that are involved are obtainable as corollaries of the quantum-mechanical treatment. Since, however, the theoretical derivations are of too great mathematical complexity to be given here, these rules will be stated without proof.

It turns out that the occurrence of resonance is governed by two independent factors, which will be discussed separately in this section and in a later one. (See Section 10·9.) For lack of better names, these factors will be called the "coupling" factor and the "stability" factor, respectively.

Although, unfortunately, the fundamental theoretical significance of "coupling" between structures cannot be described except in highly mathematical terms, the practical significance can be expressed simply by means of the three rules given below. These rules describe the most important conditions (and the only ones ordinarily encountered) which

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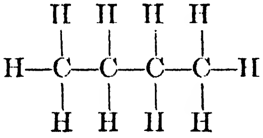
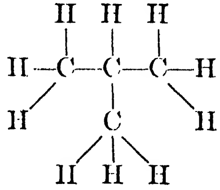
[12] See, for example, G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 6 ff.

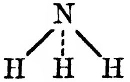
must be satisfied in order that structures may be coupled with each other, and hence in order that resonance between these structures may occur. (For further discussion of the significance of the coupling factor, see Section 10·11.)

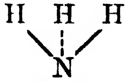
1. *Resonating structures must correspond to very nearly the same positions of all the atomic nuclei.* For example, there can be no resonance between structures I and II, since these differ markedly in the positions of a carbon nucleus and of several protons. It is of interest that this first rule is definitely required by the facts of chemistry inasmuch as, without it, the phenomenon of isomerism would have been impossible. Thus, if resonance between structures I and II could occur, then only a single butane, with a structure intermediate between I and II, could exist; the two different substances, n-butane and isobutane, respectively, could then not be separated. Indeed, if the quantum-mechanical theory had not led unambiguously to this rule, as it does, considerable doubt would thereby have been cast upon the validity of the theory.


I


II

The requirement that resonating structures correspond to at least approximately the same positions of all the atomic nuclei is not a completely precise one, since there is no sharp dividing line between the sets of structures which do, and those which do not, differ so much geometrically that resonance is impossible. For example, the question whether ammonia undergoes resonance or a rapid tautomerism between the two configurations represented by III and IV cannot be answered unambiguously. Such borderline cases, however, are fortunately very rare; in nearly all instances there is no ambiguity. The indefiniteness of this first rule will introduce no difficulties at any point in this book. In general, it may be said that, the more nearly two structures correspond to the same positions of all nuclei, the more strongly are they coupled with each other; the indefiniteness in question is thus one of deciding how weak the coupling between structures must be before it can legiti-


III


IV

mately be said no longer to exist. (For further discussion of the effect of the strength of the coupling upon the resonance, see the last paragraph of Section 10·9.)

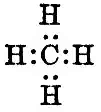
2. *Resonating structures must correspond to not too widely different average positions of all the electrons.* It is somewhat difficult to find a chemically interesting example of a set of structures which differ enough in electronic distribution for this rule to apply; indeed, electrons, being very much lighter and hence very much more mobile than atomic nuclei, cannot be so precisely localized. A rather artificial example, which might, however, be of some spectroscopic interest, is provided by the ionic free radical that could be obtained by removal of an electron from a molecule of decamethylenediamine, V, and for which the two equivalent, but presumably nonresonating, structures VI and VII can be drawn.

$H_2\ddot{N}—(CH_2)_{10}—\ddot{N}H_2$
V

$H_2\ddot{N}—(CH_2)_{10}—\dot{N}^+H_2$
VI

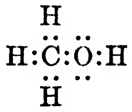
$H_2\dot{N}^+—(CH_2)_{10}—\ddot{N}H_2$
VII

3. *Resonating structures must have the same number of unpaired electrons.* An unpaired electron may be defined as one which neither partakes in the formation of an ordinary covalent (i.e., paired-electron) bond nor is part of an unshared pair of electrons upon a single atom. Thus, in the conventional electronic structures of methane, VIII, methyl alcohol, IX, and ethylene, X, all the electrons are paired; in each instance, therefore, the number of unpaired electrons is zero. On the other hand, the methyl radical, XI, has one unpaired electron, as does also its more complicated derivative, triphenylmethyl, XII. In general, any



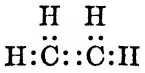
$$\begin{array}{ccc} & \mathrm{H} & \\ \mathrm{H}: & \underset{\cdot\cdot}{\ddot{\mathrm{C}}} & :\mathrm{H} \\ & \mathrm{H} & \end{array}$$

VIII



$$\begin{array}{cccc} & \mathrm{H} & & \\ \mathrm{H}: & \underset{\cdot\cdot}{\ddot{\mathrm{C}}} & :\underset{\cdot\cdot}{\ddot{\mathrm{O}}} & :\mathrm{H} \\ & \mathrm{H} & & \end{array}$$

IX



$$\begin{array}{ccccc} & \mathrm{H} & & \mathrm{H} & \\ \mathrm{H}: & \ddot{\mathrm{C}} & :: & \ddot{\mathrm{C}} & :\mathrm{H} \end{array}$$

X

$\dot{C}H_3$
XI

$(C_6H_5)_3C\cdot$
XII

molecule with an odd number of electrons must have at least one of them unpaired. Compounds consisting of such molecules are called *free radicals;* they are discussed further in Chapter 15.

Molecules with two, or more, unpaired electrons are rather rare, but they are not unknown. Although they are most common among the inorganic compounds containing atoms of the transitional groups of the periodic table, they occur also among the inorganic compounds containing only elements of low atomic weight and also among organic compounds. The most important example of such a substance is elementary oxygen O_2, which has two unpaired electrons, and which therefore does not possess the simple structure, XIII, which is usually assigned to it.

$$:\ddot{O}::\ddot{O}:$$

XIII

(Cf. page 741.) Further examples of the same type include sulfur monoxide SO, diatomic sulfur S_2, and a few other substances. Some much more complicated organic examples of substances with two unpaired electrons, the so-called *biradicals,* will be discussed later. (See Section 15·21.)

It may be asked how the number of unpaired electrons in a molecule is determined.[13] With very simple molecules, like that of oxygen, the most conclusive method is based upon a study of the spectra of the substances. However, the details of the procedure cannot be given here. With molecules of any complexity, and in particular with organic molecules, a different method, based on *magnetic* measurements, has proved more generally useful. This method makes use of the observation that every electron has a so-called "spin," which gives to it a small magnetic moment; or, in other words, that every electron behaves like a small bar magnet with a north pole and a south pole. When two electrons are paired with each other, whether they participate in the same covalent bond or belong to the same unshared pair, their spins are necessarily oriented in exactly opposite directions, so that their magnetic fields cancel one another. Consequently, only *un*paired electrons can make any contribution to the resultant magnetic moment of a molecule, and consequently only substances which consist of molecules with unpaired electrons are attracted by a magnet. (Exceptions to this rule are possible and are known, but they are not important among organic compounds.) Substances which are attracted by a magnet are said to be *paramagnetic.* The great majority of substances contain no unpaired electrons and are repelled by a magnet; such substances are said to be *diamagnetic.* Not only can the existence of unpaired electrons be demonstrated by the paramagnetism of the substances which contain them, but also the actual numbers of unpaired electrons per molecule can be calculated from the magnitudes of the attractions between the substances and a magnet. (For further details of the magnetic method, see pages 691 ff.)

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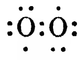
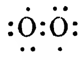
[13] For further details, see J. H. Van Vleck, *The Theory of Electric and Magnetic Susceptibilities*, Oxford University Press, Oxford, 1932.

With this much explanation of the significance of the pairing of electrons, the original question of the impossibility of resonance among structures with different numbers of unpaired electrons may again be considered. In oxygen O_2, for example, the three structures XIII, XIV, and XV can be written. The distinction between the second and third of



$:\overset{\cdot\cdot}{\underset{\cdot}{O}}:\overset{\cdot}{\underset{\cdot\cdot}{O}}:$

XIV

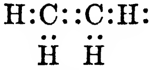


$:\overset{\cdot}{\underset{\cdot\cdot}{O}}:\overset{\cdot\cdot}{\underset{\cdot}{O}}:$

XV

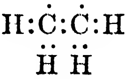
these structures lies in the choice of the orbit about each oxygen nucleus which is to be assigned the single isolated electron. Now, if the two isolated electrons in structures XIV and XV are not paired with each other, then each of these two structures has two unpaired electrons, and hence is able to resonate with the other structure. Indeed, the most satisfactory simple description of the state of the oxygen molecule is that it is a resonance hybrid of structures XIV and XV.[14] The conventional structure, XIII, however, can make no contribution through resonance to the normal state of the molecule, since it contains a different number of unpaired electrons, namely, zero. It represents instead an *excited* state, which is known spectroscopically, and which lies about 24 kcal per mole above the ground state.[15]

An example of greater organic chemical interest is provided by ethylene, for which the two structures XVI and XVII may be considered.



$H:\underset{\overset{\cdot\cdot}{H}}{C}::\underset{\overset{\cdot\cdot}{H}}{C}:H:$

XVI



$H:\underset{\overset{\cdot\cdot}{H}}{\dot{C}}:\underset{\overset{\cdot\cdot}{H}}{\dot{C}}:H$

XVII

If the two electrons represented by the isolated dots in structure XVII are paired with each other, this structure is identical with XVI, since the statement that two paired electrons are on adjacent atoms merely provides an alternative way of saying that a covalent bond exists between the two atoms. On the other hand, if the two electrons in question are not paired with each other, then structure XVII has two unpaired electrons, whereas XVI has none. In neither event is it legitimate to speak of resonance between structures XVI and XVII. (Structure XVII might nevertheless be of some spectroscopic interest, since it might represent an excited spectroscopic state. See also page 266.)

10·8 Formal Bonds. An interesting point in connection with the pairing of electrons can be brought out by a consideration of the so-called

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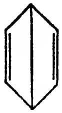
[14] L. Pauling, *J. Am. Chem. Soc.* **53**, 3225 (1931).

[15] L. Herzberg and G. Herzberg, *Astrophys. J.* **105**, 353 (1947).

Dewar structure, I, of benzene.[16] If, as now seems definitely established,



I

the six carbon atoms of the benzene molecule are located at the corners of a regular plane hexagon, the distance between any two *para* atoms is twice as great as is that between any two *ortho* atoms in the ring. Consequently, it is quite impossible for a really effective bond to exist between the *para* positions. Nevertheless, a situation more or less analogous to that implied by the Dewar structure results when two electrons, one on each of two *para* carbon atoms, are paired with each other. The significance of the pairing in such an event would then be merely that the spins (i.e., the magnetic moments) of the two electrons are pointing in exactly opposite directions. It would not be correct, however, to speak of the interaction between the distant atoms as a "bond," since its energy is much too small. As a good first approximation, in fact, it can be considered to be a "no bond" or a "broken bond." For the sake of precision in terminology, an interaction of this kind will hereafter be referred to as a *formal bond*, and it will be represented graphically by a dotted line, as in structure II. The formal bond is to be regarded as a "bookkeeping" device, introduced solely for the purpose of marking paired electrons.

II

Unlike a real bond, such an interaction makes no significant direct contribution to the stability of the structure which contains it.

It is somewhat paradoxical that structure I should have become associated with the name of Dewar since, in the paper [16] in which he mentioned this structure, Dewar assumed the Kekulé structure to be correct. However, in this same paper, he also described the construction of "ball-and-stick" molecular models which were not essentially different from those commonly employed today (except that they represented the carbon atoms as square rather than as tetrahedral). Merely to show the utility of these models and, in particular, their ability to reproduce any desired structure, he gave several examples. Among these were included the Kekulé and the "Dewar" structures, as well as a number of completely unreasonable ones, such

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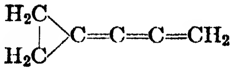
[16] J. Dewar, *Proc. Roy. Soc. Edinburgh* **6**, 82 (1867).

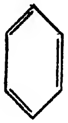
as III. He apparently did not support structure I any more than he did structure



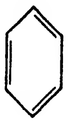
III

III. For a short time, however, structure I was seriously considered by *other* chemists.[17]

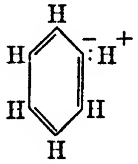
The theoretical importance of formal bonds is that, by a slight extension of the classical structural theory, they permit the drawing of additional structures, among which molecules may be presumed to resonate; and hence, that they permit the obtaining of more precise descriptions of the states of these molecules. In benzene, for example, the resonance may be considered to include not only the two Kekulé structures, IV and V, and such partially ionic structures as VI (cf. pages 400 ff.), but also the three equivalent Dewar structures, VII, II, and VIII. Since each Dewar structure contains one less effective bond than does a Kekulé structure, the structures belonging to the former type must be considerably less stable than are those belonging to the latter, and so must make appreciably smaller contributions to the state of the molecule. (See the following section.) Approximate calculations have indeed led to the conclusion that the Dewar structures are of only small (although still far from insignificant) importance in the resonance.[6]



IV



V



VI

VII

VIII

10·9 The Relative Contributions of Resonating Structures. Whenever two or more structures are coupled with each other (in the sense described in Section 10·7), resonance among them must always occur. However, the contributions of the structures may vary within wide limits; in particular, those of certain structures may be negligibly small. The "stability factor" (i.e., the second of the two factors mentioned above) then determines the relative importance of the various structures, in accordance with the general rule that, the more stable a resonating structure is, the greater is its contribution to the ground state of the molecule. As used here, the word "stable" is to be interpreted as meaning "thermochemically stable," in the sense defined in

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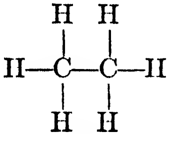
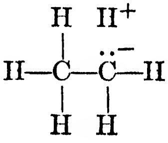
[17] See, for example, G. Städeler, *J. prakt. Chem.* **103**, 105 (1868); H. Wichelhaus, *Ber.* **2**, 197 (1869).

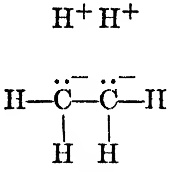
Section 9·2; the rule can accordingly be re-expressed in the form that, the lower is the energy E associated with any structure, the greater is the contribution of that structure to the hybrid.

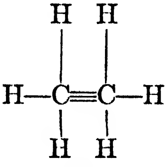
Before this rule can be put to practical use, a method must be devised by which the relative stabilities of structures can be estimated. Fortunately, a roughly qualitative method of this sort is readily available, since any structure which seems unreasonable from the viewpoint of the classical structural theory is almost certain to be an unstable one; and since, the more unreasonable a structure seems, the less stable (and hence the less important in the resonance) it is likely to be. For example, of all the structures that can be drawn for ethane, structure I is the only


I


II

one in which each linkage is of the type conventionally considered to be present in such substances, and in which each atom has its customary valence. Structure II, on the other hand, seems less reasonable since the carbon-hydrogen bond is not ordinarily regarded as ionic; this second structure is presumably therefore significantly less stable than I. Moreover, the further structure III, in which *two* of the carbon-hydrogen

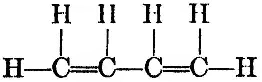

III


IV

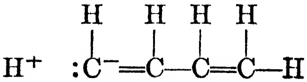
bonds are represented as ionic, is doubtless still less stable than structure II; and the rather bizarre structure IV, with sexivalent carbon, must be extremely unstable.

In structure IV, the four additional electrons that are needed for the carbon-carbon triple bond are the ones which occupy the two carbon K-shells in structures I, II, and III, but are not explicitly represented in those structures. In order that the formation of the triple bond in IV be possible, at least one of the K-shell electrons on each carbon atom must be excited at least to the M-shell. Such excitation requires an enormous amount of energy and so leads to a very unstable structure.

In general, whenever a unique structure has been assigned by the classical methods to any given molecule, then that structure seems always to be much the most stable one that can be written, and hence the one which makes the largest contribution. Under such circumstances, all further structures are less stable and therefore make smaller contributions; frequently, however, these contributions lead to appreciable modifications in the properties of the corresponding substances. With butadiene, for example, the conventional structure, V, is un-

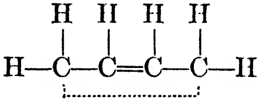

$\mathrm{H{-}\overset{H}{C}{=}\overset{H}{C}{-}\overset{H}{C}{=}\overset{H}{C}{-}H}$

V


$\mathrm{H^{+}\ :\overset{H}{C}{}^{-}{=}\overset{H}{C}{-}\overset{H}{C}{=}\overset{H}{C}{-}H}$

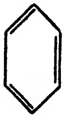
VI

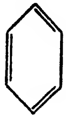
doubtedly much more important than any other. Nevertheless, structures like VI are probably significant with respect to the dipole moments of the carbon-carbon bonds; and structure VII, with a formal bond, is

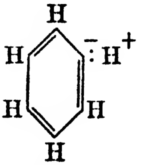

$\mathrm{H{-}\overset{H}{C}{-}\overset{H}{C}{=}\overset{H}{C}{-}\overset{H}{C}{-}H}$

VII

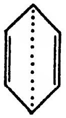
important with respect to the characteristic properties of the conjugated system. (Cf. Section 10·10.) On the other hand, whenever the structure of a substance has been left ambiguous by the classical methods, then usually the substance can be adequately described only as a resonance hybrid receiving relatively large contributions from most, if not all, of the individual structures proposed (and smaller ones, of course, from numerous further, less stable ones). With benzene, for example, the two Kekulé structures, VIII and IX, must make large and equal contributions, whereas such additional structures as X and XI must make


VIII

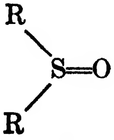

IX



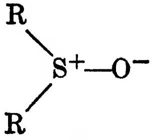
X


XI

smaller ones. Similarly, with a sulfoxide R_2SO, each of the two structures XII and XIII is probably important in the resonance. (Cf. pages 359 f. and 425.)



XII

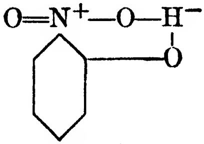


XIII

From what has just been said, it is evident that the chemists who developed the structural theory in the latter half of the nineteenth century showed a truly remarkable genius in devising a system of representation which could be fitted, without any really fundamental change, into the framework of the quantum-mechanical theories which were developed not only much later but also quite independently. This fact is an extremely fortunate one since, if the situation had proved to be otherwise, the organic chemist of today would have had either to give up the original, generally successful, but incomplete, structural theory and to make a fresh start along different lines; or else to lose all the benefit of the more recent and more precise theories which are now available.

Although familiarity with the classical structural theory thus enables one to estimate with some assurance the relative stabilities of structures, a set of formal rules, which determine the stabilities in an objective manner, would nevertheless be desirable. It may be doubted, however, whether any set of rules, covering all possible contingencies with complete rigor, is possible. At any rate, no such set has as yet been devised. The best that can be done here is accordingly to state a few general propositions which, in a wide variety of instances, have been helpful in the making of decisions.[18]

1. Any structure in which a hydrogen atom has more than two electrons in its valence shell, or in which any atom of the first row of the periodic table has more than eight electrons in its valence shell, is thermochemically so unstable that it may be neglected in qualitative discussions. Thus, the hydrogen bond in *o*-nitrophenol, for example, is presumably not due to an important contribution from any structure like XIV (cf. Section 2·6); similarly, the above structure IV for ethane can safely be ignored.



XIV

2. Since the formation of a valence bond always lowers the energy of a structure, a structure with a relatively large number of bonds should be thermochemically more stable than an analogous structure with a smaller number of bonds. Thus the Dewar structure, XI, of benzene, for example, is presumably less stable, and hence less important, than the Kekulé structures, VIII and IX, since it contains one less bond.

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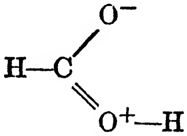
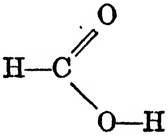
[18] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 15 ff.

(In the counting of bonds, formal bonds are of course to be ignored, since they are considered to be of negligible strength.) Moreover, tables of so-called *bond energies* have been compiled; with the aid of these bond energies, fairly precise estimates of the relative stabilities of structures can often be made, since the energy of each structure is given approximately by the sum of the energies of all the bonds which it contains. Such a refinement in the treatment will, however, be unnecessary throughout the remainder of this book.

3. Since positive and negative charges strongly attract each other, and since work must therefore be done in order to separate unlike charges, a structure which involves such a separation of charge is usually less stable thermochemically than is an analogous one which does not. Thus, structure XV of formic acid, with the positive and negative formal charges, is doubtless less stable than the conventional one, XVI, which contains the same number of bonds, but in which each atom is formally neutral. Conversely, a structure in which two like charges are close to one another (e.g., on adjacent atoms) is probably rather unstable. Thus, structure XVII of nitrous oxide N_2O is probably less stable than either of the structures XVIII and XIX, which contain the same total number of bonds.


XV


XVI

$$:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}{}^{=}\!-N^{+}\equiv O:^{+} \qquad :N\equiv N^{+}-\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:^{-} \qquad :\overset{\cdot\cdot}{N}{}^{-}\!=N^{+}=\overset{\cdot\cdot}{O}:$$

XVII XVIII XIX

4. The second and third of the above rules must be applied with considerable caution, however, since they have a number of exceptions. For example, with the gaseous molecule (or ion-pair, cf. Section 1·17) of sodium chloride, the ionic structure, XX, is probably more stable than the covalent one, XXI, even though the former structure has one less covalent bond than does the latter and, moreover, involves a separation of opposite charges. The reason for this exception is that, since one of the two atoms involved (the sodium atom) is strongly electropositive, whereas the other (the chlorine atom) is strongly electronegative, the transfer of an electron from the former atom to the latter is

$$Na^{+}Cl^{-} \qquad\qquad Na—Cl$$

XX XXI

relatively easy. In general, ionic structures like XV or XX may be expected to be more stable than the corresponding covalent ones (XVI and XXI, respectively) only if the atoms with the formal positive and negative charges are strongly electropositive and electronegative, respectively. This condition is satisfied in structure XX but not in structure XV. Under still other circumstances also, a structure with both a smaller number of bonds and a separation of charge may be more stable than an analogous one with a larger number of bonds and without the separation of charge. Thus, structure XXII for trimethylamine oxide

$$(CH_3)_3N^+\!-\!O^- \qquad\qquad (CH_3)_3N{=}O$$

XXII XXIII

is doubtless more stable than is structure XXIII, since the latter structure violates the octet rule. (Cf. rule 1, above.) With the two more or less analogous structures XXIV and XXV of a sulfoxide, however,

$$R_2S^+\!-\!\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}{:}^- \qquad\qquad R_2S{=}\overset{\cdot\cdot}{O}{:}$$

XXIV XXV

the situation is less clear. Since sulfur is not an element of the first row of the periodic table, rule 1 does not strictly apply to it, and so the second structure, XXV, cannot be immediately excluded. Nevertheless, there does seem to be some tendency for the maintenance of the octet with even such heavy atoms as sulfur, and so the first structure, XXIV, appears to be favored. On the other hand, rules 2 and 3 favor the second structure, XXV. Since the various factors operate in opposite directions, and since their relative importance cannot be readily estimated, no conclusive statement can be made regarding the relative contributions of structures XXIV and XXV. From studies of the dipole moments of such compounds, it appears probable that both structures make significant contributions.[19] (Cf. also page 422.)

In the manner just discussed, the relative stabilities of structures can usually be estimated in a fairly satisfactory manner. There still remains, however, the question how unstable a structure must be before it can be safely ignored. No simple answer can be given to this question, since a great deal depends upon the accuracy with which the distribution of charge within the molecule must be specified. The situation is thus analogous to that discussed in Section 10·6, where a hypothetical physicist was imagined to be trying to set up a mathematical expression for an empirical function, and where the number of terms which he

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[19] Cf. L. E. Sutton, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **37**, 73 ff. (1940) G. M. Phillips, J. S. Hunter, and L. E. Sutton, *J. Chem. Soc.* **1945**, 146.

had to include in his series was determined by the accuracy which he wished to obtain. With benzene, for example, it is usually sufficient to consider resonance only between the two Kekulé structures. A more accurate treatment, however, requires the inclusion of the three Dewar structures; a still more accurate one requires the inclusion of such partially ionic structures as X; and so on.

Attention should be called here to an important distinction which exists between resonance and tautomerism, and which has confused a great many people. In a tautomeric equilibrium (e.g., that between some arbitrary aldehyde A and its enol form E), the relative contributions of the two structures can be expressed in terms of the equilibrium constant K, defined in equation 10·20, where the expressions in parentheses represent the activities of the corresponding substances. The thermodynamic equation 10·21 gives the relation between the equilibrium constant K and the standard free energy change ΔF° of the reaction 10·22. Now, if ΔF° is very large, then the standard free energy

$$K = \frac{(\mathrm{E})}{(\mathrm{A})} \tag{10·20}$$

$$\Delta F^\circ = -RT \ln K \tag{10·21}$$

$$\mathrm{A} \rightleftarrows \mathrm{E} \tag{10·22}$$

of the enol form E is much higher than is that of the keto form A; hence, there is very little enol present at equilibrium. Indeed, if ΔF° is, say, 15 kcal per mole, then K has the value of 1.4×10^{-11} at 20°C; hence, at equilibrium, only one molecule in about 7×10^{10} is enolic (if the distinction between activities and concentrations may here be ignored). For many purposes, therefore, the statement would be justified that no enol form at all is present. Moreover, if ΔF° is still greater, the equilibrium concentration of the less stable tautomeride is still lower, since K decreases extremely rapidly as ΔF° increases. Thus, if ΔF° is equal to 60 kcal per mole, K has the value of 4×10^{-44} at 20°C; hence, at equilibrium, only one *molecule* of the less stable form is now present in about 4×10^{19} *moles* of the mixture! The situation described here for a tautomeric mixture is entirely different, however, from that which is supposed to obtain with a resonance hybrid. If only the coupling (see Section 10·7) between two structures is sufficiently strong, there is nothing to prevent the less stable structure from making, say, half as great a contribution as does the more stable one when the difference in energy between the two is 15 kcal per mole, or even when it is 60 kcal per mole. In other words, although the contribution of a resonating structure decreases as its stability decreases, the relative importance of a resonating structure is tremendously less dependent upon its relative thermochemical stability than is that of a tautomeric form upon its relative thermodynamic stability. In the resonating molecule, the coupling factor is extremely important since, the more strongly coupled two structures are, the greater must be the difference in their energies before the resonance between them is negligible. All structures which satisfy the conditions listed in Section 10·7 may be considered coupled with one another to at least some extent; the more nearly two structures with the same number of unpaired electrons correspond to the same relative positions of all the nuclei and of all the electrons, the more strongly they are coupled. Tautomeric structures, on the other hand, since they fail to satisfy the first of the conditions stated in Section 10·7, are completely uncoupled. (For further discussion of tautomerism, see Chapter 14.)

10·10 The Effect of Resonance upon Properties. Resonance exerts effects of various kinds upon the chemical and physical properties of the substances in which it occurs. Although these effects are mentioned from time to time throughout the book, a brief summary of some of the most important ones may be given here.[1]

As has already been mentioned (see page 396) the average distribution of electric charge in a resonating molecule, and the lengths, energies, and force constants of the individual bonds, are intermediate between the distributions, lengths, energies and force constants, respectively, that are characteristic of the individual structures involved. (Cf., however, Section 10·11.) On the other hand, the energy of a resonating molecule as a whole is always lower than is that of any one of the contributing structures; hence, resonance always stabilizes (thermochemically) any substance in which it occurs. The energy of the most stable single structure involved, minus that of the resonance hybrid, is therefore always a positive quantity. It is known as the *resonance energy* of the substance. The magnitudes of the resonance energies in many instances can be determined from thermochemical data of various kinds. With benzene,[20] for example, the observed heat of combustion of the substance (in the gaseous state) is 788 kcal per mole, whereas a value of about 829 kcal per mole would have been anticipated for the hypothetical cyclohexatriene, with the Kekulé structure.

This latter value is derived from the empirical rule that, with any hydrocarbon in which resonance is not an important factor, and to which a unique structure can

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[20] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, Chapter 3.

therefore be assigned, the heat of combustion of the gaseous substance, ΔH_c, is given approximately by the equation 10·23, in which n_h, n_s, n_d, and n_t are, respectively, the numbers of carbon-hydrogen bonds, carbon-carbon single bonds, carbon-carbon double bonds, and carbon-carbon triple bonds, in a molecule of the substance.[20]

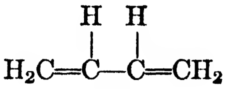
$$\Delta H_c = (53.3n_h + 50.8n_s + 118.8n_d + 205.2n_t) \text{ kcal per mole} \qquad (10\cdot23)$$

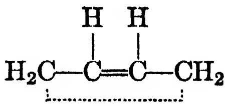
Since the observed heat of combustion of benzene is therefore less by about 41 kcal per mole than is that to be expected of a substance with the Kekulé structure, it is evident that benzene is more stable by this same 41 kcal per mole than such an imagined substance would have been. The resonance energy of benzene is therefore about 41 kcal per mole. A slightly different, but presumably more accurate, value of 36 kcal per mole for this quantity has been obtained in a completely analogous way from a comparison of the heats of hydrogenation of benzene and of cyclohexene.[20,21]

The magnitudes of the resonance energies found for other substances in these and other analogous ways vary widely. The resonance energy of a simple conjugated olefin seems always to be small; that of 1,3-butadiene, for example, is about 3 kcal per mole.[20,21] The aromatic compounds, on the other hand, have much larger resonance energies, which are usually of the order of 35 N kcal per mole, where N is the number of aromatic rings per molecule. In general, the resonance energy of a substance is greater, the greater is the number of relatively stable structures which individually have approximately the same low energy, and which therefore make approximately the same large contribution. Thus, the resonance energy of benzene, with its two Kekulé structures, I and II, is much larger (as was stated above) than is that of 1,3-butadiene, with only the one stable structure, III, and the much less stable one, IV.


I


II


$$H_2C{=}\overset{H}{\overset{|}{C}}{-}\overset{H}{\overset{|}{C}}{=}CH_2$$
III


$$H_2C{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}CH_2$$
IV

It is to be noted that, as a result of the resonance, the strength of each carbon-carbon bond in benzene, although intermediate between that of a carbon-carbon single bond and that of a carbon-carbon double bond, is nevertheless definitely greater than the arithmetic mean between these two extremes. Since the resonance energy of the substance

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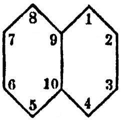
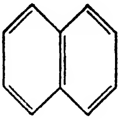
[21] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.* **58**, 146 (1936).

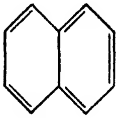
is about 36 kcal per mole, and since the six carbon-carbon bonds are equivalent, each bond is therefore stronger than the mean by about 6 kcal per mole. For this reason, the description of the "benzene" bond as a "one-and-a-half" bond (see page 392) is not strictly accurate.[22] Such an added refinement, however, is here unnecessary; consequently, the simpler, but somewhat loose, terminology will be employed without further apology throughout this book. Similarly (and with the same lack of precision), the C_1—C_2, C_3—C_4, C_5—C_6, and C_7—C_8 bonds in naphthalene, V, which resonates principally among structures VI, VII, and VIII, may be referred to as "one-and-two-thirds" bonds, and all the remaining carbon-carbon bonds in this compound may be referred to as "one-and-one-third" bonds. The distinctions which are thus made among the bonds in this substance are of considerable interest in connection with the similar distinctions implied by Thiele's structure. (See page 390.)



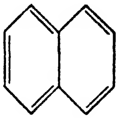
V



VI



VII



VIII

The concept of resonance energy is probably the most important single addition made by the theory of resonance to the older structural theory, since so many chemical and physical properties are affected by the thermochemical stabilities of the respective substances. Thus, one reason for both the relative ease of formation and the unreactivity of benzene (or of any other aromatic compound) is doubtless that, as a result of the resonance, such a substance has a considerably greater thermochemical stability than does any comparable nonaromatic compound.

In considering the *chemical* properties of a resonating substance, one must constantly be on his guard lest he unconsciously attribute to the substance the properties of a tautomeric mixture. (Cf. Chapter 14.) Thus, acetoacetic ester must undergo all the reactions of both the keto and the enol forms, because it is actually a mixture of these two tautomerides. On the other hand, although a resonating substance may in some instances undergo all the reactions expected of a number of the most important contributing structures, it does not have to undergo those expected of any structures, since it is not a mixture of different substances with the structures in question.

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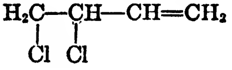
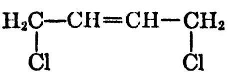
[22] See W. G. Penney, *Proc. Roy. Soc.* (London) **A158, 306 (1937)**.

A few examples should suffice to show how varied the situation may be. Thus, 1,3-butadiene reacts with chlorine to give both 1,2-dichloro-3-butene, IX, and 1,4-dichloro-2-butene, X.[23] In the first of these reactions, the substance therefore appears to have the conventional structure, III, whereas, in the latter, it appears to have the less stable structure, IV, with the formal bond. Similarly, the ozonization of *o*-xylene gives the two ozonides, XI and XII, in approximately equal amount;[24] here again the substance undergoes the reactions expected of both the important structures, XIII and XIV, respectively. On the other hand, 2,7-dihydroxynaphthalene, XV, which must receive approximately equal contributions from the three structures XVI, XVII, and XVIII, reacts almost exclusively as if it has only the one structure, XVI.[25] In particular, it reacts with a diazonium salt ArN_2X or with a halogen X_2 only at the positions marked with single asterisks, to give the respective products XIX and XX, and not at all at the positions marked by double asterisks;



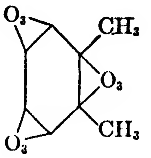
$\underset{Cl}{H_2C}-\underset{Cl}{CH}-CH=CH_2$

IX

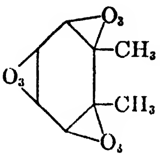


$\underset{Cl}{H_2C}-CH=CH-\underset{Cl}{CH_2}$

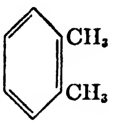
X



XI

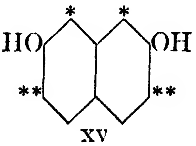


XII

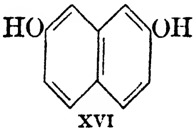


XIII

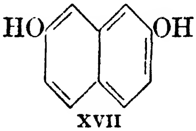
XIV



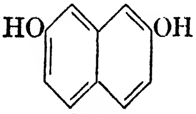
XV



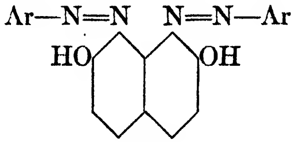
XVI



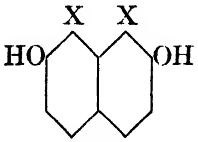
XVII



XVIII



XIX



XX

at first sight, however, the latter positions appear to be just as "*ortho*" to the phenolic hydroxyl groups as do the former. (For theoretical discussion of some analogous reactions, see pages 552 f.) Moreover,

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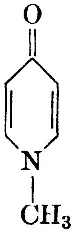
[23] I. E. Muskat and H. E. Northrup, *J. Am. Chem. Soc.* **52**, 4043 (1930).

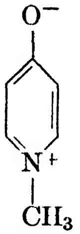
[24] A. A. Levine and A. G. Cole, *J. Am. Chem. Soc.* **54**, 338 (1932); J. P. Wibaut and P. W. Haayman, *Nature*, **144**, 290 (1939).

[25] Cf. L. F. Fieser and W. C. Lothrop, *J. Am. Chem. Soc.* **57**, 1459 (1935).

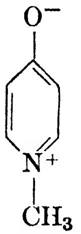
N-methyl-γ-pyridone, which presumably resonates among the structures XXI, XXII, and XXIII, undergoes none of the typical reactions of either a ketone or a tertiary amine, although structure XXI is certainly much the most important of the three.[26] The two further structures XXII and XXIII have very wide separations of charge, which render them relatively very unstable. Moreover, if these structures were of major importance, the dipole moment of the substance should be several times as great as is observed. (See also pages 638 f.) In most if not all of these instances, satisfactory interpretations of the facts can be obtained from more elaborate considerations of the reactions in question, with particular emphasis upon their probable detailed mechanisms. Such further complications cannot, however, be profitably discussed here.[27]



XXI



XXII



XXIII

10·11 Interaction Terms. It is now desirable to consider, in greater detail than would have hitherto been convenient, the reason why each property of a resonating molecule is not simply the weighted (arithmetic) mean of the corresponding properties of the contributing structures. For the sake of simplicity, the discussion will be restricted to a substance (like hydrogen chloride) for which only two structures (like structures I and II) need be taken into account; the generalization of the treatment to more complex situations should be obvious and can therefore be left to the interested reader.

$\mathrm{H{-}Cl}$
I

$\mathrm{H^+Cl^-}$
II

In Section 10·5, it was stated that, if the wave function of a molecule is represented by the symbol ψ, then the average distribution of electric charge in this molecule is defined by the function P, which is equal

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[26] Cf. N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, 1937, pages 530 ff.

[27] For further discussion of the effects of resonance upon chemical reactions, see G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, Chapter 8.

(equation 10·24) to the product of ψ and its complex conjugate ψ^*.

$$P = \psi^*\psi \qquad (10\cdot24)$$

Now, if the molecule is considered to resonate between any two structures R and S (which need not here be specified), its wave function is expressed as a linear combination (equation 10·25) of the functions ψ_r

$$\psi = a_r\psi_r + a_s\psi_s \qquad (10\cdot25)$$

and ψ_s that are set up to represent, respectively, the structures R and S. (See Section 10·5.) The function P, which defines the average charge distribution in the resonance hybrid, therefore now assumes the form shown in equation 10·26, in which the asterisks, as before, denote the

$$P = \psi^*\psi = a_r^*a_r\psi_r^*\psi_r + a_s^*a_s\psi_s^*\psi_s + a_r^*a_s\psi_r^*\psi_s + a_ra_s^*\psi_r\psi_s^* \qquad (10\cdot26)$$

complex conjugates of the respective constants or functions. This function P, however, is not the weighted arithmetic mean of the functions $\psi_r^*\psi_r$ and $\psi_s^*\psi_s$, which separately describe the charge distributions associated with the structures R and S; the weighted mean is instead the different function P' (equation 10·27), in which the constants $a_r^*a_r$ and

$$P' = a_r^*a_r\psi_r^*\psi_r + a_s^*a_s\psi_s^*\psi_s \qquad (10\cdot27)$$

$a_s^*a_s$ are the respective "weights" of the two distributions involved.

The terms $a_r^*a_s\psi_r^*\psi_s$ and $a_ra_s^*\psi_r\psi_s^*$, which appear at the right of equation 10·26, and which keep the function P from being identical with the function P', are conveniently said to represent the "interaction" between the two structures R and S. Analogous interaction terms occur also in the quantum-mechanical calculation of other properties besides the average charge distribution. In no such instance, therefore, is the calculated property of the resonance hybrid exactly equal to the weighted arithmetic mean of the corresponding properties that are associated with the individual structures. There is thus a possibility that, if the interaction terms are sufficiently large, the hybrid may not even be intermediate, with respect to the corresponding property, between the resonating structures. This possibility is, in fact, realized in every calculation of molecular energy; for, since the resonance energy is always positive (Section 10·10), the energy of the hybrid molecule is always lower than that of either structure alone.[28] (If the now threadbare analogy of the mule may once more be invoked, it may here be noted that this animal is, by popular report, more stubborn than is either of its parents.)

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[28] For a theoretical discussion of the complex problem of the effect of resonance upon force constants, see C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (London) **A193, 447, 456 (1948)**.

The resonance energy itself is, of course, due to the occurrence of interaction terms in the calculation of the energy; these terms are completely analogous to, but are naturally not identical with, the ones which occur in the calculation of the average charge distribution. If, with any specific structures, the energy interaction terms are found to be equal to zero, the resonance energy must also be equal to zero; in fact, since the structures are then not coupled with one another, resonance does not take place at all. This last statement defines the nature of the coupling, which was discussed from a more qualitative point of view in Sections 10·7 and 10·9.

Aside from the total energy, however, most properties of a resonating molecule are usually intermediate between the corresponding properties of the contributing structures. Several examples illustrating this generalization have already been given. (Cf. page 396 and also the references to earlier chapters that are listed in Section 10·1.) Indeed, it appears legitimate in any *qualitative* discussion to assume that every property (except the total energy) is always thus intermediate. This assumption has, in fact, been made throughout both this and the preceding chapters, and it will also be made throughout the following chapters.

Attention should here be called to the fact that the above discussion of interaction terms refers only to the properties of individual molecules. Clearly, therefore, none of the conclusions reached can be directly applied to purely chemical properties (cf. Section 10·10), since these involve interactions among different molecules; or to such physical properties as the melting point, boiling point, vapor tension, density, surface tension, and viscosity, since these are characteristic not of the individual molecules, but of the substance in bulk.

11.

Electrostatic Effects in Organic Chemistry[1]

11·1 The Factors Which Influence Chemical Properties. One of the major goals of chemistry will not be achieved until, from theoretical considerations alone, it is possible to calculate quantitatively the rate at which any desired reaction proceeds, the position of the equilibrium which this reaction finally reaches, and the ways in which both the rate and the equilibrium depend upon the experimental conditions. Although the known laws of physics are in principle sufficient to permit such calculations to be made, the mathematical complexity of the problem is in practice so great that the calculations in question cannot actually be performed for more than a negligible number of extremely simple reactions. At the present time, therefore, only qualitative or, at best, semiquantitative treatments are ordinarily possible. Such treatments, although they are not as complete as might be desired, may nevertheless be very useful, since they often lead to an understanding of the *relative* values of rate and equilibrium constants, and since they often explain those changes in the rate and equilibrium constants which are caused by structural or configurational modifications of the reactants. (Examples are given in the following sections.)

It is now generally believed that the three most important factors which influence the rates and equilibria in chemical reactions are (1) steric effects, (2) resonance, and (3) electrostatic interactions. In the two preceding chapters, the steric and the resonance factors were discussed; in this chapter, the electrostatic factor will be considered. (For still further discussion of electrostatic interactions, see Sections 1·3–1·15 and 10·9.)

The steric, the resonance, and the electrostatic factors are frequently assumed not only to be sharply distinguishable and entirely independent, but also to be sufficient to account for all structural effects. Actually, however, steric repulsions are themselves the results of electrostatic forces (cf. Section 1·15); furthermore, since most dipoles can be described as due to resonance between covalent and ionic structures (cf.

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[1] This chapter is based upon a memorandum which was kindly prepared for the author by Professor F. H. Westheimer.

Section 1·10), many electrostatic interactions can be regarded as special types of resonance effect. Evidently, therefore, the three factors listed are neither sharply distinguishable nor entirely independent. Finally, it should be noted that any treatment which is based upon a consideration of only these factors cannot be complete unless each of the factors is further subdivided into an energy and an entropy effect; such a refinement, however, will not here be attempted.

11·2 Electrostatic Effects upon Ionization Constants and Reaction Rates.[2] The clearest examples of electrostatic effects come from the consideration of ionization equilibria. The equilibrium constants for the reactions 11·1 and 11·2 have been measured in alcohol [3] and in

$$C_6H_5\text{—}CO_2H + C_6H_5\text{—}NH_2 \rightleftarrows C_6H_5\text{—}CO_2^- + C_6H_5\text{—}NH_3^+ \qquad (11\cdot 1)$$

$$C_6H_5\text{—}CO_2H + o\text{-}O_2N\text{—}C_6H_4\text{—}CO_2^- \rightleftarrows C_6H_5\text{—}CO_2^- + o\text{-}O_2N\text{—}C_6H_4\text{—}CO_2H \qquad (11\cdot 2)$$

water as solvent. The data, presented in Table 11·1, show that, when

TABLE 11·1

THE EFFECT OF THE SOLVENT UPON TWO DIFFERENT TYPES OF IONIC EQUILIBRIUM

	Equilibrium Constant		
Reaction of Equation	In Alcohol[3]	In Water	Ratio
11·1	1.5×10^{-5}	2.7	1.8×10^{5}
11·2	1.5×10^{-2}	0.95×10^{-2}	0.6

the solvent is changed from alcohol to water, the equilibrium constant for reaction 11·1 is increased by a factor which is greater than 10^5; but that the equilibrium constant for reaction 11·2 is essentially unaltered.

The example just cited is one where the large controlling influence is electrostatic. In reaction 11·1, the reactants are uncharged, whereas the products are oppositely charged. The two ions which are formed in this reaction strongly attract each other; in fact, the reaction can proceed to the right only because the electrostatic interaction between the ions is diminished by the action of the solvent. This effect of the solvent can be considered from two superficially different points of view. In the

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[2] For a discussion of the effects of resonance upon ionization constants and reaction rates, see, respectively, G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, Sections 7·2–7·4, and Chapter 8.

[3] H. Goldschmidt, *Z. physik. Chem.* **99**, 116 (1921).

first place, the dielectric constants of water and of alcohol (at room temperature) are approximately equal to 80 and to 24, respectively, whereas that of vacuum is equal to 1; therefore, the electrostatic forces, which are inversely proportional to the dielectric constant, are much smaller when the ions are dissolved in either of these solvents than when the ions are in the gaseous state. In the second place, when the ions are in solution, they are greatly stabilized by solvation. (Cf. Sections 1·6 and 1·12.) The two points of view are, however, not independent of one another since, in general, the only solvents which have especially high dielectric constants are the ones in which ions are strongly solvated. That such a relation should exist is hardly surprising. Indeed, a solvent can have a high dielectric constant only if it is extensively associated; hence, since such a solvent can therefore be said to "solvate itself," it should be even more effective in solvating electrically charged molecules (i.e., ions). If, for this reason, the dielectric constant is considered to be a sufficient measure of the extent to which the solvent shields ions from one another, the dependence of the equilibrium in equation 11·1 upon the solvent can be readily interpreted. Thus, the attraction between the oppositely charged ions that appear on the right side of this equation is much smaller when the solvent is water (with a dielectric constant of about 80) than it is when the solvent is alcohol (with a dielectric constant of about 24). On the other hand, the change in solvent has little or no effect on the electrostatic interaction of the uncharged reactants that appear on the left side of the equation. It therefore follows that the equilibrium shown in equation 11·1 must be displaced toward the right when the solvent is changed from alcohol to water.

The significant feature of the reaction shown in equation 11·1 is here that each of the reactants is electrically neutral, whereas each of the products is charged. Clearly, therefore, the further reaction shown in equation 11·2 is of an entirely different type. In this latter reaction, one of the reactants is charged, whereas the other is uncharged; likewise, one of the products is charged, whereas the other is uncharged. Since the electrostatic interaction between a charged and an uncharged particle is much smaller than is that between two charged particles, and since the interaction between the reactants in equation 11·2 is at least approximately balanced by that between the products, the equilibrium constant is here (relatively) little affected by the change of solvent. It is, in fact, a general rule that two acids of the same charge type (e.g., benzoic acid C_6H_5—CO_2H and *o*-nitrobenzoic acid *o*-O_2N—C_6H_4—CO_2H) have approximately the same relative strengths in two different solvents; and hence that equilibria of the type 11·2 are not greatly affected by the solvent in which such reactions are carried out. On the other hand, it is also a general rule that acids of different charge type (e.g., benzoic acid $C_6H_5—CO_2H$ and the anilinium ion $C_6H_5—NH_3^+$) vary considerably in relative strength when the solvent is changed; and hence that equilibria of the type 11·1 are greatly affected by the solvent. In the latter event, the change is large and is in the direction that is predicted by the simple electrostatic theory. (Cf. also the paragraph in fine print on page 78.)

A similar effect of solvent on reaction *rate* has been traced to an electrostatic effect. The solvolytic reactions shown in equations 11·3 and 11·4

$$(CH_3)_3C—Cl + H_2O \rightarrow (CH_3)_3C—OH + HCl \qquad (11·3)$$

$$(CH_3)_3C—Cl + CH_3OH \rightarrow (CH_3)_3C—OCH_3 + HCl \qquad (11·4)$$

involve only neutral reactants. It has, however, been shown that the cation $(CH_3)_3C^+$ is an intermediate in these reactions; the formation of this ion (equation 11·5) is the common rate-determining step of the reactions. During the solvolysis, a positive and a negative ion are there-

$$(CH_3)_3C—Cl \rightarrow (CH_3)_3C^+ + Cl^- \qquad (11·5)$$

fore produced from a neutral molecule. (This conclusion is frequently expressed in an equivalent manner by the statement that the activated complex for the reaction has a high dipole moment.) The separation of a positive from a negative charge will proceed most readily when the dielectric constant of the solvent is greatest. It is therefore not astonishing that, at 25°C, the solvolysis proceeds 30 times as fast in a solvent consisting of 57 mole per cent methanol and 43 mole per cent water as it does in a solvent consisting of 93 mole per cent methanol and only 7 mole per cent water.[4]

Reactions of the type shown in equations 11·3 and 11·4 are occasionally, and for special reasons, conducted in mixed solvents, or even in nonpolar solvents. Thus, it may happen that the reactants are not sufficiently soluble in any pure highly polar solvent, or that certain undesirable side reactions can be avoided only in some nonpolar solvent, or the like. In the absence of such factors, however, these "polar" reactions must, for electrostatic reasons, proceed best in solvents of high dielectric constant.

Electrostatic interactions are responsible not only for the *solvent* effects which have just been discussed, but also for many of the effects which *substituents* exert upon rates and equilibria. It is, in fact, in this latter field that most of the quantitative research has been done. The subject can conveniently be introduced by a consideration of two examples: a comparison of the first and second ionization constants of

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[4] A. R. Olson and R. S. Halford, *J. Am. Chem. Soc.* **59**, 2644 (1937); G. Scatchard, *J. Chem. Phys.* **7**, 657 (1939).

adipic acid; and a comparison of the ionization constants of chloroacetic acid and of acetic acid.

In the first example, the acid strengths of adipic acid, I, and of the

$$HO_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2H$$

I

univalent adipate ion, II, are compared with one another. These two

$$HO_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2^-$$

II

acids are certainly very similar; they differ, however, in two respects, of which one is statistical and the other is electrostatic. The statistical factor arises because there are two ionizable protons in un-ionized adipic acid, I, but only one such proton in the singly charged ion, II; and because there are two negatively charged carboxylate groups in the doubly charged anion, III, but only one such group in the acidic anion, II. In

$$^-O_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2^-$$

III

the absence of all electrostatic effects, this statistical factor would make the first ionization constant of any symmetrical dibasic acid (such as adipic acid) exactly 2 × 2, or 4, times as large as the second ionization constant of the same acid.[5, 6] The fact that the observed ratio of ionization constants is always greater, and is frequently much greater, than 4 is the result of the second (electrostatic) factor. Thus, the work which is required to transform adipic acid, I, into the singly charged adipate ion, II, is that expended in pulling one of the two ionizable protons away from its corresponding carboxyl group. On the other hand, the work which is required to transform the singly charged adipate ion, II, into the doubly charged ion, III, includes not only the work expended in pulling the remaining ionizable proton away from its own carboxyl group, but also that expended in removing this proton to an infinite distance from the negatively charged carboxylate group which was formed in the first step of the ionization. If this latter electrostatic effect did not exist, the amounts of work which would be required for the two stages of ionization with such a symmetrical dibasic acid would be equal; hence the two ionization constants would differ only by the abovementioned statistical factor of 4. Since, however, the electrostatic effect exists and is far from negligible, the work which is required for the first ionization is appreciably less than is that which is required for the second; hence, the ratio of the first ionization constant to the second is

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[5] E. Q. Adams, *J. Am. Chem. Soc.* **38**, 1503 (1916).

[6] N. Bjerrum, *Z. physik. Chem.* **106**, 219 (1923).

somewhat greater than 4. At 25°C, the observed values of the two ionization constants in aqueous solution[7] are, respectively, 3.70×10^{-5} and 3.86×10^{-6}; the experimental ratio is therefore 9.6.

The second example of the effect which electrostatic interactions exert upon acid strengths consists in a comparison of the ionization constant of chloroacetic acid, IV, with that of acetic acid, V. Here, the molecule

$$\underset{\text{IV}}{Cl{-}CH_2{-}CO_2H} \qquad\qquad \underset{\text{V}}{H{-}CH_2{-}CO_2H}$$

of the former substance contains a dipole (namely, that of the carbon-chlorine bond) which is not present in the molecule of the latter substance. Since this carbon-chlorine dipole has its positive and negative ends at the carbon and chlorine atoms, respectively, of the chloroacetic acid molecule, its positive end is therefore closer to the ionizable proton than is its negative end; hence, the proton is repelled by the dipole. (Cf. structure VII on page 445.) Since less work is therefore required to remove the proton from the molecule of chloroacetic acid than from the one of acetic acid, chloroacetic acid is a stronger acid than is acetic acid. The observed values of the respective ionization constants at 25°C in aqueous solution are approximately 1.5×10^{-3} and 1.8×10^{-5}; the ratio is therefore approximately 0.8×10^2.

This latter ratio is greater than is that of the first and second ionization constants of adipic acid (see above), even though the interaction between a proton and a dipole is usually smaller (other factors being equal) than is that between a proton and a charge. The reason for this apparent discrepancy is, of course, that the distance between the ionizable proton and the dipole in the molecule of chloroacetic acid is much less than is that between the corresponding proton and the charged carboxylate group in the univalent adipate ion.

The electrostatic effects which make adipic acid a stronger acid than the singly charged adipate ion, and which make chloroacetic acid a stronger acid than acetic acid, also influence reaction rates. Thus, in the alkaline hydrolysis of a carboxylic ester, the negative hydroxide ion must be brought into the neighborhood of the carboalkoxyl group; moreover, during the reaction, this ion is necessarily subject to whatever electrostatic fields may exist in the ester molecule. The hydrolyses of diethyl adipate, VI, and of monoethyl adipate, VII, provide a convenient il-

$$\underset{\text{VI}}{C_2H_5{-}O_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2{-}C_2H_5}$$

$$\underset{\text{VII}}{C_2H_5{-}O_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2H}$$

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[7] I. Jones and F. G. Soper, *J. Chem. Soc.* **1936**, 133.

lustrative example. In each of the two reactions (equations 11·6 and

$$C_2H_5—O_2C—(CH_2)_4—CO_2—C_2H_5 + OH^- \rightarrow C_2H_5—O_2C—(CH_2)_4—CO_2^- + HO—C_2H_5 \quad (11·6)$$

11·7, respectively), the hydroxide ion must be brought up to a carbo-

$$C_2H_5—O_2C—(CH_2)_4—CO_2^- + OH^- \rightarrow {}^-O_2C—(CH_2)_4—CO_2^- + HO—C_2H_5 \quad (11·7)$$

ethoxyl group. In the latter reaction (equation 11·7), however, the ion is repelled by the negative charge on the ester anion, VIII, whereas, in

$$C_2H_5—O_2C—CH_2—CH_2—CH_2—CH_2—CO_2^-$$

VIII

the former reaction (equation 11·6) no corresponding repulsion exists. If this electrostatic effect could be ignored, monoethyl adipate, VII (which contains only one carboethoxyl group per molecule), should be hydrolyzed just *half* as fast as is diethyl adipate, VI (which contains *two* carboethoxyl groups per molecule). Since, however, the repulsion is not negligible, and since it acts only in the ester anion, VIII, and not in the neutral ester, VI, its effect is to make the rate of hydrolysis of monoethyl adipate less than half that of diethyl adipate. Experimentally,[8, 9] the rate for the former ester in dilute aqueous solution at 20°C is about one-fifth as great as is that for the latter ester under the same conditions. A similar analysis of the effect of the carbon-chlorine dipole in ethyl chloroacetate, IX, explains also why this ester is saponified more rapidly than is ethyl acetate, X.

$$Cl—CH_2—CO_2—C_2H_5 \qquad H—CH_2—CO_2—C_2H_5$$

IX X

11·3 More Quantitative Treatments of Electrostatic Effects.

The reaction which is depicted in equation 11·8 may be described as the

$$HO_2C—(CH_2)_4—C^*O_2H + {}^-O_2C—(CH_2)_4—C^*O_2^- \rightleftarrows {}^-O_2C—(CH_2)_4—C^*O_2H + HO_2C—(CH_2)_4—C^*O_2^- \quad (11·8)$$

transfer of a proton (through the solvent) from a molecule of un-ionized adipic acid, I, to one of the corresponding doubly charged anion, II; in

$$HO_2C—CH_2—CH_2—CH_2—CH_2—CO_2H$$

I

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[8] C. K. Ingold, *J. Chem. Soc.* **1931,** 2170. See also C. K. Ingold, *ibid.* **1930,** 1375; C. K. Ingold and H. G. G. Mohrhenn, *ibid.* **1935,** 1482.

[9] F. H. Westheimer, W. A. Jones, and R. A. Lad, *J. Chem. Phys.* **10,** 478 (1942).

$$^{-}O_2C—CH_2—CH_2—CH_2—CH_2—CO_2{}^{-}$$

II

this equation, the asterisks designate the carboxyl and carboxylate groups which are to be thought of as not directly participating in the reaction. As is shown in equation 11·9, the equilibrium constant K for

$$K = \frac{(HO_2C—(CH_2)_4—CO_2{}^{-})^2}{(HO_2C—(CH_2)_4—CO_2H)({}^{-}O_2C—(CH_2)_4—CO_2{}^{-})}$$

$$= \frac{(H^+)(HO_2C—(CH_2)_4—CO_2{}^{-})}{(HO_2C—(CH_2)_4—CO_2H)} \Big/ \frac{(H^+)({}^{-}O_2C—(CH_2)_4—CO_2{}^{-})}{(HO_2C—(CH_2)_4—CO_2{}^{-})}$$

$$= \frac{K_1}{K_2} \qquad (11\cdot9)$$

this reaction is equal to K_1/K_2, where K_1 and K_2 are, respectively, the first and second ionization constants of adipic acid. Moreover, the standard free energy $\Delta F°$ of the reaction is, of course, related to the equilibrium constant K by the familiar thermodynamic equation 11·10,

$$\Delta F° = -RT \ln K \qquad (11\cdot10)$$

in which R is the gas constant and T is the absolute temperature. Hence, it follows that the problem of calculating the ratio K_1/K_2 of the two ionization constants of the dibasic acid is equivalent to the one of calculating the standard free energy $\Delta F°$ of reaction 11·8.

It is convenient to think of the total free energy $\Delta F°$ of reaction 11·8 as the sum of three independent terms (as in equation 11·11). The first

$$\Delta F° = \Delta F°_1 + \Delta F°_2 + \Delta F°_3 \qquad (11\cdot11)$$

of these terms, $\Delta F°_1$, is due to the statistical factor which was mentioned on page 438. Since this factor has the effect of multiplying the ratio K_1/K_2 by 4, it contributes to $\Delta F°$ a term which is equal to $-RT \ln 4$ (cf. equation 11·10); the value of $\Delta F°_1$ is therefore that shown in equation 11·12.

$$\Delta F°_1 = -RT \ln 4 \qquad (11\cdot12)$$

The second of the three terms, $\Delta F°_2$, which make up the total free energy $\Delta F°$ is equal to the work which would have to be performed in the reaction if the proton which is transferred from the one molecule to the other were not acted upon by the electrostatic fields of the particular carboxyl and carboxylate groups which are distinguished in equation 11·8 by the asterisks. In other words, this second term is equal to the work which would be required if the carboxyl and carboxylate groups, which have the asterisks, and which do not directly participate in the reaction, were not present at all. Clearly, the work involved in such a reaction would be essentially the same as that involved in reaction 11·13; since in this latter reaction, however, the products are

$$\mathrm{H{-}(CH_2)_4{-}CO_2H + H{-}(CH_2)_4{-}CO_2^- \rightleftarrows H{-}(CH_2)_4{-}CO_2^- + H{-}(CH_2)_4{-}CO_2H} \qquad (11\cdot 13)$$

identical with the reactants, the work involved here is necessarily zero. The quantity $\Delta F°_2$ must therefore be at least approximately equal to zero, as in equation 11·14.

$$\Delta F°_2 = 0 \qquad (11\cdot 14)$$

The third term, $\Delta F°_3$, which contributes to the standard free energy $\Delta F°$ of reaction 11·8, arises because the proton which is transferred must, of course, actually interact with the electrostatic fields of the carboxyl and carboxylate groups which are distinguished by the asterisks. This last term is therefore the one which was discussed qualitatively in the preceding section, and which is responsible for the fact that the ratio K_1/K_2 is greater than 4. The magnitude of $\Delta F°_3$ was first successfully calculated (for several analogous symmetrical dibasic acids, but not for adipic acid itself) by Bjerrum,[6] upon whose pioneering work is based all the subsequent quantitative investigations of the effects of electrostatic interactions upon ionic equilibria.

The derivation of Bjerrum's fundamental equation is almost obvious. Thus, reaction 11·8 can be imagined to proceed in two steps. In the first step, the proton of interest is removed to an infinite distance from the anion, III, to which it was originally linked; in the second step, this

$$\mathrm{^-O_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}C^*O_2H}$$

III

proton is brought from infinity to the position which it finally occupies in the resulting anion, IV. Consequently, $\Delta F°_3$ is the sum of the energy

$$\mathrm{HO_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}C^*O_2^-}$$

IV

that is needed (in the first step) to remove the proton from the electrostatic field of the neutral carboxyl group $\mathrm{{-}C^*O_2H}$, plus the energy that is needed (in the second step) to bring the proton back into the field of the carboxylate group $\mathrm{{-}C^*O_2^-}$. The original distance of the proton from the group $\mathrm{{-}C^*O_2H}$ is, of course, the same as its final distance from the group $\mathrm{{-}C^*O_2^-}$; this distance will hereafter be designated as r. Now, as a first approximation, the carboxyl group $\mathrm{{-}C^*O_2H}$ can be considered to consist of a carboxylate group $—C^*O_2^-$, plus a proton (which is, of course, not the one that is transferred in the reaction). The first step of the reaction therefore involves the removal of a proton from the field of both a carboxylate group $—C^*O_2^-$ and a second proton, whereas the second step involves the return of the proton into the field of a different carboxylate group. Since, as was noted above, the initial and final distances are equal to each other and to r, the effects of the fields due to the different carboxylate groups cancel one another, and only the effect of the field due to the proton (of the carboxyl group $—C^*O_2H$) remains. Hence, ΔF°_3 is equal to the work that is needed to increase the distance between two protons from r to infinity. According to classical electrostatic theory, this work has the value, per molecule, which is shown in equation 11·15; in this equation, e is the charge on the proton

$$\Delta F^\circ_3 = -\frac{e^2}{Dr} \tag{11·15}$$

(4.80×10^{-10} electrostatic unit of charge), and D is the dielectric constant of the surrounding medium.

Combination of equations 11·11, 11·12, 11·14, and 11·15 leads to equation 11·16, in which N is Avogadro's number. Combination of this

$$\Delta F^\circ = -RT \ln 4 + 0 - \frac{Ne^2}{Dr} \tag{11·16}$$

last equation with equations 11·9 and 11·10 leads in turn to the two equivalent equations 11·17 and 11·18, from either of which the ratio

$$\Delta F^\circ = -RT \ln K = -RT \ln \frac{K_1}{K_2} = -RT \ln 4 - \frac{Ne^2}{Dr} \tag{11·17}$$

$$\ln \frac{K_1}{4K_2} = \frac{Ne^2}{RTDr} \tag{11·18}$$

K_1/K_2 can be calculated if the protonic charge e, the dielectric constant D of the solvent (water), and the distance r are known. In practice, however, precise values are available only for the first two of these quantities, since the distance r varies within rather wide limits as rotation occurs about the carbon-carbon single bonds in the molecule. In fact, if the molecule is extended as completely as possible, the distance between the two carboxyl groups in the molecule of adipic acid is about 9.0 A; if the molecule is coiled round upon itself, the distance could be reduced to 0 A if it were not for the repulsive forces that act between atoms which are not bonded to one another (cf. Sections 1·15 and 9·6), and finally, if there is completely free rotation about every bond, the average distance is about 5.6 A.

In view of this uncertainty in regard to the value of the distance r for a molecule of a dibasic acid that is dissolved in water, Bjerrum's calculation is most conveniently inverted; thus, from equation 11·17 (or 11·18), and from the measured values of K_1/K_2, c, and D, the distance r is found to be equal to 8.1 A. This value is, of course, entirely reasonable; in fact, it is intermediate between the values corresponding to free rotation and to complete extension. The fact that such a simple theory therefore gives results which not only are of the correct order of magnitude, but also are quantitatively satisfactory, confirms the supposition that the ratio of the ionization constants in adipic acid is controlled by an electrostatic effect. It should here be mentioned, however, that for several other symmetrical dibasic acids, such as oxalic acid, V,

$HO_2C—CO_2H$ V

$HO_2C—C(CH_3)_2—C(CH_3)_2—CO_2H$ VI

and tetramethylsuccinic acid, VI, Bjerrum's equation gives very poor results. (More particularly, it gives values of r which are much too low. See below.)

A treatment that is similar to Bjerrum's was developed by Eucken for acids with dipolar substituents.[10] In chloroacetic acid, for example, the ionization is increased by the electrostatic interaction between the ionizable proton and the carbon-chlorine dipole. (Cf. page 439.) The quantitative treatment is based upon a consideration of reaction 11·19,

$$Cl—CH_2—CO_2H + H—CH_2—CO_2^- \rightleftarrows Cl—CH_2—CO_2^- + H—CH_2—CO_2H \quad (11 \cdot 19)$$

in which a proton is transferred from a molecule of chloroacetic acid to one of acetate ion. (Cf. equation 11·8.) An argument which is analogous to that used above with adipic acid now shows that the equilibrium constant K of reaction 11·19 is equal to K_c/K_a, where K_c and K_a are, respectively, the ionization constants of chloroacetic acid and of acetic acid. Moreover, since no statistical factor is here involved, the difference between the free energies of ionization of chloroacetic acid and of acetic acid is equal to the work required to remove the ionizable proton of the chloroacetic acid from the electrostatic field due to the carbon-chlorine dipole. According to classical electrostatic theory, the value of this work, per molecule, is $(e\mu \cos \theta)/Dr^2$, where e is again the protonic charge, μ is the magnitude of the carbon-chlorine bond moment,

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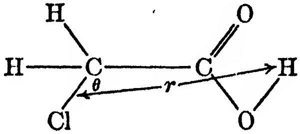
[10] A. Eucken, *Angew. Chem.* **45**, 203 (1932).

θ is the angle designated in structure VII, D is again the dielectric constant of the medium, and r is the distance (likewise designated in structure VII) between the ionizable proton and the center of the carbon-chlorine dipole. The ratio K_c/K_a of the ionization constants for the two acids is therefore given by equation 11·20. When this equation is



VII

$$\ln \frac{K_c}{K_a} = \frac{Ne\mu \cos \theta}{RTDr^2} \tag{11·20}$$

tested, it is found to give an unreasonably low value for r (about 0.6 A) if the dielectric constant D is assigned the value of 80, which is characteristic of the solvent (water). Good results can, in fact, be obtained only if a low dielectric constant, in the neighborhood of 1 to 5, is used. Smallwood [11] suggested that a low dielectric constant is actually appropriate; although his formal argument is superficially quite different from that here given, it is equivalent to the statement that, since there is no solvent between the dipole and the proton in the molecule of chloroacetic acid, the electrostatic effect is not transmitted through the solvent, but rather through the molecule, which is largely empty space, and which therefore has a low dielectric constant.

This situation is not very satisfactory. In order to get semiquantitative agreement with experiment for the long-chain dibasic acids, Bjerrum had to assume an effective dielectric constant of approximately 80; on the other hand, in order to get similar semiquantitative agreement with experiment for acids with dipolar substituents, Smallwood assumed an effective dielectric constant of 1. There can, however, be only one electrostatic law, and this single law should correctly predict the interaction of the ionizable proton both with a charged carboxylate group and with a dipole.

Bjerrum's treatment is based upon a model in which point charges (or dipoles) are assumed to be embedded in a uniform medium with a dielectric constant equal to that of the solvent (about 80 for water); and in which the existence of the molecules which carry the charges (or dipoles) is completely ignored. On the other hand, Smallwood's treatment is based upon a different model, in which the point charges and

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[11] H. M. Smallwood, *J. Am. Chem. Soc.* **54,** 3048 (1932).

dipoles are assumed to be embedded in a molecule that is infinite in extent and that has a low dielectric constant; in this model, therefore, the solvent is completely ignored. Each set of assumptions is, of course, highly arbitrary and far from the truth.

Kirkwood and Scatchard [12] proposed a more reasonable model for electrostatic problems; the application of this model to ionization equilibria was carried through by Kirkwood and Westheimer.[13] These authors assumed that the molecule is essentially a cavity in the solvent or, in other words, that it is a region into which the solvent cannot penetrate. For purposes of mathematical convenience, they assumed also that the cavity is either spherical or ellipsoidal. Surrounding the cavity, there is solvent with uniform (high) dielectric constant. Although this model is certainly crude, any model which admits the existence of both solute molecules and solvent must be a closer approximation to reality than is a still simpler model which ignores either the one or the other. The relation between this more elaborate model and the earlier ones of Bjerrum and of Smallwood is shown schematically in Figure 11·1.

With the improved model of Kirkwood *et al.*, and with the laws of classical physics, both extremes (Bjerrum's and Smallwood's) appear as limits which are approached by certain physical systems. The new equations, which are too complex to be given here, automatically reduce to Bjerrum's when the first and second ionization constants of a long and thin dibasic acid, like adipic acid, are compared with one another, and to Smallwood's equation when the ionization constant of a short dipolar acid, like chloroacetic acid, is compared with that of the parent, unsubstituted acid. The reason why the new model can thus approach two different limits is clear. The electrostatic field of a charge is inversely proportional to the distance; that of a dipole is inversely proportional to the square of the distance. (Cf., respectively, equations 11·18 and 11·20.) Consequently, the region at some distance from a *charge* (where the dielectric constant is high) is of considerable importance, whereas only the region in the immediate vicinity of a *dipole* (where the dielectric constant is low) is of comparable importance. For a similar reason, Bjerrum's treatment might be expected to be inadequate also with a short and fat dibasic acid, like oxalic acid, V, or tetramethylsuccinic acid, VI (see above); for, in the univalent anions derived from such

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[12] G. Scatchard and J. G. Kirkwood, *Physik. Z.* **33**, 297 (1932); J. G. Kirkwood, *J. Chem. Phys.* **2**, 351 (1934).

[13] J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.* **6**, 506 (1938); F. H. Westheimer and J. G. Kirkwood, *ibid.* **6**, 513 (1938); F. H. Westheimer and M. W. Shookhoff, *J. Am. Chem. Soc.* **61**, 555 (1939).

compounds, the electrostatic effects due to the charged carboxylate groups must act to a very considerable extent through the organic molecules rather than through the solvent.

In the quantitative calculations based on their theory, Kirkwood and Westheimer made a slight refinement of the model that was described above. The assumed cavity in the solvent is, of course, occupied by the acid molecule and is thus not really empty space. Since it therefore contains matter, it must be somewhat polarizable. If the cavity were in fact empty space, its dielectric constant would be 1; if it were as polarizable as is hexane, its dielectric constant would be 1.9; if it were as polarizable as is carbon tetrachloride, its dielectric constant would be 2.2. The value that was chosen for all the calculations was 2. Although this choice somewhat affects the exact quantitative results, it does not change the essential qualitative features of the treatment, and it does not alter the conclusion that the single electrostatic equation, which is based upon the above model, and which is derived from classical physics,

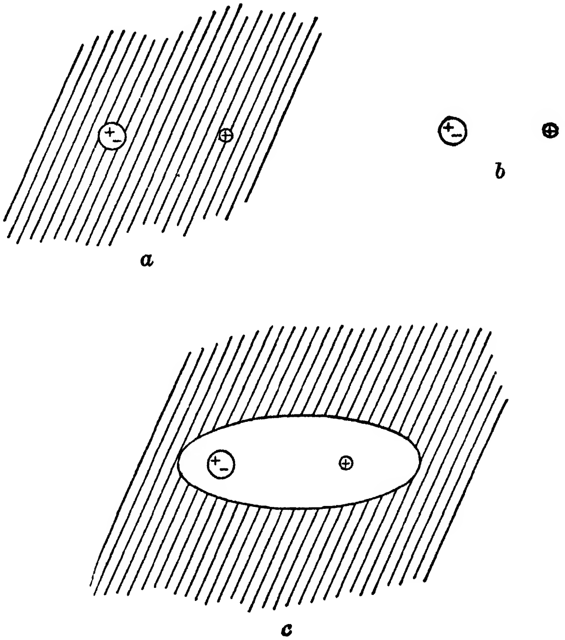

FIGURE 11·1. Schematic representations of the models used in the various semiquantitative treatments of electrostatic interactions. (*a*) Bjerrum-Eucken model, in which the molecule is ignored; (*b*) Smallwood model, in which the solvent is ignored; (*c*) Kirkwood-Westheimer model, in which both the molecule and the solvent are represented.

reduces for long-chain dibasic acids to Bjerrum's equation, and for short dipolar acids to Smallwood's. Some illustrative data are given in Table 11·2.

TABLE 11·2

Electrostatic Computations from Acid Strengths

	Computed Length of Acid Molecule in A				
Acid	Bjerrum's Model ($D = 80$)	Modified[a] Smallwood Model ($D = 1$)	Kirkwood-Westheimer Model	Fully Extended	Free Rotation
Adipic	8.1	635	7.8	9.0	5.6
Chloroacetic	0.6	5.1	3.0	3.4	3.0

[a] Smallwood applied his equation only to acids with dipolar substituents; he realized perfectly well that it would not apply to charge-charge interactions. The figure for adipic acid is given here to show that Smallwood's equation (equation 11·17 or 11·18, with D equal to 1) is approximately valid only for a restricted class of acids.

Even with the refinement mentioned in the preceding paragraph, the model of Kirkwood and Westheimer is still, of course, extremely crude; clearly, therefore, there is a possibility that a still better model could be devised. For example, the "electrical saturation" in the neighborhood of the ions might somehow be taken into account; however, data like those presented in Table 11·2 suggest that such improvements, although real, would not fundamentally change the qualitative aspects of the theory.

The effects of electrostatic interactions upon the rates of chemical reactions can also be treated in the above semiquantitative manner. Thus, if the rate constants for the alkaline hydrolyses of diethyl adipate, VIII,

$$C_2H_5—O_2C—CH_2—CH_2—CH_2—CH_2—CO_2—C_2H_5$$

VIII

and of monoethyl adipate, IX (see pages 439 f.) are designated, respectively,

$$C_2H_5—O_2C—CH_2—CH_2—CH_2—CH_2—CO_2H$$

IX

as k_1 and k_2, then the ratio k_1/k_2 can be shown (in a manner that is not essentially different from the one in which equations 11·17 and 11·18 were derived) to have the value given in equations 11·21 and 11·22.

$$\ln\frac{k_1}{k_2} = \ln 2 + \frac{NU}{RT} \qquad (11·21)$$

$$\ln \frac{k_1}{2k_2} = \frac{NU}{RT} \tag{11·22}$$

The term ln 2, which appears on the right side of equation 11·21, arises from a statistical factor, which is itself due to the fact that the diethyl ester, VIII, has two hydrolyzable carboethoxyl groups, whereas the monoethyl ester, IX, has only one such group; N is again Avogadro's number; and the quantity U is the work, per molecule, which is needed to bring a hydroxide ion from infinity to the carboethoxyl group of the ester anion, X, against the electrostatic repulsion of the negatively charged carboxylate group.

$$C_2H_5—O_2C—CH_2—CH_2—CH_2—CH_2—CO_2^-$$

X

(Since the hydrolyses which are now under discussion are considered to occur in basic solutions, the monoethyl ester, IX, is, of course, present in the form of its ion, X.) If Bjerrum's model is used, the work U is equal to e^2/Dr, where D is the dielectric constant of the solvent and r is the distance between the carboethoxyl and carboxylate groups in the ion X; if Kirkwood and Westheimer's model is used, the work is given by a more complicated expression. Since, however, the electrostatic interaction between the hydroxide ion and the carboxylate group is of the charge-charge type, and since, moreover, the ion X is long and thin, the two calculations lead to approximately the same value of U. If use is now made of the fact that the observed ratio k_1/k_2 is equal to 5,[8, 9] the computed value of the distance r is 7.7 A for Bjerrum's model and 8.2 A for Kirkwood and Westheimer's model. These two values are in satisfactory agreement both with each other and with the corresponding distances (see Table 11·2) which are derived from the ratio K_1/K_2 of the first and second ionization constants of adipic acid. (By slightly modifying Bjerrum's model, in a way which need not here be described, Ingold [8] has obtained the further value of 8.3 A for r.)

In the calculation of relative rate constants, just as in that of relative ionization constants, it is possible to estimate the electrostatic effects of dipoles (and not merely those of ionic charges); the details of the calculations should now, however, be too obvious to require further discussion here. Thus, at 6.6°C in aqueous solution, *tert*-butyl chloroacetate, XI, is hydrolyzed by hydroxide ion approximately 500 times as fast as is *tert*-butyl acetate, XII.

$$Cl—CH_2—CO_2—C(CH_3)_3$$

XI

$$H—CH_2—CO_2—C(CH_3)_3$$

XII

From this ratio of rate constants, the

calculated distance between the carboalkoxyl group and the carbon-chlorine dipole in the chloroester, XI, is found to be 3.15 A if the model of Kirkwood and Westheimer is adopted, but to be only 0.48 A if the model of Bjerrum and Eucken is adopted;[14] these values are quite close to the corresponding ones (see Table 11·2) which are derived from the ratio of the ionization constants of chloroacetic acid, VII, and acetic acid. Once more, therefore, it is apparent that, for the calculation of the electrostatic effects which are due to dipoles, the Kirkwood-Westheimer model is superior to the simpler Bjerrum-Eucken model.

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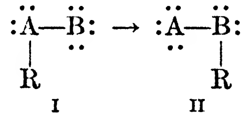
[14] F. H. Westheimer and M. W. Shookhoff, *J. Am. Chem. Soc.* **62**, 269 (1940).

12.

Molecular Rearrangements
The 1,2-Shifts

12·1 Introduction. In Chapter 4, attention was called to the fact that the principle of minimum structural change is not universally valid, inasmuch as many chemical reactions are accompanied by more or less drastic molecular rearrangements. In this chapter and in the following one, rearrangements of several different types will be surveyed, the sorts of reaction in which such rearrangements may be expected to occur will be listed, and the mechanisms that have been proposed in the attempt to account for the various anomalous reactions will be discussed.[1]

12·2 1,2-Shifts. A large number of molecular rearrangements can be described as resulting from so-called 1,2-shifts. In a purely formal sense, any such transformation can always be expressed by the general equation 12·1, in which an atom or group R, which is originally attached



$$\underset{\text{I}}{:\overset{..}{\underset{\substack{|\\ \mathrm{R}}}{\mathrm{A}}}-\overset{..}{\underset{..}{\mathrm{B}}}:} \rightarrow \underset{\text{II}}{:\overset{..}{\underset{..}{\mathrm{A}}}-\overset{..}{\underset{\substack{|\\ \mathrm{R}}}{\mathrm{B}}}:} \qquad (12\cdot 1)$$

to an atom A migrates to an adjacent atom B. Always at least some, and frequently all, of the pairs of electrons that are represented by the pairs of dots in the above structures I and II are to be considered employed in the formation of covalent bonds to further atoms or groups that are not explicitly represented. The product of the reaction which is actually isolated in any given instance is seldom, if ever, the substance corresponding to structure II; ordinarily, it is instead a substance which can be thought of as derived from II by some further reaction not involving rearrangement. As should be obvious, equation 12·1 is not intended to describe the true mechanism of the rearrangement, but merely to express as generally and as compactly as possible the significant re-

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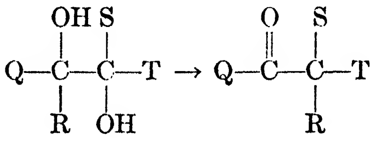
[1] For further discussions of molecular rearrangements, see W. Hückel, *Theoretische Grundlagen der Organischen Chemie*, Akademische Verlagsgesellschaft, Leipzig, 1st ed., 1931, 2nd ed., 1934, Volume I, Chapter 6; E. S. Wallis in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, Chapter 8, 2nd ed., 1943, Volume I, Chapter 12.

spect in which the principle of minimum structural change is violated in any reaction of the class now under discussion. The problem of mechanism will be discussed more fully in later sections of this chapter.

The nature and scope of the 1,2-shifts can be described most readily with the aid of specific examples, which will be chosen so as to illustrate the most important types of rearrangement belonging to this category. In each instance, it will be readily seen that the essential feature of the rearrangement is the 1,2-shift depicted in equation 12·1.

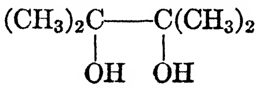
The so-called *pinacol* (or frequently the *pinacolone*) rearrangement can be described by the general equation 12·2, in which Q, R, S, and T



$$\begin{array}{c} \text{OH}\;\text{S} \qquad\qquad \text{O}\;\;\text{S} \\ \text{Q—}\underset{|}{\overset{|}{\text{C}}}\text{—}\underset{|}{\overset{|}{\text{C}}}\text{—T} \rightarrow \text{Q—}\overset{\|}{\text{C}}\text{—}\underset{|}{\overset{|}{\text{C}}}\text{—T} \\ \text{R}\;\;\text{OH} \qquad\qquad\quad \text{R} \end{array} \qquad (12\cdot2)$$

represent either hydrogen atoms or hydrocarbon radicals (which may or may not carry substituent atoms or groups). The rearrangement is brought about most frequently by the action of strong acids, such as sulfuric acid; in some instances, it occurs also at higher temperatures either in the absence of a catalyst or in the presence of certain materials, such as alumina Al_2O_3 which may be regarded as Lewis acids. (See Section 3·3.)

The most familiar example of the pinacol rearrangement consists in the transformation of tetramethylethylene glycol, III (often called



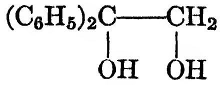
$$\begin{array}{c} (CH_3)_2\underset{|}{C}\text{——}\underset{|}{C}(CH_3)_2 \\ \quad\;\; OH \quad\;\; OH \end{array}$$

III

simply "pinacol") into methyl *tert*-butyl ketone, IV (often called simply

$(CH_3)_3C$—CO—CH_3 IV $\qquad$ CH_2OH—CH_2OH V $\qquad$ CH_3—CHO VI

"pinacolone"). The reaction is, however, extremely general since the methyl groups of the pinacol, III, can be replaced by any of a number of other atoms and groups. Thus, ethylene glycol itself, V, gives acetaldehyde, VI, over alumina at 200°C, in addition to other products formed by polymerization of the aldehyde. Moreover, aromatic as well as aliphatic compounds undergo similar reactions, as is shown, for example, by the rearrangement of 1,1-diphenylethylene glycol, VII, to diphenylacetaldehyde, VIII, and of benzpinacol, IX, to benzpinacolone, X.

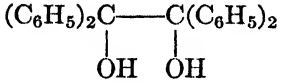


$(C_6H_5)_2\underset{OH}{\underset{|}{C}}-\underset{OH}{\underset{|}{CH_2}}$

VII

$(C_6H_5)_2CH-CHO$

VIII



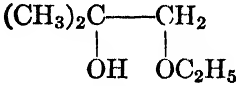
$(C_6H_5)_2\underset{OH}{\underset{|}{C}}-\underset{OH}{\underset{|}{C}}(C_6H_5)_2$

IX

$(C_6H_5)_3C-CO-C_6H_5$

X

In addition to the pinacol rearrangements proper, shown generally in equation 12·2, there exist a number of closely related transformations which apparently belong to the same class of rearrangement. Thus, the monoethyl ether, XI, of 1,1-dimethylethylene glycol is changed into

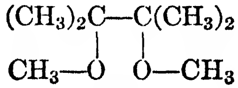


$(CH_3)_2\underset{OH}{\underset{|}{C}}-\underset{OC_2H_5}{\underset{|}{CH_2}}$

XI

$(CH_3)_2CH-CHO$

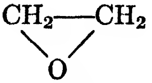
XII



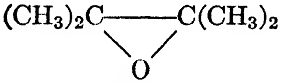
$(CH_3)_2\underset{CH_3-O}{\underset{|}{C}}-\underset{O-CH_3}{\underset{|}{C}}(CH_3)_2$

XIII

isobutyraldehyde, XII, when heated to 110°–115°C with anhydrous oxalic acid. Moreover, even the dimethyl ether, XIII, of pinacol gives pinacolone, IV, when heated to 140°C with boron oxide B_2O_3. Ethylene oxides, which also may be considered ethers of the 1,2-glycols, undergo entirely similar rearrangements. Thus, ethylene oxide, XIV, is changed



XIV

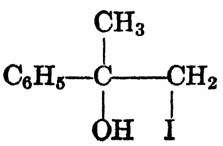


XV

CH_2OH-CH_2Cl

XVI

into acetaldehyde, VI, over alumina at 200°C, and tetramethylethylene oxide, XV, is changed into pinacolone, IV, by strong acids. Ethylene chlorohydrin, XVI, on being heated, is converted partially into acetaldehyde, VI; the methylphenylethylene iodohydrin, XVII, when treated

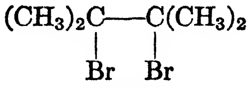


$C_6H_5-\overset{CH_3}{\overset{|}{\underset{OH}{\underset{|}{C}}}}-\underset{I}{\underset{|}{CH_2}}$

XVII

$C_6H_5-CH_2-CO-CH_3$

XVIII

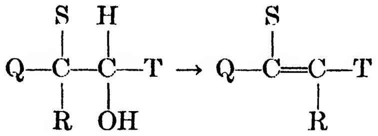


$(CH_3)_2\underset{Br}{\underset{|}{C}}-\underset{Br}{\underset{|}{C}}(CH_3)_2$

XIX

with mercuric oxide, is transformed into phenylacetone, XVIII. And finally, the action of water and lead oxide PbO at 140°–150°C upon 2,3-dimethyl-2,3-dibromobutane, XIX, produces pinacolone, IV. (The rearrangements of amino alcohols, which also are analogous to those of the pinacols, will be described later.)

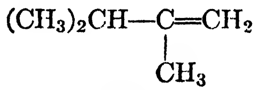
The *retropinacol* rearrangement can be represented by the general equation 12·3, in which Q, R, S, and T have the same significance as in equation 12·2. A simple example of the retropinacol rearrangement is given by the dehydration of methyl-*tert*-butylcarbinol (pinacolyl alcohol), XX, to tetramethylethylene, XXI, and *unsym*-methylisopropylethylene, XXII. When phosphoric acid on silica gel at 300°C is used as the dehydrating agent, only a small amount of the expected *tert*-butylethylene, XXIII, is formed in the reaction.[2]



$$Q-\underset{R}{\overset{S}{C}}-\underset{OH}{\overset{H}{C}}-T \rightarrow Q-\overset{S}{C}=\underset{R}{C}-T \qquad (12\cdot3)$$

$(CH_3)_3C-CHOH-CH_3$
XX

$(CH_3)_2C=C(CH_3)_2$
XXI



$$(CH_3)_2CH-\underset{CH_3}{C}=CH_2$$

XXII

$(CH_3)_3C-CH=CH_2$
XXIII

The dehydrohalogenation of a halide, like the dehydration of an alcohol, is often accompanied by a rearrangement of the retropinacol type. For example, the action of potassium acetate upon neopentyl iodide, XXIV, in absolute alcohol as solvent gives, in addition to the expected neopentyl acetate, XXV, the rearranged product trimethylethylene, XXVI.[3]

$(CH_3)_3C-CH_2I$
XXIV

$(CH_3)_3C-CH_2-O-CO-CH_3$
XXV

$(CH_3)_2C=CHCH_3$
XXVI

The retropinacol rearrangement, especially when it takes place with substances belonging to the class of compounds known as terpenes, is frequently called a *Wagner*, or a *Wagner-Meerwein*, rearrangement. For example, both the dehydration of isoborneol, XXVII (by sulfuric acid, phosphorus pentoxide, zinc chloride, or the like), and the dehydrohalogenation of isobornyl chloride, XXVIII (by the action of bases or

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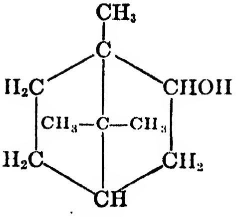
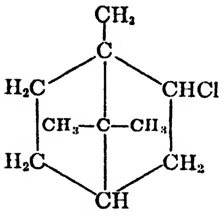
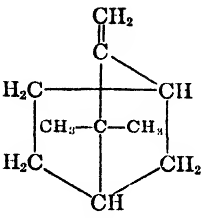
[2] F. C. Whitmore and P. L. Meunier, *J. Am. Chem. Soc.* **55**, 3721 (1933).

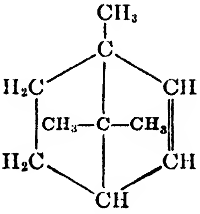
[3] F. C. Whitmore, E. L. Wittle, and A. H. Popkin, *J. Am. Chem. Soc.* **61**, 1586 (1939).

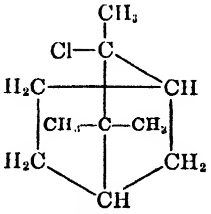

XXVII


XXVIII

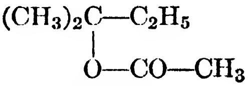

XXIX

even by simple heating), lead to camphene, XXIX, and not to bornylene, XXX. (Cf. page 96.) Conversely, the addition of hydrogen chloride to camphene leads first to camphene hydrochloride, XXXI, which then rearranges to isobornyl chloride, XXVIII.


XXX

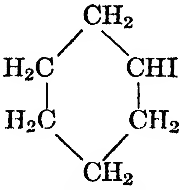

XXXI

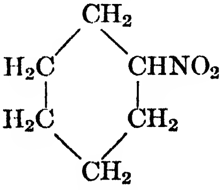
Double-decomposition reactions which are very closely related to the above retropinacol rearrangements are also known. For example, the action of silver acetate upon neopentyl iodide, XXIV, in glacial acetic acid gives a little *tert*-amylacetate, XXXII, in addition to a great deal of trimethylethylene, XXVI;[4] and that of silver nitrite upon cyclohexyl iodide, XXXIII, leads to both nitrocyclohexane, XXXIV, and 1-

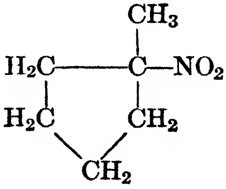


$$\begin{array}{l}\mathrm{(CH_3)_2C{-}C_2H_5}\\ \qquad\ |\\ \qquad\ \mathrm{O{-}CO{-}CH_3}\end{array}$$

XXXII


XXXIII


XXXIV


XXXV

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[4] F. C. Whitmore and G. H. Fleming, *J. Chem. Soc.* **1934**, 1269.

methyl-1-nitrocyclopentane, XXXV. Similarly, the reaction between silver cyanate and isobutyl iodide, XXXVI, yields mostly *tert*-butyl

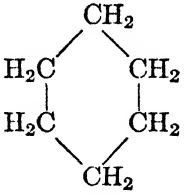
$(CH_3)_2CH\text{—}CH_2I$ XXXVI $(CH_3)_3C\text{—}NCO$ XXXVII $(CH_3)_2CH\text{—}CH_2\text{—}NCO$ XXXVIII

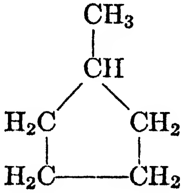
isocyanate, XXXVII, and only a little isobutyl isocyanate, XXXVIII.

Rearrangements of the foregoing type suggest the possibility of simple interchanges of halogen atoms and other atoms or groups, without the occurrence of any further reactions. One example of such a rearrangement (that of camphene hydrochloride, XXXI, to isobornyl chloride, XXVIII) has already been mentioned; a further example is provided by the transformation of *n*-propyl bromide, XXXIX, into

$CH_3\text{—}CH_2\text{—}CH_2Br$ XXXIX $CH_3\text{—}CHBr\text{—}CH_3$ XL

isopropyl bromide, XL, under the catalytic influence of aluminum bromide. That the presence of a halogen atom in the organic molecule which undergoes rearrangement is not essential to such reactions is shown by the fact that paraffin hydrocarbons also undergo similar transformations. For example, in the presence of aluminum chloride containing a little water, either cyclohexane, XLI, or methylcyclopentane, XLII, is transformed into an equilibrium mixture of the two.[5] In the rearrangement of a paraffin hydrocarbon, the presence of at least a trace of an olefin, or of something readily transformable into an olefin, is essential.[6] The function of the olefin is possibly to form an alkyl chloride RCl by reaction with the hydrogen chloride liberated from the aluminum chloride and water; this alkyl chloride may then combine with further aluminum chloride (cf. Section 2·5) to form the salt $R^+[AlCl_4]^-$, the cation of which is considered to be the effective reagent in producing the rearrangement. Frequently, the necessary hydrogen chloride is added as such to the reaction mixture; under such circum-


XLI


XLII

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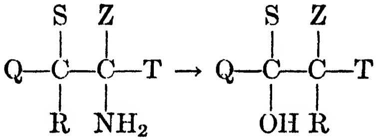
[5] A. L. Glasebrook and W. G. Lovell, *J. Am. Chem. Soc.* **61**, 1717 (1939).

[6] H. S. Bloch, H. Pines, and L. Schmerling, *J. Am. Chem. Soc.* **68**, 153 (1946); H. Pines and R. C. Wackher, *ibid.* **68**, 595 (1946); R. C. Wackher and H. Pines, *ibid.* **68**, 1642 (1946).

stances the hydrolysis of the aluminum chloride is no longer essential. Frequently, also, the olefin is replaced by an alkyl chloride. Inasmuch as olefins and alkyl chlorides are often present as impurities in paraffins, and inasmuch as only traces of these materials are required, the necessity that such substances be present was for a long time unrecognized.

The role played by the water in the isomerization of a paraffin hydrocarbon by aluminum chloride plus a trace of an olefin is certainly not *exclusively* that suggested in the preceding paragraph. Thus, although the reaction does not proceed satisfactorily in the absence of both water and hydrogen chloride, it occurs readily in the presence of water even if the hydrogen chloride evolved is completely removed by evacuation of the reaction vessel before the hydrocarbon is added. It has been suggested that, when water is present, there is formed some substance (perhaps HO—$AlCl_2$) which is so powerful a catalyst that, unlike $AlCl_3$, it does not require the aid of either hydrogen chloride or an alkyl chloride.[6] The reason for this greater activity of the partially hydrolyzed catalyst, however, is obscure.

The *Demjanow* rearrangement, which frequently occurs when a primary amine is treated with nitrous acid, proceeds in accordance with the general equation 12·4. The radical to which the amino group is joined

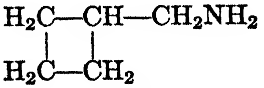


$$Q{-}\overset{S}{\underset{R}{C}}{-}\overset{Z}{\underset{NH_2}{C}}{-}T \rightarrow Q{-}\overset{S}{\underset{OH}{C}}{-}\overset{Z}{\underset{R}{C}}{-}T \qquad (12{\cdot}4)$$

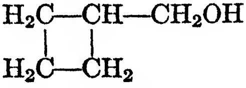
in the original substance is usually either primary or secondary, since those primary amines in which the radical is tertiary ordinarily react with nitrous acid without rearrangement. (However, see the discussion below of the amino alcohols.) As an example of the Demjanow rearrangement, the reaction between isobutylamine, XLIII, and nitrous

$(CH_3)_2CH{-}CH_2NH_2$ XLIII $(CH_3)_2CH{-}CH_2OH$ XLIV $(CH_3)_3COH$ XLV

acid may be mentioned. The alcoholic product consists of a mixture of isobutyl alcohol, XLIV, and *tert*-butyl alcohol, XLV, in the ratio of approximately 1 to 3. In reactions of this type, the product frequently contains, in addition to the alcohols, also some olefin which can be thought of as derived from the alcohols. Thus, α-cyclobutylmethylamine (cyclobutanemethylamine), XLVI, gives both the expected cyclo-

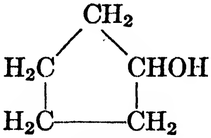


XLVI

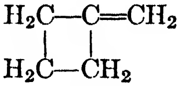


XLVII

butylcarbinol, XLVII, and the rearranged cyclopentanol, XLVIII, as

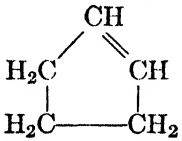


XLVIII



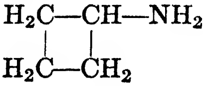
XLIX

well as the two related hydrocarbons, methylenecyclobutane, XLIX, and cyclopentene, L, respectively. Rings can be contracted as well as

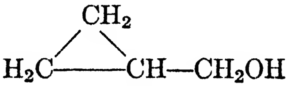


L

expanded by this rearrangement, since cyclobutylamine, LI, has been

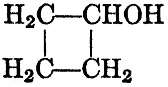


LI

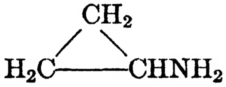


LII

found to produce cyclopropylcarbinol, LII, as well as cyclobutanol, LIII; and cyclopropylamine, LIV, gives only allyl alcohol, LV, with a "2-membered ring."



LIII

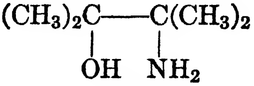


LIV

$CH_2{=}CH{-}CH_2OH$

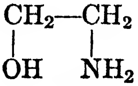
LV

Amino alcohols in which primary amino groups and hydroxyl groups are attached to adjacent carbon atoms undergo reactions which are reminiscent of both the pinacol and the Demjanow rearrangements. Thus, the substance of structure LVI gives pinacolone, IV, on treatment



$$(CH_3)_2\underset{OH}{C}{-}\underset{NH_2}{C}(CH_3)_2$$

LVI

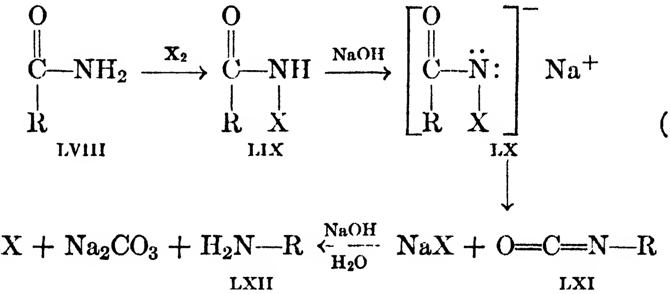


$$\underset{OH}{CH_2}{-}\underset{NH_2}{CH_2}$$

LVII

with nitrous acid; and ethanolamine, LVII, gives acetaldehyde, VI. Moreover, amino alcohols of this type undergo similar transformations under the conditions of the pinacol, as well as under those of the Demjanow, rearrangement. Thus, pinacolone can be obtained from the amino alcohol, LVI, by the heating of its hydrochloride as well as by the action upon it of nitrous acid.

The *Hofmann* rearrangement of the amide, LVIII, of a carboxylic acid,[7] which takes place under the combined influence of alkali and a halogen X_2, also can be classified as a 1,2-shift, as is shown by the sequence of reactions 12·5. The haloamide, LIX, its sodium salt, LX,



$$\underset{\text{LVIII}}{R\text{—}\overset{\overset{\large O}{\|}}{C}\text{—}NH_2} \xrightarrow{X_2} \underset{\text{LIX}}{R\text{—}\overset{\overset{\large O}{\|}}{C}\text{—}NH\text{—}X} \xrightarrow{NaOH} \underset{\text{LX}}{\left[R\text{—}\overset{\overset{\large O}{\|}}{C}\text{—}\ddot{N}{:}\text{—}X\right]^-} Na^+ \qquad (12\cdot5)$$

$$\downarrow$$

$$NaX + Na_2CO_3 + \underset{\text{LXII}}{H_2N\text{—}R} \xleftarrow[H_2O]{NaOH} NaX + \underset{\text{LXI}}{O{=}C{=}N\text{—}R}$$

and the isocyanate, LXI, are intermediates which can, in at least some instances, be isolated. Under the usual experimental conditions, however, the amine LXII is often the only product obtained. Other products that frequently are isolated include the symmetrically disubstituted urea RNH—CO—NHR, which is formed from reaction between the amine LXII and the isocyanate LXI; the urethan RNH—CO—OR′, which is formed from reaction between the alcohol R′OH, when this is used as solvent, and the isocyanate LXI; and (in the event that the radical R is primary and so representable as $R''CH_2$) the nitrile R″CN, which is formed as a result of oxidation of the amine LXII by the halogen X_2. As examples of the Hofmann rearrangement, the reactions may be cited in which acetamide, LVIII (with R equal to CH_3), is transformed into methylamine in aqueous solution, or into N-methylurethan, LXIII,

$$\underset{\text{LXIII}}{CH_3\text{—}NH\text{—}CO\text{—}O\text{—}C_2H_5} \qquad \underset{\text{LXIV}}{C_6H_5NH\text{—}CO\text{—}NHC_6H_5}$$

in alcoholic solution; in which benzamide, LVIII (with R equal to C_6H_5), is transformed into aniline and into N,N′-diphenylurea, LXIV; and in which pelargonamide, LVIII (with R equal to n-C_8H_{17}), is transformed into *n*-octylamine and *n*-heptyl cyanide.[7]

The *Lossen* rearrangement, which occurs when a hydroxamic acid, LXV (with Z equal to OH), or, more commonly, a derivative of a hydroxamic acid is heated (frequently but not always in the presence of a

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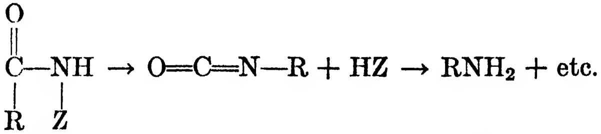
[7] For further discussion of the Hofmann rearrangement, see E. S. Wallis and J. F. Lane in R. Adams, *Organic Reactions*, John Wiley and Sons, New York, Volume III, 1946. Chapter 7.

base), and which may be represented by equation 12·6, is extremely



$$\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle O}{\overset{\|}{C}}}}-\underset{\displaystyle Z}{\underset{|}{N}}H \rightarrow O{=}C{=}N-R + HZ \rightarrow RNH_2 + \text{etc.} \qquad (12\cdot6)$$

LXV LXI LXII

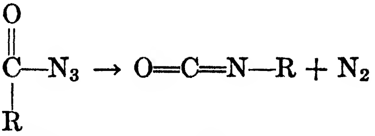
similar to the Hofmann rearrangement of an amide.[8] Examples of the Lossen rearrangement include the thermal decomposition of benzhydroxamic acid, LXV (with R equal to C_6H_5 and Z equal to OH), which gives, among other products, aniline and carbon dioxide; the action of bases upon dibenzhydroxamic acid, LXV (with R equal to C_6H_5 and Z equal to $C_6H_5—CO—O$), which gives, under suitable conditions, phenyl isocyanate, LXI (with R equal to C_6H_5), aniline, carbon dioxide, and N,N′-diphenylurea, LXIV; and numerous other reactions of similar types. When, in structure LXV, Z is a halogen atom, the rearrangement is identical with the one of Hofmann. In all instances, the products obtained are consistent with the view that the isocyanate, LXI, is always formed, although this substance can of course be transformed in familiar manners into an amine, a urea, or a urethan by the action of aqueous acids or bases, of an amine, or of an alcohol, respectively.

The original hydroxamic acid, LXV (with Z equal to OH), can be made by the action of hydroxylamine H_2NOH upon either the acid chloride or the ester of the corresponding carboxylic acid, in accordance with equation 12·7 or 12·8, respectively.

$$RCOCl + 2H_2NOH \rightarrow RCO—NHOH + [H_3NOH]^+Cl^- \qquad (12\cdot7)$$

$$RCO_2C_2H_5 + H_2NOH \rightarrow RCO—NHOH + C_2H_5OH \qquad (12\cdot8)$$

The *Curtius* rearrangement of an acid azide, LXVI, which also occurs on simple heating, and which is shown in equation 12·9, appears to be



$$\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle O}{\overset{\|}{C}}}}-N_3 \rightarrow O{=}C{=}N-R + N_2 \qquad (12\cdot9)$$

LXVI LXI

completely analogous to the Hofmann and Lossen rearrangements. The product is again an isocyanate, LXI.[9]

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[8] For further discussion of the Lossen rearrangement, see H. L. Yale, *Chem. Revs.* **33**, 209 (1943).

[9] For further discussion of the Curtius rearrangement, see P. A. S. Smith in R. Adams, *Organic Reactions*, John Wiley and Sons, New York, Volume III, 1946, Chapter 9. Cf. also H. Wolff, *ibid.*, Chapter 8.

The structure of the azide group —N_3 is best expressed as that of a resonance hybrid between structures LXVII and LXVIII.[10] Acid azides can be made by the

$$-\overset{..}{N}=N^{+}=\underset{..}{N}:^{-} \qquad\qquad -\overset{..}{\underset{..}{N}}{}^{-}-N^{+}\equiv N:$$

LXVII LXVIII

action of sodium azide NaN_3 (a commercially available substance which is prepared by the reaction between sodamide $NaNH_2$ and nitrous oxide N_2O) upon the acid chlorides, as in equation 12·10, or by that of nitrous acid upon the corresponding

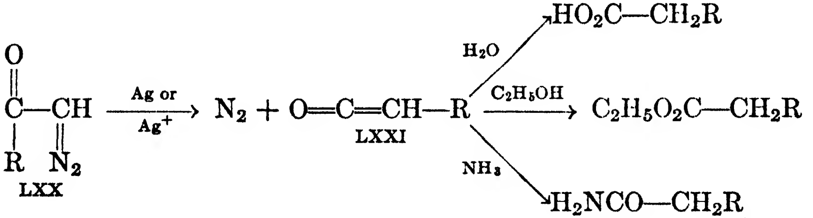
$$RCOCl + NaN_3 \rightarrow RCON_3 + NaCl \qquad (12 \cdot 10)$$

hydrazides, LXIX, as in equation 12·11. The hydrazides required in the second

$$\left.\begin{array}{l} RCOCl + 2H_2N{-}NH_2 \rightarrow [H_2N{-}NH_3]^{+}Cl^{-} + \\ RCO_2C_2H_5 + H_2N{-}NH_2 \rightarrow C_2H_5OH + \end{array}\right\} \underset{\text{LXIX}}{RCO{-}NH{-}NH_2} \xrightarrow{HNO_2} RCON_3 \qquad (12 \cdot 11)$$

of these reactions can themselves be prepared by either of the two alternative methods indicated.

The *Wolff* rearrangement of a diazo ketone, LXX, is analogous to the Hofmann, Lossen, and Curtius rearrangements.[11] As is shown in equation 12·12, the product is either a carboxylic acid or, under suitably



$$\underset{\text{LXX}}{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{N_2}{\underset{\|}{CH}}} \xrightarrow[Ag^{+}]{Ag\ or} N_2 + \underset{\text{LXXI}}{O{=}C{=}CH{-}R} \begin{cases} \xrightarrow{H_2O} HO_2C{-}CH_2R \\ \xrightarrow{C_2H_5OH} C_2H_5O_2C{-}CH_2R \\ \xrightarrow{NH_3} H_2NCO{-}CH_2R \end{cases}$$

(12·12)

modified conditions, a derivative of such an acid. The ketene LXXI, which is assumed as an intermediate, replaces the isocyanate formed in the three preceding types of rearrangement; although its existence is demanded by analogy and by the natures of the final products, it is not ordinarily isolated from the reaction mixture. (However, see below.)

The structure of a diazo ketone, containing the so-called *aliphatic diazo group* $=N_2$, is best described in terms of resonance between structures LXXII and

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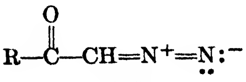
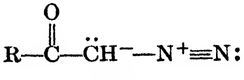
[10] Cf. N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, 1937, pages 363 ff.

[11] For further discussion of the Wolff rearrangement and of the related *Arndt-Eistert synthesis*, see W. E. Bachmann and W. S. Struve in R. Adams, *Organic Reactions*, John Wiley and Sons, New York, Volume I, 1942, Chapter 2.



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-CH{=}N^{+}{=}\underset{\bullet\bullet}{N}:^{-}$$

LXXII



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\cdot\cdot}{C}H^{-}-N^{+}{\equiv}N:$$

LXXIII

LXXIII.[12] Substances of this class can be made by the action of diazomethane CH_2N_2 upon an acid chloride, as in equation 12·13. In the carrying out of the

$$RCOCl + 2CH_2N_2 \rightarrow RCO{-}CHN_2 + CH_3Cl + N_2 \qquad (12{\cdot}13)$$

reaction, the acid chloride must be added to at least the two-fold amount of diazomethane which is demanded by this equation. If the reagents are added in the reverse order, or if a smaller amount of diazomethane is used, the diazo ketone formed by reaction 12·14 is destroyed (in accordance with equation 12·15) by the

$$RCOCl + CH_2N_2 \rightarrow RCO{-}CHN_2 + HCl \qquad (12{\cdot}14)$$

$$RCO{-}CHN_2 + HCl \rightarrow RCO{-}CH_2Cl + N_2 \qquad (12{\cdot}15)$$

hydrogen chloride that is formed simultaneously. If, however, the reaction is carried out as stated, the hydrogen chloride is removed by the excess diazomethane, as is shown in equation 12·16, and a satisfactory yield of the diazo ketone, LXX, is

$$CH_2N_2 + HCl \rightarrow CH_3Cl + N_2 \qquad (12{\cdot}16)$$

obtained. The diazomethane required for the reaction of course has a resonating structure analogous to that of the resulting diazo ketone; it can be prepared by a variety of methods, of which the one shown in equation 12·17 is probably the most

$$[CH_3{-}NH_3]^{+}Cl^{-} \xrightarrow{NH_2CONH_2} CH_3NH{-}CO{-}NH_2 \xrightarrow{HNO_2} CH_3N(NO){-}CO{-}NH_2 \xrightarrow{KOH} CH_2N_2 \qquad (12{\cdot}17)$$

convenient; the substance is usually prepared and used in ether solution without being isolated. The complete sequence of reactions by which a carboxylic acid RCO_2H is transformed, through its chloride RCOCl, into its next higher homolog $RCH_2{-}CO_2H$ is called the *Arndt-Eistert reaction*.[11]

It may perhaps not be completely apparent that the "Wolff rearrangement" really involves a rearrangement at all, since an acid, RCH_2CO_2H (or a derivative of such an acid), could conceivably be formed from the corresponding diazo ketone $R{-}CO{-}CHN_2$ by an intramolecular oxidation and reduction, without the occurrence of any 1,2-shift. Thus, if the carbonyl group of the original diazo ketone were reduced to a methylene group and if, at the same time, the $-CHN_2$ group were oxidized to a carboxyl group (or to a modified carboxyl group), the same product would be obtained as if the reaction had instead proceeded by a 1,2-shift. That this alternative interpretation is incorrect, however,

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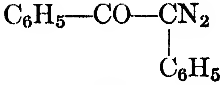
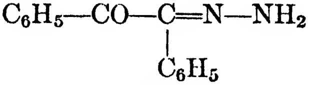
[12] Cf. N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, 1937, pages 360 ff.

is suggested by the behavior of slightly more complicated diazo ketones, with which the corresponding reactions are unambiguous. For example, phenylbenzoyldiazomethane, LXXIV (which is prepared by the oxidation of benzil monohydrazone, LXXV, with mercuric oxide HgO) decomposes at a high temperature into nitrogen and diphenylketene, LXXVI. This reaction, in which the intermediate ketene postulated in equation 12·12 is actually isolated, is evidently an example of a Wolff rearrangement; moreover, it cannot be explained on the basis of an intramolecular oxidation and reduction, since it involves a change in the carbon skeleton. Such evidence is perhaps not entirely conclusive, however, since it does not exclude the possibility that the rearrangement of phenylbenzoyldiazomethane is abnormal, and that an internal oxidation and reduction are the general rule with those other diazo ketones which contain the grouping —CO—CHN$_2$, and with which therefore no obvious change in the carbon skeleton occurs. It is accordingly of considerable interest that the reality of the 1,2-shift, even with the diazo ketones of this latter type, has been demonstrated[13] beyond any reasonable doubt with the use of carbon of mass number 13. Benzoic acid of structure LXXVII, in which the asterisk denotes the "heavy" carbon atom, has been found to lead, through the Arndt-Eistert synthesis, to phenylacetic acid of structure LXXIX. The complete sequence of reactions is shown in equation 12·18. Since the phenyl group is attached directly to the carbon atom C* in the benzoic acid, LXXVII, and presumably also in the diazo ketone, LXXVIII, but is attached instead to an adjacent atom in the phenylacetic acid, LXXIX, it is evident that a 1,2-shift has taken place. The Wolff rearrangement is therefore properly named and is not merely a reaction involving intramolecular oxidation and reduction.



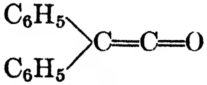
$C_6H_5—CO—\underset{C_6H_5}{\underset{|}{C}}N_2$

LXXIV



$C_6H_5—CO—\underset{C_6H_5}{\underset{|}{C}}{=}N—NH_2$

LXXV



LXXVI

$$
\begin{array}{l}
C_6H_5MgBr \xrightarrow{C^*O_2} \underset{\text{LXXVII}}{C_6H_5—C^*O_2H} \rightarrow \\
\qquad\qquad\qquad C_6H_5—C^*OCl \xrightarrow{CH_2N_2} \underset{\text{LXXVIII}}{C_6H_5—C^*O—CHN_2} \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \downarrow \qquad (12\cdot18) \\
\qquad\qquad\qquad C_6H_5—CH_3 + C^*O_2 \rightarrow \underset{\text{LXXIX}}{C_6H_5—CH_2—C^*O_2H}
\end{array}
$$

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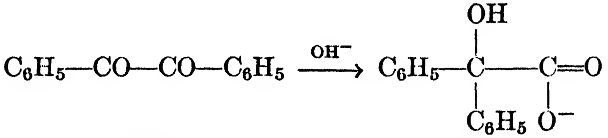
[13] C. Huggett, R. T. Arnold, and T. I. Taylor, *J. Am. Chem. Soc.* **64**, 3043 (1942).

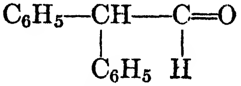
The *benzilic acid* rearrangement, by which, for example, benzil, LXXX, is transformed into the benzilate anion, LXXXI, in the presence of a strong base, also involves a 1,2-shift, as is evident from equation 12·19.



$$\underset{\text{LXXX}}{C_6H_5{-}CO{-}CO{-}C_6H_5} \xrightarrow{OH^-} \underset{\text{LXXXI}}{C_6H_5{-}\overset{OH}{\underset{C_6H_5}{C}}{-}\underset{O^-}{C}{=}O} \qquad (12\cdot 19)$$

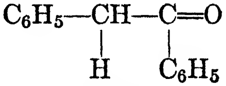
LXXX LXXXI

When a *secondary* or *tertiary aldehyde* (RR′HC—CHO or RR′R″C—CHO, respectively) is treated with concentrated sulfuric acid, it is frequently transformed into an isomeric ketone by a 1,2-shift. For example, diphenylacetaldehyde, LXXXII, is rearranged in this way to



$$C_6H_5{-}\underset{C_6H_5}{CH}{-}\underset{H}{C}{=}O$$

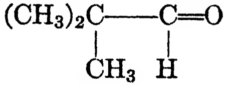
LXXXII



$$C_6H_5{-}\underset{H}{CH}{-}\underset{C_6H_5}{C}{=}O$$

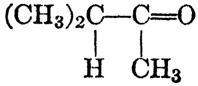
LXXXIII

desoxybenzoin, LXXXIII;[14] and trimethylacetaldehyde, LXXXIV, is



$$(CH_3)_2\underset{CH_3}{C}{-}\underset{H}{C}{=}O$$

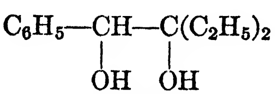
LXXXIV



$$(CH_3)_2\underset{H}{C}{-}\underset{CH_3}{C}{=}O$$

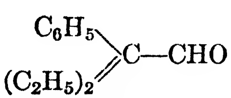
LXXXV

rearranged to methylisopropyl ketone, LXXXV. Such a reaction may perhaps account for certain anomalous results obtained with the pinacol rearrangement. Thus, the action of approximately 25 per cent sulfuric acid upon 1-phenyl-2,2-diethylethylene glycol, LXXXVI, transforms it



$$C_6H_5{-}\underset{OH}{CH}{-}\underset{OH}{C}(C_2H_5)_2$$

LXXXVI



LXXXVII

into phenyldiethylacetaldehyde, LXXXVII, whereas the action of concentrated sulfuric acid upon the same glycol transforms it instead into 4-phenyl-3-hexanone, LXXXVIII.[15] Similarly, in the vapor phase,

$C_6H_5{-}CH(C_2H_5){-}CO{-}C_2H_5$ LXXXVIII

$C_6H_5{-}CHOH{-}CHOH{-}C_6H_5$ LXXXIX

hydrobenzoin, LXXXIX, is transformed largely into diphenylacetaldehyde, LXXXII, at 250°C, but largely into desoxybenzoin, LXXXIII,

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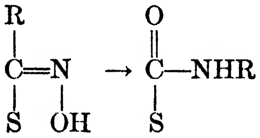
[14] S. Daniloff and E. Venus-Danilova, *Ber.* **59**, 1032 (1926).

[15] M. Tiffeneau and J. Lévy, *Bull. soc. chim.* [4] **33**, 735 (1923).

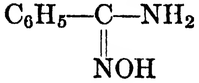
instead at 400°–450°C.[16] Again, the aldehyde may possibly be formed first under the more vigorous conditions, and then rearranged to the ketone. (However, see page 502.)

The last reaction which will be mentioned here is the *Beckmann* rearrangement, which was discussed in some detail in Section 8·4. This transformation is easily seen to involve a 1,2-shift, even though equation 12·20 which describes it differs from equation 12·1 in that the



$$\begin{array}{ccccc} \mathrm{R} & & & \mathrm{O} & \\ | & & & \| & \\ \mathrm{C} & = & \mathrm{N} & \rightarrow & \mathrm{C}\text{—}\mathrm{NHR} \\ | & & | & & | \\ \mathrm{S} & & \mathrm{OH} & & \mathrm{S} \end{array} \qquad (12\cdot 20)$$

carbon and nitrogen atoms of equation 12·20 are joined to one another by a double bond, whereas the corresponding atoms A and B of equation 12·1 are joined by only a single bond. The rearrangement of, for example, benzamidoxime, XC, to phenylurea, XCI, under the influence of



$$\begin{array}{l} C_6H_5\text{—}C\text{—}NH_2 \\ \qquad\;\, \| \\ \qquad NOH \end{array}$$

XC

$C_6H_5\text{—}NH\text{—}CO\text{—}NH_2$

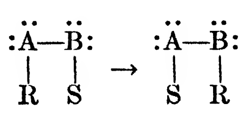
XCI

$C_6H_5\text{—}SO_2Cl$

XCII

benzenesulfonyl chloride, XCII, may be considered a special type of Beckmann rearrangement. (See also page 317.)

12·3 Early Attempts to Explain the 1,2-Shifts. A simple representation of the 1,2-shift, which was commonly employed at one time, and which is occasionally encountered even now, is illustrated by equation 12·21. According to this scheme, the two atoms or groups R and S,



$$\begin{array}{ccc} :\ddot{A}\text{—}\ddot{B}: & & :\ddot{A}\text{—}\ddot{B}: \\ |\quad\;\; | & \rightarrow & |\quad\;\; | \\ R\quad\;\; S & & S\quad\;\; R \end{array} \qquad (12\cdot 21)$$

attached to adjacent atoms A and B, simply exchange places. The final product which is isolated may be either the substance at the right of this equation or, more commonly, a different substance formed from it by subsequent changes that do not involve any further rearrangement. Several examples of the former type of reaction are mentioned on pages 455 f.; one of the latter type is shown in equation 12·22, for the transformation of pinacol, I, into pinacolone, II.

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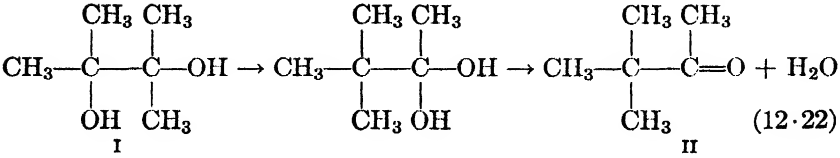
[16] Mme. Ramart-Lucas and F. Salmon-Legagneur, *Compt. rend.* **186**, 1848 (1928).

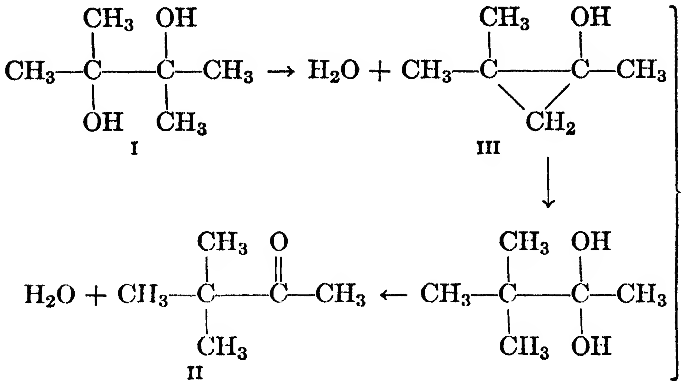


$$\underset{\text{I}}{CH_3-\overset{CH_3}{\underset{OH}{C}}-\overset{CH_3}{\underset{CH_3}{C}}-OH} \rightarrow CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{\underset{OH}{C}}-OH \rightarrow \underset{\text{II}}{CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{CH_3}{C}=O} + H_2O \qquad (12 \cdot 22)$$

Although it can readily be verified that all the rearrangements listed in the preceding section can be "explained" with the aid of equation 12·21, this equation can hardly provide an adequate description of the mechanisms of the reactions involved. Even if the structure on the right side of this equation corresponds to the final product which is actually isolated, there has been offered no explanation of the manner in which the interchange of the atoms or groups R and S has come about. On the other hand, if the structure in question is considered instead to correspond only to an unstable intermediate, the equation is still inadequate in the respect just mentioned and, moreover, also in the further respect that the intermediate which must be assumed is often highly improbable. (Cf., for example, the Curtius and Wolff rearrangements.) Chemists have therefore exerted considerable effort in the attempt to devise more complete and more reasonable mechanisms for the various reactions in question. This section will be devoted to a discussion of some of the early attempts, and to an explanation of the reasons why these attempts must be regarded as unsuccessful.

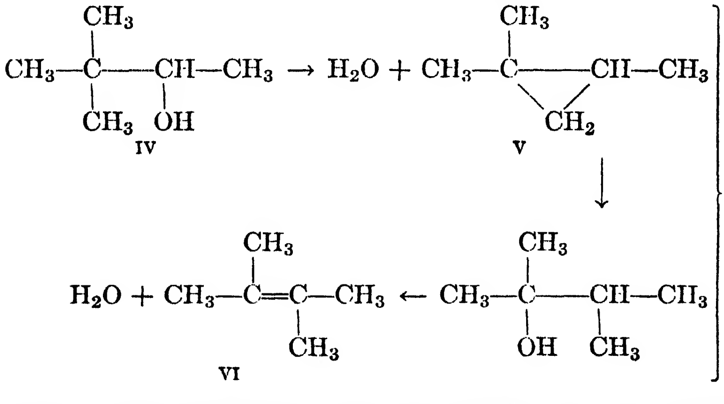
In view of the marked similarity of all the various rearrangements listed in Section 12·2, it will here be assumed that an adequate explanation of any particular 1,2-shift must be applicable also, with at most only minor and obvious changes, to any other 1,2-shift. Consequently, it will be further assumed that, if a given proposed mechanism can be shown definitely to be incorrect for any one type of 1,2-shift, it can be immediately discarded and need no longer be considered in connection with any other type of rearrangement of this same class. Such assumptions are clearly very drastic, and their legitimacy cannot be rigorously demonstrated. There is, in fact, no law of nature which states that all 1,2-shifts must necessarily go by the same mechanism, or even by similar mechanisms. Nevertheless, these assumptions will be made here on the grounds, first, that they serve to simplify and to unify the discussion; and, second, that, as will be shown in the following section, there has indeed been devised a single basic mechanism which appears to be applicable, with suitable modifications, to all the 1,2-shifts.

One of the first attempts to explain the 1,2-shifts was based upon the assumed formation of a cyclic intermediate. The rearrangement of pinacol, I, to pinacolone, II, was thus considered to proceed through the cyclopropane derivative, III, as in equation 12·23. In this way, the



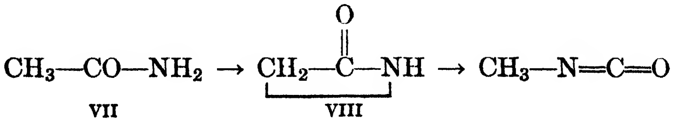
(12·23)

principle of minimum structural change could be maintained in each individual step, although the net result of the whole sequence of steps appears to constitute a violation of the principle. This same proposed mechanism could, moreover, be easily extended to most of the remaining 1,2-shifts as well. The retropinacol rearrangement of pinacolyl alcohol, IV, to tetramethylethylene, VI, for example, could be assumed to involve the intermediate formation of the cyclopropane derivative, V, as in equation 12·24; the Hofmann rearrangement of acetamide, VII,



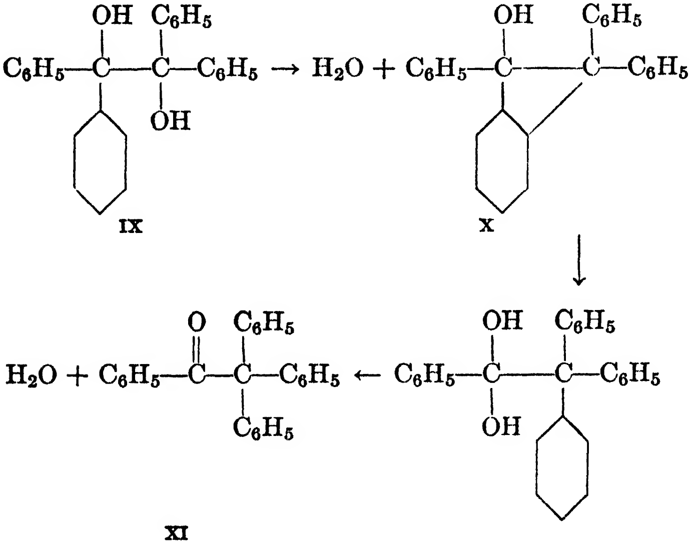
(12·24)

could be assumed to involve the intermediate VIII, as in equation 12·25;



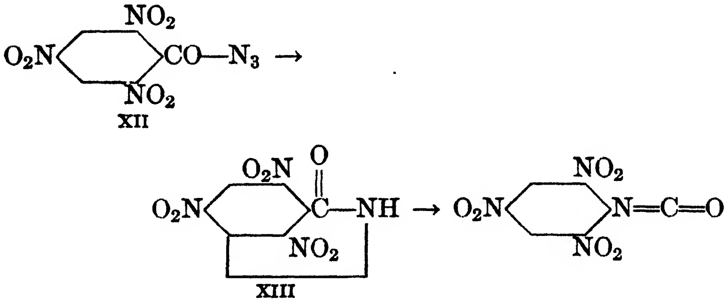
$$\underset{\text{VII}}{CH_3—CO—NH_2} \rightarrow \underset{\text{VIII}}{\underbrace{CH_2—\overset{\overset{\displaystyle O}{\|}}{C}—NH}} \rightarrow CH_3—N{=}C{=}O \qquad (12\cdot 25)$$

and so on. Even in those instances in which *three*-membered rings are impossible as intermediates, this mechanism can frequently still be considered possible, since the assumed cyclic intermediate may contain rings of other sizes. For example, the rearrangement of benzpinacol, IX, to benzpinacolone, XI, could be imagined to proceed through the intermediate X with a *four*-membered ring, as in equation 12·26; the Curtius



(12·26)

rearrangement of 2,4,6-trinitrobenzazide, XII,[17] could be imagined to proceed through the intermediate XIII with a five-membered ring (which would, however, be extraordinarily strained, cf. Chapter 9), as in equation 12·27; and so on.



(12·27)

The evidence against the above mechanism of the 1,2-shift seems to be complete. For example, if the rearrangement of the tetrachlorobenzpinacol, XIV, went through the cyclic intermediate, XV (cf. struc-

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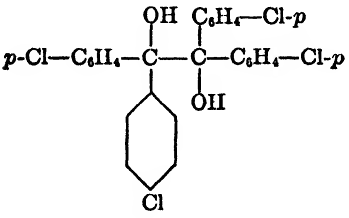
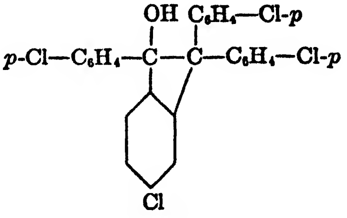
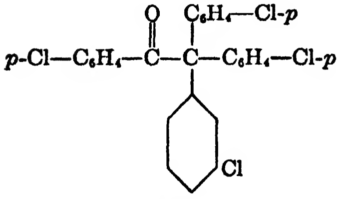
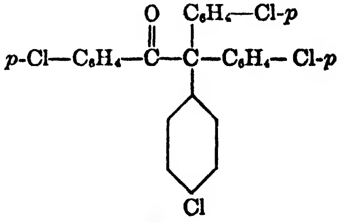
[17] V. V. Vasilevskiĭ, F. I. Bloshteĭn, and B. D. Kustrya, *J. Gen. Chem.* (U.S.S.R.) **5,** 1652 (1935); *C.A.* **30,** 3416 (1936); C. Naegeli, A. Tyabji, and L. Conrad, *Helv. Chim. Acta* **21,** 1127 (1938).

ture X), the product would have to be the tetrachlorobenzpinacolone, XVI, in which one of the chlorine atoms is no longer *para,* but is instead *meta.* The product actually obtained, however, is the different tetrachlorobenzpinacolone, XVII, in which each chlorine atom is still *para.*

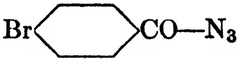

XIV

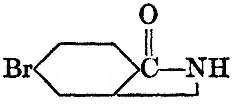

XV

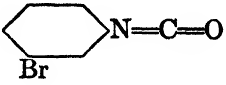

XVI


XVII

Similarly, if the Curtius rearrangement of *p*-bromobenzazide, XVIII,


XVIII


XIX


XX

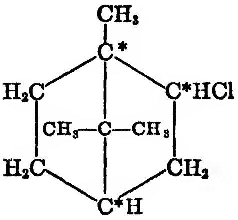
went through the cyclic intermediate, XIX (cf. structure XIII), the product would have to be *m*-bromophenylisocyanate, XX, whereas it actually is instead *p*-bromophenylisocyanate, XXI, which was identified

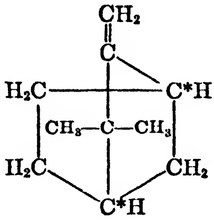

XXI

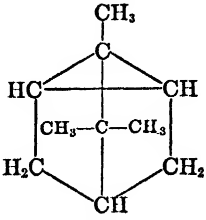

XXII

by transformation into the urethan, XXII. Numerous further examples of both the Hofmann [7] and the Curtius [9] rearrangements are known in which the assumption of cyclic intermediates analogous to VIII, XIII, and XIX would lead to incorrect predictions regarding the structures of the products.

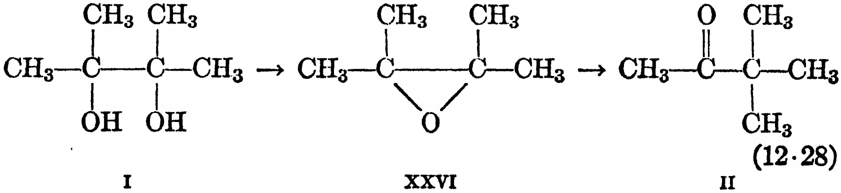
Independent evidence against this first mechanism is provided by the Wagner-Meerwein rearrangement of isobornyl chloride, XXIII, to camphene, XXIV, and by the reverse transformation of camphene into isobornyl chloride. In the first place, it may be noted that the intermediate which would have to be postulated here is the known substance tricyclene, XXV, which is not transformable into either camphene or isobornyl chloride under the conditions of the respective rearrangements. In the second place, both isobornyl chloride and camphene can be optically active since they contain the asymmetric carbon atoms designated by the asterisks, and since no *meso* form is possible with either structure. On the other hand, tricyclene is symmetrical and so cannot be optically active. Consequently, if tricyclene were an intermediate in either the forward or the reverse reaction, optically active isobornyl chloride would necessarily give racemic camphene, and optically active camphene would necessarily give racemic isobornyl chloride. It is found experimentally, however, that (+)-isobornyl chloride can be transformed into (−)-camphene, and vice versa.


XXIII

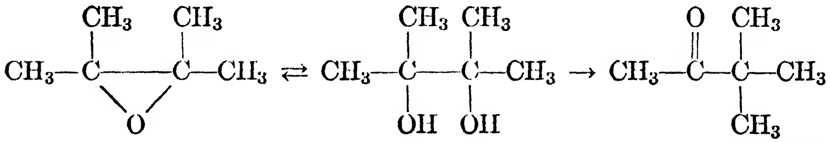

XXIV


XXV

A second mechanism which has been suggested for the 1,2-shifts assumes the formation of a different kind of cyclic intermediate. Thus, it has been postulated that the rearrangement of pinacol, I, to pinacolone, II, proceeds through the ethylene oxide, XXVI, as in equation 12·28.


(12·28)

The evidence in favor of this mechanism is that ethylene oxides like the one with structure XXVI can sometimes be shown to be formed in the course of the rearrangements, and that ethylene oxides can often themselves rearrange to the corresponding pinacolones. (See page 453.) It should be pointed out, however, that neither of these facts provides conclusive evidence that the ethylene oxides are intermediates in the rearrangements, since they could be explained equally well on the assumption that the cyclic compounds are formed by entirely independent, but reversible, side reactions, as in equation 12·29. This second mechanism,

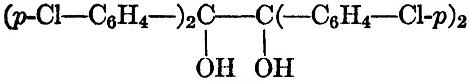


(12·29)

XXVI I II

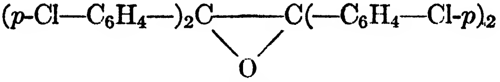
moreover, suffers somewhat from the fact that it is not completely general. Although it can be applied to the rearrangements of the glycol ethers, the halohydrins, the amino alcohols, and possibly the secondary and tertiary aldehydes, as well as to those of the glycols, it cannot be presumed to play a role in most of the remaining types of rearrangement listed above.

Several further objections can be raised to the above mechanism. First, and possibly most important, the formation of an intermediate ethylene oxide, even if correct, would in no sense account for any 1,2-shift. Indeed, the formation of the final product from the ethylene oxide would be just as hard to explain as would that from the original substance. In other words, the mechanism really begs the entire question. Moreover, direct evidence against the belief that an ethylene oxide is a necessary intermediate in a 1,2-shift comes from various sources. For example, if the rearrangement of a glycol proceeds through the ethylene oxide, the rearrangement of the former substance cannot possibly be faster than is that of the latter under the same conditions. Moreover, when no appreciable amount of ethylene oxide is observable at any time during the rearrangement of the glycol (as is usually true), the assumption that the ethylene oxide is an intermediate requires the further assumption that the rearrangement of the ethylene oxide occurs very rapidly. Under such circumstances, then, the rate of rearrangement of the glycol is merely the rate of its dehydration to the ethylene oxide, which substance is converted into the final product as rapidly as it is formed. Consequently, the ethylene oxide, when prepared in an independent manner, would have to rearrange much faster than does the corresponding glycol. This prediction is not in general borne out by the facts. For example, the rearrangements of the tetrachlorobenzpinacol, XIV, and of the ethylene oxide, XXVII, related to it have been found



$(p\text{-Cl—C}_6\text{H}_4\text{—})_2\underset{\text{OH}}{\text{C}}\text{—}\underset{\text{OH}}{\text{C}}(\text{—C}_6\text{H}_4\text{—Cl-}p)_2$

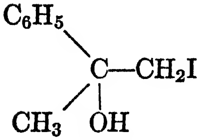
XIV



XXVII

to proceed at practically identical rates, although no trace of the oxide can be detected during the reaction of the glycol.

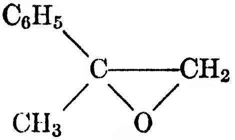
An analogous argument can be based on the fact that the iodohydrin XXVIII readily rearranges to the ketone XXIX when treated with



XXVIII

$C_6H_5\text{—}CH_2\text{—}CO\text{—}CH_3$

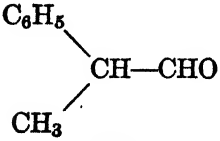
XXIX



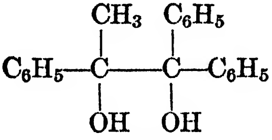
XXX

mercuric oxide, whereas the corresponding ethylene oxide, XXX, which would have to be considered an intermediate in the reaction, is completely unreactive under the identical conditions.[18]

Not infrequently, a compound rearranges to a product which is different from the one obtained from the corresponding ethylene oxide. Under such circumstances, the ethylene oxide is clearly not an intermediate in the reaction of the former substance. For example, the iodohydrin XXVIII gives rise to the ketone XXIX, as was mentioned above; but the related ethylene oxide, XXX (when treated with sulfuric acid or when merely distilled at atmospheric pressure), gives rise instead to the aldehyde XXXI. Similarly, the action of sulfuric acid upon the

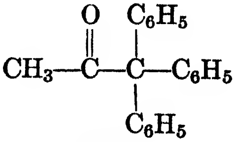


XXXI



$C_6H_5\text{—}\underset{OH}{\overset{CH_3}{C}}\text{—}\underset{OH}{\overset{C_6H_5}{C}}\text{—}C_6H_5$

XXXII



$CH_3\text{—}\overset{O}{\overset{\|}{C}}\text{—}\underset{C_6H_5}{\overset{C_6H_5}{C}}\text{—}C_6H_5$

XXXIII

glycol XXXII leads to the ketone XXXIII, whereas the action of nitrous acid upon the amino alcohol XXXIV leads instead to the dif-

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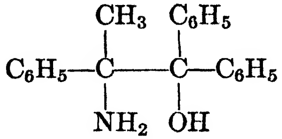
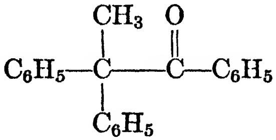
[18] M. Tiffeneau, *Ann. chim.* [8] **10**, 322 (1907).



$$C_6H_5-\underset{NH_2}{\overset{CH_3}{C}}-\underset{OH}{\overset{C_6H_5}{C}}-C_6H_5$$

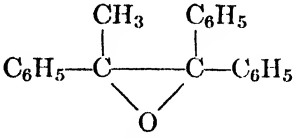
XXXIV



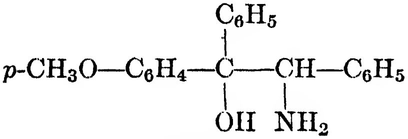
$$C_6H_5-\underset{C_6H_5}{\overset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5$$

XXXV

ferent ketone XXXV; the same ethylene oxide, XXXVI, would, however, have to be assumed as an intermediate in each reaction.[19] Moreover, the amino alcohol XXXVII gives the ketone XXXVIII when treated with nitrous acid, but the different ketone XXXIX when treated with hydrogen chloride;[20] again, however, the same ethylene oxide, XL, would have to be assumed as an intermediate in the two reactions.

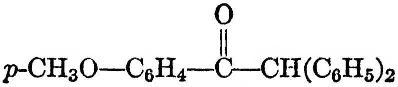


XXXVI



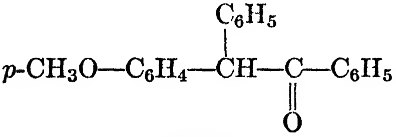
$$p\text{-}CH_3O-C_6H_4-\underset{OH}{\overset{C_6H_5}{C}}-\underset{NH_2}{CH}-C_6H_5$$

XXXVII



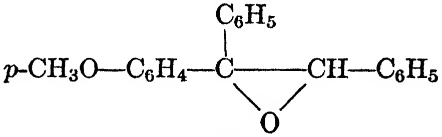
$$p\text{-}CH_3O-C_6H_4-\overset{O}{\overset{\|}{C}}-CH(C_6H_5)_2$$

XXXVIII



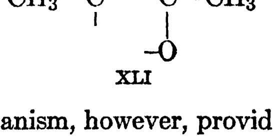
$$p\text{-}CH_3O-C_6H_4-\overset{C_6H_5}{CH}-\underset{O}{\underset{\|}{C}}-C_6H_5$$

XXXIX



XL

In an attempt to remedy some of the above defects, several authors have suggested that, instead of an ethylene oxide, the intermediate in a 1,2-shift might be a substance with a structure like XLI, with two "free valences." Such a mechanism, however, provides no better explanation of the course of the actual rearrangement than does the one which it is



$$CH_3-\underset{|}{\overset{CH_3}{C}}-\underset{-O}{\overset{CH_3}{C}}-CH_3$$

XLI

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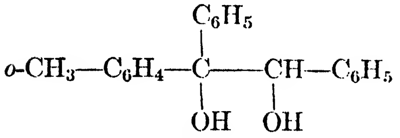
[19] A. McKenzie and J. R. Myles, *Ber.* **65**, 209 (1932).

[20] A. McKenzie and A. K. Mills, *Ber.* **62**, 1784 (1929).

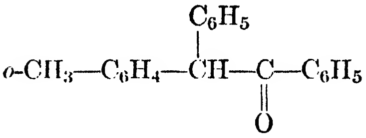
designed to replace. Furthermore, inasmuch as the nature and properties of the assumed intermediate have not been precisely defined, the mechanism cannot be experimentally confirmed. For these reasons, it has never been generally accepted, and it seems now to be largely forgotten.

The final unsuccessful mechanism to be discussed here is based upon the assumed formation of an intermediate olefin. For example, the rearrangement of the glycol XLII to the ketone XLIII might be imagined



$$o\text{-}\mathrm{CH_3{-}C_6H_4{-}}\overset{\displaystyle \mathrm{C_6H_5}}{\underset{\displaystyle \mathrm{OH}}{\mathrm{C}}}\mathrm{{-}}\underset{\displaystyle \mathrm{OH}}{\mathrm{CH}}\mathrm{{-}C_6H_5}$$

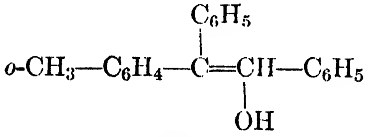
XLII



$$o\text{-}\mathrm{CH_3{-}C_6H_4{-}}\overset{\displaystyle \mathrm{C_6H_5}}{\mathrm{CH}}\mathrm{{-}}\underset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{-}C_6H_5}$$

XLIII

to occur by a loss of water and consequent formation of the unstable enol, XLIV, which then rearranges spontaneously in the usual manner



$$o\text{-}\mathrm{CH_3{-}C_6H_4{-}}\overset{\displaystyle \mathrm{C_6H_5}}{\mathrm{C}}\mathrm{{=}}\underset{\displaystyle \mathrm{OH}}{\mathrm{CH}}\mathrm{{-}C_6H_5}$$

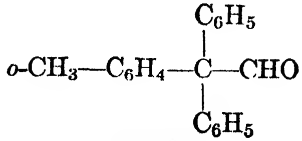
XLIV

$\mathrm{CH_3{-}CH_2{-}CH_2Br}$ XLV

$\mathrm{CH_3{-}CHBr{-}CH_3}$ XLVI

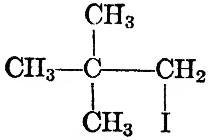
$\mathrm{CH_3{-}CH{=}CH_2}$ XLVII

to the stable keto form, XLIII.[21] (Cf. Sections 14·2 and 14·3.) Similarly, the rearrangement of *n*-propylbromide, XLV, to isopropyl bromide, XLVI, could proceed by an elimination of hydrogen bromide to give propene, XLVII, which then would add hydrogen bromide normally to give isopropyl bromide, XLVI. However, such a mechanism is obviously restricted to those rearrangements in which a *hydrogen atom* may be considered to migrate. Thus, it cannot account for the rearrangement of pinacol itself, in which a methyl group migrates, nor even for that of the above glycol XLII to the aldehyde XLVIII (which



$$o\text{-}\mathrm{CH_3{-}C_6H_4{-}}\overset{\displaystyle \mathrm{C_6H_5}}{\underset{\displaystyle \mathrm{C_6H_5}}{\mathrm{C}}}\mathrm{{-}CHO}$$

XLVIII



$$\mathrm{CH_3{-}}\overset{\displaystyle \mathrm{CH_3}}{\underset{\displaystyle \mathrm{CH_3}}{\mathrm{C}}}\mathrm{{-}}\underset{\displaystyle \mathrm{I}}{\mathrm{CH_2}}$$

XLIX

is formed simultaneously with the ketone XLIII). Moreover, it cannot

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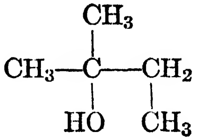
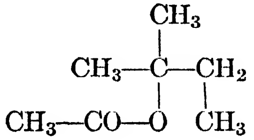
[21] R. Roger and W. B. McKay, *J. Chem. Soc.* **1933**, 332.

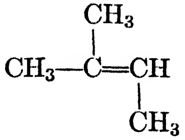
account for such further transformations as those of neopentyl iodide, XLIX, into *tert*-amyl alcohol, L, by the action of aqueous silver nitrate [3]


$CH_3-C(CH_3)(OH)-CH_2-CH_3$

L


$CH_3-C(CH_3)(O-CO-CH_3)-CH_2-CH_3$

LI


$CH_3-C(CH_3)=CH-CH_3$

LII

and into *tert*-amylacetate, LI, by the action of silver acetate in acetic acid.[4] The assumed intermediate olefin, trimethylethylene, LII, is indeed formed simultaneously as the major product in the second of these reactions, and so it is doubtless formed also to some extent in the first one; however, the formation of the olefin cannot explain the rearrangement inasmuch as this substance cannot be produced until *after* the rearrangement has already occurred by migration of a methyl group. Even in those instances in which a hydrogen atom can be considered to migrate, and in which the olefin can be formed without a preliminary unexplained rearrangement, the mechanism can still be shown to be not generally applicable. For example, in the transformation of the above *optically active* glycol, XLII, into the ketone XLIII, complete racemization does not occur. Consequently, the necessarily inactive enol, XLIV, cannot have been an intermediate in the reaction. It should be mentioned, however, that some racemization frequently occurs, and that the racemization is not infrequently found to be complete. There is, therefore, a possibility that the mechanism which is here under discussion may be involved to a greater or less extent in certain rearrangements, even though it cannot be the only mechanism operative.

12·4 The "Whitmore Mechanism" of the 1,2-Shifts. The most satisfactory mechanism that has as yet been proposed for the 1,2-shifts [22] is commonly referred to as the "Whitmore mechanism," although many of its specific underlying concepts were developed by Meerwein,[23] Stieglitz,[24] and others [24] several years before the publication of Whitmore's comprehensive and general statement of the theory.[22] No attempt will be made here, however, to discuss the mechanism from the historical point of view; this section will instead be concerned only with a description of the mechanism in its present, and possibly final, form.

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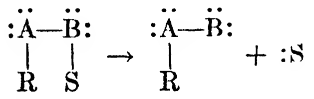
[22] F. C. Whitmore, *J. Am. Chem. Soc.* **54**, 3274 (1932).

[23] H. Meerwein and K. van Emster, *Ber.* **53**, 1815 (1920); **55**, 2500 (1922).

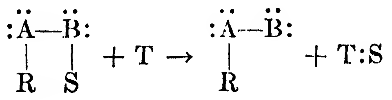
[24] Cf. the first three pages of reference 22, and especially footnote 6 on page 3275 of that reference.

It is convenient to think of a 1,2-shift as proceeding in three distinct steps, which can be arranged in a logical sequence, but which may possibly take place simultaneously in any actual rearrangement.

1. In this logical sequence of steps, the first process that is considered to occur results in the production of an unstable intermediate in which one atom has only six electrons (a so-called "open sextet") in its valence shell. Such an intermediate can be produced in any one of the following ways (which, however, frequently overlap, cf. pages 490 ff.). (*a*) Sometimes an atom or group splits off spontaneously and takes with it the pair of electrons by which it was originally linked to the rest of the molecule. This type of reaction is shown in general terms in equation 12·30, where the various symbols have the same meanings as in equations 12·1 of page 451 and 12·21 of page 465. (*b*) The fragment :S of equation 12·30 may not split off spontaneously, but may have to be pulled off by interaction with a further reagent T, as in equation 12·31.

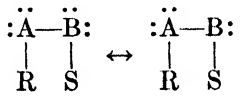


$$\begin{matrix}:\ddot{\mathrm{A}}\!-\!\ddot{\mathrm{B}}: \\ |\qquad | \\ \mathrm{R}\qquad \mathrm{S}\end{matrix} \rightarrow \begin{matrix}:\ddot{\mathrm{A}}\!-\!\ddot{\mathrm{B}}: \\ |\qquad\ \ \\ \mathrm{R}\qquad\ \ \end{matrix} + :\mathrm{S} \tag{12·30}$$



$$\begin{matrix}:\ddot{\mathrm{A}}\!-\!\ddot{\mathrm{B}}: \\ |\qquad | \\ \mathrm{R}\qquad \mathrm{S}\end{matrix} + \mathrm{T} \rightarrow \begin{matrix}:\ddot{\mathrm{A}}\!-\!\ddot{\mathrm{B}}: \\ |\qquad\ \ \\ \mathrm{R}\qquad\ \ \end{matrix} + \mathrm{T}:\mathrm{S} \tag{12·31}$$

(*c*) A structure with the necessary open sextet may contribute through resonance to the state of the initial substance, as in the expression 12·32.

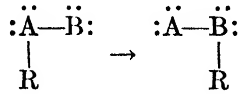


$$\begin{matrix}:\ddot{\mathrm{A}}\!-\!\ddot{\mathrm{B}}: \\ |\qquad | \\ \mathrm{R}\qquad \mathrm{S}\end{matrix} \leftrightarrow \begin{matrix}:\ddot{\mathrm{A}}\!-\!\mathrm{B}: \\ |\qquad | \\ \mathrm{R}\qquad \mathrm{S}\end{matrix} \tag{12·32}$$

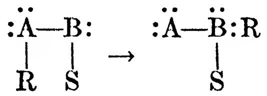
The two electrons which are missing from the atom B in the structure at the right of this expression are, of course, to be considered absorbed somehow in the various atoms and groups R, S, etc., joined to A and B. Under such circumstances, the normal structure at the left of the expression 12·32 is ordinarily supposed to be much more stable, and hence much more important, than the one at the right; the latter structure may, however, be presumed to make an appreciably greater contribution during the reaction than it does when no reaction is taking place.

2. The second step of the logical sequence of events is considered to be the one in which the actual rearrangement occurs. Considerable strain (i.e., instability) exists in the intermediate formed by reaction 12·30 or 12·31, or in the structure at the right of the expression 12·32; this strain, which is a result of the presence of an atom B with only an

open sextet, is partially relieved by the migration of both the atom or group R and its pair of electrons, in the manner shown in the appropriate one of the equations 12·33 and 12·34. Whitmore has strongly emphasized [22] the view that the two electrons move over from A to B and drag the atom or group R with them. Whether the primary motivation of the migration comes from the electron pair, however, or from R, or from the two together, the important feature of the assumed reaction is that both the electrons and R transfer their attachment from the atom to which they were originally linked to an adjacent one. The mechanism of this migration will be discussed in greater detail in Section 12·10; the point to be brought out here is merely that the migration presumably does occur.

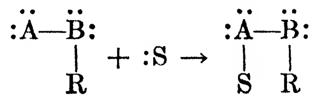


$$:\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{A}}}\!-\!\ddot{\mathrm{B}}: \;\rightarrow\; :\ddot{\mathrm{A}}\!-\!\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{B}}}: \qquad (12\cdot33)$$

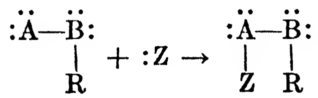


$$:\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{A}}}\!-\!\underset{\substack{|\\ \mathrm{S}}}{\mathrm{B}}: \;\rightarrow\; :\ddot{\mathrm{A}}\!-\!\underset{\substack{|\\ \mathrm{S}}}{\ddot{\mathrm{B}}}:\mathrm{R} \qquad (12\cdot34)$$

3. In the third and final step of the proposed sequence, the strain which still remains in the rearranged intermediate (in consequence of the open sextet on the atom A) is relieved, and the final isolable product is produced. This relief of strain can take place in any one of several ways. (*a*) Occasionally, the fragments formed in equations 12·30 and 12·33 recombine, as in equation 12·35. The net result of the complete sequence is then a simple interchange of the atoms or groups R and S. (*b*) Sometimes, the fragment resulting from the reaction 12·33 combines not with the fragment :S, as in equation 12·35, but with some other atom or group :Z present in the reaction mixture, as in equation 12·36.



$$:\ddot{\mathrm{A}}\!-\!\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{B}}}: \;+\; :\mathrm{S} \;\rightarrow\; :\underset{\substack{|\\ \mathrm{S}}}{\ddot{\mathrm{A}}}\!-\!\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{B}}}: \qquad (12\cdot35)$$



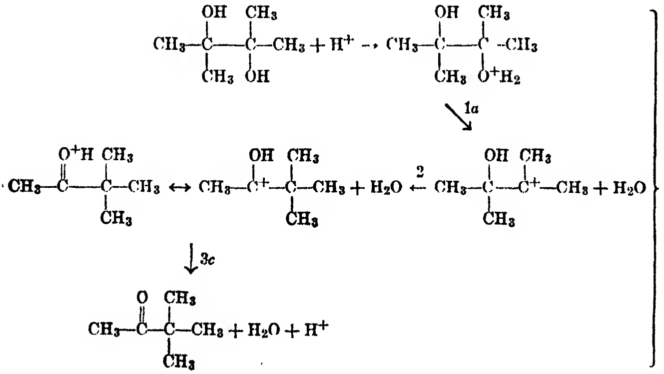
$$:\ddot{\mathrm{A}}\!-\!\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{B}}}: \;+\; :\mathrm{Z} \;\rightarrow\; :\underset{\substack{|\\ \mathrm{Z}}}{\ddot{\mathrm{A}}}\!-\!\underset{\substack{|\\ \mathrm{R}}}{\ddot{\mathrm{B}}}: \qquad (12\cdot36)$$

The net result is then a substitution reaction with rearrangement. (*c*) Frequently, the strain remaining in the rearranged fragment of equation 12·33 is relieved by the breaking off of an additional atom or group, usually in the form of an ion. As will be apparent from the specific examples given later, the net result is then a dehydration, a dehydrohalogenation, or the like, with rearrangement. (*d*) Finally, in a few instances, the structure given at the right of equation 12·33 or 12·34 is one of the less important resonating structures contributing to the state of the final product. The strain is then relieved automatically as the hypothetical intermediate with the structure in question passes over by necessity into the stable resonance hybrid. Specific examples of this type of reaction will also be given below.

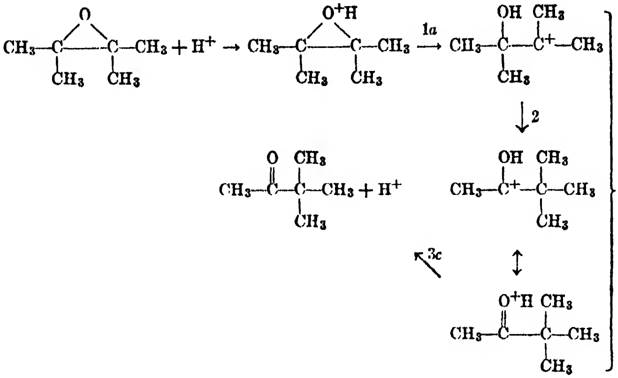
As was stated above, the three steps which have just been outlined do not need to take place in the order in which they were described. As far as anything known at present is concerned, two or perhaps all three of the steps may occur simultaneously in most, if not in all, instances. Indeed, the little evidence which is available (Section 12·9) strongly suggests that, in at least some instances, the first two steps are essentially simultaneous. In any event, the possibility of an overlapping of the steps is not at all unreasonable since it can easily be imagined that, for example, the approach of :S (equation 12·35) or of :Z (equation 12·36) may be an important factor in facilitating the simultaneous removal of :S (equation 12·30 or 12·31) and migration of R, and vice versa. It would appear to be impossible, however, for step 3 to *precede* either of the others, or for step 2 to precede step 1.

Before the experimental evidence supporting the Whitmore mechanism is discussed, the foregoing very general remarks can be made more concrete with the aid of specific examples. In the following equations, the most important types of 1,2-shifts are illustrated and interpreted by means of the scheme outlined above. For the sake of clarity, the three steps are indicated by the numerals 1, 2, and 3 above (or beside) the appropriate arrows; moreover, the natures of the first and third steps, which can follow alternative courses, are designated more precisely by the appropriate letters *a*, *b*, and *c*, or *a*, *b*, *c*, and *d*, respectively.

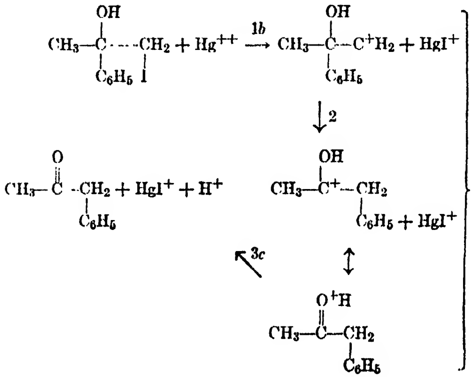
Pinacol rearrangements and their analogs:



(12·37)

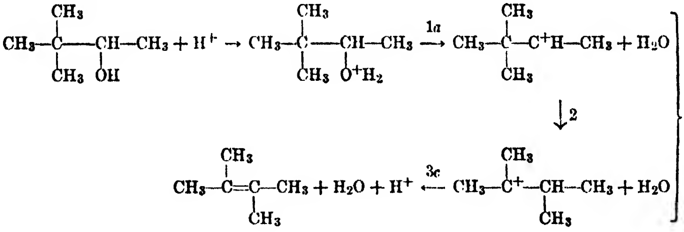


(12·38)

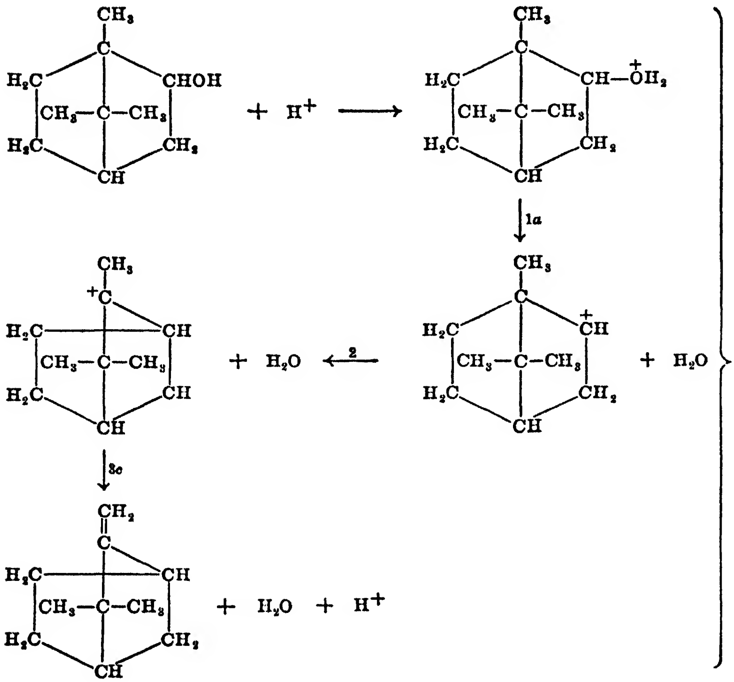


(12·39)

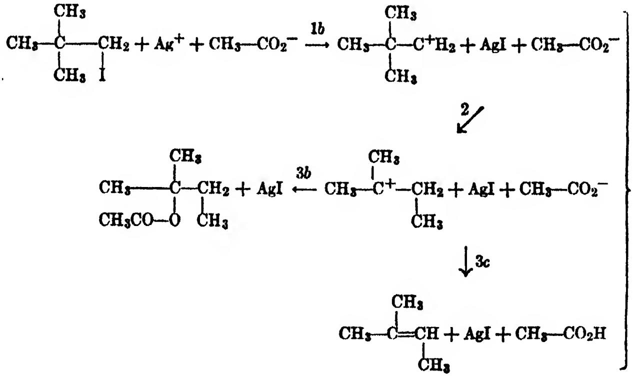
Retropinacol (Wagner-Meerwein) rearrangements:



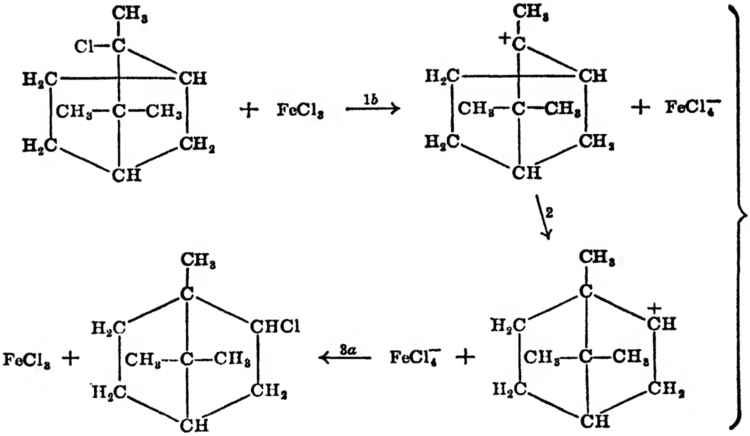
(12·40)



(12·41)

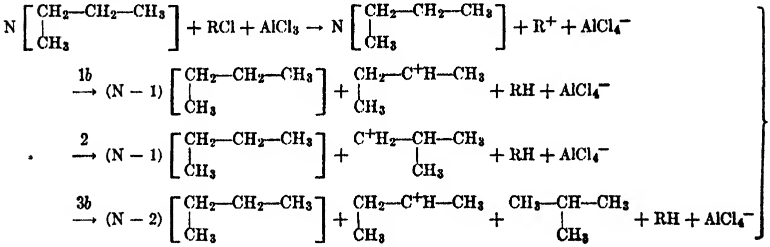


(12·42)



(12·43)

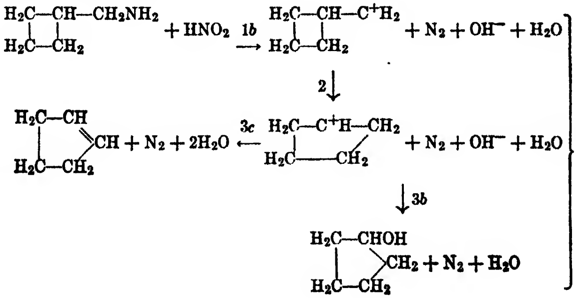
Rearrangement of paraffin hydrocarbons:



$$
\begin{aligned}
&N\left[\underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}CH_2{-}CH_3}\right] + \mathrm{RCl} + \mathrm{AlCl_3} \rightarrow N\left[\underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}CH_2{-}CH_3}\right] + \mathrm{R^+} + \mathrm{AlCl_4^-}\\
&\xrightarrow{1b} (N-1)\left[\underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}CH_2{-}CH_3}\right] + \underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}C^+H{-}CH_3} + \mathrm{RH} + \mathrm{AlCl_4^-}\\
&\xrightarrow{2} (N-1)\left[\underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}CH_2{-}CH_3}\right] + \mathrm{C^+H_2{-}}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{{-}CH_3} + \mathrm{RH} + \mathrm{AlCl_4^-}\\
&\xrightarrow{3b} (N-2)\left[\underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}CH_2{-}CH_3}\right] + \underset{\mathrm{CH_3}}{\mathrm{CH_2}}\mathrm{{-}C^+H{-}CH_3} + \mathrm{CH_3{-}}\underset{\mathrm{CH_3}}{\mathrm{CH}}\mathrm{{-}CH_3} + \mathrm{RH} + \mathrm{AlCl_4^-}
\end{aligned}
\qquad (12{\cdot}44)
$$

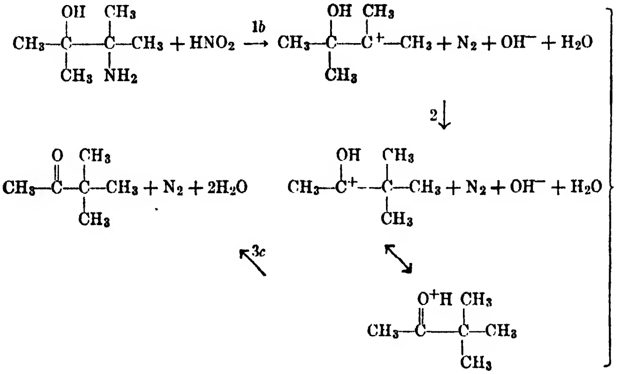
and so on by repetition of last two steps.

Demjanow rearrangements:



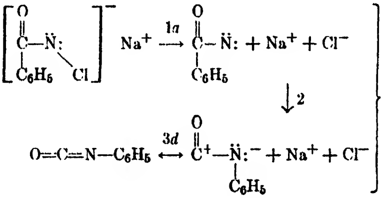
(12·45)

Rearrangement of an amino alcohol:



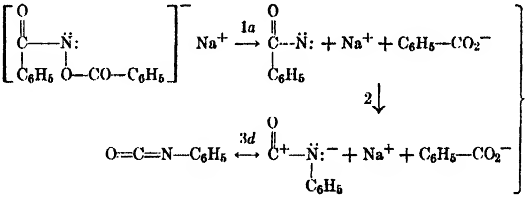
(12·46)

Hofmann rearrangement:



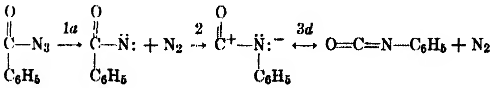
(12·47)

Lossen rearrangement:



(12·48)

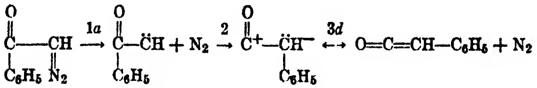
Curtius rearrangement:



$$\underset{C_6H_5}{\overset{\overset{O}{\|}}{C}}-N_3 \xrightarrow{1a} \underset{C_6H_5}{\overset{\overset{O}{\|}}{C}}-\ddot{N}: + N_2 \xrightarrow{2} \overset{\overset{O}{\|}}{C^+}-\underset{C_6H_5}{\ddot{N}}:^- \xleftrightarrow{3d} O{=}C{=}N-C_6H_5 + N_2$$

(12·49)

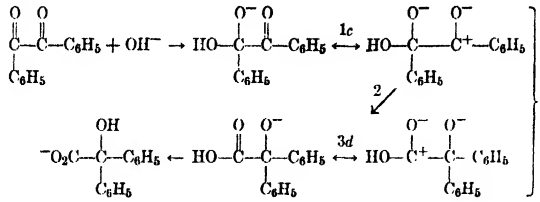
Wolff rearrangement:



$$\underset{C_6H_5}{\overset{\overset{O}{\|}}{C}}-\underset{\underset{N_2}{\|}}{CH} \xrightarrow{1a} \underset{C_6H_5}{\overset{\overset{O}{\|}}{C}}-\ddot{C}H + N_2 \xrightarrow{2} \overset{\overset{O}{\|}}{C^+}-\underset{C_6H_5}{\ddot{C}H^-} \xleftrightarrow{3d} O{=}C{=}CH-C_6H_5 + N_2$$

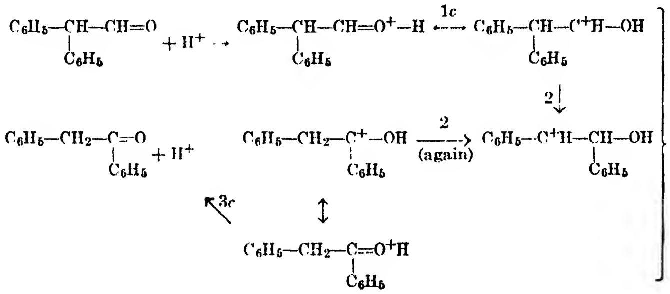
(12·50)

Benzilic acid rearrangement:



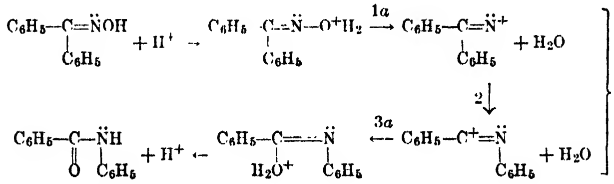
(12·51)

Rearrangement of secondary and tertiary aldehydes:



(12·52)

Beckmann rearrangement:

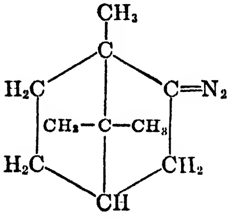


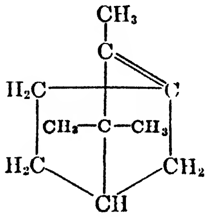
(12·53)

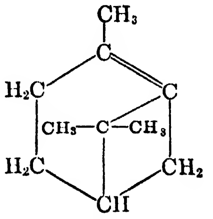
(*However, see pages 527 f.*)

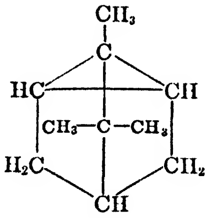
12·5 Evidence in Support of the Whitmore Mechanism. No completely conclusive proof of the correctness of the Whitmore mechanism, as applied either to all the 1,2-shifts in general or to any specific example of the 1,2-shift in particular, is possible; for, obviously, no person has ever been able to observe directly the behaviors of the individual molecules. The most that can be expected of such a mechanism, therefore, is that it permit a correlation and systematization of all the pertinent facts; that it not be in conflict with any known fact; and that it account, to as great an extent as possible, for the characteristic features of the reactions and, in particular, for the specific effects of any catalysts that may be employed. Ideally, the mechanism should be in quantitative agreement with the observed kinetics of the several reactions. It will accordingly be of interest here to consider the extent to which the Whitmore mechanism does indeed satisfy these conditions.

In the first place, it may be noted that the mechanism in question can be applied, in the manners indicated above in equations 12·37–12·53, to all the various types of 1,2-shift listed in the preceding sections. Whether or not this mechanism is correct in all instances, it is nevertheless completely successful, therefore, in correlating a large number of facts. Moreover, unlike the earlier and less successful mechanisms, it does not appear to be in direct conflict with any known fact, although it may perhaps occasionally lead one to expect the formation of a rearranged product which is not actually obtained. Thus, analogy with the rearrangements of diazo ketones (see equation 12·50 and also pages 461 f.) and of isoborneol (see equation 12·41 and also pages 454 f.) suggests that the thermal decomposition of 2-diazocamphane, I, should give a substance with structure II, or possibly one with structure III. Although the product obtained in this reaction is neither of these but instead tricyclene, IV,[25] the reaction can hardly be used as evidence against the Whitmore mechanism. The hypothetical intermediate, V, which might be postulated here, does, to be sure, have a carbon atom with only an open sextet, but the Whitmore mechanism does not require that such an intermediate always rearrange. Moreover, the mechanism does not even require that this particular intermediate be formed at all if an alternative reaction of the original substance can occur instead. For


I


II


III


IV

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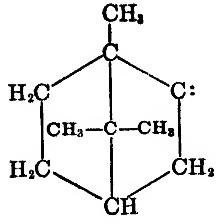
[25] U. Heubaum and W. A. Noyes, *J. Am. Chem. Soc.* **52**, 5070 (1930).



V

$(CH_3)_2CH—CH_2—NH_2$

VI

$(CH_3)_2CH—CH_2—OH$

VII

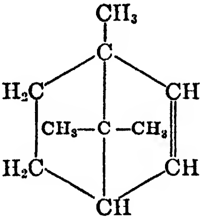
$(CH_3)_3C—OH$

VIII

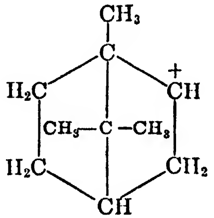
$(CH_3)_3C—NH_2$

IX

these reasons a rearrangement does not need to take place in every reaction in which one is conceivable. Thus, the action of nitrous acid upon isobutyl amine, VI, gives some of the unrearranged isobutyl alcohol, VII, in addition to the rearranged *tert*-butyl alcohol, VIII (cf. page 457); and the corresponding reaction with *tert*-butyl amine, IX, appears to proceed with no rearrangement at all. Furthermore, in the decomposition of the diazo compound, I, the formation of either one of the products II and III is highly unlikely in view of Bredt's rule (see Section 9·5); consequently the failure of a rearrangement to occur is not surprising. The fact that the product is tricyclene, IV, instead of the likewise unrearranged bornylene, X, is possibly unexpected, but it provides no evidence either for or against the Whitmore mechanism in those reactions in which a 1,2-shift does occur. In any event, it is especially important to observe that the hypothetical intermediate, V, which might be formed from diazocamphane, is not identical with the one (XI) which must be postulated in the rearrangement of isoborneol; and that there is, therefore, no necessity for the two reactions to follow similar courses.

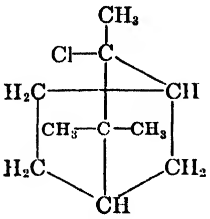


X

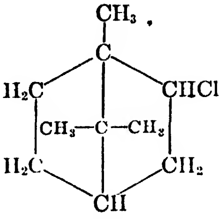


XI

Perhaps the best evidence in support of the Whitmore mechanism is provided by the fact that this mechanism usually makes possible a satisfactory interpretation of the experimental conditions under which the various rearrangements take place. Indeed, some of the early ideas which led ultimately to the theory in its present form were based upon just such considerations. Thus, Meerwein and van Emster[23] found that the rate of the rearrangement of camphene hydrochloride, XII, to isobornyl chloride, XIII, increases in most instances with the dielectric constant of the medium; they explained this fact on the assumption

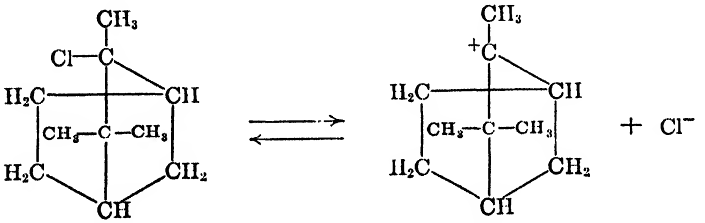


XII



XIII

that the reaction proceeds by means of the ionization shown in equation 12·54. The ion thus formed, XIV, was supposed then to rearrange



XII XIV (12·54)

to the isomeric ion, XI, which, on acquiring a chloride ion, formed isobornyl chloride, XIII. Such an ionization would, of course, be favored by a high dielectric constant of the medium. (Cf. Section 11·2.) Although certain details of Meerwein and van Emster's work have been shown by more recent studies to have been incorrect (see pages 491 ff.), the conclusion that the formation of the ion XIV is an essential step in the rearrangement is still generally held. Moreover, Meerwein and van Emster showed in their second paper [23] that this same rearrangement is made more rapid also by the presence of such substances as ferric chloride and antimony pentachloride, which could be assumed to remove a chloride ion from the camphene hydrochloride to form a stable complex ion like $FeCl_4^-$ or $SbCl_6^-$, respectively, and to leave the same organic cation, XIV, as before.

In the remaining discussion of the relationship between the Whitmore mechanism and the experimental conditions under which the rearrangements in question take place, the three types of reaction designated on page 476 as 1*a*, 1*b*, and 1*c* can conveniently be taken up separately, although, as will be discussed further below, such a procedure cannot be adopted without some arbitrariness.

In the reactions of class 1*a*, the original substance is presumed to break up spontaneously in the manner shown in equation 12·30. It might be anticipated that a rearrangement would be especially likely to follow such a course at relatively high temperatures, at which the substance in question could be expected to have a relatively great tendency to decompose. It is, in fact, observed that many rearrangements which ordinarily require the presence of catalysts can proceed without catalysts if the temperature is sufficiently high; several examples of such behavior have already been noted above. Moreover, in the Curtius rearrangement,[9] in which a catalyst is seldom used, the primary problem is to moderate, rather than to induce, the decomposition of the highly explosive azide; the reaction is accordingly carried out ordinarily by the refluxing of a dilute solution of the azide in some solvent with not too high a boiling point (frequently benzene).[26] Finally, the type of decomposition which must be postulated is usually reasonable and, in some instances, can be supported by independent evidence. Thus, the natures of the products formed in the decomposition of an alkyl or aryl azide strongly suggest the existence of intermediates (of the type $\mathrm{R{-}\ddot{N}:}$ or $\mathrm{Ar{-}\ddot{N}:}$, respectively) which are analogous to the assumed intermediate in the Curtius rearrangement. (See equation 12·49.) For example, the decomposition of methyl azide, XV, in the presence of triethyl-

$$\underset{\text{XV}}{\mathrm{CH_3{-}N_3}} \qquad \underset{\text{XVI}}{\mathrm{P(C_2H_5)_3}} \qquad \underset{\text{XVII}}{\mathrm{CH_3{-}N{=}P(C_2H_5)_3}}$$

phosphine, XVI, gives triethylphosphine methylimide, XVII, and nitrogen; the decomposition of phenyl azide, XVIII, gives azobenzene,

$$\underset{\text{XVIII}}{\mathrm{C_6H_5{-}N_3}} \qquad \underset{\text{XIX}}{\mathrm{C_6H_5{-}N{=}N{-}C_6H_5}}$$

XIX. Similarly, the decompositions of aliphatic diazo compounds $\mathrm{RR'CN_2}$ generally give products which can be explained most easily in terms of intermediates of the type $\mathrm{RR'C:}$, analogous to the assumed intermediate of the Wolff rearrangements. (See equation 12·50.) For example, the decomposition of phenyldiazomethane, XX, gives stilbene,

$$\underset{\text{XX}}{\mathrm{C_6H_5{-}CHN_2}} \qquad \underset{\text{XXI}}{\mathrm{C_6H_5{-}CH{=}CH{-}C_6H_5}} \qquad \underset{\text{XXII}}{\mathrm{CH_2N_2}} \qquad \underset{\text{XXIII}}{\mathrm{(CH_2Te)}_n}$$

XXI, and nitrogen. With diazomethane itself, XXII, the existence of short-lived methylene $\mathrm{CH_2}$ in the decomposition products is indicated

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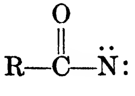
[26] For evidence that the reaction is catalyzed by acids, however, see M. S. Newman and H. L. Gildenhorn, *J. Am. Chem. Soc.* **70,** 317 (1948).

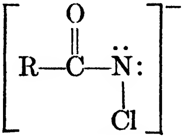
by the fact that these products react with tellurium to give polymeric telluroformaldehyde, XXIII.[27] (See also page 742.)

In the Hofmann rearrangement, the formation of the postulated intermediate XXIV should be easier from the anion XXV than from the



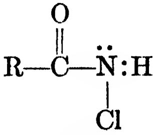
$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}{:}}$$

XXIV



$$\left[\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{Cl}{\underset{|}{\ddot{N}}}{:}}\right]^-$$

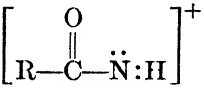
XXV



$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{Cl}{\underset{|}{\ddot{N}}}{:}H}$$

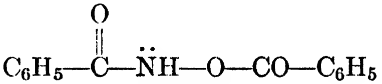
XXVI

neutral haloamide XXVI, since only one bond must be broken in the former reaction, whereas two bonds would have to be broken in the latter; moreover, the formation of this intermediate XXIV from the anion XXV should be easier than that of the alternative intermediate, XXVII,



$$\left[\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}{:}H}\right]^+$$

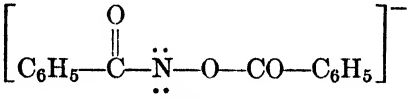
XXVII



$$\mathrm{C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}H{-}O{-}CO{-}C_6H_5}$$

XXVIII

from the neutral haloamide XXVI, since more work should be required to separate the negative halide ion from the cation XXVII than from the neutral fragment XXIV. In any event, the essential role of the base in the rearrangement is readily understood. For a completely analogous reason, the Lossen rearrangement of, for example, dibenzhydroxamic acid, XXVIII, proceeds most rapidly in basic solution, in which the substance exists in the form of a salt containing the anion XXIX.



$$\left[\mathrm{C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}\ddot{\underset{\cdot\cdot}{N}}{-}O{-}CO{-}C_6H_5}\right]^-$$

XXIX

Moreover, the ease of rearrangement of an acyl hydroxamic acid with structure XXX increases, for given R, with the ionization constant of

$$\mathrm{R{-}CO{-}NH{-}O{-}CO{-}R'}$$

XXX

the acid $R'CO_2H$, and hence with the stability of the anion $R'CO_2^-$, which must be assumed to be split off in step 1*a* of the reaction;[8] this fact also seems entirely reasonable, even though one might not have been justified in predicting it in advance. On the other hand, the ease of rearrangement of an acyl hydroxamic acid of this same type, XXX, de-

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[27] F. O. Rice and A. L. Glasebrook, *J. Am. Chem. Soc.* **56**, 2381 (1934).

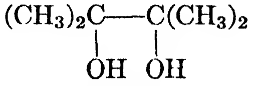
creases as the ionization constant of the acid RCO_2H increases, and hence presumably as the stability of the anion XXXI, which must be

$$[R{-}CO{-}\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}{-}O{-}CO{-}R']^-$$

XXXI

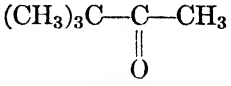
decomposed, increases;[8] again the observed regularity in behavior is entirely reasonable.

In the rearrangement of pinacol, XXXII, to pinacolone, XXXIII,



$$(CH_3)_2\underset{\underset{OH}{|}}{C}{-}\underset{\underset{OH}{|}}{C}(CH_3)_2$$

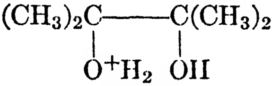
XXXII



$$(CH_3)_3C{-}\underset{\underset{O}{\|}}{C}{-}CH_3$$

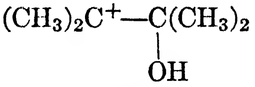
XXXIII

the catalytic effect of an acid like sulfuric acid can be related to the greater ease of breaking up the oxonium cation, XXXIV, into the cation



$$(CH_3)_2\underset{\underset{O^+H_2}{|}}{C}{-}\underset{\underset{OH}{|}}{C}(CH_3)_2$$

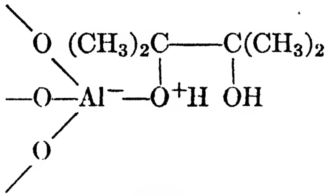
XXXIV



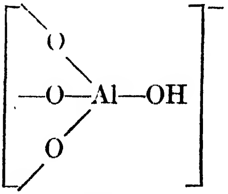
$$(CH_3)_2C^+{-}\underset{\underset{OH}{|}}{C}(CH_3)_2$$

XXXV

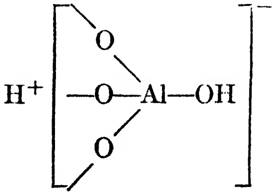
XXXV plus neutral water than of breaking up the original pinacol, XXXII, into the same cation, XXXV, plus the negative hydroxide ion. Similarly, the catalytic effect of a Lewis acid like aluminum oxide can be related to the relatively great ease of breaking up the oxonium addition compound (which is represented schematically by structure XXXVI) into the cation XXXV and the stable anion XXXVII; al-



XXXVI



XXXVII



XXXVIII

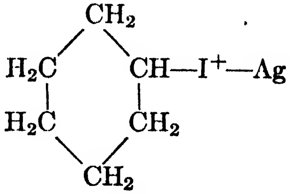
though oppositely charged ions must here still be separated, the decomposition should be easier than the analogous one with pinacol itself since the anion XXXVII, which is derived from the doubtless very strong acid XXXVIII, ought to be formed more readily than is the hydroxide ion, which is derived instead from the almost nonacidic water.

The production of the ion XXXV by the action either of an acid in the classical sense or of a Lewis acid could with equal right be classified as resulting from a reaction of type 1*a*, in which the molecules of the original substance decompose spontaneously, or from one of class 1*b*, in which a reagent attacks these molecules and detaches from them the appropriate fragments. Thus, on the one hand, the "original substance" may be thought of as the oxonium compound, XXXIV or XXXVI, which is doubtless present to some extent in the reaction mixture, and which is presumed to decompose into the cation XXXV without any outside assistance; or, on the other hand, the "original substance" may be thought of as pinacol itself, XXXII, which also is doubtless present in the reaction mixture, but which apparently has little, if any, tendency to decompose spontaneously into the cation XXXV. In the former event, the reaction would be classified as one of type 1*a*; in the latter, it would be classified instead as one of type 1*b*. With the pinacol rearrangement, in which there is reason to believe that the assumed oxonium cation, XXXIV, and addition compound, XXXVI, not only exist but also play essential roles in the rearrangement, the former point of view seems to offer the deeper insight into the nature of the reaction since it provides a more detailed picture of the processes which are considered to occur. It has, accordingly, been adopted in the foregoing discussion of the pinacol rearrangement and of several other reactions of similar type. (Cf. pages 478 ff.) The alternative point of view is, however, equally logical and in practice often proves to be the more convenient; it will, accordingly, be employed hereafter whenever the particular occasions warrant.

Examples of rearrangements in which the first steps seem more definitely to follow the course 1*b* are given by the reaction of silver acetate with neopentyl iodide (cf. equation 12·42, page 480), and by that of silver nitrite with cyclohexyl iodide (cf. page 455). Although, of course, it could be postulated that addition compounds with the structures XXXIX and XL, respectively, are formed, and that these

$(CH_3)_3C—CH_2—I^+—Ag$

XXXIX

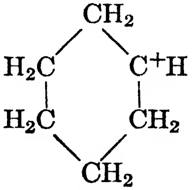


XL

decompose spontaneously in accordance with scheme 1*a* to the ions XLI and XLII, respectively, there is no evidence for the existence of such complexes. It seems more logical, therefore, to consider that the silver ions merely pull off the iodide ions in accordance with scheme 1*b*, and leave the respective organic cations, XLI and XLII. In any event, the role of the silver ion in the reaction is readily understandable; both the tendency of this ion to form stable complexes with halide ions and the extreme insolubility of silver iodide are consistent with the belief that silver-iodine bonds are readily formed and are strong. In analogous ways, the various further rearrangements brought about by the action of salts either of silver or of other heavy metals can also be easily interpreted.

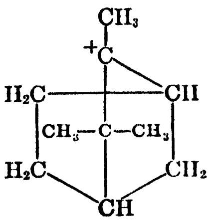
$(CH_3)_3C—C^+H_2$

XLI

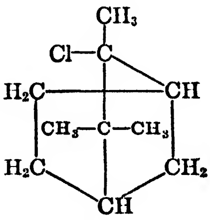


XLII

The rearrangement of camphene hydrochloride to isobornyl chloride under the catalytic influence of ferric chloride or antimony pentachloride (see above) may also be interpreted in an obvious manner as proceeding through a step of class 1*b*. The "uncatalyzed" rearrangement studied by Meerwein and van Emster,[23] on the other hand, might appear to proceed instead through a step of class 1*a* (cf. equation 12·54, page 486); this conclusion was indeed drawn by Meerwein and van Emster on the basis of their kinetic data. Nevertheless, Bartlett and Pöckel [28] have been able to show by a more careful investigation that the production of the ion XIV does not result from a *spontaneous* ionization of camphene hydrochloride, XII, but rather from a reaction in which the chloride ion is pulled off from the molecule of camphene hydrochloride



XIV



XII

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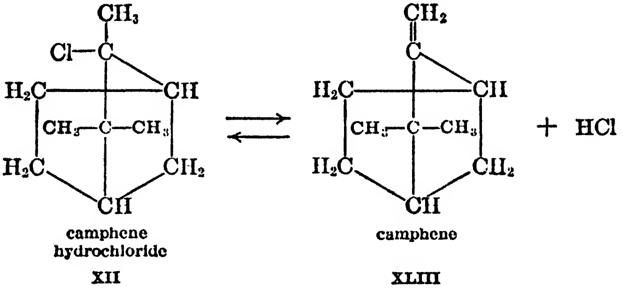
[28] P. D. Bartlett and I. Pöckel, *J. Am. Chem. Soc.* **60**, 1585 (1938).

by a molecule of hydrogen chloride, presumably as a result of hydrogen-bond formation. The reaction is therefore again of class 1*b*.

This interpretation, requiring that a stable hydrogen bond be possible between two chlorine atoms, may appear to be inconsistent with the statement made earlier in Section 2·6 that fluorine, oxygen, and nitrogen are the only elements which can ordinarily enter into such unions. It may be noted, however, that even a small pull exerted by the molecule of hydrogen chloride upon the chlorine atom of the camphene hydrochloride molecule might be expected to lead to a marked increase in the ease with which the chloride ion breaks away. It is probably not necessary, therefore, to assume that the hydrogen bond postulated here is as strong as the ones between, for example, oxygen atoms.

The evidence supporting the mechanism of Bartlett and Pöckel is of sufficient interest to be described here briefly. Camphene hydrochloride in solution dissociates rapidly and reversibly into camphene, XLIII, and hydrogen chloride, in the manner shown in equation 12·55. (In the nitrobenzene solvent used by Bartlett and Pöckel, the hydrogen chloride that is formed neither dissociates further into ions nor associates.) If the solution is prepared from pure camphene hydrochloride, the concentrations of camphene and of hydrogen chloride are identical at all times during the rearrangement. Consequently, the equilibrium constant K of the dissociation can be expressed as in equation 12·56, in



(12·55)

$$K = \frac{[\mathrm{C}]\,[\mathrm{HCl}]}{[\mathrm{CHCl}]} = \frac{[\mathrm{HCl}]^2}{[\mathrm{CHCl}]} \qquad (12\cdot56)$$

which C stands for camphene, and CHCl stands for camphene hydrochloride. Under such circumstances, the concentration of hydrogen chloride is proportional to the square root of that of camphene hydrochloride. If the reaction follows the course assumed by Bartlett and Pöckel, its rate $-d[\mathrm{CHCl}]/dt$ should be that given by equation 12·57, and

$$-\frac{d[\mathrm{CHCl}]}{dt} = k[\mathrm{CHCl}]\,[\mathrm{HCl}] = k[\mathrm{CHCl}]^{3/2}\sqrt{K} \qquad (12\cdot57)$$

so should be proportional to the three-halves power of the concentration of camphene hydrochloride. On the other hand, if a large excess of camphene is added to the reaction mixture, so that the concentration of camphene [C] can be considered to have the constant value A during the course of the rearrangement, then the equilibrium expression assumes the form 12·58 instead of 12·56, and the concentration of hydrogen

$$K = \frac{[\mathrm{C}]\,[\mathrm{HCl}]}{[\mathrm{CHCl}]} = \frac{[\mathrm{A}]\,[\mathrm{HCl}]}{[\mathrm{CHCl}]} \qquad (12\cdot 58)$$

chloride becomes proportional to that of camphene hydrochloride. The rate of the rearrangement, which is now given by equation 12·59 instead

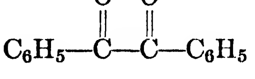
$$-\frac{d[\mathrm{CHCl}]}{dt} = k[\mathrm{CHCl}]\,[\mathrm{HCl}] = k[\mathrm{CHCl}]^2\,\frac{K}{A} \qquad (12\cdot 59)$$

of by equation 12·57, is accordingly proportional to the square of the concentration of camphene hydrochloride. Since these predictions were found by Bartlett and Pöckel to be in complete agreement with the data, and since Meerwein and van Emster's original assumption of a spontaneous ionization of the camphene hydrochloride would require that, under each set of conditions, the rate of rearrangement be proportional to the first power of the concentration of camphene hydrochloride, as in equation 12·60, the only reasonable conclusion is that Bartlett and

$$-\frac{d[\mathrm{CHCl}]}{dt} = k[\mathrm{CHCl}] \qquad (12\cdot 60)$$

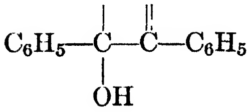
Pöckel's interpretation of the reaction is the correct one.

The benzilic acid rearrangement can be considered to involve a step of type 1*c*. (Cf. equation 12·51, page 483.) The postulated intermediate which is presumed to undergo the actual rearrangement is here an anion formed by the addition of a hydroxide ion to a molecule of benzil, XLIV.



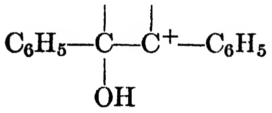
$C_6H_5-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-C_6H_5$

XLIV



$C_6H_5-\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}-\overset{\overset{O}{\|}}{C}-C_6H_5$

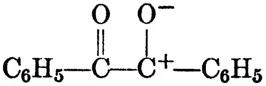
XLV



$C_6H_5-\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}-\overset{\overset{O^-}{|}}{C^+}-C_6H_5$

XLVI

This ion doubtless resonates between structures XLV and XLVI, of which the second, and presumably less important, one has the required open sextet. The function of the base in making the rearrangement occur should now be apparent; structure XLVI, as a result of its less unfavorable distribution of electric charge, must make a larger contribution to the state of the negative ion than the analogous structure, XLVII, makes to that of the neutral benzil molecule. Very satisfactory



$$C_6H_5{-}\overset{\overset{\textstyle O}{\|}}{C}{-}\overset{\overset{\textstyle O^-}{|}}{C^+}{-}C_6H_5$$

XLVII

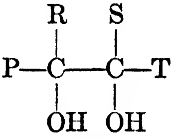
evidence for this mechanism of the benzilic acid rearrangement has been obtained from kinetic studies.[29] The rate of the reaction has been found to be proportional to the concentration of benzil and also to that of hydroxide ion, but to be independent of the concentrations of such other strong Brønsted (or Lewis) bases as phenoxide ion, XLVIII, and *o*-

$C_6H_5{-}O^-$
XLVIII

o-$Cl{-}C_6H_4{-}O^-$
XLIX

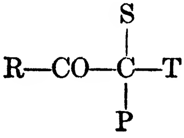
chlorophenoxide ion, XLIX. The rearrangement is therefore catalyzed specifically by hydroxide ion, but not by bases in general. This conclusion shows that the anion resonating between structures XLV and XLVI must be an intermediate in the reaction.

12·6 Migratory Aptitudes in the 1,2-Shift. Although the Whitmore mechanism makes possible a satisfactory interpretation of any 1,2-shift, it does not always in any given instance permit an unambiguous prediction of the structure of the final product. For example, a pinacol of general structure I, in which P, R, S, and T are considered to



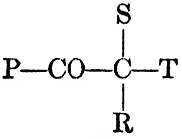
$$P{-}\underset{\underset{\textstyle OH}{|}}{\overset{\overset{\textstyle R}{|}}{C}}{-}\underset{\underset{\textstyle OH}{|}}{\overset{\overset{\textstyle S}{|}}{C}}{-}T$$

I



$$R{-}CO{-}\underset{\underset{\textstyle P}{|}}{\overset{\overset{\textstyle S}{|}}{C}}{-}T$$

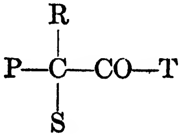
II



$$P{-}CO{-}\underset{\underset{\textstyle R}{|}}{\overset{\overset{\textstyle S}{|}}{C}}{-}T$$

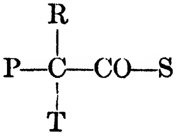
III

represent different atoms or groups, could conceivably rearrange to any one of the four structurally isomeric products II–V (or to a mixture of



$$P{-}\underset{\underset{\textstyle S}{|}}{\overset{\overset{\textstyle R}{|}}{C}}{-}CO{-}T$$

IV



$$P{-}\underset{\underset{\textstyle T}{|}}{\overset{\overset{\textstyle R}{|}}{C}}{-}CO{-}S$$

V

these products). Although the Whitmore mechanism can be applied to the reaction, no matter which of the possible courses it may be found to follow, the product cannot be predicted in advance without informa-

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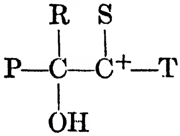
[29] F. H. Westheimer, *J. Am. Chem. Soc.* **58,** 2209 (1936). See also I. Roberts and H. C. Urey, *ibid.* **60,** 880 (1938).

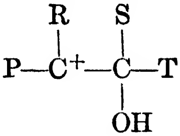
tion regarding what may be called the *migratory aptitudes* of the various atoms and groups or, in other words, without information regarding the relative tendencies of the substituents P, R, S, and T to shift from their original to their final points of attachment.

At least two different factors must be considered in any complete discussion of migratory aptitudes, although neither of these factors is necessarily important in every type of 1,2-shift. The situation can again be illustrated with a discussion of the generalized pinacol, I. With this substance, the first step in the rearrangement is considered to be the loss of a hydroxide ion to give an organic cation with either structure VI or structure VII.



$$P-\underset{OH}{\overset{R}{C}}-\overset{S}{C}{}^{+}-T$$

VI



$$P-\overset{R}{C}{}^{+}-\underset{OH}{\overset{S}{C}}-T$$

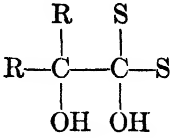
VII

If the ion VI is formed, then only P or R (and not S or T) can migrate in the second step; hence the final product must be, respectively, II or III. On the other hand, if the ion VII is formed instead, then only S or T (and not P or R) can migrate; hence, the final product has instead to be, respectively, IV or V. Evidently, therefore, the course of the rearrangement is partially determined by the relative ease with which the two hydroxyl groups can be removed with their binding electrons. The second factor determining migratory aptitudes comes into play in the second step of the rearrangement, in which the actual shift takes place. Thus, if the ion VI is the one formed, then there still remains the question whether P or R migrates. Similarly, if the ion VII is the one formed, then there still remains the question whether S or T migrates.

In summary, and in more general terms, the two factors under discussion may be described as, first, the one that determines the structure of the intermediate with the open sextet of electrons (in those instances in which more than one such intermediate is possible); and, second, the one that determines the identity of the atom or group of this intermediate which actually migrates (in those instances in which there is more than one atom or group in the intermediate which could migrate). Although it might appear that the expression "migratory aptitude" could be strictly applied only to the second of these two factors (see also below), it is nevertheless commonly employed to designate the resultant of the two.

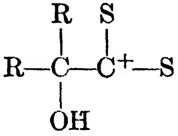
Inasmuch as the two factors which determine migratory aptitudes depend upon different properties of the atoms or groups concerned, they can most conveniently be treated separately. The following section will, accordingly, deal only with the first of these factors; the discussion of the second will for the moment be postponed.

12·7 Migratory Aptitudes as Determined by the Identity of the Intermediate. A particularly convenient group of compounds for the consideration of the first factor, without any interference from the second, is provided by the so-called *unsymmetrical* pinacols of general structure I. Considerable, although not exclusive, attention will accordingly be given to such substances in this section. With any compound of this type, the product of the rearrangement is determined solely by the tendencies of the two hydroxyl groups to separate as anions. Thus, if the intermediate that is formed has structure II, only the atom or group R can migrate; hence the product is necessarily the aldehyde or ketone III. On the other hand, if the intermediate that is formed has instead structure IV, then only the atom or group S can migrate; hence, the product is necessarily the isomer V. It will be noted that, in either event, the relative "migratory aptitudes" of R and S are determined, not by any intrinsic tendencies to migrate which these atoms or groups may possess, but rather by the effects which these atoms or groups exert upon the ionizations of the adjacent hydroxyl groups. Moreover, it will be noted further that the relationship between the resultant migratory aptitude and the effectiveness in promoting ionization is an *inverse* one, since the group which migrates does so because the adjacent hydroxyl group is *not* detached in the first step of the rearrangement. In other words, the migratory aptitude of an atom or group (to the extent that it is determined by the single factor now under discussion) can be considered equivalent to the *in*effectiveness of that atom or group in favoring the production of an open sextet upon the atom to which it is attached.



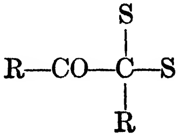
$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle OH}{C}}{-}\overset{\displaystyle S}{\underset{\displaystyle OH}{C}}{-}S}$$

I



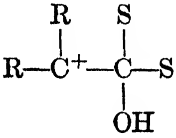
$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle OH}{C}}{-}\overset{\displaystyle S}{C^{+}}{-}S}$$

II



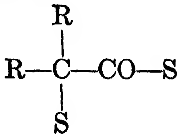
$$\mathrm{R{-}CO{-}\overset{\displaystyle S}{\underset{\displaystyle R}{C}}{-}S}$$

III



$$\mathrm{R{-}\overset{\displaystyle R}{C^{+}}{-}\overset{\displaystyle S}{\underset{\displaystyle OH}{C}}{-}S}$$

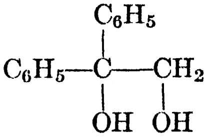
IV



$$\mathrm{R{-}\overset{\displaystyle R}{\underset{\displaystyle S}{C}}{-}CO{-}S}$$

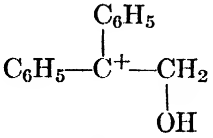
V

In the rearrangement of a pinacol, the intermediate with an open sextet that is formed in the greater amount seems usually to be the thermodynamically more stable one, i.e., the one which would be present to the greater extent in an equilibrium mixture of the two. (Cf. Section 9·2. For some difficulties with this generalization, however, see below.) For example, the rearrangement of 1,1-diphenylethylene glycol, VI,



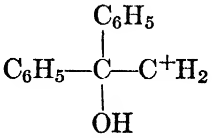
$C_6H_5\text{—}\overset{C_6H_5}{\underset{OH}{C}}\text{—}\underset{OH}{CH_2}$

VI



$C_6H_5\text{—}\overset{C_6H_5}{C^+}\text{—}\underset{OH}{CH_2}$

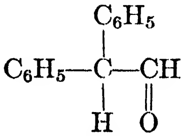
VII



$C_6H_5\text{—}\overset{C_6H_5}{\underset{OH}{C}}\text{—}C^+H_2$

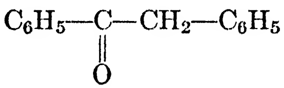
VIII

might go through either of the two intermediates VII and VIII, with production finally of either diphenylacetaldehyde, IX, or desoxybenzoin,



$C_6H_5\text{—}\overset{C_6H_5}{\underset{H}{C}}\text{—}\underset{O}{\underset{\|}{CH}}$

IX



$C_6H_5\text{—}\underset{O}{\underset{\|}{C}}\text{—}CH_2\text{—}C_6H_5$

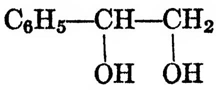
X

X, respectively. The significant difference between the two possible cations VII and VIII is that, in the former, the positive formal charge is represented as on a carbon atom to which two phenyl groups are joined, whereas, in the latter, the charge is represented instead as on a carbon atom to which two hydrogen atoms are joined. There is very good evidence that the proximity of aromatic radicals, as in structure VII, stabilizes a carbonium cation (see Section 2·5); for example, triphenylcarbinol, XI, reacts with concentrated sulfuric acid to form the "halochromic salt," XII, containing a cation analogous to the one with structure VII; on the other hand, ordinary alcohols, either without aryl

$(C_6H_5)_3COH$
XI

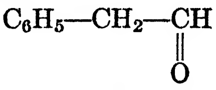
$[(C_6H_5)_3C]^+HSO_4^-$
XII

groups or with aryl groups more distant from the hydroxyl group, do not give rise to such ions. In general, the stability of the ion increases with the number of aryl groups. Consequently, the inference can be drawn that the ion VII should be formed in preference to the ion VIII, and that the product isolated should be diphenylacetaldehyde, IX, instead of desoxybenzoin, X. This expectation is, in fact, confirmed by experiment. Similarly, phenylethylene glycol, XIII, would be expected to



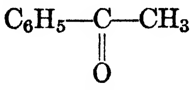
$C_6H_5\text{—}\underset{OH}{CH}\text{—}\underset{OH}{CH_2}$

XIII



$C_6H_5\text{—}CH_2\text{—}\underset{O}{\underset{\|}{CH}}$

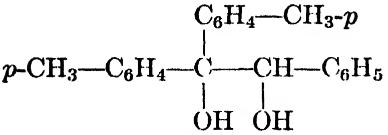
XIV



$C_6H_5\text{—}\underset{O}{\underset{\|}{C}}\text{—}CH_3$

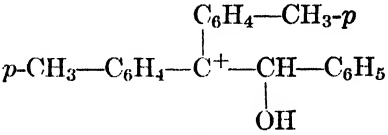
XV

give phenylacetaldehyde, XIV, rather than acetophenone, XV; again the expectation is confirmed by experiment. Moreover, since the stability of the cation increases with the number of aryl groups, 1,1-di-*p*-tolyl-2-phenylethylene glycol, XVI, should give rise to the intermediate



$$p\text{-}CH_3—C_6H_4—\underset{OH}{\overset{C_6H_4—CH_3\text{-}p}{C}}—\underset{OH}{CH}—C_6H_5$$

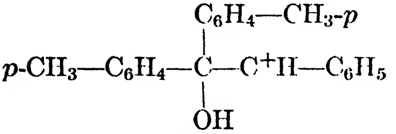
XVI



$$p\text{-}CH_3—C_6H_4—\overset{C_6H_4—CH_3\text{-}p}{C^+}—\underset{OH}{CH}—C_6H_5$$

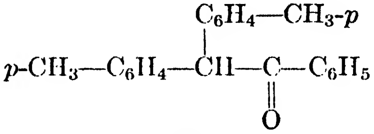
XVII

XVII, and not to the alternative one, XVIII; this prediction is in agreement with the fact that the product of the reaction is α,α-di-*p*-tolylacetophenone, XIX, and not the isomeric *p*-methyl-α-*p*-tolyl-α-phenylacetophenone, XX, which would have had to be formed from the cation XVIII.



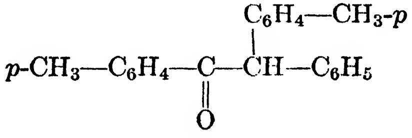
$$p\text{-}CH_3—C_6H_4—\underset{OH}{\overset{C_6H_4—CH_3\text{-}p}{C}}—C^+H—C_6H_5$$

XVIII



$$p\text{-}CH_3—C_6H_4—\overset{C_6H_4—CH_3\text{-}p}{CH}—\underset{O}{\underset{\|}{C}}—C_6H_5$$

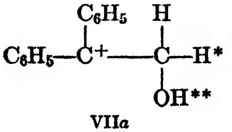
XIX



$$p\text{-}CH_3—C_6H_4—\underset{O}{\underset{\|}{C}}—\overset{C_6H_4—CH_3\text{-}p}{CH}—C_6H_5$$

XX

In the foregoing examples, in which aromatic groups are compared with hydrogen atoms, the possibility exists that, in at least some instances, the reactions do not take place by the Whitmore mechanism, but instead by dehydrations to enols which then rearrange to the stable keto forms. (See, however, pages 474 f.) Even if the reactions proceeded in this manner, however, the above considerations would not necessarily be without significance, since the ions VII and XVII might still be assumed as intermediates in the dehydrations. The distinction between the two points of view is that, if the Whitmore mechanism is correctly applied to these reactions, the hydrogen atom marked by the single asterisk in structure VII*a* migrates

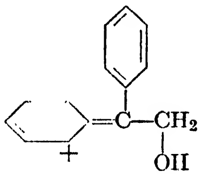


$$C_6H_5—\overset{C_6H_5}{C^+}—\underset{OH^{**}}{\overset{H}{C}}—H^*$$

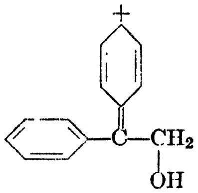
VII*a*

to the adjacent carbon atom, and then the proton marked by the double asterisk is removed; whereas, if the enolic dehydration is here correct, the proton marked by the single asterisk is first removed, and then the one marked by the double asterisk migrates to the adjacent carbon atom, presumably not by means of a direct jump from one atom to another, but rather by means of a reaction in which a base removes the proton H** from the oxygen atom, and an acid that is also present in the medium gives a doubtless different proton to the carbon atom. In either event, the electrons must redistribute themselves, through resonance. This same ambiguity in mechanism must clearly occur also in all those other reactions, discussed below, in which hydrogen atoms are considered to migrate, and in which therefore the enolic dehydration is conceivable.

The theory of resonance provides a simple and logical explanation of the stabilization of ions like VII by the aromatic groups present. Thus, in the original pinacol, VI, the only important resonance is that in the two benzene rings separately. Since there is accordingly no significant interaction between these two rings, the resonance energy of the substance should be approximately twice that of benzene itself—i.e., some 70–80 kcal per mole. In the particular cation that is considered to be the more stable, however, the resonance can include not only the structures represented above by VII, in which the formal charge is on the carbon atom between the two rings, but also such further structures as XXI and XXII, in which the charge is on an *ortho* or *para* carbon atom of one of the rings. If the resonance in the ion were restricted to the structures included in the symbol VII, just as that in the pinacol itself is restricted to those included in the symbol VI, then the resonance energy should again be approximately twice that of benzene, since then the rings would not be interacting with each other. However, the resonance in the ion cannot be thus restricted; it must instead include the further structures like XXI and XXII. Consequently, the resonance energy of the ion must be greater than twice that of benzene; hence, as a result of this resonance, the ion is stabilized with respect to the neutral glycol, VI. In the alternative ion, VIII, on the other hand, there is no possibility for resonance with quinoid structures analogous to XXI and XXII; since the resonance energy of this ion, like that of the glycol itself, must therefore be approximately twice that of benzene, the ion is not stabilized by the resonance to any greater extent than is the glycol. It follows, therefore, that this second ion, VIII, should be less stable than the first one. (The theoretically important distinction between thermochemical and thermodynamic stability is not likely to alter the conclusions just reached; hence it is here ignored.)

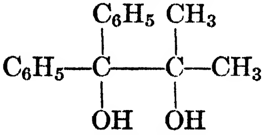


XXI



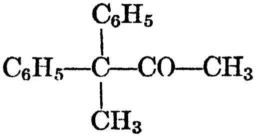
XXII

Alkyl groups are usually intermediate between aryl groups and hydrogen atoms in facilitating the removal of hydroxide ions from the carbon atoms to which they are attached. Thus, the fact that 1,1-diphenyl-2,2-dimethylethylene glycol, XXIII, rearranges to 1-methyl-1,1-di-



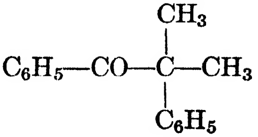
$$C_6H_5-\overset{\displaystyle C_6H_5}{\underset{\displaystyle OH}{C}}-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}-CH_3$$

XXIII



$$C_6H_5-\overset{\displaystyle C_6H_5}{\underset{\displaystyle CH_3}{C}}-CO-CH_3$$

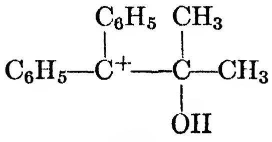
XXIV



$$C_6H_5-CO-\overset{\displaystyle CH_3}{\underset{\displaystyle C_6H_5}{C}}-CH_3$$

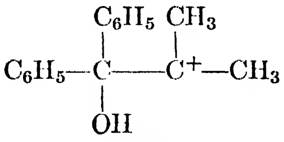
XXV

phenylacetone, XXIV, and not to α-phenylisobutyrophenone, XXV, shows that the ion XXVI is formed in preference to the ion XXVII; and



$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle C_6H_5}{|}}{C}{}^{+}{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}CH_3}$$

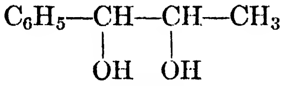
XXVI



$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}\overset{\overset{\displaystyle CH_3}{|}}{C}{}^{+}{-}CH_3}$$

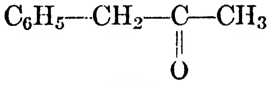
XXVII

accordingly that phenyl groups are more effective than are methyl groups in stabilizing structures in which they are joined to atoms with open sextets. Similarly, since 1-phenyl-2-methylethylene glycol, XXVIII,



$$\mathrm{C_6H_5{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}CH_3}$$

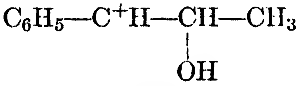
XXVIII



$$\mathrm{C_6H_5{-}CH_2{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}CH_3}$$

XXIX

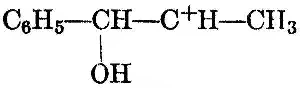
leads to phenylacetone, XXIX, the intermediate XXX is evidently



$$\mathrm{C_6H_5{-}C^{+}H{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}CH_3}$$

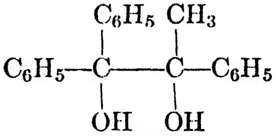
XXX

formed in preference to XXXI; and, since 1,1,2-triphenyl-2-methyl-



$$\mathrm{C_6H_5{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}C^{+}H{-}CH_3}$$

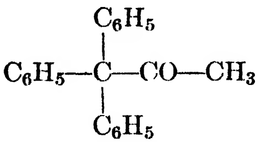
XXXI



$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}C_6H_5}$$

XXXII

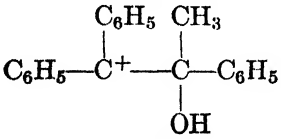
ethylene glycol, XXXII, leads to 1,1,1-triphenylacetone, XXXIII, the



$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{C}}{-}CO{-}CH_3}$$

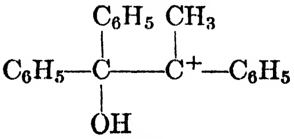
XXXIII

ion XXXIV is evidently formed in preference to XXXV. On the other



$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle C_6H_5}{|}}{C}{}^{+}{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}C_6H_5}$$

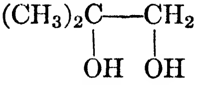
XXXIV



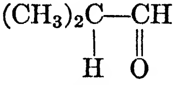
$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}{-}\overset{\overset{\displaystyle CH_3}{|}}{C}{}^{+}{-}C_6H_5}$$

XXXV

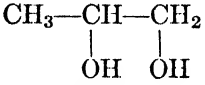
hand, alkyl groups appear to be more effective than hydrogen atoms in facilitating the ionization of adjacent hydroxyl groups. Thus, isobutylene glycol, XXXVI, rearranges to isobutyraldehyde, XXXVII, propyl-


$(CH_3)_2\underset{OH}{\underset{|}{C}}-\underset{OH}{\underset{|}{CH_2}}$

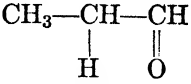
XXXVI


$(CH_3)_2\underset{H}{\underset{|}{C}}-\underset{O}{\underset{\|}{CH}}$

XXXVII

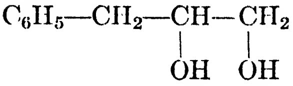

$CH_3-\underset{OH}{\underset{|}{CH}}-\underset{OH}{\underset{|}{CH_2}}$

XXXVIII

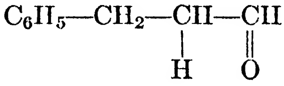

$CH_3-\underset{H}{\underset{|}{CH}}-\underset{O}{\underset{\|}{CH}}$

XXXIX

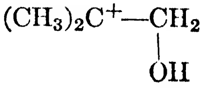
ene glycol, XXXVIII, rearranges to propionaldehyde, XXXIX, and benzylethylene glycol, XL, rearranges to benzylacetaldehyde, XLI;


$C_6H_5-CH_2-\underset{OH}{\underset{|}{CH}}-\underset{OH}{\underset{|}{CH_2}}$

XL

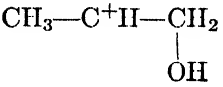

$C_6H_5-CH_2-\underset{H}{\underset{|}{CH}}-\underset{O}{\underset{\|}{CH}}$

XLI

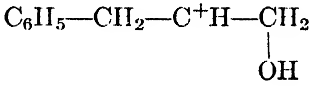

$(CH_3)_2C^+-\underset{OH}{\underset{|}{CH_2}}$

XLII

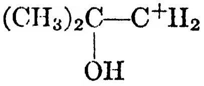
hence, it follows that the ions XLII, XLIII, and XLIV are formed in


$CH_3-C^+H-\underset{OH}{\underset{|}{CH_2}}$

XLIII

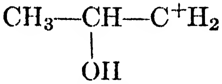

$C_6H_5-CH_2-C^+H-\underset{OH}{\underset{|}{CH_2}}$

XLIV

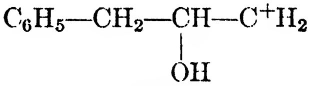

$(CH_3)_2\underset{OH}{\underset{|}{C}}-C^+H_2$

XLV

preference to the ions XLV, XLVI, and XLVII, respectively.

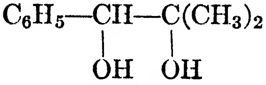

$CH_3-\underset{OH}{\underset{|}{CH}}-C^+H_2$

XLVI

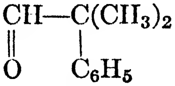

$C_6H_5-CH_2-\underset{OH}{\underset{|}{CH}}-C^+H_2$

XLVII

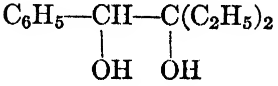
Although, as was shown above, a phenyl group makes the departure of an adjacent hydroxyl group easier than does an alkyl group, such a group appears frequently to be less effective in this respect than *two* alkyl groups since, for example, the rearrangement of 1-phenyl-2,2-dimethylethylene glycol, XLVIII, with 20 per cent sulfuric acid gives


$C_6H_5-\underset{OH}{\underset{|}{CH}}-\underset{OH}{\underset{|}{C}}(CH_3)_2$

XLVIII

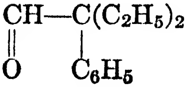

$\underset{O}{\underset{\|}{CH}}-\underset{C_6H_5}{\underset{|}{C}}(CH_3)_2$

XLIX

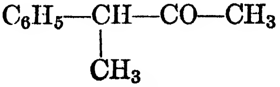

$C_6H_5-\underset{OH}{\underset{|}{CH}}-\underset{OH}{\underset{|}{C}}(C_2H_5)_2$

L

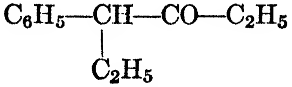
dimethylphenylacetaldehyde, XLIX, and that of 1-phenyl-2,2-diethylethylene glycol, L, under the same conditions similarly gives diethylphenylacetaldehyde, LI. The situation is, however, not so straight-


$\underset{O}{\underset{\|}{CH}}-\underset{C_6H_5}{\underset{|}{C}}(C_2H_5)_2$

LI

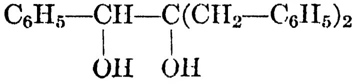

$C_6H_5-\underset{CH_3}{\underset{|}{CH}}-CO-CH_3$

LII


$C_6H_5-\underset{C_2H_5}{\underset{|}{CH}}-CO-C_2H_5$

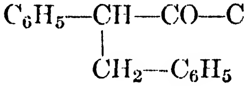
LIII

forward as it might appear to be, since the same two glycols, XLVIII and L, are transformed by treatment with *concentrated* sulfuric acid into the ketones LII and LIII, respectively. A possible interpretation of the facts is that, under either set of conditions, the pinacols themselves rearrange to the corresponding aldehydes, XLIX and LI; but that, in the presence of concentrated sulfuric acid, these aldehydes then rearrange further to the respective ketones LII and LIII. Some support for this interpretation can indeed be advanced, since the aldehydes in question have been found actually to undergo the postulated rearrangements under the stated conditions. (See also pages 464 f.) That such an interpretation is not generally valid, however, is shown by the behavior of the apparently analogous 1-phenyl-2,2-dibenzylethylene glycol, LIV,



$$C_6H_5{-}\underset{\text{OH}}{\underset{|}{\text{CH}}}{-}\underset{\text{OH}}{\underset{|}{\text{C}}}(CH_2{-}C_6H_5)_2$$

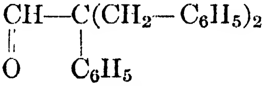
LIV



$$C_6H_5{-}\underset{CH_2-C_6H_5}{\underset{|}{\text{CH}}}{-}CO{-}CH_2{-}C_6H_5$$

LV

which rearranges to the ketone LV with either dilute or concentrated sulfuric acid, and never to the aldehyde LVI. Moreover, in this instance

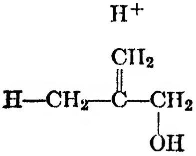


$$\underset{\text{O}}{\underset{\|}{\text{CH}}}{-}\underset{C_6H_5}{\underset{|}{\text{C}}}(CH_2{-}C_6H_5)_2$$

LVI

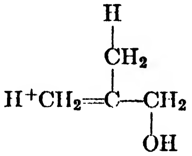
at any rate, the aldehyde cannot be an intermediate in the formation of the ketone, since the *optically active* glycol, LIV, gives the optically active ketone, LV. If the necessarily inactive aldehyde, LVI, were an intermediate in the rearrangement, the finally resulting ketone would instead have to be completely racemic. The corresponding experiments with the optically active forms of the dimethyl and diethyl compounds, XLVIII and L, respectively, have not been reported; consequently, the possibility of the intermediate formation of the aldehydes XLIX and LI in the reactions of these glycols with concentrated sulfuric acid cannot be definitely excluded.

The resonance theory can provide a simple interpretation of the ability of alkyl (as well as of aryl) groups to stabilize the cations in which they are attached to the positive centers. Thus, the ion represented above as XLII can resonate with the additional structures LVII and LVIII; hence it is stabilized by the resulting reso-



$$H{-}CH_2{-}\overset{\overset{H^+}{CH_2}}{\overset{\|}{\text{C}}}{-}\underset{\text{OH}}{\underset{|}{CH_2}}$$

LVII



$$H^+CH_2{=}\overset{\overset{\text{H}}{\overset{|}{CH_2}}}{\overset{|}{\text{C}}}{-}\underset{\text{OH}}{\underset{|}{CH_2}}$$

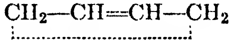
LVIII

nance energy. On the other hand, neither the alternative cation, XLV, nor the original isobutylene glycol, XXXVI, is stabilized in any similar manner. The conclusion can therefore be drawn that the ion resonating among the structures XLII, LVII, and LVIII should be formed in preference to the alternative one, XLV. (Again, the distinction between thermochemical and thermodynamic stability is here ignored.)

Resonance with structures like LVII and LVIII, in which an atom or group is not joined by any sort of bond to the atom to which it is ordinarily considered to be linked, is called *hyperconjugation* or, frequently, *no-bond resonance*.[30] It differs in no really fundamental respect from the familiar type of conjugation exhibited, for example, by 1,3-butadiene. In the ion resonating among the structures XLII, LVII, and LVIII, for example, the interaction between a given one of the carbon atoms and one of the hydrogen atoms is represented as a single bond in the most stable structure, XLII, but as a bond of order one less (i.e., as a "no-bond") in a less stable structure, either LVII or LVIII; in butadiene, similarly, a bond between a given two of the carbon atoms is represented as a double bond in the most stable structure, LIX, but as a bond of order one less (i.e., as an ordinary single bond) in a less stable structure, LX. Moreover, both in the ion and in butadiene, a different bond is represented as single in the most stable structure but as a bond of order one greater (i.e., as a double bond) in a less stable structure. In both these respects, the analogy between the hyperconjugation in the ion and the ordinary conjugation in butadiene is complete. Attention should perhaps at this point, however, be called to the incorrectness of the popular misconception that the assumption of resonance with such structures as LVII and LVIII implies that the "no-bonded" atoms or groups are in danger of breaking away from the rest of the molecule. In the corresponding most stable, and hence most important, structures, these atoms or groups are always represented as linked to the appropriate atoms. Consequently, in the resonance hybrid, they are definitely linked by valence bonds to the atoms in question; the assumption of the no-bond resonance does not, therefore, require a dissociation of the molecule. The only effect of the hyperconjugation upon these bonds, in fact, is to weaken them to a small extent, just as the ordinary conjugation in butadiene may be considered to weaken slightly the bonds that are represented as double in the conventional, and most stable, structure LIX.

$H_2C{=}CH{-}CH{=}CH_2$

LIX



$CH_2{-}CH{=}CH{-}CH_2$

LX

With the above rules governing the relative effectiveness of aryl groups, alkyl groups, and hydrogen atoms in facilitating the removal of an adjacent hydroxyl group in the form of hydroxide ion, one can in many instances, as has been shown in the preceding pages, predict which of the possible intermediates will be formed in greater amount from a given pinacol. In many other instances, however, more detailed information is required regarding the relative effectiveness of two different

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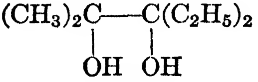
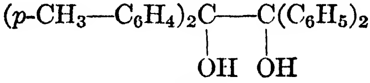
[30] For further discussion of hyperconjugation, see, for example, R. S. Mulliken, C. A. Rieke, and W. G. Brown, *J. Am. Chem. Soc.* **63**, 41 (1941); G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 85 ff.; C. L. Deasy, *Chem. Revs.* **36**, 145 (1945). For still earlier suggestions of the phenomenon, see G. W. Wheland, *J. Chem. Phys.* **2**, 474 (1934); J. W. Baker and W. S. Nathan, *J. Chem. Soc.* **1935**, 1844.

aryl groups, or of two different alkyl groups. For example, nothing that has been said so far would enable one to predict which of the two possible intermediates derived from either of the pinacols, LXI and LXII,



$(CH_3)_2C(OH)-C(OH)(C_2H_5)_2$

LXI

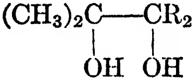


$(p\text{-}CH_3-C_6H_4)_2C(OH)-C(OH)(C_6H_5)_2$

LXII

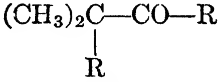
would be formed to the greater extent. (However, see below.) In any reaction of this type, a mixture of products is usually obtained; hence, each of the possible intermediate cations must be assumed to be formed to some extent.

As a result of a considerable amount of experimental study, several more or less general statements can be made regarding the smaller differences among the various alkyl groups or among the various aryl groups in their abilities to facilitate the loss of hydroxide ions from the carbon atoms to which they are attached. Thus, the methyl group seems to be the most effective of the alkyl groups, since the glycol LXIII,



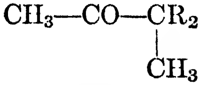
$(CH_3)_2C(OH)-C(OH)R_2$

LXIII



$(CH_3)_2C(R)-CO-R$

LXIV

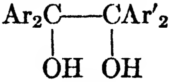


$CH_3-CO-C(CH_3)R_2$

LXV

with R equal to ethyl, *n*-propyl, or *n*-butyl, rearranges to a mixture of the two ketones LXIV and LXV, in which the former predominates. On the other hand, a comparison of the rearrangements of the pinacols, XLVIII, L, and LIV, discussed above, suggests that the benzyl group is relatively *in*effective.

The aryl groups have been investigated in a somewhat more detailed manner.[31] In fact, a fairly, although not completely, successful attempt has been made with these groups to put the experimental data upon a quantitative basis, so that the composition of the product formed in the rearrangement of an unsymmetrical glycol of form LXVI could be cal-



$Ar_2C(OH)-C(OH)Ar'_2$

LXVI

culated in advance. The underlying principle of the treatment can be illustrated by the following examples.

The rearrangement of 1,1-diphenyl-2,2-di-*p*-biphenylylethylene glycol, LXVII, gives a mixture consisting of 46 per cent α-phenyl-α,α-di-*p*-

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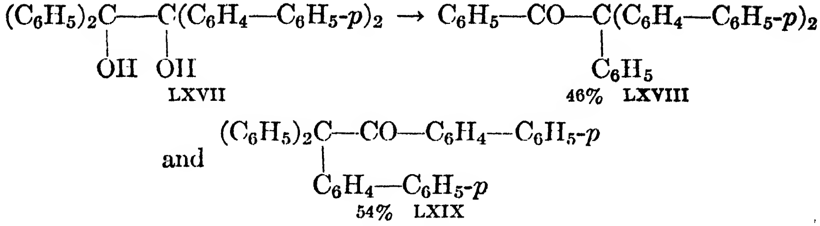
[31] W. E. Bachmann and H. R. Steinberger, *J. Am. Chem. Soc.* **56**, 170 (1934). See also H. Adkins in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 846 f., 2nd ed., 1943, Volume I, pages 1068 ff.



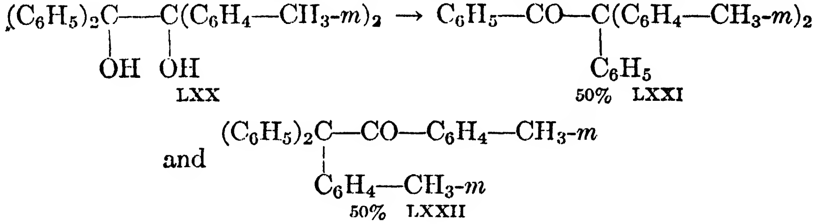
$$(C_6H_5)_2\underset{\displaystyle OH}{C}-\underset{\displaystyle OH}{C}(C_6H_4-C_6H_5\text{-}p)_2 \rightarrow C_6H_5-CO-\underset{\displaystyle C_6H_5}{C}(C_6H_4-C_6H_5\text{-}p)_2$$

LXVII 46% LXVIII

$$\text{and}\quad (C_6H_5)_2\underset{\displaystyle C_6H_4-C_6H_5\text{-}p}{C}-CO-C_6H_4-C_6H_5\text{-}p$$

54% LXIX

biphenylylacetophenone, LXVIII, resulting from migration of a phenyl group; and of 54 per cent *p*,α,α-triphenyl-α-*p*-biphenylylacetophenone, LXIX, resulting from migration of a *p*-biphenylyl group. The migratory aptitudes of the phenyl and *p*-biphenylyl groups in an unsymmetrical pinacol of type LXVI can therefore be considered to be in the ratio of 46:54, or of 1.00:1.18. As was mentioned above, these relative migratory aptitudes can be taken here and below to correspond inversely to the relative abilities of the groups in question to facilitate the ionization of the adjacent hydroxyl group. If the migratory aptitude of the phenyl group is by definition assigned the value 1.00, that of the *p*-biphenylyl group is then 1.18. Similarly, from the fact that 1,1-diphenyl-2,2-di-*m*-tolylethylene glycol, LXX, gives equal quantities of the two



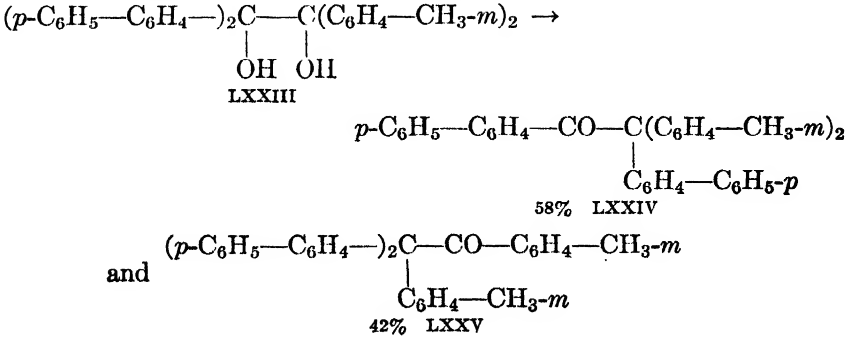
$$(C_6H_5)_2\underset{\displaystyle OH}{C}-\underset{\displaystyle OH}{C}(C_6H_4-CH_3\text{-}m)_2 \rightarrow C_6H_5-CO-\underset{\displaystyle C_6H_5}{C}(C_6H_4-CH_3\text{-}m)_2$$

LXX 50% LXXI

$$\text{and}\quad (C_6H_5)_2\underset{\displaystyle C_6H_4-CH_3\text{-}m}{C}-CO-C_6H_4-CH_3\text{-}m$$

50% LXXII

possible pinacolones, LXXI and LXXII, the migratory aptitude of the *m*-tolyl group is seen to be equal to that of the phenyl group, and so to have the value 1.00. Consequently, in 1,1-di-*p*-biphenylyl-2,2-di-*m*-tolylethylene glycol, LXXIII, the ratio of the migratory aptitudes of



$$(p\text{-}C_6H_5-C_6H_4-)_2\underset{\displaystyle OH}{C}-\underset{\displaystyle OH}{C}(C_6H_4-CH_3\text{-}m)_2 \rightarrow$$

LXXIII

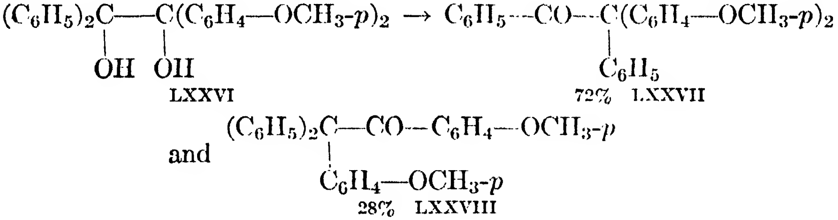
$$p\text{-}C_6H_5-C_6H_4-CO-\underset{\displaystyle C_6H_4-C_6H_5\text{-}p}{C}(C_6H_4-CH_3\text{-}m)_2$$

58% LXXIV

$$\text{and}\quad (p\text{-}C_6H_5-C_6H_4-)_2\underset{\displaystyle C_6H_4-CH_3\text{-}m}{C}-CO-C_6H_4-CH_3\text{-}m$$

42% LXXV

the *p*-biphenylyl and *m*-tolyl groups is 1.18:1.00; hence, the ratio of the amounts of the two ketones LXXIV and LXXV in the rearrangement product can be predicted to be 1.18:1.00 or 54:46. The observed ratio of 58:42 is in fairly good agreement with this predicted value. The agreement is, however, not always so satisfactory. Thus, from the fact that 1,1-diphenyl-2,2-di-*p*-anisylethylene glycol, LXXVI, gives 72 per



$$(C_6H_5)_2\underset{\mathrm{OH}}{C}-\underset{\mathrm{OH}}{C}(C_6H_4-OCH_3\text{-}p)_2 \rightarrow C_6H_5-CO-\underset{C_6H_5}{C}(C_6H_4-OCH_3\text{-}p)_2$$

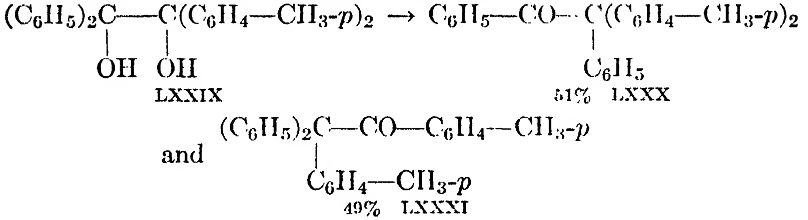
LXXVI

72% LXXVII

$$\text{and}\quad (C_6H_5)_2\underset{C_6H_4-OCH_3\text{-}p}{C}-CO-C_6H_4-OCH_3\text{-}p$$

28% LXXVIII

cent of the ketone LXXVII, in which a phenyl group has migrated, and 28 per cent of the ketone LXXVIII, in which a *p*-anisyl group has migrated, the migratory aptitude of the *p*-anisyl group is seen to be 28/72 or 0.39; and from the further fact that 1,1-diphenyl-2,2-di-*p*-tolylethylene glycol, LXXIX, gives 51 per cent of the ketone LXXX, in



$$(C_6H_5)_2\underset{\mathrm{OH}}{C}-\underset{\mathrm{OH}}{C}(C_6H_4-CH_3\text{-}p)_2 \rightarrow C_6H_5-CO-\underset{C_6H_5}{C}(C_6H_4-CH_3\text{-}p)_2$$

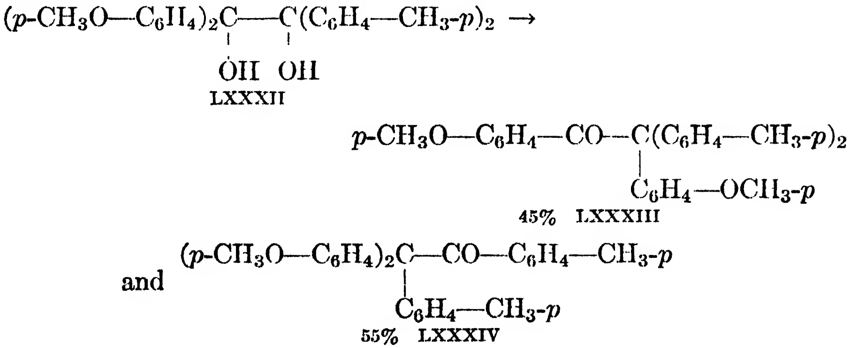
LXXIX

51% LXXX

$$\text{and}\quad (C_6H_5)_2\underset{C_6H_4-CH_3\text{-}p}{C}-CO-C_6H_4-CH_3\text{-}p$$

49% LXXXI

which a phenyl group has migrated, and 49 per cent of the ketone LXXXI, in which a *p*-tolyl group has migrated, the migratory aptitude of the *p*-tolyl group is seen to be 49/51 or 0.96. Consequently, the prediction can be made that 1,1-di-*p*-anisyl-2,2-di-*p*-tolylethylene glycol, LXXXII, should give the ketones LXXXIII and LXXXIV, where



$$(p\text{-}CH_3O-C_6H_4)_2\underset{\mathrm{OH}}{C}-\underset{\mathrm{OH}}{C}(C_6H_4-CH_3\text{-}p)_2 \rightarrow$$

LXXXII

$$p\text{-}CH_3O-C_6H_4-CO-\underset{C_6H_4-OCH_3\text{-}p}{C}(C_6H_4-CH_3\text{-}p)_2$$

45% LXXXIII

$$\text{and}\quad (p\text{-}CH_3O-C_6H_4)_2\underset{C_6H_4-CH_3\text{-}p}{C}-CO-C_6H_4-CH_3\text{-}p$$

55% LXXXIV

the *p*-anisyl and *p*-tolyl groups, respectively, have migrated, in the ratio of 0.39:0.96 or of 29:71, so that the product of the rearrangement should be 29 per cent LXXXIII and 71 per cent LXXXIV. Here the prediction is in rather poor agreement with experiment, since the product has been found actually to be 45 per cent LXXXIII and 55 per cent LXXXIV. These two examples, which have been discussed in some detail, represent approximately the extent of agreement between calculated and observed compositions of products in the rather limited number of rearrangements (of aromatic unsymmetrical pinacols, LXVI) for which data are available. In the second column of Table 12·1 are listed the migratory aptitudes of the various aryl groups that have been studied. It is to be understood that these values may be used only with the unsymmetrical pinacols of type LXVI, with which the migratory aptitudes are determined solely by the extents to which the corresponding groups facilitate (or, rather, *fail* to facilitate) the loss of hydroxide ions from the adjacent carbon atoms (see above); it is to be understood also that, in view of what has already been said regarding the accuracy of the calculated compositions, the treatment based upon these values can, at best, be expected merely to suggest the correct orders of magnitude, and not to give the precise values, of the yields of the two isomeric ketones obtained in any given reaction.

The sensitivity of the migratory aptitudes of the various aryl groups to apparently minor changes in structure is shown by the last column of Table 12·1, in which are listed the values of the migratory aptitudes that

TABLE 12·1

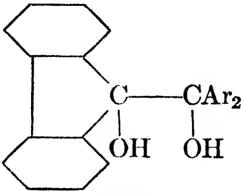
MIGRATORY APTITUDES IN UNSYMMETRICAL AROMATIC PINACOLS $Ar_2C(OH)—C(OH)Ar'_2$ [31]

Aryl Group	*Migratory Aptitude* I [a]	II [b]
p-Biphenylyl	1.18	....
Phenyl	1.00	1.00
m-Tolyl	1.00	0.33
p-Tolyl	0.96	0.046
p-Chlorophenyl	0.75	....
p-Phenetyl (*p*-$C_2H_5—O—C_6H_4$)	0.49	0.012
p-Anisyl (*p*-$CH_3—O—C_6H_4$)	0.39	0.006
p-Fluorophenyl	0.099	....
Biphenylene (*o,o'*-$C_6H_4—C_6H_4$)	....	0.31

[a] The values in this column apply to those unsymmetrical pinacols in which neither Ar_2 nor Ar'_2 represents the bivalent biphenylene group.

[b] The values in this column apply to those unsymmetrical pinacols in which either Ar_2 or Ar'_2 represents the bivalent biphenylene group.

are exhibited by some of the same groups as before, when these groups are present in pinacols of the type LXXXV, containing the so-called *biphenylene* group. As before, the phenyl group is here arbitrarily assigned the value 1.00. Although the pinacols of this second group are still unsymmetrical ones, and although they thus appear to be just like those of the first group, the relative migratory aptitudes are seen to be entirely different. The order of decreasing magnitude is the same in the two series (so far as such a comparison is permitted by the rather small number of data), but the extent of the variation is much greater in the second series than in the first. The reason for this striking difference is not known. The various migratory aptitudes in the biphenylene pinacols, LXXXV, cannot be checked against one another for internal consistency, in the way in which those of the pinacols of type LXVI can be (see above), since no pinacol of the former type can contain more than one kind of aromatic group in addition to the biphenylene group that is necessarily always present. (Pinacols with substituents in the biphenylene group have not been studied in the manner described.)



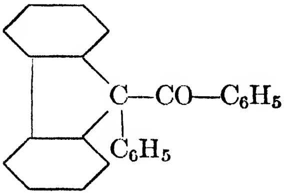
LXXXV

It will be of interest now to consider the extent to which the migratory aptitudes of the various groups listed in Table 12·1 can be correlated with other properties of these groups. From what has been said above regarding the inverse relationship between, on the one hand, the migratory aptitudes in unsymmetrical pinacols of the type LXVI or LXXXV and, on the other hand, the stabilities of the corresponding intermediate cations, it might be anticipated that the replacement of a phenyl group in triphenylcarbinol, XI, by a different aromatic group with lower migratory aptitude would lead to an increase in the stability of the derived triarylmethyl cation, LXXXVI; and conversely, that the replacement of a phenyl group in the carbinol by a different group of higher migratory aptitude would lead to a decrease in the stability of the derived cation. It appears, however, that the expected correlation does not exist. Thus, although the *p*-anisyl group *p*-CH_3—O—C_6H_4, which has a low migratory aptitude, does indeed give rise to relatively stable

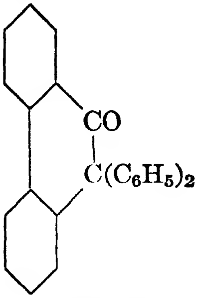
$(C_6H_5)_3COH$
XI

$(C_6H_5)_2C^+$—Ar
LXXXVI

triarylmethyl cations,[32] the *p*-biphenylyl group *p*-C_6H_5—C_6H_4, which has a high migratory aptitude, also gives rise to relatively stable cations.[32] Perhaps the most striking discrepancy is provided by the behavior of diphenylbiphenyleneethylene glycol (LXXXV, with Ar equal to C_6H_5), from which the two ketones LXXXVII and LXXXVIII are

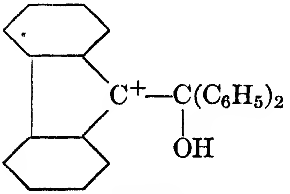


LXXXVII

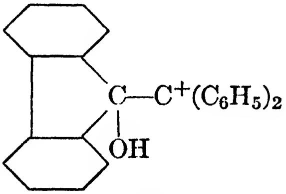


LXXXVIII

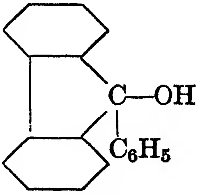
obtained in the ratio of approximately 3:1 (more precisely, 1.00:0.31, see Table 12·1). It appears necessary to suppose, therefore, that the intermediate cation LXXXIX is formed in preference to the ion XC,



LXXXIX



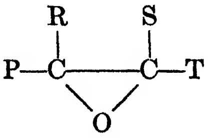
XC



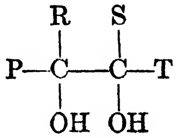
XCI

even though the former would be expected to be much the less stable, inasmuch as 9-phenylfluorenol, XCI, is known to form a halochromic salt with strong acids much less readily than triphenylcarbinol, XI, does.[32] Apparently, therefore, the theory is not at present sufficiently refined to account for the relatively small differences among the various aromatic groups.

In the rearrangement of an ethylene oxide with the general structure XCII, just as in that of the corresponding pinacol, XCIII, there is a

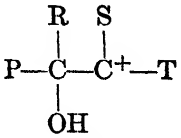


XCII



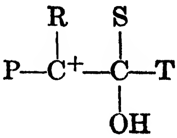
$$P-\underset{OH}{\overset{R}{C}}-\underset{OH}{\overset{S}{C}}-T$$

XCIII



$$P-\underset{OH}{\overset{R}{C}}-\overset{S}{C}^{+}-T$$

XCIV



$$P-\overset{R}{C}^{+}-\underset{OH}{\overset{S}{C}}-T$$

XCV

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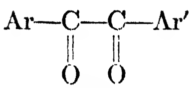
[32] Cf. K. Ziegler and E. Boye, *Ann.* **458**, 229 (1927).

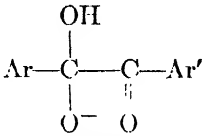
possibility that either one of the two intermediate ions, XCIV or XCV, may be formed. (Cf. pages 494 f.) Although this further type of reaction has not been studied as thoroughly as has the pinacol rearrangement proper, the rule appears to be justified that, in at least most instances, an ethylene oxide leads to the same final product, or mixture of products, as does the pinacol from which it is derived. Consequently, it may be assumed that the oxide, XCII, and the related glycol, XCIII, ordinarily give rise to the same intermediate cation (either XCIV or XCV).

The benzilic acid rearrangement also is subject to some ambiguity, since an unsymmetrical benzil like XCVI could be imagined to give rise



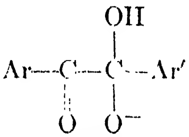
$$\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}Ar'}$$

XCVI



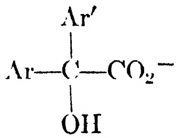
$$\mathrm{Ar{-}\overset{\overset{OH}{|}}{\underset{\underset{O^-}{|}}{C}}{-}\underset{\underset{O}{\|}}{C}{-}Ar'}$$

XCVII



$$\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{OH}{|}}{\underset{\underset{O^-}{|}}{C}}{-}Ar'}$$

XCVIII

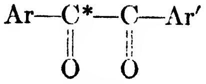


$$\mathrm{Ar{-}\overset{\overset{Ar'}{|}}{\underset{\underset{OH}{|}}{C}}{-}CO_2^-}$$

XCIX

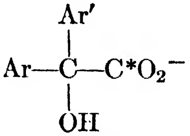
to either one of the two intermediate anions, XCVII and XCVIII. (See equation 12·51, page 483.) It is to be noted, however, that, no matter which intermediate is formed, the same substituted benzilate ion, XCIX, must result. The problem of migratory aptitudes is, therefore, not involved.

It is nevertheless of interest that, although the question whether the benzilic acid rearrangement proceeds through the intermediate anion XCVII or XCVIII cannot be answered by the usual methods of organic chemistry, it could be answered with the use of isotopic tracers. Thus, if the carbon atom designated by the asterisk in structure XCVI*a* were



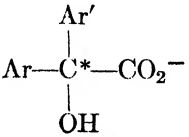
$$\mathrm{Ar{-}\underset{\underset{O}{\|}}{C^*}{-}\underset{\underset{O}{\|}}{C}{-}Ar'}$$

XCVI*a*



$$\mathrm{Ar{-}\overset{\overset{Ar'}{|}}{\underset{\underset{OH}{|}}{C}}{-}C^*O_2^-}$$

XCIX*a*



$$\mathrm{Ar{-}\overset{\overset{Ar'}{|}}{\underset{\underset{OH}{|}}{C^*}}{-}CO_2^-}$$

XCIX*b*

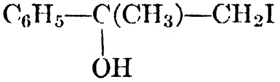
C^{13} or the radioactive C^{14}, the two different products XCIX*a* and XCIX*b* would be experimentally distinguishable. Such experiments have never been made. In the at least superficially analogous rearrangement of phenylglyoxal, C, to the mandelate ion, CI, however, the hydrogen

$\mathrm{C_6H_5{-}CO{-}CHO}$
C

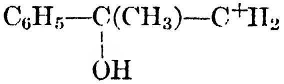
$\mathrm{C_6H_5{-}CHOH{-}CO_2^-}$
CI

atom, rather than the phenyl group, has in this way been shown to migrate.[33]

Most of the remaining types of 1,2-shift differ from the rearrangements of pinacols, of ethylene oxides, and of benzils in that they are not subject to any ambiguity with respect to the identity of the intermediate with the open sextet. This circumstance results from the fact that the molecules which undergo such rearrangements ordinarily have only one atom or group (and not two) which could be expected to break away readily under the conditions employed. Thus, in the reaction of the iodohydrin, CII, with mercuric oxide, the mercuric ion may be presumed


$C_6H_5\text{—}\underset{\underset{\text{OH}}{|}}{C}(CH_3)\text{—}CH_2I$

CII


$C_6H_5\text{—}\underset{\underset{\text{OH}}{|}}{C}(CH_3)\text{—}C^+H_2$

CIII

to have a specific affinity for the iodine atom, but not for the hydroxyl group or for any atom of this group; consequently, the intermediate must be CIII rather than CIV. The fact that the final product is phenyl-

$C_6H_5\text{—}C^+(CH_3)\text{—}CH_2I$

CIV

acetone, CV, and not α-phenylpropionaldehyde, CVI (see page 453), is

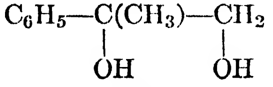
$C_6H_5\text{—}CH_2\text{—}CO\text{—}CH_3$

CV

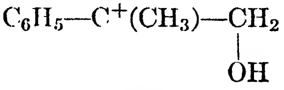
$C_6H_5\text{—}CH(CH_3)\text{—}CHO$

CVI

in agreement with this interpretation. On the other hand, with the corresponding *glycol*, CVII, the stabilizing effects of the phenyl and methyl


$C_6H_5\text{—}\underset{\underset{\text{OH}}{|}}{C}(CH_3)\text{—}\underset{\underset{\text{OH}}{|}}{CH_2}$

CVII


$C_6H_5\text{—}C^+(CH_3)\text{—}\underset{\underset{\text{OH}}{|}}{CH_2}$

CVIII

groups ensure that the different cation CVIII is formed, instead of CIII, and hence that, when this glycol is rearranged, the product obtained is α-phenylpropionaldehyde, CVI.

In the retropinacol (or Wagner-Meerwein) rearrangement, the original molecule usually possesses only a single halogen atom or hydroxyl group that can break away as an anion; consequently, only a single intermediate cation is possible. For example, neopentyl iodide, CIX, can give rise only to the intermediate CX; and isoborneol, CXI, can give rise only to the intermediate CXII. Similarly, in the Demjanow re-

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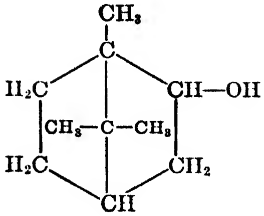
[33] W. v. E. Doering, T. I. Taylor, and E. F. Schoenewaldt, *J. Am. Chem. Soc.* **70**, 455 (1948); O. K. Neville, *ibid.* **70**, 3499 (1948).

$(CH_3)_3C—CH_2I$

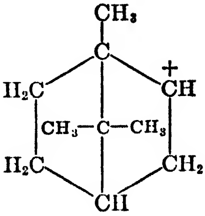
CIX

$(CH_3)_3C—\overset{+}{C}H_2$

CX

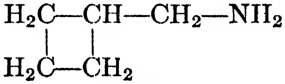


CXI

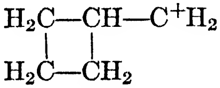


CXII

arrangement, the intermediate with the open sextet is uniquely determined if the apparently necessary assumption is made that the carbon atom to which the amino group was originally joined becomes the seat of the open sextet in the intermediate. Thus, α-cyclobutylmethylamine, CXIII, can give rise only to the intermediate CXIV. Moreover,

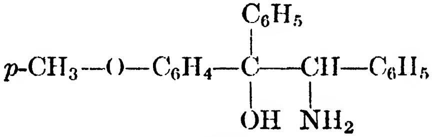


CXIII



CXIV

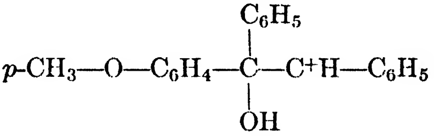
and for the same reason, the amino alcohol CXV can give rise only to the



$$p\text{-}CH_3—O—C_6H_4—\underset{OH}{\overset{C_6H_5}{C}}—\underset{NH_2}{CH}—C_6H_5$$

CXV

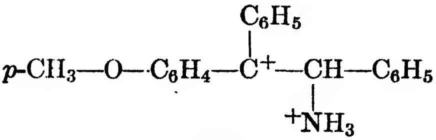
intermediate CXVI when it is treated with nitrous acid, although it is



$$p\text{-}CH_3—O—C_6H_4—\underset{OH}{\overset{C_6H_5}{C}}—C^+H—C_6H_5$$

CXVI

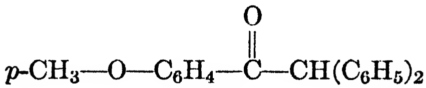
more likely to give rise instead to the alternative intermediate CXVII



$$p\text{-}CH_3—O—C_6H_4—\overset{C_6H_5}{C^+}—\underset{^+NH_3}{CH}—C_6H_5$$

CXVII

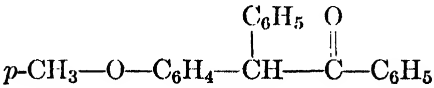
when treated with a strong acid like hydrochloric acid, toward which it would behave in the manner characteristic of a pinacol. This circumstance doubtless contains the explanation of the fact, noted on page 473, that the amino alcohol CXV is transformed into the ketone CXVIII



$$p\text{-}CH_3\text{—}O\text{—}C_6H_4\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}CH(C_6H_5)_2$$

CXVIII

(and so must have passed through the intermediate CXVI) when it is treated with nitrous acid; but is transformed instead into the different ketone CXIX (and so must have passed through the different inter-

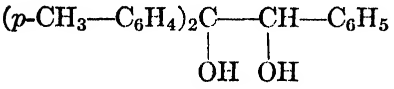


$$p\text{-}CH_3\text{—}O\text{—}C_6H_4\text{—}\overset{\overset{\displaystyle C_6H_5}{|}}{CH}\text{——}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}C_6H_5$$

CXIX

mediate CXVII) when it is treated with hydrogen chloride. No further discussion of the remaining 1,2-shifts should now be required, since these reactions differ in no significant respect from those already discussed. As was noted at the beginning of the preceding paragraph, most of these other rearrangements permit no ambiguity.

12·8 Intrinsic Migratory Aptitudes. Attention may now be turned to the second of the two factors that determine migratory aptitudes, namely, to the factor which operates only after the intermediates with the open sextets have already been formed, and which may be referred to as the *intrinsic* tendency of the atoms or groups concerned to change their points of attachment. Unfortunately, however, there are no generally valid rules which govern all the 1,2-shifts. In fact, even the gross distinction among aryl groups, alkyl groups, and hydrogen atoms corresponds to no reliable differences in migratory aptitudes. In possibly the majority of rearrangements, once the intermediates with the open sextets have been formed, hydrogen atoms migrate in preference to aryl groups, and aryl groups in turn migrate in preference to alkyl groups. This generalization cannot, however, be relied upon, since numerous exceptions to it are known. For example, the pinacol rearrangement of 1,1-di-*p*-tolyl-2-phenylethylene glycol, I, gives α,α-di-



$$(p\text{-}CH_3\text{—}C_6H_4)_2\underset{\underset{\displaystyle OH}{|}}{C}\text{——}\underset{\underset{\displaystyle OH}{|}}{CH}\text{—}C_6H_5$$

I

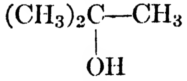
$$(p\text{-}CH_3\text{—}C_6H_4)_2CH\text{—}CO\text{—}C_6H_5$$

II

p-tolylacetophenone, II, with migration of a hydrogen atom in preference to a phenyl group; the Demjanow rearrangement of isobutyl amine, III, gives *tert*-butyl alcohol, IV, with migration of a hydrogen atom in

$(CH_3)_2CH—CH_2—NH_2$

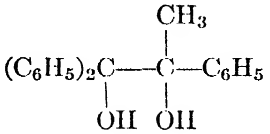
III



$$(CH_3)_2\underset{\underset{\displaystyle OH}{|}}{C}—CH_3$$

IV

preference to a methyl group; and the pinacol rearrangement of 1,1,2-triphenylpropane-1,2-diol, V, gives 1,1,1-triphenylacetone, VI, with



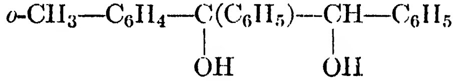
$$(C_6H_5)_2\underset{\underset{\displaystyle OH}{|}}{C}—\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}—C_6H_5$$

V

$(C_6H_5)_3C—CO—CH_3$

VI

migration of a phenyl group in preference to a methyl group. On the other hand, the rearrangement of 1,2-diphenyl-1-*o*-tolylethylene glycol, VII, gives predominantly *o*-tolyldiphenylacetaldehyde, VIII, with migration of a phenyl group in preference to a hydrogen atom; the Demjanow rearrangement of α-cyclopropylmethylamine, IX, gives cyclobutanol,

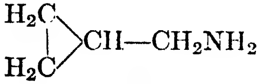


$$o\text{-}CH_3—C_6H_4—\underset{\underset{\displaystyle OH}{|}}{C}(C_6H_5)—\underset{\underset{\displaystyle OH}{|}}{C}H—C_6H_5$$

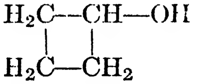
VII

$o\text{-}CH_3—C_6H_4—C(C_6H_5)_2—CHO$

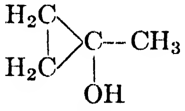
VIII



IX

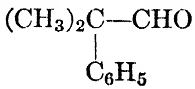


X



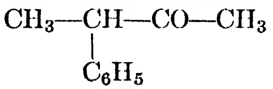
XI

X, with alteration in the size of the ring (i.e., with migration of what may be considered an alkyl substituent), rather than 1-methylcyclopropanol, XI (i.e., rather than with migration of a hydrogen atom); and the rearrangement of dimethylphenylacetaldehyde, XII, gives 2-phenylbutane-3-one, XIII, with migration of a methyl group in preference to a phenyl group. Since inconsistencies of the types described in these two sets of reactions are not at all uncommon, it is impossible to give any simple, and at the same time completely general, rules for the intrinsic migratory tendencies of atoms and groups.



$$(CH_3)_2\underset{\underset{\displaystyle C_6H_5}{|}}{C}—CHO$$

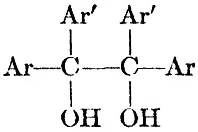
XII



$$CH_3—\underset{\underset{\displaystyle C_6H_5}{|}}{C}H—CO—CH_3$$

XIII

In spite of the difficulties just referred to, however, considerable success has been achieved with the so-called *symmetrical* pinacols of general structure XIV, in which Ar and Ar′ represent two different aryl



$$\begin{array}{ccc} & \mathrm{Ar'} \quad \mathrm{Ar'} & \\ & | \qquad | & \\ \mathrm{Ar}- & \mathrm{C}-\!\!-\mathrm{C} & -\mathrm{Ar} \\ & | \qquad | & \\ & \mathrm{OH} \quad \mathrm{OH} & \end{array}$$

XIV

groups.[34] For a number of such groups, the migratory aptitudes listed in Table 12·2 have been assigned in a way that is completely analogous

TABLE 12·2

Migratory Aptitudes in Symmetrical Aromatic Pinacols $\mathrm{ArAr'C(OH)—C(OH)ArAr'}$[34]

Aryl Group	*Migratory Aptitude*	*Aryl Group*	*Migratory Aptitude*
p-Anisyl	500	*p*-Iodophenyl	1.0
p-Phenetyl	500	*p*-Bromophenyl	0.7
p-Tolyl	15.7	*p*-Chlorophenyl	0.7
p-Biphenylyl	11.5	*o*-Anisyl	0.3
p-Isopropylphenyl	9	*m*-Bromophenyl	0.0
p-Ethylphenyl	5	*m*-Chlorophenyl	0.0
m-Tolyl	1.95	*o*-Bromophenyl	0.0
m-Anisyl	1.6	*o*-Chlorophenyl	0.0
Phenyl	1.00		

to the one discussed in Section 12·7 in connection with the *un*symmetrical pinacols. (See also below.) As before, the values given here to the various groups are based upon the arbitrary assignment of the value 1.00 to the phenyl group. As might have been anticipated, the migratory aptitudes listed in Table 12·2 for the symmetrical pinacols are not at all similar to those listed in Table 12·1 for the unsymmetrical pinacols; in fact, the range in migratory aptitudes is much greater for the symmetrical pinacols than for the unsymmetrical ones, and the order of increasing migratory aptitude in either table is approximately the reverse of that in the other table. The reason for this difference between the two sets of migratory aptitudes is, of course, that in the two types of pinacol the values for any given group are determined by entirely different factors. Thus, as was mentioned above (see Section 12·7), the so-called migratory aptitude of a group present in an unsymmetrical pinacol is a measure of its inability to facilitate the departure of an adjacent hydroxide ion; whereas, on the other hand, the migratory aptitude of the same group in a symmetrical pinacol, XIV, is instead a

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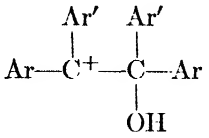
[34] W. E. Bachmann and J. W. Ferguson, *J. Am. Chem. Soc.* **56**, 2081 (1934). See also H. Adkins in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed. 1938, Volume I, pages 844 ff., 2nd ed., 1943, Volume I, pages 1066 ff.

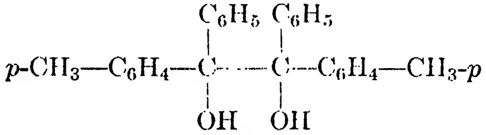
measure of its intrinsic tendency to migrate since, with such a pinacol, only a single intermediate cation, XV, is possible, no matter which hydroxyl group is removed in the first step of the rearrangement.



$$\begin{array}{ccccc} & \mathrm{Ar'} & & \mathrm{Ar'} & \\ & | & & | & \\ \mathrm{Ar}— & \mathrm{C}^+ & — & \mathrm{C} & —\mathrm{Ar} \\ & & & | & \\ & & & \mathrm{OH} & \end{array}$$

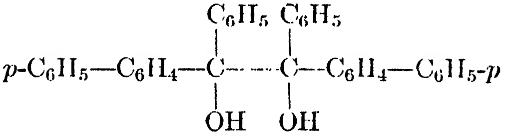
XV

Rather unexpectedly, perhaps, in view of the inconsistencies mentioned above, the migratory aptitudes given in Table 12·2 have been found to permit fairly accurate predictions of the compositions of the mixtures of ketones that are obtained by rearrangement of symmetrical aromatic pinacols. For example, the rearrangements of 1,2-di-*p*-tolyl-1,2-diphenylethylene glycol, XVI, and of 1,2-di-*p*-biphenylyl-1,2-diphenylethylene glycol, XVII, lead to the values of 15.7 and 11.5 for the *p*-tolyl and *p*-biphenylyl groups, respectively. (See Table 12·2.)



$$\begin{array}{ccccc} & \mathrm{C_6H_5} & & \mathrm{C_6H_5} & \\ & | & & | & \\ p\text{-}\mathrm{CH_3—C_6H_4}— & \mathrm{C} & — & \mathrm{C} & —\mathrm{C_6H_4—CH_3}\text{-}p \\ & | & & | & \\ & \mathrm{OH} & & \mathrm{OH} & \end{array}$$

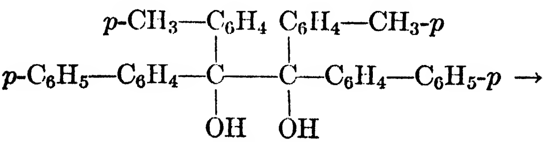
XVI



$$\begin{array}{ccccc} & \mathrm{C_6H_5} & & \mathrm{C_6H_5} & \\ & | & & | & \\ p\text{-}\mathrm{C_6H_5—C_6H_4}— & \mathrm{C} & — & \mathrm{C} & —\mathrm{C_6H_4—C_6H_5}\text{-}p \\ & | & & | & \\ & \mathrm{OH} & & \mathrm{OH} & \end{array}$$

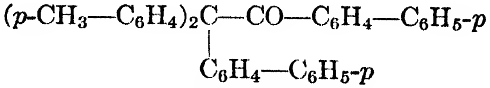
XVII

With the use of these values, the prediction can be made that the rearrangement of 1,2-di-*p*-tolyl-1,2-di-*p*-biphenylylethylene glycol, XVIII, should give the two ketones XIX and XX in the ratio of 15.7:11.5, or of



$$\begin{array}{ccccc} & p\text{-}\mathrm{CH_3—C_6H_4} & & \mathrm{C_6H_4—CH_3}\text{-}p & \\ & | & & | & \\ p\text{-}\mathrm{C_6H_5—C_6H_4}— & \mathrm{C} & — & \mathrm{C} & —\mathrm{C_6H_4—C_6H_5}\text{-}p \rightarrow \\ & | & & | & \\ & \mathrm{OH} & & \mathrm{OH} & \end{array}$$

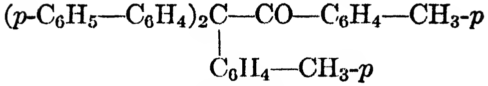
XVIII



$$\begin{array}{l} (p\text{-}\mathrm{CH_3—C_6H_4})_2\mathrm{C—CO—C_6H_4—C_6H_5}\text{-}p \\ \qquad\qquad\qquad\;\, | \\ \qquad\qquad\qquad\mathrm{C_6H_4—C_6H_5}\text{-}p \end{array}$$

57% XIX

and



$$(p\text{-}C_6H_5\text{—}C_6H_4)_2\underset{\displaystyle C_6H_4\text{—}CH_3\text{-}p}{\underset{|}{C}}\text{—}CO\text{—}C_6H_4\text{—}CH_3\text{-}p$$

43% XX

58:42. When the experiment was carried out, the product was found to consist of 57 per cent, XIX, and of 43 per cent, XX. Although the agreement is not always quite so good as in this example, entirely satisfactory results have been obtained in a number of other such rearrangements, and serious disagreements seem never to have been encountered. (However, see below.)

Also rather unexpectedly, the observed migratory aptitudes of the various aryl groups can be correlated in a fairly satisfactory manner with other properties of the same groups. Thus, inspection of the figures in Table 12·2 shows that (with the exception of the *ortho*-substituted groups, with which steric effects of the type considered in Section 9·7 might be expected to be large and unpredictable) the migratory aptitudes increase in the same order as do the susceptibilities of the corresponding benzene derivatives to an attack by one of the familiar substituting reagents like nitric acid or a halogen. For example, nitration takes place at a *meta* position of toluene somewhat more rapidly than it does at any one of the six equivalent positions of benzene; and it takes place at the *para* position of toluene much more rapidly still.[35] Correspondingly, the migratory aptitude of the *m*-tolyl group is somewhat greater than is that of the phenyl group, and that of the *p*-tolyl group is much larger still. Similarly, nitration takes place at the *para* position of chlorobenzene somewhat more slowly than it does at any position in benzene, and it takes place at the *meta* position of chlorobenzene much more slowly still. Correspondingly, the migratory aptitude of the *p*-chlorophenyl group is somewhat smaller than is that of the phenyl group, and that of the *m*-chlorophenyl group is much smaller still. And finally, the extreme reactivity of anisole $CH_3\text{—}O\text{—}C_6H_5$ toward nitric acid or the like, at the *para* position, is paralleled by the exceptionally large migratory aptitude of the *p*-anisyl group $p\text{-}CH_3\text{—}O\text{—}C_6H_4$. This correlation between migratory aptitude and speed of substitution is hardly surprising since the migration (i.e., the second of the three steps involved in the Whitmore mechanism, see pages 476 f.) can itself be thought of as a substitution reaction in which a carbon atom joined to the benzene ring is replaced by an adjacent atom. Moreover, the usual rules of orientation which apply to nitration, halogenation, and the like might be expected to apply here also since, in all these different reactions, the

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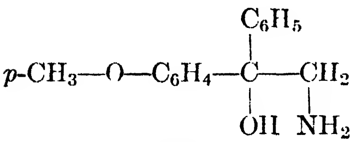
[35] C. K. Ingold, A. Lapworth, E. Rothstein, and D. Ward, *J. Chem. Soc.* **1931,** 1959.

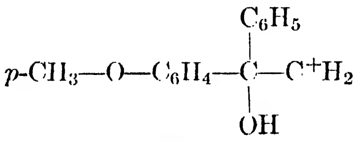
attack upon the benzene ring is considered to be made by a reagent with an open sextet.[36] Unfortunately, however, no similar treatment is possible for the migratory aptitudes of alkyl groups, as compared either with one another or with aryl groups or hydrogen atoms. (See also the following paragraph.)

Although, as was mentioned above, the migratory aptitudes listed in Table 12·2 give a rather good account of the products resulting from the rearrangements of symmetrical pinacols, these migratory aptitudes cannot be safely applied to all rearrangements of even closely related substances. For example, the action of nitrous acid upon the amino alcohol, XXI, would be expected to give first the intermediate XXII



$$p\text{-}CH_3{-}O{-}C_6H_4{-}\underset{OH}{\overset{C_6H_5}{C}}{-}\underset{NH_2}{CH_2}$$

XXI



$$p\text{-}CH_3{-}O{-}C_6H_4{-}\underset{OH}{\overset{C_6H_5}{C}}{-}C^+H_2$$

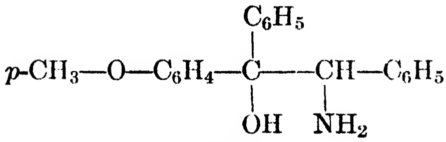
XXII

and then, in view of the great intrinsic migratory aptitude of the *p*-anisyl group, the ketone XXIII. This expectation is in agreement with

$$C_6H_5{-}CO{-}CH_2{-}C_6H_4{-}O{-}CH_3\text{-}p$$

XXIII

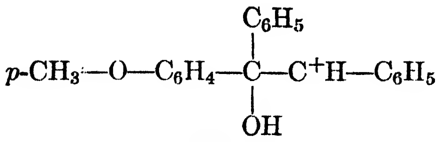
experiment.[37] Similarly, the closely related amino alcohol, XXIV, would



$$p\text{-}CH_3{-}O{-}C_6H_4{-}\underset{OH}{\overset{C_6H_5}{C}}{-}\underset{NH_2}{CH}{-}C_6H_5$$

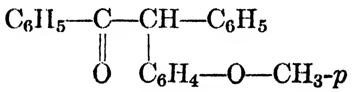
XXIV

be expected to give the intermediate XXV and then, again with migra-



$$p\text{-}CH_3{-}O{-}C_6H_4{-}\underset{OH}{\overset{C_6H_5}{C}}{-}C^+H{-}C_6H_5$$

XXV



$$C_6H_5{-}\underset{O}{\overset{}{C}}{-}\underset{C_6H_4-O-CH_3\text{-}p}{CH}{-}C_6H_5$$

XXVI

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[36] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 256 ff.

[37] A. Orechow and M. Roger, *Compt. rend.* **180**, 70 (1925).

tion of the *p*-anisyl group, the ketone XXVI. In this instance, however, the expectation is not in agreement with experiment, since the product actually obtained is the isomeric ketone, XXVII.[20] Here apparently

$$p\text{-}CH_3\text{—}O\text{—}C_6H_4\text{—}CO\text{—}CH(C_6H_5)_2$$

XXVII

the phenyl group of the intermediate migrates in preference to the *p*-anisyl group. No explanation of this anomaly can at present be given. The existence of such inconsistencies indeed serves to make even more surprising the success obtained in predicting the courses of the rearrangements of the symmetrical pinacols; and it casts more than a little doubt upon the adequacy of the theoretical interpretation given above for the observed migratory aptitudes of the various aryl groups in the symmetrical pinacols.

In many rearrangements, the problem of relative intrinsic migratory aptitudes does not enter, since the intermediate with the open sextet contains only a single atom or group that could conceivably migrate. This situation is encountered, for example, in the Hofmann, Curtius, and Lossen rearrangements, in which the intermediate, with general structure XXVIII, can be transformed only into the isocyanate, XXIX.

$R\text{—}\dot{C}O\text{—}\ddot{N}\!:$ XXVIII

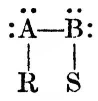
$R\text{—}N\text{=}C\text{=}O$ XXIX

$R\text{—}CO\text{—}CH\!:$ XXX

$R\text{—}CH\text{=}C\text{=}O$ XXXI

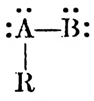
Similarly, the intermediate XXX in the Wolff rearrangement can pass over only into the ketene, XXXI.

12·9 The Stereochemistry of the 1,2-Shifts. According to the Whitmore mechanism, a 1,2-shift occurs in three steps: first (in at least most instances), an atom or group S and its pair of binding electrons are removed from the original substance, I; second, a further atom or group



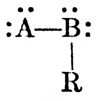
$$\begin{array}{cc} :\ddot{A}\text{—} & \ddot{B}: \\ | & | \\ R & S \end{array}$$

I



$$\begin{array}{cc} :\ddot{A}\text{—} & \ddot{B}: \\ | & \\ R & \end{array}$$

II



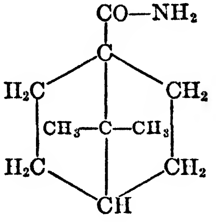
$$\begin{array}{cc} :\ddot{A}\text{—} & \ddot{B}: \\ & | \\ & R \end{array}$$

III

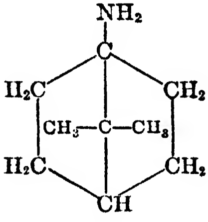
R of the resulting intermediate, II, migrates to the position vacated by S; and, third, the second intermediate, III, thus produced is finally stabilized in some way. (Cf. Section 12·4.) Comparison of structures I and III shows that the sequence of steps is equivalent to a substitution reaction in which the atom or group R replaces S upon the atom B. If B happens to be an asymmetric atom, the question therefore arises whether the substitution under discussion proceeds with a Walden inversion, or with retention of configuration, or with racemization. Moreover, the shift can be regarded equally well as a substitution reaction upon the atom or group R, since the atom A that is joined to R in structures I and II is replaced by B in structure III. Consequently, in those rearrangements in which R is not a single atom but is instead a radical, and in which moreover the particular atom by which R is joined first to A and then to B is asymmetric, the further question arises whether the substitution at this atom of the radical R proceeds with Walden inversion, or with retention of configuration, or with racemization.

It seems now to be generally agreed that, although more or less racemization is frequently observed, there is a marked tendency for inversion at the atom B, but for retention of configuration in the group R. The two sets of evidence which can be advanced in support of these two independent conclusions will be discussed separately in the remainder of this section.

The second of the two questions raised above (namely, the question of inversion, retention, or racemization in the group R) can conveniently be taken up first. Some evidence suggesting that the configuration is retained in the group that migrates has, in fact, already been mentioned in a previous chapter (see page 276), where it was stated that the amide IV undergoes the Hofmann rearrangement normally and



IV



V

gives rise ultimately to the amine V.[38] Since an inversion of configuration in the hydrocarbon radical is here made geometrically impossible by the rigidity of the bridge structure, the fact that the rearrangement occurs at all shows conclusively that an inversion is at least not a necessary feature of the reaction. (See page 276 for a discussion of the significance of an inversion of configuration about an atom which, like the one joined to the carboxamide group in structure IV and to the amino group in structure V, is not asymmetric.) Further evidence pointing to the same conclusion is provided by the fact that, as has been shown in numerous examples in the preceding sections, aromatic groups, such as the phenyl group, with which again no inversion of configuration is geometrically possible, can migrate in most types of 1,2-shift.

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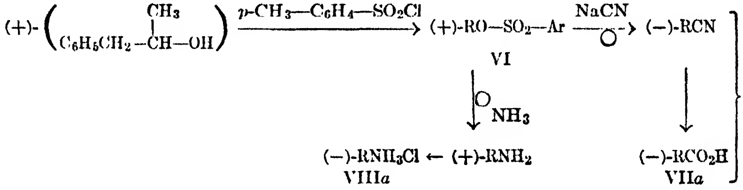
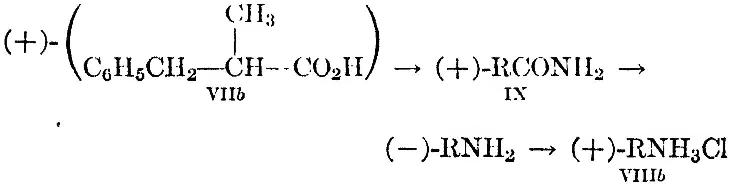
[38] P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.* **61**, 3184 (1939).

It could, of course, be argued that the rearrangement of the particular amide IV, as well as those other 1,2-shifts in which aromatic groups migrate, may be abnormal, and that the possibility of an inversion in the remaining 1,2-shifts, in which analogous geometrical factors are not involved, is not excluded. Completely conclusive evidence has, however, been obtained from a study of several further rearrangements in which comparable geometrical factors are not involved, but in which the configurations are still found to be retained. One such study[39] involves the two sequences of reactions 12·61 and 12·62. From the first of these,[40]



(12·61)



$$(+)\text{-}\left(\begin{matrix}\text{CH}_3\\ |\\ \text{C}_6\text{H}_5\text{CH}_2\text{—CH—CO}_2\text{H}\end{matrix}\right) \rightarrow (+)\text{-RCONH}_2 \rightarrow (-)\text{-RNH}_2 \rightarrow (+)\text{-RNH}_3\text{Cl} \qquad (12\cdot 62)$$

VIIb IX VIIIb

if the reasonable assumption is made that the reactions of the *p*-toluenesulfonic ester, VI, with both cyanide ion and ammonia are accompanied by inversion (see pages 284 f.), the conclusion can be drawn that the configuration of the 1-phenylisopropyl radical R is the same in the levorotatory acid, VII*a*, as in the levorotatory amine hydrochloride, VIII*a*. Consequently the configuration of this radical must be the same in the dextrorotatory acid, VII*b* (reactions 12·62), as in the dextrorotatory amine hydrochloride, VIII*b*. It follows, therefore, that no inversion of configuration could have occurred in the Hofmann rearrangement of the amide IX,[41] since none could have occurred in the reactions by which the amide was made from the parent acid. Moreover, since the acid, VII*b*, can be transformed into the same amine hydrochloride, VIII*b*, by the Lossen[42] and Curtius[43] rearrangements (of the benzoyl derivative, X, of the hydroxamic acid, and of the azide, XI, respectively),

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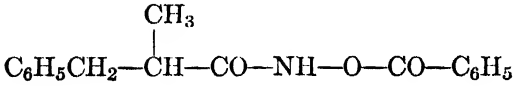
[39] J. Kenyon and D. P. Young, *J. Chem. Soc.* **1941**, 263.

[40] J. Kenyon, H. Phillips, and V. P. Pittman, *J. Chem. Soc.* **1935**, 1072.

[41] E. S. Wallis and S. C. Nagel, *J. Am. Chem. Soc.* **53**, 2787 (1931).

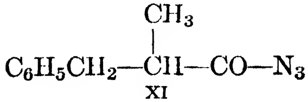
[42] E. S. Wallis and R. D. Dripps, *J. Am. Chem. Soc.* **55**, 1701 (1933).

[43] L. W. Jones and E. S. Wallis, *J. Am. Chem. Soc.* **48**, 169 (1926).



$C_6H_5CH_2—CH(CH_3)—CO—NH—O—CO—C_6H_5$

X

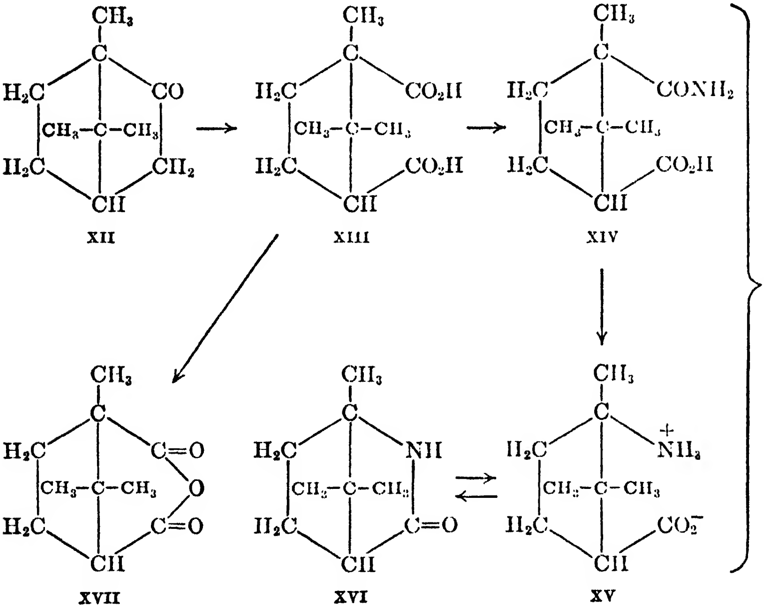


$C_6H_5CH_2—CH(CH_3)—CO—N_3$

XI

as well as by the Hofmann rearrangement, it follows that the configuration is retained also in these other reactions. In none of these reactions is the rearrangement accompanied by any racemization so extensive that it cannot be assumed to have occurred before or after, rather than during, the actual migration.

More conclusive evidence that no inversion of configuration occurs in the migrating group in the Hofmann rearrangement is contained in the series of reactions 12·63.[44] That the two carboxyl groups in camphoric



(12·63)

acid, XIII, are *cis* with respect to each other is shown, first, by the preparation of the substance by the oxidation of camphor, XII, for which only the *cis* configuration is possible (cf. Section 9·5); and, second, by its ready transformation into the anhydride, XVII, for which again only the *cis* configuration is possible. Moreover, the amino acid, XV, resulting from the Hofmann rearrangement of the half-amide, XIV, must also be a *cis* compound in view of its easy conversion into, and regeneration

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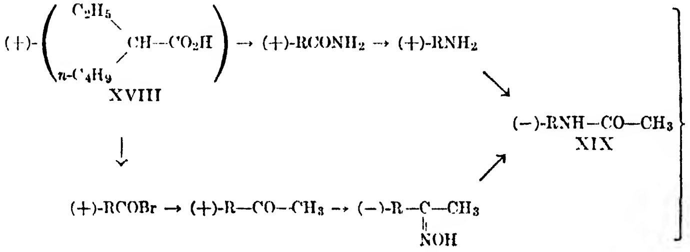
[44] W. A. Noyes, *Am. Chem. J.* **16,** 500 (1894); W. A. Noyes and R. S. Potter, *J. Am. Chem. Soc.* **34,** 1067 (1912); **37,** 189 (1915); W. A. Noyes and L. F. Nickell, *ibid.* **36,** 118 (1914); S. Archer, *ibid.* **62,** 1872 (1940).

from, the lactam, XVI. Consequently, since the configurations of the initial and final compounds in the rearrangement are identical, no inversion can have occurred.

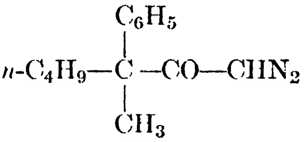
If, on the basis of the above evidence, it is accepted that the Hofmann rearrangement takes place with retention of configuration, the Beckmann rearrangement also can be shown to proceed with retention.[39] In the sequence of reactions 12·64, the (+)-ethyl-*n*-butylacetic acid,



(12·64)

XVIII, is transformed by two different routes into the same (−)-N-3-heptylacetamide, XIX. Consequently, an inversion in the heptyl group must have occurred *both* in the Hofmann rearrangement in the first route from the compound XVIII to the product XIX *and* in the Beckmann rearrangement in the second route; or else *no* inversion occurred in *either* reaction. For the reasons stated above, the second alternative is presumably the correct one.

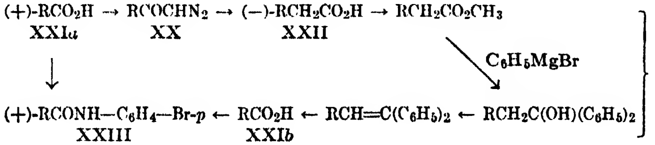
The most conclusive evidence for the retention of the configuration in the migrating group in a 1,2-shift is that derived from a study of the Wolff rearrangement of the optically active diazo ketone of structure (not configuration) XX. The pertinent data[45] are summarized in the



$$n\text{-}C_4H_9-\overset{\displaystyle C_6H_5}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CO-CHN_2$$

XX

sequence of reactions 12·65, in which R represents the 2-phenyl-2-



(12·65)

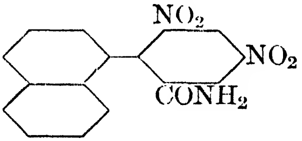
[45] J. F. Lane and E. S. Wallis, *J. Am. Chem. Soc.* **63**, 1674 (1941).

hexyl radical at the left of the carbonyl group in structure XX. In this series of reactions, (+)-α-phenyl-α-methylhexanoic acid, XXI*a*, is transformed by the Arndt-Eistert synthesis (see page 462) into (−)-β-phenyl-β-methylheptanoic acid, XXII, which is then degraded by the so-called Barbier-Wieland degradation to α-phenyl-α-methylhexanoic acid, XXI*b*. The identity of the original and final acids, XXI*a* and XXI*b*, respectively, was shown by a comparison of the properties of the derived *p*-bromoanilides, XXIII. It follows, therefore, that no net inversion has taken place in the series of reactions by which the acid XXI*a* is transformed into the identical acid XXI*b*. Moreover, since the Wolff rearrangement, in which the acid XXII is produced from the diazo ketone XX, is the only step of the entire sequence in which the asymmetric carbon atom is directly affected, and since this reaction is accordingly the only one in which an inversion could have occurred, it follows further that the rearrangement must have taken place with retention of configuration.

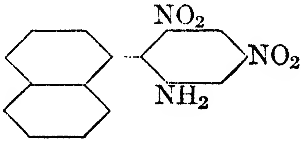
On the basis of the above evidence, it is now generally believed that no Walden inversion ever occurs in the group R which transfers its attachment from the atom A to the adjacent atom B in structures I–III. It is to be noted that, if this assumption is valid, the 1,2-shifts constitute an important class of exceptions to the general rule stated earlier (see page 286) that an inversion occurs in every substitution reaction proceeding in one step.

Although, in accordance with the Whitmore mechanism, a rearrangement of this class is considered to proceed in altogether three steps, the substitution in the group R occurs only in the second one of these steps; it is, accordingly, a one-step process taking place with retention of configuration. (For discussion of the further condition that the displaced group must be leaving while the entering one is coming up, see the last paragraph of this section.)

The fact that the migrating group is ordinarily not racemized to any significant extent in a 1,2-shift suggests rather strongly that this group, in the course of its migration, never breaks completely away from the rest of the molecule. In other words, the group in question has apparently begun to be bonded in some way to the atom to which it is linked in the final product before it has lost all contact with the atom to which it was linked in the original substance. (For a more detailed discussion of this process, see the following section.) If, for example, the radical R of an amide $RCONH_2$ exists free to any extent in the reaction mixture (presumably as the anion $R:^-$), the carbon atom which, in this fragment, is left forming only three covalent bonds would be expected to assume a nearly (if not quite) planar configuration. Consequently, if this atom were originally asymmetric, it should in the ion R:$^-$ pass over readily to the enantiomorphic configuration (if, indeed, it is not actually planar, and hence symmetric); hence, the final product that is isolated should be at least extensively, and perhaps completely, racemized. Against this reasoning, there might be raised the objection that the carbon atom in question, even though it forms only three covalent bonds in the ion R:$^-$, has nevertheless a complete octet of electrons in its valence shell; and therefore that the possibility cannot be definitely excluded that an atom in such a state could maintain its dissymmetric configuration for an appreciable length of time. This alternative interpretation of the lack of racemization can, however, be made highly improbable in the following way. The amide XXIV can be obtained in



XXIV



XXV

optically active form, as a result of a restriction of rotation about the bond between the benzene and the naphthalene rings. (Cf. Sections 6·12 and 6·13.) When the dextrorotatory enantiomorph of this substance is subjected to the Hofmann rearrangement, the resulting amine, XXV, is found to be dextrorotatory and not appreciably racemized.[46] However, if the ion R:$^-$ in this instance had existed as such in the course of the rearrangement, racemization would necessarily have occurred, since the blocking carboxamide group $-CONH_2$, which prevents coplanarity of the rings, and which thus makes possible the optical activity of the amide XXIV, would no longer be present. In this reaction, the question therefore does not arise whether a carbon atom forming only three bonds, but possessing a full octet, can maintain a pyramidal configuration. It appears necessary, in fact, to presume that the migrating group is never without some blocking group, and hence that it is never detached from the remainder of the molecule. The argument would not be altered if the migrating group were assumed to break away, not as an anion R:$^-$, but instead as either a neutral radical R· or a cation R$^+$. A completely analogous reaction, which leads to the same conclusion, is given by the Wolff rearrangement of the dextrorotatory form of the diazo ketone, XXVI; the resulting acid, obtained in the form of

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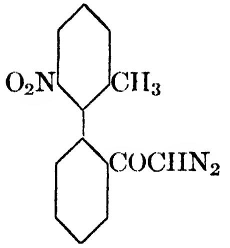
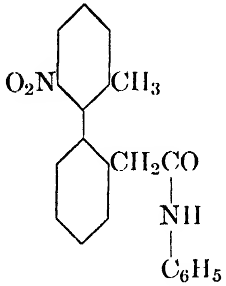
[46] E. S. Wallis and W. W. Moyer, *J. Am. Chem. Soc.* **55**, 2598 (1933).



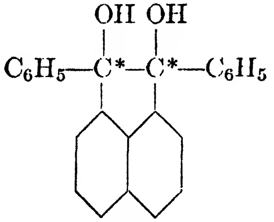
XXVI



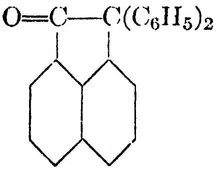
XXVII

its dextrorotatory anilide, XXVII, was found to be again not unduly racemized.[47]

Attention can now be transferred to the stereochemical details of the substitution at atom B of structures I, II, and III. The evidence leading to the belief that a Walden inversion does occur at atom B can be illustrated with reference to the pinacol rearrangement of 7,8-diphenylacenaphthene-7,8-diol, XXVIII.[48] Since the molecule of this glycol



XXVIII



XXIX

possesses the two equivalent asymmetric carbon atoms designated by the asterisks, the compound can exist in both a racemic and a *meso* form. In the racemic form, the two hydroxyl groups are on opposite sides of the five-membered ring to which they are joined (i.e., are *trans* with respect to each other), as are likewise the two phenyl groups. In the *meso* form, on the other hand, the two hydroxyl groups are on the same side of the ring (i.e., are *cis* with respect to each other), as are likewise again the two phenyl groups. Moreover, inasmuch as one of the stereoisomeric forms has been resolved, the question as to which inactive form is racemic and which is *meso* has been answered unambiguously. Now, when the *meso-* (i.e., *cis-*) glycol is treated with either sulfuric or *p*-toluenesulfonic acid, it is transformed smoothly into 7,7-diphenylacenaphthenone, XXIX; but when the racemic (i.e., *trans-*) glycol is

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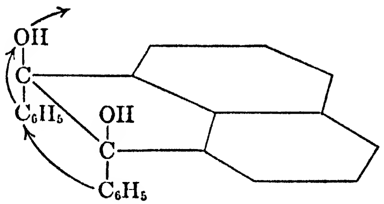
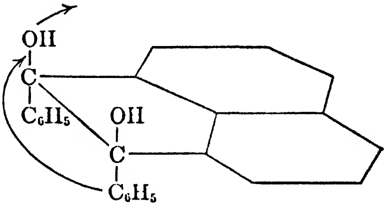
[47] J. F. Lane and E. S. Wallis, *J. Org. Chem.* **6,** 443 (1941).

[48] P. D. Bartlett and R. F. Brown, *J. Am. Chem. Soc.* **62,** 2927 (1940).

treated similarly, it reacts sluggishly. The resulting production of the same 7,7-diphenylacenaphthenone, XXIX, as before is apparently preceded by the isomerization of the *trans* to the *cis* compound. It appears, therefore, that only the *cis*, and not the *trans*, form can undergo the rearrangement in question. Furthermore, the phenyl group that migrates replaces a hydroxyl group which, in the original *cis*-glycol, was joined to the adjacent carbon atom and was located on the opposite side of the five-membered ring. Since it is hardly likely, under these circumstances, that the phenyl group could assume the same relative position in space that the hydroxyl group which it replaces formerly did, the conclusion is drawn that the substitution of a phenyl for a hydroxyl group takes place with inversion. If the reaction followed instead the alternative course, so that the configuration was not altered, the phenyl group in its migration would have to move, not by the most direct route from its original to its final position, but rather in a long arc passing either around one of the other aromatic rings present or else around the remaining hydroxyl group; it may be doubted whether such an indirect path is possible. The situation is illustrated in diagrams XXX and XXXI, in which the direct, and one of the conceivable indirect, routes, respectively, are indicated by the appropriate arrows. The planes of the rings in these figures are to be thought of as lying nearly at right angles to that of the paper.

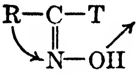


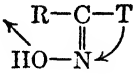
XXX

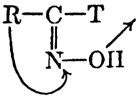


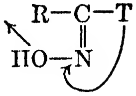
XXXI

The data regarding the steric course of the Beckmann rearrangement, which were presented in an earlier chapter (see Section 8·4), can be considered to support the views expressed in the preceding paragraph, even though the nitrogen atom to which the migrating group becomes attached in such a rearrangement cannot be asymmetric. If the correctness of the *anti* shift in the Beckmann transformation is accepted as definitely established, then the migrating group must approach the nitrogen atom (the analog of the atom B in structures I–III) from the side opposite the hydroxyl group which it replaces. The situation can be described by means of diagrams XXXII and XXXIII, in which the arrows again represent the directions in which the various groups move.


XXXII

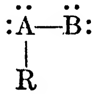

XXXIII


XXXIV


XXXV

The alternative possibility, that the migrating group R or T assumes the position in space formerly occupied by the displaced hydroxyl group, is seen from the corresponding diagrams XXXIV and XXXV to be highly unreasonable. Since, as was noted above, the nitrogen atom at which the substitution occurs cannot be asymmetric, the reaction cannot be said strictly to involve an inversion of configuration about that atom; nevertheless, since the entering group presumably attacks the nitrogen atom from the rear, and since such an attack from the rear may be considered the essential feature of a Walden inversion (cf. pages 289 f.), the occurrence of the *anti* shift in the Beckmann rearrangement supports the belief that a Walden inversion takes place at the atom B (of structures I–III) in those instances in which this atom is asymmetric.

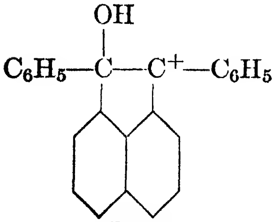
On the basis of the above considerations, the question whether the first two steps postulated in the Whitmore mechanism of the 1,2-shifts are consecutive or simultaneous can now profitably be considered. If these two steps are consecutive, so that the first is complete before the second begins to occur, the intermediate II with the open sextet at atom

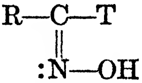


$$\begin{array}{l} :\ddot{A}\!-\!\ddot{B}: \\ \;| \\ \;R \end{array}$$

II

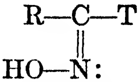
B must be supposed to exist as such to at least a minute extent in the reaction mixture. Under such circumstances, however, the atom B could hardly be expected to maintain its asymmetric configuration, since there is reason to believe that an atom with only six electrons in its valence shell would be planar, or nearly so, rather than pyramidal. Inversion of configuration at atom B could then not be the general rule. For example, if the ion XXXVI (the analog of the intermediate II) derived


XXXVI



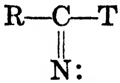
$$\begin{array}{c} R\!-\!C\!-\!T \\ \| \\ :N\!-\!OH \end{array}$$

XXXVII



$$\begin{array}{c} R\!-\!C\!-\!T \\ \| \\ HO\!-\!N: \end{array}$$

XXXVIII



$$\begin{array}{c} R\!-\!C\!-\!T \\ \| \\ N: \end{array}$$

XXXIX

from 7,8-diphenylacenaphthene-7,8-diol, XXVIII, exists for any length of time before the phenyl group and its pair of binding electrons migrate, the *cis* and the *trans* forms of this glycol would have to give rise to the same intermediate ion, XXXVI. Consequently, the striking difference in behavior of the two stereoisomers would be difficult (although perhaps not impossible) to explain. Moreover, in the Beckmann rearrangement, two stereoisomeric oximes, XXXVII and XXXVIII, would necessarily give rise to the same intermediate, XXXIX; consequently, if this intermediate exists as such, the two different oximes would have to lead ultimately to the same final product. Again, therefore, the experimental observations are contrary to what would have been expected if the first two steps of the rearrangement were consecutive. The conclusion thus appears inescapable that these two steps are simultaneous. In other words, the atom or group R of structures I–III, the phenyl group of the glycol XXVIII, and the groups R and T of the oximes XXXVII and XXXVIII, respectively, must be migrating to their new positions while the groups which they replace are departing. Only in this way, apparently, can the above-mentioned differences in behavior of stereoisomers be explained. Moreover, it may be noted further that the assumption of simultaneity accounts nicely for the inversion of configuration since, as long as the departing group is still in the neighborhood of the atom to which it was originally joined, the migrating group can hardly approach from any side except the rear. If the two steps were assumed instead to be consecutive, and if, as would then be necessary, the atom with the open sextet in the intermediate were assumed to maintain its configuration, the replacement might be expected to proceed with retention, and not with inversion, of configuration.

12·10 The Mechanism of the Actual Migration in the 1,2-Shifts.[49] As has been stated at numerous places in the preceding sections, the second step in the Whitmore mechanism of a 1,2-shift consists in the migration of an atom or group, together with its pair of binding electrons, to a position adjacent to the one occupied in the original substance. The manner in which this migration takes place can now be discussed in more detail than was hitherto possible.

Several features of the migration, which have already been mentioned, must be taken into account in any completely satisfactory picture of the process. These features are, first, the retention of stereochemical configuration in the migrating group; second, the inversion of configuration at the atom to which the migrating group ultimately becomes attached; third, the failure of the migrating group ever to become completely free

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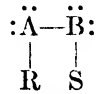
[49] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 216 ff., 279 ff.

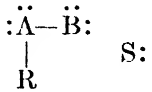
from the remainder of the molecule at any time during the reaction; and, fourth, the simultaneity of the migration with the logically preceding step, in which an open sextet is produced. (See the preceding section.) As will be shown below, a relatively simple mechanism of the transformation, satisfying these four conditions, can indeed be devised with the aid of the concept of resonance.

In the following discussion, the generalized structures I*a*, II, and III*a*



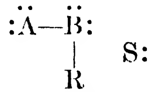
$$\begin{array}{cc} :\ddot{A}\text{—}\ddot{B}: & \\ | \quad\;\; | & \\ R \quad\;\; S & \end{array}$$

I*a*



$$\begin{array}{cc} :\ddot{A}\text{—}\ddot{B}: & \\ | \qquad\quad & S: \\ R \qquad\quad & \end{array}$$

II

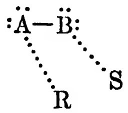


$$\begin{array}{cc} :\ddot{A}\text{—}\ddot{B}: & \\ \qquad\quad | & S: \\ \qquad\quad R & \end{array}$$

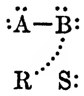
III*a*

of the original substance and of the two assumed intermediates, respectively, will be employed. For later convenience, the fragment S:, which breaks away from the molecule I*a*, is represented explicitly in structures II and III*a*, even though it is not to be considered bonded in any way to the remaining atoms of these structures. Two simplifications will be employed in the treatment: first, the atom or group S of structure I*a*, together with its binding electrons, will be assumed to break away spontaneously (i.e., the reaction will be assumed to follow the course 1*a* of page 476); and, second, the concluding step of the rearrangement (i.e., the transformation of the intermediate III*a* into the stable product which is finally isolated) will be ignored. Neither of these simplifications, however, is an essential part of the treatment; in a manner which should become obvious later, either or both of them could be eliminated, if desired, at the expense of an increase in the complexity of the argument.

So long as the rearrangement has not progressed to any appreciable extent, the reacting system can be described, with an accuracy sufficient for most purposes, by structure I*a* of the original substance. Similarly, after the migration has taken place, the system can be described, with a similar accuracy, by structure III*a*. (It will be remembered that the third step of the rearrangement, in which the intermediate III*a* is stabilized, is here being ignored.) Nevertheless, the system cannot be described with complete accuracy, either at the outset or at the end of the migration, except in terms of resonance among a large number (actually an infinite number; see page 403) of structures, of which structures I*a* and III*a*, respectively, are merely the most important ones. Ordinarily, these additional structures make such small contributions to the states of the system that they can be ignored; certain ones of them, however, turn out to be essential to an understanding of the migration itself. Thus structure I*b*, in which the electrons are paired as in I*a*, but in which the relative positions of the atomic nuclei are those characteristic of III*a*, may be considered to make a small contribution to the state of the intermediate described heretofore simply as III*a*. (The dotted lines between A and R, and between B and S, represent formal bonds, as usual. See Section 10·8.) Similarly, structure III*b*, in which the electrons are paired as in III*a*, but in which the relative positions of the nuclei are those characteristic of I*a*, may be considered to make a minute contribution to the state of the original molecule. (The dotted line again represents a formal bond.) In other words, resonance can occur between structures I*a* and III*b*, with the former much the more important, and also between structures III*a* and I*b*, again with the former much the more important; for, in the two structures of either pair, the positions of the nuclei and the numbers of unpaired electrons are the same. On the other hand, however, no resonance can occur either between structures I*a* and I*b* or between structures III*a* and III*b*, for here the nuclear positions are widely different. (Cf. Section 10·7.)



I*b*



III*b*

Structures I*a* and I*b*, in which the electrons are paired in the same manner, but between which, as was just noted, no resonance can occur, can conveniently be regarded as merely two different geometrical phases of a single structure, which may be called structure I. The point of view adopted here is readily seen to be not essentially different from the one which is adopted implicitly whenever two different conformations (i.e., geometrical phases; cf. page 176) of a molecule like that of ethane are said to correspond to the same structure. Moreover, in a completely similar manner, the two structures III*a* and III*b* can likewise be regarded as merely two different geometrical phases of a single structure, which may be called structure III. As the group R migrates from its position in the original substance to that in the product, each of these two structures I and III passes through an infinite number of intermediate geometrical phases, just as a molecule of ethane, in going from any one conformation to any other, passes through an infinite number of intermediate conformations.

In Figure 12·1, an attempt is made to show in a schematic manner how the energies of the two structures I and III vary in the course of the migration. The abscissa x is a parameter which is related to the positions of the atomic nuclei; it is defined well enough for the purposes of this discussion by the statement that it assumes the value 0 at the beginning of the migration, when the atomic positions are as in structures I*a* and III*b*; the value 1 at the end of the migration, when the atomic positions are as in structures III*a* and I*b*; and intermediate values during the migration, when the atomic positions are intermediate between the extremes. At the outset, when x is equal to 0, structure I reduces simply to I*a*, which is unstrained and so has a low energy. As the migration proceeds (i.e., as x increases), the energy of this structure rises since the lengths of the A—R and B—S bonds are increased, and since the B—A—R bond angle is distorted. Finally, when the migration is complete, with x equal to 1, structure I reduces simply to I*b*, which is very highly strained and so has a very high energy. This variation in the energy of structure I is shown qualitatively by curve *APB* of Figure 12·1. Conversely, structure III, which reduces to the strained III*b* when x is equal to 0, and to the unstrained III*a* when x is equal to 1, becomes progressively more stable as the migration proceeds; its energy, accordingly, decreases along some such curve as *CPD*.

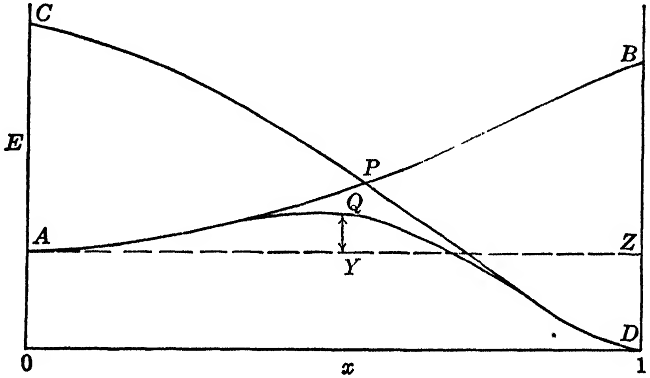


FIGURE 12·1. The energies E of structure I (curve *APB*), of structure III (curve *CPD*), and of their resonance hybrid (curve *AQD*) as functions of a parameter x which defines the extent of the migration.

For each value of x (i.e., for each set of relative positions of all the atomic nuclei), resonance must occur between structures I and III. As a result of this resonance, the energy of the actual system is lower than that corresponding to either individual structure. Consequently, the true dependence of the energy of the system upon the parameter x is that shown schematically by the curve *AQD*, which lies below both the curves *APB* and *CPD* but becomes practically coincident with the lower one of these at each extreme. As the group R migrates from its initial to its final position, S moves away from the molecule, x increases from

0 to 1, and the system may be said to progress along this curve AQD. At the point Q, where the energy is a maximum, the system is described as being the *activated complex*, or the *transition state*, for the reaction. The energy which must be supplied to produce this activated complex, and which is accordingly represented in the figure by the vertical distance YQ, is of course the activation energy $\Delta E^{\ddagger}$ of the reaction. Only those molecules which have an amount of energy equal to or greater than $\Delta E^{\ddagger}$ are able to "climb the hill" from A to Q and to pass over into the next "valley" at D. In other words, only such molecules are able to undergo the reaction. (Cf. Section 6·6.) It may be presumed that the valley at D ordinarily lies lower than does the original one at A; and that the difference in energy at these two points, which is represented in the figure by the distance ZD, and which is equal to the energy $-\Delta E$ liberated in the reaction, provides the major part of the driving force that makes the reaction take place at all.

It should be noted that the system at the point D is considered usually not to be in its final state but to be instead in an intermediate state in which the molecule still possesses an open sextet. Consequently, the major part of the driving force of the reaction may be provided instead by the further decrease in energy that occurs when this intermediate is stabilized in the third, and final, step of the rearrangement. Such considerations, however, do not affect the principles involved. The point D may then lie above the point Z, and not below it as it does in Figure 12·1. Moreover, it should be noted further that the theoretically important distinction between the changes in internal energy and in standard free energy, ΔE and ΔF°, respectively, has been ignored here; it may be doubted, however, whether any serious error has been introduced thereby into the above purely qualitative discussion.

As the migration proceeds, structure I becomes progressively less stable, as was pointed out above, while structure III becomes progressively more stable. Consequently, although resonance between the two structures occurs at all times, the contribution of structure I steadily decreases, while that of structure III steadily increases. When x has reached the value corresponding to the point P (which is also at least approximately the value corresponding to the point Q), the energies are equal, and so the two structures make nearly, if not exactly, the same contribution. Finally, at the completion of the migration, structure I, which was originally "the" structure of the system, has become of negligible importance, and structure III, which was originally of negligible importance, has become "the" structure. The whole process has then taken place in a completely continuous manner without sudden transitions or "quantum jumps" of any kind.

It will now be of interest to consider whether the mechanism described above really satisfies the conditions imposed at the beginning of this section. That it does indeed do so is practically obvious. In the first place, the retention of the configuration of the migrating group R is ensured by the manner in which R merely "slides over" from atom A to atom B. In the process, the atom B can approach the group R only from the front; hence, in R, no inversion is possible. In the second place, an inversion at the atom B seems necessary since, as the group R comes up from one side, the departing atom or group S: can move only in the opposite direction if it is not to collide with R and thus to make the approach of R impossible. In the third place, the group R is certainly never completely free from the rest of the molecule, since it is always bonded either to atom A or to atom B, or else (through resonance) partly to both A and B at the same time. And, in the fourth place, the departure of the atom or group S: and the migration of R (i.e., the first two steps of the rearrangement) are actually considered to be simultaneous. As a matter of fact, in consequence of this simultaneity, the intermediate with structure II, which in previous sections was assumed to be formed in the first step and to react further in the second step, has been completely by-passed. As is readily verified, this intermediate, which was listed, for reasons of continuity, at the beginning of this section, was never again referred to in the subsequent discussion. From the point of view here developed, therefore, the first two steps have completely coalesced, so that the formerly assumed intermediate II has been eliminated. If the third step of the rearrangement is considered to be simultaneous with the first two, the further intermediate III*a* also is found, in a completely similar manner, to disappear.

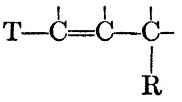
13.

Molecular Rearrangements

Further Types

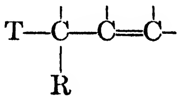
13·1 Introduction. The discussion of the 1,2-shift in the preceding chapter has been exceptionally long and detailed because the rearrangements belonging to this class can assume a very large number of different forms, and because a relatively great amount of information is available regarding the occurrence, course, and mechanisms of such reactions. The discussion of the remaining types of rearrangement in this chapter, on the other hand, will be considerably more brief, because the scopes of these further reactions are comparatively narrow, and because, in many instances, comparatively little is known about their mechanisms. A number of these reactions appear to proceed by a dissociation into fragments, which may be ions, radicals, or reactive molecules, and which subsequently recombine to form the final products. Such transformations, since they do not take place *intramolecularly*, should perhaps not be classified as rearrangements at all. Nevertheless, several reactions of this type will be discussed here, since (superficially at any rate) they bear a very close resemblance to the true intramolecular rearrangements.

13·2 The Allylic Rearrangement. Very frequently, a substance which can be represented schematically by structure I, and which therefore contains the so-called *allylic* system, undergoes an easy rearrangement to an isomeric substance, which can be represented similarly by the isomeric structure II, with a different allylic system. For example, either crotyl bromide, III, or methylvinylcarbinyl bromide, IV, rear-



$$\mathrm{T{-}\overset{|}{C}{=}\overset{|}{C}{-}\underset{\underset{R}{|}}{\overset{|}{C}}{-}}$$

I

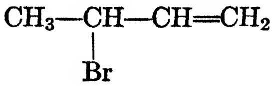


$$\mathrm{T{-}\underset{\underset{R}{|}}{\overset{|}{C}}{-}\overset{|}{C}{=}\overset{|}{C}{-}}$$

II

$CH_3{-}CH{=}CH{-}CH_2Br$

III



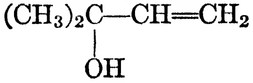
$$\mathrm{CH_3{-}\underset{\underset{Br}{|}}{CH}{-}CH{=}CH_2}$$

IV

ranges to an equilibrium mixture of the two (containing 86 per cent of the compound III and 14 per cent of the compound IV) in a few days at room temperature, or in less than 5 minutes at 100°C.[1] Moreover, a substance containing any particular allylic system, I, frequently undergoes a substitution reaction, in which the atom or group R is replaced by a different atom or group S, and in which the product is derived from the isomeric allylic system, II. For example, the pentenyl bromide, V, gives the rearranged alcohol, VI, on hydrolysis, although it gives the

$(CH_3)_2C{=}CH{-}CH_2Br$

V



$$(CH_3)_2\underset{OH}{\underset{|}{C}}{-}CH{=}CH_2$$

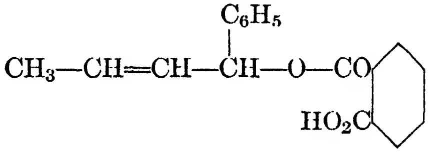
VI

expected ether, VII, on treatment with sodium ethoxide. (Cf. page

$(CH_3)_2C{=}CH{-}CH_2{-}O{-}C_2H_5$

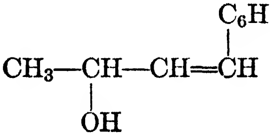
VII

126.) Similarly, hydrolysis of the ester VIII leads to the rearranged



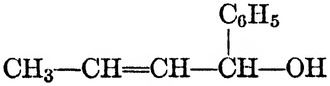
VIII

alcohol IX when the reaction is carried out under mild conditions, but



$$CH_3{-}\underset{OH}{\underset{|}{CH}}{-}CH{=}\overset{C_6H_5}{\overset{|}{CH}}$$

IX



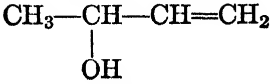
$$CH_3{-}CH{=}CH{-}\overset{C_6H_5}{\overset{|}{CH}}{-}OH$$

X

to the normal product X when the reaction is carried out with 5 *N* sodium hydroxide (cf. pages 282 f.); and the action of hydrogen bromide upon either of the alcohols XI and XII gives a mixture of the

$CH_3{-}CH{=}CH{-}CH_2OH$

XI



$$CH_3{-}\underset{OH}{\underset{|}{CH}}{-}CH{=}CH_2$$

XII

bromides III and IV.[2]

Of the explanations that have been proposed for the above rather erratic allylic rearrangements, the one that is at present most favored

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[1] W. G. Young and S. Winstein, *J. Am. Chem. Soc.* **57**, 2013 (1935).

[2] W. G. Young and J. F. Lane, *J. Am. Chem. Soc.* **60**, 847 (1938).

can be illustrated with the reactions of the unsaturated chlorides XIII

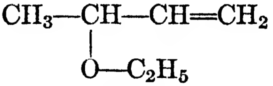
$$\mathrm{CH_3{-}CH{=}CH{-}CH_2Cl} \qquad\qquad \mathrm{CH_3{-}CHCl{-}CH{=}CH_2}$$

XIII XIV

and XIV, which have structures analogous to those of the respective bromides III and IV.[3] When these substances are treated with sodium ethoxide in ethyl alcohol, they are transformed into their ethyl ethers, XV and XVI, respectively, without rearrangement. Since the rate of

$$\mathrm{CH_3{-}CH{=}CH{-}CH_2{-}O{-}C_2H_5}$$

XV



$$\mathrm{CH_3{-}\underset{\displaystyle O{-}C_2H_5}{\underset{|}{CH}}{-}CH{=}CH_2}$$

XVI

each of these reactions is proportional both to the concentration of the organic chloride and to that of ethoxide ion, the mechanism of the substitution may be considered to consist in an attack by the ethoxide ion upon the carbon atom to which the chlorine atom is attached. Presumably the reaction is accompanied by an inversion of configuration at the atom at which it occurs. (Cf. pages 286 ff.) The mechanism thus appears to be analogous in all respects to those of the corresponding reactions of most saturated primary and secondary halides. On the other hand, when the chlorides XIII and XIV are dissolved in ethyl alcohol containing no sodium ethoxide, a slow solvolysis takes place, and there is produced a mixture of the two ethers XV and XVI. Moreover, approximately the same mixture of ethers is obtained from each of the two chlorides. Obviously, therefore, a second mechanism of ether formation, which, unlike the first one, leads to partial rearrangement, is possible under these more mild conditions. This second mechanism, however, becomes manifest only when the concentration of ethoxide ion is extremely low or, in other words, when the rate of the first-mentioned reaction, which is proportional to the concentration of ethoxide ion, becomes extremely small. Obviously also, the rate of the solvolysis reaction proceeding by this second mechanism must be independent of the concentration of ethoxide ion, since the reaction still proceeds at an appreciable rate in the presence of the hydrogen chloride which is one of its products. The reagent which provides the ethoxyl group, accordingly, cannot be the ethoxide ion but must instead be un-ionized ethyl alcohol. In order that the production of the same mixture of ethers from each of the two chlorides may be accounted for, it is necessary to presume that both chlorides give rise to a common intermediate, which then reacts with the solvent. Most usually, this intermediate is thought to be a cation resonating between the two

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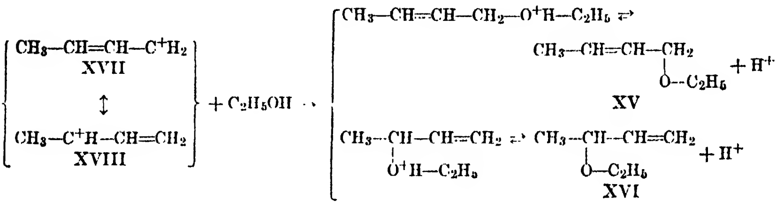
[3] A. G. Catchpole and E. D. Hughes, *J. Chem. Soc.* **1948**, 4.

structures XVII and XVIII. As is shown in the sequences of reactions 13·1 and 13·2, this postulated cation (XVII↔XVIII) could indeed be

$$\begin{array}{c} CH_3{-}CH{=}CH{-}CH_2Cl \rightleftarrows \\ \text{XIII} \\ \\ CH_3{-}CHCl{-}CH{=}CH_2 \rightleftarrows \\ \text{XIV} \end{array} \left[\begin{array}{c} CH_3{-}CH{=}CH{-}C^+H_2 \\ \text{XVII} \\ \updownarrow \\ CH_3{-}C^+H{-}CH{=}CH_2 \\ \text{XVIII} \end{array}\right] + Cl^- \qquad (13\cdot1)$$

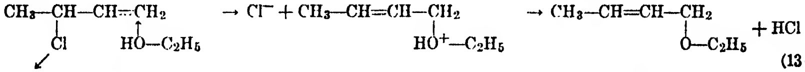


$$\left[\begin{array}{c} CH_3{-}CH{=}CH{-}C^+H_2 \\ \text{XVII} \\ \updownarrow \\ CH_3{-}C^+H{-}CH{=}CH_2 \\ \text{XVIII} \end{array}\right] + C_2H_5OH \rightarrow \left[\begin{array}{l} CH_3{-}CH{=}CH{-}CH_2{-}O^+H{-}C_2H_5 \rightleftarrows \underset{\text{XV}}{CH_3{-}CH{=}CH{-}\underset{O-C_2H_5}{CH_2}} + H^+ \\ \\ CH_3{-}\underset{O^+H-C_2H_5}{CH}{-}CH{=}CH_2 \rightleftarrows \underset{\text{XVI}}{CH_3{-}\underset{O-C_2H_5}{CH}{-}CH{=}CH_2} + H^+ \end{array}\right] \qquad (13\cdot2)$$

formed equally well from either of the unsaturated chlorides; it must have the same resonating structure regardless of its source; and it could lead to the observed mixture of products. (For the significance of the double-headed arrows here and below, see page 391.) Moreover, the stabilization of the cation by the resonance is doubtless an important factor leading to its relatively great ease of formation. The mechanism is therefore consistent with all the significant features of the reactions, even though it does not enable one to predict in advance the relative amounts of the ethers XV and XVI which are formed.

If it is assumed, as above, that a substitution reaction of an allylic compound can proceed either by a direct replacement without rearrangement, or by a preliminary dissociation to a resonating ionic intermediate (or by both mechanisms at the same time), the identity of the product can always be explained. For example, the rearrangement of either of the bromides III and IV (see above) to the equilibrium mixture is easily understandable in terms of a reversible ionization of the bromides and of resonance in the resulting cation. (Cf. equations 13·1.) Furthermore, the hydrolysis of the pentenyl bromide, V, to the alcohol VI can be explained as proceeding through the corresponding ion, which here gives only one product, whereas the formation of the ether VII from the same bromide and sodium ethoxide can be explained as the result of a direct attack by ethoxide ion. And finally, the reactions of the alcohols XI and XII with hydrogen bromide must go partly through the resonating ion, XVII ↔ XVIII, and partly by direct attack upon the carbon atoms to which the hydroxyl groups are attached; this conclusion follows from the fact that crotyl alcohol, XI, although it leads to a mixture of the bromides III and IV, gives somewhat more crotyl bromide, III, than does the isomeric alcohol, XII.[2]

An alternative mechanism of the allylic rearrangement, which is less favorably regarded than is the ionic one just discussed, but which may be valid in some instances, can be described as of the "push-and-pull" type. For example, the formation of ethyl crotyl ether, XV, by the action of ethyl alcohol upon methylvinylcarbinyl chloride, XIV, can be imagined to be dependent upon an attack by the alcohol molecule upon the carbon atom in the position that is gamma with respect to the chlorine atom replaced. This mechanism, which is represented schematically in equation 13·3, seems much less reasonable for the particular



$$\begin{array}{l}CH_3—CH—CH{=}CH_2\\ \quad\; |\\ \quad Cl \qquad HO—C_2H_5\end{array} \rightarrow Cl^- + \begin{array}{l}CH_3—CH{=}CH—CH_2\\ \qquad\qquad\quad\; |\\ \qquad\qquad HO^+—C_2H_5\end{array} \rightarrow \begin{array}{l}CH_3—CH{=}CH—CH_2\\ \qquad\qquad\quad\; |\\ \qquad\qquad\; O—C_2H_5\end{array} + HCl \qquad (13\cdot3)$$

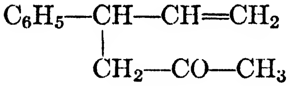
XIV XV

reaction now under discussion than does the one based upon ionization, since it could only with considerable difficulty be reconciled with the observed compositions of the products obtained in the several reactions mentioned above. On the other hand, since the actions of acetoacetic ester, XIX, upon cinnamyl alcohol, XX, and upon phenylvinylcarbinol,

$$\underset{\text{XIX}}{CH_3—CO—CH_2—CO_2—C_2H_5} \qquad \underset{\text{XX}}{C_6H_5—CH{=}CH—CH_2OH}$$

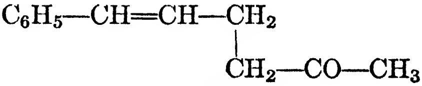
XXI, give in each instance *only* the rearranged products, XXII and

$$\underset{\text{XXI}}{C_6H_5—CHOH—CH{=}CH_2}$$



$$\begin{array}{l}C_6H_5—CH—CH{=}CH_2\\ \qquad\quad\; |\\ \qquad\quad CH_2—CO—CH_3\end{array}$$

XXII



$$\begin{array}{l}C_6H_5—CH{=}CH—CH_2\\ \qquad\qquad\qquad\quad\; |\\ \qquad\qquad\qquad\quad CH_2—CO—CH_3\end{array}$$

XXIII

XXIII, respectively,[4] some sort of push-and-pull mechanism for these reactions seems to be required, even though the details of the reactions are not entirely clear. Moreover, the Claisen rearrangement frequently involves a simultaneous allylic rearrangement which is definitely of the push-and-pull type. (See the following section.)

The distinction between the ionic and the push-and-pull mechanisms of the allylic rearrangement is that in the former, but not in the latter, the resonating intermediate ion (XVII ↔ XVIII, or the like) is assumed actually to exist as such in the reaction mixture. There is, however, no sharp dividing line between the two points of view, since the question

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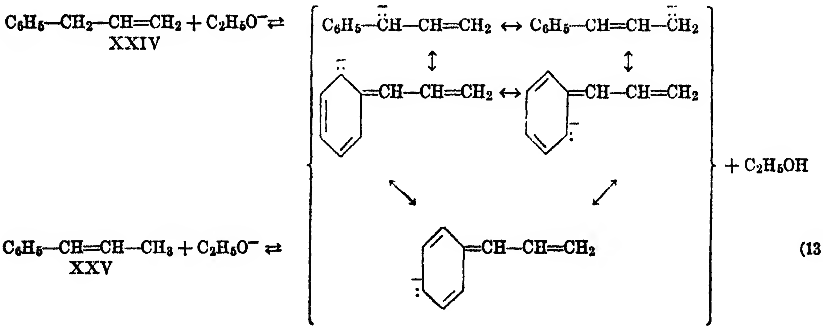
[4] M. F. Carroll, *J. Chem. Soc.* **1940**, 1266. See also C. L. Wilson, *Trans. Faraday Soc.* **37**, 631 (1941). For a study of this reaction, see W. Kimel and A. C. Cope, *J. Am. Chem. Soc.* **65**, 1992 (1943). For a general discussion of push-and-pull mechanisms, with further examples, see R. E. Kepner, S. Winstein, and W. G. Young, *ibid.* **71**, 115 (1949).

whether a given intermediate in a given reaction is or is not sufficiently independent to be said to "exist as such" is a rather nebulous one. It is, in fact, possible to imagine a continuous gradation of mechanisms ranging from the extreme ionic to the extreme push-and-pull type. Conceivably, most allylic rearrangements are of intermediate type. With the exception of certain rare reactions, such as the above-mentioned ones of acetoacetic ester with cinnamyl alcohol and with phenylvinylcarbinol, and of the Claisen rearrangement, the ionic mechanism seems ordinarily, however, to be quite satisfactory. In any event, it should be noted that, no matter which mechanism is adopted, the intermediate resonating ion need not be assumed ever to be present in a concentration sufficiently high that its existence is demonstrable by a measurement of conductivity or by any other analogous experiment.

In the examples of the allylic rearrangement that have been mentioned so far, the substituent R of structures I and II is of such nature that it can form a stable anion. The organic residue which is stabilized by resonance is therefore necessarily a cation. Other examples are known, however, in which R may be presumed to break away as a cation and so to leave behind a resonating organic anion. Thus, when allylbenzene, XXIV, is refluxed with alcoholic potassium hydroxide, it is transformed

$$\underset{\text{XXIV}}{C_6H_5\text{—}CH_2\text{—}CH\text{=}CH_2} \qquad \underset{\text{XXV}}{C_6H_5\text{—}CH\text{=}CH\text{—}CH_3}$$

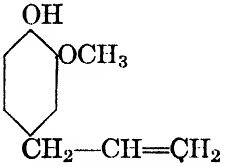
into the isomeric propenylbenzene, XXV. The mechanism of this rearrangement is doubtless that shown in equation 13·4. The stabiliza-

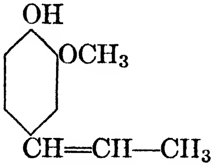


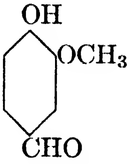
(13·4)

tion of the intermediate ion by the resonance is doubtless, as in the preceding examples, an important factor in facilitating the rearrangement. Moreover, the fact that propenylbenzene is formed from allylbenzene, rather than vice versa, can be related to the stabilization of the former substance by the resonance which results from the conjugation of the ethylenic double bond with the aromatic ring. (Cf. Section 10·10.)

Many reactions of the foregoing type, in which unconjugated double bonds are changed into conjugated ones, are known and can be interpreted in a similar way. Thus, the transformation of eugenol, XXVI,


XXVI

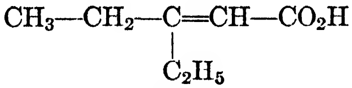

XXVII


XXVIII

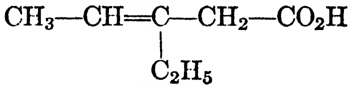
into isoeugenol, XXVII, is an essential step in an important method of manufacturing vanillin, XXVIII. Moreover, α,β and β,γ-unsaturated carbonyl compounds can similarly be interconverted; rather unexpectedly, however, the conjugated α,β-compound does not always predominate in the equilibrium mixture. Thus, although with the pentenoic acids, XXIX and XXX, the equilibrium is greatly in favor

$CH_3{-}CH_2{-}CH{=}CH{-}CO_2H$ XXIX $CH_3{-}CH{=}CH{-}CH_2{-}CO_2H$ XXX

of the conjugated α,β-compound, XXIX, with the β-ethylpentenoic acids, XXXI and XXXII, the opposite is true. The rather erratic

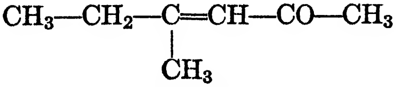

XXXI

$CH_3{-}CH_2{-}\underset{\underset{C_2H_5}{|}}{C}{=}CH{-}CO_2H$

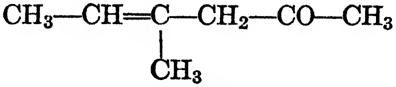

XXXII

$CH_3{-}CH{=}\underset{\underset{C_2H_5}{|}}{C}{-}CH_2{-}CO_2H$

manner in which the position of the equilibrium is affected by apparently minor changes in structure is shown by a comparison of the pair of isomeric methyl ketones, XXXIII and XXXIV, with the pair of closely

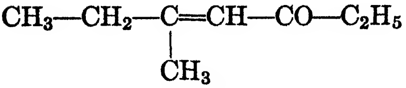

XXXIII

$CH_3{-}CH_2{-}\underset{\underset{CH_3}{|}}{C}{=}CH{-}CO{-}CH_3$

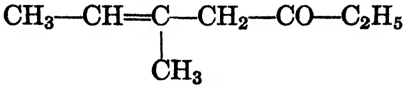

XXXIV

$CH_3{-}CH{=}\underset{\underset{CH_3}{|}}{C}{-}CH_2{-}CO{-}CH_3$

related ethyl ketones, XXXV and XXXVI. With the former substances,


XXXV

$CH_3{-}CH_2{-}\underset{\underset{CH_3}{|}}{C}{=}CH{-}CO{-}C_2H_5$

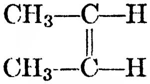

XXXVI

$CH_3{-}CH{=}\underset{\underset{CH_3}{|}}{C}{-}CH_2{-}CO{-}C_2H_5$

the equilibrium is considerably in favor of the unconjugated ketone, XXXIV, whereas, with the latter, it is in favor of the conjugated ketone, XXXV.[5] Although the complete explanation of these variations is not at present known, one of the factors involved probably arises from a stabilizing effect exerted by alkyl substituents that are attached to unsaturated atoms. This effect is illustrated, for example, by the fact that the heat of hydrogenation of 1-butene, XXXVII, is greater than

$$CH_2{=}CH{-}CH_2{-}CH_3$$

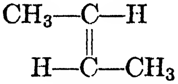
XXXVII



$$\begin{matrix} CH_3{-}C{-}H \\ \| \\ CH_3{-}C{-}H \end{matrix}$$

XXXVIII

the heats of hydrogenation of *cis*- and *trans*-2-butenes, XXXVIII and XXXIX, respectively, by 1.8 and 2.7 kcal per mole, respectively,[6] even



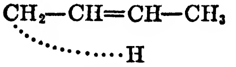
$$\begin{matrix} CH_3{-}C{-}H \\ \| \\ H{-}C{-}CH_3 \end{matrix}$$

XXXIX

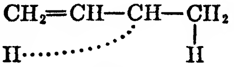
$$CH_3{-}CH_2{-}CH_2{-}CH_3$$

XL

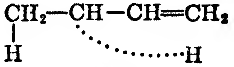
though the product of each reaction is the same substance, *n*-butane, XL. This stabilization is possibly due to the hyperconjugation resulting from resonance with such structures as XLI–XLIII, with formal bonds. (See Section 10·10 and pages 502 f.) With 1-butene, resonance occurs



XLI



XLII



XLIII

between structures XXXVII and XLI; hence the double bond is here "hyperconjugated" with only one alkyl group. With 2-butene, on the other hand, resonance occurs among structures XXXVIII (or XXXIX), XLII, and XLIII; hence the double bond is now "hyperconjugated" with two different alkyl groups. The latter hydrocarbon, therefore, has the greater resonance energy and hence is (thermochemically) the more stable.

Allylic rearrangements may occur also in the reactions of the Grignard reagents that are prepared from allyl halides. A typical example is provided by the sequence of reactions 13·5. (Benzyl chloride, XLIV,

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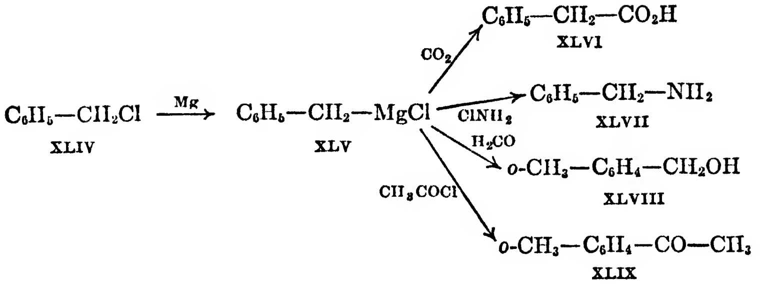
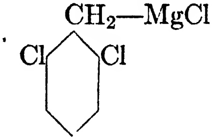
[5] For further examples of this type of rearrangement of unsaturated carbonyl compounds, see J. W. Baker, *Tautomerism*, D. Van Nostrand Company, New York, 1934, pages 154 ff.

[6] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.* 57, 876 (1935).

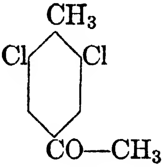


(13·5)

may be considered to be a special type of allyl halide, in which the double bond of structures I and II is replaced by a phenyl group.) The first two of these reactions, in which phenylacetic acid, XLVI, and benzylamine,[7] XLVII, are produced, are perfectly normal; the latter two reactions, however, in which *o*-methylbenzyl alcohol, XLVIII, and *o*-methylacetophenone,[8] XLIX, are produced, involve allylic rearrangements. Moreover, since the reaction between acetyl chloride and 2,6-dichlorobenzylmagnesium chloride, L, gives 3,5-dichloro-4-methylacetophenone,



L



LI

LI, it is evident that, when both *ortho* positions are blocked, the anomalous reaction can occur at the *para* position of the benzene ring.[8]

In each of the above rearrangements of the benzyl Grignard reagents, two reactions, namely, the formation of the Grignard reagent and its further transformation, always intervene between the original benzyl chloride and the final anomalous product. Consequently, there is a possibility that the rearrangement might have occurred in either of these reactions. The assumption is commonly made, however, that the Grignard reagent is normal, as is shown in formulas XLV and L, and that therefore the rearrangement occurs in the concluding step. Perhaps the best justification for this belief is derived from the fact that the Grignard reagent, XLV, gives some unrearranged products, such as phenylacetic acid, XLVI, and benzylamine, XLVII. In order to explain these products, one must assume either that two rearrangements, which exactly cancel each other, have occurred, or else that no rearrangement

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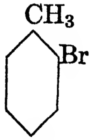
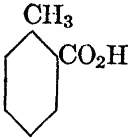
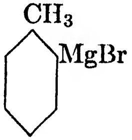
[7] G. H. Coleman and R. A. Forrester, *J. Am. Chem. Soc.* **58**, 27 (1936).

[8] P. R. Austin and J. R. Johnson, *J. Am. Chem. Soc.* **54**, 647 (1932).

at all has occurred. The latter possibility, since it is the simpler, may be accepted as probably correct in the absence of any information to the contrary. Moreover, the fact [8] that the Grignard reagent prepared from *o*-bromotoluene, LII, when treated with carbon dioxide, gives


LII

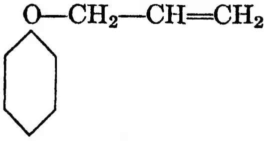

LIII

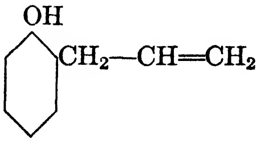

LIV

o-toluic acid, LIII, and not phenylacetic acid, XLVI, is also most easily interpreted on the assumption that this latter Grignard reagent has the expected structure LIV, whereas the one from benzyl chloride, XLIV, has structure XLV. The evidence is, however, not completely conclusive, and so there remains a possibility that the structures assigned above to the Grignard reagents are incorrect.

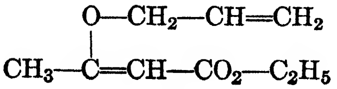
13·3 The Claisen Rearrangement.[9] When a simple or substituted allyl ether of a phenol or enol is heated to about 200°C, it usually undergoes a rearrangement, in which the allyl group loses its attachment to the ether oxygen atom and becomes linked instead to a carbon atom of the phenolic or enolic system. The simplest example of this reaction is provided by the rearrangement of allyl vinyl ether, I, to allylacetaldehyde, II.[10] Moreover, allyl phenyl ether, III, is similarly transformed

$$\underset{\text{I}}{CH_2{=}CH{-}CH_2{-}O{-}CH{=}CH_2} \qquad \underset{\text{II}}{CH_2{=}CH{-}CH_2{-}CH_2{-}CHO}$$

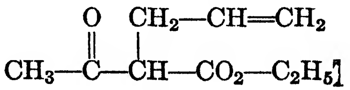

III


IV

into *o*-allylphenol, IV; and ethyl O-allylacetoacetate, V, is transformed


V

$$CH_3{-}\overset{\overset{\displaystyle O{-}CH_2{-}CH{=}CH_2}{|}}{C}{=}CH{-}CO_2{-}C_2H_5$$


VI

$$CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{\overset{\displaystyle CH_2{-}CH{=}CH_2}{|}}{C}H{-}CO_2{-}C_2H_5$$

into ethyl *α*-allylacetoacetate, VI. This last-mentioned reaction is of

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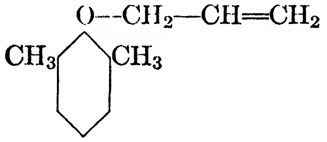
[9] For further details regarding the Claisen rearrangement, and for many further references to the original literature, see D. S. Tarbell in R. Adams, *Organic Reactions*, John Wiley and Sons, New York, Volume II, 1944, Chapter 1.

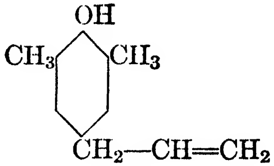
[10] C. D. Hurd and M. A. Pollack, *J. Am. Chem. Soc.* **60**, 1905 (1938).

historical interest since it was the first example of the Claisen rearrangement to be discovered.

With the allyl aryl ethers, the migrating group ordinarily goes to the *ortho* position of the aromatic ring if there is at least one such position that is not already occupied. On the other hand, it can go instead to the *para* position if both *ortho* positions are blocked by substituents. Allyl 2,6-dimethylphenyl ether, VII, for example, gives 2,6-dimethyl-4-allylphenol, VIII.[11] On the other hand, if both the *para* position and the two *ortho* positions are blocked, the rearrangement does not occur unless, as happens in a few instances, one of the blocking groups is ejected in the reaction. Migration to a vacant *meta* position has never been observed. The rearrangement, regardless of whether it is *ortho* or *para*, usually takes place smoothly without a catalyst (although ammonium chloride is reported occasionally to make the reaction faster); the yield is frequently almost quantitative.

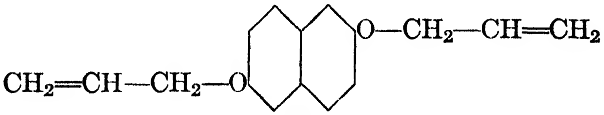


VII

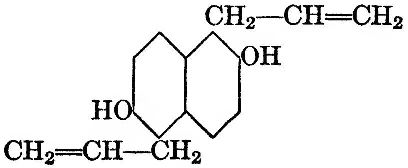


VIII

In the naphthalene series, an allyl group can migrate from a β oxygen atom only to the adjacent α carbon atom, and not to the adjacent β carbon atom, even though the latter atom might seem to be just as "*ortho*" as the former. For example, 2,6-diallyloxynaphthalene, IX, gives only 1,5-diallyl-2,6-dihydroxynaphthalene, X, and no 1,7- or



IX



X

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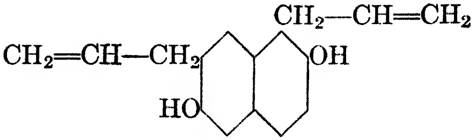
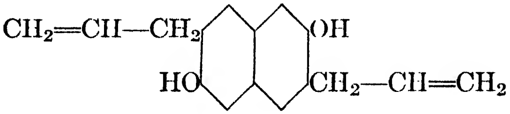
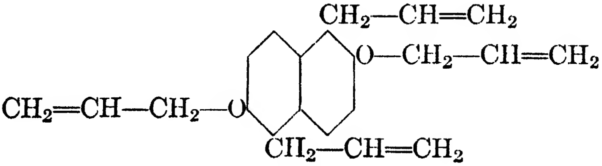
[11] D. S. Tarbell and J. F. Kincaid, *J. Am. Chem. Soc.* **62**, 728 (1940).

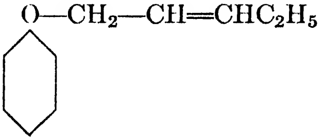
3,7-diallyl-2,6-dihydroxynaphthalene (XI or XII, respectively). Indeed, if the 1 and 5 positions are blocked, as in 1,5-diallyl-2,6-diallyloxynaphthalene, XIII, no rearrangement takes place at all.[12] The situation is therefore analogous to that encountered in the substitution reactions of 2,7-dihydroxynaphthalene. (Cf. page 430.)

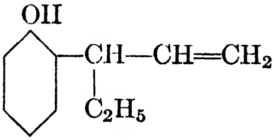

XI


XII


XIII

A very interesting feature of the Claisen rearrangement is that, at least with the allyl aryl ethers when the migrations are to the *ortho* positions, an allylic rearrangement occurs simultaneously in the migrating allyl group; or, in other words, that the carbon atom by which this group is attached to the ring in the final product is gamma with respect to the atom by which it was linked to the oxygen atom in the original ether. Thus γ-ethylallyl phenyl ether, XIV, rearranges to *o*-(α-ethylallyl)-phenol, XV (however, see page 555), and, conversely, α-ethylallyl phenyl ether, XVI, rearranges to *o*-(γ-ethylallyl)-phenol, XVII.[13,14]


XIV


XV

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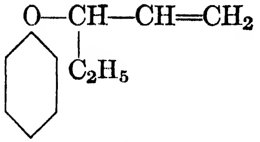
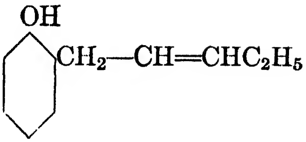
[12] L. F. Fieser and W. C. Lothrop, *J. Am. Chem. Soc.* **57**, 1459 (1935).

[13] W. M. Lauer and W. F. Filbert, *J. Am. Chem. Soc.* **58**, 1388 (1936).

[14] C. D. Hurd and M. A. Pollack, *J. Org. Chem.* **3**, 550 (1939).

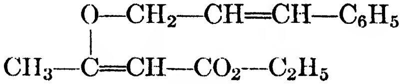


XVI



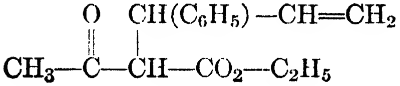
XVII

In the analogous rearrangements of the enolic ethers, a similar *inversion* of the allyl group is found sometimes to occur, and sometimes not to occur. Thus, ethyl O-cinnamylacetoacetate, XVIII, gives ethyl α-(α-phenylallyl)-acetoacetate, XIX, with inversion at 110°C in the presence of ammonium chloride,[15] but it gives instead ethyl α-cinnamylacetoacetate, XX, without inversion at 260°C.[16] (This use of the word "inversion" must, of course, be sharply distinguished from that in the discussion of stereochemistry. No reference is here intended to the *configuration* of the substituted allyl group or to that of any atom contained in it.)



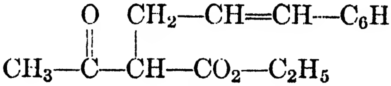
$$CH_3-C(O-CH_2-CH{=}CH-C_6H_5){=}CH-CO_2-C_2H_5$$

XVIII



$$CH_3-C({=}O)-CH(CH(C_6H_5)-CH{=}CH_2)-CO_2-C_2H_5$$

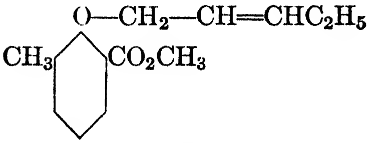
XIX



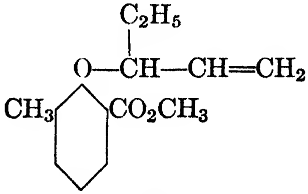
$$CH_3-C({=}O)-CH(CH_2-CH{=}CH-C_6H_5)-CO_2-C_2H_5$$

XX

The question whether an inversion occurs in the allyl group when it migrates to the *para* position is still far from settled. Only one example, in fact, has as yet been reported in which all the data required for the drawing of a conclusion are available. Thus, each of the two isomeric ethers, XXI and XXII, gives the same product, XXIII.[17] The rear-



XXI



XXII

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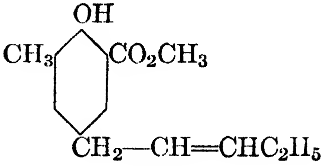
[15] W. M. Lauer and E. I. Kilburn, *J. Am. Chem. Soc.* **59**, 2586 (1937).

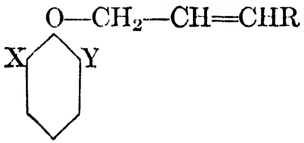
[16] E. Bergmann and H. Corte, *J. Chem. Soc.* **1935**, 1363.

[17] O. Mumm, H. Hornhardt, and J. Diederichsen, *Ber* **72**, 100 (1939); O. Mumm and J. Diederichsen, *ibid.* **72**, 1523 (1939).

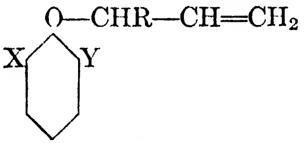


XXIII

rangement of the compound XXI therefore proceeds without inversion, whereas that of the compound XXII proceeds with inversion. Although, of course, it is extremely unsafe to generalize on the basis of so little evidence, one is nevertheless tempted to state as a general rule that, in any *para* rearrangement, two isomeric ethers which are related as are the two with the structures XXIV and XXV will always give the same

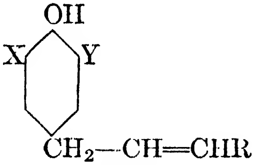


XXIV



XXV

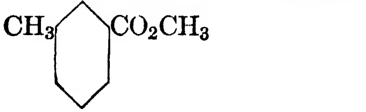
product, XXVI. Only further experiment can determine whether or



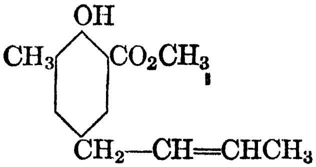
XXVI

not this rule is indeed valid.

Although the rule just stated cannot at the present time be accepted in its entirety except with the greatest reserve, part of it is supported by a small amount of additional evidence. Several further ethers of the general form XXIV have been rearranged, and, in each reaction, the product obtained has had structure XXVI. For example, the ether XXVII gives the product XXVIII,[18] and the ether XXIX gives the



XXVII



XXVIII

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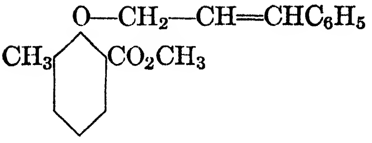
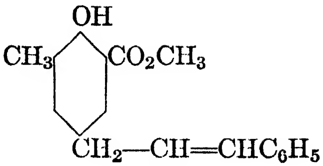
[18] O. Mumm and F. Möller, *Ber.* **70**, 2214 (1937).



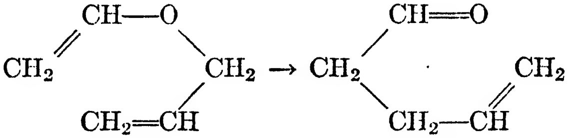
XXIX



XXX

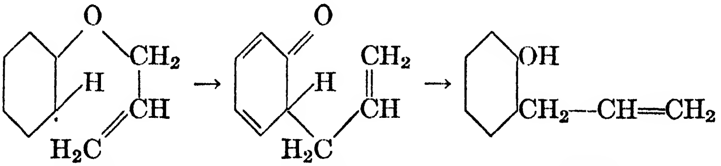
product XXX.[18] In none of these reactions has there been an inversion in the allyl group. The isomeric compounds of general form XXV, however, have not yet been investigated in any of these further instances; consequently, it is not known whether, as predicted, these compounds also lead with inversion to the same products, XXVIII and XXX, respectively, that their isomers do.

A reasonable mechanism for the rearrangement of an allyl ether of an enol is shown in equation 13·6 for the simplest example of this type of



XXXI XXXII (13·6)

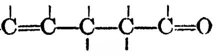
reaction. It may be assumed that the molecule of the original allyl vinyl ether, I, in the course of its thermal motions, achieves the geometrical conformation XXXI. The transition from structure XXXI to structure XXXII should then be fairly easy since it requires only a redistribution of the electrons, in addition to a comparatively small alteration in the relative positions of a few of the atomic nuclei. Similarly, the *ortho* rearrangement of an allyl aryl ether, XXXIII, can be imagined to proceed in the analogous manner represented in equation 13·7. The original product, XXXIV, which is analogous to the substance XXXII in equation 13·6, is here the unstable ketonic form of *o*-allylphenol; it would doubtless rearrange spontaneously to the stable phenolic form, XXXV, as rapidly as it is formed (presumably by giving up a proton to some base that is present, and simultaneously accepting a different proton from some acid. See page 255 and also Section 14·4.)



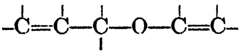
XXXIII XXXIV XXXV (13·7)

In the rearrangement of allyl vinyl ether, the details of the transition from structure XXXI to structure XXXII can be seen most clearly with the aid of a diagram like that of Figure 12·1 on page 532. When x is equal to 0, the conformation of the molecule is that corresponding to structure XXXI; when x is equal to 1, the conformation is that corresponding to structure XXXII. As the reaction proceeds, the value of x increases from 0 to 1. The energy E of structure XXXI therefore rises (in consequence of the resulting distortion) along the curve APB of the abovementioned diagram, while that of structure XXXII falls along the curve CPD. The energy of the molecule itself, however, goes along the curve AQD, which corresponds to the resonance hybrid of structures XXXI and XXXII. The activated complex (at the point Q) receives at least approximately equal contributions from the two structures. Only those molecules which possess an excess energy equal to or greater than the activation energy YQ are able to pass from A to D and thus to make the transition between the structures. Clearly, in the rearrangement of allyl phenyl ether also, the transition from structure XXXIII to structure XXXIV can be interpreted in a completely analogous manner.

If the figure referred to in the preceding paragraph is considered in any specific rearrangement to provide an accurate representation of the dependence of the energies of the respective structures and of their resonance hybrid upon the value of x, the driving force of the reaction (i.e., the factor which makes it proceed in the observed direction rather than in the opposite one) is seen to arise from the circumstance that the point D lies below Z, and hence is lower than A. In those rearrangements in which the original ether is derived from a simple enol, and not from a phenol, the figure in question does indeed seem to be correct in the respect mentioned, since, in any such reaction, the ketonic system, XXXVI, appears always to be more stable


$-\overset{|}{C}=\overset{|}{C}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-\overset{|}{C}=O$

XXXVI


$-\overset{|}{C}=\overset{|}{C}-\underset{|}{\overset{|}{C}}-O-\overset{|}{C}=\overset{|}{C}-$

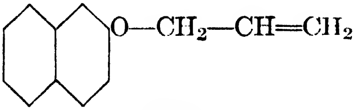
XXXVII

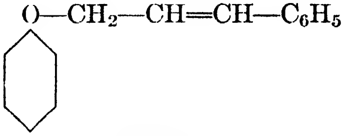
than the isomeric ethylenic one, XXXVII. In those other rearrangements, however, in which the original ether is derived from a phenol, the situation is not so clear, since, for example, the assumed intermediate, XXXIV, has lost the stabilization resulting from the resonance in the benzene ring. It is entirely possible, therefore, that the ketone XXXIV may actually be less stable than the original ether, XXXIII. Under such circumstances, the reaction must be considered to proceed to completion only because the unstable intermediate, XXXIV, is transformed into the stable phenol, XXXV, as fast as it is formed. (The foregoing discussion is, of course, based on the simplifying assumption that the changes in entropy are of secondary importance, and that the distinction between internal energy and free energy can therefore be ignored. Inasmuch as the changes in internal energy which take place in these reactions seem to be large in magnitude, this assumption is not unreasonable.)

The belief that the rearrangement of an allyl vinyl ether or the *ortho* rearrangement of an allyl aryl ether may, and usually does, occur in the manner indicated in equations 13·6 and 13·7, respectively, is supported by various types of evidence. The reaction has been found to follow first-order kinetics (i.e., to proceed at a rate which is proportional to the concentration of the ether alone);[19] the rate-determining step must

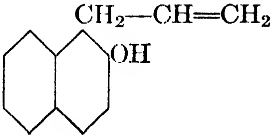
[19] J. F. Kincaid and D. S. Tarbell, *J. Am. Chem. Soc.* **61**, 3085 (1939).

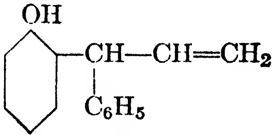
therefore involve only a single molecule of the ether. Any bimolecular mechanism, in which two molecules collide and interchange allyl groups, can accordingly be excluded. Moreover, of the possibilities which thus remain, the one that the ether dissociates unimolecularly into two fragments which then recombine in a different way is rendered improbable by the fact that, when a mixture of two different ethers is rearranged, each substance behaves as if it were alone, and no *cross products* are formed. For example, a mixture of allyl β-naphthyl ether, XXXVIII,


XXXVIII

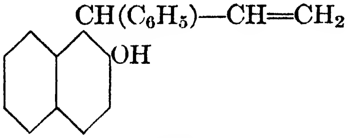

XXXIX

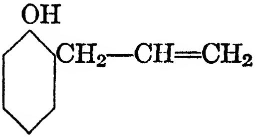
and cinnamyl phenyl ether, XXXIX, gives only 1-allyl-2-naphthol, XL,


XL


XLI

and o-(α-phenylallyl)-phenol, XLI, and no 1-(α-phenylallyl)-2-naphthol, XLII, or o-allylphenol, IV.[20] This nonoccurrence of cross products


XLII


IV

would be hard to reconcile also with the bimolecular mechanism mentioned above. Further evidence opposed to the dissociation-and-recombination mechanism is contained in the fact that isomeric ethers like those with structures XIV and XV (page 546), for example, give isomeric products. If the γ-ethylallyl radical ever broke away from the ether XIV, and if the α-ethylallyl radical ever broke away from the ether XV, the resulting allylic fragments would necessarily be identical, whether they were ions or neutral radicals, since resonance would have to occur between the two structures XLIII and XLIV. (In these structures, the asterisks designate carbon atoms which possess unshared pairs

$C^*H_2—CH{=}CH—C_2H_5$
XLIII

$CH_2{=}CH—C^*H—C_2H_5$
XLIV

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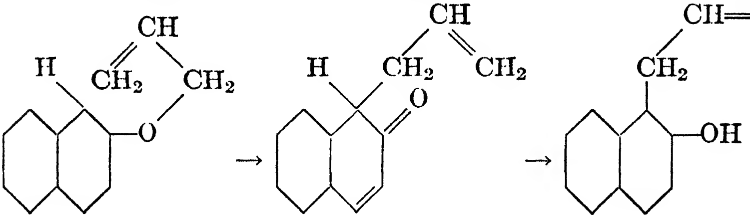
[20] C. D. Hurd and L. Schmerling, *J. Am. Chem. Soc.* **59**, 107 (1937).

of electrons and negative formal charges if the fragment is an anion; or open sextets and positive formal charges if the fragment is a cation; or single unpaired electrons and zero formal charges if the fragment is a neutral radical.) Consequently, since only a single fragment resonating between structures XLIII and XLIV is possible, the two ethers XIV and XV would have to lead to the same final product, or to the same mixture of products, if any dissociation of this kind occurred.

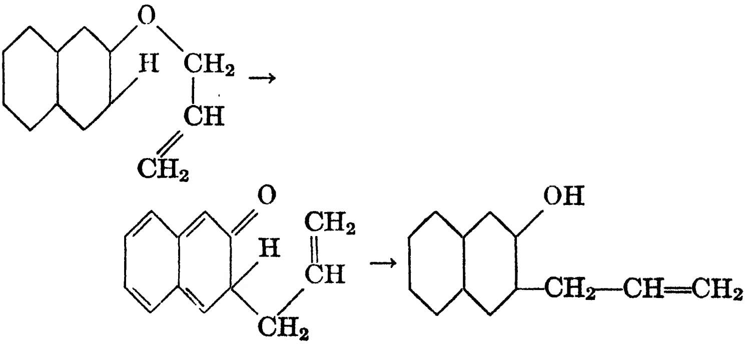
It appears necessary, therefore, to suppose that the rearrangement takes place intramolecularly, as is assumed in the mechanism outlined originally. (See equations 13·6 and 13·7.) The most striking success of this mechanism is that it accounts for the observed inversion in the allyl group. In fact, this one feature of the rearrangement would be sufficient alone (at any rate, in the *ortho* rearrangement of the allyl aryl ethers, in which the inversion seems always to occur) to exclude almost any other mechanism that might be proposed, since some sort of push-and-pull mechanism is clearly required. (Cf. page 539.)

Still a further success of the intramolecular mechanism of the *ortho* rearrangement is that it leads to a simple explanation for the inability of the allyl group in an allyl β-naphthyl ether to migrate to the adjacent beta position. For an alpha migration, which occurs with ease, equation 13·7 assumes the form 13·8, whereas for a beta migration, which does not occur, it would have to assume the form 13·9. In the assumed intermediate XLV of equation 13·8, the resonance energy of one of the



XLV

(13·8)

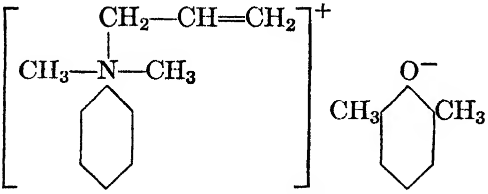


XLVI

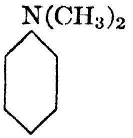
(13·9)

two benzene rings is lost just as, in the assumed intermediate XXXIV of equation 13·7, that of the one benzene ring present is lost. The two reactions, therefore, appear completely analogous; hence, if one takes place, there is no obvious reason why the other should not do so too. However, in the assumed intermediate XLVI of equation 13·9, the resonance energy of *both* benzene rings is necessarily lost. Consequently, this intermediate would have to be extremely unstable, and so its formation might be expected to be extremely difficult. In terms of Figure 12·1 of page 532 the situation appears to be that the point *D* now lies far above *Z* (and not below it as shown in the figure); hence, the amount of the ketonic substance, XLVI, that can be present at any time must be very small. Furthermore, the activation energy *YQ* must be very large.

The mechanism of the *para* rearrangement of an allyl aryl ether is rather uncertain. The mechanism that is favored for the *ortho* rearrangement is clearly inapplicable here, not only because it fails to account for the frequent lack of inversion in the allyl group, but also because it is made geometrically impossible by the relatively great distance between the ether oxygen atom and the *para* carbon atom. A dissociation-and-recombination mechanism seems rather more satisfactory, since it neither requires nor prohibits inversion, and since, in addition, it is in agreement with the observation that this reaction also follows first-order kinetics.[11] Indeed, if the above rule that two isomeric ethers of general structure XXIV and XXV always give the same rearranged product, XXVI, is found to be valid, a mechanism of this type would seem to be required. On the other hand, however, the fact that the thermal decomposition of the allyldimethylanilinium salt, XLVII, of 2,6-dimethyl-

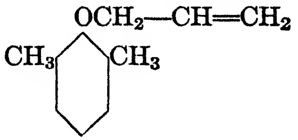


XLVII

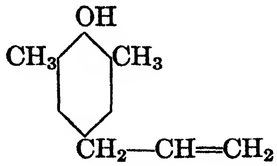


XLVIII

phenol gives only dimethylaniline, XLVIII, and allyl 2,6-dimethylphenyl ether, VII, but no 4-allyl-2,6-dimethylphenol, VIII, has been advanced



VII



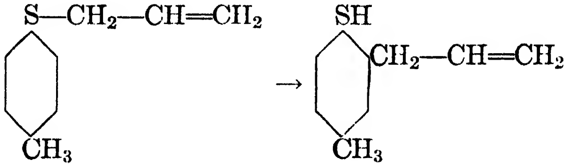
VIII

as evidence against this mechanism.[21] Clearly, the problem requires further investigation. In those rearrangements of the allyl ethers of enols in which inversions do not occur, the situation is of course similarly unsettled.

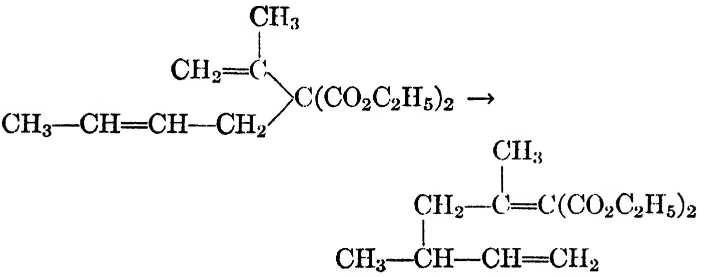
Various analogs of the Claisen rearrangement have been reported. A few typical examples are given in the equations 13·10–13·13. To the limited extent to which such reactions have been investigated, it appears that these further rearrangements proceed by first-order kinetics, are at least frequently accompanied by inversion, and do not lead to the production of cross products. An obvious suitable generalization of the intramolecular mechanism outlined in equations 13·6 and 13·7, therefore, seems reasonable here (except, perhaps, for the reaction of equation 13·13), although a dissociation into radicals or ions, followed by a recombination, is not excluded in all instances.

$$C_6H_5-\overset{O-CH_2-CH=CHCH_3}{\overset{|}{C}}=N-C_6H_5 \rightarrow C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{CH(CH_3)-CH=CH_2}{\overset{|}{N}}-C_6H_5$$

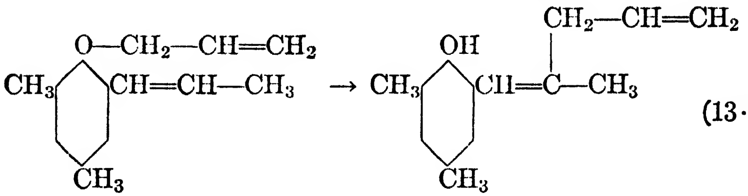
(13·10)[18]



(13·11)[22]



(13·12)[23]



(13·13)

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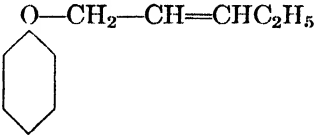
[21] D. S. Tarbell and J. R. Vaughan, Jr., *J. Am. Chem. Soc.* **65**, 231 (1943).

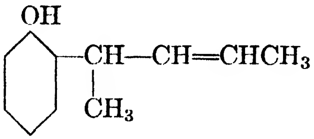
[22] C. D. Hurd and H. Greengard, *J. Am. Chem. Soc.* **52**, 3356 (1930).

[23] A. C. Cope, C. M. Hofmann, and E. M. Hardy, *J. Am. Chem. Soc.* **63**, 1852 (1941)

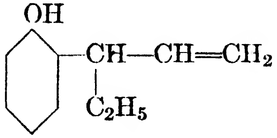
A few examples of *abnormal* rearrangements of allyl aryl ethers are known. Thus, γ-ethylallyl phenyl ether, XIV, gives *o*-(α,γ-dimethylallyl)-phenol, XLIX, as well as some of the expected product *o*-(α-ethylallyl)-phenol, XV.[13,14] Nothing is known about the mechanism of this anomalous reaction.



XIV

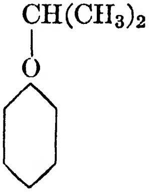


XLIX

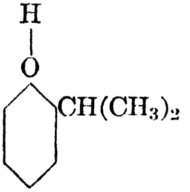


XV

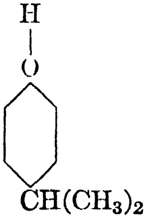
13·4 Rearrangements of Alkyl Aryl Ethers. When an alkyl aryl ether is treated with a strong acid (in the generalized sense of Lewis), it frequently undergoes a transformation into an alkylphenol, with migration of the alkyl group to the *ortho* or *para* position of the ring. For example, isopropyl phenyl ether, I, when refluxed in an acetic acid solution containing sulfuric acid, rearranges to *o*-isopropylphenol, II.[24] In the presence of aluminum chloride instead of acetic and sulfuric acids, this same ether, I, gives a mixture of *o*-isopropylphenol, II, and *p*-isopropylphenol, III, in which the latter predominates.[25] Other catalysts of similar type which have been employed include hydrogen chloride, zinc chloride (frequently in glacial acetic acid), and boron trifluoride.



I



II



III

In general, the ease of the rearrangement increases with the complexity of the alkyl group. Thus, although anisole, IV, has apparently never

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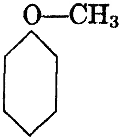
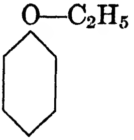
[24] J. B. Niederl and S. Natelson, *J. Am. Chem. Soc.* **53**, 1928 (1931).

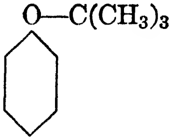
[25] R. A. Smith, *J. Am. Chem. Soc.* **56**, 717 (1934).



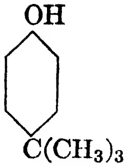
IV



V



VI



VII

been successfully transformed into either *o*- or *p*-cresol, a patent has been taken out for the production of ethylphenol (presumably either the *ortho* or the *para* isomer, or a mixture of the two) from phenetole, V, at a high temperature and pressure in the presence of silica gel or fuller's earth.[26] In most of the rearrangements of this class that have been studied, the migrating alkyl group is either secondary or tertiary, and the reactions occur with greater ease than those in which the migrating groups are primary. With *tert*-butyl phenyl ether, VI, in fact, the rearrangement (to give mostly *p-tert*-butylphenol, VII) takes place without a catalyst at the boiling point of the compound; the ether, therefore, cannot be purified by distillation at atmospheric pressure.[27]

The various mechanisms that have been proposed for the rearrangement of an alkyl aryl ether may be divided into three main classes. (1) Some authors have suggested that the reaction is intramolecular, so that the migrating alkyl group never loses contact with the molecule to which it was originally joined, and so that it never becomes attached to a different molecule. The manner in which such a migration could occur is, however, not entirely clear. (Cf., however, pages 578 f.) Certainly, nothing very closely analogous to the "inverting" migration of an allyl group to the *ortho* position (see equation 13·7 on page 549) is possible here. (2) Other authors have considered that the reaction proceeds by a dissociation-and-recombination mechanism. If this suggestion is correct, the alkyl group splits off as an olefin, as an alkyl halide, sulfate, or the like, or as an organic ion or free radical which then attacks the *ortho* or *para* position of the benzene ring. Only in rare instances, therefore, can the alkyl group be joined to the same ring in the product as in the original ether. (3) Still other authors have considered the possibility that one molecule of the ether acts as an alkylating agent toward a second molecule. If this suggestion is correct, the alkyl group is never joined to the same ring in the product as in the original ether. (However, see pages 559 f.)

The evidence which is at present available is somewhat conflicting, but, on the whole, it favors the second of the above mechanisms. (How-

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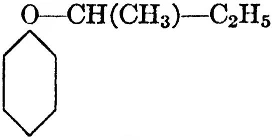
[26] Schering-Kahlbaum A.-G., Brit. **294,238**. See *C.A.* **23**, 1908 (1929).

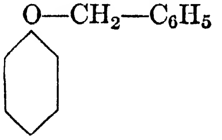
[27] R. A. Smith, *J. Am. Chem. Soc.* **55**, 3718 (1933).

ever, see pages 559 ff.) In the first place, a breaking up of the ether into fragments is known to occur in at least some instances, since both the free phenol and the olefin that is derived from the migrating alkyl group are frequently found among the major products, along with the rearranged alkylphenol. For example, the action of acetic and sulfuric acids upon *sec*-butyl phenyl ether, VIII, gives mostly phenol

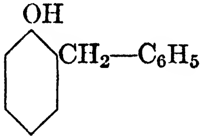


VIII

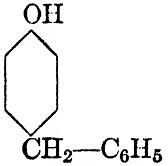
and butene (of unstated structure).[28] It is not definitely established whether in this reaction the olefin is an essential intermediate in the rearrangement or merely a by-product. In any event, however, the formation of an olefin is not a necessary condition for rearrangement, since benzyl phenyl ether, IX, which cannot give rise to an olefin, rearranges to *o*- and *p*-benzylphenol X and XI, respectively, in the presence of zinc chloride or hydrogen chloride (or of both).[29] In this reaction, however, benzyl chloride $C_6H_5—CH_2Cl$ could serve as the active intermediate; indeed, there is evidence [29] that this substance is actually produced. Although, in a formal sense, and frequently also with respect to chemical properties, the benzyl group is of the allyl type, the rearrangement of the ether IX is more closely related to the rearrangements of the alkyl aryl ethers than it is to those of the allyl aryl ethers discussed in the preceding section. In those reactions in which the existence of an olefin can be demonstrated, there is a possibility that this unsaturated compound is itself formed from an alkyl halide or the like, or possibly from an alkyl cation (or vice versa). The nature of the primary intermediate cannot be decided from the information that is now available.



IX



X



XI

Further evidence favoring the second of the three mechanisms outlined above is that the assumed recombination of the assumed fragments is a reaction of a type that can be expected to occur under the experi-

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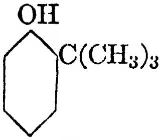
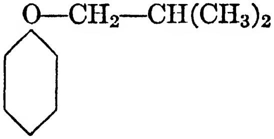
[28] M. M. Sprung and E. S. Wallis, *J. Am. Chem. Soc.* **56**, 1715 (1934).

[29] W. F. Short and M. L. Stewart, *J. Chem. Soc.* **1929**, 553.

mental conditions employed. In fact, the alkylation of an aromatic substance by an olefin, alkyl halide, or the like in the presence of a strong Lewis acid is merely an example of the familiar Friedel-Crafts reaction (or of a likewise familiar close analog of this reaction). Moreover, some sort of organic cation is commonly assumed as an intermediate both in the Friedel-Crafts reaction and in its analogs.[30] The assumption of a dissociation and subsequent recombination is therefore entirely reasonable, whether the alkyl group is considered to break away as an olefin, or as an alkyl halide or the like, or as an organic cation. Mention may be made also of the fact that the alkylphenols that result from the rearrangements under discussion are usually obtainable more conveniently by the direct alkylation of the phenol by means of the olefin or alkyl halide. Thus, *o-tert*-butylphenol, XII, and (principally) *p-tert*-butylphenol, VII, can be prepared not only by the rearrangement of *tert*-butyl phenyl ether, VI, but also by the action either of isobutylene and sulfuric acid[31] or of *tert*-butyl chloride and aluminum chloride[32] upon phenol. Moreover, the rearrangement of isobutyl phenyl ether, XIII, like that of *tert*-butyl phenyl ether, VI, gives mostly *p-tert*-butylphenol, VII; this transformation of the isobutyl into a *tert*-butyl group is what would have been expected if the isobutyl group splits off in the reaction, since isobutyl compounds in the Friedel-Crafts reaction usually lead to *tert*-butyl products. (The rearrangement within the butyl group itself may, of course, be described as a 1,2-shift. See Chapter 12.) The final type of evidence to be advanced here in favor of the dissociation-and-recombination mechanism is that the rearrangement always, or nearly always, results in the formation of cross products of one kind or another. Thus, as an extreme example, the action of boron trifluoride upon isopropyl phenyl ether, I, gives phenol, XIV, *o*-isopropylphenol, II, 2,4-diisopropylphenol, XV, 2,4,6-triisopropylphenol, XVI, and the respective isopropyl ethers, XVII, XVIII, and XIX of the last three phenols,



XII



XIII

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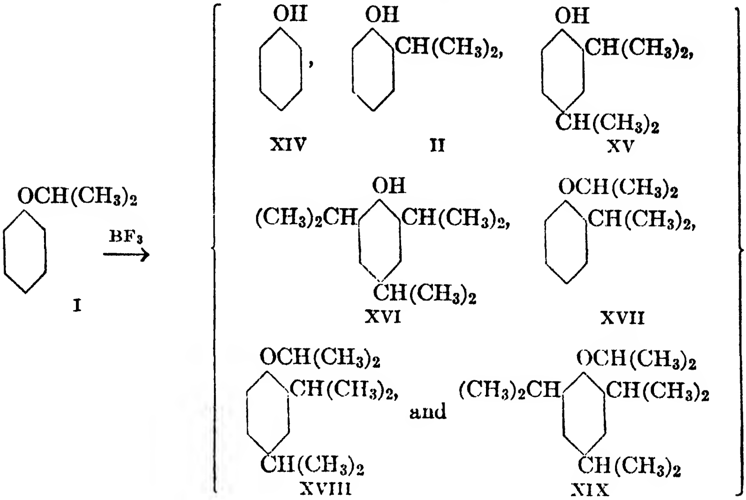
[30] Cf., for example, D. V. Nightingale, *Chem. Revs.* **25**, 329 (1939); C. C. Price, *ibid.* **29**, 37 (1941); *Mechanisms of Reactions at Carbon-Carbon Double Bonds*, Interscience Publishers, New York, 1946, pages 41 ff.; W. F. Luder and S. Zuffanti, *The Electronic Theory of Acids and Bases*, John Wiley and Sons, New York, 1946, Chapter 10.

[31] S. Natelson, *J. Am. Chem. Soc.* **56**, 1583 (1934).

[32] R. P. Perkins, A. J. Dietzler, and J. T. Lundquist, U. S. **1,972,599**. See *C.A.* **28**, 6532 (1934).

as is shown in equation 13·14.[33] Moreover, the action of aluminum chloride upon isopropyl phenyl ether, I, in the presence of phenyl ether, XX, gives *o*- and *p*-isopropylphenyl phenyl ether, XXI and XXII, respectively, in addition to *o*- and *p*-isopropylphenol, II and III, respectively; and in the presence of benzene, the corresponding reaction gives isopropylbenzene, XXIII.[25] In these reactions, the isopropyl groups have obviously been transferred from one molecule to another; hence, any kind of purely intramolecular migration is definitely excluded.



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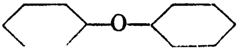
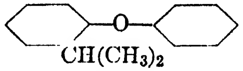
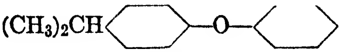


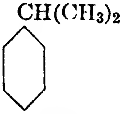
XX



XXI



XXII



XXIII

Much of the above evidence is as consistent with the assumption that each ether molecule alkylates another molecule, as with the one that dissociation and recombination occur. Only the fact that the formation of olefins, alkyl halides, and the like can sometimes be demonstrated favors the latter mechanism over the former. On the other hand, the further fact that aliphatic alcohols and ethers, such as ethyl alcohol and ethyl ether, can be used as alkylating agents in reactions of the Friedel-Crafts type suggests that dissociation of the original ether is

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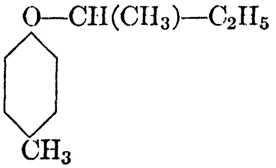
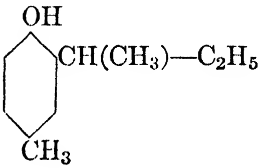
[33] F. J. Sowa, S. D. Hinton, and J. A. Nieuwland, *J. Am. Chem. Soc.* **55**, 3402 (1933).

at least not necessary. The distinction between the two mechanisms is, however, not a completely sharp one in the absence of detailed information regarding the mechanism of the Friedel-Crafts reaction; it is entirely possible, in fact, as was mentioned above, that the actual alkylating agent is always something like an organic cation, regardless of the nature of the original reagent added to the reaction mixture. For this reason, the second and third of the mechanisms described on page 556 are perhaps not essentially different.

The most important evidence opposed to the above interpretation of the rearrangement is derived from a study of certain optically active ethers. Thus, when Sprung and Wallis treated (+)-*sec*-butyl *p*-tolyl ether, XXIV, with either sulfuric acid or zinc chloride in glacial acetic acid, they obtained a product which was still dextrorotatory, and which they considered to be 2-*sec*-butyl-4-methylphenol, XXV.[28] The *sec*-butyl group thus appears able to migrate without complete racemization. The conclusion therefore follows that neither 1-butene nor 2-butene can be an intermediate since each of these olefins is optically inactive. Moreover, the further possibility that some such intermediate as *sec*-butyl chloride or the *sec*-butyl cation, XXVI, is involved seems also rather unlikely, since there is no reason to suppose that either of these intermediates could retain its optical activity under the experimental conditions. In fact, when a mixture of (+)-*sec*-butyl mesityl ether, XXVII, and *p*-cresol, XXVIII, is treated with sulfuric acid in glacial acetic acid, the 2-*sec*-butyl-4-methylphenol, XXV, which is formed has been found to be completely racemic.[34] Since this latter reaction, in which all the optical activity is lost, is necessarily intermolecular, a reasonable inference is that the preceding one, in which the activity is



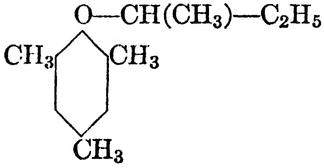
XXIV



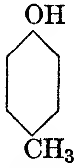
XXV

$CH_3—C^+H—C_2H_5$

XXVI



XXVII



XXVIII

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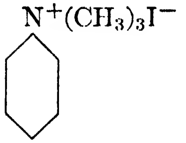
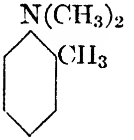
[34] W. I. Gilbert and E. S. Wallis, *J. Org. Chem.* 5, 184 (1940).

partially retained, is probably intramolecular. Before such a conclusion could be considered definitely established, however, the problem would have to be subjected to a much more extensive study than has yet been given it. The isolation of cross products in numerous instances (see above) shows conclusively that the reaction is sometimes intermolecular, but not that it always is; possibly both the inter- and the intramolecular mechanisms are correct, so that some reactions proceed by the one route, others proceed by the other route, and still others proceed partly by both routes at the same time.

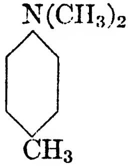
13·5 The Hofmann Rearrangement of the Salts of Alkyl Aryl Amines. In this reaction, which must be carefully distinguished from the Hofmann rearrangement of an amide (see page 459), an alkyl group migrates from the amino nitrogen atom to the *ortho* or *para* position of the benzene ring. For example, when trimethylanilinium iodide, I, is heated to 250°–280°C, it is transformed into a mixture of



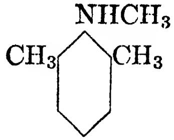
I



II

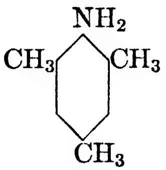


III

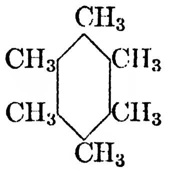


IV

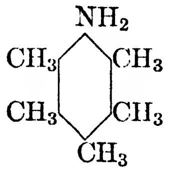
the hydroiodides of N,N-dimethyl-*o*-toluidine, II, N,N-dimethyl-*p*-toluidine, III, and N-methyl-*vic*-*m*-xylidine, IV. At the still higher temperature of 300°–330°C, the major product is the hydroiodide of mesidine, V, although smaller amounts of hexamethylbenzene, VI, and



V



VI



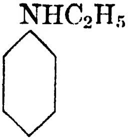
VII

the hydroiodide of 2,3,4,5,6-pentamethylaniline, VII, are also obtained. Presumably, the formation of the toluidines, the xylidine, and the mesidine results from the sequence of reactions 13·15. The formation

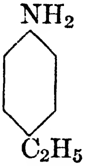
$$C_6H_5\text{—}N^+(CH_3)_3I^- \rightarrow CH_3\text{—}C_6H_4\text{—}N^+H(CH_3)_2I^- \rightarrow$$
$$(CH_3)_2C_6H_3\text{—}N^+H_2CH_3I^- \rightarrow (CH_3)_3C_6H_2\text{—}N^+H_3I^- \quad (13\cdot15)$$

of the two minor products, VI and VII, which contain respectively six and five methyl groups per molecule, and which must therefore be regarded as cross products, shows that the reaction is at least not entirely intramolecular.

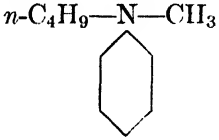
The rearrangement is not restricted to the quaternary salts like I since, as is suggested in the reaction scheme 13·15, the salts of secondary or tertiary amines behave similarly. Thus, the hydrochloride of N-ethylaniline, VIII, when heated to 300°–330°C, gives the hydrochloride of



VIII

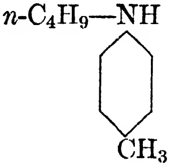


IX

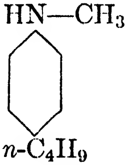


X

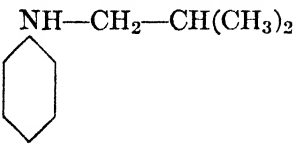
p-ethylaniline, IX; and the hydrochloride of N-methyl-N-*n*-butylaniline, X, gives the hydrochloride of *p*-methyl-N-*n*-butylaniline, XI, and possibly that of *p*-*n*-butyl-N-methylaniline, XII, as well as a mixture of the hydrochlorides of primary amines resulting from the migration of both alkyl groups.[35] Moreover, the substances which undergo the rearrangements do not have to be salts of acids like the hydrogen halides, since they can instead be addition compounds formed between the amines in question and certain acids in the generalized sense of Lewis. (Cf. Section 3·3.) For example, N-isobutylaniline, XIII, rearranges to *p*-isobutylaniline, XIV, when heated either with zinc bromide to 280°–310°C or with cobaltous chloride to 260°–270°C.[36] Sometimes both a hydrogen halide and a metallic salt are used.[36]



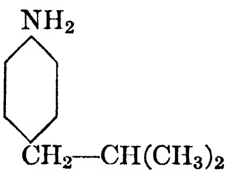
XI



XII



XIII



XIV

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[35] J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.* **117**, 103 (1920).

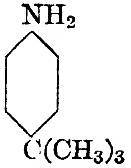
[36] W. J. Hickinbottom and G. H. Preston, *J. Chem. Soc.* **1930**, 1566; W. J. Hickinbottom and A. C. Waine, *ibid.* **1930**, 1558.

In view of the obvious close similarity of this type of rearrangement to the type discussed in the preceding section, no attempt need be made here to discuss the mechanism of the reaction in any great detail. As before, three possibilities have been suggested: (1) The reaction may be intramolecular (although, as was mentioned above, it cannot be exclusively intramolecular); (2) the amine salt may decompose into fragments which consist of an amine plus something like an olefin, or an alkyl halide, or an alkyl cation, and which subsequently recombine; or (3) one molecule may alkylate another. Also, as before, it is possible that two, or even all three, mechanisms may be correct, and that different reactions may follow different courses.

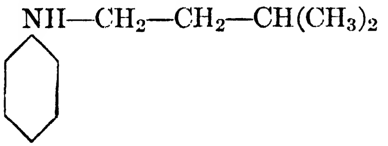
Olefins and alkyl halides have been found among the reaction products. For example, when the hydrobromide of N-isobutylaniline, XIII, is heated to 240°–270°C, it decomposes partially to isobutylene, XV, and

$(CH_3)_2C{=}CH_2$
XV

$(CH_3)_2CH{-}CH_2Br$
XVI


XVII

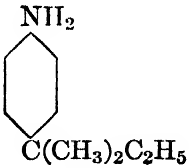
isobutyl bromide, XVI; and the residue is found to contain the hydrobromide of *p*-*tert*-butylaniline, XVII.[37] In view of the rearrangement of the isobutyl group to the *tert*-butyl group in the process, the possibility that isobutylene, XV, is an intermediate is strongly suggested. The situation is completely analogous with N-isoamylaniline, XVIII, which


XVIII

$(CH_3)_2C{=}CHCH_3$
XIX

$(CH_3)_2CH{-}CH_2{-}CH_2Br$
XX

under the same conditions, gives trimethylethylene, XIX, isoamyl bromide, XX, and *p*-*tert*-amylaniline, XXI.[37] Again, the rearrangement


XXI

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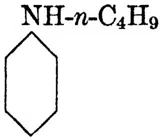
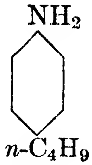
[37] W. J. Hickinbottom and S. E. A. Ryder, *J. Chem. Soc.* **1931**, 1281

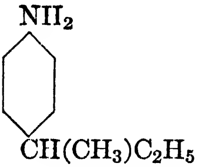
within the alkyl group itself suggests that the olefin is an intermediate. That the reaction does not always proceed in this manner is shown, however, by several of the reactions mentioned above. For example, the fact that N-isobutylaniline, XIII, when it is heated with either zinc bromide or cobaltous chloride, gives *p*-isobutylaniline, XIV, with no change in the isobutyl group, shows that isobutylene, XV, could not be an intermediate in this reaction. Moreover, the further fact that the hydrochloride of N-*n*-butylaniline, XXII, gives that of *p*-*n*-butylaniline, XXIII, rather than that of *p*-*sec*-butylaniline, XXIV, shows that neither 1-butene, XXV, nor 2-butene, XXVI, could be involved, since either of these olefins would lead to a *sec*-butylaniline.[36]



XXII



XXIII



XXIV

$CH_2{=}CH{-}C_2H_5$

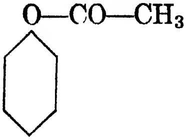
XXV

$CH_3{-}CH{=}CH{-}CH_3$

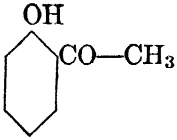
XXVI

The foregoing discussion should be sufficient to show that the rearrangement of the amine salts presents a very complex problem, about which much remains to be learned.

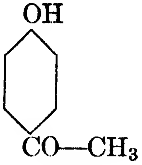
13·6 The Fries Rearrangement.[38] When phenyl acetate, I, is treated with aluminum chloride, it is transformed into a mixture of *o*-hydroxyacetophenone, II, and *p*-hydroxyacetophenone, III. Most



I



II



III

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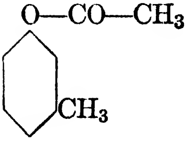
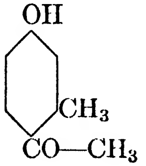
[38] For the examples of the Fries rearrangement discussed in this section, see K. W. Rosenmund and W. Schnurr, *Ann.* **460**, 56 (1928); A. H. Blatt in R. Adams, *Organic Reactions*, John Wiley and Sons, Inc., New York, Volume I, 1942, Chapter 11.

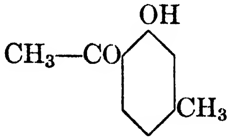
other phenolic esters of carboxylic acids behave similarly. The migration of the acyl group is always, as in the example just given, to the *ortho* or *para* position with respect to the hydroxyl group; it is never to the *meta* position. The relative amounts of the *ortho* and *para* products that are formed usually vary with the temperature of the reaction; in general, the proportion of the *ortho* hydroxy ketone that is obtained increases as the temperature is raised. An extreme example of this phenomenon is provided by the behavior of *m*-cresyl acetate, IV, which



IV

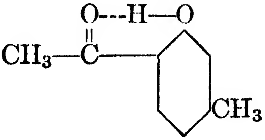


V

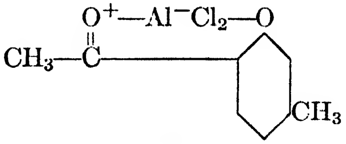


VI

gives only 2-methyl-4-hydroxyacetophenone, V, at 25°C, and only 2-hydroxy-4-methylacetophenone, VI, at 165°C. Moreover, the former substance, V, which is obtained at the lower temperature, is transformed into the latter one, VI, when it is heated with aluminum chloride at 170°C. A reasonable explanation of this behavior is that the rearrangement is reversible, and that, although the *para* compound, V, is formed more rapidly than is its isomer, VI, the *ortho* compound, VI, is the more stable of the two. Consequently, at a low temperature, at which only the fastest one of the possible reactions occurs at an appreciable rate, the *para* compound, V, is formed exclusively; but at a higher temperature, at which all the possible reactions (both the forward and the reverse ones) take place more or less rapidly, the equilibrium mixture, which consists essentially of only the *ortho* compound, VI, is obtained instead. The observed greater stability of the *ortho* compound is possibly due to the presence in its molecule of an intramolecular hydrogen bond, the existence of which, as in structure VII, is shown independently by, for



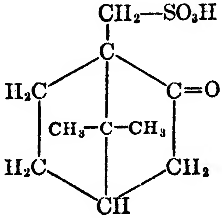
VII



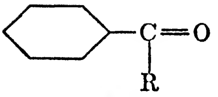
VIII

example, the fact that the *ortho* hydroxy compound, VI (or, rather, VII) is much more volatile than is its *para* isomer, V. (Cf. page 51.) This explanation, however, takes no account of the fact that, in the presence of the aluminum chloride, structures V and VII can hardly be adequate representations of the respective substances. A more reasonable explanation is therefore that the *ortho* hydroxy ketone permits the formation of some such aluminum chloride complex as VIII, whereas the *para* hydroxy ketone does not permit the formation of any very close analog of this substance. Since the union of the two oxygen atoms through the aluminum atom in structure VIII is doubtless much stronger than is the hydrogen bond in structure VII, the equilibrium may be much more favorable to the *ortho* compound in the presence of the aluminum chloride than in the absence of this substance.

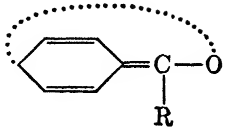
Evidence confirming the assumed reversibility of the Fries rearrangement is provided by the fact that the reaction by which a phenolic ester and a hydroxy ketone are interconverted can sometimes be made to proceed in the reverse direction, so that the ester is formed from the ketone, instead of vice versa. For example, the action of a trace of camphor sulfonic acid, IX, at 150°C transforms 2-methyl-4-hydroxyacetophenone, V, back into *m*-cresyl acetate, IV. Investigation of a considerable number of examples has led to the rule that this reverse Fries migration takes place generally if, and only if, the hydroxyl group is *para* to the acyl group, and if, and only if, some further substituent in the hydroxy ketone is *ortho* to the acyl group. The explanation of this rule is possibly that any *ortho* hydroxy ketone is always too stable to revert to the phenolic ester (presumably on account of the hydrogen bond, as in structure VII, since no aluminum chloride complex, as in structure VIII, is possible in the absence of aluminum chloride); whereas any *p*-hydroxy ketone is sufficiently unstable to react if a substituent *ortho* to the acyl group exerts a steric repulsion upon that group. This steric effect may not be due merely to a lack of space (cf. Section 9·6) for the acyl group and its *ortho* neighbor; it may be partially due also to a special kind of resonance effect. In any aromatic ketone, the conjugation of the carbonyl group with the benzene ring may be expected to lead to an appreciable stabilization of the molecule as a result of the resonance between such structures as X and XI. (Cf. Sections 10·8 and



IX



X



XI

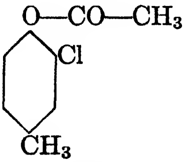
10·10.) Now, if the presence of an *ortho* substituent results in a rotation of the acyl group about the bond by which it is linked to the ring, so that the R—C=O group does not lie in the plane of the ring, the quinoid structures like XI, in which this bond is represented as a double bond, are made much less stable. Consequently, the effectiveness of the resonance with these structures is reduced, and the stabilization resulting from the conjugation is largely lost. Although the effect of this *steric inhibition of resonance* is thus in the correct direction, there is, unfortunately, no reliable way of estimating whether it is of sufficient magnitude to account for the facts.

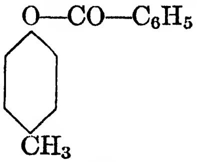
The reaction by which *m*-cresyl acetate, IV, and 2-methyl-4-hydroxyacetophenone, V, are interconverted can thus be made to go essentially to completion in either direction by suitable choice of the condensing agent (aluminum chloride or camphor sulfonic acid). This observation shows that at least one of these condensing agents is not simply a catalyst, since a catalyst cannot affect the position of the equilibrium; one of these acids must instead, therefore, enter into the reaction in some more direct manner. Undoubtedly, as has already been assumed, the product of the reaction when an equivalent quantity of aluminum chloride is used is not the ketone V that is finally isolated, but is instead an addition compound formed between this ketone and aluminum chloride. (Cf. structure VIII, suggested above for the corresponding addition compound of the *ortho* isomer.) The tendency to form such an addition compound is presumably one of the factors driving the reaction to completion. (The further assumption must apparently be made that the addition compound formed from the ketone V is more stable than the one formed from the ester IV, although, of course, less stable than the compound VIII.) On the other hand, when only a trace of camphor sulfonic acid is used, no such stable addition compound is possible; under these circumstances, the equilibrium is evidently in favor of the ester.

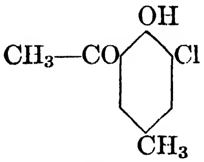
It is now generally agreed that the Fries rearrangement proceeds by a dissociation-and-recombination mechanism, as in equation 13·16.

$$C_6H_5O\text{—}CO\text{—}CH_3 + AlCl_3 \rightarrow C_6H_5OAlCl_2 + CH_3\text{—}COCl \rightarrow CH_3CO\text{—}C_6H_4OH \cdot AlCl_3 \quad (13\cdot16)$$

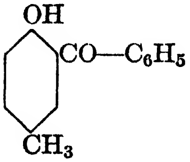
The evidence supporting this mechanism is that, when a mixture of esters is rearranged, cross products are obtained. Thus, when a mixture of 2-chloro-4-methylphenyl acetate, XII, and *p*-tolyl benzoate, XIII, is

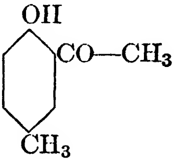

XII

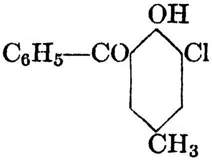

XIII


XIV

treated with aluminum chloride at 150°C, the mixture of ketones produced contains not only 2-hydroxy-3-chloro-5-methylacetophenone, XIV, and 2-hydroxy-5-methylbenzophenone, XV, but also the two possible

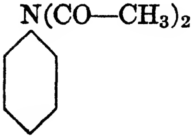

XV

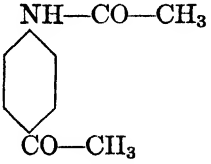

XVI

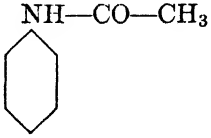

XVII

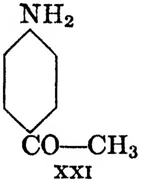
cross products, 2-hydroxy-5-methyl-acetophenone, XVI, and 2-hydroxy-3-chloro-5-methylbenzophenone, XVII.

A reaction which appears to be an analog of the Fries rearrangement is provided by the transformation of N,N-diacetylaniline, XVIII, into


XVIII

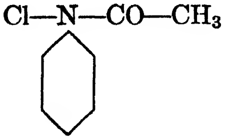

XIX

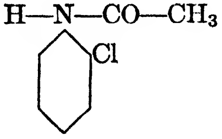

XX

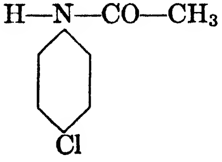

XXI

p-acetylacetanilide, XIX, by the action of zinc chloride at 150°–160°C. Acetanilide, XX, itself, however, does not rearrange similarly to *p*-aminoacetophenone, XXI.

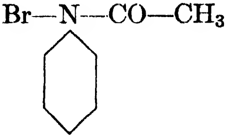
13·7 The Rearrangements of N-Chloro- and N-Bromoanilides and of Their Analogs. N-Chloroacetanilide, I, when treated


I

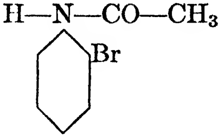

II


III

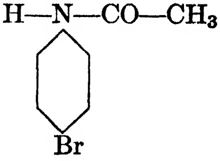
with hydrogen chloride, is transformed into a mixture of *o*-chloroacetanilide, II, and *p*-chloroacetanilide, III; the relative amounts of the two isomeric products vary with the experimental conditions. Similarly, N-bromoacetanilide, IV, when treated with hydrogen bromide,



IV



V



VI

is transformed into *o*-bromoacetanilide, V, and *p*-bromoacetanilide, VI. This type of reaction is a very general one, since most other anilides, in which a halogen atom is joined to the nitrogen atom, behave in analogous manners.

When these rearrangements are carried out in aqueous solvents (often containing more or less acetic acid), only the hydrogen halides are found to act as catalysts.[39] Other acids, such as sulfuric or acetic acid, are without pronounced effect. Moreover, both the action of hydrogen chloride upon N-bromoacetanilide, IV, and that of hydrogen bromide upon N-chloroacetanilide, I, lead to the same brominated products, V and VI. These various facts suggest that, at least under the conditions stated, the reactions are not true intramolecular rearrangements but instead are reactions which proceed by dissociations and subsequent recombinations. For example, the production of *o*- and *p*-chloroacetanilide from N-chloroacetanilide and hydrogen chloride can be imagined to involve the steps shown in equations 13·17 and 13·18.

$$C_6H_5\text{—NCl—CO—}CH_3 + HCl \rightleftarrows C_6H_5\text{—NH—CO—}CH_3 + Cl_2 \qquad (13\cdot17)$$

$$C_6H_5\text{—NH—CO—}CH_3 + Cl_2 \rightarrow Cl\text{—}C_6H_4\text{—NH—CO—}CH_3 + HCl \qquad (13\cdot18)$$

Similarly, the production of *o*- and *p*-bromoacetanilide from N-bromoacetanilide and hydrogen bromide can be imagined to involve the steps shown in equations 13·19 and 13·20. In each instance, the presence

$$C_6H_5\text{—NBr—CO—}CH_3 + HBr \rightleftarrows C_6H_5\text{—NH—CO—}CH_3 + Br_2 \qquad (13\cdot19)$$

$$C_6H_5\text{—NH—CO—}CH_3 + Br_2 \rightleftarrows Br\text{—}C_6H_4\text{—NH—CO—}CH_3 + HBr \qquad (13\cdot20)$$

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[39] For a general discussion of the rearrangement and of its mechanism, see K. J. P. Orton, F. G. Soper, and G. Williams, *J. Chem. Soc.* **1928**, 998.

of the halide ion that is derived from the hydrogen halide is obviously required. (For a discussion of the further reactions in which both chlorine and bromine are involved at the same time, see below.) Moreover, the belief that this interpretation of the reactions is correct has been supported also by extensive investigations of their kinetics. The most nearly conclusive evidence is doubtless that derived from a study [40] of the reaction of N-chloroacetanilide in the presence of hydrogen chloride containing radioactive chlorine (designated in the following as Cl*). In this work, it was shown that the exchange reaction 13·21 is slow, that

$$C_6H_5—NCl—CO—CH_3 + HCl^* \rightleftarrows C_6H_5—NCl^*—CO—CH_3 + HCl \quad (13·21)$$

the further exchange reaction 13·22 is fast, and that the rate at which

$$Cl_2 + HCl^* \rightleftarrows Cl—Cl^* + HCl \quad (13·22)$$

the radioactive *o*- and *p*-chloroacetanilides are produced is equal to that at which radioactive chloride ion disappears from the solution (provided that a suitable correction is made for the occurrence of side reactions). The only reasonable interpretation of these facts seems to be that the *o*- and *p*-chloroacetanilides are formed by the chlorine that is in equilibrium at all times with this radioactive chloride ion, as in equation 13·22. If a purely intramolecular rearrangement had occurred, no appreciable amount of radioactive chloride ion could have been removed from the solution (except in the above-mentioned side reactions), since the exchange reaction 13·21 is relatively slow.

The formation of *p*-bromoacetanilide, VI, from N-chloroacetanilide, I, and hydrogen bromide is an inevitable corollary of the proposed mechanism, as is seen from the equations 13·23 and 13·24. Since chlorine is a

$$C_6H_5—NCl—CO—CH_3 + 2HBr \rightleftarrows C_6H_5—NH—CO—CH_3 + Br_2 + HCl \quad (13·23)$$

$$C_6H_5—NH—CO—CH_3 + Br_2 \rightarrow Br—C_6H_4—NH—CO—CH_3 + HBr \quad (13·24)$$

much stronger oxidizing agent than is bromine, there is no possibility that an appreciable amount of either elementary chlorine or bromine chloride, BrCl, (see below) could be produced; hence there is no possibility that more than a trace of *p*-chloroacetanilide could be formed.

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[40] A. R. Olson, C. W. Porter, F. A. Long, and R. S. Halford, *J. Am. Chem. Soc.* **58,** 2467 (1936); A. R. Olson, R. S. Halford, and J. C. Hornel, *ibid.* **59,** 1613 (1937).

On the other hand, the formation of the same *p*-bromoacetanilide from N-bromoacetanilide and hydrogen chloride is not so obviously necessary. The equations 13·25 and 13·26 can, of course, be written, but

$$C_6H_5\text{—NBr—CO—}CH_3 + HCl \rightleftarrows C_6H_5\text{—NH—CO—}CH_3 + BrCl \quad (13\cdot25)$$

$$C_6H_5\text{—NH—CO—}CH_3 + BrCl \rightarrow Br\text{—}C_6H_4\text{—NH—CO—}CH_3 + HCl \quad (13\cdot26)$$

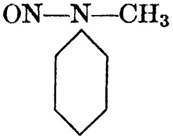
the situation is here complicated by the presence of the chloride ion, rather than of the bromide ion, in excess. Although the bromine chloride BrCl would be expected to act as a brominating agent (equation 13·26), and not as a chlorinating agent, there is no assurance that this substance is formed in sufficient amount to account for the observed course of the reaction. In the complicated equilibrium that exists in the solution, chlorine, hypochlorous acid, bromine, and hypobromous acid may be present, as well as the bromine chloride and chloride ion. Unless more information were available regarding the relative amounts of these substances, and regarding the relative rates of their reactions with acetanilide, the identity of the product could not be predicted. In any event, however, the fact that this product is *p*-bromoacetanilide rather than *p*-chloroacetanilide is not at all unreasonable.

Although the rearrangements of N-chloro- and N-bromoanilides in aqueous solvents containing hydrogen halides may be presumed to occur by the above dissociation-and-recombination mechanism, the situations under other experimental conditions may be entirely different. For example, in a nonaqueous solvent like chlorobenzene, the reaction has been found to be catalyzed by all acids investigated, and not by only the hydrogen halides.[41] The effectiveness of an acid as a catalyst increases with its strength. Under these circumstances, the free halogen can hardly be an intermediate; in fact, evidence that no halogen is formed has been obtained. Moreover, the reaction can be brought about also, in the absence of a catalyst, by the action of ultraviolet light. It is possible, but by no means proved, that the absorption of the light leads here to the production of bromine atoms. In general, nothing very definite can be said at the present time regarding the mechanisms of these reactions that take place in the absence of hydrogen halides.

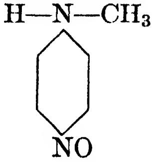
Several further classes of reaction are known in which a substituent migrates from a nitrogen atom attached to a benzene ring to the *ortho*

[41] R. P. Bell, *Proc. Roy. Soc.* (London) **A143**, 377 (1934); *J. Chem. Soc.* **1936**, 1154; R. P. Bell and P. V. Danckwerts, *ibid.* **1939**, 1774.

or *para* position. The *Fischer-Hepp* rearrangement of an aromatic nitrosoamine, for example, can be illustrated by the transformation of N-nitroso-N-methylaniline, VII, into *p*-nitroso-N-methylaniline, VIII.



VII



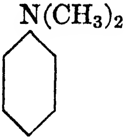
VIII

This reaction, which takes place in the presence of aqueous or alcoholic hydrochloric or hydrobromic acid, is considered to proceed, in the manner shown in equations 13·27 and 13·28, by a dissociation into the free

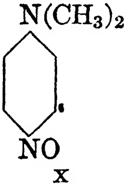
$$C_6H_5—N(NO)—CH_3 + HCl \rightleftarrows C_6H_5—NH—CH_3 + NOCl \qquad (13·27)$$

$$C_6H_5—NH—CH_3 + NOCl \rightarrow p\text{-}ON—C_6H_4—NH—CH_3 + HCl \qquad (13·28)$$

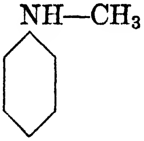
secondary amine and nitrosyl halide, which then recombine. That the rearrangement is, at any rate, not exclusively intramolecular is shown by the occurrence of cross products when the reaction is carried out in the presence of easily nitrosated substances. For example, N-nitroso-N-methylaniline, VII, and N,N-dimethylaniline, IX, in ethyl alcohol



IX



X



XI

containing hydrogen chloride give *p*-nitroso-N,N-dimethylaniline, X, and N-methylaniline, XI.[42] That a nitrosyl halide, rather than nitrous acid, is formed as an intermediate is suggested by the fact that the reaction occurs readily and with good yield in the presence of either hydrochloric or hydrobromic acid, poorly and with low yield in the presence of sulfuric acid, and apparently not at all in the presence of nitric acid.[42]

The rearrangement of a *diazoamino compound* into the corresponding aminoazo compound is also considered to proceed by a dissociation and recombination. The transformation of diazoaminobenzene, XII, for

[42] P. W. Neber and H. Rauscher, *Ann.* **550**, 182 (1942).

$$\underset{\text{XII}}{C_6H_5\text{—}N\text{=}N\text{—}NH\text{—}C_6H_5} \qquad \underset{\text{XIII}}{C_6H_5\text{—}N\text{=}N\text{—}C_6H_4\text{—}NH_2\text{-}p}$$

example, into *p*-aminoazobenzene, XIII, takes place in the presence of excess aniline and a little aniline hydrochloride; this reaction can be represented as in equations 13·29 and 13·30. Evidence for this mechanism is provided by the fact that, under suitable circumstances, cross products are formed. Thus, if dimethylaniline, IX, and its hydrochloride are substituted for aniline and its hydrochloride in the rearrangement, the major product obtained is *p*-dimethylaminoazobenzene, XIV.[43]

$$C_6H_5\text{—}N\text{=}N\text{—}NH\text{—}C_6H_5 + C_6H_5\text{—}N^+H_3Cl^- \rightleftarrows C_6H_5\text{—}N_2{}^+Cl^- + 2C_6H_5\text{—}NH_2 \quad (13\cdot29)$$

$$C_6H_5\text{—}N_2{}^+Cl^- + 2C_6H_5\text{—}NH_2 \rightarrow C_6H_5\text{—}N\text{=}N\text{—}C_6H_4\text{—}NH_2\text{-}p + C_6H_5\text{—}N^+H_3Cl^- \quad (13\cdot30)$$

$$\underset{\text{XIV}}{C_6H_5\text{—}N\text{=}N\text{—}C_6H_4\text{—}N(CH_3)_2\text{-}p} \qquad \underset{\text{XV}}{C_6H_5\text{—}OH}$$

Similarly, when diazoaminobenzene, XII, is heated with phenol, XV, *p*-hydroxyazobenzene, XVI, is obtained. And finally, when diazoaminobenzene, XII, is dissolved in either very dilute alcoholic hydrogen chloride or cold acetic acid, it is transformed into the more complex diazoamino compound, XVII;[44] this substance presumably results from the coupling of the diazonium salt with *p*-aminoazobenzene, XIII.

$$\underset{\text{XVI}}{C_6H_5\text{—}N\text{=}N\text{—}C_6H_4\text{—}OH\text{-}p}$$

$$\underset{\text{XVII}}{C_6H_5\text{—}N\text{=}N\text{—}C_6H_4\text{—}NH\text{—}N\text{=}N\text{—}C_6H_5}$$

Still other reactions of the same general type are known; in most instances, however, they have not been so extensively studied and are not so well understood. Some of the most important of these further rearrangements are illustrated in the reactions of equations 13·31–13·38.

$$C_6H_5\text{—}NCl_2 \xrightarrow{HCl} 2,4\text{-}Cl_2C_6H_3\text{—}N^+H_3\ Cl^- \quad (13\cdot31)$$

$$C_6H_5\text{—}NH\text{—}NO_2 \xrightarrow{H_2SO_4} o\text{-}O_2N\text{—}C_6H_4\text{—}N^+H_3\ HSO_4{}^- \quad (13\cdot32)$$

$$C_6H_5\text{—}NH\text{—}SO_3Na \xrightarrow{180°C} p\text{-}NaO_3S\text{—}C_6H_4\text{—}NH_2 \quad (13\cdot33)$$

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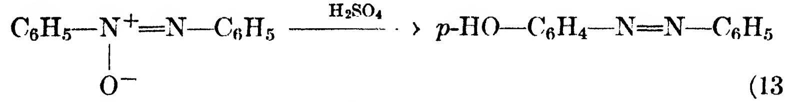
[43] E. Rosenhauer and H. Unger, *Ber.* **61**, 392 (1928).

[44] J. C. Earl, *Ber.* **63**, 1666 (1930).

$$C_6H_5\text{—NH—}SO_3K \xrightarrow[\substack{CH_3\text{—}CO_2H \\ \text{at } 0°C}]{H_2SO_4 \text{ in}} o\text{-}KO_3S\text{—}C_6H_4\text{—}NH_2 \qquad (13\cdot34)$$

$$C_6H_5\text{—NHOH} \xrightarrow{H_2SO_4} p\text{-HO—}C_6H_4\text{—}N^+H_3\ HSO_4^- \qquad (13\cdot35)$$

$$C_6H_5\text{—NHOH} \xrightarrow{HCl} p\text{-Cl—}C_6H_4\text{—}N^+H_3\ Cl^- \qquad (13\cdot36)$$



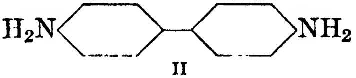
$$C_6H_5\text{—}\underset{\displaystyle O^-}{\overset{|}{N^+}}\text{=N—}C_6H_5 \xrightarrow{H_2SO_4} p\text{-HO—}C_6H_4\text{—N=N—}C_6H_5 \qquad (13\cdot37)$$

$$C_6H_5\text{—}N^+(CH_3)_2\text{—}O^- \xrightarrow{SO_2} o\text{-HO—}C_6H_4\text{—}N(CH_3)_2 \qquad (13\cdot38)$$

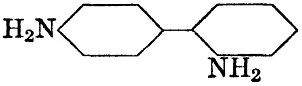
13·8 The Benzidine and Related Rearrangements.[45] In the presence of a strong acid like hydrochloric or sulfuric acid, hydrazobenzene, I, rearranges to the *p,p'*-diamine, benzidine, II. At the same time, a small amount of the isomeric *o,p'*-diamine, diphenyline, III, is also formed. In the naphthalene series, an *o,o'*-diamine may also be formed; 1,2-di-α-naphthylhydrazine, IV, for example, gives both the *p,p'*-diamine, V, and the *o,o'*-diamine, VI (but, rather unexpectedly, none of the *o,p'*-product, VII). Migrations to *meta* positions are never observed.

$C_6H_5\text{—NH—NH—}C_6H_5$

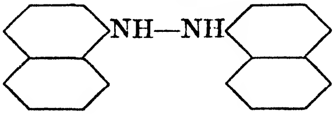
I



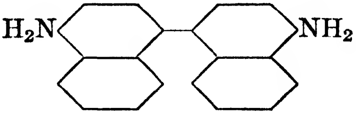
II



III



IV



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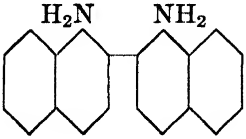
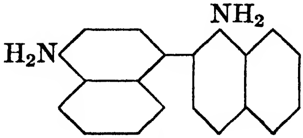


VI



VII

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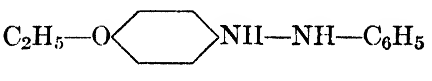
[45] For general reviews of the benzidine rearrangement and its analogs, see P. Jacobson, *Ann.* **428,** 76 (1922); R. Robinson, *J. Chem. Soc.* **1941,** 220; E. D. Hughes and C. K. Ingold, *ibid.* **1941,** 608.

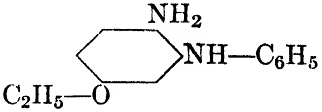
These rearrangements, at first sight, appear analogous to the ones which were discussed in the preceding sections, and in which substituents migrate from nitrogen atoms to the *ortho* or *para* positions of attached benzene rings. Thus, the formation of benzidine, II, from hydrazobenzene, I, could be imagined to proceed, as in equation 13·39, in two

$$\underset{\text{I}}{C_6H_5—NH—NH—C_6H_5} \rightarrow \underset{\text{VIII}}{C_6H_5—NH—C_6H_4—NH_2} \rightarrow \underset{\text{II}}{H_2N—C_6H_4—C_6H_4—NH_2} \quad (13·39)$$

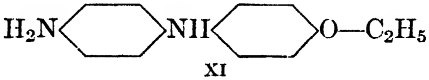
steps, in each of which singly the structural change is of the type mentioned. Although this mechanism is now definitely known to be incorrect, it was at one time considered to be supported by the fact that the presence of the assumed intermediates (e.g., VIII) in the reaction mixtures can in some instances be demonstrated. *p*-Ethoxyhydrazobenzene, IX, for example, gives 2-amino-5-ethoxydiphenylamine, X, and a little 4-amino-4′-ethoxydiphenylamine, XI; and *p*-acetamidohydrazobenzene, XII, gives 4-acetamido-4′-aminodiphenylamine, XIII. As is evident from these examples, the *semidine* rearrangement (as this side reaction is often called) may be to either the *ortho* or the *para* position, and, with an unsymmetrically substituted hydrazobenzene, it may involve the migration of either one of the two NHAr groups.



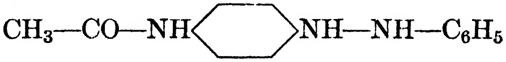
IX



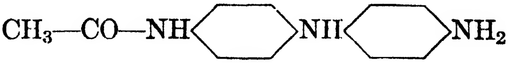
X



XI



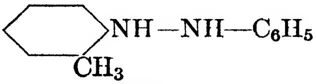
XII



XIII

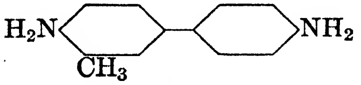
Although semidines like VIII, X, XI, and XIII can frequently be formed under the conditions of the benzidine rearrangement, they cannot, as mentioned above, be intermediates in the latter reaction. The evidence upon which this view is based is simply that benzidines cannot be formed from the semidines under the conditions under which they can be formed from the corresponding hydrazobenzenes. Evidently, therefore, the benzidine and semidine rearrangements are two entirely independent, although sometimes simultaneous, reactions.

If the benzidine rearrangement does not proceed by the two-step process of equation 13·39, a second reasonable interpretation of the reaction is then that it takes place by a dissociation into fragments which subsequently recombine. These fragments might be ions, radicals, or reactive neutral molecules. The available evidence at the present time, however, is opposed also to this further possibility. In Jacobson's review of the field in 1922,[45] this author listed 65 different reactions in which an unsymmetrical hydrazo compound Ar—NH—NH—Ar′ is rearranged to a benzidine. In each instance, the product that is obtained has been found to contain both aromatic groupings Ar and Ar′; in no instance is a product containing two like groupings isolated.[45a] For example, 2-methyl-hydrazobenzene, XIV, gives only 3-methylbenzidine, XV, and

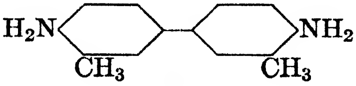


XIV

neither unsubstituted benzidine, II, nor 3,3′-dimethylbenzidine, XVI.

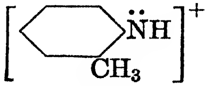


XV

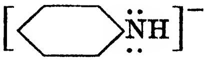


XVI

If the original hydrazobenzene, XIV, had broken up into fragments during the reaction, the symmetrical products, II and XVI, might have been expected to accompany the unsymmetrical one, XV. The argument is, however, not entirely conclusive, as can be seen from the following considerations. If, for the sake of definiteness, the hydrazobenzene, XIV, is supposed to give rise exclusively to the cation XVII and the anion



XVII

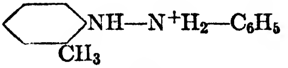


XVIII

XVIII, then only the unsymmetrical benzidine, XV, which is actually observed, would be expected to result, since the formation of either of the symmetrical products, II and XVI, by union of ions with like charge is relatively improbable.

[45a] See also G. W. Wheland and J. R. Schwartz, *J. Chem. Phys.* **17**, 425 (1949).

Since the benzidine rearrangement is acid catalyzed, the molecule which would have to be assumed to break up into fragments is doubtless not an electrically neutral molecule of the hydrazo compound, such as XIV, but is instead a cation, such as XIX, which is derived from the hydrazo molecule by the addition of a proton.

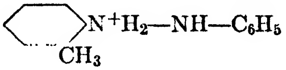


XIX

$C_6H_5—NH_2$

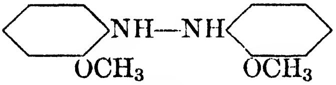
XX

Consequently, the fragments thus produced would presumably consist, not of a cation like XVII and an *anion* like XVIII, but of a cation like XVII and a *neutral molecule* like XX. As is easily seen, however, these considerations need not affect the objection raised in the preceding paragraph. In fact, the above argument remains valid unless either the original hydrazo compound is assumed to dissociate into two *electrically neutral* radicals, or else the two isomeric hydrazo cations, e.g., XIX and XXI, are assumed to be formed in comparable amounts. The first of these assumptions, however, is unlikely since it fails to account for the catalysis by hydrogen ion; the second can hardly be generally true since the relative basicities of the two nitrogen atoms in the hydrazo molecule must vary widely with the natures of the substituents in the two aromatic rings.

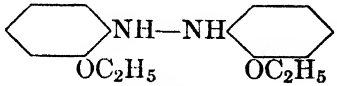


XXI

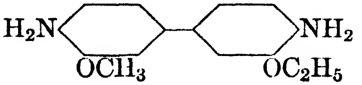
In order to remove all possibility that the benzidine rearrangement may proceed by dissociation and recombination, Ingold and Kidd[46] studied the rearrangement of a mixture of 2,2′-dimethoxyhydrazobenzene, XXII, and 2,2′-diethoxyhydrazobenzene, XXIII. If the hydrazo compounds break up into any sort of fragments, whether these be ions, radicals, or reactive molecules, the cross product 3-methoxy-3′-ethoxybenzidine, XXIV, should be formed as well as 3,3′-dimethoxybenzidine, XXV, and 3,3′-diethoxybenzidine, XXVI. The authors were unable, however, to find any evidence of this cross product.



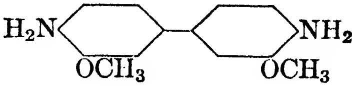
XXII



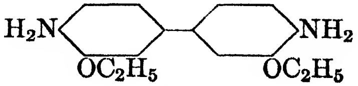
XXIII



XXIV



XXV



XXVI

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[46] C. K. Ingold and H. V. Kidd, *J. Chem. Soc.* **1933**, 984.

The rearrangements of hydrazobenzenes to *o,p'*- and *o,o'*-benzidines or to *o*- or *p*-semidines have not been so extensively studied as have the rearrangements to *p,p'*-benzidines. The view is generally held, however, that these further rearrangements also do not go by dissociation and recombination, since cross products and the like have not been observed.

If, on the basis of the above evidence, the rearrangement of hydrazobenzene, I, to benzidine, II, is considered to be a true intramolecular rearrangement, the serious problem of explaining how the two *para* carbon atoms of the original hydrazo compound find each other at so great a distance still remains to be examined. One suggestion that has been made is that, in the course of its thermal motions, the hydrazo molecule becomes distorted so that the two benzene rings come to lie more or less flat against each other in approximately parallel planes. In this way, the two *para* positions can be brought fairly close together in space. Against this explanation, however, can be raised the objection that benzene rings seem to be surprisingly thick. From information regarding the ways in which the molecules of aromatic hydrocarbons are packed in crystals, it may in fact be judged that an aromatic ring has a thickness of about 3.5 A, as compared with a distance of only about 2.8 A between two carbon atoms that are *para* to one another in the same ring.[47] Consequently, it may be doubted whether the carbon atoms at the ends of the molecule of hydrazobenzene can come close enough to one another to interact strongly until *after* the central nitrogen-nitrogen bond has first been broken. Moreover, although such an explanation could be extended to the reactions in which *o,o'*-benzidines are formed, it seems to be inadequate to account for those other reactions in which either *o,p'*-benzidines or semidines are formed instead.

A different suggestion regarding the mechanism of the benzidine and related rearrangements has been made by Dewar.[48] According to this scheme, the migration takes place in such a way that at all times the migrating group is held in some manner by the electrons of the benzene ring. Since the original molecule, therefore, never breaks up into fragments of any kind, the rearrangement is intramolecular. The significance of this mechanism is, however, not entirely clear, since the forces by which the migrating group is considered to be bonded to the ring during the migration are not precisely defined.[49] Presumably, the mechanism implies that, during the rearrangement, the molecule is a resonance hybrid receiving contributions from many different structures, in each

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[47] J. M. Robertson, *Chem. Revs.* **16**, 417 (1935).

[48] M. J. S. Dewar, *Nature* **156**, 784 (1945) *J. Chem. Soc.* **1946**, 406.

[49] Cf., however, M. J. S. Dewar, *Discussions of the Faraday Society*, No. 2, The Labile Molecule, 1947, pages 50 ff; C. A. Coulson and M. J. S. Dewar, *ibid.*, pages 54 ff.

of which the migrating group is covalently bonded to one of the atoms of the ring; and that, as the migration takes place, there is a corresponding continuous variation in the relative contributions of the several resonating structures. The process which is thus envisaged may therefore be described as a sequence of partially overlapping 1,2-shifts, proceeding in a manner which is essentially the same as the one that was outlined in Section 12·10 for a simpler type of transformation.

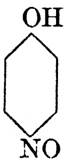
It is evident that, up to the present time, the mechanisms of the benzidine rearrangement and of its analogs have not been definitely established. Even the exact way in which the acid catalyst participates in the reaction is disputed by Robinson and by Hughes and Ingold.[45] No attempt, therefore, will be made here to pursue the problem any further.

14.

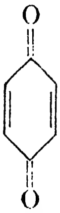
Tautomerism

14·1 The Nature of Tautomerism. Not infrequently, a material which seems to consist of a single pure substance cannot be adequately described by means of any individual structure. (Cf. Section 4·2.) For example, the action of nitrous acid upon phenol, I, gives a product

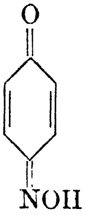
I



II

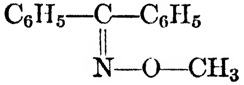


III



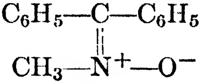
IV

which might be assumed to be *p*-nitrosophenol, II; and the action of hydroxylamine upon *p*-benzoquinone, III, gives a product which might be assumed to be the monoxime, IV. The two products are found, however, to be not isomeric but identical. On the basis of its methods of preparation, therefore, the product which is formed in either of these reactions appears to have *both* of the structures II and IV. Moreover, the action of sodium hydroxide and methyl sulfate upon benzophenone oxime leads to a mixture of the O-methyl derivative, V, and the N-methyl



$$\begin{array}{ccccc} C_6H_5 & — & C & — & C_6H_5 \\ & & \| & & \\ & & N & — & O—CH_3 \end{array}$$

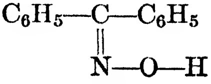
V



$$\begin{array}{ccccc} C_6H_5 & — & C & — & C_6H_5 \\ & & \| & & \\ CH_3 & — & N^+ & — & O^- \end{array}$$

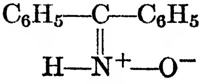
VI

derivative, VI. (Cf. page 336.) On the basis of its reactions, therefore, the original oxime appears to have *both* of the structures VII and VIII.



$$\begin{array}{ccccc} C_6H_5 & — & C & — & C_6H_5 \\ & & \| & & \\ & & N & — & O—H \end{array}$$

VII



$$\begin{array}{ccccc} C_6H_5 & — & C & — & C_6H_5 \\ & & \| & & \\ H & — & N^+ & — & O^- \end{array}$$

VIII

Numerous further illustrations of these types of anomalous behavior will be given below.

Whenever the methods of preparation or the reactions (or both) of an apparently pure substance require the assignment of two or more distinct structures which differ markedly in the relative positions of at least one atomic nucleus, *tautomerism* (from the Greek ταὐτό, the same, +μέρος, part) is said to occur. The reactions cited in the preceding paragraph, therefore, show that *p*-nitrosophenol (or *p*-benzoquinone monoxime) and benzophenone oxime are tautomeric compounds. On the other hand, whenever a substance must be described by two or more structures that correspond to practically the same positions of all the atomic nuclei, and that differ only in the average distributions of the electrons, *resonance* rather than tautomerism can ordinarily be considered to occur. (See Chapter 10.)

The word "tautomerism" is occasionally replaced by some different expression, such as "desmotropism," "pseudomerism," "metamerism," "kryptomerism," "allelotropism," "merotropy," or "dynamic isomerism." The slightly different shades of meaning often associated with these various terms are usually ignored by most chemists, however, and so they need not be discussed here. In this book, only the word "tautomerism" will be employed; it may be considered equivalent to any one, or to all, of the expressions listed. When two or more tautomeric structures differ in the position of a *hydrogen* atom, as well as in the distribution of the valence bonds, the tautomerism is frequently described as *prototropy* (from "proton" + the Greek τρέπειν, to turn). All the above types of tautomerism, and most of the further ones mentioned in this chapter, are examples of prototropy. (See, however, Sections 14·12 and 14·13.)

In at least most instances in which the material of interest is in a fluid state (i.e., when it is liquid or gaseous, or in solution in a liquid solvent), a tautomeric compound is now generally considered not to be a single pure substance, as it appears to be, but instead to be a mixture of two or more different substances, which have the structures indicated by the methods of preparation or by the reactions. (With respect to this use of the expression "tautomeric compound," see the paragraph in fine print below.) Thus, in a melted or dissolved sample of the product formed by the action either of nitrous acid on phenol or of hydroxylamine on *p*-benzoquinone, some of the molecules presumably have structure II, whereas the others have the isomeric structure IV; similarly, in a melted or dissolved sample of benzophenone oxime, some of the molecules may have structure VII, whereas the others have the isomeric structure VIII. The situation visualized here is therefore fundamentally different from the one which is considered to obtain with a resonating substance, all molecules of which are thought to have the same intermediate structure.

Although a tautomeric compound in the solid state may be a pure substance with a single definite structure, this possibility is here of little practical importance. The chemical reactions by which structures are determined are almost invariably carried out in the liquid or gaseous state or in solution, and so only the natures of the reagents and products under such conditions are relevant to the discussion of tautomerism. Consequently, except when explicit statements to the contrary are made, all further remarks in this chapter regarding the natures of tautomeric compounds may be considered to apply only when these compounds are in a fluid state.

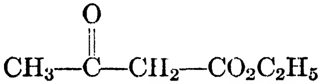
A material exhibiting tautomerism, since it is regarded as a mixture, is in a strict sense neither a substance nor a compound. Nevertheless, in order that common usage may be retained to as great an extent as possible, and in order also that awkward circumlocutions may be avoided, such materials will be referred to throughout this chapter as compounds. In doubtless the great majority of instances, a tautomeric compound (in this sense) consists almost exclusively of a single substance (or *tautomer* or *tautomeride*), and it contains at most only traces of other substances (or tautomers or tautomerides). In such an event, it seems permissible to describe the material not only as a compound but also as a substance, and to say that it possesses the one most important structure. Thus, acetoacetic ester, which has been found to consist of appreciable amounts of two tautomers (see the following section), will be referred to as a compound, but not as a substance; whereas benzophenone oxime, which presumably consists almost entirely of a single tautomer with structure VII, will be referred to both as a compound and as a substance, and it will be described by structure VII. This system of terminology, although not entirely correct, is a convenient one which in practice is found to lead to no confusion.

The reason why a tautomeric compound appears to be a single pure substance is, in general, two-fold. In the first place, as was mentioned above, such a compound usually is very nearly a single pure substance, since ordinarily only one of the tautomers exists to an appreciable extent in the equilibrium mixture. In the second place, even when two or more tautomers are present in significant amounts, their interconversion is relatively rapid. Consequently, a separation of the mixture into its components is difficult; moreover, each component of the mixture can undergo the reactions characteristic of any of its tautomers, since it can readily be transformed into that tautomer.

The transition of any given substance into a tautomer of it may be thought of as a special type of molecular rearrangement, since it involves merely the transformation of the substance in question into an isomeric substance. The characteristic which distinguishes tautomeric changes from the remaining types of rearrangement is that the tautomeric changes are always both reversible and rapid under the usual experimental conditions, whereas ordinary rearrangements need be neither reversible nor rapid. Obviously, such a distinction is not a very sharp one; there is, in fact, no definite dividing line between those isomers which are tautomers of one another and those which are not. Since, however, most examples are found to fall naturally into one category or the other, no practical difficulty is caused by this slight indefiniteness in the terminology. (However, see Section 14·12.)

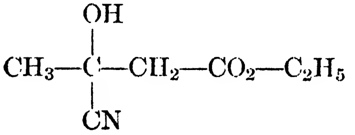
The foregoing rather general discussion of tautomerism will in the following sections be amplified and made more concrete by the consideration of a number of specific examples.

14·2 Acetoacetic Ester. One of the first examples of a tautomeric compound to receive careful and detailed study was acetoacetic ester (ethyl acetoacetate). On the one hand, this compound seems to be a saturated keto ester with structure I, since it forms the cyanohydrin, II,



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-CO_2C_2H_5$$

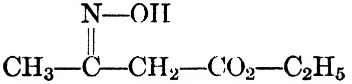
I



$$CH_3-\underset{\underset{\displaystyle CN}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-CH_2-CO_2-C_2H_5$$

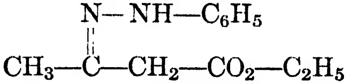
II

with hydrogen cyanide, the oxime, III, with hydroxylamine, the phenyl-



$$CH_3-\overset{\overset{\displaystyle N-OH}{\|}}{C}-CH_2-CO_2-C_2H_5$$

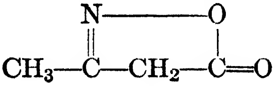
III



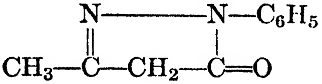
$$CH_3-\overset{\overset{\displaystyle N-NH-C_6H_5}{\|}}{C}-CH_2-CO_2-C_2H_5$$

IV

hydrazone, IV, with phenyl hydrazine, and so on. The fact that the oxime, III, and the phenylhydrazone, IV, are readily transformed by the loss of ethyl alcohol into the respective heterocyclic products, V

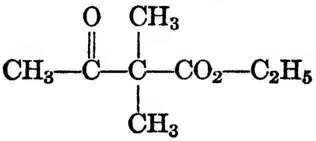


V



VI

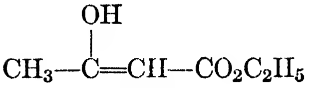
and VI, does not in any way affect the discussion. Moreover, when treated with an excess of both sodium ethoxide and methyl iodide, acetoacetic ester is transformed into a product to which the ketonic structure, VII, can be definitely assigned. On the other hand, the



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-CO_2-C_2H_5$$

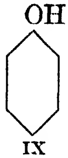
VII

compound seems also to be an unsaturated hydroxy ester with structure VIII, since it absorbs bromine very rapidly, gives an intense red color

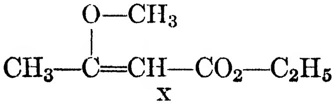


$CH_3-\overset{OH}{\overset{|}{C}}=CH-CO_2C_2H_5$

VIII



IX



$CH_3-\overset{O-CH_3}{\overset{|}{C}}=CH-CO_2-C_2H_5$

X

with ferric chloride, and is an acid with an ionization constant of about 3×10^{-11} in aqueous solution.[1] In all three of these latter respects, acetoacetic ester resembles phenol, IX, which contains a hydroxyl group joined to an unsaturated carbon atom. Moreover, the action of diazomethane CH_2N_2 upon acetoacetic ester gives a product to which structure X can be definitely assigned.

In the reactions cited (and also in a number of other reactions which might have been mentioned), acetoacetic ester appears to have both of the structures I and VIII. Since these two structures differ in the position of a hydrogen atom, which for convenience in future reference may be called the *enolic* or the *tautomeric* hydrogen atom, the compound is seen to exhibit tautomerism (prototropy) rather than resonance. For a number of years, organic chemists tried more or less unsuccessfully to explain this anomalous behavior. One attempted explanation, which is now of only historical interest, was given in 1885 by Laar,[2] who proposed that the enolic hydrogen atom, which is joined to a carbon atom in structure I but to an oxygen atom in structure VIII, is not joined permanently to either atom in the actual molecule, but is instead constantly undergoing oscillations about an intermediate position. For the description of this imagined situation, Laar coined the word "tautomerism." Although this explanation was never generally adopted and was soon shown conclusively to be incorrect, the word "tautomerism" has nevertheless been retained.

By the end of the nineteenth century, most chemists had accepted the view that acetoacetic ester is an equilibrium mixture of two distinct substances, the so-called *keto* form with structure I and the so-called *enol* form with structure VIII. The evidence supporting this view was largely that a number of other compounds with properties similar to those of acetoacetic ester had been separated into components to which structures analogous to I and VIII could be assigned. As one example among several, tribenzoylmethane was isolated in two isomeric forms; one form gives no immediate color with ferric chloride and, when treated

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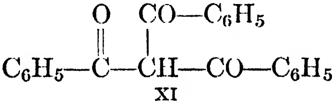
[1] G. Schwarzenbach and E. Felder, *Helv. Chim. Acta* **27**, 1701 (1944).

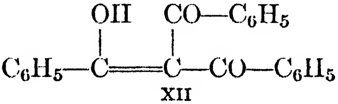
[2] C. Laar, *Ber.* **18**, 648 (1885).

with a base, is transformed only slowly into a salt; whereas the other form gives an immediate red color with ferric chloride and is transformed rapidly into a salt. The first of these substances, which is obtained by the action of sodium ethoxide and benzoyl chloride upon dibenzoylmethane in alcoholic solution, doubtless has the keto structure, XI; the second, which is obtained from the first by careful neutralization



$$C_6H_5-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle CO-C_6H_5}{|}}{CH}-CO-C_6H_5$$

XI



$$C_6H_5-\overset{\overset{\displaystyle OH}{|}}{C}=\overset{\overset{\displaystyle CO-C_6H_5}{|}}{C}-CO-C_6H_5$$

XII

of the sodium salt, doubtless has the enolic structure, XII. The solid enol form reverts in a few days to the solid keto form at room temperature, and more rapidly at higher temperatures.

Acetoacetic ester itself was not separated into its components until considerably later. The first practical method to be devised was that of Knorr, who found that the pure keto form, which melts at −39°C, can be crystallized at −78°C from any one of several organic solvents, such as ether or a mixture of ether and alcohol; and that a fairly pure liquid enol form can be obtained by the careful addition of slightly less than the calculated quantity of hydrogen chloride to a suspension of the sodium salt of acetoacetic ester in ether or petroleum ether at −78°C. Either form can be kept without change more or less indefinitely at the low temperature at which it is obtained, or for days or even weeks at room temperature if catalysts are excluded with sufficient care; return to the equilibrium mixture is, however, rapid at room temperature in the presence of acids, bases, tobacco smoke, etc.

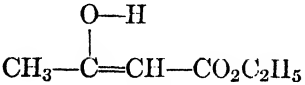
A more recent, and simpler, method of separation, devised by K. H. Meyer, is based upon the two facts: first, that quartz has a less pronounced catalytic effect than does glass, which is somewhat basic, upon the interconversion; and, second, that the enol form is appreciably more volatile than the keto form. Accordingly, the pure keto form can be obtained by placing the equilibrium mixture in a quartz distilling flask and boiling out the small amount (see below) of enol form that is present. Fairly pure enol can be obtained from the equilibrium mixture by a careful distillation from a (catalytic) glass flask into a (noncatalytic) quartz receiver; although the equilibrium mixture contains relatively little enol form, the entire material is ultimately obtained as the enol, since the equilibrium is constantly re-established in the distilling flask as the enol is distilled out.

The fact that the enol form, VIII, of acetoacetic ester is more volatile than the keto form, I, is rather unexpected, since substances with hydroxyl groups in their molecules ordinarily have higher boiling points than do analogous substances with carbonyl groups. For example, allyl alcohol, XIII, boils at 97°C, whereas the isomeric acetone, XIV,

$$CH_2{=}CH{-}CH_2{-}OH \qquad CH_3{-}CO{-}CH_3$$

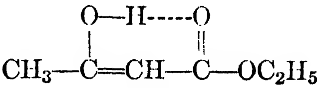
XIII XIV

boils at the considerably lower temperature of 57°C. The explanation of this anomaly is apparently that the enol form does not have exactly structure VIII with a free hydroxyl group, but has instead structure XV



$$CH_3{-}\overset{\overset{\large O-H}{|}}{C}{=}CH{-}CO_2C_2H_5$$

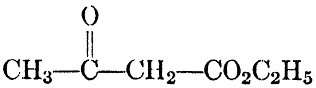
VIII



$$CH_3{-}\overset{\overset{\large O-H\cdots\cdots O}{|}}{C}{=}CH{-}\overset{\|}{C}{-}OC_2H_5$$

XV

with an intramolecular hydrogen bond. (Cf. pages 51 ff.) Since, therefore, no hydroxyl group is available for the formation of an intermolecular hydrogen bond, association does not occur (or at any rate is greatly reduced), and the substance boils at a lower temperature than does the presumably more polar keto form, I.



$$CH_3{-}\overset{\overset{\large O}{\|}}{C}{-}CH_2{-}CO_2C_2H_5$$

I

As with tribenzoylmethane (see above), the enol form of acetoacetic ester *immediately* exhibits only the properties of an unsaturated alcohol with structure VIII (or XV), whereas the keto form *immediately* exhibits only those of a saturated ketone with structure I. Either form can, however, undergo also the reactions characteristic of the other, if sufficient time is allowed for the tautomeric change to occur. For example, although the enol form gives an intense red color at once when treated with ferric chloride, the keto form gives a color only slowly.

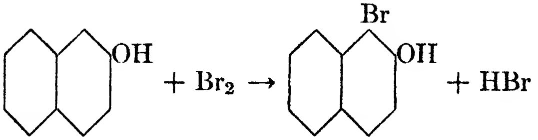
Several methods have been used for the determination of the position of the keto-enol equilibrium in a sample of acetoacetic ester. Some of these methods are based upon an examination of a physical property, such as the density, refractive index, or absorption spectrum. Any method of this type can be used, of course, only if the quantitative relationship between the value of the measured property and the composition of the mixture has previously been determined in some independent manner.

If the pure keto and enol forms are available, artificial mixtures with any desired compositions can be prepared and examined; in this way, the required relationship can be derived. This procedure is not completely satisfactory, however, because considerable difficulty is encountered not only in obtaining and keeping the pure keto and enol forms, but also in demonstrating, in the absence of any independent tests, that the materials obtained are actually the pure tautomers.

A different method of analysis, which does not require the isolation of the keto and enol forms, is therefore desirable. The most common such method is based upon the fact that the enol form absorbs bromine rapidly, whereas the keto form does not (except in so far as it may be transformed into the enol form). This so-called "Kurt Meyer method," in its simplest form, consists merely in the titration of the ester, or of a solution of it in any desired solvent, with a standard solution of bromine. The end-point is reached when the color of the bromine is no longer discharged rapidly. However, the hydrogen bromide, which is formed as one of the products of the reaction (cf. equation 14·1 below), catalyzes the conversion of the keto to the enol form (cf. equation 7·1 on page 255). Consequently, since fresh enol is constantly being produced from the keto form, the titration must be carried out very rapidly, and the correct end-point (which is, at best, not a very sharp one) can easily be passed. For this reason, the procedure is frequently modified in the following way. An amount of bromine which is known to be more than enough to react with all the enol form present, but which need not be precisely measured, is added rapidly to the ester or to its solution. The excess bromine is then destroyed immediately by the addition of more than the necessary quantity of β-naphthol (or of some other substance which reacts very fast with bromine). The reactions which have occurred up to this point are the ones shown in equations 14·1 and 14·2. From each

$$\mathrm{CH_3{-}C(OH){=}CH{-}CO_2C_2H_5 + Br_2 \rightarrow}$$

$$\underset{\text{XVI}}{\mathrm{CH_3{-}CO{-}CHBr{-}CO_2C_2H_5}} + \mathrm{HBr} \qquad (14{\cdot}1)$$



(14·2)

molecule of the enol form that is present in the original sample, exactly one molecule of the bromoester, XVI, has been produced. The analysis of the mixture for this bromoester is carried out by the addition of excess potassium iodide and by subsequent titration of the iodine that is liberated in accordance with equation 14·3. Each molecule of iodine I_2 that

$$CH_3—CO—CHBr—CO_2C_2H_5 + H^+ + 2I^- \rightarrow CH_3—CO—CH_2—CO_2C_2H_5 + Br^- + I_2 \quad (14·3)$$

is produced corresponds to one molecule of enol form in the original sample. A serious disadvantage of this more elaborate procedure is that the final reduction (equation 14·3) is often awkwardly slow. (For still another modification of the Kurt Meyer method, see page 592.)

The positions of the equilibria in acetoacetic ester under a variety of conditions are shown in Table 14·1. The percentage of enol present is seen to vary markedly with the nature of the solvent and, in general, to increase as the polarity of the solvent decreases. The significance of this fact will be discussed more fully in Section 14·6.

TABLE 14·1

POSITIONS OF THE EQUILIBRIA IN SOLUTIONS OF ACETOACETIC ESTER[a]

Solvent	*% Enol*	*Solvent*	*% Enol*
Water	0.4	50% Ethyl alcohol	2.18
Acetic acid	5.74	Propyl alcohol (0°C)	12.45
Methyl alcohol (0°C)	6.87	Ethyl acetate	12.9
50% Methyl alcohol	1.52	Amyl alcohol	15.33
25% Methyl alcohol	0.83	Benzene	16.2
Acetone	7.30	Toluene	19.8
Pure ester	7.71	Xylene	23.4
Chloroform	8.19	Ethyl ether	27.1
Nitrobenzene	10.1	Carbon disulfide	32.4
Ethyl alcohol (0°C)	12.00	Hexane	46.4
Ethyl alcohol	10.52	Vapor phase[b]	45.3–51.6
96% Ethyl alcohol	8.7		

[a] Except as noted, the values given refer to 18°C and are taken from K. H. Meyer, *Ann.* **380,** 212 (1911). The concentrations of the solutions investigated are not stated, but are apparently rather low.

[b] J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.* **54,** 4039 (1932); R. Schreck, *ibid.* **71,** 1881 (1949).

Inasmuch as the percentage of enol at equilibrium is different in the pure ester and in a dilute solution in any one of the solvents listed in Table 14·1, the position of the keto-enol equilibrium must vary with concentration; for, as the solution becomes more concentrated, the equilibrium must approach the position characteristic of the pure ester. Some data bearing upon this point are presented in Table 14·2. Evidently the solutions are far from perfect; for, if the activities of the solutes were proportional to their concentrations, the law of mass action would require that the position of the equilibrium in each solvent be independent of concentration, and that it be the same as in the pure ester. The justification of this statement is that, in equation 14·4 which

$$CH_3—CO—CH_2—CO_2C_2H_5 \rightleftarrows CH_3—C(OH)═CH—CO_2C_2H_5 \quad (14·4)$$

describes the equilibrium, the same total number of molecules (namely, one) appears on each side of the reverse arrows.

TABLE 14.2

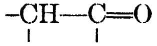
VARIATIONS IN THE POSITIONS OF THE KETO-ENOL EQUILIBRIUM IN ACETOACETIC ESTER WITH CHANGES IN CONCENTRATION[a]

Solvent	*Wt. ester in grams*	*Wt. solvent in grams*	*% Enol*
Ethyl alcohol	1.773	0.9340	7.8
	0.4808	48	13.2
Benzene	1.952	0.486	8.3
	0.284	12.982	20.6
Carbon disulfide	1.883	0.395	8.0
	0.345	36.099	39.2
n-Hexane	1.877	0.211	9.3
	0.113	6.552	58.6

[a] The figures in this table apply to "room temperature," and are taken from K. H. Meyer and P. Kappelmeier, *Ber.* **44**, 2718 (1911). In the original paper, data are given also for a large number of intermediate concentrations in each of the four solvents studied. In each solvent, the percentage of enol increases continuously between the extremes as the concentration of the ester decreases.

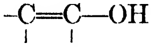
14·3 Keto-enol Tautomerism in Some Simple Carbonyl Compounds. Before the rather complex keto-enol systems (of which acetoacetic ester is a typical example) are discussed further, it will be desirable here to survey the situations which are encountered with certain more simple systems. This section will accordingly be restricted to a consideration of those compounds which, in their keto forms, contain only *isolated* carbonyl groups, and which, in their enol forms, are *not phenolic.* (A carbonyl group may be termed "isolated" if it is not close enough to a second carbonyl group, or the like, in the same molecule to be significantly affected by it; a compound may be termed "not phenolic" if it contains no hydroxyl group that is directly joined to an aromatic ring.) The types of keto-enol tautomerism which are thus excluded from consideration in this section will be taken up in later sections.

Any molecule containing the keto grouping, I, can be considered able to undergo a tautomeric change to an isomeric molecule containing the enol grouping, II. In the compounds of the restricted class defined in the preceding paragraph, the equilibria appear always to be greatly in favor of the keto forms. Acetaldehyde, for example, consists almost exclusively of molecules with the keto structure, III, and hardly at all of molecules with the alternative enol structure, IV. Moreover, all attempts to prepare a substance, vinyl alcohol, with this latter structure have led instead to ordinary acetaldehyde. The compound can therefore be regarded as a *substance*, in the sense defined on page 582, and it can be said to have the keto structure III. Similarly, acetone can be considered to be a substance with the keto structure V, although a relatively small number of enolic molecules with structure VI are doubtless also present at equilibrium (see below); and acetic acid can be considered to be a substance with the keto structure VII, although a relatively small number of enolic molecules with structure VIII may also be present.



$-\underset{|}{\mathrm{C}}\mathrm{H}-\underset{|}{\mathrm{C}}{=}\mathrm{O}$

I



$-\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{C}}-\mathrm{OH}$

II

$CH_3—CH{=}O$

III

$H_2C{=}CH—OH$

IV

$CH_3—CO—CH_3$

V

$CH_2{=}C(OH)—CH_3$

VI

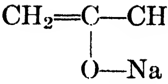
$CH_3—CO—OH$

VII

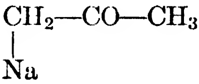
$CH_2{=}C(OH)_2$

VIII

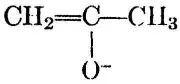
The evidence supporting the belief that simple carbonyl compounds of the types just mentioned are in equilibrium with small amounts of their respective enols is somewhat indirect, but it seems to be entirely conclusive. With the few rather special exceptions noted below (see pages 593 ff.), the enol forms have never been isolated. Nevertheless, the substances undergo a number of reactions which at least suggest the enolic structure. For example, acetone, V, reacts with metallic sodium, with liberation of hydrogen and with formation of a salt. At one time, this reaction was considered to prove the presence of the enol form, VI, since the belief was then held that only this form, with a structure analogous to that of a phenol, could be sufficiently acidic to behave in the manner observed. At the present time, however, the argument is not considered to be conclusive; there is, in fact, reason to suppose that even the keto form, V, in which the enolic hydrogen atom is joined to a carbon atom rather than to an oxygen atom, may be sufficiently acidic to react with an alkali metal. In any event, the salt that is formed cannot be considered derived, in a structural sense, solely from the enol form. Being a sodium salt, it is doubtless ionized, so that its structure is not expressible by diagram IX any more than by diagram X. Moreover,


$CH_2{=}\underset{\underset{O-Na}{|}}{C}-CH_3$

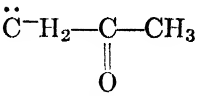
IX


$\underset{\underset{Na}{|}}{CH_2}-CO-CH_3$

X

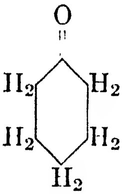

$CH_2{=}\underset{\underset{O^-}{|}}{C}-CH_3$

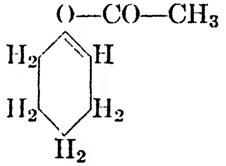
XI

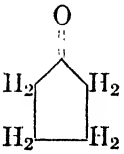

$\ddot{C}^-H_2-\underset{\underset{O}{\|}}{C}-CH_3$

XII

even its anion cannot be described by the single enol structure XI, since resonance must occur to at least a small extent with the presumably less stable, and hence less important, keto structure, XII. (See Section 14·10 for a more detailed discussion of the completely analogous problem that arises in connection with the primary and secondary nitro compounds.) Further similarly suggestive, but inconclusive, evidence is provided by the fact that, under certain conditions, compounds with isolated carbonyl groups may give rise to enolic derivatives. For example, cyclohexanone, XIII, is transformed by the action of acetic anhydride and sodium acetate into the enol acetate, XIV. Several other substances with analogous structures, such as cyclopentanone, XV, diethyl ketone, XVI, and isovaleraldehyde, XVII, have been reported


XIII


XIV


XV

$(C_2H_5)_2C{=}O$

XVI

$(CH_3)_2CH-CH_2-CHO$

XVII

to undergo reactions of this same type.

Much more conclusive evidence for the presence of traces of enol in equilibrium with simple carbonyl compounds has been obtained from kinetic studies of the acid-catalyzed halogenations, racemizations, and deuterium exchanges of ketones. The data bearing upon this problem have already been discussed [illegible] earlier chapter (see pages 255 ff.), and consequently need not be [illegible]ted here. It will be sufficient, therefore, merely to call attention to the fact that this kinetic evidence for enolization is much less complete with aldehydes and with carboxylic acids and their derivatives than it is with ketones. Indeed, in the reactions of the *acid* derivatives, the rate-determining steps are certainly not always, and are possibly never, enolizations.[3]

The enol contents of a few simple ketones have been measured by an ingenious modification of the Kurt Meyer method.[4] This modification was developed originally [5] for the determination of the positions of the equilibria in systems in which the tautomeric changes occur exceptionally fast; it was subsequently found, however, to be advantageous also for the study of systems in which the enol contents are extremely small.

The principles of this procedure are the following. First of all, two different aqueous stock solutions are prepared. One of these solutions contains both the ketone of interest and chloride ion Cl^-, at known concentrations. The purpose of the chloride ion is to serve as a "tracer," or as an "indicator" of the amount of this solution that is present in the finally resulting mixture. The second stock solution contains both bromide ion Br^- and bromate ion BrO_3^-, at known concentrations; it is slightly acidic, and its *p*H is adjusted so that elementary bromine is liberated at a satisfactorily slow rate by the reaction between the bromide and bromate ions (equation 14.5). The two stock solutions are rapidly mixed with each other (and

$$6H^+ + 5Br^- + BrO_3^- \rightarrow 3Br_2 + 3H_2O \qquad (14\cdot5)$$

also with distilled water, which acts as a "carrier") by being allowed to flow at controlled rates into and through a small vessel. The reaction mixture is then immediately brought into contact with a platinum electrode. At the outset, when the concentration of the bromine in the second stock solution is extremely low, and when the enol is accordingly in excess in the reaction vessel, all the bromine is instantly removed by reaction with the enol. However, since the concentration of the bromine is increasing steadily as more of this halogen is being formed, there is ultimately reached a time at which the amount of free bromine available in the reaction vessel is exactly equivalent to the amount of enol; and after which the bromine, rather than the enol, is in excess. The reaching of this equivalence-point is made evident by a large and sudden change in the emf of the platinum electrode, as measured against a saturated calomel electrode. When this change in potential is observed, therefore, the concentrations of enol and of bromine in the reaction vessel are exactly equal. The calculation of the fraction of enol in the ketone then requires only knowledge of the concentration of elementary bromine in the stock solution in which it is being generated, and of the ratio in which the two stock solutions are being mixed with each other. The first of these necessary data can be obtained by an immediate analysis of a portion of the appropriate stock solution; the second, by an analysis of the reaction mixture streaming past the platinum electrode. (For further details regarding both the experimental procedure and the method of calculating the results, the original papers [4,5] should be consulted.)

[3] See, for example, M. S. Kharasch and L. [illegible]bbs, *J. Org. Chem.* **6,** 705 (1941).

[4] G. Schwarzenbach and C. Wittwer, *Helv. [illegible]Acta* **30,** 669 (1947).

[5] G. Schwarzenbach and E. Felder, *Helv. Chi[illegible]ta* **27,** 1044 (1944); G. Schwarzenbach and C. Wittwer, *ibid.* **30,** 656 (1947).

In the way just outlined, the values listed in Table 14·3 have been obtained. As expected, the enol contents of the simple ketones are extremely small. Relatively large unexplained variations occur, however, with apparently minor changes in structure. It would be most interesting, therefore, to have data for a much larger group of compounds, and also data regarding the dependence of the enol contents upon the solvent, the concentration, and the temperature.

TABLE 14.3

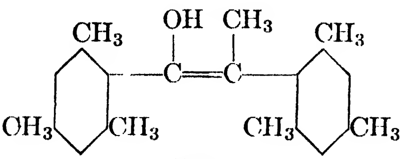
ENOL CONTENTS OF SOME MONOKETONES AT EQUILIBRIUM IN THE LIQUID STATE

Compound	*% Enol* [a]
Acetone	2.5×10^{-4}
Cyclopentanone	4.8×10^{-3}
Cyclohexanone	2.0×10^{-2}

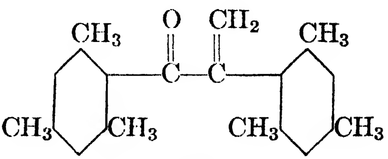
[a] G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta* **30**, 669 (1947).

The values given in Table 14·3 apply to the pure liquid ketones since, although the determinations were made in aqueous solution, insufficient time for the establishment of the new equilibria was allowed to elapse between the preparations of the solutions and the subsequent measurements. If the solutions were allowed to stand at room temperature for several hours or days, the enol contents very slowly decreased; the equilibria are therefore even less favorable to the enol forms in aqueous solution than in the pure liquids.

A comparatively small number of highly substituted vinyl alcohols that are the enolic forms of compounds with isolated carbonyl groups have been prepared. A typical example is provided by 1,2-dimesityl-1-propene-1-ol, XVIII, which is obtained by reduction of the unsaturated ketone XIX.[6] This enol has some rather unexpected properties; it is insoluble in aqueous sodium hydroxide, and it gives no color with ferric chloride. It does, however, decolorize bromine slowly and permanganate rapidly (the latter reaction leading to regeneration of the ketone XIX [7]).



XVIII



XIX

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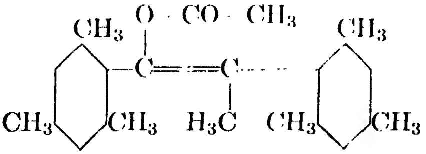
[6] R. C. Fuson, J. Corse, and C. H. McKeever, *J. Am. Chem. Soc.* **62**, 3250 (1940).

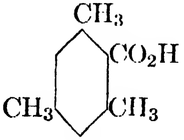
[7] R. C. Fuson, D. J. Byers, and N. Rabjohn, *J. Am. Chem. Soc.* **63**, 2639 (1941).

Its structure is shown by its infrared absorption spectrum,[6] and also by the fact that the ozonolysis of either it or its acetate, XX, gives 2,4,6-

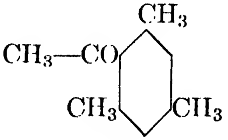


XX

trimethylbenzoic acid, XXI, and acetomesitylene, XXII.[7] Its most

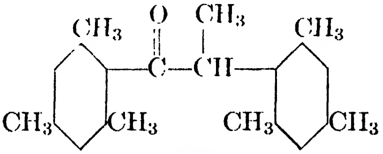


XXI



XXII

striking feature is that it does not rearrange to the keto form, XXIII

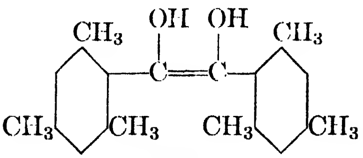


XXIII

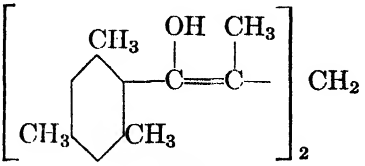
spontaneously, or even when refluxed for moderate periods of time either with alcoholic hydrogen chloride or piperidine, or with phosphoric acid.[6] Only when it is refluxed in methyl alcoholic hydrogen chloride for 13 hours, in fact, is the isomerization effected.[7] That the rearrangement is reversible, even though extraordinarily slow, is shown by the regeneration of the enol when a strongly basic solution containing both the keto form and sodium ethoxide in absolute ethyl alcohol is first refluxed for 13 hours and then acidified.[7]

The properties of the enol XVIII and its keto form XXIII indicate that here, as with the simpler tautomeric pairs considered above, the keto form is present in the larger amount at equilibrium. The reasoning which leads to this conclusion is the following. The isomerization of the enol to the keto form takes place in the presence of an acid, which could be expected to act as a catalyst, but which could not be expected to alter significantly the relative amounts of the two forms present at equilibrium. On the other hand, the reverse transformation of the keto to the enol form takes place only in the presence of a strong base, which could be expected both to catalyze the interconversion and also to affect the equilibrium by transforming the compound into a salt. In other words, in the acidic medium the keto and enol forms are presumably present as such, and so the composition of the final mixture presumably corresponds to the position of the equilibrium. In the strongly basic medium, however, only relatively small amounts of the keto and enol forms can be present as such, since most of the material has been transformed into an anion; this anion, on treatment with an acid, then gives the enol form. If this interpretation is correct, the equilibrium between the anion and the enol form must be reached more rapidly than is that between the anion and the keto form (cf. Section 14·10 for a discussion of the analogous situation with the primary and secondary nitro compounds); consequently, the enol form should react fairly rapidly with a base to form a salt. The fact that this substance does not, however, dissolve in aqueous sodium hydroxide then suggests that the sodium salt must be rather insoluble in the strongly basic medium employed.

The reason why the enol XVIII can be isolated, even though it is apparently the less stable form, is of course that the rate of its conversion into the keto form XXIII is exceptionally small. Presumably steric hindrance, resulting from the presence of the large number of bulky methyl groups in the immediate neighborhood of the oxygen atom, is responsible for the extreme sluggishness of the reactions. (Cf. Section 9·7.) This interpretation receives considerable support from the observation that stable enols analogous to 1,2-dimesityl-1-propene-1-ol, XVIII, have been obtained only when there is very great steric hindrance. Furthermore, the rate of the transformation of the enol into the keto form increases as the steric hindrance decreases. Thus, although 1,2-dimesityl-1-propene-1-ol, XVIII, rearranges extremely slowly, the less hindered enediol, XXIV, which apparently exists in two stereo-isomeric (*cis-trans*) forms, rearranges readily in the presence of either hydrogen chloride or piperidine,[8] the still less hindered dienol, XXV,



XXIV



XXV

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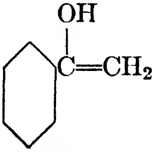
[8] R. C. Fuson and J. Corse, *J. Am. Chem. Soc.* **61**, 975 (1939); R. B. Thompson, *ibid.* **61**, 1281 (1939); R. C. Fuson, C. H. McKeever, and J. Corse, *ibid.* **62**, 600 (1940).

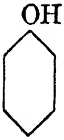
rearranges spontaneously at room temperature,[9] and the practically unhindered enol, XXVI, has never been isolated at all.



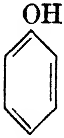
XXVI

Although the now available evidence for the enolization of simple carbonyl compounds is completely convincing only with the ketones, there is no reason to doubt that enolization occurs also to a small extent with aldehydes and with carboxylic acids and their derivatives. This belief is supported not only by the similarities in the general behaviors of the different classes of compound, but also by the measured positions of the equilibria in certain related, but more complex, systems. (See Section 14·5.) The inference may, in fact, be drawn that aldehydes are probably *more* enolic than are analogous ketones, but that acids and their derivatives are probably less enolic than such ketones.

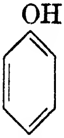
14·4 Phenols. If phenol, I, possessed the simple Kekulé structure



I



II



III

II or III, it would be an enol, strictly comparable with the enols discussed in the preceding section. Since, however, it is instead a resonance hybrid receiving equal contributions from structures II and III, it is perhaps not legitimately classifiable as an enol. Nevertheless, in view of the close structural relationship between phenol and the enols proper, and in view also of the similarities in chemical properties, phenol can most conveniently be regarded as an enol of a special type. In any event, the problem of tautomerism arises with phenol, just as it does with the previously considered carbonyl compounds.

Phenol is almost, if not quite, completely enolic. No convincing evidence for the existence of molecules with either of the two possible keto structures, IV and V, has been obtained, although the possibility

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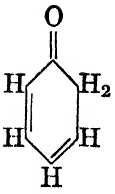
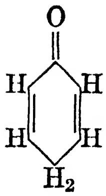
[9] R. C. Fuson, W. E. Ross, and C. H. McKeever, *J. Am. Chem. Soc.* **61**, 414 (1939).

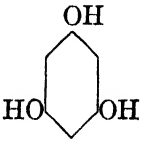


IV

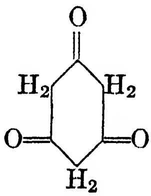


V

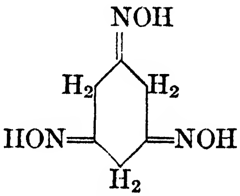
that a relatively very few such molecules may be present at equilibrium has not been excluded. The situation is therefore the opposite of that encountered with, for example, the largely ketonic acetic acid. On the other hand, the trihydric phenol phloroglucinol reacts in accordance both with the triphenolic structure, VI, and with the triketonic structure, VII. Thus, it gives a color with ferric chloride and is acidic; but also it is changed into the trioxime, VIII, by the action of hydroxylamine. Moreover, when treated with methyl iodide and sodium methoxide, it gives not only the trimethyl ether, IX, but also the methylated ketone, X (as well as such "mixed" products as the diketo ether, XI). Resorcinol, XII, is intermediate in its properties between phenol and phloroglucinol.



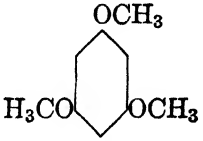
VI



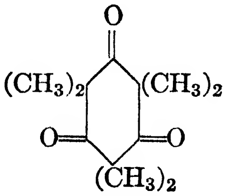
VII



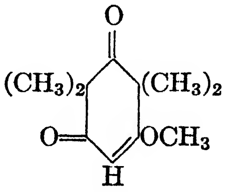
VIII



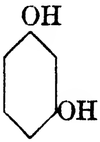
IX



X

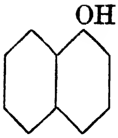


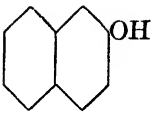
XI

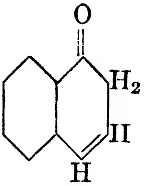


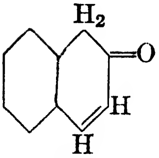
XII

The hydroxy derivatives of the more highly condensed aromatic hydrocarbons are usually analogous to those of benzene itself. Both 1-naphthol, XIII, and 2-naphthol, XIV, for example, have every appearance

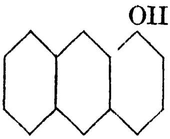

XIII

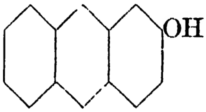

XIV

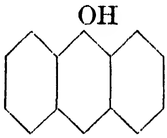

XV

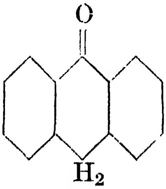

XVI

of being true phenols, and not unsaturated ketones with structures like XV and XVI, respectively. Similarly, 1-anthrol, XVII, and 2-anthrol,


XVII

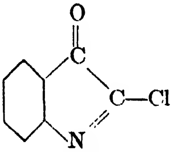

XVIII

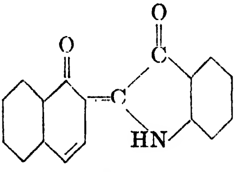

XIX


XX

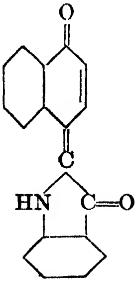
XVIII, seem also to be phenols. 9-Anthrol, XIX, however, rearranges readily to the more stable keto form, 9-anthrone. XX. (For a discussion of heterocyclic phenols, see Section 14·11.)

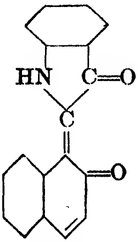
Although, as has just been stated, 1- and 2-naphthol and 1- and 2-anthrol seem to be true phenols, there is nevertheless some evidence which at least suggests the respective ketonic structures for these compounds. Thus, in the presence of phosphorus oxychloride in benzene solution, isatin chloride, XXI, reacts with 1-naphthol.


XXI

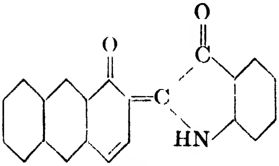

XXII

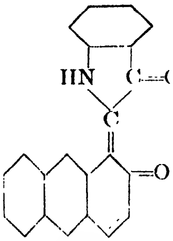
XIII, to give a mixture of the products XXII and XXIII; and with 2-naphthol, XIV, to give the product XXIV. Similarly, the corresponding compounds XXV

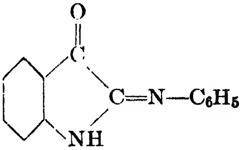

XXIII

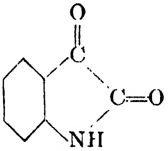

XXIV

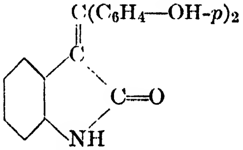
and XXVI result from the action of isatin-α-anil, XXVII, upon 1-anthrol, XVII, and 2-anthrol, XVIII, respectively, in warm acetic anhydride. In contrast, the reaction between isatin, XXVIII, and phenol itself, I, in the presence of concentrated sulfuric acid leads to the diphenolic compound XXIX. Although the experimental conditions in these several reactions are not entirely comparable, it appears evident that ketonic products can be obtained from the naphthols and anthrols more easily than from phenol.


XXV


XXVI

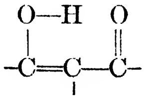

XXVII

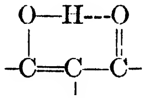

XXVIII

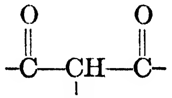

XXIX

14·5 1,3-Dicarbonyl Compounds.

Two carbonyl groups that are separated by a single carbon atom cannot be considered isolated from each other (see page 589), if the carbon atom between them is joined to at least one hydrogen atom. With the 1,3-dicarbonyl compounds, in fact, the enol forms (with the grouping I or often, more precisely, II)


$$\begin{array}{ccc} \mathrm{O{-}H} & & \mathrm{O} \\ | & & \| \\ -\mathrm{C}{=} & \mathrm{C} & {-}\mathrm{C}- \\ & | & \end{array}$$
I

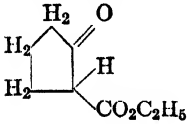
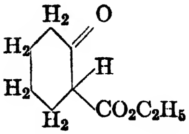
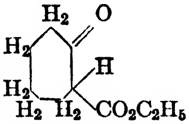
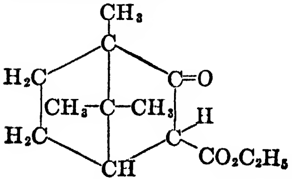
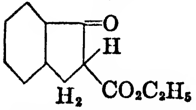

$$\begin{array}{ccc} \mathrm{O{-}H} & {\cdots} & \mathrm{O} \\ | & & \| \\ -\mathrm{C}{=} & \mathrm{C} & {-}\mathrm{C}- \\ & | & \end{array}$$
II


$$\begin{array}{ccc} \mathrm{O} & & \mathrm{O} \\ \| & & \| \\ -\mathrm{C}{-} & \mathrm{CH} & {-}\mathrm{C}- \\ & | & \end{array}$$
III

seem always to be markedly more stable with respect to their corresponding keto forms (with the grouping III) than might have been anticipated in view of the low enol contents of analogous monocarbonyl compounds. An important example illustrating this generalization is provided by acetoacetic ester, which has already been discussed in some detail. (See Section 14·2.) Numerous further examples of several different types are, however, also known; this section will be devoted to a survey of these various classes of 1,3-dicarbonyl compound.

TABLE 14·4

KETO-ENOL EQUILIBRIA IN SOME β-KETOESTERS

	% Enol			
Compound	Gas Phase[a]	Pure Liquid[b]	0.1 *M* in Hexane[a]	0.1 *M* in *A*bs. Alcohol[b, c]
$CH_3COCH_2CO_2CH_3$	53.7–55.0	5.7–6.0	....	....
$CH_3COCH_2CO_2C_2H_5$	45.3–51.6[a, f]	7.3–7.8	48–50	9–11
$CH_3COCH(CH_3)CO_2C_2H_5$	13.5–14.5	4.0–4.2	10.3–12.9	5.1
$CH_3COCH(C_2H_5)CO_2C_2H_5$	9.8–10.2	2.9–3.1	14.0–15.0	3.0–4.0
$CH_3COCH(n\text{-}C_3H_7)CO_2C_2H_5$	13.1–13.4	6.8–7.2	14.3–14.5	....
$CH_3COCH(i\text{-}C_3H_7)CO_2C_2H_5$	6.0–6.25	4.8–5.0	5.85–6.1	....
$CH_3COCH(n\text{-}C_4H_9)CO_2C_2H_5$	13.0–15.0	6.0–6.2	9.0–11	5.7–6.4
$CH_3COCH(sec\text{-}C_4H_9)CO_2C_2H_5$	8.0–10.0[d]	8.3–8.5	8.6–9.9	9.0–9.5
$CH_3COCH(sec\text{-}C_4H_9)CO_2C_2H_5$	54.0–56.0[e]	....	....	....
$CH_3COCH(C_6H_5)CO_2C_2H_5$	78–82[d]	29.5–31.5	66–68	30.4–31.0
$CH_3COCH(C_6H_5)CO_2C_2H_5$	9.0–10.0[e]	....	....	....
$CH_3COCH(CH_2C_6H_5)CO_2C_2H_5$	11.0–14.0	4.8–5.0	11–13	5.0–5.5
	26.7–28.3[f]	4.5	....	6.4
	89.9–91.7[f]	76	....	60
	....	18	....	14
	....	0.5	....	0.5
	....	25	....	23.3
$C_6H_5COCH_2CO_2CH_3$	....	18.5	....	24
$C_6H_5COCH_2CO_2C_2H_5$	....	21.4	....	24
$C_6H_5CH_2COCH(C_6H_5)CO_2C_2H_5$	....	Solid	....	31
$C_6H_5COCH(CH_2C_6H_5)CO_2C_2H_5$	....	4	....	4.1

NOTES FOR TABLE 14·4

[a] The data in this column are for 25°C and, except as noted, are taken from J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.* **54,** 4039 (1932).

[b] The data in this column above the double horizontal line are taken from J. B. Conant and A. F. Thompson, Jr. (reference *a*), and are for 25°C; the data below the double horizontal line are taken from W. Dieckmann, *Ber.* **55,** 2470 (1922).

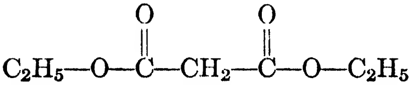
[c] The values above the double horizontal line are for 0.1 *M* solutions at 25°C; those below the double horizontal line are for 1 per cent solutions at 20°C.

[d] Value for 25°C, obtained by extrapolation of data obtained at higher temperatures.

[e] This value is for 95°C.

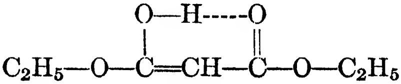
[f] R. Schreck, *J. Am. Chem. Soc.* **71,** 1881 (1949).

With respect to enol content, malonic ester (ethyl malonate), with the keto and enol structures IV and V, respectively, is doubtless inter-



$C_2H_5-O-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-O-C_2H_5$

IV



$C_2H_5-O-\overset{\overset{O-H\cdots\cdots}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}-O-C_2H_5$

V

mediate between the almost nonenolic monocarbonyl compounds like acetone and ethyl acetate, on the one hand, and the appreciably enolic β-ketoesters, like acetoacetic ester, on the other. Thus, this compound must be somewhat enolic, since it has some acidic character and since it couples, like a phenol, with benzene diazonium chloride. Nevertheless, its enol content must be very small since it is insoluble in aqueous sodium hydroxide, gives no color with ferric chloride, and instantly absorbs extremely little, if any, bromine.[10] The enol form has not as yet been isolated, although unstable solutions of it, which revert rapidly to solutions of the equilibrium ester, have been obtained by acidification of the sodium salt.[10] With the remaining esters of dicarboxylic acids, the keto forms of which contain the grouping III, the situations are closely analogous to that with malonic ester itself. In all such compounds which have so far been studied, the enol contents at equilibrium seem to be significantly greater than that in, say, acetone or ethyl acetate, but much less than that in, say, acetoacetic ester.

In a β-ketoester, the enolic hydrogen atom is joined to a carbon atom that lies between one ketonic and one ester group. Most, if not all, compounds of this class (like the most familiar representative, acetoacetic ester) are sufficiently enolic that their enol contents can be determined by the Kurt Meyer method (see pages 587 f.), and that their enol forms can be isolated by one or another of the procedures outlined above (see page 585). The positions of the keto-enol equilibria vary a great deal, however, with the solvent (if any), with the concentration, with the temperature, and with the structure of the compound. To

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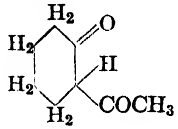
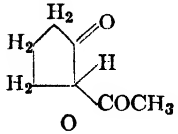
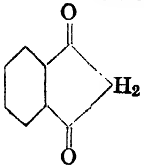
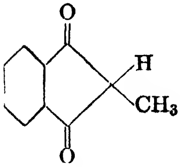
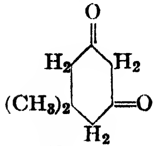
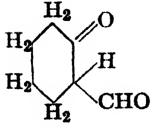
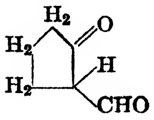
[10] K. H. Meyer, *Ber.* **45,** 2864 (1912).

TABLE 14·5

Keto-enol Equilibria in Some 1,3-Diketones

	% Enol				
Compound	Gas Phase[a]	Pure Liquid[a]	0.1 M in Hexane[a]	0.1 M in Abs. Alcohol[a]	In Water[b]
$CH_3COCH_2COCH_3$	91–93	76–80	91.4–92	82.5–83.5	15.5
$CH_3COCH(CH_3)COCH_3$	43.5–44.5	30–31	58.5–59.4	30.6–32.3	2.80
$CH_3COCH(C_2H_5)COCH_3$	34.0–37.0[c]	26–27	26.2–26.7	27.0–30.4	.....
$CH_3COCH(C_2H_5)COCH_3$	58.0–60.0[d]	......	....	....	.....
$CH_3COCH(CH_2C_6H_5)COCH_3$	68.0–72.0	61–62	66–70	45.0–47.5	.....
$CH_3COCHBrCOCH_3$	....	.....	....	....	8.1
$CH_3COCH(SO_2CH_3)COCH_3$	....	.....	....	....	1.1
	....	.....	....	....	29.1
	....	.....	....	....	15.1
	....	.....	....	....	1.60
	....	.....	....	....	1.03
	....	.....	....	....	95.3
	....	.....	....	....	48.4[e]
	....	.....	....	....	40.6[e]

NOTES FOR TABLE 14·5

[a] The data in this column are taken from J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.* **54**, 4039 (1932), and are for 25°C.

[b] The data in this column are taken from G. Schwarzenbach and E. Felder, *Helv. Chim. Acta* **27**, 1044 (1944), and are for 0.01–0.001 *M* solutions at 20°C.

[c] Value for 25°C, obtained by extrapolation of the data obtained at higher temperatures.

[d] This value is for 95°C.

[e] A keto*aldehyde*.

the extent that a generalization can legitimately be based upon the data now available, the variations of enol content with solvent[11] and with concentration are usually similar to those observed with acetoacetic ester itself (see Tables 14·1 and 14·2); that is to say, the enol forms are usually favored in the less polar solvents, and the equilibria shift toward the positions characteristic of the pure liquid esters as the concentrations are increased. (The theoretical interpretation of these variations will be discussed in the following section.) Very little can be said about the dependence of keto-enol equilibria upon temperature, since this problem has so far been relatively neglected. (However, see Table 14.4.) As with acetoacetic ester itself, the enol forms are in general more volatile than the keto forms. The presence of hydrogen bonds in the enols, which are accordingly not strictly hydroxylic compounds, is therefore indicated.

Even under a given set of experimental conditions, the positions of the equilibria in different β-ketoesters may be very different. For example, the data given in Table 14·4 show that minor changes in structure can have surprisingly great effects. In general, an alkyl substituent upon the carbon atom to which the enolic hydrogen atom is attached decreases the enolization. The inclusion of the ketonic carbon atom in an alicyclic ring may lead to large, but completely erratic, variations in the enol content. The significance of these conclusions is rendered somewhat uncertain, however, by the fact that, with α-*sec*-butyl- and α-phenylacetoacetic ester, the equilibria shift rapidly with the temperature, and in opposite directions. Possibly, therefore, any correlation made with the aid of such data as those in Table 14·4 might be valid only for a single temperature; and some entirely different correlation might be valid instead at some different temperature.

1,3-Diketones are usually somewhat more enolic than are analogous β-ketoesters. They show, however, the same sorts of variation in enol content with the experimental conditions and with structure. Generalization is, however, again difficult. The positions of the equilibria in a number of typical systems are shown in Table 14·5. As with the β-ketoesters, a number of these dicarbonyl compounds have been separated

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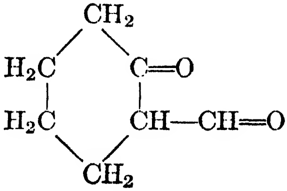
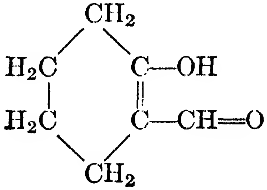
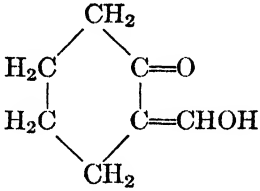
[11] Cf. J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.* **54**, 4039 (1932).

into their keto and enol components. The enols, since they are ordinarily more volatile than the keto forms, presumably contain intramolecular hydrogen bonds (except for the last three *diketones* listed, with which such hydrogen bonds are geometrically impossible).

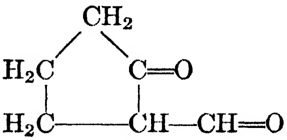
β-Ketoaldehydes are usually even more enolic than analogous 1,3-diketones. Thus, as is shown in Table 14·5, 2-formylcyclohexane-1-one, VI, and 2-formylcyclopentane-1-one, IX, have appreciably higher enol contents than do their acetyl analogs. With any compound of this type, two *different types* of enol are possible, since the enolic hydrogen atom could become attached, in the enol form, to the oxygen atom of either the ketonic or the aldehydic carbonyl group. Thus, 2-formylcyclohexane-1-one, VI, could be in equilibrium with either VII or VIII, or

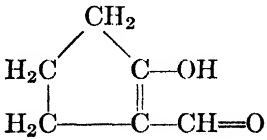

VI


VII

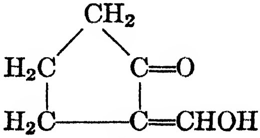

VIII

with both; and 2-formylcyclopentane-1-one, IX, could be in equilibrium


IX


X

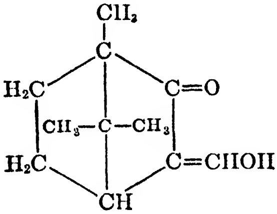
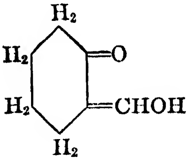
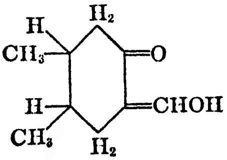
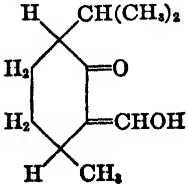
with either X or XI, or with both. The view which is most commonly


XI

held is, however, that the so-called *hydroxymethylene* structures VIII and XI are correct, or, at any rate, that these structures represent the predominant (if perhaps not the only) enolic forms present. Indeed, these compounds are usually called hydroxymethylenecyclohexanone and hydroxymethylenecyclopentanone, respectively. Other compounds with analogous structures ordinarily possess similar properties; they also are usually called hydroxymethylene ketones. Since these compounds doubtless contain intramolecular hydrogen bonds, the distinction between the two types of enolic structure is, however, very slight. As is implied by the general use of the designation "hydroxymethylene ketone," the *pure* compounds (whether solid or liquid) seem to be en-

TABLE 14·6

KETO-ENOL EQUILIBRIA IN SOME HYDROXYMETHYLENE KETONES

Compound	*State*	*% Enol* [a]
$C_2H_5CO{-}C(CH_3){=}CHOH$	Solid	100
	Solid	100
	Liquid	100
	Liquid	89
	Liquid	97

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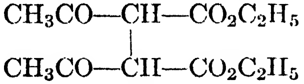
[a] K. v. Auwers and H. Jacobsen, *Ann.* **426**, 161 (1922).

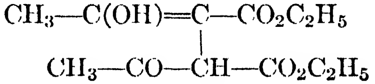
tirely enolic, or nearly so. Thus, by application of the Kurt Meyer method, v. Auwers and Jacobsen[12] have obtained the results shown in Table 14·6. The effect of the solvent upon the positions of the equilibria with a number of compounds belonging to this class has been investigated by Sen and Mondal,[13] who found that the enol contents decrease with the time in alcoholic solution, but increase slightly in either benzene or ether solution.

When two or more pairs of carbonyl groups that are in the 1,3-positions with respect to each other are present in the same molecule, the possibilities for keto-enol tautomerism are increased. Diacetylsuccinic ester, for example, has been obtained as the diketo form, XII, the keto-enol



$$\begin{array}{rcl}\mathrm{CH_3CO{-}} & \mathrm{CH} & \mathrm{{-}CO_2C_2H_5}\\ & | & \\ \mathrm{CH_3CO{-}} & \mathrm{CH} & \mathrm{{-}CO_2C_2H_5}\end{array}$$

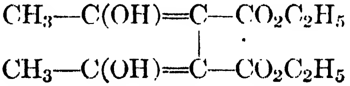
XII



$$\begin{array}{rcl}\mathrm{CH_3{-}C(OH){=}} & \mathrm{C} & \mathrm{{-}CO_2C_2H_5}\\ & | & \\ \mathrm{CH_3{-}CO{-}} & \mathrm{CH} & \mathrm{{-}CO_2C_2H_5}\end{array}$$

XIII

form, XIII, and the dienol form, XIV. Actually, altogether five



$$\begin{array}{rcl}\mathrm{CH_3{-}C(OH){=}} & \mathrm{C} & \mathrm{{-}CO_2C_2H_5}\\ & | & \\ \mathrm{CH_3{-}C(OH){=}} & \mathrm{C} & \mathrm{{-}CO_2C_2H_5}\end{array}$$

XIV

different forms of this ester are reported to have been isolated; two of these are doubtless *stereo*isomers of other forms.

It is possible for the molecule of a keto form to contain a hydrogen atom that is alpha to *three* carbonyl groups. Any such compound might be expected to be more enolic than an analogous one in which the corresponding hydrogen atom is alpha to only two carbonyl groups. This expectation is sometimes in agreement with experiment. Thus, tricarbomethoxymethane, XV, is 8–16 per cent enolic in the gas phase,[11]

$\mathrm{HC(CO_2CH_3)_3}$ XV $\quad$ $\mathrm{H_2C(CO_2C_2H_5)_2}$ XVI $\quad$ $\mathrm{CH_3{-}CO{-}CH(CO_2C_2H_5)_2}$ XVII

although the enol content of the analogous malonic ester, XVI, is so small that the attempt to measure it has failed. Similarly, acetylmalonic ester, XVII, is 71 per cent enolic in absolute alcoholic solution, whereas both acetoacetic ester and malonic ester are much less enolic. Nevertheless, examples in which the variation is in the opposite direction are also known. Thus, although dibenzoylmethane, XVIII, is apparently

$\mathrm{H_2C(CO{-}C_6H_5)_2}$ XVIII $\quad$ $\mathrm{HC(CO{-}C_6H_5)_3}$ XIX

---

[12] K. v. Auwers and H. Jacobsen, *Ann.* **426,** 161 (1922).

[13] H. K. Sen and K. Mondal, *J. Indian Chem. Soc.* **5,** 609 (1928).

almost completely enolic either in the pure state or in alcoholic solution, tribenzoylmethane, XIX, is reported[14] to be markedly less enolic.

14·6 The Variation of Enol Content with Solvent. It has been stated (pages 588 and 603) that acetoacetic ester is more enolic in a nonpolar solvent than in a polar one, and that most other 1,3-dicarbonyl compounds which have been investigated behave similarly. The reason for this striking regularity can be understood with the aid of the van't Hoff-Dimroth relation, a somewhat different form of which was discussed in an earlier chapter. (See Section 2·9.)

For the reaction shown in equation 14·6, the value of the equilibrium

$$\text{keto} \rightleftarrows \text{enol} \tag{14·6}$$

constant K, given by equation 14·7, varies from solvent to solvent if

$$K = \frac{C_E}{C_K} \tag{14·7}$$

the concentrations C_E and C_K of the enol and keto forms, respectively, are expressed either in moles per liter or in any of the other conventional units. However, the constant G, defined by equation 14·8, should be

$$G \equiv \frac{C_E/S_E}{C_K/S_K} = K\frac{S_K}{S_E} \tag{14·8}$$

more or less independent of the solvent if the solubilities S_E and S_K of the enol and keto forms, respectively, in the solvents of interest are not too great. Now, if equation 14·8 is put into the equivalent form 14·9,

$$K = G\frac{S_E}{S_K} \tag{14·9}$$

the ordinary equilibrium constant K is seen to be equal to a constant G (which is characteristic of the particular keto-enol system, but is approximately independent of the solvent) multiplied by the ratio S_E/S_K of the solubilities of the two forms. It follows, therefore, that the relative amount of any given enol form present at equilibrium is greatest in that solvent in which its *relative* solubility S_E/S_K is greatest, and least in that solvent in which its relative solubility is least. It follows also that, with acetoacetic ester and its analogs, the solubilities of the enol forms, relative to those of the corresponding keto forms, are greatest in the least polar solvents and least in the most polar solvents.

---

[14] W. Dieckmann, *Ber.* **55**, 2470 (1922).

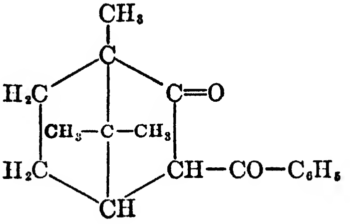
The extent to which equation 14·9 permits a quantitatively accurate interpretation of the observed variations in the positions of the keto-enol equilibria is illustrated by the data of Table 14·7. The compound to which these data refer is benzoylcamphor, I. Although here the ratio S_E/S_K of the solubilities varies by a factor of 8, the value of G is constant within less than ±5 per cent.

TABLE 14·7

VARIATION WITH SOLVENT OF THE KETO-ENOL EQUILIBRIUM IN BENZOYLCAMPHOR[a]

Solvent	K	S_E/S_K	G
Ethyl ether	6.81	6.39	1.06
Ethyl acetate	1.98	1.81	1.09
Ethyl alcohol	1.67	1.57	1.06
Methyl alcohol	0.869	0.748	1.15
Acetone	0.852	0.80	1.06

[a] O. Dimroth, *Ann.* **399**, 91 (1913).



I

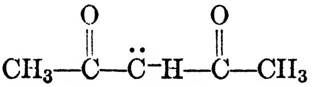
The above conclusion that the relative solubilities of the enol forms increase as the polarity of the solvent decreases may at first sight seem somewhat surprising. Since hydroxylic compounds are ordinarily more polar than analogous ketonic ones, and since "like dissolves like," the enol forms might have been expected to have their least, rather than their greatest, relative solubilities in the nonpolar solvents. The situation here is therefore completely analogous to the one encountered earlier (pages 585 f.), when attention was called to the fact that the enol form of acetoacetic ester is more volatile than the keto form. The two related anomalies can be explained in the same way, i.e., as a consequence of the intramolecular hydrogen bond in the enol form. The enol form is accordingly less polar than the keto form, and not more polar, as might have been supposed. The situations with the remaining 1,3-dicarbonyl compounds, with which the enol forms are more volatile than the keto forms and are favored in the nonpolar solvents, are of course completely analogous to that with acetoacetic ester.

The enol contents of acetone and of other simple monoketones have been found to be smaller in aqueous solution than in the pure liquid. (See page 593.) In view of the foregoing considerations, this observation seems anomalous; for, with these compounds, there is no possibility of intramolecular hydrogen bonds, and hence no obvious reason why the relative solubilities of the enol forms should be less in water than in the corresponding ketones. Perhaps the equilibria are displaced by hydration of the keto forms. The problem deserves further study.

The nature of the solvent can affect the keto-enol equilibrium of a 1,3-dicarbonyl compound in still a different way. When the enol content of any such compound in a solvent like water or alcohol is measured by the Kurt Meyer method, the amount of bromine absorbed is found to be appreciably greater in a strongly basic solution than it is in an approximately neutral one. Indeed, in the most basic solutions, the amount of bromine absorbed may approach the value corresponding to an enol content of 100 per cent (as, for example, with acetylacetone, II). This phenomenon is undoubtedly due, however, not primarily to a shift in the equilibrium between the un-ionized keto and enol forms, II and III,

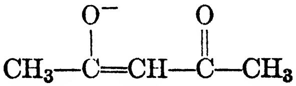
$$\underset{\text{II}}{CH_3-CO-CH_2-CO-CH_3} \qquad \underset{\text{III}}{CH_3-C(OH){=}CH-CO-CH_3}$$

respectively, but rather to the transformation of the compound into a salt. The anion of this salt, which absorbs bromine just as the enol form, III, does, must resonate among the keto and enol structures, IV, V,



$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\cdot\cdot}{C}{}^{-}H-\overset{\overset{O}{\|}}{C}-CH_3$$

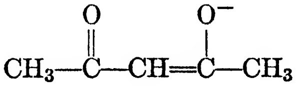
IV



$$CH_3-\overset{\overset{O^-}{|}}{C}{=}CH-\overset{\overset{O}{\|}}{C}-CH_3$$

V

and VI. Since the salt is therefore not strictly an enol, the statement



$$CH_3-\overset{\overset{O}{\|}}{C}-CH{=}\overset{\overset{O^-}{|}}{C}-CH_3$$

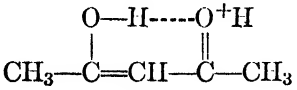
VI

that the equilibrium shifts toward the enol form in basic solution is not quite correct. (See also page 591.)

The absorption of bromine by a 1,3-dicarbonyl compound may increase in strongly acidic solution as well as in strongly basic solution. Acetylacetone, II,[15] for example, has an apparent enol content of about 75 per cent in concentrated sulfuric acid, although it is only 15.5 per cent enolic in water. (See Table 14·5.) The explanation here is presumably that, in the acidic medium, the equilibrium which is measured is no longer the one between electrically neutral keto and enol forms, II and

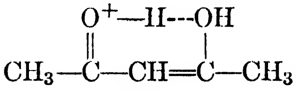
[15] G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta* **30**, 659 (1947).

III, respectively, but rather one between ketonic and enolic oxonium cations. (Cf. Section 2·3.) The direction in which the equilibrium is observed to be displaced then shows that the enol form is more basic than the keto form; this conclusion seems reasonable since the resulting enolic cation must be stabilized by the resonance between the two (almost) equivalent structures VII and VIII, whereas the ketonic cation,



$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O{-}H\cdots\cdots}{|}}{C}{=}CH{-}\overset{\overset{\displaystyle O^{+}H}{\|}}{C}{-}CH_3}$$

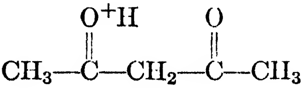
VII



$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O^{+}{-}H\cdots}{\|}}{C}{-}CH{=}\overset{\overset{\displaystyle OH}{|}}{C}{-}CH_3}$$

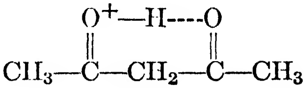
VIII

IX (or perhaps X), cannot be stabilized in any such way. (Cf. Section 10·10.)



$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O^{+}H}{\|}}{C}{-}CH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3}$$

IX

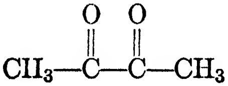


$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O^{+}{-}H\cdots\cdots}{\|}}{C}{-}CH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3}$$

X

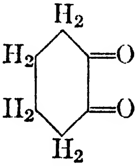
14·7 Other Types of Dicarbonyl Compound.

An acyclic 1,2-diketone, such as biacetyl, I, is ordinarily yellow and predominantly ketonic. A cyclic 1,2-diketone, such as cyclohexane-1,2-dione, II, on the other hand, is ordinarily colorless and highly enolic, as in structure III. The marked difference between these two classes of compound is shown by the data of Table 14·8.

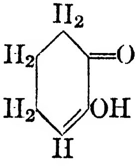


$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3}$$

I



II



III

With certain types of aromatic 1,2-diketone, even if the carbon atoms of the two carbonyl groups are not parts of rings, the enol contents may be rather large. Such substances, therefore, resemble the cyclic compounds listed in Table 14·8 more closely than they do biacetyl, even though in structure they seem more analogous to the latter acyclic compound. For example, benzyl methyl diketone, IV, is about 60 per cent enolic in the pure liquid at 100°C,[16] and benzyl phenyl diketone, V, is 29.6 per cent enolic under the same conditions.[16] Each of these two compounds has been separated into its keto and enol forms. Since, under

$\mathrm{C_6H_5{-}CH_2{-}CO{-}CO{-}CH_3}$
IV

$\mathrm{C_6H_5{-}CH_2{-}CO{-}CO{-}C_6H_5}$
V

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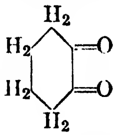
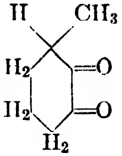
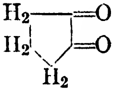
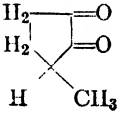
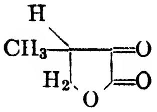
[16] H. Moureu. *Ann. chim.* [10] **14**, 283 (1930).

TABLE 14.8

KETO-ENOL EQUILIBRIA IN SOME 1,2-DIKETONES

Compound	*% Enol*[a]
	40
	60
	100
	100
	100
$CH_3—CO—CO—CH_3$ [b]	5.6×10^{-3}

[a] Except as noted, the values in this column are taken from G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta* **30**, 663 (1947), and refer to dilute aqueous solution.

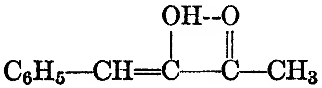
[b] The value for this compound is taken from G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta* **30**, 669 (1947), and is for the pure liquid ketone.

10 mm pressure, the keto form, IV, boils at 104°–108°C, whereas the corresponding enol form, VI, boils at the higher temperature of 133°–

$$C_6H_5—CH{=}C(OH)—CO—CH_3$$

VI

134°C, it is improbable that an intramolecular hydrogen bond exists in the latter substance. This conclusion is in agreement with the generalizations stated in Section 2·6; for, if an intramolecular hydrogen bond did exist in the enol, as in structure VII, the ring would consist of only



$$C_6H_5—CH{=}\overset{\text{OH--O}}{C—C}—CH_3$$

VII

five members (including the hydrogen atom), and it would contain only one double bond.

In a 1,4-diketone, such as acetonylacetone, VIII, the two carbonyl

$$\mathrm{CH_3{-}CO{-}CH_2{-}CH_2{-}CO{-}CH_3}$$

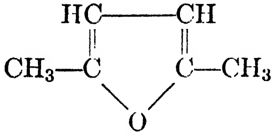
VIII

groups are fairly completely isolated from each other; there is, at any rate, no really convincing evidence that any compound of this type is significantly more enolic than a simple monoketone. That the isolation of the carbonyl groups is not absolute, however, is suggested (without being in any sense proved) by certain reactions which can be most simply interpreted in terms of a dienolic structure like IX. Thus,

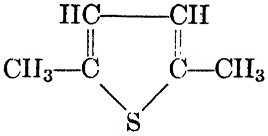
$$\mathrm{CH_3{-}C(OH){=}CH{-}CH{=}C(OH){-}CH_3}$$

IX

acetonylacetone, VIII, is transformed into 2,5-dimethylfuran, X, when

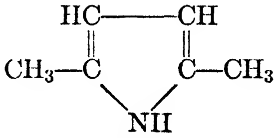


X



XI

distilled with zinc chloride, into 2,5-dimethylthiophene, XI, when heated with phosphorus pentasulfide P_2S_5, and into 2,5-dimethylpyrrole, XII,



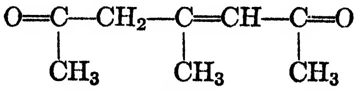
XII

when heated with alcoholic ammonia.

When two carbonyl groups are separated from each other by a saturated chain of more than two atoms, they can be considered completely isolated; under such circumstances, the possibility that the enolization is greater than usual is not supported by even inconclusive evidence of the type just mentioned in connection with the 1,4-diketones. However, when the chain separating the carbonyl groups is unsaturated, the enol contents may be appreciable. Glutaconic dialdehyde, XIII, for example,

$$\mathrm{O{=}CH{-}CH_2{-}CH{=}CH{-}CH{=}O}$$

XIII



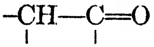
$$\mathrm{O{=}\underset{CH_3}{C}{-}CH_2{-}\underset{CH_3}{C}{=}CH{-}\underset{CH_3}{C}{=}O}$$

XIV

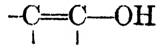
seems to be relatively very enolic; in particular, it forms an especially stable sodium salt.[17] Moreover, the related ketone, XIV, seems also to be appreciably enolic, although rather less so than the aldehyde, XIII.[17]

14·8 Variations in Enol Content with Structure. An important theoretical problem is presented by the above-mentioned extreme variations in the enol contents of carbonyl compounds, ranging from practically 0 per cent in, say, acetone to practically 100 per cent in, say, phenol. Although, unfortunately, this problem has not yet been completely solved, several of the factors involved in it are now fairly well understood.

All attempts that have been made to account for the observed differences in the positions of the keto-enol equilibria have been based upon the assumption that the keto grouping, I, is normally more stable than


$-\underset{|}{C}H-\underset{|}{C}=O$

I


$-\underset{|}{C}=\underset{|}{C}-OH$

II

the enol grouping, II. The almost completely ketonic acetone is therefore considered to illustrate the normal situation, whereas the appreciably enolic acetoacetic ester and the almost completely enolic phenol are considered instead to illustrate anomalous situations requiring explanation. This view is, indeed, required not only by the chemical facts but also by certain thermochemical considerations. As is well known, the heat of combustion of a (nonresonating) substance can usually be calculated with moderate accuracy as the sum of contributions from each of the valence bonds present. (Cf. pages 427 f.) When this procedure is applied to the keto and enol groupings, I and II, respectively, the former is found to correspond to the lower heat of combustion, and hence to be the more stable, by something like 15–18 kcal per mole.[18] In other words, the *sum of the bond energies* for the keto grouping, I, is greater than is the corresponding sum for the enolic grouping, II, by something like 15–18 kcal per mole. This figure, although it cannot of course be relied upon as more than approximately correct, is so large that the error in its exact value is doubtless insignificant. Consequently, even when the maximum reasonable allowance is made for a possibly adverse entropy effect, the conclusion that the equilibrium mixture should consist largely of the keto form seems inescapable.

The enol form of phenol resonates between the two Kekulé structures, III and IV; like benzene, it is presumably stabilized by this resonance

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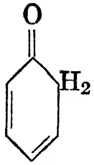
[17] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta* **23**, 1147, 1162 (1940).

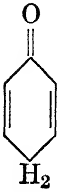
[18] Cf. Table 3·4 on page 64 of G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944.

III

IV



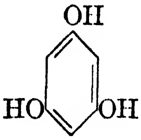
V



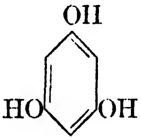
VI

to the extent of about 35–40 kcal per mole. (Cf. Section 10·10.) The two possible keto forms, V and VI, on the other hand, contain only simple conjugated systems, rather than intact benzene rings, and so they are presumably much less stabilized by the resonance. Consequently, although either keto form should be more stable than the enol form if resonance did not exist (since the sum of the bond energies is greater for the former than for the latter structure), the effect of the resonance is sufficient to reverse the order and to make the enol form much the most stable one of the three.

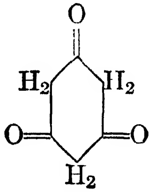
In phloroglucinol, the trienolic form resonates between the Kekulé structures, VII and VIII, whereas the triketo form can be assigned the



VII

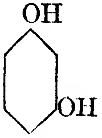


VIII

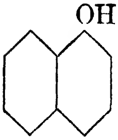


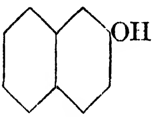
IX

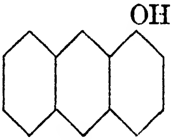
unique structure IX. Although the resonance therefore favors the trienolic form of this compound somewhat more than it does the enolic form of phenol, the situation here is modified by the presence of *three* enolic, and of *three* ketonic, groupings in the respective molecules. Since, in the absence of resonance, the keto grouping is much more stable than the enolic one, the difference in bond energies favors the triketo form, IX, of phloroglucinol even more than it favors the keto forms, V and VI, of phenol. The effects of the resonance and of the bond energies are therefore in opposite directions; if the resonance alone were important, phloroglucinol should be somewhat more enolic than phenol but, if the bond energies alone were important, phloroglucinol should be much less enolic than phenol. Although a prediction of the exact position of the equilibrium in phloroglucinol could hardly be based upon such roughly qualitative considerations, the observation (see page 597) that this compound is definitely less exclusively enolic than is phenol is at least not unreasonable. Moreover, the further observation that resorcinol, X, which is intermediate in structure between phenol and phloroglucinol, is intermediate also in properties is likewise not unreasonable.

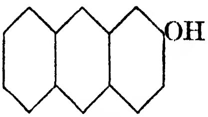

X

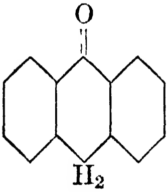
The high enol contents of 1-naphthol, XI, 2-naphthol, XII, 1-anthrol, XIII, and 2-anthrol, XIV, can easily be accounted for in the manner just outlined. The fact that the ketonic 9-anthrone, XV, is more stable than its enolic tautomer, 9-anthrol, XVI, is, however, somewhat unexpected. A possible explanation is that the loss of resonance stabilization in the transition from the 9-anthrol structure, XVI, to the 9-anthrone structure, XV, may be markedly less than the loss in the transition from the phenol structure, XVII, to either one of the cyclohexadienone structures, V and VI. Indeed, the resonance energy of the anthracene ring system might be expected to be less than three times that of benzene, since the three rings in the more complex system are not independent of each other.[19] Neither the experimental data regarding the resonance energies nor the theoretical calculations that are now available are of sufficient accuracy, however, to permit a trustworthy conclusion.

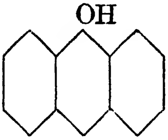

XI

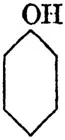

XII


XIII


XIV


XV


XVI


XVII

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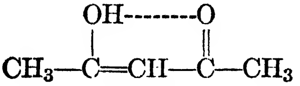
[19] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 207 f.

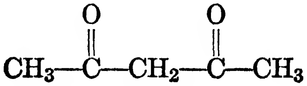
Although fairly satisfactory interpretations of the keto-enol equilibria in phenols are thus usually possible, no equally satisfactory interpretations of the equilibria in systems of other types have as yet been given. The difficulties that are encountered in the attempt to explain the smaller variations among the 1,2- and 1,3-dicarbonyl compounds are illustrated in the following discussion.

In acetylacetone, the enol form, XVIII, possesses both an intramolecular hydrogen bond and a conjugated system that are not present in the keto form, XIX.



$CH_3-\overset{\overset{\text{OH}\cdots\cdots\cdots}{|}}{C}=CH-\overset{\overset{\text{O}}{\|}}{C}-CH_3$

XVIII



$CH_3-\overset{\overset{\text{O}}{\|}}{C}-CH_2-\overset{\overset{\text{O}}{\|}}{C}-CH_3$

XIX

It is natural, therefore, to suppose that the enol is stabilized to the extent of some 5–10 kcal per mole by the hydrogen bond, and to the extent of some 2–3 kcal per mole by the conjugated system. These figures of 5–10 and 2–3 kcal per mole represent, respectively, the order of magnitude of the energy of a hydrogen bond between two oxygen atoms,[20] and that of the resonance stabilization of a simple conjugated system.[21] At least the major part of the difference between the bond energies of the keto and enol systems is therefore counterbalanced by these two factors. No adequate explanation of the high enol content of acetylacetone can, however, be based upon only such considerations as these, since still other unrecognized factors appear also to be important. For example, the cyclic 1,2-diketones listed in Table 14·8 are, in general, even more enolic than acetylacetone (cf. Table 14·5); the former compounds, however, are, on geometrical grounds, prevented from containing hydrogen bonds, and they are no more extensively conjugated in their enol forms than in their keto forms. Moreover, the striking difference between the cyclic and the acyclic 1,2-diketones finds no explanation in terms of either hydrogen bonds or conjugation. It looks, in fact, rather as if there is some as yet unexplained factor which greatly favors the enolization of cyclic ketones. Thus, the enol content of cyclohexanone is about 80 times as great as is that of acetone (cf. Table 14·3); and 5,5-dimethylcyclohexane-1,3-dione, XX (Dimedon), which can have no intramolecular hydrogen bond,

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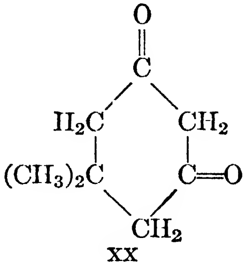
[20] Cf. L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, 1st ed., 1939, page 313, 2nd ed., 1940, page 333; M. Davies, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **43**, 5 (1946).

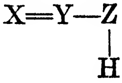
[21] Cf. G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 55 ff.



XX

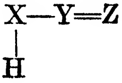
is more enolic than acetylacetone, which does have one (cf. Table 14·5). On the other hand, the erratic variations in enol content that are observed with the five different 2-carboethoxycycloalkane-1-ones listed in Table 14·4 suggest that the mere presence of a ring is not alone sufficient to ensure extensive enolization. Clearly, the situation is still very obscure. Further progress toward the final solution of the problem must apparently await further experimental data.

14·9 Some Further Types of Prototropy. A rather large number of different sorts of prototropy (see Section 14·1) are now recognized. In most, but not all, of these sorts, the tautomeric structures can be expressed in general terms by the symbols I and II, in which X, Y, and Z represent unspecified multivalent atoms, and H represents a hydrogen atom. Keto-enol tautomerism, for example, belongs to this class, since the groupings I and II become identical with the keto and enol groupings,



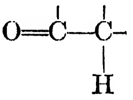
$\mathrm{X{=}Y{-}\underset{\substack{|\\ H}}{Z}}$

I



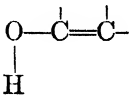
$\mathrm{\underset{\substack{|\\ H}}{X}{-}Y{=}Z}$

II



$\mathrm{O{=}\overset{|}{C}{-}\underset{\substack{|\\ H}}{\overset{|}{C}}{-}}$

III

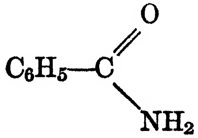


$\mathrm{\underset{\substack{|\\ H}}{O}{-}\overset{|}{C}{=}\overset{|}{C}{-}}$

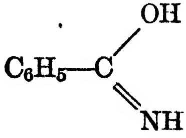
IV

III and IV, respectively, if X, Y, and Z are considered to stand specifically for O, C, and C, respectively.

Another type of protropy that can be represented by the general structures I and II is the *lactam-lactim* tautomerism of the amides of carboxylic acids. Although benzamide, for example, is usually considered to consist largely of the lactam form, V (however, see below),

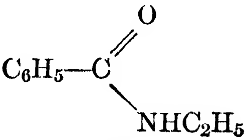


V

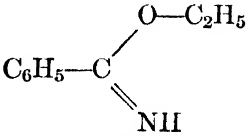


VI

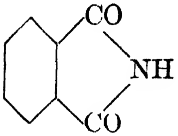
there is a possibility that more or less lactim form, VI, is also present. The evidence regarding the position, or even the existence, of the equilibrium in such a system, however, is not conclusive. The action of ethyl iodide alone upon benzamide leads to an N-ethyl derivative, of which the lactam structure is VII; whereas the action of a mixture of ethyl iodide and silver oxide leads instead to the O-ethyl derivative (or imino ether), VIII. The first reaction is consistent with the lactam structure, V, whereas the second appears instead to favor the lactim structure, VI. Such reactions, however, cannot lead to a convincing assignment of structure; for, even if they both gave the same product, they would not be sufficient, in the absence of information regarding their detailed mechanisms, to establish the structure of the original benzamide. The reactions of the more acidic imides of dibasic acids with diazomethane CH_2N_2 are similarly inconclusive. Both phthalimide, IX, and succinimide, X, for example, give as their only definitely identified products the N-methyl derivatives, XI [22,23] and XII,[23] respectively;



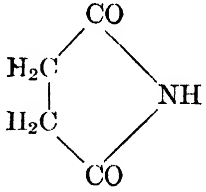
VII



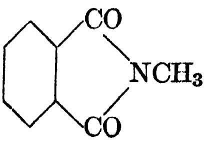
VIII



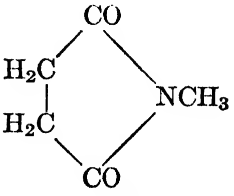
IX



X



XI



XII

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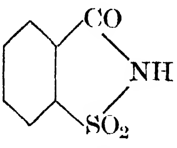
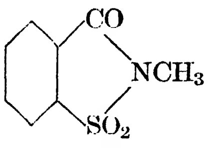
[22] F. Arndt and H. Scholz, *Ann.* **510,** 62 (1934).

[23] G. Labruto, *Gazz. chim. ital.* **63,** 266 (1933); *C.A.* **27,** 3926 (1933).

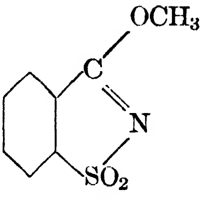
whereas saccharin, XIII, gives both the N-methyl derivative, XIV, and



XIII



XIV



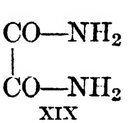
XV

the O-methyl derivative, XV, in the ratio of about 4 to 1.[22] Even if, as is commonly assumed, rearrangements do not occur in any of these reactions, the formation of N-methylimides as the major or sole products does not prove that the unsubstituted imides are largely or exclusively in their lactam forms. The evidence cited does not, in fact, rule out the possibility that the lactam forms are only minor components, which, however, react with the diazomethane much faster than the predominant lactim forms do. The largely ketonic acetoacetic ester, XVI, for example, gives the enolic ether, XVII, when similarly treated with diazomethane. (Cf. page 584.) Still a different chemical approach to the problem of the tautomerism in the amides is based upon the fact that compounds with carbon-nitrogen double bonds are oxidized by perbenzoic acid $C_6H_5—CO_3H$, with fairly complete disruption of the molecules into fragments which in most instances have been incompletely characterized.[24] Urea, XVIII, oxamide, XIX, hippuric acid, XX, and

$CH_3—CO—CH_2—CO_2C_2H_5$
XVI

$CH_3—C(OCH_3)═CH—CO_2C_2H_5$
XVII

$H_2N—CO—NH_2$
XVIII

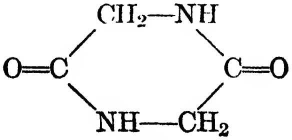


$$\begin{array}{l} CO—NH_2 \\ | \\ CO—NH_2 \end{array}$$

XIX

$C_6H_5—CO—NH—CH_2—CO_2H$
XX

glycine anhydride (diketopiperazine), XXI, are not oxidized by this



XXI

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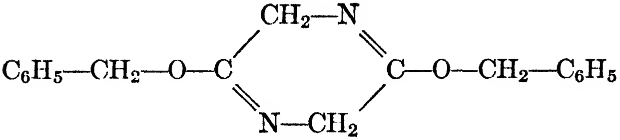
[24] M. M. Botwinnik and N. J. Gawrilow, *J. prakt. Chem.* [2] **148**, 170 (1937).

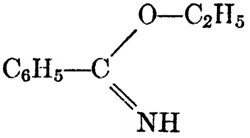
reagent, whereas the O,O′-dibenzyl derivative, XXII, of the last-named



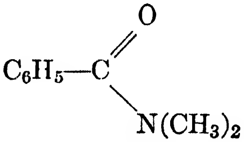
XXII

compound is oxidized; it appears, therefore, that the amides, XVIII–XXI, contain little, if any, of the lactim forms, whereas the dibenzyl derivative, XXII, is of course necessarily a pure lactim. On the other hand, the NH_2 and NH groups of primary and secondary amines are oxidized, even though those of the amides are not. Clearly, the reactions of perbenzoic acid with these various types of compound are not at present well enough understood to permit the drawing of trustworthy conclusions.

The physical, as well as the chemical, properties of amides have been used in the study of the lactam-lactim tautomerism. The most significant of these properties is perhaps the ultraviolet absorption spectrum. Hantzsch,[25] for example, has found that the spectrum of benzamide, V or VI (in alcohol), is very similar to that of the imino ether, XXIII, but

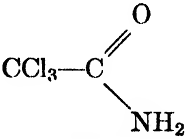


XXIII

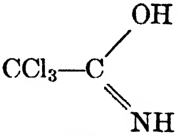


XXIV

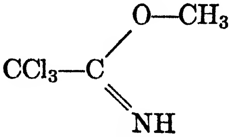
rather different from that of N,N-dimethylbenzamide, XXIV. Since the structures of the derivatives XXIII and XXIV are hardly open to question, the natural inference is that benzamide exists largely in the lactim form, VI. Analogous results were obtained, and a similar conclusion was drawn, from a spectroscopic comparison of trichloroacetamide, XXV or XXVI (in either chloroform or aqueous methyl alcohol), with



XXV



XXVI



XXVII

the related imino ether, XXVII, and piperidide, XXVIII.[25] If this

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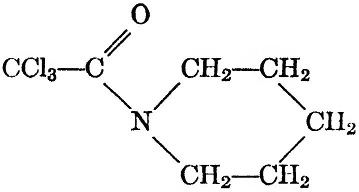
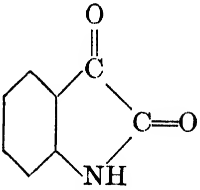
[25] A. Hantzsch, *Ber.* **64**, 661 (1931). Cf. also Ramart, Naik, and Trivedi, *Bull. soc. chim* [5] **1**, 525 (1934); Ramart-Lucas, *ibid.* [5] **3**, 723 (1936).



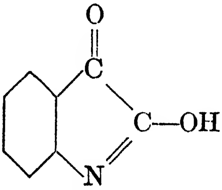
XXVIII

spectroscopic evidence is accepted as both decisive and generally valid, then the common view that the amides of carboxylic acids have predominantly the lactam structures must be discarded, and the opposite view that these compounds are instead lactims must be adopted in its place. On the other hand, Richards and Thompson [26] have interpreted the *infrared* spectra of the amides as supporting the lactam structures with extensive association due to hydrogen bonding. The most that can safely be said at the present time, therefore, is that, although both the lactam and the lactim forms of amides probably exist, the positions of the equilibria are not known with certainty.

Lactam-lactim tautomerism is of considerable historical interest, since isatin is stated to have been the first example of a tautomeric compound to be recognized explicitly as such. Baeyer,[27] in his classical work on the structure and synthesis of indigo, observed that this compound appears to have both of the structures XXIX and XXX, and he suggested that it is really a mixture of the two substances.

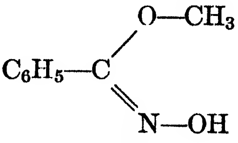


XXIX

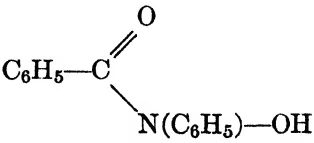


XXX

Various analogs of the amides exhibit completely analogous types of tautomerism. *Benzhydroxamic acid,* for example, gives rise not only to derivatives like XXXI, in which the substituent is joined to the oxygen



XXXI



XXXII

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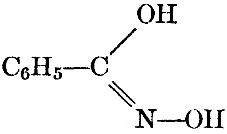
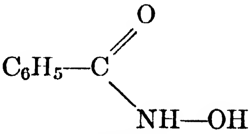
[26] R. E. Richards and H. W. Thompson, *J. Chem. Soc.* **1947,** 1248.

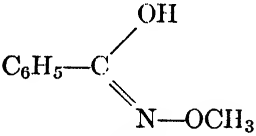
[27] A. Baeyer and S. Oekonomides, *Ber.* **15,** 2093 (1882). Cf. also A. Baeyer, *ibid.* **33,** Sonderheft LI (1900).

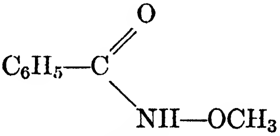
atom of the carbonyl group, but also to derivatives like XXXII, in which the substituent is joined to the nitrogen atom. The parent acid thus appears to have both of the structures XXXIII and XXXIV. This

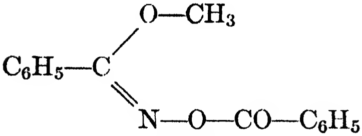

XXXIII

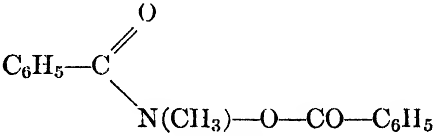

XXXIV

compound, however, has never been separated into the isomeric forms with the two structures indicated. The situations with the remaining hydroxamic acids are entirely similar. Moreover, the tautomerism persists with some of the derivatives of the hydroxamic acids. Thus, only a single compound is known corresponding to the two structures XXXV and XXXVI. On the other hand, replacement of the tautomeric hydrogen atom can lead to a pair of separable, and not easily interconvertible isomers, as, for example, the two derivatives XXXVII and XXXVIII of benzhydroxamic acid. In no instance in which tautomerism occurs in either a hydroxamic acid or a derivative of one, is the position of the presumed equilibrium known.


XXXV

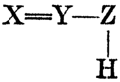

XXXVI


XXXVII

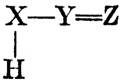

XXXVIII

Although all the compounds of structures XXXI–XXXVIII are commonly referred to as *hydroxamic* acids, or as derivatives of hydroxamic acids, the word "hydroxamic" applies strictly only to those which contain carbonyl groups (i.e., the even-numbered structures). The remaining structures (i.e., the odd-numbered ones) should instead be described by the word "hydroximic."

The *amidines*, like the hydroxamic acids, are tautomeric compounds analogous to the amides, and describable by the general structures I and

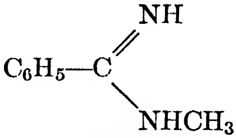

$X{=}Y{-}\underset{\substack{|\\ H}}{Z}$

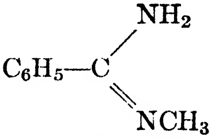
I

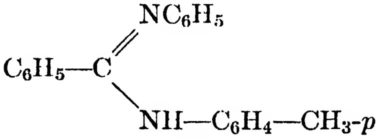

$\underset{\substack{|\\ H}}{X}{-}Y{=}Z$

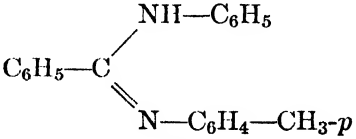
II

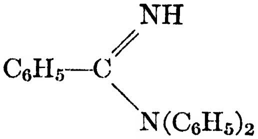
II. Thus, only one N-methylbenzamidine is known, even though the two nonequivalent structures XXXIX and XL can be written. Similarly, only one N-phenyl-N′-*p*-tolylbenzamidine is known, even though again two structures, XLI and XLII, can be written. On the other hand, N,N-diphenylbenzamidine, XLIII, and N,N′-diphenylbenzamidine, XLIV, are distinct substances since they differ in the position of a phenyl group, and not merely in that of a hydrogen atom. The *guanidines* may be considered to form a special class of amidines. As might therefore have been anticipated, only a single methylguanidine corresponds to the two structures XLV and XLVI, although two different dimethylguanidines with structures XLVII and XLVIII are known.

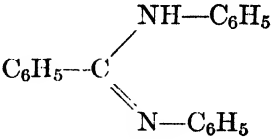

XXXIX

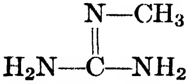

XL


XLI


XLII

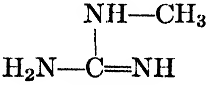

XLIII


XLIV



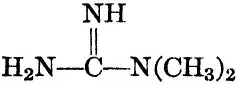
$$\mathrm{H_2N{-}\overset{\overset{\displaystyle N{-}CH_3}{\|}}{C}{-}NH_2}$$

XLV



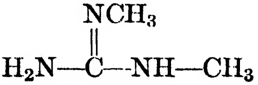
$$\mathrm{H_2N{-}\overset{\overset{\displaystyle NH{-}CH_3}{|}}{C}{=}NH}$$

XLVI



$$\mathrm{H_2N{-}\overset{\overset{\displaystyle NH}{\|}}{C}{-}N(CH_3)_2}$$

XLVII



$$\mathrm{H_2N{-}\overset{\overset{\displaystyle NCH_3}{\|}}{C}{-}NH{-}CH_3}$$

XLVIII

Primary and secondary *nitroso compounds* exhibit a somewhat different type of tautomerism, which is, however, still a prototropy that can be represented by the general structures I and II. The most usual situation can be illustrated with nitrosoethane, XLIX, and 2-nitrosopropane, L;

$$CH_3\text{—}CH_2\text{—}N{=}O \qquad (CH_3)_2CH\text{—}N{=}O$$

XLIX L

these substances have never been isolated, since all attempts to obtain them have led instead to the respective isomeric *isonitroso* compounds, acetaldoxime, LI, and acetone oxime, LII. (Cf., however, the following

$$CH_3\text{—}CH{=}N\text{—}OH \qquad (CH_3)_2C{=}N\text{—}OH$$

LI LII

paragraph.) Only a few exceptional secondary nitroso compounds are stable enough to be isolated; three typical examples are given by 1-chloro-1-nitrosoethane, LIII, ethyl α-nitrosopropionate, LIV, and

$$CH_3\text{—}CHCl\text{—}NO \qquad CH_3\text{—}CH(NO)\text{—}CO_2C_2H_5$$

LIII LIV

2-chloro-3-nitroso-2-methylbutane, LV. Each of these compounds can

$$(CH_3)_2CCl\text{—}CH(NO)\text{—}CH_3$$

LV

easily be transformed either into its dimeric form or into the corresponding more stable isonitroso form. No oxime (isonitroso compound) has ever been observed, however, to undergo the reverse transformation into a primary or secondary nitroso compound or into the dimer of such a compound. Although the equilibria are always greatly in favor of the oxime forms, their exact positions are unknown. *Tertiary* nitroso compounds, such as nitrosobenzene, LVI, or 2-methyl-2-nitrosopropane,

$$C_6H_5\text{—}NO \qquad (CH_3)_3C\text{—}NO$$

LVI LVII

LVII, on the other hand, cannot exhibit such tautomerism; they are accordingly stable substances that can be isolated. (The closely related tautomerism of the primary and secondary *nitro* compounds will be discussed in the following section.)

Evidence for the existence of the primary nitroso compound, nitrosomethane $CH_3\text{—}NO$ has recently been obtained.[28] The photochemical decomposition of *tert*-butyl nitrite $(CH_3)_3C\text{—}ONO$ gives acetone and, among other products, a colorless solid with a composition and molecular weight corresponding to the dimeric formula $(CH_3\text{—}NO)_2$. When this substance is melted or vaporized, or when its solution is heated, a green color is produced. The green material, which is possibly nitrosomethane $CH_3\text{—}NO$, returns to the original colorless solid if it is immediately cooled, but it is transformed by prolonged heating into trimeric formaldoxime $(H_2C{=}NOH)_3$.

[28] C. S. Coe and T. F. Doumani, *J. Am. Chem. Soc.* **70**, 1516 (1948).

Diazoamino compounds contain a tautomeric system that again is expressible in terms of the general structures I and II. Thus, the same product results from the action of *p*-toluenediazonium nitrate upon aniline as from that of benzenediazonium nitrate upon *p*-toluidine. From its first method of preparation, the compound appears to have structure LVIII, whereas, from its second method of preparation, it appears to

$$p\text{-}CH_3—C_6H_4—N=N—NH—C_6H_5$$

LVIII

have the isomeric structure LIX. Its reactions also are those expected

$$p\text{-}CH_3—C_6H_4—NH—N=N—C_6H_5$$

LIX

of both structures. Reduction with acid stannous chloride, for example, leads not only to aniline and *p*-tolylhydrazine, LX, but also to *p*-toluidine

$$p\text{-}CH_3—C_6H_4—NH—NH_2 \qquad C_6H_5—NH—NH_2$$

LX LXI

and phenylhydrazine, LXI. Moreover, hydrolysis with dilute sulfuric acid gives *p*-cresol, aniline, phenol, and *p*-toluidine. On the other hand, when the compound is warmed with a mixture of dimethylaniline and its hydrochloride, it behaves as if it has only structure LVIII, since the products obtained are aniline and *p*-dimethylamino-*p*′-methylazobenzene, LXII. Such a reaction is not, however, a conclusive proof of

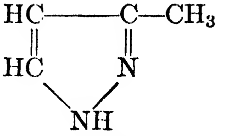
$$p\text{-}(CH_3)_2N—C_6H_4—N=N—C_6H_4—CH_3\text{-}p$$

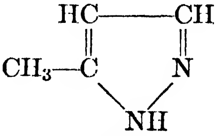
LXII

structure; the identities of the products formed from a tautomeric compound are determined by the relative rates of the various possible reactions, as well as by the composition of the tautomeric mixture. All other diazoamino compounds, to the extent that they have been studied, are analogous to the one just discussed. With none of these compounds is anything known definitely about the position of the equilibrium.

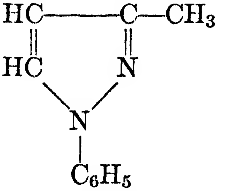
The rearrangements of compounds with isolated double bonds to ones with conjugated double bonds, or vice versa, have been discussed in a previous chapter. (See pages 540 ff.) Reactions of this type might be described as tautomeric changes between structures that are related to each other in the manner shown by the general symbols I and II. There seems, however, to be no advantage in adopting such a terminology; the transformations in question are usually so slow that they are most conveniently regarded as molecular rearrangements, and not as tautomerizations.

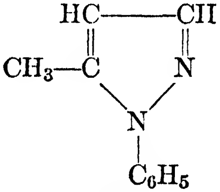
Several types of prototropy are known, in which the relationships between the pairs of tautomeric structures are similar to, but somewhat more complicated than, the one between structures I and II. Thus, the two structures LXIII and LXIV correspond to the same compound.


LXIII

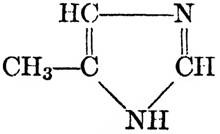

LXIV

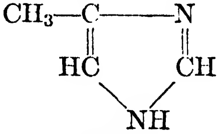
The tautomerism of this *methylpyrazole* is undoubtedly due, not to a mobility of the methyl group, but rather to the mobility of the hydrogen atom that is joined to one nitrogen atom in the first structure but to the other nitrogen atom in the second structure. If this hydrogen atom is replaced by a heavier substituent, as in the compounds LXV and LXVI,


LXV


LXVI

the expected pair of isomeric substances exists. Similarly, the two further structures LXVII and LXVIII, with a different type of heterocyclic

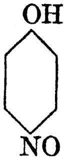

LXVII


LXVIII

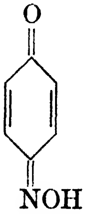
ring, represent a single compound. As before, the tautomerism of this *methylimidazole* (or *methylglyoxaline*) is also doubtless due to the mobility of a hydrogen atom rather than to that of a methyl group.

Both the pyrazole and the imidazole rings contain the groupings I and II. The tautomerism of a pyrazole differs from any of the simpler types considered previously, since here the tautomeric change requires the migration of two double bonds, and not merely the migration of one such bond. The tautomerism of an imidazole, on the other hand, is indistinguishable from that of an amidine; in fact, an imidazole is merely a special type of amidine.

The product that is obtained by the action of nitrous acid upon phenol is identical with the one that is obtained by the action of hydroxylamine upon *p*-benzoquinone. (See Section 14·1.) Tautomerism therefore exists between *p*-nitrosophenol, LXIX, and *p*-benzoquinone

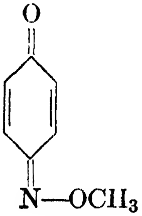


LXIX

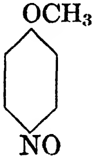


LXX

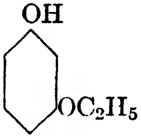
monoxime, LXX. This further type of protropy, like that of the cyclic compounds of the two preceding paragraphs, can be thought of as an extension of the more restricted type described by structures I and II. The chemical properties of the compound do not permit a decision between structures LXIX and LXX. Since, however, the ultraviolet absorption spectrum resembles that of the O-methyl ether, LXXI, of



LXXI

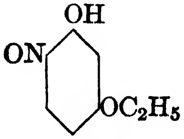


LXXII

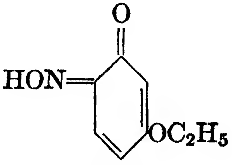


LXXIII

the oxime rather than that of *p*-nitrosoanisole, LXXII,[29] the compound may be assumed to have predominantly the quinone monoxime structure, LXX. The extent to which the quinone monoxime structures are correct also for the remaining tautomeric compounds of this class is not known. Very rarely, the two tautomeric forms have been reported to be isolable in the solid state. For example, the compound resulting from the action of nitrous acid on resorcinol monoethyl ether, LXXIII, can be obtained in two easily interconvertible crystalline modifications; one of these may have the nitroso structure, LXXIV, whereas the other



LXXIV



LXXV

may have the oxime structure, LXXV.

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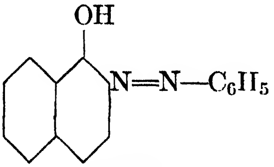
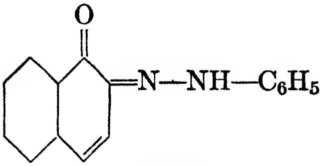
[29] L. C. Anderson and M. B. Geiger, *J. Am. Chem. Soc.* **54**, 3064 (1932); L. C. Anderson and R. L. Yanke, *ibid.* **56**, 732 (1934).

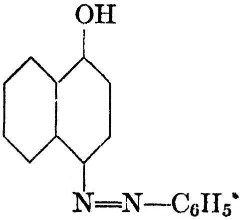
The tautomerism between the *o-* and *p-hydroxyazo compounds,* on the one hand, and the *quinone monophenylhydrazones,* on the other, is analogous to that between the nitrosophenols and the quinone monoximes. Thus, only a single known compound corresponds to the two structures LXXVI and LXXVII; similarly, only a single known compound corresponds to the two further structures LXXVIII and LXXIX.



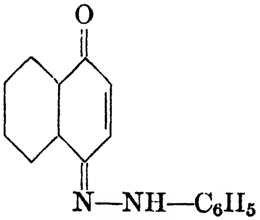
LXXVI



LXXVII



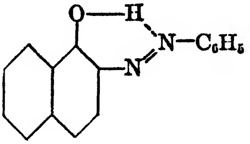
LXXVIII



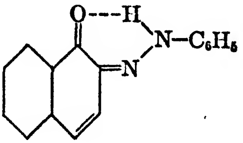
LXXIX

In the *ortho* series, the compounds are usually considered to be the quinone monophenylhydrazones (e.g., LXXVII), since they do not dissolve in an aqueous base, as the hydroxyazo compounds (e.g., LXXVI) would be expected to do. In the *para* series, on the other hand, the compounds are usually considered to be the hydroxyazo compounds (e.g., LXXVIII), since they do dissolve in an aqueous base.

In the *ortho* compound, a hydrogen bond undoubtedly exists between the nitrogen and oxygen atoms. (Cf. Section 2·6.) The hydroxyazo and the quinone monophenylhydrazone structures should therefore be written as LXXX and LXXXI, respectively, rather than as LXXVI and LXXVII respectively. Inasmuch as the position of the proton between the nitrogen and oxygen atoms is presumably not the same in structure LXXX as in structure LXXXI, resonance between the two structures presumably does not occur. (See Section 10·7.) Since, however, only a very slight change in the position of the proton is sufficient to transform either structure into the other, the tautomerism may be expected to be exceptionally mobile.



LXXX



LXXXI

In some classes of prototropy which are now recognized, the relation between the tautomeric structures cannot be expressed either by the general symbols I and II or by any logical extension of them. *Hydrogen cyanide,* for example, appears to have both of the structures LXXXII

$$\underset{\text{LXXXII}}{H—C\equiv N} \qquad \underset{\text{LXXXIII}}{H—N═C} \qquad \underset{\text{LXXXIV}}{R—C\equiv N} \qquad \underset{\text{LXXXV}}{R—N═C}$$

and LXXXIII, since it gives rise not only to the normal cyanides (nitriles) with structure LXXXIV, but also to the isocyanides (isonitriles) with structure LXXXV. (The valence state of the carbon atom in the isocyanides LXXXIII and LXXXV will be discussed later. See the paragraph in fine print at the end of Section 15·2.) The tautomerism of the oximes between structures LXXXVI and LXXXVII is also not

$$\underset{\text{LXXXVI}}{R_2C═N—OH} \qquad \underset{\text{LXXXVII}}{R_2C═N^+H—O^-}$$

describable by the symbols I and II; since this type of prototropy has already been discussed, it need not be mentioned further here. (See Section 8·3.) Finally, the ring-chain tautomerism of hydroxy aldehydes and hydroxy ketones, which may be regarded as a further type of prototropy, will be discussed later in Section 14·13.

14·10 Nitro-aci-nitro Tautomerism. A primary or secondary nitro compound is always weakly acidic; hence it can be transformed into a salt by the action of a strong base. The neutralization is, however, a slow reaction, the rate of which can be measured in the following way.[30] The conductivity of an aqueous solution of, for example, nitromethane, I, is extremely small, since the compound is only slightly

$$\underset{\text{I}}{CH_3—NO_2} \qquad \underset{\text{II}}{Ba^{++}[CH_2═NO_2]^-_2}$$

ionized. If barium hydroxide is added to such a solution, the conductivity rises immediately to the value which would have been observed if the nitro compound had not been present; as the slow neutralization reaction takes place, however, the conductivity decreases gradually until, after about 15 minutes at 0°C, it reaches the lower value that is characteristic of the salt II. Moreover, the regeneration of the nitro compound from the salt is also a slow reaction; when an equivalent quantity of hydrogen chloride is added to the solution of the salt, the conductivity is initially high, but it decreases within about 15 minutes at 0°C to the conductivity which is due merely to the barium chloride present.

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[30] A. Hantzsch, *Ber.* **32,** 575 (1899); A. Hantzsch and A. Veit, *ibid.* **32,** 607 (1899).

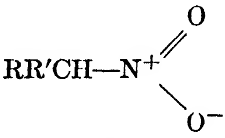
Another significant feature of the reaction between the salt and the strong acid is that the solution is weakly acidic immediately after the addition of the exactly equivalent amount of hydrogen chloride. The solution becomes essentially neutral, of course, when the regeneration of the nitro compound is complete. It may be inferred, therefore, that the nitro compound can exist in two distinct forms. One of these forms, which is called the *nitro* (or *normal*) form, is the more stable but less acidic of the two; the other, which is called the *aci* (or *iso*) form, is the less stable but more acidic of the two. In the aqueous solution of nitromethane, the compound is largely in the relatively nonacidic nitro form when the salt is treated with hydrogen chloride, the relatively (but still only weakly) acidic aci form is rapidly produced, but it then slowly rearranges to the more stable normal form. The equilibrium thus assumed can be compactly expressed by equation 14·10, in which the

$$\begin{tikzcd}
\text{nitro form} \arrow[rr, shift left, "\text{slow}"] \arrow[dr, shift left] & & \text{aci form} \arrow[ll, shift left] \arrow[dl, shift left] \\
& H^+ + \text{anion} \arrow[ul, shift left, "\text{slow}"] \arrow[ur, shift left, "\text{fast}"] &
\end{tikzcd} \qquad (14 \cdot 10)$$

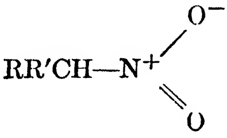
pairs of reverse arrows imply merely the existence of the equilibria indicated, and do not necessarily describe the paths by which the various compounds are transformed into, or derived from, one another.

Obviously, equation 14·10 is identical in form with the one applying to the equilibrium of a keto and an enol form with each other and with the corresponding anion. The most significant difference is that ordinarily, in the keto-enol system, all the equilibria are rapidly established. (Cf., however, pages 593 ff.)

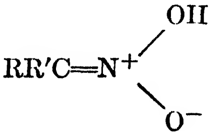
The nitro form of any primary or secondary nitro compound $RR'CH—NO_2$ is now generally considered to be a resonance hybrid receiving equal contributions from the two equivalent structures III



III

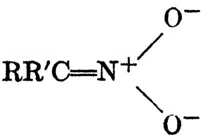


IV



V

and IV; the aci form is considered to have structure V; and the anion is considered to have structure VI (possibly somewhat modified by



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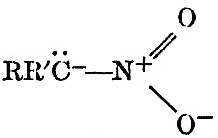

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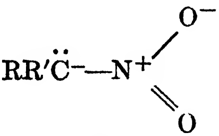


VIII

resonance with the two doubtless less stable, and hence less important, structures VII and VIII). It is important that, although there are two un-ionized forms of the nitro compound, there is only one anion, and hence only one salt.

The tautomerism between the nitro and aci forms is closely analogous to all the various types of prototropy which can be described by the general symbols I and II of page 617, and which have been discussed in the preceding sections. A *tertiary* nitro compound, such as 2-nitro-2-methylpropane, IX, or nitrobenzene, X, has no hydrogen atom that is

$(CH_3)_3C{-}NO_2$
IX

$C_6H_5{-}NO_2$
X

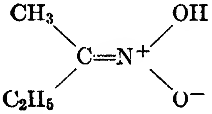
alpha to the nitro group in the nitro form; such a compound can therefore have no aci form. The observed restriction of nitro-aci-nitro tautomerism to primary and secondary nitro compounds is thus explained.

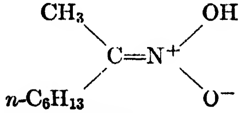
Structures V of the aci form and VI of the anion were in considerable doubt for a number of years. In 1927, Kuhn and Albrecht[31] reported that optically active 2-nitrobutane, XI, can be transformed into its sodium salt, and then regenerated,

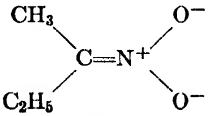
$CH_3{-}CH(NO_2){-}C_2H_5$
XI

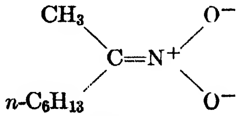
$CH_3{-}CH(NO_2){-}n{-}C_6H_{13}$
XII

without complete racemization; somewhat later, Shriner and Young[32] reported that the analogous 2-nitroöctane, XII, behaves similarly. Structures XIII and XIV


XIII


XIV


XV


XVI

for the two aci forms, and the further structures XV and XVI for the two negative ions, therefore, appear to be definitely excluded. These structures, in fact, cannot correspond to dissymmetric configurations; consequently, if they are correct, the regenerated nitro compounds must be racemic. In spite of the numerous attempts which were made to devise different structures not suffering from this apparent defect,[33] the observed retention of optical activity remained an unsolved mystery

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[31] R. Kuhn and H. Albrecht, *Ber.* **60**, 1297 (1927).

[32] R. L. Shriner and J. H. Young, *J. Am. Chem. Soc.* **52**, 3332 (1930).

[33] Cf. R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, pages 308 ff., 2nd ed., 1943, Volume I, pages 388 ff.

until comparatively recently. In 1947 and 1948, however, Kornblum and his coworkers[34] showed that, in each instance, the apparent incompleteness of racemization is due both to an incompleteness of the neutralization, and also to the presence of optically active impurities in the sample of nitro compound used. The complete neutralization of the pure nitro compound leads always to complete racemization. There is, therefore, no longer any reason to doubt that structures V, VI, XIII–XVI are correct.

The belief that every primary or secondary nitro compound is a tautomeric mixture of a nitro and an aci form has been confirmed by several sorts of independent (and more direct) evidence. Thus, although ordinary phenylnitromethane is almost entirely in the nitro form, XVII,

$$\underset{\text{XVII}}{C_6H_5{-}CH_2{-}NO_2} \qquad \underset{\text{XVIII}}{C_6H_5{-}CH{=}NO_2H}$$

the aci form, XVIII, can be obtained by careful treatment of the sodium salt with hydrogen chloride. Several other nitro compounds have likewise been prepared both in the ordinary (i.e., largely nitro) form and also in the aci form. In every instance, the aci form is unstable and reverts more or less rapidly to the ordinary mixture.

The aci and nitro forms may be distinguished from one another by the fact that the aci, but not the nitro, forms give characteristic colors with ferric chloride and rapidly absorb bromine. In both these respects, the relation between the aci and the nitro forms is similar to that between enol and keto forms. The reaction with bromine has, in fact, been used for the measurement of the positions of the equilibria in several nitro compounds, just as it has been used in the study of many keto-enol systems. (See pages 587 f.) *p*-Nitrophenylnitromethane, XIX and

$$\underset{\text{XIX}}{p\text{-}O_2N{-}C_6H_4{-}CH_2{-}NO_2} \qquad \underset{\text{XX}}{p\text{-}O_2N{-}C_6H_4{-}CH{=}NO_2H}$$

XX, for example, has in this way been found to contain 0.18 per cent of the aci form, XX, in ethyl alcohol, and 0.79 per cent in dilute aqueous methyl alcohol.

The direction in which the proportion of aci form varies with the solvent shows that the relative solubility of the aci form is greater in the partly aqueous solvent than it is in the less polar one. (See Section 14·6.) This conclusion is entirely reasonable, since the aci form, XX, contains a hydroxyl group, whereas the nitro form, XIX, does not.

In pyridine, *p*-nitrophenylnitromethane is reported to contain 16 per cent of the aci form, XX. This extreme variation in the equilibrium may be due to an extreme variation in the relative solubilities of the two forms. On the other hand, it may

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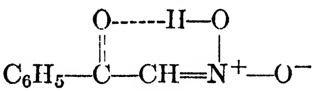
[34] N. Kornblum, N. N. Lichtin, J. T. Patton, and D. C. Iffland, *J. Am. Chem. Soc.* **69**, 307 (1947); N. Kornblum, J. T. Patton, and J. B. Nordmann, *ibid.* **70**, 746 (1948).

instead be only apparent; for, since pyridine is basic, a nitro compound dissolved in this solvent may be partly in the anionic form which, like the aci form, absorbs bromine. (Cf. page 609.)

ω-Nitroacetophenone, XXI and XXII, contains 10.3 per cent of the

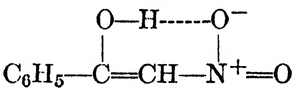
$$\underset{\text{XXI}}{C_6H_5{-}CO{-}CH_2{-}NO_2} \qquad \underset{\text{XXII}}{C_6H_5{-}CO{-}CH{=}NO_2H}$$

aci form, XXII, in toluene, but only 2.7 per cent in 67 per cent aqueous methyl alcohol. With this compound, the shift of the equilibrium away from the aci form in the more polar solvent shows that the relative solubility of the aci form is less in the aqueous alcohol than it is in toluene. The aci form may therefore be assumed not to contain a free hydroxyl group, as in structure XXII, but instead to have structure XXIII with an intramolecular hydrogen bond. Another possibility,



$$C_6H_5{-}\overset{\overset{O\cdots\cdots H{-}O}{\|\qquad\quad |}}{C}{-}CH{=}N^+{-}O^-$$

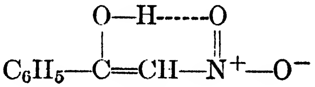
XXIII



$$C_6H_5{-}\overset{\overset{O{-}H\cdots\cdots O^-}{|\qquad\quad |}}{C}{=}CH{-}N^+{=}O$$

XXIV

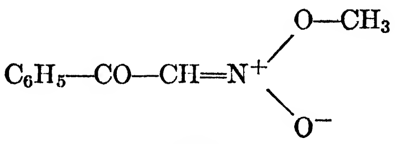
however, is that the substance is a resonance hybrid of the two *enolic* structures, XXIV and XXV; if this resonating structure is correct, the



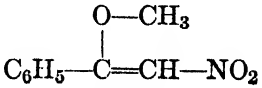
$$C_6H_5{-}\overset{\overset{O{-}H\cdots\cdots O}{|\qquad\quad \|}}{C}{=}CH{-}N^+{-}O^-$$

XXV

substance should be called an enol instead of an aci-nitro compound. The chemical properties of the compound do not permit a decision between the two possibilities. The action of diazomethane CH_2N_2,[35] for example, leads to both the nitronic ester, XXVI, and the enolic



XXVI



$$C_6H_5{-}\overset{\overset{O{-}CH_3}{|}}{C}{=}CH{-}NO_2$$

XXVII

ether, XXVII; these two products are formed in a ratio of approximately 2:1. Perhaps the two forms are in tautomeric equilibrium with each other, as well as with the nitro-keto form, XXI. Resonance among all three structures XXIII, XXIV, and XXV is presumably impossible since the first of these structures probably differs from the other two in the position of the proton in the hydrogen bond.

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[35] F. Arndt and J. D. Rose, *J. Chem. Soc.* **1935**, 1.

With most simple nitro compounds, the proportions of aci form that are present at equilibrium are too small to be measured by the method based upon the absorption of bromine. For the study of such compounds, however, an entirely different method has been devised.[36] The equilibrium constants for the various equilibria in equation 14·10 (which is here repeated for ease of reference) are given in equations 14·11–14·13, in which the expressions in parentheses represent the

$$\begin{tikzcd} \text{nitro form} \arrow[rr, shift left, "\text{slow}"] \arrow[dr, shift left] & & \text{aci form} \arrow[ll, shift left] \arrow[dl, shift left, "\text{fast}"] \\ & \text{H}^+ + \text{anion} \arrow[ul, shift left, "\text{slow}"] \arrow[ur, shift left] & \end{tikzcd} \qquad (14\cdot10)$$

$$K_i = \frac{(\text{aci form})}{(\text{nitro form})} \qquad (14\cdot11)$$

$$K_n = \frac{(\text{H}^+)\ (\text{anion})}{(\text{nitro form})} \qquad (14\cdot12)$$

$$K_{ac} = \frac{(\text{H}^+)\ (\text{anion})}{(\text{aci form})} \qquad (14\cdot13)$$

activities of the appropriate substances or ions. The quantity K_i may be called the *isomerization constant;* the further quantities K_n and K_{ac} may be called the *true ionization constants* of, respectively, the nitro and aci forms. These three constants are not independent of one another, since the second is the product of the other two (equation 14·14). If

$$K_n = K_iK_{ac} \qquad (14\cdot14)$$

the tautomerism of the nitro compound is ignored in any determination of the acid strength of the compound, an *apparent* ionization constant K_{app} (equation 14·15) will be obtained. Now, if the nitro compound

$$K_{app} = \frac{(\text{H}^+)(\text{anion})}{(\text{nitro form}) + (\text{aci form})} = \frac{(\text{H}^+)(\text{anion})}{(\text{nitro form})(1 + K_i)} = \frac{K_n}{1 + K_i} = \frac{K_iK_{ac}}{1 + K_i} \qquad (14\cdot15)$$

is largely in the nitro form, the isomerization constant K_i is very small compared to unity; hence the apparent ionization constant K_{app} is equal, within less than the experimental error, to the true ionization constant K_n of the nitro form. Therefore, since K_n can thus be measured

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[36] D. Turnbull and S. H. Maron, *J. Am. Chem. Soc.* **65**, 212 (1943).

experimentally, the isomerization constant K_i can be calculated from equation 14·14 if the true ionization constant K_{ac} of the aci form is known. This last constant also can be measured experimentally. Each of the equilibria involving the nitro form (equation 14·10) is established fairly slowly, whereas the one between the aci form and its ions is established very rapidly; consequently, if the salt of the nitro compound is treated with a strong acid, the true ionization constant K_{ac} of the immediately liberated aci form can be determined before an appreciable amount of the nitro form has been produced. In this way, the data of Table 14·9 have been obtained.

TABLE 14·9

Equilibrium Constants in Some Simple Nitro Compounds[a]

Compound	$K_{app} = K_n$	K_{ac}	K_i
Nitromethane[b]	6.1×10^{-11}	5.6×10^{-4}	1.1×10^{-7}
Nitroethane	3.5×10^{-9}	3.9×10^{-5}	8.9×10^{-5}
2-Nitropropane	2.1×10^{-8}	7.7×10^{-6}	2.75×10^{-3}

[a] The data in this table are for a dilute aqueous solution at 25°C. They are taken from D. Turnbull and S. H. Maron, *J. Am. Chem. Soc.* **65**, 212 (1943). Cf. also G. W. Wheland and J. Farr, *ibid.* **65**, 1433 (1943).

[b] The value of K_{ac} for nitromethane was estimated by Turnbull and Maron (reference *a*) from data of R. Junell, Dissertation, Upsala, Sweden, 1935. The value of K_i for this compound was obtained by a combination of this estimated K_{ac} with the measured value of K_{app}.

The interpretation of the equilibria of equation 14·10 was obscured for some time by an erroneous theory, which was proposed by Hantzsch in order to explain some erroneous data. Thus, Hantzsch and Barth[37] reported that, although an aqueous solution of nitromethane, I, is not at all acidic and has no measurable conductivity,

$$\underset{\text{I}}{CH_3{-}NO_2} \qquad \underset{\text{XXVIII}}{Na^+[CH_2{=}NO_2]^-}$$

a solution of its sodium salt, XXVIII, is so little hydrolyzed that it appears to be derived from a moderately strong acid. The suggestion was accordingly made that the ionization of the nitro compound, dissolved in pure water, is determined by the very small constant K_n, whereas the hydrolysis of the salt is determined instead by the much larger constant K_{ac}. The nitro form was thus regarded as not a true acid, but rather as a *pseudo* acid; and the aci form was regarded as the true acid, from which the salt is derived. In support of this theory of pseudo acidity, Hantzsch and Barth presented data for many additional compounds, each of which, like nitromethane, was reported to be, itself, relatively nonacidic but to form relatively unhydrolyzed salts. Somewhat later, however, Kauffmann[38] pointed out that the

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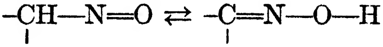
[37] A. Hantzsch and A. Barth, *Ber.* **35**, 210 (1902).

[38] H. Kauffmann, *Z. physik. Chem.* **47**, 618 (1904); *Ber.* **37**, 2468 (1904). See also J. v. Zadwidzki, *ibid.* **37**, 2298 (1904).

theory is contrary to the law of mass action; and that, if the measurements are made under the conditions of complete equilibrium, the ionization constant obtained either from the conductivity of the solution or from the hydrolysis of the salt must be the apparent constant K_{app}. Ley and Hantzsch[39] then re-examined nitromethane and found that, contrary to the previous conclusion, but as required by the correct theory, the ionization constants measured by the two methods are identical (within experimental error), and equal to about 10^{-11}. (Cf. Table 14·9.)

The distinction between a "pseudo acid," like the nitro form of a nitro compound, and a "true acid," like the aci form, is therefore not as fundamental as was originally supposed; both forms, in fact, must be regarded as true acids, since each is in equilibrium with hydrogen ion plus an anion. Probably the most important way in which the nitro form differs from an ordinary acid is that it is neutralized slowly by a base, and is regenerated slowly from its salt. For the description of these properties, the expression "secondary acid," suggested by Lewis,[40] seems preferable to Hantzsch's expression "pseudo acid."

The nitro-aci-nitro tautomerism is closely related to the nitroso-isonitroso tautomerism considered in the preceding section, since the essential structural change in each can be expressed in general terms by equation 14·16. In spite of this resemblance, however, the equilibria are extremely different; the structure at the left of equation 14·16 is

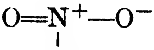


$$-\underset{|}{C}H-N=O \rightleftarrows -\underset{|}{C}=N-O-H \qquad (14\cdot16)$$

always much the more stable one with a nitro compound, whereas it is always much the less stable one with a nitroso compound. One (and perhaps the most important) reason for this striking difference in properties is that the nitro form of a nitro compound must be stabilized to a considerable extent by the resonance between the two equivalent structures, XXIX and XXX, of the nitro group. The aci-nitro, nitroso, and

$$^{-}O-\underset{|}{N}^{+}=O$$

XXIX



$$O=\underset{|}{N}^{+}-O^{-}$$

XXX

isonitroso compounds, on the other hand, cannot be stabilized in the same manner, since each is adequately described by a single structure.

14·11 Heterocyclic "Phenols." The tautomerism of a carbocyclic phenol is necessarily of the keto-enol type (cf. Section 14·4); that of an analogous heterocyclic compound may or may not belong instead to one of the other classes of prototropy discussed in Section 14·9. With

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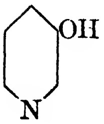
[39] H. Ley and A. Hantzsch, *Ber.* **39**, 3149 (1906).

[40] G. N. Lewis, *J. Franklin Inst.* **226**, 293 (1938); G. N. Lewis and G. T. Seaborg, *J. Am. Chem. Soc.* **61**, 1886 (1939).

β-hydroxypyridine, for example, the tautomeric structures include the enolic one, I (which implies resonance between the Kekulé-like structures, II and III), and the three different ketonic ones, IV, V, and VI. With α-hydroxypyridine, however, lactam-lactim as well as keto-enol tautomerism is involved; the relation between structures VII and VIII is that between a lactam and its lactim, but the relation between structure VIII and either IX or X is that between an enol and its keto form. With γ-hydroxypyridine, for which the corresponding structures are XI, XII, XIII, and XIV, the situation is analogous to the one just described for the α-isomer.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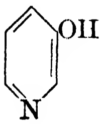
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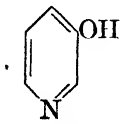
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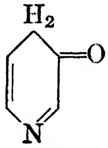
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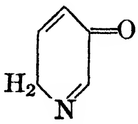
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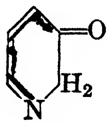
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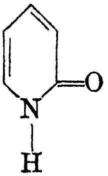
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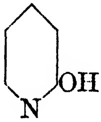
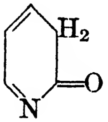

VIII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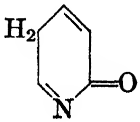
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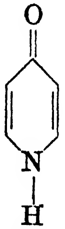
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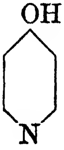
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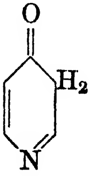
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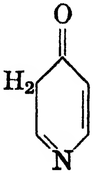
XIV

β-Hydroxypyridine appears to be a true phenol with structure I.[41,42] In particular, it has acidic as well as basic properties, and it gives a color with ferric chloride. Moreover, the action of ethyl bromide upon its sodium salt leads to only the O-ethyl ether, XV, and that of diazo-

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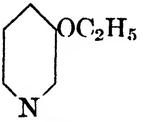
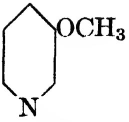
[41] Cf. N. V. Sidgwick, T. W. J. Taylor, and W. Baker, *The Organic Chemistry of Nitrogen*, Oxford University Press, Oxford, 1937, pages 530 ff.

[42] H. Specker and H. Gawrosch, *Ber.* **75**, 1338 (1942).



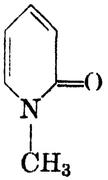
XV



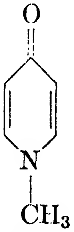
XVI

methane upon the compound itself leads to only the O-methyl ether, XVI. The phenolic structure has been supported also by studies of the molecular refraction [43] and of the ultraviolet absorption spectrum [42] of the parent compound.

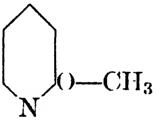
The structures of α- and γ-hydroxypyridines are still not entirely clear.[41, 42] Each compound has acidic as well as basic properties, and the γ-compound gives a color with ferric chloride. The action of methyl iodide leads to the N-methyl derivatives, XVII and XVIII, but that



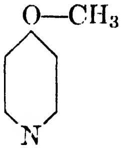
XVII



XVIII



XIX



XX

of diazomethane leads instead to the O-methyl derivatives, XIX and XX. The molecular refractions [43] and the ultraviolet absorption spectra [42] of the α- and γ-hydroxypyridines are similar to those of the N-methyl derivatives, XVII and XVIII, but different from those of either the O-methyl ethers, XIX and XX, or the phenolic β-hydroxypyridine, I. Presumably, therefore, the parent compounds are not really hydroxypyridines, as in structures VIII and XII, but are instead α- and γ-pyridones with structures VII and XI, respectively. These last structures, however, are themselves not entirely satisfactory, since neither the unsubstituted compounds nor their N-methyl derivatives, XVII and XVIII, have the properties of unsaturated ketones or of amines. Thus, they do not react with phenylhydrazine to form phenylhydrazones,[44] with Grignard reagents to form amino alcohols, or with alkyl halides to form quaternary ammonium salts. (Cf. page 431.) It seems most probable that the various compounds are resonance

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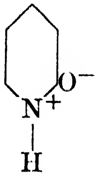
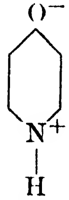
[43] K. v. Auwers, *Ber.* **63**, 2111 (1930).

[44] See, however, D. N. Bedekar, R. P. Kaushal, and S. S. Deshapande, *J. Indian Chem. Soc.* **12**, 465 (1935).

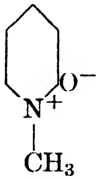
hybrids of the pyridone structures, VII, XI, XVII, and XVIII, and the respective zwitterion structures, XXI–XXIV.[45]



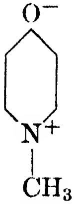
XXI



XXII

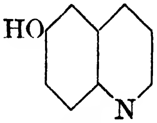


XXIII

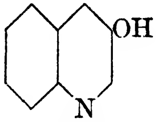


XXIV

Any *hydroxyquinoline* (such as the one with structure XXV), in which

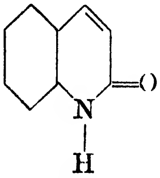


XXV

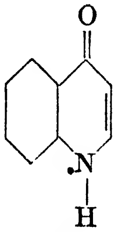


XXVI

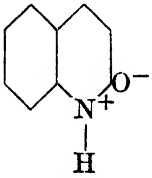
the hydroxyl group is attached to a carbon atom of the benzene ring, is a true phenol, like the naphthol to which it is structurally related. Any other hydroxyquinoline, however, in which the hydroxyl group is attached to a carbon atom of the pyridine ring, is analogous to the corresponding hydroxypyridine. Thus, although β-hydroxyquinoline, XXVI, appears to be a phenol like β-hydroxypyridine, the α-hydroxy compound, carbostyril, and the γ-hydroxy compound, kynurin, appear instead to be resonance hybrids of the respective quinolone structures, XXVII and XXVIII, and zwitterion structures, XXIX and XXX.



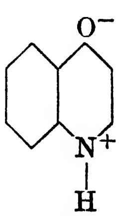
XXVII



XXVIII



XXIX



XXX

Little is known, in general, regarding the tautomeric equilibria in the hydroxy derivatives of the remaining heterocyclic ring systems. *Cyanuric acid*, for example, has some characteristics of the trilactam structure, XXXI, and some of the trilactim structure, XXXII. Thus, this

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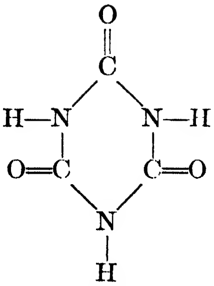
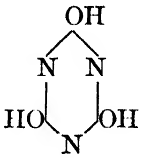
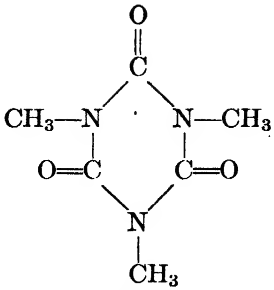
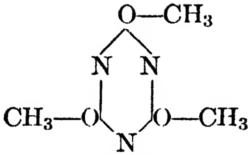
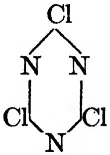
[45] Cf. F. Arndt and A. Kalischek, *Ber.* **63**, 587 (1930); F. Arndt, *ibid.* **63**, 2963 (1930).


XXXI

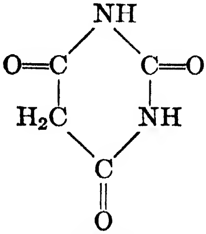

XXXII

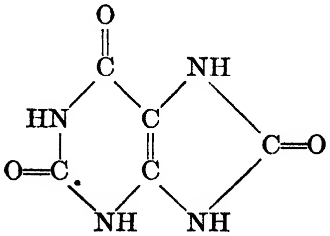

XXXIII

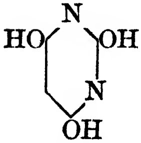

XXXIV

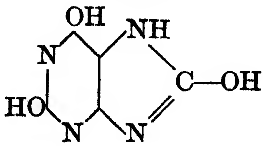

XXXV

substance leads to the derivatives XXXIII, XXXIV, and XXXV of definitely known structure. Since the chemical properties of the parent compound are indecisive, recourse has been had to such physical properties as the ultraviolet absorption spectrum. On the whole, the evidence supports the most commonly held belief that the compound is largely, if not entirely, in the trilactam form, XXXI.[46] Similarly, barbituric acid and uric acid are usually considered to have, respectively, the keto-lactam structures, XXXVI and XXXVII, rather than the enol-lactim structures, XXXVIII and XXXIX.


XXXVI


XXXVII


XXXVIII


XXXIX

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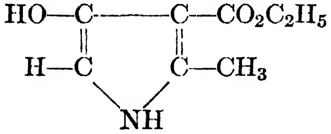
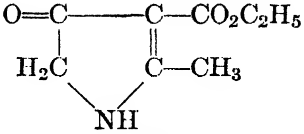
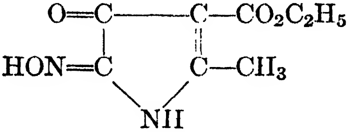
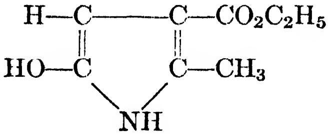
[46] Cf. I. M. Klotz and T. Askounis, *J. Am. Chem. Soc.* **69**, 801 (1947).

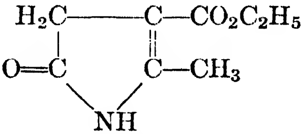
In the *pyrrole* series, keto-enol tautomerism occurs; according to Fischer and Orth,[47] however, the enolic form usually predominates. 2-Methyl-3-carboethoxy-4-hydroxypyrrole, for example, seems to have structure XL, since it gives the well-known pine-splint test for a true pyrrole; moreover, it behaves as a phenol, since it gives a color with ferric chloride. The two further facts that it forms a salt with strong bases, and that it couples with diazonium compounds, are also in agreement with the hydroxypyrrole structure, XL; both phenols and true pyrroles, in fact, ordinarily undergo both these types of reaction. On the other hand, the compound acts also to some extent as if it has the isomeric structure XLI, since it is transformed by the action of nitrous acid into the oxime XLII (and into more complex products that are apparently derived from this oxime). Most other monohydroxypyrroles (such as the one for which the enolic and ketonic structures are XLIII and XLIV, respectively) are closely similar to the one just discussed. Succinimide, however, is considered to have structure XLV, and not

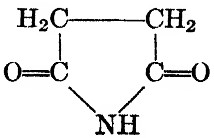

XL

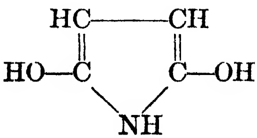

XLI


XLII


XLIII


XLIV


XLV


XLVI

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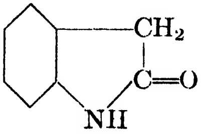
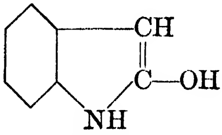
[47] H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Akademische Verlagsgesellschaft, Leipzig, 1934, Volume I, pages 124 ff.

to be 2,5-dihydroxypyrrole, XLVI; similarly, oxindole is considered to have structure XLVII, and not to be 2-hydroxyindole, XLVIII.

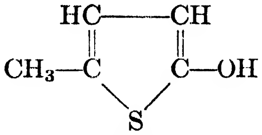


XLVII

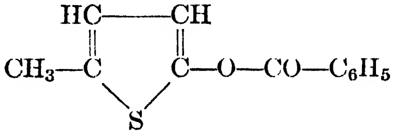


XLVIII

Extremely little is known about the *hydroxythiophenes*.[48] Thiotenol (2-hydroxy-5-methylthiophene), XLIX, is the simplest compound of

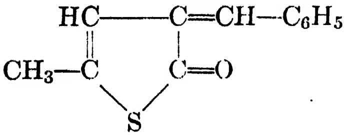


XLIX

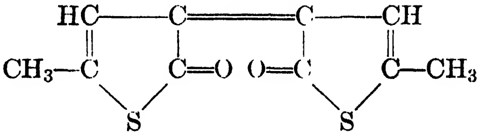


L

this class to have been studied.[49] It reacts with benzoyl chloride to form the benzoate, L, but with benzaldehyde to form the condensation product, LI. Moreover, by the action of ferric chloride, it is oxidized

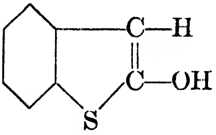


LI

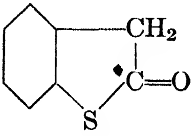


LII

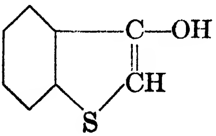
to the substance LII, which may be regarded as the simplest known indigoid dye. The somewhat more complicated, but more thoroughly investigated, 2-hydroxythionaphthene (LIII and LIV) and 3-hydroxythionaphthene (LV and LVI) likewise behave as tautomeric compounds.



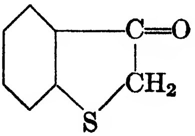
LIII



LIV



LV



LVI

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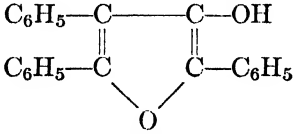
[48] Cf. W. Steinkopf, *Die Chemie des Thiophens*, Theodor Steinkopff, Dresden and Leipzig, 1941, pages 62 ff.

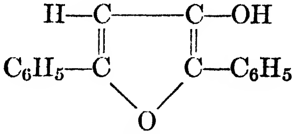
[49] W. Steinkopf and F. Thormann, *Ann.* **540**, 1 (1939).

With none of these hydroxythiophenes is anything known about the positions of the equilibria between the keto and enol forms.

Until comparatively recently, no enol forms of *hydroxyfurans* were known, although the keto forms and the O-acyl derivatives of several such compounds had been prepared. In 1936, however, Kohler and his coworkers [50] prepared 3-hydroxy-2,4,5-triphenylfuran, LVII, and 3-hydroxy-2,5-diphenylfuran, LVIII.

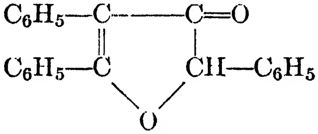


LVII

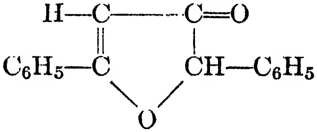


LVIII

Each of these compounds absorbs bromine rapidly, gives a color with ferric chloride, and can be transformed more or less completely into the corresponding furanone, LIX or LX, respectively.



LIX



LX

14·12 Anionotropy. All the examples of tautomerism that have been considered up to this point belong to the type known as prototropy, since the several members of each set of tautomeric structures differ in the position of a proton, as well as in the arrangement of the valence bonds. (Cf. Section 14·1.) There exists, however, still a further, much less varied, kind of tautomerism, where the structures differ in the position of an atom or group that is able to form a stable anion; such tautomerism is commonly referred to as *anionotropy.*

The most important examples of anionotropy are encountered among the allylic compounds like crotyl chloride, I, and methylvinylcarbinyl chloride, II.

$CH_3—CH{=}CH—CH_2Cl$ I

$CH_3—CHCl—CH{=}CH_2$ II

Either one of these substances gives the reactions of both, and either one can easily be converted into an equilibrium mixture of the two. Since, however, such transformations have already been discussed in a previous chapter (see Section 13·2), it will here be sufficient merely to call attention to the fact that these reactions of the allylic compounds are at the borderline between the isomeric changes

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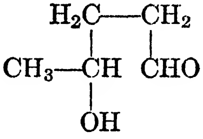
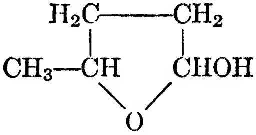
[50] E. P. Kohler, F. H. Westheimer, and M. Tischler, *J. Am. Chem. Soc.* **58**, 264 (1936); E. P. Kohler and D. W. Woodward, *ibid.* **58**, 1933 (1936).

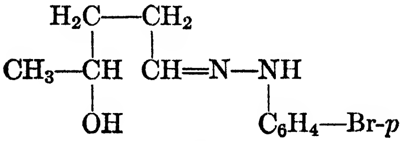
which are most conveniently classified as molecular rearrangements, and the ones which are instead most conveniently classified as interconversions of tautomers. In practice, both methods of classification are commonly employed; the equilibrium between the unsaturated chlorides I and II, for example, may be described as illustrating either the allylic rearrangement or anionotropy.

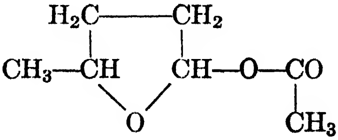
14·13 Ring-chain Tautomerism. In a formal sense, ring-chain tautomerism can be regarded as a special kind of prototropy or anionotropy, since the tautomeric structures always differ in the position either of a proton or of an anionic atom or group. The relation between a pair of ring-chain tautomers is, however, not very similar to that between any of the pairs of tautomers discussed previously; consequently, it is convenient to consider that this further variety of tautomerism forms a distinct class.

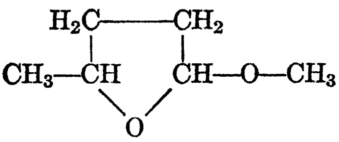
A typical example of ring-chain tautomerism (which is more closely related to prototropy than it is to anionotropy) is provided by the compound that appears to be both γ-hydroxyvaleraldehyde, I, and 2-hydroxy-5-methyltetrahydrofuran, II. This compound, in fact, is transformed into the *p*-bromophenylhydrazone, III, by the action of *p*-bromophenylhydrazine; into the cyclic acetate, IV, by the action of acetic anhydride; and into the cyclic acetal, V, by the action of methyl alcoholic hydrogen chloride. Moreover, the further compound which appears to be both δ-hydroxycaproaldehyde, VI, and 2-hydroxy-6-methyltetra-

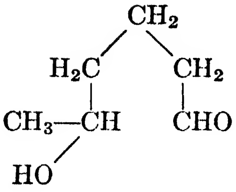

I


II

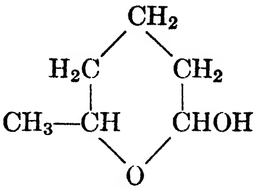

III


IV


V

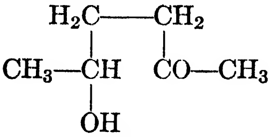


VI

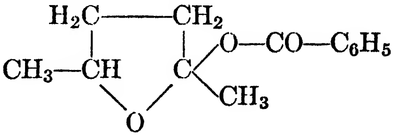


VII

hydropyran, VII, behaves similarly. Such tautomerism is exhibited not only by hydroxyaldehydes, but also by many hydroxy ketones. Thus, the reaction of 5-hydroxy-2-hexanone, VIII, with benzoyl

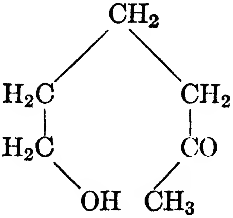


VIII

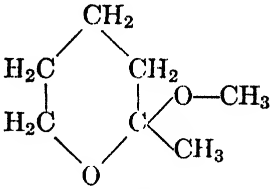


IX

chloride and sodium hydroxide leads to the cyclic benzoate, IX; and that of 6-hydroxy-2-hexanone, X, with methyl alcoholic hydrogen

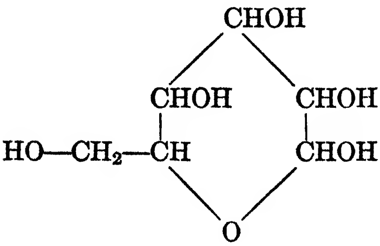


X

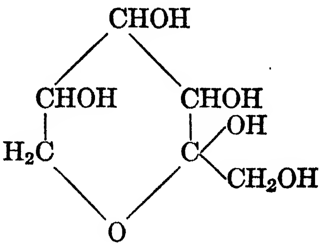


XI

chloride leads to the cyclic acetal, XI. Ring-chain tautomerism of this type is especially well known among the carbohydrates; glucose and fructose, for example, are largely (if not entirely) cyclic hemiacetals with structures XII and XIII, respectively.



XII



XIII

From a study of molecular refractions, v. Auwers[51] has concluded that, with the two hydroxy aldehydes, I and VI, the equilibria are greatly

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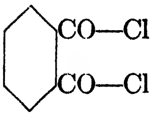
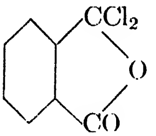
[51] K. v. Auwers, *Ber.* **56**, 1672 (1923).

in favor of the respective cyclic forms, II and VII; but that the hydroxy ketone, X, is acyclic. This difference between the aldehydes and ketones is not general, however, since fructose, XIII, as well as glucose, XII, is cyclic. As might have been expected (see Chapter 9), the tendency of a hydroxy aldehyde or hydroxy ketone to exhibit ring-chain tautomerism is greatest when the ring in the cyclic form contains either five or six atoms.[52] (Cf. also equation 9·2 on page 374.)

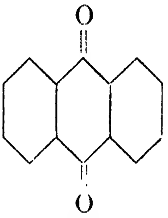
A different type of ring-chain tautomerism (which is more closely related to anionotropy than it is to prototropy) is that of the acid chlorides of dibasic acids. Phthaloyl chloride, for example, reacts as if it has both of the structures XIV and XV. Thus, when treated with benzene and aluminum chloride, this compound gives not only anthraquinone, XVI, but also diphenylphthalide, XVII; when treated with hydrazine, it gives the product XVIII; when treated with zinc and hydrochloric acid, it is reduced to phthalide, XIX; and so on. That the two tautomers actually exist has been proved by the isolation of each. The symmetrical form, XIV, is obtained by treatment of phthalic anhydride with phosphorus pentachloride.[53] The unsymmetrical form, XV, which can be prepared by heating its isomer, XIV, with aluminum chloride, reverts partially to the symmetrical form when it is melted (at 87°–89°C).[52] Succinyl chloride is similarly tautomeric, since its reactions require consideration of both the structures XX and XXI; this compound has not, however, been obtained in the two postulated forms.



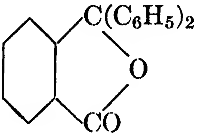
XIV



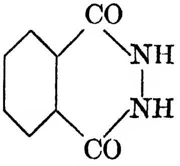
XV



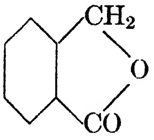
XVI



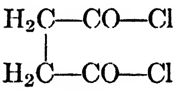
XVII



XVIII

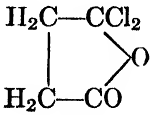


XIX



$$\begin{array}{l} H_2C—CO—Cl \\ \quad | \\ H_2C—CO—Cl \end{array}$$

XX



XXI

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[52] For several closely related examples of ring-chain tautomerism, see A. Kirrmann and C. Prévost, *Bull. soc. chim.* [4] **53**, 253 (1933).

[53] Cf. E. Ott, H. Gilman, and F. J. Prochaska in A. H. Blatt, *Organic Syntheses*, John Wiley and Sons, New York, Collective Volume 2, 1943, page 528.

15.

Free Radicals[1]

15·1 Types of Anomalous Valence. In an earlier chapter (see page 91), it was stated that the structural theory of organic chemistry can be reconciled with the observed numbers of isomers only if certain variations in the valences of the elements are recognized. Some of these variations have already been discussed. Thus, an increase in the covalence of an atom, and the acquiring of a formal positive charge by that atom, have been taken as criteria for the formation of an onium compound. (See Sections 2·3 and 2·4.) The valences of the elements in these onium compounds, however, can hardly be regarded as anomalous, since they are easily interpreted by the electronic theory of valence. The characteristic examples of anomalous valence occur rather in the groups of compounds known as *free radicals.*

Before the nature of free radicals is examined more carefully, it will be desirable first to consider the distinction between two different types of anomalous valence. These types can be illustrated, respectively, by the unknown compound CH_5 and by the known, but extremely reactive, methyl radical CH_3. A molecule composed of one carbon and five hydrogen atoms would be *physically unstable;* in other words, it would break apart spontaneously into smaller fragments (such as a molecule of methane plus a hydrogen atom, or a methyl radical plus a hydrogen molecule). Since a carbon atom cannot form more than four strong bonds, and since a hydrogen atom cannot form more than one strong bond, there could be no important forces operating to hold together the molecule of such a compound as CH_5. Obviously, therefore, this compound cannot exist. The methyl radical CH_3, on the other hand, is physically stable, since a carbon atom *can* form three strong bonds. The

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[1] For further discussion of free radicals, see W. E. Bachmann in H. Gilman, *Organic Chemistry*, John Wiley and Sons, New York, 1st ed., 1938, Volume I, Chapter 5, 2nd ed., 1943, Volume I, Chapter 6; W. A. Waters, *The Chemistry of Free Radicals*, Oxford University Press, Oxford, 1946; E. W. R. Steacie, *Atomic and Free Radical Reactions*, Reinhold Publishing Corporation, New York, 1946; *Free Radical Mechanisms*, Reinhold Publishing Corporation, New York, 1946; E. Müller, *Angew. Chem.* **51**, 657 (1938); *Neuere Anschauungen der organischen Chemie*, Julius Springer, Berlin, 1940, Chapter IV.

reason why the substance cannot be prepared in large quantity and kept for an extended period of time is, therefore, not that its molecules break apart spontaneously; indeed, a single molecule that is completely isolated from all contact with other molecules of any kind would doubtless remain unchanged indefinitely. The reason is instead that the substance is so extraordinarily reactive that each molecule undergoes some sort of chemical change before it has had a very large number of collisions with other molecules. That the radical should be so reactive is hardly surprising, for, since in general the stability of a molecule increases with the number of its bonds (see Section 10·9), a molecule in which a carbon atom has less than its normal valence might be expected to have a powerful tendency to go over into products in which every atom does have its full normal valence.

Since no physically unstable compound can exist, all examples of anomalous valence taken up in this chapter will necessarily belong to the second of the two types just discussed. The compounds considered hereafter will therefore be physically stable, but will contain atoms that form fewer than their customary numbers of bonds. Such compounds might be expected to be always as extremely reactive as the methyl radical; this expectation is, however, not correct. Although some of the compounds described in the following sections are, to be sure, similar to the methyl radical in reactivity, others exist in equilibrium with normal compounds in which no atoms have anomalous valences, and still others must be classified as rather *un*reactive. All gradations between widely separated extremes are known.

15·2 The Distinguishing Characteristics of Free Radicals. The methyl group, CH_3, is clearly a radical; when it is not combined with some other atom or radical, it may be called a *free* radical. Not infrequently, however, there is more or less uncertainty whether a given isolated, but interconnected, group of atoms should or should not be similarly described. It would be desirable, therefore, to formulate a precise definition of the expression "free radical," so that this source of uncertainty might be eliminated.

A common impression of free radicals is that they are extremely reactive colored substances, which are transformed into colorless products by dimerization, by reaction with oxygen, or by combination with other free radicals. Although these properties are indeed possessed by many free radicals, they are neither necessary nor sufficient. Thus, some free radicals are rather unreactive (as noted above), some are colorless, some do not dimerize, some are inert toward oxygen, and some show no tendency to combine with other free radicals. Moreover, many compounds that are not conveniently regarded as free radicals do have one or more of the properties listed. Consequently, these properties do not provide the precise definition desired.

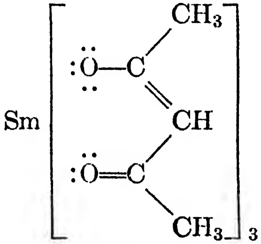
The least unsatisfactory statement of the distinguishing characteristics of a free radical is probably that a substance is a free radical if, and only if, each of its molecules contains an *unpaired electron.* (See pages 416 f.) The methyl radical CH_3, for example, contains an odd number of electrons, of which at least one must therefore be unpaired; hence this substance is a free radical. Nitrosobenzene, I, on the other hand, has

$$C_6H_5—NO$$

I

been found[2] to have no unpaired electrons; hence it is not a free radical, even though it is a colored compound that associates to a colorless dimer.

Although the foregoing definition is logical and convenient when applied to purely organic compounds, it is sometimes not entirely satisfactory when applied to compounds containing elements of the transition groups. For example, the apparently un-ionized samarium acetylacetonate, II, and the ferricyanide ion, III, contain odd numbers of electrons; consequently, although neither is very closely analogous to the typical free radicals taken up in the later sections of this chapter, each must be considered a free radical. (Samarium acetylacetonate has five unpaired electrons per molecule;[3] ferricyanide ion has one.[4]) It may therefore seem unwise to adopt a definition which classifies such "inorganic" substances and ions as free radicals. Nevertheless, the definition in question will be used throughout this chapter, since it leads to no difficulties with any of the compounds to which it will be applied.



II

$$[Fe(CN)_6]^{\equiv}$$

III

The compounds of "bivalent carbon" illustrate a special class of anomalous valence. The present view regarding the constitution of these compounds[5] is that

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[2] E. B. Wilson, Jr., *J. Am. Chem. Soc.* **56,** 747 (1934).

[3] For the electronic configuration of the samarium ion, see J. H. Van Vleck, *The Theory of Electric and Magnetic Susceptibilities,* Oxford University Press, Oxford, 1932, page 243.

[4] Cf. L. Pauling, *J. Am. Chem. Soc.* **53,** 1367 (1931).

[5] Cf. L. Pauling, *The Nature of the Chemical Bond,* Cornell University Press, Ithaca, 1st ed., 1939, pages 127 f., 183 f., 2nd ed., 1940, pages 135 f., 198 f.

carbon monoxide CO is a resonance hybrid of structures IV and V; that an isocyanide

$$\begin{array}{cccccc} :\mathrm{C}{=}\ddot{\mathrm{O}}: & :\mathrm{C}^{-}{\equiv}\mathrm{O}:^{+} & \mathrm{R}{-}\ddot{\mathrm{N}}{=}\mathrm{C}: & \mathrm{R}{-}\mathrm{N}^{+}{\equiv}\mathrm{C}:^{-} & \mathrm{HO}{-}\ddot{\mathrm{N}}{=}\mathrm{C}: & \mathrm{HO}{-}\mathrm{N}^{+}{\equiv}\mathrm{C}:^{-} \\ \text{IV} & \text{V} & \text{VI} & \text{VII} & \text{VIII} & \text{IX} \end{array}$$

RNC is a resonance hybrid of structures VI and VII; and that fulminic acid HONC is a resonance hybrid of structures VIII and IX. These interpretations are supported by the fact that there are no known stable compounds with structures like X, in which the "bivalent" carbon atom forms two single bonds, or like XI, in

$$\begin{array}{ccc} \mathrm{CH_3{-}C{-}CH_3} & \qquad & \mathrm{C{=}C(CH_3)_2} \\ \text{X} & & \text{XI} \end{array}$$

which this atom is joined by a double bond to an atom without an unshared pair of electrons. In other words, "bivalent carbon" does not occur except when resonance of the assumed type is possible. Further, and more direct, evidence in favor of the assumption of resonance can also be given.[5] Since structures IV–IX do not contain any unpaired electrons, the substances to which they refer are not free radicals.

15·3 Production of Short-lived Free Radicals in the Gas Phase. The methyl free radical is so extremely reactive that it cannot be isolated, and (even without isolation) it cannot be kept for more than a fraction of a second. Any free radical with these properties is said to be *short-lived*, or to be of *short life*. It is evident that special methods must be devised for the preparation and study of such free radicals, since the usual techniques of organic chemistry would obviously be inadequate.

Paneth and Hofeditz were the first chemists to obtain satisfactory evidence for the existence of a free radical of short life. Their procedure (often referred to as the *Paneth technique*) can be illustrated with a description of their preparation of methyl CH_3.[6] The vapor of lead tetramethyl $Pb(CH_3)_4$ in a current of hydrogen or nitrogen, is passed through a quartz tube, the pressure in which is held at about 1–2 mm by the action of a high-speed vacuum pump. A small portion of the tube is then heated strongly, so that the lead tetramethyl is decomposed, and a "mirror" of metallic lead is deposited on the inside of the tube. The gaseous products of the decomposition, which are swept along by the hydrogen or nitrogen, are able to "dissolve," or to remove, a previously formed lead mirror farther along the tube. Since the only likely stable products (hydrogen, methane, ethane, ethylene, and acetylene) have been shown to have no effect upon such a mirror, it seems necessary to infer that the reaction product responsible for the disappearance of the mirror is free methyl CH_3, and that this radical reacts with the metallic lead to regenerate the volatile lead tetramethyl. This inference is supported by the fact that, if the tube is heated at a point beyond the one at which the lead mirror is being dissolved, a new mirror

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[6] F. Paneth and W. Hofeditz, *Ber.* **62**, 1335 (1929).

is formed, doubtless as a result of the decomposition of this regenerated lead tetramethyl. Moreover, when a metallic mirror of zinc or one of antimony is similarly dissolved, zinc dimethyl $Zn(CH_3)_2$, or a mixture of antimony trimethyl $Sb(CH_3)_3$ and tetramethylbistibine $(CH_3)_2Sb—Sb(CH_3)_2$, can be obtained by condensation of the exit gases.[6, 7]

The rate at which a mirror is dissolved by the free radical decreases with increasing distance between the mirror and the point at which the radical is formed.[6] Thus, an antimony mirror prepared in a certain standardized manner disappears in 4 sec at 4 cm, but only after 150 sec at 37 cm. Evidently, therefore, as the radical moves along the tube, it is rapidly transformed into less reactive products. From a determination of the dependence of the rate of disappearance of the mirror upon the distance, and from a knowledge of the velocity with which the gases flow through the tube, the half-life of the radical can be calculated. Under the conditions employed by Paneth and Hofeditz, this half-life was found to be about 6×10^{-3} sec. Although there is therefore no possibility of isolating the radical at room temperature, an attempt has nevertheless been made to isolate it at a lower temperature by cooling the gases in liquid air as soon as possible after the radical has been generated; the product obtained in this way consisted, however, only of stable hydrocarbons.

The Paneth technique has been applied to the thermal decomposition (*pyrolysis*) of several other organometallic compounds besides lead tetramethyl. Bismuth trimethyl $Bi(CH_3)_3$, for example, is as satisfactory as the lead compound for the production of methyl radicals; it suffers, however, from the fact that it is sensitive toward oxygen and hence is inconvenient to work with.[6] On the other hand, zinc dimethyl $Zn(CH_3)_2$ and antimony trimethyl $Sb(CH_3)_3$ are relatively unsatisfactory.[6] Other metals which have been employed include mercury, germanium, silicon, and tin.[8] The ethyl radical C_2H_5 has been made by the decomposition of lead tetraethyl $Pb(C_2H_5)_4$; it resembles the methyl radical closely in its properties and in its half-life.[9] Similarly, the benzyl radical $C_6H_5—CH_2$ has been made by the decomposition of tin tetrabenzyl $Sn(CH_2—C_6H_5)_4$.[10] Attempts to prepare *n*-propyl *n*-C_3H_7 and isobutyl *i*-C_4H_9 from the lead compounds have, however, failed;[9,10] these more complex radicals (if, indeed, they are produced at

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[7] F. A. Paneth and H. Loleit, *J. Chem. Soc.* **1935**, 366.

[8] E. W. R. Steacie, *Atomic and Free Radical Reactions*, Reinhold Publishing Corporation, New York, 1946, page 510.

[9] F. Paneth and W. Lautsch, *Ber.* **64**, 2702 (1931).

[10] F. A. Paneth and W. Lautsch, *J. Chem. Soc.* **1935**, 380.

all) rapidly decompose further into still smaller fragments. Although gaseous products that dissolve metallic mirrors are formed, the resulting metal alkyls contain largely, if not entirely, methyl groups, rather than propyl or isobutyl groups. Paneth and Lautsch [10] have reported that the decomposition of lead tetraphenyl $Pb(C_6H_5)_4$ gives a great deal of carbon but no radical that can dissolve a metallic mirror; Dull and Simons,[11] on the other hand, have reported that the product obtained in this way reacts with mercury to give mercury diphenyl $Hg(C_6H_5)_2$. The major product of the reaction is biphenyl $C_6H_5—C_6H_5$, which is doubtless formed by dimerization of the phenyl radical.

Metal alkyls are by no means the only compounds which, on pyrolysis, give rise to free radicals of short life. In fact, decomposition into radicals seems to be the rule rather than the exception. That this generalization should be correct is not surprising. If, for example, a bond between two atoms A and B (which may be of either the same or different elements) is broken pyrolytically, the reaction can be expected to proceed more easily in the manner shown in equation 15·1 than in the alternative

$$\mathrm{A—B} \rightarrow \mathrm{A}\cdot + \mathrm{B}\cdot \qquad (15\cdot1)$$

$$\mathrm{A—B} \rightarrow \mathrm{A}^{+} + \mathrm{B}\!:^{-} \qquad (15\cdot2)$$

manner shown in equation 15·2; for, in equation 15·1, the radicals which are separated from each other are electrically neutral, whereas, in equation 15·2, the ions which are similarly separated have opposite electric charges. Thus, if two charges, equal respectively to $+e$ and $-e$ (where e is 4.80×10^{-10} electrostatic unit, the magnitude of the electronic charge) are initially at a distance of 1.5 A (an average bond length) from each other, and if these charges are separated so that they no longer interact appreciably, the rupture of the "ionic bond" requires an energy of more than 200 kcal per mole to overcome the electrostatic attraction (see Section 1·4); on the other hand, the rupture of a single covalent bond with the production of free radicals (equation 15·1) never requires much more than about 100 kcal per mole, and usually requires significantly less than that amount of energy.

One example of a compound which is not a metal alkyl, but which is decomposed thermally to free radicals, is given by azomethane, I; this

$$\underset{\text{I}}{CH_3—N{=}N—CH_3} \qquad \underset{\text{II}}{(CH_3)_2CH—N{=}N—CH(CH_3)_2}$$

substance at 475°C gives rise to methyl radicals, which can be detected

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[11] M. F. Dull and J. H. Simons, *J. Am. Chem. Soc.* **55**, 3898 (1933).

by their ability to dissolve lead mirrors.[12,13] Similarly, azoisopropane, II, at 450°–550°C gives radicals that dissolve antimony mirrors;[13] these radicals have been found, however, to be methyl rather than isopropyl.[14] Numerous other examples have been investigated by Rice and his coworkers. Thus, a number of paraffin hydrocarbons decompose at temperatures between 800° and 1000°C into radicals which attack metallic mercury.[15] The resulting mercury dialkyls HgR_2 were treated with mercuric bromide $HgBr_2$, and thereby transformed into alkyl mercuric bromides RHgBr, which were then identified by their characteristic x-ray diffraction patterns. Regardless of the size of the original paraffin molecules, the only substances definitely shown to be formed were methyl mercuric bromide CH_3HgBr (which was always the major product), and ethyl mercuric bromide C_2H_5HgBr (which was present, when at all, in smaller amount). The instability of the larger alkyl radicals is therefore again evident. Similar results have been obtained also in the pyrolyses of several aliphatic ketones, alcohols, ethers, and amines;[16] the products obtained from all these compounds are able to dissolve antimony mirrors.

Photochemical, as well as thermal, decompositions have been used for the production of short-lived free radicals. For example, irradiation of gaseous acetone, III, methyl ethyl ketone, IV, and diethyl ketone, V,

$$\underset{\text{III}}{CH_3\text{—}CO\text{—}CH_3} \qquad \underset{\text{IV}}{CH_3\text{—}CO\text{—}C_2H_5} \qquad \underset{\text{V}}{C_2H_5\text{—}CO\text{—}C_2H_5}$$

with the light of a quartz mercury-vapor lamp gives radicals which dissolve mirrors of antimony, tellurium, and lead,[17] and which also attack elementary mercury, arsenic, and iodine.[18] That the radical produced from acetone in this *photolysis* is methyl has been shown by the isolation of dimethyl telluride $(CH_3)_2Te$, dimethyl ditelluride $(CH_3)_2Te_2$, mercury dimethyl $Hg(CH_3)_2$, and arsenic trimethyl $As(CH_3)_3$;[18] that the radical produced from diethyl ketone is ethyl has been shown similarly by the isolation of arsenic triethyl $As(C_2H_5)_3$. Methyl-*n*-butyl ketone, acetaldehyde, and propionaldehyde were reported[17] to form no radicals; in later work, however, it was found[18] that methyl radicals can be detected in the decomposition of acetaldehyde if precautions are taken to prevent the surface of the metal from

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[12] J. A. Leermakers, *J. Am. Chem. Soc.* **55**, 3499 (1933).

[13] F. O. Rice and B. L. Evering, *J. Am. Chem. Soc.* **55**, 3898 (1933).

[14] F. O. Rice and A. T. W. Aten, Jr., quoted by F. O. Rice, *Chem. Revs.* **17**, 53, 60 (1935)

[15] F. O. Rice, *Trans. Faraday Soc.* **30**, 152 (1934).

[16] F. O. Rice and W. R. Johnston, *J. Am. Chem. Soc.* **56**, 214 (1934).

[17] T. G. Pearson, *J. Chem. Soc.* **1934**, 1718.

[18] T. G. Pearson and R. H. Purcell, *J. Chem. Soc.* **1935**, 1151.

becoming covered with a protective layer of polymerized acetaldehyde. Photolysis of di-*n*-propyl ketone, VI, gives the *n*-propyl free radical

$$CH_3{-}CH_2{-}CH_2{-}CO{-}CH_2{-}CH_2{-}CH_3$$

VI

$CH_3{-}CH_2{-}CH_2$, which reacts with mercury to form mercury di-*n*-propyl $Hg(n\text{-}C_3H_7)_2$; rather unexpectedly, photolysis of diisopropyl ketone, VII, also gives the *n*-propyl radical.[19] (It is of interest that this

$$(CH_3)_2CH{-}CO{-}CH(CH_3)_2$$

VII

propyl radical has not been made by *thermal* decompositions in the gas phase. See above.) The phenyl radical also has been made photochemically. When either benzophenone $C_6H_5{-}CO{-}C_6H_5$ or acetophenone $C_6H_5{-}CO{-}CH_3$ in the gaseous state is irradiated with ultraviolet light, it forms a product that attacks a tellurium mirror. The free radicals obtained from acetophenone have been the most extensively studied; they react with the tellurium to produce diphenyl telluride $(C_6H_5)_2Te$, phenylmethyl telluride $C_6H_5{-}Te{-}CH_3$, and dimethyl telluride $(CH_3)_2Te$.[20]

Simple alkyl and aryl radicals have been made in the gas phase by reactions of still further types. Thus, sodium vapor attacks methyl bromide, ethyl bromide, and bromobenzene, with production of methyl, ethyl, and phenyl radicals, respectively.[21] The sodium-free gaseous products react with iodine vapor to form methyl iodide, ethyl iodide, and iodobenzene (plus large amounts of biphenyl), respectively;[21] they remove tellurium mirrors, and the *alkyl* radicals remove antimony mirrors.[22] Similarly, free benzyl $C_6H_5{-}CH_2$, which is formed by the action of sodium vapor on benzyl chloride $C_6H_5{-}CH_2Cl$, also removes tellurium mirrors.[23] Moreover, as will be discussed in greater detail in the following section, many of the familiar gas-phase reactions of aliphatic compounds are now considered to involve free alkyl radicals as active intermediates.

Acyl, as well as alkyl and aryl, radicals are also known. That the photochemical decomposition of acetone gives not only methyl radicals

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[19] H. H. Glazebrook and T. G. Pearson, *J. Chem. Soc.* **1936,** 1777. Cf., however, M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.* **63,** 526 (1941).

[20] H. H. Glazebrook and T. G. Pearson, *J. Chem. Soc.* **1939,** 589.

[21] M. Polanyi and D. W. G. Style, *Naturwissenschaften* **20,** 401 (1932); E. Horn, M. Polanyi, and D. W. G. Style, *Z. physik. Chem.* **B23,** 291 (1933); *Trans. Faraday Soc.* **30,** 189 (1934); E. Horn and M. Polanyi, *Z. physik. Chem.* **B25,** 151 (1934).

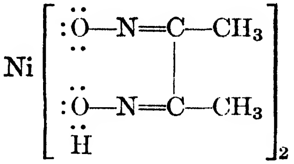
[22] A. O. Allen and C. E. H. Bawn, *Trans. Faraday Soc.* **34,** 463 (1938).

[23] F. A. Paneth and W. Lautsch, *J. Chem. Soc.* **1935,** 380.

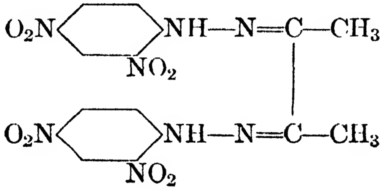
CH_3 (shown by the formation of dimethyl telluride[24]), but also acetyl radicals $CH_3—CO$, has been demonstrated by the isolation[24,25] of biacetyl, VIII, of nickel dimethylglyoxime, IX, and of biacetyl 2,4-dinitrophenylhydrazone (presumably the bis-hydrazone, X[26]); this biacetyl is, of course, formed by the dimerization of the acetyl radical. Evidence for the production of formyl HCO by the photolysis of acetaldehyde has also been obtained.[27] Unlike the alkyl and aryl radicals, the acyl radicals are not obtained by thermal decompositions (doubtless because at elevated temperatures they rapidly decompose into alkyl or aryl radicals and carbon monoxide); and they do not dissolve metallic mirrors.

$CH_3—CO—CO—CH_3$

VIII



IX



X

15·4 Reactions of Gaseous Short-lived Free Radicals. Several important reactions of free radicals have already been mentioned. Of these, the ones which have been most extensively discussed in the preceding section are the ones by which alkyl or aryl derivatives of various (often metallic) elements are formed by direct combination of the radicals with those elements. Thus, the reactions with lead, antimony, zinc, mercury, arsenic, iodine, and tellurium have been taken as evidence for the existence of free radicals. In addition to these elements, bismuth, tin, selenium, and others have also been used in the same way.[28] It is

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[24] H. H. Glazebrook and T. G. Pearson, *J. Chem. Soc.* **1937,** 567.

[25] R. Spence and W. Wild, *Nature* **138,** 206 (1936); *J. Chem. Soc.* **1937,** 352. Cf. also M. Barak and D. W. G. Style, *Nature* **135,** 307 (1935).

[26] Cf. B. Tankó, *Biochem. Z.* **247,** 482 (1932); H. H. Strain, *J. Am. Chem. Soc.* **57,** 758 (1935).

[27] Cf. W. A. Waters, *The Chemistry of Free Radicals,* Oxford University Press, Oxford, 1946, page 118; E. W. R. Steacie, *Atomic and Free Radical Reactions,* Reinhold Publishing Corporation, New York, 1946, pages 362 ff.; *Free Radical Mechanisms,* Reinhold Publishing Corporation, New York, 1946, pages 230 ff.

[28] Cf. E. W. R. Steacie, *Atomic and Free Radical Reactions,* Reinhold Publishing Corporation, New York, 1946, page 48; *Free Radical Mechanisms,* Reinhold Publishing Corporation, New York, 1946, page 36.

commonly assumed that the reactions between radicals and many solid elements take place at the first collisions.

A further (more briefly mentioned) reaction of the gaseous radicals of short life is their dimerization to stable products that are no longer free radicals. Biphenyl and biacetyl, for example, were stated above to be formed by the combination of phenyl and of acetyl radicals, respectively. Moreover, the rapid spontaneous disappearance of methyl radicals in Paneth and Hofeditz's original experiment [6] must be attributed to their dimerization, since ethane was found to be the major product of the reaction in the absence of other reagents.[29,30] Similarly, the ethyl radical dimerizes to *n*-butane;[29,30] this reaction is favored at low temperatures.

It might be thought that an active radical like methyl or ethyl would necessarily combine with another such radical to form a stable paraffin hydrocarbon at the first collision, since the two radicals should be held together by the new covalent bond that results from the interaction between the formerly unpaired electrons. The situation is somewhat more complicated, however, than it appears at first sight to be. When the new bond is created, a considerable amount of energy (the bond energy) is made available. As a result of the law of conservation of energy, this energy must go somewhere since it cannot simply cease to exist. The probability that it will be transformed into rotational energy, or that it will be radiated as light of some wave length, can be shown to be negligibly small; the probability that it will be transformed into translational energy of the molecule as a whole can be shown to be exactly zero, since any such process would violate the law of conservation of momentum. Only three possibilities therefore remain. The first of these is that the energy cause the dissociation of the resulting molecule either into the radicals from which it was originally formed or else into different fragments; the second is that the energy be used to excite the vibrations of the molecule; the third is that the energy be dissipated by intermolecular collisions. When the radicals that combine are as small as methyl or ethyl, the possibility which is most likely to be realized in the gas phase is the first one. For, if the energy is instead transformed into vibrational energy, the probability that at some instant it will reside exclusively (or nearly exclusively) in some individual bond is so great that the molecule is almost certain to break up into radicals by rupture of that bond before there has been sufficient time for a collision

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[29] F. A. Paneth, W. Hofeditz, and A. Wunsch, *J. Chem. Soc.* **1935**, 372; F. Paneth and K. F. Herzfeld, *Z. Elektrochem.* **37**, 577 (1931).

[30] F. Paneth and W. Lautsch, *Ber.* **64**, 2708 (1931); W. J. Moore, Jr., and H. S. Taylor, *J. Chem. Phys.* **8**, 396, 466 (1940).

with another molecule. Consequently, the observed dimerizations of methyl and of ethyl can hardly occur in the gas phase; they must therefore take place predominantly on the wall of the tube, which acts as the "other molecule," collision with which is needed for the dissipation of the excess energy. Even so, however, not every collision results in reaction; it has been found, for example, that, before a methyl radical is destroyed, it must collide about 1000 times with a cold glass or quartz wall, or about 10,000 times with a hot wall at 500°C when helium is used as the carrier gas.[29]

An alkyl radical with more than two carbon atoms decomposes readily into smaller radicals, as has already been mentioned. Another type of reaction by which a radical more complex than methyl can be destroyed is called *disproportionation;* two ethyl radicals, for example, can be transformed by a mutual hydrogenation and dehydrogenation into one molecule of ethane C_2H_6 and one of ethylene C_2H_4.[31] The mechanism of disproportionation is not known.

Still a further type of reaction undergone by gaseous free radicals of short life can be expressed by the general equation 15·3. For example,

$$\text{(radical)} + \text{(molecule)} \rightarrow \text{(radical)}' + \text{(molecule)}' \qquad (15\cdot3)$$

when the methyl radical is swept along in a current of hydrogen, more or less methane is formed,[29] presumably by reaction 15·4. (Here, and

$$\dot{\mathrm{C}}\mathrm{H_3} + \mathrm{H_2} \rightarrow \mathrm{CH_4} + \mathrm{H}\cdot \qquad (15\cdot4)$$

hereafter, a single isolated dot beside an atomic symbol represents an unpaired electron.) Moreover, the chlorination of a paraffin hydrocarbon RH is considered to proceed by the chain of reactions 15·5 and

$$:\underset{\cdot\cdot}{\dot{\mathrm{Cl}}}: + \mathrm{RH} \rightarrow \mathrm{R}\cdot + \mathrm{HCl} \qquad (15\cdot5)$$

15·6. A chlorine atom (which is of course a free radical since it contains

$$\mathrm{R}\cdot + \mathrm{Cl_2} \rightarrow \mathrm{RCl} + :\underset{\cdot\cdot}{\dot{\mathrm{Cl}}}: \qquad (15\cdot6)$$

an odd number of electrons) initiates the chain in reaction 15·5 by removing a hydrogen atom from the hydrocarbon and by producing the radical R·; although in the process this original chlorine atom is converted into stable hydrogen chloride, and hence is made inactive, it is

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[31] Cf. R. L. Geddes and E. Mack, Jr., *J. Am. Chem. Soc.* **52**, 4372 (1930); W. J. Moore, Jr., and H. S. Taylor, *J. Chem. Phys.* **8**, 396 (1940); E. W. R. Steacie, *Free Radical Mechanisms*, Reinhold Publishing Corporation, New York, 1946, pages 224 ff.; *Atomic and Free Radical Reactions*, Reinhold Publishing Corporation, New York, 1946, pages 329 ff.

replaced in the subsequent reaction 15·6. The chain can obviously continue by repetition of the reactions 15·5 and 15·6 until the hydrocarbon RH or the chlorine Cl_2 has been used up, or until the chain is broken by some such reaction as 15·7, 15·8, 15·9, or 15·10; any one of

$$2\mathrm{R}\cdot \rightarrow \mathrm{R{-}R} \tag{15·7}$$

$$2:\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \rightarrow \mathrm{Cl}_2 \tag{15·8}$$

$$\mathrm{R}\cdot + :\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \rightarrow \mathrm{RCl} \tag{15·9}$$

$$:\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: + \mathrm{O}_2 \rightarrow \mathrm{ClO}_2 \tag{15·10}$$

these reactions would presumably have to take place on the wall since three-body collisions in the gas phase are extremely rare (see above).

The most satisfactory evidence for the proposed mechanism of chlorination is doubtless that obtained from a kinetic study of the photochemical chlorination of gaseous chloroform,[32] which substance may be presumed to react in the same way as does a paraffin hydrocarbon. Since, however, an adequate discussion of this work would require an undesirably long digression into the theory of reaction rates, only certain other types of evidence, of a more qualitative nature, will be described here.

Part of this other evidence is derived from a consideration of the conditions under which the reaction takes place. A mixture of ethane and chlorine, for example, can remain unchanged for an indefinite period of time if it is kept in the dark and at room temperature; the substitution reaction proceeds rapidly, however, if the mixture is illuminated with ultraviolet light (or even with visible light of sufficiently short wave length); if it is heated in the dark to a temperature above about 250°C; or if, in the dark and at a comparatively low temperature, it is made to contain a trace of a free radical like ethyl.[33] These methods of initiating the reaction are just the ones which could have been expected to be effective if the mechanism of equations 15·5 and 15·6 is correct. The absorption of light by molecular chlorine Cl_2 has been shown[34] spectroscopically to result in the production of the atomic chlorine Cl that is needed for the reaction; at 250°C and higher, a small amount of atomic chlorine can be formed by the thermal dissociation of the molec-

[32] H. J. Schumacher and K. Wolff, *Z. physik. Chem.* **B25**, 161 (1934).

[33] Cf. W. E. Vaughan and F. F. Rust, *J. Org. Chem.* **5**, 449 (1940).

[34] H. Kuhn, *Z. Physik.* **39**, 77 (1926).

ular chlorine; and a trace of ethyl radical (or the like) can start the reaction chain in accordance with equation 15·6.

Further evidence for the proposed mechanism is that a minute trace of atomic chlorine or of a free radical is sufficient to permit the formation of a relatively enormous amount of chlorinated product. Since the *chain carriers*, $:\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:$ and R·, are constantly regenerated, a single chlorine atom or a single radical should in principle be able to start a chain reaction by which any given amount of hydrocarbon is finally chlorinated. In practice, however, a reaction carried out in such a manner would be immeasurably slow and, indeed, would almost certainly be stopped by one of the chain-breaking reactions 15·7–15·10 long before it is complete. Consequently, the numbers of chlorine atoms and of radicals present at any instant must be large in an absolute sense, although they may be extremely small in comparison with Avogadro's number. For example, the amount of atomic chlorine that is formed either photochemically or thermally can at most be only a minute fraction of the amount of molecular chlorine present. Consequently, each of the original chlorine atoms must lead to the production of a great many molecules of final product. Moreover, the chlorinations of ethane and of propane have been found to go practically to completion at 132°–140°C in the presence of as little as 0.002 mole per cent of lead tetraethyl.[33] No reaction occurs at this temperature, however, in the absence of the lead tetraethyl, which acts as a source of ethyl radicals. Evidently, therefore, the reaction must be initiated by these ethyl radicals, and it must proceed in such a manner that each radical leads to the production of many molecules of product.

In this reaction, the lead tetraethyl is frequently referred to as a *catalyst*, since only a trace, or "catalytic amount," of it is required. This substance is, however, destroyed in the reaction, and so it is not strictly a catalyst.

Still further evidence that the chlorination of a paraffin hydrocarbon is of the radical-chain type is provided by the fact that the reaction is *inhibited* by a small amount of oxygen.[33] Thus, a single molecule of oxygen, by breaking a single chain (equation 15·10), can prevent the formation of a great many molecules of product. Consequently, a trace of this element is sufficient to decrease greatly the rate of the reaction. Since the oxygen is transformed in the process into a substance, or into substances, that cannot inhibit the chlorination, and since new chains are constantly being initiated, the oxygen must in time be completely used up. Consequently, if at the outset all the oxygen has not been removed from the original reagents, the reaction has an *induction period;*

in other words, it commences slowly, but becomes rapid somewhat later, after the oxygen has been consumed.

An alternative mechanism, which is in as good agreement with the above evidence as the one proposed originally (equations 15·5 and 15·6), is shown in equations 15·11 and 15·12. This second path is, however,

$$:\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: + \mathrm{RH} \rightarrow \mathrm{RCl} + \mathrm{H}\cdot \tag{15·11}$$

$$\mathrm{H}\cdot + \mathrm{Cl_2} \rightarrow \mathrm{HCl} + :\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \tag{15·12}$$

rendered rather improbable by other considerations. In order for a reaction to take place by a chain mechanism, each individual step must be extremely fast; in fact, the chains are broken so rapidly by reactions like those of equations 15·7–15·10 that any such mechanism becomes impracticable unless the chain carriers react at very nearly their first collisions with the appropriate reagent molecules. Consequently, no step in a chain can require a large activation energy. Moreover, since the activation energy of any endothermic reaction must always be at least as great as the heat absorbed in the reaction, it follows also that no step in a chain reaction can be strongly endothermic. If, for definiteness, the hydrocarbon RH is taken to be methane CH_4, the heats of the reactions 15·5, 15·6, 15·11, and 15·12 can be calculated from data in the literature. Thus, equation 15·15 is the sum of equations 15·13 and

$$\mathrm{CH_4} \rightarrow \dot{\mathrm{C}}\mathrm{H_3} + \mathrm{H}\cdot - 102\ \mathrm{kcal}^{35} \tag{15·13}$$

15·14; consequently, the reaction of equation 15·15 is almost thermally

$$\mathrm{H}\cdot + :\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \rightarrow \mathrm{HCl} + 102.9\ \mathrm{kcal}^{36} \tag{15·14}$$

neutral. With hydrocarbons that are more complex than methane, the reactions corresponding to 15·15 can be shown in a similar way to

$$\mathrm{CH_4} + :\overset{\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \rightarrow \dot{\mathrm{C}}\mathrm{H_3} + \mathrm{HCl} + 0.9\ \mathrm{kcal} \tag{15·15}$$

be more exothermic than 15·15.[35] On the other hand, equation 15·19 is the sum of equations 15·16, 15·17, and 15·18; consequently, the

$$\mathrm{CH_4} + \mathrm{Cl_2} \rightarrow \mathrm{CH_3Cl} + \mathrm{HCl} + 24\ \mathrm{kcal}^{37} \tag{15·16}$$

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[35] H. C. Andersen, G. B. Kistiakowsky, and E. R. Van Artsdalen, *J. Chem. Phys.* **10**, 305 (1942); H. C. Andersen and G. B. Kistiakowsky, *ibid.* **11**, 6 (1943); D. P. Stevenson, *ibid.* **10**, 291 (1942).

[36] Cf. F. R. Bichowsky and F. D. Rossini, *The Thermochemistry of the Chemical Substances*, Reinhold Publishing Corporation, New York, 1936, pages 20, 22.

[37] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, 1st ed., 1939, 2nd ed., 1940, Tables 10–1 and 10–2.

$$2{:}\underset{\cdot\cdot}{\dot{\mathrm{Cl}}}{:} \rightarrow \mathrm{Cl_2} + 57.8\ \mathrm{kcal}^{36} \qquad (15\cdot17)$$

$$\mathrm{HCl} \rightarrow \mathrm{H}\cdot + {:}\underset{\cdot\cdot}{\dot{\mathrm{Cl}}}{:} - 102.9\ \mathrm{kcal}^{36} \qquad (15\cdot18)$$

reaction of equation 15·19 is definitely endothermic and hence im-

$$\mathrm{CH_4} + {:}\underset{\cdot\cdot}{\dot{\mathrm{Cl}}}{:} \rightarrow \mathrm{CH_3Cl} + \mathrm{H}\cdot - 21\ \mathrm{kcal} \qquad (15\cdot19)$$

probable. In a similar manner, each of the remaining reactions, 15·20

$$\dot{\mathrm{C}}\mathrm{H_3} + \mathrm{Cl_2} \rightarrow \mathrm{CH_3Cl} + {:}\underset{\cdot\cdot}{\dot{\mathrm{Cl}}}{:} \qquad (15\cdot20)$$

and 15·12, can be shown to be strongly exothermic. It follows, therefore, that, although the alternative sequence (reactions 15·11 and 15·12, or 15·19 and 15·12) is made unlikely by the probable slowness of its first step (15·11 or 15·19), the original sequence (reactions 15·5 and 15·6, or 15·15 and 15·20) is entirely reasonable. (See also page 714.)

Most, if not all, other substitution reactions of gaseous paraffin hydrocarbons are considered to go by radical-chain mechanisms which are more or less analogous to the one just discussed. Since, however, comparatively little is known regarding the natures of the various individual steps, these reactions will not be discussed further here.[1]

A different type of reaction of short-lived free radicals in the gas phase can be expressed generally by equation 15·21. Since the product of the

$$(\text{radical}) + (\text{molecule}) \rightarrow (\text{radical})' \qquad (15\cdot21)$$

reaction is itself a free radical, it may be able to combine with a second molecule of the other reagent to form still a third radical, as in equation (15·22). Moreover, this process may continue still further. For ex-

$$(\text{radical})' + (\text{molecule}) \rightarrow (\text{radical})'' \qquad (15\cdot22)$$

ample, when mercury diethyl $\mathrm{Hg(C_2H_5)_2}$ is decomposed thermally in an atmosphere of ethylene, a liquid product $\mathrm{(CH_2)}_n$ is formed.[38] This polymerized product may be considered the result of successive reactions, the first three of which are shown in equations 15·23, 15·24, and 15·25.

$$\mathrm{Hg(C_2H_5)_2} \rightarrow \mathrm{Hg} + 2\mathrm{C_2H_5} \qquad (15\cdot23)$$

$$\mathrm{C_2H_5} + \mathrm{H_2C{=}CH_2} \rightarrow \mathrm{C_2H_5{-}CH_2{-}}\dot{\mathrm{C}}\mathrm{H_2} \qquad (15\cdot24)$$

$$\mathrm{C_2H_5{-}CH_2{-}}\dot{\mathrm{C}}\mathrm{H_2} + \mathrm{H_2C{=}CH_2} \rightarrow \mathrm{C_2H_5{-}CH_2{-}CH_2{-}CH_2{-}}\dot{\mathrm{C}}\mathrm{H_2} \qquad (15\cdot25)$$

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[38] H. S. Taylor and W. H. Jones, *J. Am. Chem. Soc.* **52**, 1111 (1930).

Each step of the polymerization consists of a simple combination of two molecules, of which one is a free radical and the other is not; consequently, the participation of a third body in each collision that results in combination is presumably necessary here (at any rate at the outset, when both molecules are small), just as it is necessary in the dimerization of a small radical. (See above.) The wall presumably does not act as this third body, because the reaction does not proceed more rapidly when the reaction vessel is packed with glass wool so that the wall surface is greatly increased. Possibly a molecule of ethylene acts as the third body; if so, equation 15·24, for example, should be replaced by equation 15·26 (unless, of course, the ethyl radical and ethylene molecule are

$$C_2H_5 + 2H_2C{=}CH_2 \rightarrow C_2H_5{-}CH_2{-}\dot{C}H_2 + H_2C{=}CH_2 \qquad (15\cdot 26)$$

already big enough to combine directly and without intervention of a third body).

The sequence of reactions (just discussed) must stop at some time, since the polymerization cannot go on forever. Several possibilities for the termination of the chain can be considered. Two radicals may combine with each other (equation 15·27); this reaction would be

$$\begin{aligned} &C_2H_5{-}(CH_2{-}CH_2)_m{-}CH_2{-}\dot{C}H_2 \\ &\qquad + C_2H_5{-}(CH_2{-}CH_2)_n{-}CH_2{-}\dot{C}H_2 \rightarrow \\ &\qquad\qquad C_2H_5{-}(CH_2{-}CH_2)_{m+n+2}{-}C_2H_5 \qquad (15\cdot 27) \end{aligned}$$

analogous to the dimerization of, for example, the methyl radical. (See above.) On the other hand, two radicals may interact by disproportionation (equation 15·28) in the manner described on page

$$\begin{aligned} &C_2H_5{-}(CH_2{-}CH_2)_m{-}CH_2{-}\dot{C}H_2 \\ &\qquad + C_2H_5{-}(CH_2{-}CH_2)_n{-}CH_2{-}\dot{C}H_2 \rightarrow \\ &\qquad C_2H_5{-}(CH_2{-}CH_2)_m{-}CH_2{-}CH_3 \\ &\qquad\qquad + C_2H_5{-}(CH_2{-}CH_2)_n{-}CH{=}CH_2 \qquad (15\cdot 28) \end{aligned}$$

657 for ethyl radicals. Finally, *chain transfer* (equation 15·29) may

$$\begin{aligned} &C_2H_5{-}(CH_2{-}CH_2)_n{-}CH_2{-}\dot{C}H_2 + H_2C{=}CH_2 \rightarrow \\ &\qquad C_2H_5{-}(CH_2{-}CH_2)_n{-}CH{=}CH_2 + H_3C{-}\dot{C}H_2 \qquad (15\cdot 29) \end{aligned}$$

occur; although the chain by which the radical $C_2H_5{-}(CH_2{-}CH_2)_n{-}\dot{C}H_2{-}CH_2$ was formed is thus terminated, a new chain can be started by the ethyl radical that is simultaneously formed. It is not known which of these possibilities is correct; possibly two, or even all three, of them are realized to a greater or less extent.

Free radicals that have been produced in still other ways can also cause the polymerization of olefins. Thus, the polymerization of ethylene has been induced by the radicals formed in the pyrolysis of azomethane[39] or in the photolysis of acetaldehyde, propionaldehyde, *n*-butyraldehyde, acetone, and diethyl ketone;[40] and the polymerizations of propylene and of isobutylene have been induced by the radicals formed in the photolysis of acetaldehyde.[40] (For the polymerization of acetaldehyde by radicals, see pages 653 f.)

15·5 Production and Reactions of Short-lived Free Radicals in Solution. The methods by which short-lived free radicals are produced, and the reactions which such radicals undergo, are apparently of the same general types in solution as in the gas phase. At any rate, there are a considerable number of reactions which can be most easily interpreted if this generalization is assumed to be correct. Thus, the pyrolysis of an organometallic compound in solution seems to give an unstable free radical plus the metallic element. When, for example, a solution of mercury diphenyl in ethyl alcohol is heated to 150°–200°C, elementary mercury, benzene, and acetaldehyde are formed.[41] Presumably, the mercury diphenyl decomposes to mercury and phenyl, and then the latter substance attacks the solvent instead of dimerizing. (Cf. equation 15·3 on page 657.) Moreover, photolysis of methyl ethyl ketone in "medicinal paraffin" gives carbon monoxide, methane, ethane, ethylene, and acetaldehyde; at the end of the reaction, the solvent has become unsaturated.[42] Presumably, the ketone decomposes to alkyl and acyl radicals, which attack the solvent and react in other familiar ways. Finally, the chlorination of a paraffin hydrocarbon in solution may be considered to proceed by the mechanism described above for the gas-phase reaction.

The foregoing reactions in the liquid phase were selected for their particularly close relation to the previously discussed reactions in the gas phase; they form, however, only a small fraction of the reactions in solution which are now considered to involve free radicals as intermediates. The number of such reactions is, in fact, so large that no attempt can be made here to survey the entire field. The following discussion (like the preceding one) is, therefore, to be considered illustrative rather

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[39] O. K. Rice and D. V. Sickman, *J. Am. Chem. Soc.* **57**, 1384 (1935).

[40] C. J. Danby and C. N. Hinshelwood, *Proc. Roy. Soc.* (London) **A179**, 169 (1941).

[41] G. A. Razuvaev and M. M. Koton, *J. Gen. Chem.* (U.S.S.R.) **1**, 864 (1931); *C.A.* **26**, 2719 (1932).

[42] R. G. W. Norrish and C. H. Bamford, *Nature* **140**, 195 (1937); C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.* **1938**, 1531.

than exhaustive. (For still other examples, see Sections 7·9 and 7·11.)

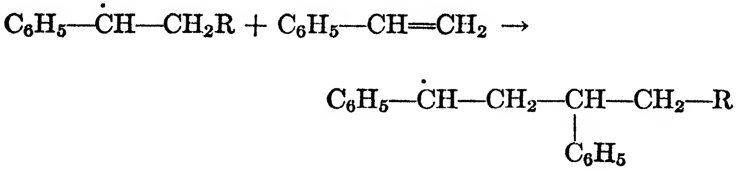
It will be convenient to divide the various free-radical reactions into two main classes, which can be taken up separately. Thus, some such reactions appear to proceed by *chain* mechanisms, whereas others appear not to do so. Examples of both these types (especially in the gas phase) have already been given, and the experimental criteria by which the two may be distinguished have been discussed. For few, if any, liquid-phase reactions, however, have the mechanisms been conclusively demonstrated.

The most extensively studied radical-chain reactions in the liquid phase are undoubtedly the polymerizations of olefins. It would lie entirely outside the scope of this book, however, to describe in detail the various experimental procedures by which these important reactions are carried out on either the industrial or the laboratory scale; it will be sufficient, rather, merely to say here that one of the most common procedures involves the treatment of the olefin with a peroxide.[45] For example, the polymerization of styrene, I, when induced by benzoyl

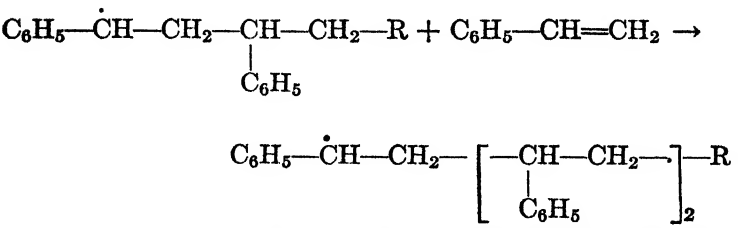
$$\underset{\text{I}}{C_6H_5\text{—}CH\text{=}CH_2} \qquad \underset{\text{II}}{C_6H_5\text{—}CO\text{—}O\text{—}O\text{—}CO\text{—}C_6H_5}$$

peroxide, II, may be presumed to proceed by the steps shown in equations 15·30–15·33, in which R· represents either the phenyl radical

$$C_6H_5\text{—}CH\text{=}CH_2 + R\cdot \rightarrow C_6H_5\text{—}\dot{C}H\text{—}CH_2\text{—}R \qquad (15\cdot30)$$



$$C_6H_5\text{—}\dot{C}H\text{—}CH_2R + C_6H_5\text{—}CH\text{=}CH_2 \rightarrow C_6H_5\text{—}\dot{C}H\text{—}CH_2\text{—}\underset{\substack{|\\ C_6H_5}}{CH}\text{—}CH_2\text{—}R \qquad (15\cdot31)$$



$$C_6H_5\text{—}\dot{C}H\text{—}CH_2\text{—}\underset{\substack{|\\ C_6H_5}}{CH}\text{—}CH_2\text{—}R + C_6H_5\text{—}CH\text{=}CH_2 \rightarrow C_6H_5\text{—}\dot{C}H\text{—}CH_2\text{—}\left[\text{—}\underset{\substack{|\\ C_6H_5}}{CH}\text{—}CH_2\text{—}\right]_2\text{—}R \qquad (15\cdot32)$$

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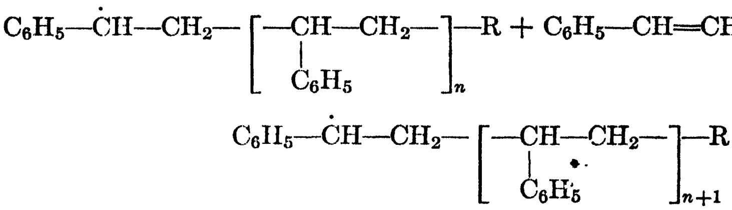
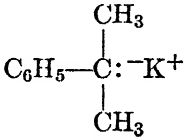
[45] Cf. C. C. Price, *Mechanisms of Reactions at Carbon-Carbon Double Bonds*, Interscience Publishers, New York, 1946, Chapters IV–VII.



$$\mathrm{C_6H_5{-}\dot{C}H{-}CH_2{-}}\left[\begin{array}{c}\mathrm{{-}CH{-}CH_2{-}}\\ |\\ \mathrm{C_6H_5}\end{array}\right]_n\mathrm{{-}R} + \mathrm{C_6H_5{-}CH{=}CH_2} \rightarrow \mathrm{C_6H_5{-}\dot{C}H{-}CH_2{-}}\left[\begin{array}{c}\mathrm{{-}CH{-}CH_2{-}}\\ |\\ \mathrm{C_6H_5}\end{array}\right]_{n+1}\mathrm{{-}R} \qquad (15\cdot33)$$

C_6H_5 or the benzoate radical $C_6H_5-CO_2$. (Cf. equations 15·24 and 15·25.) As in the analogous radical-induced polymerization of ethylene in the gas phase, the termination of the chain may result from the union of two radicals, from disproportionation, or from chain transfer, or from any two or all three of these reactions simultaneously.

The polymerization of an olefin may be carried out also in other ways which do not involve radical chains. Such a compound, for example, can be polymerized by the action of a strong acid like sulfuric acid or stannic chloride, or by a strong base like potassium phenylisopropyl, III.[43] These further reactions are irrelevant to the discussion in this chapter, however, and so they need not here be further discussed.



$$\mathrm{C_6H_5{-}}\overset{\displaystyle \mathrm{CH_3}}{\underset{\displaystyle \mathrm{CH_3}}{\mathrm{C}}}\mathrm{\!:^-K^+}$$

III

Whether the radical R· that initiates the polymerization of styrene (equation 15·30) is phenyl or benzoate, the phenyl group of the original benzoyl peroxide is contained in the molecule of the final polymer. This conclusion is supported by the fact that, if *p*-bromobenzoyl peroxide,

$$p\text{-}\mathrm{Br{-}C_6H_4{-}CO{-}O{-}O{-}CO{-}C_6H_4{-}Br}\text{-}p$$

IV

IV, is used instead of benzoyl peroxide, II, the resulting polymer contains aromatically linked bromine.[44,45] Similarly, the action of *p*-chlorobenzoyl peroxide, V, upon allyl acetate, VI, gives a polymer that contains chlorine.[45] Since, on hydrolysis of this latter polymer, some *p*-chlorobenzoic acid, VII, can be obtained, it is evident that *p*-chlorobenzoate

$$p\text{-}\mathrm{Cl{-}C_6H_4{-}CO{-}O{-}O{-}CO{-}C_6H_4{-}Cl}\text{-}p$$

V

$$\mathrm{H_2C{=}CH{-}CH_2{-}O{-}CO{-}CH_3} \qquad p\text{-}\mathrm{Cl{-}C_6H_4{-}CO_2H}$$

VI VII

---

[44] C. C. Price, R. W. Kell, and E. Krebs, *J. Am. Chem. Soc.* **64**, 1103 (1942); P. D. Bartlett and S. G. Cohen, *ibid.* **65**, 543 (1943).

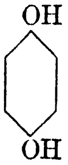
[45] P. D. Bartlett and R. Altschul, *J. Am. Chem. Soc.* **67**, 812 (1945).

groups are present in the polymer, and therefore that, as suggested above, carboxylate as well as aryl radicals can initiate the chains. Indeed, Bartlett and Altschul[45] have estimated that, under their experimental conditions, the polymerized allyl acetate contains between four and five times as many *p*-chlorobenzoate groups as it does simple *p*-chlorophenyl groups.

A further reaction which is considered to go by a radical-chain mechanism is the so-called *abnormal* addition of hydrogen bromide to an olefin. The addition of this acid is usually *normal* (i.e., in agreement with *Markownikoff's rule*) if oxygen and peroxides are carefully excluded, but it may be abnormal (i.e., contrary to Markownikoff's rule) if oxygen or peroxides are present. (Oxygen possibly exerts its effect by first converting the olefin into a peroxide.) Thus, the product formed from propylene, VIII, is predominantly isopropyl bromide, IX, under the

$$\underset{\text{VIII}}{CH_3\text{—}CH\text{=}CH_2} \qquad \underset{\text{IX}}{CH_3\text{—}CHBr\text{—}CH_3} \qquad \underset{\text{X}}{CH_3\text{—}CH_2\text{—}CH_2Br}$$

former conditions, but predominantly *n*-propyl bromide, X, under the latter.[46] Since only a trace of oxygen or peroxide may be sufficient to induce a relatively very large amount of abnormal addition, and since the abnormal addition can be more or less completely inhibited by traces of such "antioxidants" as hydroquinone, XI, or diphenylamine, XII



XI

$(C_6H_5)_2NH$

XII

(cf. page 311), the reaction presumably goes by a chain mechanism. The sequence of steps given in equations 15·34 and 15·35 is the one most

$$CH_3\text{—}CH\text{=}CH_2 + :\underset{\bullet\bullet}{\overset{\bullet}{Br}}: \rightarrow CH_3\text{—}\dot{C}H\text{—}CH_2Br \qquad (15\cdot34)$$

$$CH_3\text{—}\dot{C}H\text{—}CH_2Br + HBr \rightarrow CH_3\text{—}CH_2\text{—}CH_2Br + :\underset{\bullet\bullet}{\overset{\bullet}{Br}}: \qquad (15\cdot35)$$

commonly assumed; the original bromine atom is considered to result from the action of the oxygen, or of the peroxide, or of some free radical formed in the thermal decomposition of the peroxide, upon the hydrogen bromide. The inhibition of the reaction by an antioxidant is presumably due to the ability of such a substance to act as a chain breaker.

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[46] For further discussion of abnormal additions to olefins, and for references to the original literature, see F. R. Mayo and C. Walling, *Chem. Revs.* **27**, 351 (1940).

Abnormal additions of hydrogen bromide can be induced also by the action of ultraviolet light or of certain metals like iron.[46] The light doubtless causes dissociation of the hydrogen bromide, or of some other component of the reaction mixture, into radicals; the metal probably reacts with the acid to form hydrogen atoms which can initiate the chains.

The abnormal addition of hydrogen bromide is possible with most olefins in which the ethylenic double bond is not conjugated with a carbonyl group. Abnormal additions of hydrogen chloride or of hydrogen iodide, however, do not ordinarily occur with such olefins.[47] When a compound contains the grouping $-\underset{\diagdown\ \ |}{C}=\underset{|}{C}-\underset{|}{C}=O$, the addition of any hydrogen halide HX always gives a product with the grouping $-\underset{|}{C}X-\underset{|}{C}H-\underset{|}{C}=O$, regardless of the identity of the halogen X, regardless of the presence or absence of oxygen, peroxides, or antioxidants, and regardless of Markownikoff's rule. The reason why, with *un*conjugated olefins, hydrogen chloride and hydrogen iodide behave differently from hydrogen bromide is presumably that, with hydrogen chloride, the reaction analogous to 15·35 is slow because the hydrogen-chlorine bond is so strong; whereas, with hydrogen iodide, the reaction analogous to 15·34 is slow because the carbon-iodine bond is so weak. A few other reagents, such as mercaptans, thioacids, and bisulfites can also add abnormally to olefins in the presence of oxidizing agents.[46]

A further reaction, which bears some resemblance both to the polymerization of olefins and to the abnormal addition of hydrogen bromide, can be illustrated by the addition of, for example, bromotrichloromethane $CBrCl_3$ to an olefin. Thus, if both styrene, I, and a few mole per cent of acetyl peroxide, XIII, are dissolved in this halogen compound,

$$\underset{\text{XIII}}{CH_3-CO-O-O-CO-CH_3} \qquad \underset{\text{XIV}}{C_6H_5-CHBr-CH_2-CCl_3}$$

and if the solution is then warmed to 60°–70°C for 4 hours, a good yield of 1,1,1-trichloro-3-bromo-3-phenylpropane, XIV, is obtained.[48] A second product which is formed at the same time is a high-boiling material that doubtless contains more than one styrene residue per molecule. (In the reaction with bromotrichloromethane, this high-boiling material is only a minor by-product; in the analogous reaction with carbon tetrachloride, on the other hand, the corresponding material is the major

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[47] For some abnormal additions of hydrogen chloride to olefins in the gas phase at high temperatures, see J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Am. Chem. Soc.* **70**, 2767 (1948); W. E. Hanford and J. Harmon, U. S. **2,418,832**; *C.A.* **42**, 581 (1948).

[48] M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Am. Chem. Soc.* **69**, 1105 (1947).

product.) Similar reactions take place with other olefins, such as 1-octene, propylene, ethylene, and isobutylene; and with other halogen compounds, such as carbon tetrachloride, carbon tetrabromide, chloroform, bromoform, and di- and trichloroacetic acids. These reactions occur also in the absence of the acetyl peroxide if the solution of the olefin in the halogen compound is irradiated with ultraviolet light; or if (with bromotrichloromethane, but not with the other halogen compounds named) the acetyl peroxide is replaced by a mixture of iodine and either magnesium or Raney nickel. The action of the ultraviolet light doubtless produces free radicals photochemically; the mixture of iodine and a metal probably contains a free radical like MgI.

The reactions just mentioned have every appearance of proceeding by radical chains. A reasonable mechanism for the addition of, for example, bromotrichloromethane to styrene is given in equations 15·36–15·39. The material of higher molecular weight, which is also obtained,

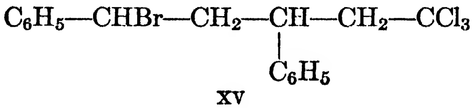
$$CH_3{-}CO{-}O{-}O{-}CO{-}CH_3 \rightarrow 2\dot{C}H_3 + 2CO_2 \qquad (15{\cdot}36)$$

$$\dot{C}H_3 + CBrCl_3 \rightarrow CH_3Br + \dot{C}Cl_3 \qquad (15{\cdot}37)$$

$$\dot{C}Cl_3 + C_6H_5{-}CH{=}CH_2 \rightarrow C_6H_5{-}\dot{C}H{-}CH_2{-}CCl_3 \qquad (15{\cdot}38)$$

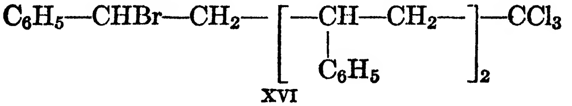
$$C_6H_5{-}\dot{C}H{-}CH_2{-}CCl_3 + CBrCl_3 \rightarrow C_6H_5{-}CHBr{-}CH_2{-}CCl_3 + \dot{C}Cl_3 \qquad (15{\cdot}39)$$

probably contains the polymerized styrene that would have been formed in the absence of the halogen compound (cf. equations 15·30–15·33), and also some such further products as XV and XVI. These latter



$$C_6H_5{-}CHBr{-}CH_2{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}CH_2{-}CCl_3$$

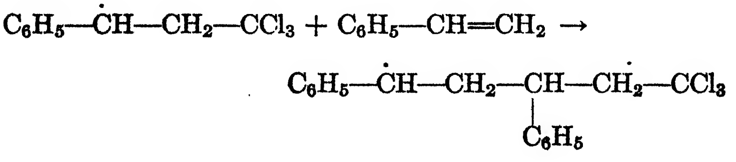
XV



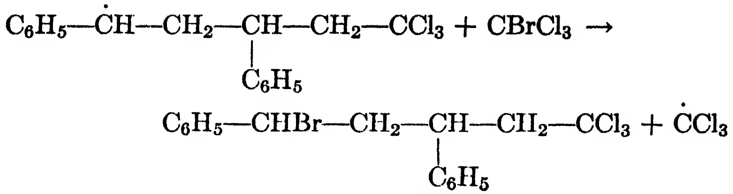
$$C_6H_5{-}CHBr{-}CH_2{-}\left[{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}CH_2{-}\right]_2{-}CCl_3$$

XVI

substances could result from the reactions of equations 15·40–15·43,

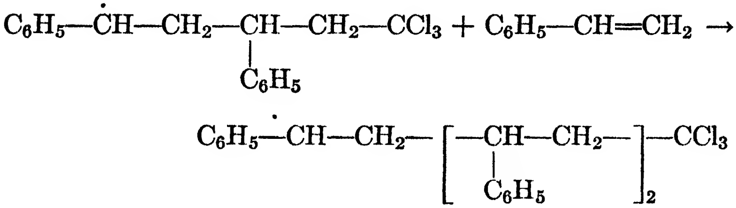


$$C_6H_5{-}\dot{C}H{-}CH_2{-}CCl_3 + C_6H_5{-}CH{=}CH_2 \rightarrow C_6H_5{-}\dot{C}H{-}CH_2{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}CH_2{-}CCl_3 \qquad (15{\cdot}40)$$

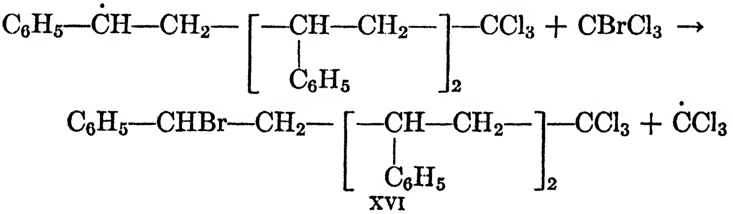


$$\mathrm{C_6H_5{-}\dot{C}H{-}CH_2{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}CCl_3 + CBrCl_3 \rightarrow C_6H_5{-}CHBr{-}CH_2{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}CCl_3 + \dot{C}Cl_3} \qquad (15\cdot41)$$

XV



$$\mathrm{C_6H_5{-}\dot{C}H{-}CH_2{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}CCl_3 + C_6H_5{-}CH{=}CH_2 \rightarrow C_6H_5{-}\dot{C}H{-}CH_2{-}\left[{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}\right]_2{-}CCl_3} \qquad (15\cdot42)$$

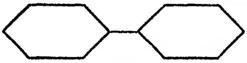


$$\mathrm{C_6H_5{-}\dot{C}H{-}CH_2{-}\left[{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}\right]_2{-}CCl_3 + CBrCl_3 \rightarrow C_6H_5{-}CHBr{-}CH_2{-}\left[{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}\right]_2{-}CCl_3 + \dot{C}Cl_3} \qquad (15\cdot43)$$

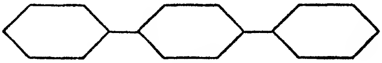
XVI

where the original radical of equation 15·40 is the one formed in equation 15·38.

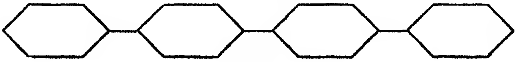
A number of Grignard reactions, which take place in the presence of metallic salts, also appear to involve radical chains. One example will be sufficient. If phenylmagnesium bromide is treated with bromobenzene, no reaction occurs. However, if 3–10 mole per cent of cobaltous chloride $CoCl_2$ is also present, an excellent yield of biphenyl, XVII, is obtained.[49] The by-products include benzene, *p*-terphenyl, XVIII, *p*-quaterphenyl, XIX, and other high-boiling materials. That the biphenyl is formed largely from the Grignard reagent and not from the bromobenzene is shown by the fact that this latter substance can be replaced by other organic bromides, such as *p*-bromotoluene or ethyl bromide, without any significant change in the yield of biphenyl. That



XVII



XVIII



XIX

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[49] M. S. Kharasch and E. K. Fields, *J. Am. Chem. Soc.* **63**, 2316 (1941).

the bromobenzene is nevertheless altered in the reaction is shown by the fact that its bromine is found by titration to be converted into bromide ion. The mechanism proposed by Kharasch and Fields is shown in equations 15·44–15·46. The phenyl radicals produced in

$$C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl \qquad (15\cdot 44)$$

$$2C_6H_5CoCl \rightarrow C_6H_5—C_6H_5 + 2CoCl \qquad (15\cdot 45)$$

$$CoCl + C_6H_5Br \rightarrow CoClBr + C_6H_5 \qquad (15\cdot 46)$$

reaction 15·46 apparently dimerize to form a small part of the biphenyl isolated, extract a hydrogen atom from the solvent (ether) to form benzene, and react with benzene, biphenyl, *p*-terphenyl, and so on to form, respectively, biphenyl, *p*-terphenyl, *p*-quaterphenyl, and so on. (See also below.) The CoClBr formed in reaction 15·46 replaces the $CoCl_2$ consumed in reaction 15·44, so that the chain can continue.

A number of other reactions are considered to involve free radicals as intermediates, but not to proceed by any sorts of chain mechanisms. For example, if sodium benzene diazotate, XX, N-nitrosoacetanilide,

$C_6H_5—N{=}N—ONa$
XX

$C_6H_5—N(NO)—CO—CH_3$
XXI

XXI (which is tautomeric with benzenediazonium acetate, XXII), or

$C_6H_5—N_2^+ \; O_2^-C—CH_3$
XXII

$C_6H_5—CO—O—O—CO—C_6H_5$
II

benzoyl peroxide, II, is decomposed thermally in the presence of benzene, more or less biphenyl, XVII, is formed.[50] The reaction of sodium benzene diazotate is commonly classified with all others of the same type as a *Gomberg reaction*. If toluene, XXIII, or nitrobenzene, XXIV, is

$C_6H_5—CH_3$
XXIII

$C_6H_5—NO_2$
XXIV

used instead of benzene, a *mono*substituted biphenyl is obtained. In each instance, therefore, one of the two phenyl groups in the product comes from each reagent. The reactions can therefore be considered to be substitutions brought about in the benzene, toluene, or nitrobenzene, respectively, by the reagent that is thermally decomposed. These substitutions are, however, significantly different from such familiar ones as nitration and halogenation, because they obey entirely different rules of orientation. Thus, although the methyl and nitro groups are ordinarily considered to be, respectively, *ortho-para* and *meta*

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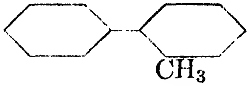
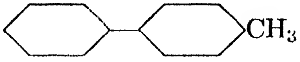
[50] Cf. D. H. Hey and W. A. Waters, *Chem. Revs.* **21**, 169 (1937); D. H. Hey, *Ann. Repts. Progress Chem.* (Chem. Soc. London) **37**, 268 (1940).

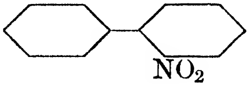
directing, both are *ortho-para* directing in the reactions which are now being discussed, since the major products are, respectively, the *o*- and *p*-methylbiphenyls, XXV, and XXVI, and the *o*- and *p*-nitrobiphenyls, XXVII and XXVIII. All substituent groups, in fact, regardless of their normal orienting effects, are found similarly to be *ortho-para* directing.[51] Largely for this reason, the reactions now under discussion are considered to proceed by a dissociation of the sodium benzene diazotate, N-nitrosoacetanilide, or benzoyl peroxide into phenyl radicals, which then attack the benzene, toluene, or nitrobenzene molecules. Since no chains are involved, stoichiometric (and not merely "catalytic") quantities of all reagents are required.



XXV



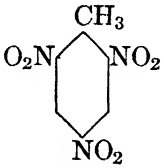
XXVI



XXVII

XXVIII

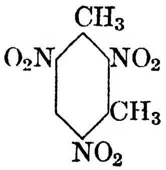
Alkyl, as well as aryl, groups can sometimes be introduced into an aromatic ring (in poor yield). Thus, when a solution of trinitrotoluene, XXIX, and acetyl peroxide, XIII, in acetic acid is refluxed, a small quantity of trinitro-*m*-xylene, XXX, is obtained.[52] Several other nitro compounds have been methylated in a similar manner. The acetyl peroxide, moreover, can be replaced by lead tetraacetate, XXXI. It



XXIX

$CH_3—CO—O—O—CO—CH_3$

XIII



XXX

$Pb(O_2C—CH_3)_4$

XXXI

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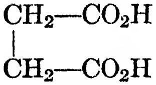
[51] For a theoretical discussion of orientation with respect to the different types of reagent, see G. W. Wheland, *The Theory of Resonance*, John Wiley and Sons, New York, 1944, section 8·11.

[52] L. F. Fieser, R. C. Clapp, and W. H. Daudt, *J. Am. Chem. Soc.* **64**, 2052 (1942).

may be presumed that the active methylating agent in either type of reaction is the free methyl radical. (See also below.)

When a solution of acetyl peroxide, XIII, in acetic acid is refluxed (without any trinitrotoluene or the like), succinic acid, XXXII, methane,



$$\begin{array}{l} CH_2\text{—}CO_2H \\ | \\ CH_2\text{—}CO_2H \end{array}$$

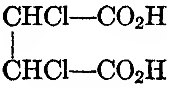
XXXII

$CH_3\text{—}CO_2CH_3$ XXXIII

$CH_2Cl\text{—}CO_2H$ XXXIV

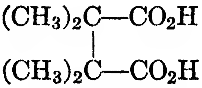
$(CH_3)_2CH\text{—}CO_2H$ XXXV

carbon dioxide, and a trace of methyl acetate, XXXIII, are formed.[53] On the basis of the peroxide decomposed, the yield of succinic acid is about 50 per cent. If the solvent used is chloroacetic acid, XXXIV, or isobutyric acid, XXXV, instead of acetic acid, the dibasic acid produced is not succinic acid, XXXII, but is instead dichlorosuccinic acid, XXXVI, or tetramethylsuccinic acid, XXXVII, respectively. The most



$$\begin{array}{l} CHCl\text{—}CO_2H \\ | \\ CHCl\text{—}CO_2H \end{array}$$

XXXVI



$$\begin{array}{l} (CH_3)_2C\text{—}CO_2H \\ \quad\;\;\; | \\ (CH_3)_2C\text{—}CO_2H \end{array}$$

XXXVII

reasonable mechanism of the reaction is the one shown in equations 15·47–15·49. (Cf. also equation 15·36.) The methyl acetate is possibly

$$CH_3\text{—}CO\text{—}O\text{—}O\text{—}CO\text{—}CH_3 \rightarrow CH_3\text{—}CO\text{—}\underset{\cdot\cdot}{\dot{O}}: + \dot{C}H_3 + CO_2 \qquad (15\cdot47)$$

$$\dot{C}H_3 + CH_3\text{—}CO_2H \rightarrow CH_4 + \dot{C}H_2\text{—}CO_2H \qquad (15\cdot48)$$

$$2\dot{C}H_2\text{—}CO_2H \rightarrow HO_2C\text{—}CH_2\text{—}CH_2\text{—}CO_2H \qquad (15\cdot49)$$

formed from the acetate radical $CH_3\text{—}CO\text{—}\underset{\cdot\cdot}{\dot{O}}:$, either by disproportionation or by reaction with unchanged acetyl peroxide. The acetate radical can also, of course, decompose further into carbon dioxide and the methyl radical, as is presupposed in equation 15·36. (Cf. equation 15·51, below.)

The Kolbe synthesis of a paraffin hydrocarbon by electrolysis of the salt of a carboxylic acid probably involves free radicals as intermediates. Thus, the production of ethane from sodium acetate may be interpreted

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[53] M. S. Kharasch and M. T. Gladstone, *J. Am. Chem. Soc.* 65, 15 (1943).

in the way shown in equations 15·50–15·52, where e^- represents an

$$CH_3—CO_2^- \rightarrow CH_3—CO_2 + e^- \qquad (15\cdot50)$$

$$CH_3—CO_2 \rightarrow \dot{C}H_3 + CO_2 \qquad (15\cdot51)$$

$$2\dot{C}H_3 \rightarrow CH_3—CH_3 \qquad (15\cdot52)$$

electron. The acetate radical, which is formed at the anode by discharge of the acetate anion, decomposes into carbon dioxide and the methyl radical; the latter then dimerizes to ethane. If, as has been suggested, acetyl peroxide, XIII, or peracetic acid, XXXVIII, takes part in the

$CH_3—CO—O—OH$

XXXVIII

reaction, the conclusion that the ethane results from the union of methyl radicals is not necessarily affected, since these assumed substances would doubtless, themselves, decompose to methyl radicals. As by-products, which may be made the principal products by suitable modifications of the conditions, methane, methyl acetate, XXXIII, and methyl alcohol are also obtained. The methane does not result, as might have been supposed, from an attack by the methyl radical upon the solvent (water); it results rather from an attack by the radical upon unchanged acetic acid or acetate ion. This conclusion follows from the fact that the electrolysis of "heavy" acetic acid $CD_3—CO_2D$ in ordinary water H_2O gives only "heavy" methane CD_4; and that, conversely, the electrolysis of ordinary acetic acid $CH_3—CO_2H$ in "heavy" water D_2O gives only ordinary methane CH_4.[54]

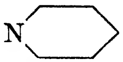
As in the original paper by Clusius and Schanzer,[54] "heavy" and ordinary acetic acid are here assigned the structures $CD_3—CO_2D$ and $CH_3—CO_2H$, respectively. Actually, of course, since there is rapid interchange of the hydrogen atom of a hydroxyl group OH and the deuterium atom of a deuteroxyl group OD, "heavy" acetic acid in ordinary water is largely $CD_3—CO_2H$, and ordinary acetic acid in "heavy" water is largely $CH_3—CO_2D$. These considerations, however, have no effect upon the conclusions reached above.

The sources of the methyl acetate and methyl alcohol are not clear; possibly these substances are formed by direct union of the methyl radical with an acetate or hydroxyl radical, respectively. Alternatively, the methyl acetate might be formed from the acetate radical by disproportionation (see above), and the methyl alcohol might be formed from the methyl acetate by hydrolysis. In the electrolysis of the salts of the

[54] K. Clusius and W. Schanzer, *Z. physik. Chem.* **A192**, 273 (1943). For further studies of the mechanism of the Kolbe synthesis, see P. Hölemann and K. Clusius, *Z. physik. Chem.* **B35**, 261 (1937); W. Schanzer and K. Clusius, *Z. physik. Chem.* **A190**, 241 (1942); A. Kruis and W. Schanzer, *ibid.* **A191**, 301 (1942); and also reference 55.

higher carboxylic acids, olefins also are formed; potassium propionate, for example, usually gives more ethylene than it gives butane. Since little, if any, ethane is formed simultaneously,[55] only a small part of the ethylene, at most, can result from the disproportionation of the ethyl radical; the major source of this olefin is therefore somewhat obscure.

Electrolysis of sodium acetate in acetic acid containing trinitrotoluene, XXIX, leads to the production of a small amount of trinitro-*m*-xylene,



XXXIX

XL

XXX.[52] The methyl radical, when prepared electrolytically, is therefore seen to react in the same way that it does when prepared by the thermal decomposition of acetyl peroxide or of lead tetraacetate. (See above.) Moreover, electrolysis of benzoic acid in pyridine, XXXIX, gives some 4-phenylpyridine, XL (together with other products).[56]

When a solution of sodium ethyl NaC_2H_5 in zinc diethyl $Zn(C_2H_5)_2$ is electrolyzed, a mixture of ethane and ethylene is liberated at the anode.[57] These hydrocarbons doubtless result from the disproportionation of the ethyl radical that is formed by the discharge of the ethide anion $C_2H_5^-$. If the anode is made of lead, lead tetraethyl $Pb(C_2H_5)_4$ is also formed. Moreover, electrolysis of *n*-propylmagnesium bromide in ethyl ether provides propane, propylene, *n*-hexane, ethylene, and various other products.[58] The first three of these substances must be derived from the propyl radical liberated at the anode, whereas the ethylene may result from the attack by this radical upon the solvent.

Free radicals can be produced electrolytically not only at the anode but also at the cathode. The reduction of acetone, XLI, at a mercury

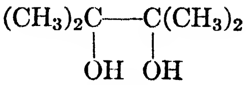
$$CH_3—CO—CH_3$$

XLI

cathode, for example, gives some mercury diisopropyl, XLII;[59] possibly,

$$Hg[CH(CH_3)_2]_2$$

XLII



$$\underset{\text{OH}}{(CH_3)_2C}—\underset{\text{OH}}{C(CH_3)_2}$$

XLIII

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[55] P. Hölemann and K. Clusius, *Ber.* **70,** 819 (1937).

[56] F. Fichter and H. Stenzl, *Helv. Chim. Acta* **22,** 970 (1939).

[57] F. Hein, E. Petzchner, K. Wagler, and F. A. Segitz, *Z. anorg. allgem. Chem.* **141,** 161 (1924).

[58] W. V. Evans and D. Braithwaite, *J. Am. Chem. Soc.* **61,** 898 (1939).

[59] C. J. Haggerty, *Trans. Am. Electrochem. Soc.* **56,** 421 (1929).

the initial product is the isopropyl radical $\dot{C}H(CH_3)_2$, which then reacts with the metal of the electrode. Since pinacol, XLIII, is a further product of the electrolytic reduction of acetone, the existence of the radical ion, XLIV, or of the neutral radical, XLV, is also suggested. The

$$\underset{\text{XLIV}}{(CH_3)_2\dot{C}\text{—}O^-} \qquad\qquad \underset{\text{XLV}}{(CH_3)_2\dot{C}\text{—}OH}$$

nonelectrolytic formation of pinacol (for example, by reduction of acetone with amalgamated magnesium) may also involve one or both of these latter radicals. (See Section 15·16.)

15·6 The Early History of Aliphatic Chlorination.[60] Each of the two preceding sections contained references to the general reaction in which a hydrogen atom in the molecule of an aliphatic compound is replaced by a chlorine atom. This reaction is an important one, not only because of its practical utility and theoretical interest, but also because of the vital role which it played in the development of chemical structural theory; hence, a brief digression into its early history is here not entirely out of place.

One evening, during the reign of King Charles X of France, the guests who were attending a party at the Tuileries were greatly annoyed by the fact that the candles gave off irritating fumes and large quantities of smoke. Dumas, who was at that time one of the leading French chemists, was asked to investigate the matter. He soon established that the irritating fumes were composed of hydrogen chloride; on pursuing the problem further, he found also that the candles had been bleached with chlorine and that they contained organically bound chlorine. His interest in the action of elementary chlorine upon organic substances being thus aroused, he then embarked upon a systematic study of the reaction. In the course of his investigations, he proved that chlorine can enter into a great many organic substances besides candle wax, and that it does so by replacing part (or all) of the hydrogen which was originally present. Moreover, since he found that the chlorinated products were usually rather analogous in chemical and physical properties to the respective substances from which they were made, he concluded further that the replacement of a hydrogen atom by a chlorine atom is not necessarily accompanied by any drastic change in what would now be called the *structure* of the molecule.

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[60] This section is, in part, based upon H. B. Friedman, *J. Chem. Education* **7**, 633 (1930); cf. also A. W. Hofmann, *Ber.* **17**, Ref., 629, 667 (1884).

In the light of present-day chemical knowledge, these discoveries by Dumas may seem rather uninteresting and, in fact, almost trivial. At the time when they were made, however, they were revolutionary, because they were irreconcilable with the only scientific theory of chemical binding which had as yet been proposed. This theory, the so-called *dualistic theory* of Davy and Berzelius,[61] related all chemical forces to the attractions between electric charges with opposite signs. Thus, sodium atoms were considered to be positively charged (or perhaps merely to acquire positive charges when they approach other atoms); oxygen atoms, on the other hand, were considered to be negatively charged. Hence, sodium oxide Na_2O was thought to result, in an obvious manner, from the electrostatic attractions among the constituent atoms. (For the sake of convenience, modern atomic weights and empirical formulas are used here and throughout this paragraph.) Similarly, sulfur trioxide SO_3 was thought to be formed by the union of positive sulfur and negative oxygen atoms. The neutralization of charge was not considered, however, to be always complete. Since the positiveness of sodium atoms was supposed to be greater than the negativeness of oxygen atoms, sodium oxide was thought to have a residual positive charge; since the positiveness of sulfur atoms was thought to be less than the negativeness of oxygen atoms, sulfur trioxide was similarly thought to have a residual negative charge. The positive sodium oxide and the negative sulfur trioxide were then supposed to unite to form sodium sulfate $Na_2O + SO_3$ (or, in modern notation, Na_2SO_4). The sodium oxide was then the "base" which neutralized the "acid" sulfur trioxide. By an obvious extension of this procedure, a logical and self-consistent explanation could be given for the formation of even such a complex substance as the alum $Na_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$.

On the basis of Davy and Berzelius's dualistic theory, the idea that a "negative" chlorine atom can replace a "positive" hydrogen atom without an essential change in the constitution of the molecule is, of course, quite unacceptable. Berzelius and his supporters, in the attempt to preserve their theory, therefore tried for several years to explain Dumas's observations by assuming that the way in which the chlorine-substituted molecules are built up from their atoms is entirely different from that in which the corresponding unsubstituted molecules are built up. Since, however, all these attempts were ultimately unsuccessful, the dualistic theory was finally abandoned.

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[61] For further details, see any book on the history of chemistry.

The reason for the failure of the dualistic theory became apparent when, in the first decades of this century, the distinction between electrostatic and covalent binding was at last recognized. (See Sections 1·3–1·12.) Clearly, in fact, since this theory can satisfactorily account for only the interactions between oppositely charged ions, it cannot explain the existence of covalent forces. At the present time, of course, the dualistic theory (when properly re-expressed in modern terms) is again accepted as valid within the limited field to which it is particularly suited.

The *substitution theory,* which succeeded the dualistic theory, was based on the assumption that an atom of one element can be replaced by an atom of almost any other element without a significant change in the properties of the substance. Since the true atomic weights of the various elements had not yet been established, and since the concepts of valence and of structure (as they are now understood) were still extremely rudimentary, this assumption was not entirely unreasonable. Some of the enthusiastic proponents of the theory, however, carried the idea to extremes which, even at the time, were recognized by the more sober chemists as absurd.

In the course of the bitter controversies which ensued, the eminent German chemist Wöhler composed a satirical letter, in which he ridiculed the extreme claims that were then being made by some adherents of the substitution theory. Although he had apparently intended this letter for only private circulation, his close friend and associate, Liebig, published it [62] in *Annalen der Chemie und Pharmacie* (now called *Justus Liebigs Annalen der Chemie*), of which Liebig and Wöhler were then editors. Since Paris was the chief center of the views which he wished to ridicule, Wöhler wrote his letter in French (rather than in German which was then, as it is now, the usual language for articles in the *Annalen*); and he gave his address as Paris. Moroever, in order to make his purpose especially clear, he signed his name as "S. C. H. Windler." (The German word *Schwindler* means both swindler and humbug.) Since the letter is rather amusing, a translation of it is given below. The various chemical formulas, which are expressed in the notation of the dualistic theory, are not modernized. The interpretation of these formulas is, however, apparent if it is remembered that that of manganous acetate, for example, was expressed as $MnO + C_4H_6O_3$ or, in more modern symbols, as $MnO + CH_3—CO—O—CO—CH_3$; the MnO is here the "base" and the $CH_3—CO—O—CO—CH_3$ is the "acid" from which the salt is considered to be formed.

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[62] S. C. H. Windler (F. Wöhler), *Ann.* **33**, 308 (1840). The translation of this letter which is given here is adapted, with permission, from the one of H. B. Friedman (reference 60).

CONCERNING THE LAW OF SUBSTITUTION AND THE THEORY OF TYPES *

Paris, March 1, 1840

Sir:

I hasten to communicate to you one of the most striking facts of organic chemistry. I have verified the theory of substitution in an extremely remarkable and completely unexpected manner. It is only now that one can appreciate the great value of this ingenious theory and that one can dimly foresee the tremendous discoveries which it promises to realize for us. The discovery of chloroacetic acid and the constancy of type in the chlorinated compounds derived from ether and from ethyl chloride have led me to experiments which I shall now describe. I allowed a stream of chlorine to pass through a solution of manganous acetate under the direct influence of sunlight. After 24 hours, I found in the liquid a fine crystallization of a yellow salt with a violet tint. The solution contained only the same salt and hydrochloric acid. I have analyzed this salt; it is manganous chloroacetate. So far nothing extraordinary, a simple substitution of the hydrogen of acetic acid by an equivalent amount of chlorine, already known from the beautiful researches on chloroacetic acid. This salt, heated to 110° in a stream of dry chlorine, was converted with liberation of oxygen gas into a new golden yellow compound, the analysis of which led to the formula $MnCl_2 + C_4Cl_6O_3$ for its composition. There was thus substitution of the oxygen of the base by chlorine, as has been observed in a great many circumstances. The new substance was dissolved in very pure chloral with the aid of heat, and I made use of this liquid, unaffected by chlorine, to continue the treatment by that reagent. I let dry chlorine flow for four hours, keeping the liquid always very near its boiling point. During this time, a white material constantly precipitated; this was found on careful examination to be manganous chloride. When there was no further precipitation, I cooled the liquid for some time, and I obtained a third substance in [the form of] silky yellow needles with a green cast. It was $C_4Cl_{10}O_3$, or, in other words, it was manganous acetate in which all the hydrogen and the manganous oxide were replaced by chlorine. Its formula ought to be written as $Cl_2Cl_2 + C_4Cl_6O_3$. There were thus six atoms of chlorine in the acid, the four other atoms representing manganous oxide. Like hydrogen, manganese and oxygen can be replaced by chlorine; one could see nothing surprising in this substitution.

But this is still not the end of this remarkable series of substitutions. On allowing chlorine again to act upon a solution of this material in water, there was a liberation of carbonic acid, and on cooling the liquid to +2° there was deposited a yellowish mass formed of small plates, closely resembling the hydrate of chlorine. Also, it contained only chlorine and water. But, on measuring the density of its vapor, I have found that it was formed from 24 atoms of chlorine and 1 atom of water. Here then was the most perfect substitution of all the elements of manganous acetate. The formula of the substance must be expressed as $Cl_2Cl_2 + Cl_8Cl_6Cl_6 + aq$. Although I know that in the bleaching action of chlorine there is replacement of hydrogen by chlorine, and that the fabrics, which are bleached in England according to the laws of substitution, conserve their type, † I believe nevertheless that the replacement of carbon by chlorine, atom for atom, is a discovery which belongs to me. Please make note in your journal and accept, etc.

S. C. H. WINDLER

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* Communication by letter to J. L.

† I have just learned that in the shops of London there are already fabrics of spun chlorine, very much in demand in the hospitals and preferred over all others for night caps, drawers, etc.

As a result of the attacks upon it by Wöhler and by others, the substitution theory soon gave way to a succession of *type theories*, which in turn were at last replaced by the modern *structural theory*. These later developments, however, need not here be further described since they are not so directly concerned with the substitution reactions of aliphatic compounds.[61]

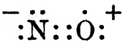
It should be noted that the substitution, type, and (early) structural theories were, in one important respect, less complete than the dualistic theory which they replaced. That is to say, they contained no explanation for the (covalent) bonds which they assumed to exist. Not until the application of quantum-mechanical methods to the problem, in fact, was this problem finally solved. (Cf. Sections 1·8, 10·4, and 10·5.)

15·7 Some Simple Inorganic Free Radicals of Long Life. In addition to the short-lived free radicals discussed in the preceding sections, a number of long-lived radicals are also known; such substances can be isolated and kept more or less indefinitely without significant change. Although the majority of these long-lived free radicals are complex organic substances, a few of them are simple inorganic compounds. Indeed, the longest known and most familiar of all the free radicals that are now recognized belong to this latter type.

A molecule of nitric oxide NO contains an odd number of electrons; the substance is necessarily, therefore, a free radical even though it is not strongly colored, and even though it has no great tendency to dimerize. Gaseous nitric oxide is generally considered to be colorless and completely monomeric; on the other hand, the compound in the liquid and solid states is light blue and appears to be largely dimeric.[63] Nitric oxide is probably a resonance hybrid of structures I and II.[64]

$:\dot{N}::\ddot{O}:$

I



$^{-}:\ddot{N}::\dot{O}:^{+}$

II

Like many other free radicals, it reacts with oxygen; the reaction is, however, anomalous in that the product, nitrogen dioxide NO_2 is a second free radical which is more obviously colored than is the original free radical. Moreover, nitric oxide combines with many organic free radicals to form stable products. (See the following sections.)

Nitrogen dioxide NO_2 also has an odd number of electrons per molecule; hence it also is a free radical. This compound is colored and, even in the gaseous state, exists in equilibrium with its less colored dimer,

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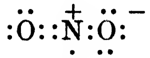
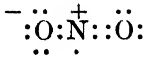
[63] Cf. H. L. Johnston and W. F. Giauque, *J. Am. Chem. Soc.* **51**, 3194 (1929); E. Lips *Helv. Phys. Acta* **8**, 247 (1935); H. Bizette and B. Tsai, *Compt. rend.* **206**, 1288 (1938).

[64] L. Pauling, *J. Am. Chem. Soc.* **53**, 3225 (1931).

nitrogen tetroxide N_2O_4. The monomeric radical probably resonates among such structures as III–VI.[64] Further simple inorganic free radi-

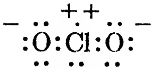

III

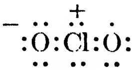

IV


V


VI

cals include chlorine dioxide ClO_2, which may resonate among structures VII–IX,[65] and the superoxide ion O_2^-, which must resonate between


VII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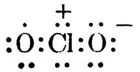
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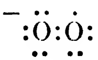
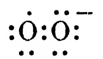

X


XI

structures X and XI.[66] Both chlorine dioxide and the superoxide ion (as in potassium superoxide KO_2) are colored; the former is yellow, whereas the latter is orange. Neither the molecule nor the ion, however, associates to a dimer.

15·8 Triarylmethyls. The organic free radicals of long life were discovered a number of years before the simpler ones of short life. The first such radical to be prepared and to be recognized as such was triphenylmethyl, I.

$$(C_6H_5)_3C\cdot$$
I

In the last years of the nineteenth century, Gomberg was interested in the completely phenylated paraffin hydrocarbons; after having successfully prepared tetraphenylmethane, II, he next turned his atten-

$(C_6H_5)_4C$ II

$(C_6H_5)_3C—C(C_6H_5)_3$ III

$(C_6H_5)_3CBr$ IV

$(C_6H_5)_3CCl$ V

tion to hexaphenylethane, III.[67] In his first attempt to synthesize this compound, he treated triphenylmethyl bromide, IV, with metallic sodium. Since this procedure proved unsatisfactory, and since triphenylmethyl chloride, V, gave no better results than the bromide, he next replaced the sodium by "molecular" (i.e., very finely divided) silver. Under these conditions, he obtained a white, high-melting solid that was only slightly soluble in any of the usual organic solvents. He presumed that this product was the desired hexaphenylethane. On analysis, however, he found that its contents of carbon and of hydrogen were too low. At first, he suspected that the combustion of the compound was incomplete; but, after many unsuccessful attempts to increase the

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[65] L. O. Brockway, *Proc. Natl. Acad. Sci. U. S.* **19**, 303 (1933).

[66] E. W. Neuman, *J. Chem. Phys.* **2**, 31 (1934).

[67] M. Gomberg, *Ber.* **33**, 3150 (1900); *J. Am. Chem. Soc.* **22**, 757 (1900).

measured percentages of carbon and hydrogen, he at last concluded that the substance contained oxygen, and so was not a hydrocarbon after all.

The oxygen in the product could have come from either one (or both) of only two possible sources; it might have come from an impurity in the silver used, or it might have come from the air. Experiments with carefully purified silver, however, gave the same oxygenated product as before; moreover, in still further experiments, in which metallic zinc or mercury was used instead of silver, he again obtained this same product. Since it was therefore evident that the oxygen must have come from the air, Gomberg next carried out the reaction in an atmosphere of carbon dioxide. In this way, he obtained a white solid hydrocarbon, which dissolved readily in organic solvents to form yellow solutions, and which absorbed oxygen rapidly from the air with production of the above relatively insoluble white compound.

The properties of the new oxygen-free substance were found to be very different from the ones expected of hexaphenylethane, III. Thus, as has already been mentioned, the compound is colored when in solution, and it absorbs oxygen from the air. The product formed in this reaction with oxygen was identified as the peroxide, VI, by its preparation from triphenylmethyl chloride, V, and sodium peroxide Na_2O_2. An unexpected reaction takes place also with elementary iodine; the product in this instance is triphenylmethyl iodide, VII. Chlorine and bromine behave like iodine; but, with these more active halogens, the reactions are more extensive, and substitutions as well as additions occur.

$(C_6H_5)_3C{-}O{-}O{-}C(C_6H_5)_3$
VI

$(C_6H_5)_3CI$
VII

On the basis of the properties just described, Gomberg concluded that his hydrocarbon was not hexaphenylethane, III, but the free radical, triphenylmethyl, I. For a while, the subsequent work in the field tended both to support and to discredit this bold hypothesis. On the one hand, several further reactions of the compound were discovered; thus, the actions of nitric oxide, nitrogen dioxide, diazomethane CH_2N_2 (cf. page 742), and hydrogen in the presence of platinum were found to give, respectively, triphenylnitrosomethane, VIII, a mixture of triphenylmethyl nitrite, IX, and a little triphenylnitromethane, X, 1,1,1,3,3,3-hexaphenylpropane, XI, and triphenylmethane, XII. Moreover, several

$(C_6H_5)_3CNO$
VIII

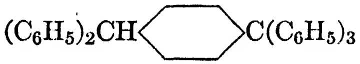
$(C_6H_5)_3C{-}ONO$
IX

$(C_6H_5)_3CNO_2$
X

$(C_6H_5)_3C{-}CH_2{-}C(C_6H_5)_3$
XI

$(C_6H_5)_3CH$
XII

analogous hydrocarbons, in which one or more of the phenyl groups are replaced by other aromatic groups, were prepared and were found to have entirely similar properties (see below). In all these reactions of the supposed hexaarylethanes, the central carbon-carbon bonds seem to be so extraordinarily weak that they may logically be considered already broken. On the other hand, however, cryoscopic measurements of the molecular weight led to values that were in better agreement with the assumption that the original oxygen-free compound was hexaphenylethane, III, than they were with the assumption that it was triphenylmethyl, I. Thus, in 1904 Gomberg and Cone studied solutions in six different solvents under an atmosphere of nitrogen. They obtained molecular weights varying erratically from 412 to 532.5, and their average molecular weight was 477. The theoretical molecular weight of hexaphenylethane is 486; that of triphenylmethyl is 243. Although the experimental values obtained by Gomberg and Cone are obviously not precise, they strongly suggest that the compound is, at any rate, not pure triphenylmethyl. Finally, the situation was obscured further by the fact that, under the influence of various reagents, such as hydrogen chloride in dry benzene or metallic sodium in dry ether, the compound is irreversibly transformed into the stable hydrocarbon, *p*-benzhydryltetraphenylmethane, XIII; this substance was frequently mistaken for hexaphenylethane.



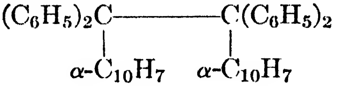
XIII

In spite of the difficulties and apparent inconsistencies just mentioned, there was soon general agreement that Gomberg's white oxygen-free solid is really hexaphenylethane, III, but that this compound in solution dissociates slightly into the yellow triphenylmethyl radical, I (equation 15·53). The reactions with reagents like oxygen, nitric oxide, nitrogen

$$\underset{\text{III}}{(C_6H_5)_3C{-}C(C_6H_5)_3} \rightleftharpoons \underset{\text{I}}{2(C_6H_5)_3C\cdot} \qquad (15\cdot53)$$

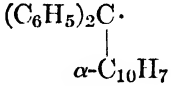
dioxide, and hydrogen are therefore readily explainable as due to the trace of radical present; when this small amount of radical is removed from the equilibrium mixture by reaction with any of these reagents, more radical is formed by the dissociation of the ethane, until finally the entire material has been converted. (However, see pages 687 f.) On the other hand, the observed high molecular weight is also readily explainable as due to the great preponderance of hexaphenylethane over triphenylmethyl at equilibrium. (Cf. pages 690, 694.)

The evidence supporting the above interpretation of Gomberg's hydrocarbon seems completely conclusive. Although the dissociation of hexaphenylethane itself into triphenylmethyl radicals is too small to be proved by a cryoscopic determination of molecular weight, other hexaarylethanes are more highly dissociated. For example, the apparent molecular weight of 1,1,2,2-tetraphenyl-1,2-di-α-naphthylethane, XIV,



$$\underset{\alpha\text{-}C_{10}H_7}{(C_6H_5)_2C}\text{——}\underset{\alpha\text{-}C_{10}H_7}{C(C_6H_5)_2}$$

XIV



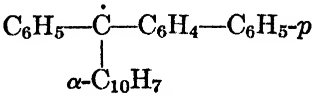
$$\underset{\alpha\text{-}C_{10}H_7}{(C_6H_5)_2C\cdot}$$

XV

in benzene (at the melting point of the solution) was reported by Schlenk to be 372 in a 2.7 per cent solution and 363 in a 2.3 per cent solution, as compared with the theoretical values of 586 and 293 for the undissociated ethane, XIV, and radical, XV, respectively. In a more detailed study of this same substance in a number of solvents with different melting points, Gomberg and Schoepfle[68] found that, in general, the apparent molecular weight increases with decreasing melting point of the solvent and, in any given solvent, with increasing concentration. Their values ranged from about 256 in a 1.1 per cent solution in naphthalene (80°C) to about 354 in a 2.7 per cent solution in nitrobenzene (6°C). Although these figures are again not very precise (cf. the following section), they are presumably good enough to show an appreciable dissociation of the ethane XIV. (Cf., however, Section 15·20.) Hexa-*p*-biphenylylethane, XVI, was considered by Schlenk, Weickel, and Herzenstein to be

$(p\text{-}C_6H_5\text{—}C_6H_4)_3C\text{—}C(C_6H_4\text{—}C_6H_5\text{-}p)_3$ XVI $\qquad (p\text{-}C_6H_5\text{—}C_6H_4)_3C\cdot$ XVII

completely dissociated into tri-*p*-biphenylylmethyl radicals, XVII, since its apparent molecular weight in benzene was found to range between 434 and 487, whereas the calculated molecular weight of tri-*p*-biphenylylmethyl, XVII, is 471. Furthermore, this compound is apparently dissociated even in the solid state, since it forms greenish black crystals, whereas the ethane XVI would be expected to be white. Phenyl-α-naphthyl-*p*-biphenylylmethyl, XVIII, was also considered by Schlenk



$$C_6H_5\text{—}\underset{\alpha\text{-}C_{10}H_7}{\dot{C}}\text{—}C_6H_4\text{—}C_6H_5\text{-}p$$

XVIII

to be completely monomeric since it closely resembles tri-*p*-biphenylylmethyl, XVII, in its properties.

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[68] M. Gomberg and C. S. Schoepfle, *J. Am. Chem. Soc.* **39**, 1652 (1917); **41**, 1655 (1919).

Further evidence supporting the belief that hexaphenylethane and its analogs are dissociated to a greater or less extent into free radicals is provided by the fact that solutions of these compounds often disobey *Beer's law.*[69] This law applies to the absorption of monochromatic light by a solution of a colored substance in a colorless solvent. It can be stated most easily in the form shown in equation 15·54, where I is the

$$\frac{I}{I_0} = 10^{-\epsilon md} \qquad (15 \cdot 54)$$

intensity of the light after it has passed through d centimeters of the solution; I_0 is the intensity of the light from the same source after it has passed through d centimeters of the pure solvent; m is the concentration of the solution in moles per liter; and ϵ is the so-called *molar extinction coefficient,* the value of which varies with the colored solute and with the wave length of the light used, but not with either the concentration m or the path length d.

Actually, equation 15·54 expresses not only Beer's law, but also *Lambert's law;* the first of these two laws refers to the dependence of I/I_0 upon the concentration m, whereas the second refers to the dependence upon the path length d. Solutions of hexaarylethanes disobey only Beer's law.

The significance of equation 15·54 can be explained with the aid of the following experiment. A vertical cylindrical tube contains a solution of some colored substance (say, potassium permanganate) in some colorless solvent (say, water); the intensity of the color is observed by allowing monochromatic light to pass lengthwise (i.e., vertically) through the tube. If, now, the solution in the tube is diluted by the addition of more solvent, the concentration m decreases, but the path length d increases in the same ratio. Since the product md is therefore unaltered, the intensity of the color, observed in the same way as before, must also be unaltered if the solution obeys Beer's law. This law then merely expresses the fact that the fraction of the light absorbed (i.e., $1 - I/I_0$) is determined only by the number of colored molecules through which the light passes; this number is, of course, not affected by the addition of more colorless solvent.

As was mentioned above, solutions of hexaphenylethane and its analogs do not obey Beer's law. In particular, the extinction coefficients ϵ are not constants independent of the concentrations m; instead, they increase as the solutions are made more dilute. In other words, if the experiment described in the preceding paragraph were carried out with, for example, a solution of hexaphenylethane in ether, the observed intensity of the color would not remain constant but would increase on the addition of more solvent. (The experiment would, of course, have to be carried out in such a way that all traces of oxygen, halogens, strong acids, etc., are rigorously excluded.) Apparently, therefore, the number

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[69] J. Piccard, *Ann.* **381,** 347 (1911); K. Ziegler and L. Ewald, *ibid.* **473,** 163 (1929).

of colored molecules increases when the solution is diluted, even though the total weight of solute remains unchanged. This behavior is exactly what would be expected if an equilibrium exists between the colorless hexaarylethane and the colored triarylmethyl radical (equation 15·53). With decreasing concentration, the equilibrium is required by the law of mass action to be displaced in such a direction that the number of solute molecules is increased; hence the degree of dissociation of the ethane is required to increase. (For further discussion of this colorimetric method of demonstrating the dissociation of a compound into free radicals, see pages 689 ff.)

The most conclusive evidence for the existence of free radicals of long life has been obtained from studies of magnetic properties. (Cf. page 417.) Free radicals, since they contain unpaired electrons, must be attracted by a magnet (i.e., they must be paramagnetic). In this respect, such substances differ from practically all others which are not free radicals, and which therefore contain no unpaired electrons. Consequently, a measurement of the magnetic susceptibility (cf. pages 691 f.) of a substance is sufficient to decide the question whether the substance is, or is not, a free radical. Thus, Taylor[70] found that 1,1,2,2-tetraphenyl-1,2-di-α-naphthylethane, XIV, in benzene is appreciably less diamagnetic than it should have been if it consisted solely of molecules with structure XIV; he concluded, therefore, that a certain amount of the paramagnetic diphenyl-α-naphthylmethyl radical, XV, was also present. More recently, this magnetic method has been refined and greatly extended, so that it is now the most reliable and the most generally useful one for the detection of free radicals. (For further details, see pages 691 ff.)

15·9 The Degrees of Dissociation of Hexaarylethanes. The discussion in the preceding section has shown in a rather qualitative way that (in solution and sometimes also in the solid state) hexaarylethanes are to a greater or less extent dissociated into triarylmethyl radicals. Nothing has as yet been said, however, about the methods by which the degrees of dissociation may be measured quantitatively.

The most obvious method by which such information might be obtained consists in a precise determination of the apparent molecular weight of the compound. Thus, if m moles of an ethane R—R is dissolved in 1 liter of solution, and if the fraction of this ethane which is dissociated into the radical R· is designed as α, then the concentrations of the ethane and of the radical are, respectively, $m(1 - \alpha)$ and $2\alpha m$ moles per liter. The total number of moles of solute in 1 liter of solution

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[70] N. W. Taylor, *J. Am. Chem. Soc.* **48**, 854 (1926).

is therefore $m(1 - \alpha) + 2\alpha m$, or $m(1 + \alpha)$. If, now, the molecular weight of the ethane is M, the apparent molecular weight M_{app} is equal (equation 15·55) to mM, the weight of solute in 1 liter of solution,

$$M_{app} = \frac{mM}{m(1 + \alpha)} = \frac{M}{1 + \alpha} \qquad (15\cdot55)$$

divided by $m(1 + \alpha)$, the number of moles of solute in the same volume of solution. Since the true molecular weight, M, of the ethane can be calculated from the molecular formula, and since the apparent molecular weight M_{app} can be measured experimentally, the degree of dissociation α can be determined from either of the two equivalent equations 15·55 and 15·56.

$$\alpha = \frac{M}{M_{app}} - 1 \qquad (15\cdot56)$$

Although the above procedure appears to be simple and straightforward, it has in practice proved to be far from satisfactory. The experimental errors in the determination of the apparent molecular weights M_{app} seem always to be so great that the resulting degrees of dissociation α can at best be only approximately correct. That something, in any event, is seriously wrong with this method is shown most strikingly by the fact that not infrequently the measured apparent molecular weights are less than $\frac{1}{2}M$, the molecular weight of the radical. For example, as was pointed out on page 683, M_{app} for 1,1,2,2-tetraphenyl-1,2-di-α-naphthylethane at the melting point of its solution in naphthalene has been found to be about 256; since M for the same compound is 586, the degree of dissociation, when calculated by equation 15·55 or 15·56 turns out, therefore, to be 1.3. A dissociation of 130 per cent is, however, quite meaningless. At one time, Gomberg and Schoepfle [68] suggested that the diphenyl-α-naphthylmethyl radicals themselves dissociate further into still smaller fragments; this interpretation, however, has been generally regarded as untenable. Several other hexaarylethanes, besides the tetraphenyldi-α-naphthylethane just mentioned, have been found cryoscopically to have apparent dissociations greater than 100 per cent; hence it is evident that reliable quantitative data cannot be obtained by this method. (Cf. also Section 15·20.)

Other, and still less satisfactory, methods for estimating the dissociation of a hexaarylethane have also been used. If, for example, a solution of hexaphenylethane is exposed to the air for a very short time, its color is rapidly discharged as the radical is transformed into the peroxide. The color soon returns, however, as more of the radical is formed by the dissociation of the remaining ethane. This process can be repeated several times before all the ethane has been destroyed. The disappearance and reappearance of the color show that, in the original solution, an appreciable fraction of the hexaphenylethane was undissociated. On the other hand, if a solution of hexa-*p*-biphenylylethane is similarly treated, the color does not come back even once. Evidently, therefore, only a relatively small fraction of this ethane can be undissociated. It might be supposed that this qualitative method of estimating the degree of dissociation could be made more quantitative if the amount of oxygen required for the first discharge of the color is measured, and if the reasonable assumption is made that each molecule of oxygen that is absorbed accounts for the disappearance of two molecules of the radical, as in equation 15·57. Such a procedure, however, could lead to no

$$2R\cdot + O_2 \rightarrow R—O—O—R \qquad (15\cdot57)$$

completely reliable results. In the first place, the rate at which the free radical is produced from the ethane is so great that, when the radical is "titrated" with oxygen, the end-point cannot be accurately judged. In the second place, equation 15·57 probably does not describe the only way in which the oxygen reacts. Indeed, kinetic studies have strongly suggested (see the following paragraph in fine print) that the absorption of oxygen is at least partly a chain reaction proceeding in the steps shown in equations 15·58–15·60; if this mechanism is correct, therefore, the

$$R—R \rightarrow 2R\cdot \qquad (15\cdot58)$$

$$R\cdot + O_2 \rightarrow R—\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}—\underset{\cdot\cdot}{\overset{\cdot}{O}}: \qquad (15\cdot59)$$

$$R—\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}—\underset{\cdot\cdot}{\overset{\cdot}{O}}: + R—R \rightarrow R—O—O—R + R\cdot \qquad (15\cdot60)$$

assumption that each molecule of oxygen removes two of the *originally present* molecules of free radical R· is incorrect. If the absorption of nitric oxide NO were measured, rather than that of oxygen, the second of these two complications would apparently no longer exist (see below), but the first would probably still be of sufficient importance to make the method unsatisfactory.

The rate at which nitric oxide NO is absorbed by a solution of hexaphenylethane is proportional to the concentration of hexaphenylethane; but, if the partial pressure of the nitric oxide over the solution is at least one atmosphere, the rate is independent of this partial pressure and nearly independent of the solvent.[71] Presum-

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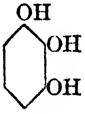
[71] K. Ziegler, P. Orth, and K. Weber, *Ann.* **504**, 131 (1933).

ably, therefore, the rate-determining step is the dissociation of the hexaphenylethane (equation 15·58); the triphenylmethyl radicals then combine with the nitric oxide (equation 15·61) as fast as they are formed. Consequently, the rate of the absorption of nitric oxide is equal to the rate of dissociation of the ethane (provided that suitable precautions are taken to avoid the complications due to side reactions and to the slight reversibility of reaction 15·61.) The rate at which oxygen is absorbed is, however, greater than the rate at which nitric oxide is absorbed, and hence greater than the rate of dissociation.[72, 73] Consequently, the reaction with oxygen cannot proceed solely by the steps 15·58 and 15·57, since the former of these is slower than the overall reaction. This conclusion supports the above mechanism (equations 15·58–15·60) for the oxidation of hexaphenylethane. Additional support is provided by the fact that, in the presence of an excess of pyrogallol, I, hexaphenylethane is not oxidized to triphenylmethyl peroxide, II, but instead to triphenylmethyl hydroperoxide, III, which is presumably derived from the radical IV.[73, 74]

$$R\cdot + NO \rightarrow R\text{—}NO \qquad (15{\cdot}61)$$



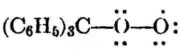
I

$(C_6H_5)_3C\text{—}O\text{—}O\text{—}C(C_6H_5)_3$

II

$(C_6H_5)_3C\text{—}O\text{—}O\text{—}H$

III



$$(C_6H_5)_3C\text{—}\ddot{\underset{\cdot\cdot}{O}}\text{—}\dot{\underset{\cdot\cdot}{O}}:$$

IV

Under such conditions, one mole of oxygen is absorbed for each mole of triphenylmethyl radical (not for each mole of hexaphenylethane), and the rate of the reaction is equal to the rate of absorption of nitric oxide (i.e., to the rate of dissociation of the hexaphenylethane).

A different method for estimating the degree of dissociation of a hexaarylethane is suggested by the fact that, although the ethane itself is usually colorless, the free radical derived from it is always colored. Consequently, an intensely colored solution may be presumed to contain a comparatively high concentration of free radical, and a weakly colored solution may be presumed to contain a comparatively low concentration of free radical. In general, however, different free radicals have qualitatively different colors, and, under identical conditions, they absorb quantitatively different amounts of light. Consequently, no *simple* procedure based upon an observation of the color of a solution can lead to a reliable quantitative estimate of the extent of dissociation of any hexaarylethane. (However, see below.) Possibly, the most significant information that can be obtained in this manner, without recourse to

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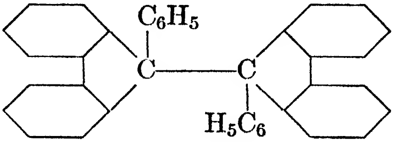
[72] R. C. Mithoff and G. E. K. Branch, *J. Am. Chem. Soc.* **52**, 255 (1930).

[73] K. Ziegler and L. Ewald, *Ann.* **504**, 162 (1933).

[74] K. Ziegler, L. Ewald, and A. Seib, *Ann.* **504**, 182 (1933); K. Ziegler and P. Herte, *ibid.* **551**, 206 (1942).

elaborate techniques, is that the color of the solution of a given ethane at a given concentration in a given solvent usually becomes more intense as the temperature is raised, and less intense as the temperature is lowered. It may be concluded, therefore, that the equilibrium is usually displaced toward the free radical at the higher temperature, and hence that the dissociation of the ethane is an endothermic reaction. Moreover, the fact that solutions of diphenylbifluoryl, V, are colorless at room temperature and become brown only at higher temperatures shows that the dissociation of this hexaarylethane is exceptionally small.



V

The first really quantitative method developed for the determination of the degree of dissociation of a hexaarylethane may be considered an elaboration of the above qualitative colorimetric one. As has already been noted, a solution of such a compound does not obey Beer's law, since the extinction coefficient ϵ of equation 15·54 is not a constant, independent of the concentration. It may be presumed, however, that this anomalous behavior of the solution is due merely to the variation of α, the fraction of the ethane dissociated. If one liter of the solution is prepared from m moles of the hexaarylethane, the concentration of the free radical, which is the only colored solute, is of course not m moles per liter, but $2m\alpha$ moles per liter; consequently, the equation which would be expected to apply rigorously to the solution is not 15·54 but 15·62. In this latter equation, ϵ' is the true extinction coefficient of the

$$\frac{I}{I_0} = 10^{-2m\alpha\epsilon' d} \qquad (15\cdot62)$$

triarylmethyl radical; it, rather than ϵ, the apparent extinction coefficient of the hexaarylethane, is the quantity that ought to be independent of concentration. Like the apparent extinction coefficient ϵ, this true one ϵ' is a function of the wave length of the monochromatic light employed.

If the value of ϵ' at some specified wave length were known, then α could be calculated from the measured value of ϵ at that same wave length; for, as is shown by a comparison of equations 15·54 and 15·62, the relation among ϵ, ϵ', and α is the one given in equation 15·63. Al-

$$\epsilon = 2\alpha\epsilon' \qquad (15\cdot63)$$

though the value of ϵ' is not known at the outset, it can be obtained from a study of the dependence of ϵ upon the concentration m. If the solution is made more and more dilute, α increases and, in fact, approaches unity as m approaches zero. Consequently, if the measured values of ϵ are extrapolated to infinite dilution, ϵ' can be set equal to one-half of the thus obtained limiting value. Since ϵ' is then known, α can be calculated for each concentration m investigated. Moreover, the internal consistency of the experimental data and the accuracy of the derived value of ϵ' can be presumed to be satisfactory if the equilibrium constant K, defined in equation 15·64, is really a constant inde-

$$K = \frac{(\mathrm{R}\cdot)^2}{(\mathrm{R}-\mathrm{R})} = \frac{4\alpha^2 m}{1-\alpha} \qquad (15\cdot 64)$$

pendent of concentration. Since all the particles that take part in the equilibrium are electrically neutral, no interionic forces exist; consequently, large deviations from the simple mass-law expression, 15·64, like the ones encountered in solutions of electrolytes, are not to be expected here. Ziegler and Ewald [69] have found that K is indeed constant, within about ±5 per cent, in each of the systems which they studied.

The only compound that has been extensively investigated by the above colorimetric method is hexaphenylethane; the data obtained are summarized in Table 15·1. The considerable variation of the equilibrium constant with the solvent is, of course, due to differences in the relative solubilities of the ethane and of the radical in the various solvents (cf. Section 14·6); there is, however, no independent way in which these solubilities can be measured. The fact that, in each solvent, the equilibrium constant K increases with the temperature shows that the dissociation of the ethane is endothermic. (See above.) From the tempera-

TABLE 15·1

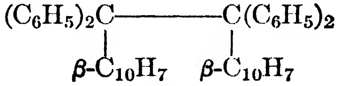
DISSOCIATION OF HEXAPHENYLETHANE [a]

Solvent	$K \times 10^4$ *at 20°C*	ΔH *in kcal per mole*
Propionitrile	1.2	11.1
Ethyl benzoate	1.67	12.0
Acetophenone	1.70	11.5
Dioxane	2.5	11.6
Bromobenzene	3.7	11.5
Ethylene bromide	3.9	11.4
Benzene	4.1	11.3
Chloroform	6.9	10.5
Carbon disulfide	19.2	11.0

[a] The data in this table are taken from K. Ziegler and L. Ewald, *Ann.* **473**, 163 (1929).

ture coefficients of K, the respective changes in heat content ΔH can be calculated; perhaps unexpectedly, ΔH is found to be nearly independent of solvent even though, at any given temperature, the equilibrium constant K varies widely with solvent.

The only hexaarylethane besides hexaphenylethane which has been studied by the quantitative colorimetric procedure is 1,1,2,2-tetraphenyl-1,2-di-β-naphthylethane, VI; the equilibrium constant for this



$$\begin{array}{ccc}(C_6H_5)_2C & \text{———} & C(C_6H_5)_2 \\ | & & | \\ \beta\text{-}C_{10}H_7 & & \beta\text{-}C_{10}H_7\end{array}$$

VI

compound was shown [69] not to vary with the concentration, but its absolute value was not determined. With a number of other ethanes, the method has been found to be inapplicable. (See page 706.)

The quantitative method that has been most extensively used for the determination of the extents of dissociation of hexaarylethanes is based upon the fact that, as was mentioned in Section 15·8, the undissociated ethane is diamagnetic, whereas the free radical is paramagnetic.

Before the principles of this method can be further described, a brief digression into the theory of magnetism is desirable. The force F which acts (*in vacuo*) between two magnetic poles that have strengths p and p', and that are at a distance r from each other, is given by equation 15·65; by convention, the strength of a north

$$F = \frac{pp'}{r^2} \tag{15·65}$$

pole always has a positive sign, whereas that of a south pole always has a negative sign. When the force F is positive, the two poles repel each other; when F is negative, they attract each other. Equation 15·65 may be considered to define the pole strengths p and p'. A *magnet* consists of a north pole and a south pole, which have strengths of the same magnitude but, naturally, of opposite sign. The *magnetic moment* μ of a magnet is equal to the product pl of the strength p of the north pole and the distance l between the north and south poles (equation 15·66). When a

$$\mu = pl \tag{15·66}$$

magnetic pole is in a magnetic field, it is acted upon by a force that is equal to the product of the pole strength p and the *field strength* H (equation 15·67); this rela-

$$F = Hp \tag{15·67}$$

tion defines the latter quantity. If any object which is not a magnet (i.e., which has a moment μ equal to zero) is placed in a magnetic field of strength H, a magnetic moment is induced in this object; the induced moment μ_i is proportional to the field strength, as is shown in equation 15·68. The proportionality constant χ is called

$$\mu_i = \chi H \tag{15·68}$$

the *magnetic susceptibility* of the object in which the moment is induced; it has a positive sign if the matter of which the object is composed is paramagnetic, but a negative sign if the matter is diamagnetic. The situation is shown schematically in Figure 15·1, in which *N* and *S* represent, respectively, the north and south poles of the magnet that produces the field of strength *H*; and *n* and *s* represent, respectively, the north and south poles of the magnet induced in the object. In Figure 15·1*a*, the matter is diamagnetic; since like poles repel one another, the object is pushed out from the region between the poles *N* and *S*. In Figure 15·1*b*, the matter is paramagnetic; since unlike poles attract one another, the object is pulled into the region between the poles *N* and *S*.

The magnetic susceptibility of any object depends, of course, upon the substance, or substances, of which that object is composed. Moreover, the susceptibility is proportional to the amount of matter that is contained in the object; hence its value is not uniquely determined until the amount of matter is specified. In the following discussion, reference will be made only to *molar* susceptibilities χ_m (i.e., to susceptibilities per mole of substance).

The experimental methods by which magnetic susceptibilities are measured need not be discussed here. It may be mentioned, however, that these methods involve the measurement of the magnitude and direction of the force that acts upon the substance of interest when the substance is between the north and south poles of a powerful magnet. (Cf. Figure 15·1.)[75]

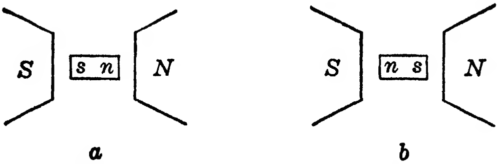


FIGURE 15·1. The induction of magnetic moments in a diamagnetic object (Figure 15·1*a*) and in a paramagnetic object (Figure 15·1*b*).

Theory and experiment have combined to show that the molar magnetic susceptibility χ_m of any nonmetallic and nonferromagnetic substance can be expressed in the form shown in equation 15·69, where *N*

$$\chi_m = A + \frac{N^2\mu^2}{3RT} \tag{15·69}$$

is now Avogadro's number, μ is the magnetic moment of a single molecule, *R* is the gas constant, and *T* is the absolute temperature.[75] The quantity *A* is called the *diamagnetic term* since its sign is always negative; its value, which is essentially independent of temperature, can be calculated with fair accuracy as the sum of the atomic susceptibilities of all the atoms in the molecule, plus certain correction terms associated with the presence of double bonds, of aromatic rings, or of other structural features.[75] In other words, *A* is a partly additive and partly constitutive property, like the molecular refraction, molecular volume,

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[75] Cf. L. Michaelis in A. Weissberger, *Physical Methods of Organic Chemistry*, Interscience Publishers, New York, Volume II, 1946, Chapter XXIV; P. W. Selwood, *Magnetochemistry*, Interscience Publishers, New York, 1943.

parachor, heat of combustion, etc. With most of the organic substances considered in this chapter, the *magnitude* of A, which is of course positive, is of the order of a few hundred times 10^{-6} electromagnetic unit of magnetic susceptibility. If equation 15·69 is solved for the magnetic moment μ, equation 15·70 is obtained; all quantities on the right side

$$\mu = \sqrt{\frac{3RT}{N^2}(\chi_m - A)} \tag{15·70}$$

of this latter equation are known constants, or can be calculated in the way just described, or can be obtained by direct measurement. Consequently, the value of the magnetic moment μ can be determined.

It is a consequence of quantum mechanics that the moment μ of a molecule with j unpaired electrons is equal to $\sqrt{j(j+2)}\beta$,[75] where β is the so-called *Bohr magneton* with the value given in equation 15·71.

$$\beta = \frac{eh}{4\pi mc} = 0.927 \times 10^{-20} \text{ erg gauss}^{-1} \tag{15·71}$$

In this equation, e and m are, respectively, the magnitude of charge and the mass of an electron; h is Planck's constant; and c is the velocity of light. When the numerical values of N, R, T, and β are inserted in equation 15·69, the paramagnetic term $(N^2\mu^2)/(3RT)$ is found to be equal, at 20°C, to about $420j(j+2) \times 10^{-6}$. Since, so long as j is not equal to zero, the magnitude of this positive term is ordinarily larger that is that of the negative diamagnetic term A (see above), the susceptibility χ_m is usually positive; consequently, any free radical may be expected to be paramagnetic. With a free radical that contains just one unpaired electron per molecule, j is equal to 1, the magnetic moment μ is equal to $\sqrt{3}\beta$, and the paramagnetic term is equal, at 20°C, to about 1260×10^{-6}.

The method by which the degree of dissociation α of a hexaarylethane is determined should now be evident. The apparent magnetic susceptibility per mole of ethane is measured, and from this resulting figure is subtracted the calculated (negative) value of A. The difference $\chi_m - A$ is then equal to $(2\alpha N^2\mu^2)/(3RT)$, or to $2\alpha \times 1260 \times 10^{-6}$ (see above); the factor 2α is introduced here because each mole of ethane gives rise at equilibrium to 2α moles of free radical. All data required for the computation of α are therefore available.

It is important to observe that α is obtained from a linear interpolation of the susceptibility χ_m, and not from one of the moment μ. Thus, although the apparent magnetic moment of an ethane is equal to zero if there is no dissociation, and to $\sqrt{3}\beta$ (per methyl radical) if the dissociation is complete, an apparent moment of, say, $\frac{1}{2}\sqrt{3}\beta$ (per methyl radical) corresponds to an α that is equal, not to $\frac{1}{2}$, but to $\frac{1}{4}$. The reason for this fact is that the magnetic susceptibility is a linear function of α, but a quadratic one of μ (see above).

The magnetic method has been applied to a large number of hexaarylethanes; in Table 15·2 are listed the equilibrium constants K that can

TABLE 15·2

EQUILIBRIUM CONSTANTS OF SOME HEXAARYLETHANES

Ethane	$K \times 10^3$	*Remarks*
Hexaphenyl	0.22	In benzene at 22°–24°C [a]
	0.18	In benzene at 20°C [b]
	0.17	In toluene at 20°C [c]
Tetraphenyldi-*o*-tolyl	33	In benzene at 25°C [d]
Tetraphenyldi-*m*-tolyl	1.8	In benzene at 25°C [d]
Tetraphenyldi-*p*-tolyl	1.1	In benzene at 25°C [d]
Tetraphenyldi-*o*-ethylphenyl	65	In benzene at 25°C [d]
Tetraphenyldi-*p*-*tert*-butylphenyl	2.4	In benzene at 25°C [d]
Tetraphenyldi-*p*-cyclohexylphenyl	3.2	In benzene at 26°C [e]
Diphenyltetra-*o*-tolyl	1500	In benzene at 25°C [d]
Diphenyltetra-*m*-tolyl	2.1	In benzene at 25°C [d]
Diphenyltetra-*p*-tolyl	1.3	In benzene at 25°C [d]
Diphenyltetra-*p*-*tert*-butylphenyl	3.2	In benzene at 25°C [d]
Diphenyltetra-*p*-cyclohexylphenyl	3.8–5.7	In benzene at 27°–28°C [e]
Hexa-*m*-tolyl	110	In benzene at 25°C [d]
Hexa-*p*-tolyl	12	In benzene at 25°C [d]
Hexa-*p*-*sec*-butylphenyl	65	In benzene at 25°C [d]
Hexa-*p*-cyclohexylphenyl	20	In benzene at 25°C [e]
Tetraphenyldi-*o*-chlorophenyl	6.5	In benzene at 25°C [f]
Tetraphenyldi-*m*-chlorophenyl	1.8	In benzene at 25°C [f]
Tetraphenyldi-*p*-chlorophenyl	1.1	In benzene at 25°C [f]
Hexa-*p*-fluorophenyl	0.60	In benzene at 25°C [g]
Tetraphenyldi-*o*-anisyl	0.60	In benzene at 25°C [h]
Tetraphenyldi-*m*-anisyl	0.28	In benzene at 25°C [h]
Tetraphenyldi-*p*-anisyl	0.81	In benzene at 25°C [h]
Hexa-*o*-anisyl	120	In benzene at 25°C [h]
Tetraphenyldi-*m*-biphenylyl	2.9–3.3	In benzene at 26°–27°C [i]
Tetraphenyldi-*p*-biphenylyl	3.8–4.7	In benzene at 26°–28°C [i]
Tetraphenyldi-α-naphthyl	11	In toluene at 20°C [c]
Tetraphenyldi-β-naphthyl	1.5	In benzene at 25°C [j]
Diphenyltetra-*p*-biphenylyl	16	In benzene at 25°C [j]
Diphenyldi-*p*-biphenylyldi-α-naphthyl	250	In benzene at 25°C [j]
Diphenyltetra-β-naphthyl	7.8	In benzene at 25°C [j]
Hexa-*m*-biphenylyl	85	In benzene at 25°C [k]
Hexa-*o*-biphenylyl	37	In benzene at 25°C [j]
	Completely dissociated	In benzene [l]
	Completely dissociated	In solid state [l]
Hexa-β-naphthyl	30	In benzene at 25°C [j]
Hexa-*p*-nitrophenyl	Largely dissociated	In solid state [m]

NOTES FOR TABLE 15·2

[a] E. Müller and I. Müller-Rodloff, *Ann.* **521,** 89 (1936).

[b] M. F. Roy and C. S. Marvel, *J. Am. Chem. Soc.* **59,** 2622 (1937).

[c] R. Preckel and P. W. Selwood, *J. Am. Chem. Soc.* **63,** 3397 (1941); the values given above are calculated from the ones for ΔF_{20} given by Preckel and Selwood in their Table IV.

[d] C. S. Marvel, J. F. Kaplan, and C. M. Himel, *J. Am. Chem. Soc.* **63,** 1892 (1941).

[e] C. S. Marvel and C. M. Himel, *J. Am. Chem. Soc.* **62,** 1550 (1940).

[f] C. S. Marvel, F. C. Dietz, and C. M. Himel, *J. Org. Chem.* **7,** 392 (1942).

[g] C. S. Marvel, H. W. Johnston, J. W. Meier, T. W. Mastin, J. Whitson, and C. M. Himel, *J. Am. Chem. Soc.* **66,** 914 (1944).

[h] C. S. Marvel, J. Whitson, and H. W. Johnston, *J. Am. Chem. Soc.* **66,** 415 (1944).

[i] C. S. Marvel, M. B. Mueller, and E. Ginsberg, *J. Am. Chem. Soc.* **61,** 2008 (1939).

[j] C. S. Marvel, J. W. Shackleton, C. M. Himel, and J. Whitson, *J. Am. Chem. Soc.* **64,** 1824 (1942).

[k] C. S. Marvel, E. Ginsberg, and M. B. Mueller, *J. Am. Chem. Soc.* **61, 77** (1939).

[l] E. Müller, I. Müller-Rodloff, and W. Bunge, *Ann.* **520,** 235 (1935).

[m] F. L. Allen and S. Sugden, *J. Chem. Soc.* **1936,** 440.

be derived from some of the thus obtained degrees of dissociation (equation 15·64). A direct comparison between these figures and the ones obtained by independent reliable methods can be made only with hexaphenylethane itself. With this compound, the magnetic value of the dissociation constant K in benzene is approximately half as great as the spectroscopic value (Table 15·1); the reason for this discrepancy is not known. Whether similar discrepancies would be found with the remaining ethanes is, of course, also not known. Although the two methods, each of which is presumably trustworthy, differ somewhat in regard to the value of K, they agree in regard to its temperature coefficient; ΔH, the heat of dissociation, has been calculated by Müller and Müller-Rodloff [76] from the magnetic measurements to be 11.6 ± 1.7 kcal per mole in benzene, and by Preckel and Selwood [77] to be 10.2 ± 1.2 kcal per mole in toluene. (Cf. Table 15·1.)

The discrepancy between the magnetic and spectroscopic values of the equilibrium constant of hexaphenylethane may be no greater than the experimental errors. In view of the extreme precautions that have to be taken to protect the hexaphenylethane from even traces of oxygen and other reagents, the experiments are difficult by either procedure, and their results are certainly less precise than are those obtained in analogous experiments with less sensitive compounds. In general, most of the values listed in Table 15·2 may be inferred from the internal consistency of the data to have probable errors of the order of ±50 per cent. Nevertheless, the satisfactory agreement among the three independent magnetic measurements for hexaphenylethane suggests that the experimental errors in *these* measurements are not large enough to account for the discrepancy. (Cf., however, the widely dis-

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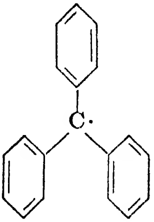
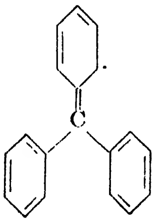
[76] E. Müller and I. Müller-Rodloff, *Ann.* **521,** 89 (1936).

[77] R. Preckel and P. W. Selwood, *J. Am. Chem. Soc.* **63,** 3397 (1941).

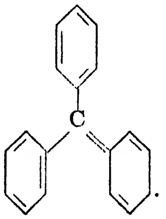
cordant results for hexa-*p*-biphenylylethane.) Apparently, therefore, the spectroscopic work is less precise than it seems to be, or else some systematic error affects either the magnetic or the spectroscopic value of K (or both). A possible source of difficulty, which has not hitherto received adequate consideration, is the following: In the magnetic experiments, the diamagnetic term A (equation 15·69) is not measured directly but is only estimated. There is, however, reason to doubt the legitimacy of using, in this estimation, the same value for the atomic susceptibility of *tri*valent carbon that has been found to apply to *quadri*valent carbon. Moreover, the magnetic susceptibility of a diamagnetic substance has been found to be very sensitive with respect to the extent of conjugation within the molecules of that substance.[78] In undissociated hexaphenylethane, each benzene ring is, of course, a completely conjugated system, but it is independent of all the other benzene rings, from which it is "insulated" by one or more saturated carbon atoms. In the triphenylmethyl radical, on the other hand, no benzene ring is entirely independent of the other two, since resonance can occur among a large number of structures, of which VII, VIII, and IX are typical examples. (Cf. page 709.) Consequently, when a molecule of hexaphenylethane dissociates into two triphenylmethyl radicals, the extent of the conjugation is increased by the coalescence of the smaller systems. This change might be expected to have a significant effect upon the diamagnetic term A. Since no allowance has been made for any such effect, the calculated degree of dissociation may therefore be not exactly correct. (For a possible source of systematic error in the *spectroscopic* measurements, see pages 705 f.)



VII



VIII



IX

From a survey of Table 15·2, it is evident that the introduction of substituents into the benzene rings of hexaphenylethane increases the dissociation, and that the effects of such substituents may be very great. In general, methoxyl groups are the least effective of all those studied; halogen atoms are slightly more effective than methoxyl groups; and alkyl groups are much more effective still. The ability of an alkyl group to increase the dissociation of the ethane increases somewhat with its weight. A phenyl group, as a substituent on a benzene ring, is somewhat more effective than an alkyl group. The nitro group is one of the most effective of all. The positions of the substituents are often even more important than their natures; *ortho* substituents almost always produce the greatest increases in dissociation, and *para* substituents usually produce the least. Moreover, the replacement of the phenyl groups of

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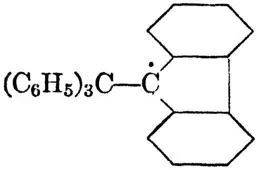
[78] For a discussion of some extreme examples, see L. Pauling, *J. Chem. Phys.* **4**, 673 (1936).

hexaphenylethane by naphthyl groups may be thought of as equivalent to the introduction of substituents. The β-naphthyl group, when joined to one of the two ethane carbon atoms, is approximately as effective as a *m*- or *p*-alkylphenyl group, but less effective than a biphenylyl group; the α-naphthyl group, on the other hand, is the most effective of all those for which data are given in Table 15·2.

15·10 Analogs of the Triarylmethyls. The dissociation of any tetraarylethane into diarylmethyl radicals is, in general, less than is that of an analogous hexaarylethane into triarylmethyl radicals. In fact, the evidence that the tetraaryl compounds dissociate at all is much less complete than is the evidence that the hexaaryl compounds do so. Pentaphenylethyl, I, and triphenylbiphenyleneethyl, II, for example,

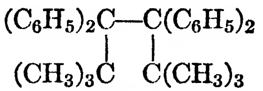
$(C_6H_5)_3C{-}\dot{C}(C_6H_5)_2$

I



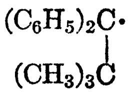
II

are considered to be largely, if not entirely, monomeric; the evidence upon which this conclusion is based consists, however, only of cryoscopic determinations of the apparent molecular weights (cf. pages 685 f.) and of the fact that the substances in the solid state are, respectively, yellow and violet. (Each of these radicals, although it contains altogether five phenyl groups, is a diarylmethyl since its trivalent carbon atom is directly joined to only two aryl groups.) Moreover, tetraphenyldi-*tert*-butylethane, III, is considered to be slightly dissociated



$$\begin{array}{ccc}(C_6H_5)_2C & - & C(C_6H_5)_2\\ | & & |\\ (CH_3)_3C & & C(CH_3)_3\end{array}$$

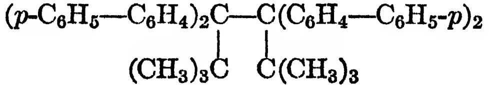
III



$$\begin{array}{c}(C_6H_5)_2C\cdot\\ |\\ (CH_3)_3C\end{array}$$

IV

into diphenyl-*tert*-butylmethyl radicals, IV,[79] since its solutions, which are faintly colored at room temperature, become more intensely yellow if the temperature is raised, and return to their original color if the temperature is then lowered (however, see page 706); the substance also rapidly absorbs oxygen and reacts with sodium. (See Section 15·12.) Tetra-*p*-biphenylyldi-*tert*-butylethane, V, is considered to be more highly



$$\begin{array}{ccc}(p\text{-}C_6H_5{-}C_6H_4)_2C & - & C(C_6H_4{-}C_6H_5\text{-}p)_2\\ | & & |\\ (CH_3)_3C & & C(CH_3)_3\end{array}$$

V

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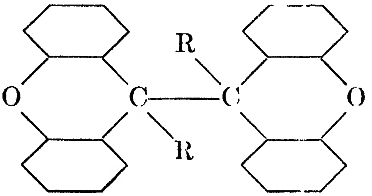
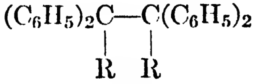
[79] J. B. Conant and N. M. Bigelow, *J. Am. Chem. Soc.* **50**, 2041 (1928).

dissociated than is the corresponding tetraphenyl compound, III, since it is more intensely colored in solution, and since it reacts more rapidly with oxygen and with sodium.[80] Conant and his coworkers have obtained similar evidence to show that the dialkylbixanthyls of general structure VI are more highly dissociated than are the analogous dialkyl-



VI



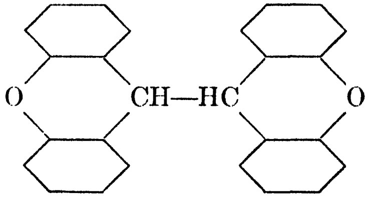
$$\begin{matrix}(C_6H_5)_2C & - & C(C_6H_5)_2 \\ | & & | \\ R & & R\end{matrix}$$

VII

tetraphenylethanes, VII, without the oxygen bridges; in these compounds, primary alkyl groups appear to be less effective than secondary alkyl groups in promoting the dissociation of the ethane.[81] Hydrogen atoms are still less effective, since neither tetraphenylethane, VIII, nor

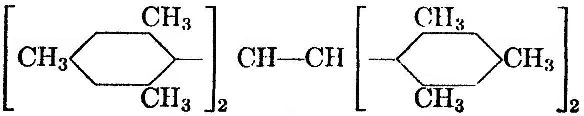
$(C_6H_5)_2CH—CH(C_6H_5)_2$

VIII



IX

bixanthyl, IX, gives any evidence of dissociating into free radicals. (Cf., however, pages 703 f.) On the other hand, tetramesitylethane, X,



X

forms a red solution which becomes more intensely colored as the temperature is raised, which fades as the temperature is lowered, and

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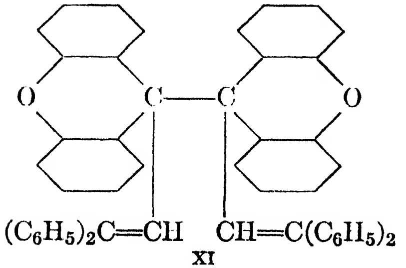
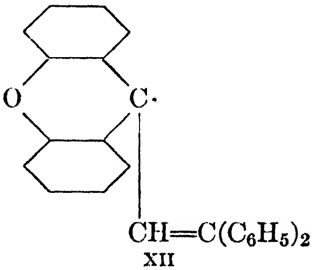
[80] J. B. Conant and R. F. Schultz, *J. Am. Chem. Soc.* **55**, 2098 (1933).

[81] J. B. Conant and A. W. Sloan, *J. Am. Chem. Soc.* **47**, 572 (1925); J. B. Conant and L. F. Small, *ibid.* **47**, 3068 (1925); J. B. Conant, L. F. Small, and A. W. Sloan, *ibid.* **48**, 1743 (1926); J. B. Conant and B. S. Garvey, Jr., *ibid.* **49**, 2080 (1927); J. B. Conant and M. W. Evans, *ibid.* **51**, 1925 (1929).

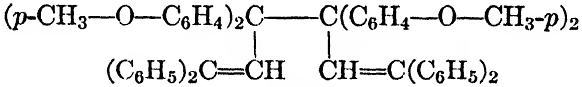
which does not obey Beer's law;[82] several other tetraphenylethanes with many *ortho* methyl groups behave similarly.[83]

Di-(β,β-diphenylvinyl)-bixanthyl, XI, may be considered inter-


XI


XII

mediate in structure between the tetraarylethanes and the hexaarylethanes; for although, in this substituted ethane, only four aryl groups are joined to the central carbon atoms, the two remaining substituents, like aryl groups, are unsaturated. The dissociation into 9-(β,β-diphenylvinyl)-xanthyl, XII, is rather extensive.[84] A cryoscopic determination of the apparent molecular weight in naphthalene has led to the conclusion that the bixanthyl is 60 per cent dissociated; moreover, the substance is colored in solution, and it reacts rapidly with such reagents as oxygen and sodium. Similar evidence suggests that the further ethanes XIII–XV are also appreciably dissociated.[84, 85]

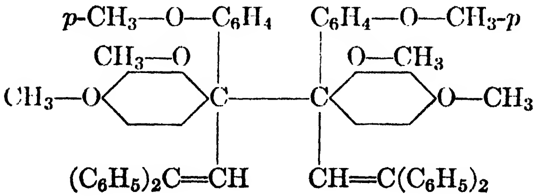


$$\begin{array}{cc} (p\text{-}CH_3\text{—}O\text{—}C_6H_4)_2C & \text{——}C(C_6H_4\text{—}O\text{—}CH_3\text{-}p)_2 \\ | & | \\ (C_6H_5)_2C{=}CH & CH{=}C(C_6H_5)_2 \end{array}$$

XIII

$$\begin{array}{cc} (C_6H_5)_2C & \text{——}C(C_6H_5)_2 \\ | & | \\ (C_6H_5)_2C{=}CH & CH{=}C(C_6H_5)_2 \end{array}$$

XIV


XV

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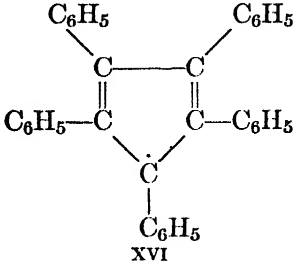
[82] W. T. Nauta and P. J. Wuis, *Rec. trav. chim.* **57**, 41 (1938).

[83] J. Coops, W. T. Nauta, M. J. E. Ernsting, and A. C. Faber, *Rec. trav. chim.* **59**, 1109 (1940); J. Coops, W. T. Nauta, and M. J. E. Ernsting, *ibid.* **60**, 245 (1941).

[84] K. Ziegler, G. Bremer, F. Thiel, and F. Thielmann, *Ann.* **434**, 34 (1923).

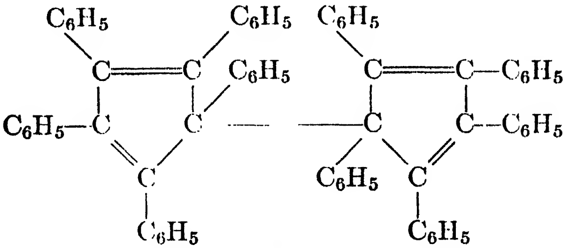
[85] K. Ziegler and C. Ochs, *Ber.* **55**, 2257 (1922).

Pentaphenylcyclopentadienyl, XVI, is a monoarylmethyl radical,



XVI

with two unsaturated substituents; this compound does not associate appreciably to the dimer XVII. In the solid state, it forms dark red crystals; a cryoscopic determination of its molecular weight in benzene has agreed well with the monomeric formula XVI; and (most significant of all) its magnetic susceptibility shows the presence of one unpaired electron per molecule of monomer.[86]



XVII

15·11 Preparation of Triarylmethyls and Their Analogs.

The reaction of an aryl-substituted alkyl halide with "molecular" silver, or with metallic mercury or zinc is frequently the most satisfactory method for the preparation of a dissociable ethane. This procedure is, in fact, the one that was adopted by Gomberg (see Section 15·8) in his original preparation of hexaphenylethane and of triphenylmethyl. Other metals besides the three mentioned have also been used. Finely divided copper, for example, has also been found satisfactory. The alkali metals can be used, but they are not advantageous because they react further with the radicals formed. (See Section 15·12.)

The converse of the reaction of an organic halogen compound with a metal is the reaction of an organometallic compound with a halogen. This type of reaction also can be used for the preparation of a dissociable ethane. Although the halogen reacts further with the ethane and with the free radical derived from it, the procedure can be modified so that

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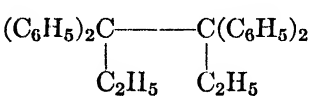
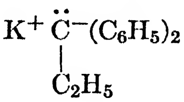
[86] E. Müller and I. Müller-Rodloff, *Ber.* **69**, 665 (1936).

it no longer suffers from this disadvantage. Thus, the very slightly dissociated 3,3,4,4-tetraphenylhexane, I, can be made in poor yield by



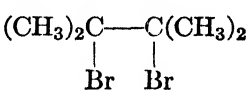
$$\begin{array}{ccc}(C_6H_5)_2C & — & C(C_6H_5)_2\\ | & & |\\ C_2H_5 & & C_2H_5\end{array}$$

I



$$\begin{array}{l}K^+\ \ddot{C}^-(C_6H_5)_2\\ \quad\ \ |\\ \quad C_2H_5\end{array}$$

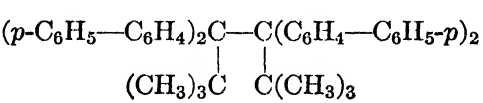
II



$$\begin{array}{ccc}(CH_3)_2C & — & C(CH_3)_2\\ | & & |\\ Br & & Br\end{array}$$

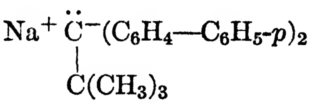
III

the action of either bromine or iodine upon potassium 1,1-diphenylpropyl, II, or in much better yield by the action of 2,3-dibromo-2,3-dimethylbutane, III (which acts as a source of bromine), upon the same potassium compound, II.[87] Similarly, the more highly dissociated tetra-*p*-biphenylyldi-*tert*-butylethane, IV, has been made by the action



$$\begin{array}{ccc}(p\text{-}C_6H_5—C_6H_4)_2C & — & C(C_6H_4—C_6H_5\text{-}p)_2\\ | & & |\\ (CH_3)_3C & & C(CH_3)_3\end{array}$$

IV



$$\begin{array}{l}Na^+\ \ddot{C}^-(C_6H_4—C_6H_5\text{-}p)_2\\ \qquad\ |\\ \quad C(CH_3)_3\end{array}$$

V

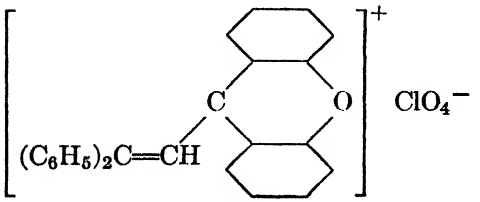
of the dibromide III upon the sodium compound V.[80] Further methods of preparation, which likewise involve the removal of the metal from an organometallic compound, can be illustrated with the formation of hexaphenylethane and triphenylmethyl by the reaction of sodium triphenylmethyl, VI, with either oxygen or triphenylmethyl chloride, VII.

$Na^+ :C^-(C_6H_5)_3$
VI

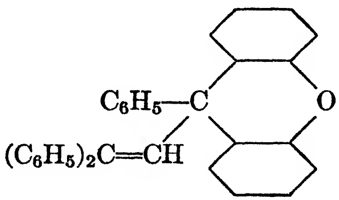
$(C_6H_5)_3C—Cl$
VII

The first of these reactions gives a poor yield, because the oxygen cannot be prevented from destroying a considerable amount of the radical;[87] the second, on the other hand, gives an excellent yield. Metallic mercury can also be used to extract the alkali metal from a compound like sodium triphenylmethyl. (Cf. Section 15·12.)

When the halochromic salt, VIII (see Section 2·5), is treated with



VIII



IX

phenylmagnesium bromide, the reaction follows two independent courses. On the one hand, the phenyl group of the Grignard reagent couples with the substituted xanthyl group of the salt VIII to give

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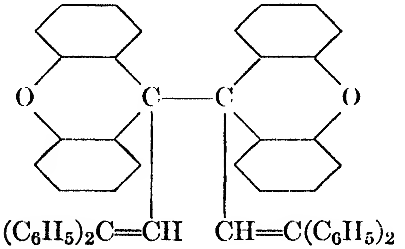
[87] K. Ziegler and B. Schnell, *Ann.* **437**, 227 (1924).

9-phenyl-9-(β,β-diphenylvinyl)-xanthene, IX; on the other hand, two phenyl groups also combine with each other to give biphenyl $C_6H_5—C_6H_5$, while two of the xanthyl groups form the highly dissociated bixanthyl, X.[84] (See above.) In the second of these two reactions,


X

$(C_6H_5)_3C—OH$
XI

the Grignard reagent acts as a reducing agent, since it gives one electron to the carbonium cation. (See Section 2·5.) Other reducing agents can be used similarly; thus, hexaphenylethane precipitates when vanadous chloride VCl_2 and concentrated hydrochloric acid are added to a solution of triphenylcarbinol, XI, in either acetone or acetic acid. Titanous chloride $TiCl_3$ can be used instead of vanadous chloride.

15·12 Reactions of Triarylmethyls and Their Analogs. Many reactions of triarylmethyls and of similar free radicals have already been mentioned in previous sections. Consequently, only a few isolated topics remain to be discussed here.

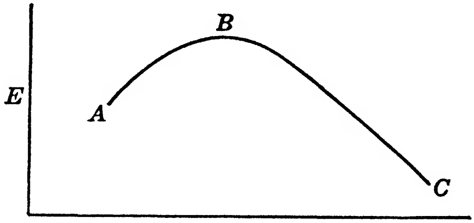


FIGURE 15·2. The variation of the energy *E* of the system in the dimerization of triphenylmethyl (route *A* → *B* → *C*) or in the dissociation of hexaphenylethane (route *C* → *B* → *A*).

The association of a free radical to its dimer might be expected to proceed with extreme ease, since the reaction involves merely the combination of the two "free valences" on the two radicals concerned, and hence does not require the rupture of any bonds. It is possibly rather surprising, therefore, that the reaction by which, for example, hexaphenylethane is formed from triphenylmethyl requires an activation energy of about 8 kcal per mole of ethane formed. Figure 15·2 contains a schematic plot of the energy of a system consisting of two triphenylmethyl radicals (or of one hexaphenylethane molecule) as the dimerization takes place (or as the ethane dissociates). The points *A*, *B*, and *C* correspond, respectively, to the dissociated radicals, to the activated complex or transition state for both the forward and reverse reactions, and to the undissociated ethane. The energy difference between *A* and *C* is equal to ΔH, the heat of dissociation of the ethane; its value is about 11 kcal per mole of ethane. (Cf. Table 15·1, page 690.) The energy difference between *B* and *C* is the activation energy for the dissociation of the ethane; its value has been found [71] from the temperature coefficient of the rate of dissociation (see pages 687 f.) to be about 19 kcal. The energy difference between *A* and *B* is equal to the activation energy for the association reaction; its value, which is obtained by subtraction, is therefore about 8 kcal. (Cf. also page 710.)

One of the most characteristic properties of the *short*-lived free radicals is their ability to form organometallic compounds by reacting with metallic elements. As might have been anticipated, this property is less apparent with the relatively stable and unreactive triarylmethyls and their analogs. In fact, the alkali metals are the only metals which are sufficiently active to combine readily with such free radicals. Sodium triphenylmethyl, I, for example, is formed when triphenylmethyl, II, is

$$\underset{\text{I}}{\mathrm{Na^+\,:C^-(C_6H_5)_3}} \qquad \underset{\text{II}}{\mathrm{(C_6H_5)_3C\cdot}} \qquad \underset{\text{III}}{p\text{-}\mathrm{(C_6H_5)_2CH{-}C_6H_4{-}C(C_6H_5)_3}}$$

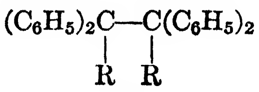
treated with either sodium or sodium amalgam. Under the former conditions, the hydrocarbon III (cf. page 682) is also formed to a greater or less extent.[88] Under the latter conditions, the reaction does not go to completion, since the equilibrium of equation 15·72 is established;

$$\mathrm{(C_6H_5)_3\dot{C}} + \mathrm{NaHg}_x \rightleftarrows \mathrm{Na^+\,\ddot{C}^-(C_6H_5)_3} + x\mathrm{Hg} \qquad (15\cdot72)$$

with an excess of sodium amalgam, however, the free radical can be almost completely converted into the organosodium compound, whereas, with a large amount of pure mercury, the alkali metal can be almost completely removed from the organosodium compound.[89] The remaining alkali metals, to the comparatively limited extent to which they have been investigated, behave like sodium.

The fact that tetraphenylethane, IV, is cleaved slowly by sodium-

$$\underset{\text{IV}}{\mathrm{(C_6H_5)_2CH{-}CH(C_6H_5)_2}} \qquad \underset{\text{V}}{\mathrm{K^+\,:C^-H(C_6H_5)_2}}$$



$$\underset{\text{VI}}{\mathrm{(C_6H_5)_2\underset{\displaystyle R}{\underset{|}{C}}{-}\underset{\displaystyle R}{\underset{|}{C}}(C_6H_5)_2}}$$

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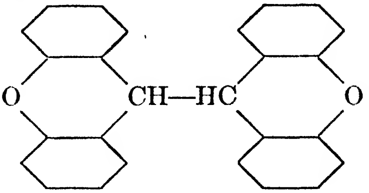
[88] Cf. W. E. Bachmann and F. Y. Wiselogle, *J. Am. Chem. Soc.* **58**, 1943 (1936).

[89] H. E. Bent, *J. Am. Chem. Soc.* **52**, 1498 (1930); **53**, 1786 (1931).

potassium alloy with production of potassium diphenylmethyl, V, suggests that even this hydrocarbon is slightly dissociated into free radicals. The dialkyltetraphenylethanes, VI, can similarly be cleaved,[87] but 1,2-diphenylethane (bibenzyl), VII, does not react.[90] Since bixanthyl,

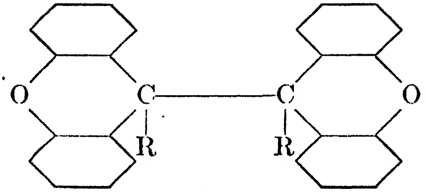
$C_6H_5—CH_2—CH_2—C_6H_5$

VII



VIII

VIII, and the dialkylbixanthyls, IX, are cleaved even more easily than



IX

are the corresponding tetraphenylethanes, the former compounds are presumably more dissociated than are the latter.

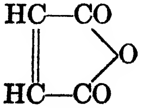
A further characteristic reaction of the short-lived free radicals is their addition to unsaturated compounds. (See pages 661 f. and 664 ff.) Triarylmethyls also undergo this reaction to some extent. Triphenylmethyl, for example, adds to butadiene, X, to form 1,1,1,6,6,6-hexaphenyl-3-hexene, XI, and to several other conjugated diolefins to form analogous products.[91] The addition can take place also with compounds that are not conjugated diolefins; for example, the reactions of triphenylmethyl with maleic anhydride, XII,[91] styrene, XIII,[92] vinyl acetate,

$$CH_2{=}CH—CH{=}CH_2$$

X

$$(C_6H_5)_3C—CH_2—CH{=}CH—CH_2—C(C_6H_5)_3$$

XI



XII

$C_6H_5—CH{=}CH_2$

XIII

$CH_2{=}CH—O—CO—CH_3$

XIV

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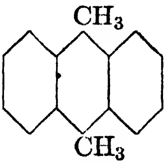
[90] J. B. Conant and B. S. Garvey, Jr., *J. Am. Chem. Soc.* **49**, 2599 (1927).

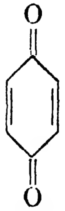
[91] J. B. Conant and B. F. Chow, *J. Am. Chem. Soc.* **55**, 3475 (1933); J. B. Conant and H. W. Scherp, *ibid.* **53**, 1941 (1931).

[92] C. S. Marvel, J. Dec, and J. A. Corner, *J. Am. Chem. Soc.* **67**, 1855 (1945).

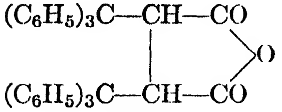
XIV,[92] 9,10-dimethylanthracene, XV,[93] and *p*-benzoquinone, XVI, give



XV

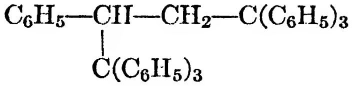


XVI



$$\begin{array}{l} (C_6H_5)_3C{-}CH{-}CO \\ \qquad\qquad\;\; | \qquad\;\; \rangle O \\ (C_6H_5)_3C{-}CH{-}CO \end{array}$$

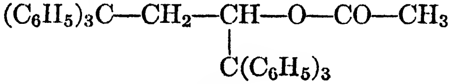
XVII



$$\begin{array}{l} C_6H_5{-}CH{-}CH_2{-}C(C_6H_5)_3 \\ \qquad\quad\;\; | \\ \qquad\;\; C(C_6H_5)_3 \end{array}$$

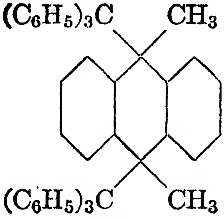
XVIII

the products XVII, XVIII, XIX, XX, and XXI, respectively.

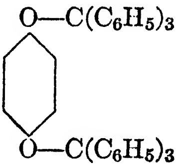


$$\begin{array}{l} (C_6H_5)_3C{-}CH_2{-}CH{-}O{-}CO{-}CH_3 \\ \qquad\qquad\qquad\quad\;\; | \\ \qquad\qquad\qquad\; C(C_6H_5)_3 \end{array}$$

XIX



XX

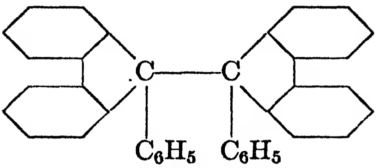


XXI

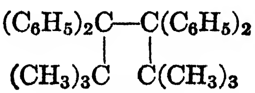
Triarylmethyls and their analogs, like the simpler free radicals of short life, may disproportionate by a mutual hydrogenation and dehydrogenation. Thus, triphenylmethyl itself, under the influence of light, is slowly transformed into a mixture of triphenylmethane, XXII, and

$(C_6H_5)_3CH$

XXII



XXIII



$$\begin{array}{l} (C_6H_5)_2C{-}C(C_6H_5)_2 \\ \qquad\quad\; | \quad\;\; | \\ (CH_3)_3C \;\; C(CH_3)_3 \end{array}$$

XXIV

the practically undissociated diphenylbifluoryl, XXIII. Long-lived free radicals with alkyl substituents undergo irreversible decompositions

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[93] B. M. Mikhaĭlow, *Bull. acad. sci. U.R.S.S. Classe sci. chim.* **1945**, 627; *C.A.* **40**, 4711 (1946).

which are not at present completely understood, but which are commonly regarded as disproportionations of some kind. Thus, if a solution of tetraphenyldi-*tert*-butylethane, XXIV, is heated to 100°C for a few minutes, the more intense color which is thus produced no longer fades when the solution is cooled.[79] The solution of hexa-*p*-tolylethane, XXV,

$$(p\text{-}CH_3—C_6H_4)_3C—C(C_6H_4—CH_3\text{-}p)_3$$

XXV

has been shown [94, 77] by magnetic measurements to be rapidly transformed into a product which contains no free radical at all. Since no great change in the color of the solution is observed during the disappearance of the free radical, the colorimetric method of analysis (see Section 15·9) is clearly inapplicable to this substance. All other hexaarylethanes containing primary or secondary alkyl substituents behave similarly; they retain their contents of free radical somewhat longer, however, than hexa-*p*-tolylethane, XXV, does. On the other hand, hexaarylethanes with tertiary alkyl substituents are more stable and show relatively little tendency to disproportionate.

15·13 The Theory of the Stabilities of Triarylmethyls and Their Analogs. In the dissociation of unsubstituted ethane into simple methyl radicals, the energy required to break the carbon-carbon bond is about 85 kcal per mole; [35] for the dissociation of hexaphenylethane into triphenylmethyl radicals, the energy required is instead only about 11 kcal per mole. (Cf. Table 15·1, page 690.) This striking difference in what may be called the *strength* of the central carbon-carbon bond is of course responsible for the fact that, although no appreciable dissociation of ethane itself occurs at ordinary temperatures, hexaphenylethane in solution exists in equilibrium with an easily detectable amount of triphenylmethyl. There still remains, however, the important theoretical problem of explaining how the presence of six phenyl groups can so greatly weaken the bond in question.

One of the early attempts to explain the dissociation of hexaphenylethane was based upon the idea that phenyl groups form exceptionally strong bonds and so use up disproportionate amounts of the "affinities" of the atoms to which they are attached. (Cf. pages 389 f.) In the triphenylmethyl radical, therefore, the central carbon atom is presumed to have comparatively little affinity left for a fourth bond to the corresponding atom of a second radical. This explanation, however, suffers from its vagueness. The nature of the assumed affinity is not defined, and the reason why phenyl groups form especially strong bonds is not

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[94] C. S. Marvel, W. H. Rieger, and M. B. Mueller, *J. Am. Chem. Soc.* **61**, 2769 (1939); C. S. Marvel, M. B. Mueller, C. M. Himel, and J. F. Kaplan, *ibid.* **61**, 2771 (1939).

given. Moreover, tetraphenylmethane, I, in which the central carbon

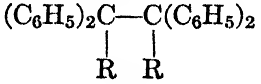
$$\underset{\text{I}}{(C_6H_5)_4C} \qquad \underset{\text{II}}{(C_6H_5)_3C—C(C_6H_5)_2—C(C_6H_5)_2—C(C_6H_5)_3}$$

atom is linked to four phenyl groups, is an unusually stable substance; this fact is hard to reconcile with the theory that three such groups use up nearly all the affinity of that atom. Finally, if this theory were correct, the central carbon-carbon bond in decaphenylbutane, II, ought to be stronger than the corresponding one in tetraphenylethane, III,

$$\underset{\text{III}}{H—C(C_6H_5)_2—C(C_6H_5)_2—H} \qquad \underset{\text{IV}}{(C_6H_5)_3C—\dot{C}(C_6H_5)_2}$$

since the two triphenylmethyl groups of the former compound should be less firmly bonded to the central carbon atoms than are the corresponding hydrogen atoms of the latter compound. The facts are not, however, in agreement with this prediction; decaphenylbutane is largely dissociated into pentaphenylethyl radicals, IV (see page 697), whereas tetraphenylethane is not appreciably dissociated at all.

A second early suggestion regarding the dissociations of hexaphenylethane and of its analogs is that, in the undissociated ethane, the bulky aryl groups interfere *sterically* with one another. It is, in fact, reasonable to suppose that the three phenyl groups in a triphenylmethyl radical, for example, occupy so large a volume that two such radicals cannot come close enough together for a strong bond to be formed between them. (Cf. Sections 9·6 and 9·7.) This theory is supported by a large amount of evidence; it is at present considered to account for at least a part, but probably not for all, of the observed weakening of the central bond. Thus, a naphthyl group is more effective in causing the dissociation of a hexaarylethane than is a smaller phenyl group. Moreover, an α-naphthyl group, with which the steric effect should be especially great, is more effective than a β-naphthyl group, with which the steric effect should be considerably smaller. With the tetraarylethanes of general structure V, the dissociation increases with the size and complexity of



$$(C_6H_5)_2\underset{R}{C}—\underset{R}{C}(C_6H_5)_2$$

V

$$\underset{\text{VI}}{(CH_3)_3C—C(CH_3)_3}$$

the atom or group R (cf. pages 697 f.); the hexaarylethanes with *ortho* substituents are more highly dissociated than are their less hindered isomers with *meta* or *para* substituents (cf. Table 15·2, pages 694 f.). Finally, even in hexa*methyl*ethane, VI, in which the six methyl groups can produce only a relatively small amount of steric repulsion, the central carbon-carbon bond has been found[95] to be somewhat longer, and hence presumably somewhat weaker, than an ordinary carbon-carbon single bond.

The most conclusive evidence that a steric factor is important in aiding the dissociation of hexaphenylethane has been derived from studies of heats of hydrogenation.[96] By a combination of thermochemical data, the heat ΔH of the reaction 15·73 can be calculated to be

$$CH_3{-}CH_3 + H_2 \rightarrow 2CH_4 \qquad (15\cdot 73)$$

about -13 kcal per mole of ethane in the gas phase; the heat ΔH of the corresponding reaction 15·74 has been found by direct measurement

$$(C_6H_5)_3C{-}C(C_6H_5)_3 + H_2 \rightarrow 2(C_6H_5)_3CH \qquad (15\cdot 74)$$

to be about -35 kcal per mole of hexaphenylethane in solution in ethyl acetate. Although these two values are not strictly comparable, since they apply to different states of aggregation, the difference of about 22 kcal between them is so great that it must be real. Evidently, therefore, the carbon-carbon bond in ethane is much harder to break by hydrogenation (as well as by dissociation into free radicals) than is the corresponding bond in hexaphenylethane. Moreover, since the resonance factor (discussed below) cannot account for the observed difference between these heats of hydrogenation, the most reasonable explanation is that the bond in the hexaphenylethane molecule has been weakened sterically.

That this steric effect cannot be the only factor promoting the dissociation of hexaphenylethane is suggested by two types of data. In the first place, it is difficult to see how substituents in the *para* positions could increase the repulsions between the two triarylmethyl radicals, although they do increase the dissociation of the hexaarylethane. (Cf. Table 15·2, pages 694 f.) In the second place, the difference in the heats of hydrogenation of ethane and of hexaphenylethane is only about one-third as great as the observed difference in the heats of dissociation. Consequently, there must exist still some further effect that accounts for the remaining two-thirds of the total weakening of the bond.

The major factor responsible for the dissociation of hexaphenylethane and its analogs is probably a resonance effect.[97] In hexaphenylethane, each of the six benzene rings separately resonates between the two Kekulé structures. Since these benzene rings are independent of one

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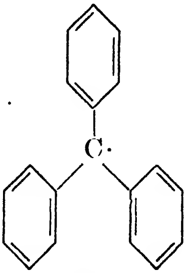
[95] S. H. Bauer and J. Y. Beach, *J. Am. Chem. Soc.* **64**, 1142 (1942).

[96] H. E. Bent and G. R. Culbertson, *J. Am. Chem. Soc.* **58**, 170 (1936).

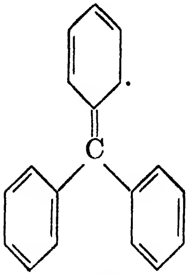
[97] Cf. L. Pauling and G. W. Wheland, *J. Chem. Phys.* **1**, 362 (1933); G. W. Wheland, *J. Am. Chem. Soc.* **63**, 2025 (1941); *The Theory of Resonance*, John Wiley and Sons, New York, 1944, pages 192 ff.

another, and since the resonance energy of benzene is about 36 kcal mole (see Section 10·10), the stabilization of the undissociated ethane by the resonance should amount to approximately 6 × 36, or 216, kcal per mole. In the triphenylmethyl radical, each benzene ring similarly resonates between the two Kekulé structures; consequently, there can be written altogether 2^3, or 8, essentially equivalent structures like VII,

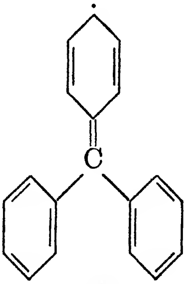


VII

in which the unpaired electron is on the central carbon atom. If no further resonance were possible, the two radicals derived from one molecule of hexaphenylethane should again be stabilized by approximately 6 × 36, or 216, kcal for each mole of ethane; the resonance would then have no effect on the relative stabilities of the ethane and of the radicals, and hence no effect upon the equilibrium. The radical, however, can be stabilized further by resonance with a great many additional structures, such as VIII–XI; since structures analogous to these last ones are



VIII



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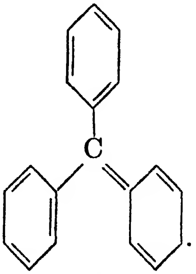
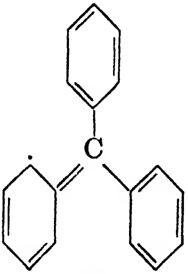


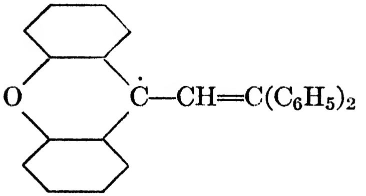
X



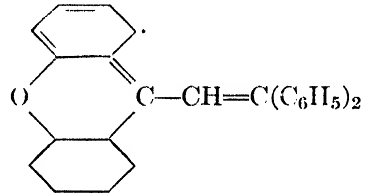
XI

not possible for the undissociated ethane, the resonance energy of the ethane must be less than that of the radicals formed from it. Consequently, the resonance favors the dissociation of hexaphenylethane. Since no analogous resonance can occur either in unsubstituted ethane $H_3C—CH_3$, or in the simple methyl radical $\dot{C}H_3$, resonance must be *one* of the factors responsible for the great difference between the dissociation of hexaphenylethane and that of ethane. The belief that resonance is the *major* factor is supported by approximate numerical calculations,[97] which have shown that, when hexaphenylethane dissociates into triphenylmethyl radicals, the increase in the total resonance energy is of the same order of magnitude as the observed weakening of the carbon-carbon bond of the ethane. (The appreciable activation energy required in the dimerization of triphenylmethyl may be due to the considerable loss of resonance stabilization in the ethane. Cf. pages 702 f.)

With such analogs of the triarylmethyls as 9-(β,β-diphenylvinyl)-xanthyl (represented hitherto by structure XII), resonance can occur

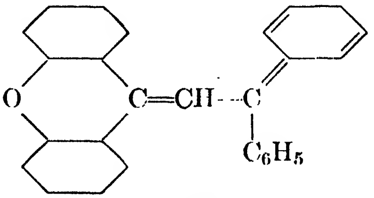


XII



XIII

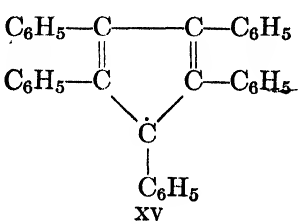
with structures in which the unpaired electron is on an *ortho* or *para* carbon atom of any desired benzene ring. In structure XIII, for example, one of the rings of the xanthyl system is involved; whereas, in structure XIV, one of the rings of the β,β-diphenylvinyl group is involved



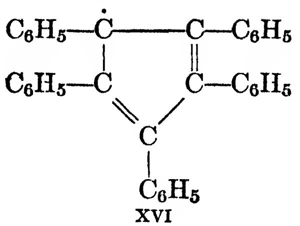
XIV

instead. Since structures of neither of these two latter types can be drawn for the corresponding ethane, the resonance again favors the dissociation of the ethane into radicals; moreover, since resonance in the radical occurs with structures like XIV, the β,β-diphenylvinyl group is more effective in stabilizing the radical than a saturated alkyl group would have been.

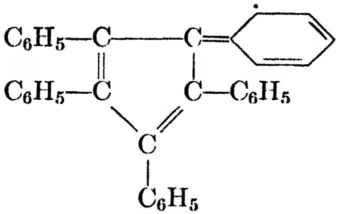
In pentaphenylcyclopentadienyl, the possibilities for resonance are especially great; the unpaired electron can be upon any one of the five equivalent carbon atoms of the central ring, or upon an *ortho* or *para* carbon atom of any one of the five equivalent benzene rings. (Cf. the illustrative structures XV–XVIII.) The radical should therefore be



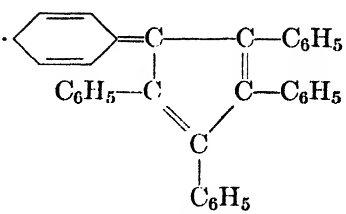
XV



XVI

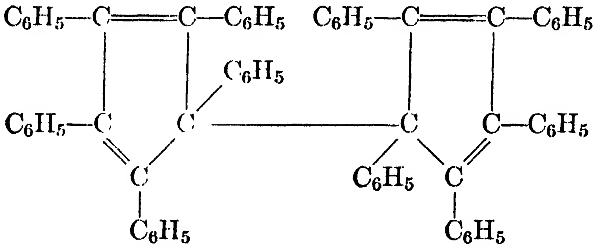


XVII



XVIII

exceptionally stable. On the other hand, the dimer XIX is stabilized only by the resonance in the benzene rings separately, and (to a very small extent) by the simple conjugation of the ethylenic double bonds of the five-membered rings with each other and with the phenyl groups. The observed complete dissociation of the dimer is therefore not unreasonable.



XIX

Although the combined steric and resonance factors can thus apparently account for the gross features of the dissociations of substituted ethanes into free radicals, many of the finer details are as yet unexplained. The effects of *meta* and *para* alkyl groups, and of *meta* phenyl groups, for example, are quite appreciable even though they cannot be easily related to either steric or resonance effects. Evidently, much remains to be done before the problem can be considered completely solved.[97]

15·14 Ionization of Hexaphenylethane. When hexaphenylethane is dissolved in liquid sulfur dioxide, the resulting solution is yellow. That this color is not due to the presence of triphenylmethyl radicals is suggested, however, by the fact that the solution conducts the electric current, even though the likewise yellow solutions of the same ethane in organic solvents do not. Obviously, therefore, hexaphenylethane dissolved in sulfur dioxide gives rise to ions of some sort.

One possibility is that the hexaphenylethane dissociates into two oppositely charged ions, as in equation 15·75. This possibility can be

$$(C_6H_5)_3C\text{—}C(C_6H_5)_3 \rightleftarrows (C_6H_5)_3C^+ + (C_6H_5)_3C\!:^- \qquad (15\cdot75)$$

excluded, however, on two grounds. First, although the triphenylmethyl cation, I (as in triphenylmethyl perchlorate, II) is yellow, the

$$\underset{\text{I}}{(C_6H_5)_3C^+} \qquad \underset{\text{II}}{(C_6H_5)_3C^+ClO_4^-} \qquad \underset{\text{III}}{(C_6H_5)_3C\!:^-} \qquad \underset{\text{IV}}{Na^+\,:C^-(C_6H_5)_3}$$

triphenylmethyl anion, III (as in sodium triphenylmethyl, IV) is an intense red; a solution containing equal amounts of these two ions could hardly, therefore, have the observed yellow color. (See also the following paragraph.) Second, the triphenylmethyl anion is known to react with sulfur dioxide to form the triphenylmethane sulfinate anion, V.

$$\underset{\text{V}}{(C_6H_5)_3C\text{—}SO_2^-}$$

Since, however, this last ion is colorless, the alternative assumption that the ionization is in accordance with equation 15·76, rather than 15·75,

$$(C_6H_5)_3C\text{—}C(C_6H_5)_3 + SO_2 \rightleftarrows$$
$$(C_6H_5)_3C^+ + (C_6H_5)_3C\text{—}SO_2^- \qquad (15\cdot76)$$

is in agreement with the qualitative observations. Quantitative measurements, however, have shown that equation 15·76 also is incorrect.[98] The extinction coefficient of the triphenylmethyl cation, I, at some specified wave length can be obtained from an examination of a solution of triphenylmethyl bromide, VI in sulfur dioxide, in which solvent the

$$\underset{\text{VI}}{(C_6H_5)_3C\text{—}Br} \qquad\qquad \underset{\text{VII}}{(C_6H_5)_3C^+Br^-}$$

bromide apparently exists in the ionized form VII. In solution in sulfur dioxide, the apparent extinction coefficient of hexaphenylethane at the same wave length is found to be twice as great, per mole of ethane, as is that of the cation I. Since each molecule of ethane must therefore give rise to two triphenylmethyl cations, and not to only one, the ionization must be of the type shown in equation 15·77 or 15·78.

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[98] L. C. Anderson, *J. Am. Chem. Soc.* **57**, 1673 (1935).

$$(C_6H_5)_3C{-}C(C_6H_5)_3 + 2SO_2 \rightleftarrows 2(C_6H_5)_3C^+ + 2SO_2^- \qquad (15\cdot77)$$

$$(C_6H_5)_3C{-}C(C_6H_5)_3 + SO_2 \rightleftarrows 2(C_6H_5)_3C^+ + SO_2^= \qquad (15\cdot78)$$

Although both the triphenylmethyl free radical, VIII, and cation I

$$(C_6H_5)_3C\cdot$$

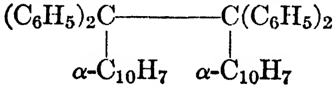
VIII

are yellow, their absorption spectra are entirely different.[98] The spectra of hexaphenylethane in sulfur dioxide and in, say, ether are, therefore, easily distinguishable since, in the former solvent, the observed spectrum is that of the cation, whereas, in the latter solvent, it is that of the neutral radical. With other ethanes, the colors in the two solvents could appear different even to the unaided eye; thus, since the diphenyl-α-naphthylmethyl radical, IX, and cation X are respectively reddish brown and

$$(C_6H_5)_2\dot{C}{-}\alpha\text{-}C_{10}H_7 \qquad\qquad (C_6H_5)_2C^+{-}\alpha\text{-}C_{10}H_7$$

IX X

green, a solution of tetraphenyldi-α-naphthylethane, XI, in ether is

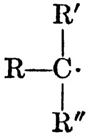


$$\begin{array}{ccc} (C_6H_5)_2C & \text{———} & C(C_6H_5)_2 \\ | & & | \\ \alpha\text{-}C_{10}H_7 & & \alpha\text{-}C_{10}H_7 \end{array}$$

XI

reddish brown, whereas one in sulfur dioxide should be green. The color of the solution in the latter solvent has not, however, been reported.

15·15 Configurations of Alkyl Radicals. There is little direct evidence regarding the stereochemical configuration of a carbon atom that forms three single bonds and has, in addition, one unpaired electron. It is commonly assumed, however, that such an atom is planar or, if normally pyramidal, is able easily to become planar. If this assumption is correct, no trivalent carbon atom can then be a center of molecular dissymmetry; in other words, no free radical with general structure I,

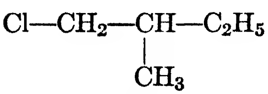


$$\begin{array}{c} R' \\ | \\ R{-}C\cdot \\ | \\ R'' \end{array}$$

I

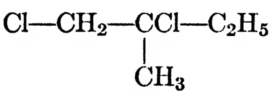
in which R, R′, and R″ represent different atoms or groups, can be optically active, unless, of course, at least one of the atoms or groups R, R′, and R″ is itself dissymmetric. (Cf. the discussion of the ammonia molecule, Section 8·2.) In view of the experimental difficulties encountered in all studies of free radicals, the fact that no radical of this type, I, has as yet been resolved can hardly be considered proof that resolution is impossible.

Some indirect evidence that a trivalent carbon atom cannot maintain a dissymmetric configuration for more than a small fraction of a second is provided by an investigation of the chlorination of (+)-1-chloro-2-methylbutane, II.[99] (However, see below.) The 1,2-dichloro-2-methylbutane, III, formed in this reaction, is found, when separated from its various, simultaneously produced isomers, to be completely racemic. Presumably, therefore, the intermediate free radical, IV (cf. equations 15·5 and 15·6, page 657), was racemized by passing into, or through, the planar configuration before it was transformed into the product III.



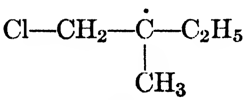
$$Cl{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}H}{-}C_2H_5$$

II



$$Cl{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}Cl}{-}C_2H_5$$

III

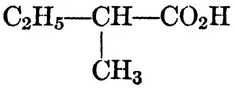


$$Cl{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{\overset{\bullet}{C}}}{-}C_2H_5$$

IV

The racemization observed in the course of the above reaction provides some additional evidence against the alternative chain mechanism considered on page 660 (equations 15·11 and 15·12) for the chlorination of aliphatic compounds. If the chlorine atom replaces the hydrogen atom directly in a one-step process (equation 15·11), the reaction may be expected to proceed with a Walden inversion (cf. Section 7·8), but not with the observed complete racemization. The occurrence of racemization rather than inversion, therefore, supports the belief that reaction 15·11 is not involved.

Evidence which suggests that an alkyl radical can nevertheless maintain a dissymmetric configuration for an appreciable length of time, and which therefore conflicts with the evidence just presented, is provided by the reaction between (+)-methylethylacetic acid, V, and acetyl peroxide, VI. (Cf. page 672.)[100] The dimethyldiethylsuccinic acid, VII, that is obtained in this reaction has been found to be slightly, but definitely, dextrorotatory. Consequently, if the proposed free-radical

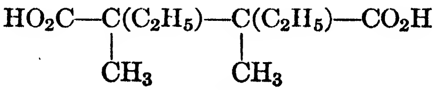


$$C_2H_5{-}\underset{\displaystyle CH_3}{\underset{|}{C}H}{-}CO_2H$$

V

$$CH_3{-}CO{-}O{-}O{-}CO{-}CH_3$$

VI



$$HO_2C{-}\underset{\displaystyle CH_3}{\underset{|}{C}}(C_2H_5){-}\underset{\displaystyle CH_3}{\underset{|}{C}}(C_2H_5){-}CO_2H$$

VII

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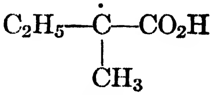
[99] H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Am. Chem. Soc.* **62**, 3435 (1940).

[100] M. S. Kharasch, J. G. Kuderna, and W. H. Urry, personal communication.

mechanism (cf. equations 15·47–15·49) is correct, the intermediate radical, VIII, must be able to retain its optical activity for at least a



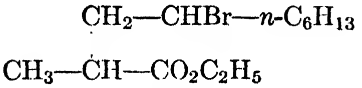
$$C_2H_5—\overset{\cdot}{\underset{CH_3}{\underset{|}{C}}}—CO_2H$$

VIII

short time. Moreover, the addition of (—)-ethyl α-bromopropionate, IX, to 1-octene, X, under the influence of a trace of acetyl peroxide,

$$\underset{\text{IX}}{CH_3—CHBr—CO_2C_2H_5} \qquad \underset{\text{X}}{CH_2{=}CH—n\text{-}C_6H_{13}}$$

VI (cf. pages 667 f.) leads similarly to a product XI with a small,



$$\overset{CH_2—CHBr—n\text{-}C_6H_{13}}{\overset{|}{CH_3—CH—CO_2C_2H_5}}$$

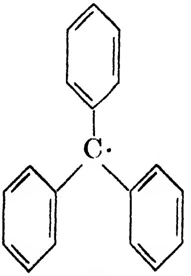
XI

$$\underset{\text{XII}}{CH_3—\dot{C}H—CO_2C_2H_5}$$

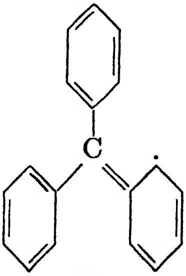
but definite, levorotation.[101] Again, the intermediate radical, XII (cf. equations 15·36–15·39), must be assumed to be not instantaneously racemized.

The observed inactivity of the 1,2-dichloro-2-methylbutane, III, obtained by chlorination of (+)-1-chloro-2-methylbutane, II, may indicate that the radical IV has a lower optical stability than either of the radicals VIII and XII. On the other hand, it may indicate merely that the molecular rotation of the optically pure dichloride, III, is comparatively small, so that the residual activity of the almost (but not quite) completely racemized material has in this instance escaped detection. In either event, the conclusion that the chlorination does not proceed by a one-step reaction with Walden inversion (see above) is not invalidated.

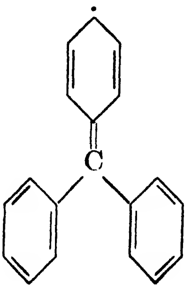
The triphenylmethyl radical might be expected to be completely planar, since all the resonating structures, XIII–XV, etc., can be free



XIII



XIV



XV

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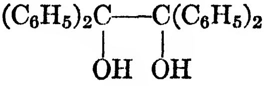
[101] M. S. Kharasch and P. S. Skell, personal communication.

of strain at the same time only if the three phenyl groups are coplanar with one another and with the central carbon atom. Such complete planarity is, however, impossible inasmuch as it would require that the *ortho* hydrogen atoms attached to different rings lie unreasonably close to one another. (Cf. Section 9·6.) Consequently, some departure from planarity is unavoidable. The true shape of the radical is not known. One possibility is that each of the benzene rings is rotated slightly about the bond by which it is joined to the central carbon atom, so that the molecule resembles a three-bladed propeller. Since each of the carbon-carbon bonds about which the rotation is thus considered to occur is a double bond in some of the structures involved, a certain amount of strain would therefore be introduced. Moreover, if the departure from strict planarity is instead assumed to be of some different type, an analogous strain would still be present. Consequently, the stabilization of the radical by the resonance must be somewhat smaller than it would otherwise have been; there is no reason, however, to suppose that this decrease in the stabilization is so great as seriously to affect the earlier theoretical discussion (Section 15·13).

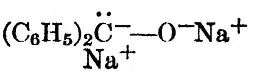
15·16 Metal Ketyls. A solution of benzophenone, I, in an inert solvent like dry ether or benzene becomes intensely blue if it is treated with metallic sodium or with sodium amalgam. The color thus produced is discharged rapidly by numerous reagents. With oxygen, for example, the original colorless benzophenone, I, is regenerated, and sodium peroxide Na_2O_2 is formed; with iodine, benzophenone is again regenerated, and sodium iodide is formed; with carbon dioxide, benzilic acid, II, can be isolated from the material first formed; with water, an equimolecular mixture of benzophenone, I, and benzhydrol, III, is produced; and with dilute aqueous acetic acid, benzpinacol, IV, is obtained almost exclusively.[102] With excess sodium or sodium amalgam, on the other hand, the solution slowly assumes the intense violet color of the disodium derivative, V.

$$\underset{\text{I}}{(C_6H_5)_2C{=}O} \qquad \underset{\text{II}}{(C_6H_5)_2C(OH){-}CO_2H} \qquad \underset{\text{III}}{(C_6H_5)_2CHOH}$$



$$\underset{OH}{(C_6H_5)_2C}{-}\underset{OH}{C(C_6H_5)_2}$$

IV



$$(C_6H_5)_2\underset{Na^+}{\overset{\cdot\cdot}{C}^{-}}{-}O^-Na^+$$

V

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[102] W. E. Bachmann, *J. Am. Chem. Soc.* **55**, 1179 (1933).

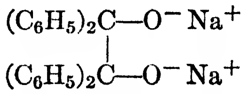
The sensitive blue product of the original reaction between benzophenone and sodium is called benzophenone sodium; it is an example of a rather large group of compounds known as *metal ketyls*. Most aromatic ketones, in fact, give rise to analogous ketyls; even a few ketones like hexamethylacetone, VI,[103] and pivalophenone, VII,[104] with highly

$$\underset{\text{VI}}{(CH_3)_3C\text{—}CO\text{—}C(CH_3)_3} \qquad \underset{\text{VII}}{C_6H_5\text{—}CO\text{—}C(CH_3)_3}$$

branched aliphatic groups, are reported to behave similarly. Moreover, the sodium can be replaced[102] by any of the remaining alkali metals, lithium, potassium, rubidium, or cesium, or by beryllium (plus beryllium iodide), magnesium (plus magnesium iodide or in an amalgam), or calcium. Finally, the reduction of an aromatic ketone to the corresponding pinacol (as, for example, the reduction of benzophenone, I, to benzpinacol, IV) by the action of a mixture of metallic magnesium and magnesium iodide MgI_2 in dry ether or benzene[105] doubtless proceeds through a metal ketyl in which the hypothetical magnesium subiodide MgI takes the place of an alkali metal. This interpretation of the reaction is supported by the appearance of an intense color during the reduction. Analogy suggests that the pinacol reductions of simple aliphatic ketones, like acetone, by metal-acid combinations may also involve metal ketyls as intermediates; there is, however, no conclusive experimental evidence supporting this view.

The empirical formula of benzophenone sodium has been found to be $C_{13}H_{10}ONa$. The substance, since it therefore contains one atom of sodium for each molecule of benzophenone, may have either the monomeric structure, VIII, or the dimeric structure, IX. In the former event,

$$\underset{\text{VIII}}{(C_6H_5)_2\dot{C}\text{—}O^- \, Na^+}$$



$$\begin{array}{l} (C_6H_5)_2C\text{—}O^- \, Na^+ \\ \qquad\quad | \\ (C_6H_5)_2C\text{—}O^- \, Na^+ \end{array}$$

IX

the compound is a free radical; in the latter, it is the disodium salt of benzpinacol, IV. The free radical structure is supported by the intense color and great reactivity of the ketyl; the dimeric structure, on the other hand, is supported by the easy transformation of the ketyl into benzpinacol. A reasonable interpretation of the data is accordingly

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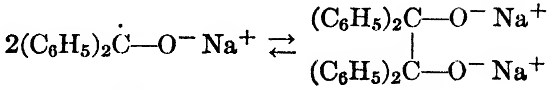
[103] A. E. Favorsky and I. N. Nazarow, *Bull. soc. chim.* [5] **1**, 46 (1934).

[104] I. N. Nazarow, *Compt. rend. acad. sci.* (U.R.S.S.) [N.S.] **1**, 325 (1934); *C.A.* **28**, 4407 (1934).

[105] M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.* **49**, 236 (1927).

that, in solution, an equilibrium exists between the monomeric and dimeric forms (equation 15·79).



$$2(C_6H_5)_2\dot{C}—O^-\,Na^+ \rightleftarrows \begin{array}{l}(C_6H_5)_2C—O^-\,Na^+\\ \quad\quad\quad\;\, |\\ (C_6H_5)_2C—O^-\,Na^+\end{array} \qquad (15\cdot79)$$

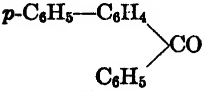
VIII IX

Schlenk and Thal considered that the equilibrium in a solution of benzophenone potassium in ether is greatly, if not completely, in favor of the monomeric free radical. Their evidence for this belief was that they found the boiling point of a solution of benzophenone not to change on the addition of potassium; since, therefore, the total number of solute molecules remained unaltered during the formation of the potassium ketyl, no appreciable amount of dimer could have been formed. More recent investigators,[106] however, were not able to confirm Schlenk and Thal's experimental result; instead, they found that the boiling point of the solution decreased as the ketyl was formed, and that the extent of the decrease corresponded approximately to complete dimerization. In view of the anomalies found in the apparent molecular weights of the hexaarylethanes (see Section 15·9), it may be doubted whether any significant information can be obtained from such experiments as these.

The problem of measuring the positions of the equilibria in solutions of metal ketyls was not solved until the magnetic method was applied. (See pages 691 ff.) In this way, the dissociations of the metal pinacolates have been found to vary widely with the solvent and with the

TABLE 15·3

Dissociations of Some Metal Pinacolates in Solution

Ketone	*Metal*	*Solvent*	*Concentration in Wt. %*	*Temperature in °C*	*Per cent Dissociation*
$(C_6H_5)_2CO$	Na	Benzene	1.7	25	<1 [a]
"	K	Dioxane	15	24	83 [b]
 $\begin{array}{l}p\text{-}C_6H_5—C_6H_4\\ \qquad\qquad\quad\;\;\rangle CO\\ \quad C_6H_5\end{array}$	Na	Benzene	9.4	27	1.7 [a]
"	Na	Dioxane	3.0	26	41 [a]
"	K	Dioxane	17	24	83 [b]

[a] R. N. Doescher and G. W. Wheland, *J. Am. Chem. Soc.* **56**, 2011 (1934).
[b] S. Sugden, *Trans. Faraday Soc.* **30**, 18 (1934).

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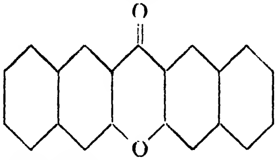
[106] R. N. Doescher and G. W. Wheland, *J. Am. Chem. Soc.* **56**, 2011 (1934).

identities of both the ketone and the metal.[106,107] Some data which illustrate the variations in degree of dissociation are given in Table 15·3. Similar variations have been observed also in the solid state, as is shown by the data of Table 15·4. A further example of the effect of the metal upon the properties of the ketyl is given by the fact that, although benzophenone sodium is dark blue, benzophenone lithium is light green in solution,[102] and the magnesium iodide derivative of benzophenone forms a red solution.[102,105]

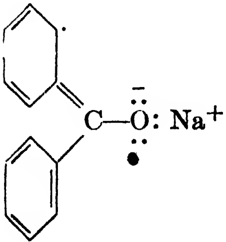
TABLE 15·4

DISSOCIATIONS OF SOME METAL PINACOLATES IN THE SOLID STATE AT 17°–18°C [a]

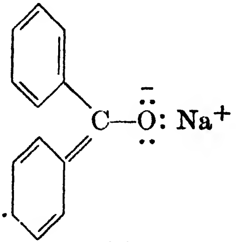
Ketone	*Metal*	*Per cent Dissociation*
	K	0
$(C_6H_5)_2CO$	Li	4
"	K	77
$[p\text{-}(CH_3)_2N{-}C_6H_4{-}]_2CO$	Li	29
"	Na	79
"	K	96

[a] E. Müller and W. Janke, *Z. Elektrochem.* **45**, 380 (1939). See also F. L. Allen and S. Sugden, *J. Chem. Soc.* **1936**, 440.

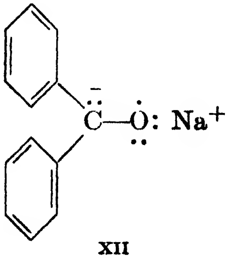
The theoretical explanation of the dissociations of the above tetraaryl pinacolates is presumably similar to that suggested in Section 15·13 for the analogous dissociations of the hexaarylethanes. On the one hand, the bulky aryl groups doubtless interfere sterically with one another, so that they lengthen, and weaken, the central carbon-carbon bonds of the dimers; on the other hand, resonance with such structures as X, XI, XII,



X



XI



XII

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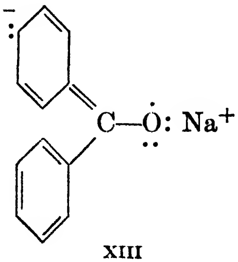
[107] S. Sugden, *Trans. Faraday Soc.* **30**, 18 (1934).

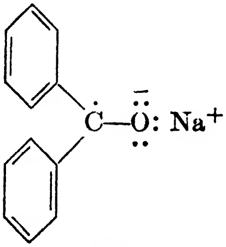
and XIII, which can be written for the free radicals but not for the



XIII

undissociated pinacolates, must also favor the dissociation. Finally, the electrostatic repulsions between the two negatively charged halves of the pinacolate ions must be at least partially responsible for the fact that the dissociations occur only in the ions and not in the electrically neutral pinacols.

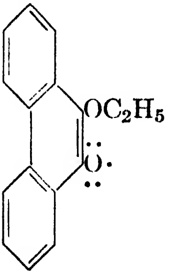
The monomeric metal ketyls are most commonly classified with the triarylmethyls as free radicals containing trivalent carbon. Such a classification is, however, not strictly correct. Although each resonating structure of a triarylmethyl (cf. page 709) contains a trivalent carbon atom with an unpaired electron, the situation is different with the metal ketyls. In each of structures X, XI, and XIV, for example, the atom



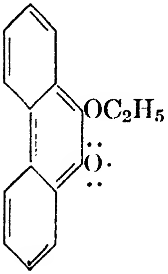
XIV

with the anomalous valence is indeed a carbon atom, but in structures XII and XIII it is instead an oxygen atom. To the extent, therefore, that structures like these last two contribute to the states of the resonance hybrids, the metal ketyls might with some justification be described as free radicals containing univalent oxygen. There is, accordingly, an ambiguity regarding the identity not only of the specific atom, but even of the element, which has the anomalous valence. Similar ambiguities will be encountered also in all the further types of free radical discussed in the following sections.

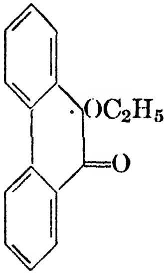
15·17 Free Radicals Containing "Univalent Oxygen." There exist a number of free radicals which, for historical rather than logical reasons (cf. the preceding paragraph), are said to contain univalent oxygen. One of the first compounds of this class to be investigated was the one which may be presumed to resonate among such structures as I–V. (Only the first two of these structures really contain univalent oxygen.) This compound is apparently formed (however, see the following paragraph) by the dissociation of the peroxide, VI, which is itself prepared by the oxidation of the hydroxy ether, VII, with potassium ferricyanide.[108] Although the peroxide is colorless in the solid state, its solutions in such solvents as ether, benzene, and chloroform are greenish blue and do not obey Beer's law. (See pages 684 f. and 689 ff.) Moreover,



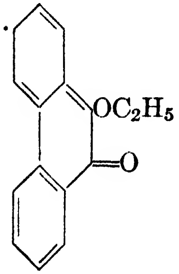
I



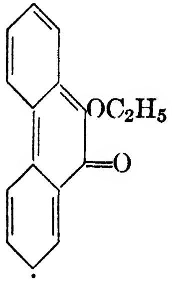
II



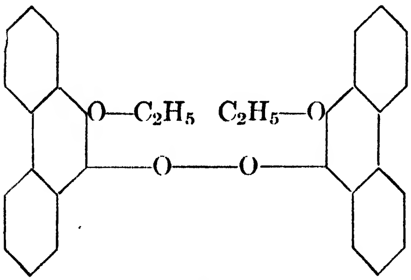
III



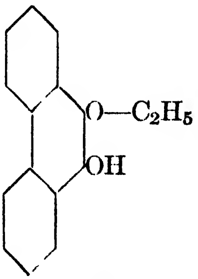
IV



V



VI



VII

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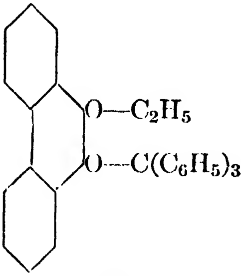
[108] S. Goldschmidt and W. Schmidt, *Ber.* **55**, 3197 (1922).

the apparent molecular weight of the peroxide (by the freezing-point method in benzene) is abnormally low. The compound also combines with triphenylmethyl, as is shown by the disappearance of the color of each reagent; the diether VIII, which is presumably formed, has not been obtained, but its existence has been made probable by the isolation of its hydrolysis products, triphenylcarbinol, IX, and the hydroxy ether, VII. Unlike the free radicals considered heretofore, this compound is insensitive toward oxygen; it can, accordingly, be worked with in an open vessel. A number of other peroxides which have structures analogous to VI, and which have been made in a similar way by the oxidation of phenols, have also been found to have similar properties.[108, 109]



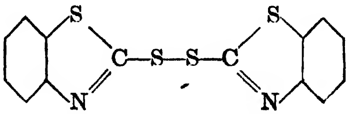
VIII

$(C_6H_5)_3C—OH$

IX

Although the chemical evidence which has just been cited seems clearly to indicate that the peroxide, VI, dissociates into free radicals, magnetic measurements[110] have nevertheless shown that, in benzene solution in the dark, there is little, if any dissociation (less than 2 per cent). When the solution is illuminated with (mostly) visible light, however, the magnetic measurements show that an appreciable dissociation does occur. Cutforth and Selwood point out that, since Goldschmidt and his coworkers presumably took no pains to shield their solutions from light, and since the dissociation is slow,[108] there is not necessarily any contradiction between the earlier chemical experiments and the more recent magnetic ones.

The structure of 2,2′-dithiobisbenzothiazole (2-benzothiazolyl disulfide), X, is



X

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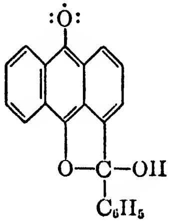
[109] S. Goldschmidt, *Ber.* **55**, 3194 (1922); S. Goldschmidt and C. Steigerwald, *Ann.* **438**, 202 (1924); S. Goldschmidt, A. Vogt, and M. A. Bredig, *ibid.* **445**, 123 (1925).

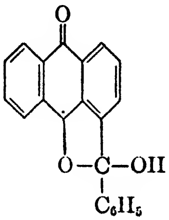
[110] H. G. Cutforth and P. W. Selwood, *J. Am. Chem. Soc.* **70**, 278 (1948).

somewhat analogous to that of the peroxide, VI. The solution of this disulfide in toluene becomes colored when the temperature is raised to above 80°C, and then fades when the temperature is again lowered. Magnetic measurements[110] have shown that, in toluene, the compound dissociates appreciably into free radicals containing "univalent sulfur" (even in the dark), and that the degree of dissociation increases with the temperature.

A closely related group of free radicals with "univalent oxygen" is represented by the substance for which such resonating structures as XI–XIV can be written. This compound may be prepared directly[111]



XI



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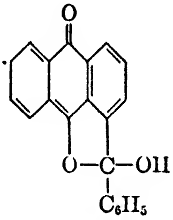
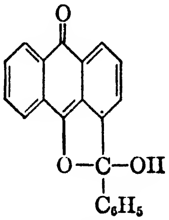
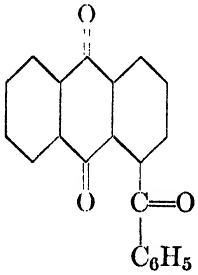


XIII

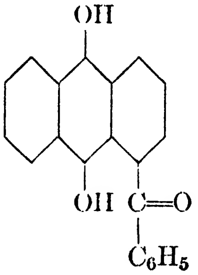


XIV

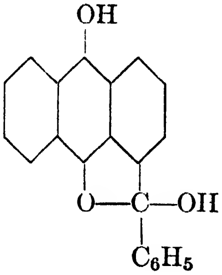
by gentle reduction of the quinone XV, or indirectly[112] by more extensive



XV



XVI



XVII

reduction of the same quinone XV, all the way to the hydroquinone XVI, subsequent rearrangement of the latter to the hemiacetal XVII, and final oxidation of the hemiacetal. Several analogous free radicals, in which one or more substituents are joined to the aromatic rings, have also been prepared by the corresponding reactions.[111,112] All these substances are colored (usually violet); unlike the simpler compounds just discussed, they are somewhat (but not very) sensitive toward oxygen, and they have little if any tendency to dimerize.

The original evidence that the free radicals now under discussion do not dimerize consisted of measurements of apparent molecular weight

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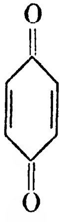
[111] R. Scholl and H. Hähle, *Ber.* **54**, 2376 (1921); **56**, 918, 1065 (1923); R. Scholl, H. Dehnert, and H. Semp, *ibid.* **56**, 1633 (1923); R. Scholl, S. Hass, and H. v. Hoessle, *ibid.* **64**, 1158 (1931).

[112] L. F. Fieser and W. Y. Young, *J. Am. Chem. Soc.* **54**, 4095 (1932).

in nitrobenzene at both the boiling and freezing points.[111] Much more conclusive evidence was obtained later,[112] however, by a *potentiometric* method based upon the following principles. If a platinum electrode is immersed in a solution containing an oxidizing agent A and a reducing agent B, a potential is set up. If the "single electrode" which is thus established is a reversible one, its potential E can be measured against that of some standard electrode. The thermodynamic relation between E and the activities (A) and (B) of the oxidizing and reducing agents, respectively, is shown in equation 15·80, where R is the gas constant,

$$E = E^\circ + \frac{RT}{nF} \ln \frac{(A)}{(B)} \qquad (15\cdot80)$$

T is the absolute temperature, n is the number of electrons (per molecule) transferred from B to A, F is the faraday (about 96,500 coulombs), and the constant E° is the so-called *standard* electrode potential, the value of which is characteristic of the oxidizing and reducing agents. Now, if a solution of the reducing agent B is titrated potentiometrically by the addition of some oxidizing agent C, which is strong enough to transform an equivalent quantity of B (practically) completely into A, and if the measured potential E is plotted against the amount of oxidizing agent C that has been added, the value of n can, with the aid of equation 15·80, be determined from the shape of the resulting curve. When Fieser and Young [112] titrated a slightly acidic solution of 1-benzoylanthrahydroquinone, XVI, with *p*-benzoquinone, XVIII, immediately after the former substance had been prepared by the catalytic reduction of the quinone XV, they obtained a curve with n equal to 2; the reversible 1-step 2-electron change involved under these circumstances is doubtless merely the oxidation of the hydroquinone XVI to the quinone XV. On the other hand, if the solution of the hydroquinone was allowed to stand for some time before the titration with the *p*-benzoquinone was carried out, or if the solution was heated, a different result was obtained; the titration curve under these conditions was found to consist of two distinct parts, the first of which had n equal to 2, but the second of

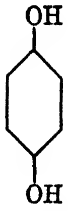


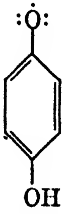
XVIII

which had n equal to 1. The oxidation must therefore have followed two independent courses. The most reasonable interpretation of the data is that, when the hydroquinone XVI was allowed to stand, or when it was heated, it was *partially* transformed into the hemiacetal XVII. The observed reversible 2-electron change was, in fact, positively identified as the direct oxidation of the residual hydroquinone to the quinone XV. The likewise reversible 1-electron change, on the other hand, was considered to be the oxidation of the hemiacetal, XVII, to the above free radical resonating among the various structures like XI–XIV. Since the two parts of the titration curve were distinct and clearly separable from one another, the two independent oxidation processes cannot have overlapped; that is to say, the oxidation of the hydroquinone XVI to the quinone XV must have been essentially complete before the oxidation of the hemiacetal XVII to the free radical began; or, in other words, no appreciable quantity of the free radical could have been formed before practically all the hydroquinone was oxidized. This fact is extremely fortunate since, if the two oxidations had overlapped, the interpretation of the titration curve would have been made much more difficult.

Whether the above explanation of the data is exactly correct or not, the occurrence of a 1-electron change shows conclusively that some sort of free radical was formed in the oxidation. For, in any 1-electron change, either the original reagent or the final product must have an odd number of electrons per molecule, and so at least one of these two substances must be a free radical.

The most thoroughly studied class of free radicals containing "univalent oxygen" consists of the semiquinones that were discussed from a different point of view in Section 2·7. The simplest example of such a free radical is the semiquinone which is obtained as an intermediate in the reduction of p-benzoquinone, XVIII, to p-benzohydroquinone, XIX,


XIX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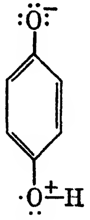
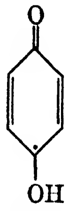
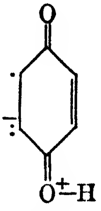
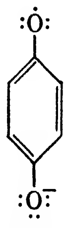

XXI

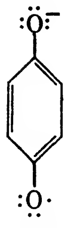

XXII


XXIII

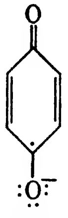
or in the oxidation of the latter compound to the former. In neutral or acidic solution, this semiquinone can be regarded as a resonance hybrid of such electrically neutral structures as XX–XXIII; in basic solution, however, it must instead be regarded as a hybrid of such anionic structures as XXIV–XXVII. (See also below.) Like some of the above free



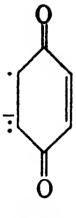
XXIV



XXV



XXVI



XXVII

radicals containing "univalent oxygen," the semiquinones are not sensitive to oxygen. That the semiquinones are indeed free radicals was first shown by a potentiometric method based upon the principles discussed above.[113] The interpretation of the data was here made difficult, however, by three different complications which were not encountered by Fieser and Young.[112] In the first place, many of the semiquinones have greater or less tendencies to dimerize. In the second place, the semiquinones are stable only in basic solutions, in which both they and their corresponding hydroquinones are, to varying extents, transformed into their negative ions; the complete equilibrium which must be studied in any given instance is, therefore, not one between a single oxidizing agent and a single reducing agent, but is instead one among several oxidizing agents and several reducing agents. And, in the third place, all three oxidation stages, i.e., the quinone, the semiquinone, and the hydroquinone, are usually present together in the same solution; the various steps of the studied oxidation or reduction therefore overlap. For these reasons, the mathematical treatment of the potentiometric data.[113] is extremely complicated. In spite, however, of these several difficulties, which need not here be further described, Michaelis and his coworkers have been able in a number of instances to measure precisely the relative concentration of each component of the complex equilibrium mixture under varying conditions of concentration and *p*H.

Semiquinones have been shown to be free radicals not only by the above potentiometric method, but also by the magnetic method used with other types of free radical.[114] The results obtained by the two independent procedures are in satisfactory qualitative and quantitative agreement with each other.

The stabilities of the semiquinones must be due largely to resonance.

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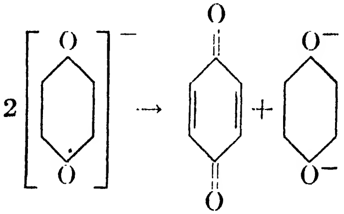
[113] Cf. L. Michaelis, *Chem. Revs.* **16**, 243 (1935); L. Michaelis and M. P. Schubert, *ibid.* **22**, 437 (1938).

[114] Cf., for example, L. Michaelis, G. F. Boeker, and R. K. Reber, *J. Am. Chem. Soc.* **60**, 202 (1938).

The steric factor, which is important with such radicals as the triarylmethyls (see Section 15·13), may, to be sure, be partly responsible for the relatively small tendency of the semiquinones to dimerize; it cannot, however, account for the greatly reduced tendency of these compounds, especially in basic solution, to disproportionate into equimolecular mixtures of the corresponding quinones and hydroquinone ions (as, for example, in equation 15·81). Further evidence for the importance of


(15·81)

resonance can be derived from a consideration of the effect of alkalinity upon the stability. In neutral or acidic solution, the radical resonates principally among electrically neutral structures like XX–XXIII (see above), several of which are relatively unstable on account of their wide separations of electric charge. (See Section 10·9.) In basic solution, however, the radical resonates principally among anionic structures like XXIV–XXVII, no one of which is made especially unstable by a separation of charge. The resonance must, therefore, be much more effective in stabilizing the anionic radical than it is in stabilizing the electrically neutral one; consequently, the semiquinone should be most stable in a basic medium, as it is in fact found to be.

15·18 Free Radicals Containing "Bivalent Nitrogen." Since the single bond between the two nitrogen atoms in hydrazine $H_2N—NH_2$ is apparently rather weaker than the one between the two carbon atoms in ethane $H_3C—CH_3$, tetraphenylhydrazine, I, may be expected to

$$\underset{\text{I}}{(C_6H_5)_2N—N(C_6H_5)_2} \qquad\qquad \underset{\text{II}}{(C_6H_5)_2\dot{N}:}$$

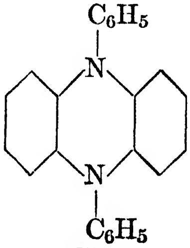
dissociate into diphenylamino radicals, II, more readily than tetraphenylethane, III, dissociates into diphenylmethyl radicals, IV. This

$$\underset{\text{III}}{(C_6H_5)_2CH—CH(C_6H_5)_2} \qquad\qquad \underset{\text{IV}}{(C_6H_5)_2\dot{C}H}$$

prediction appears to be correct; for, although tetraphenylethane does not dissociate appreciably in solution even at fairly high temperatures, tetraphenylhydrazine gives some evidence of doing so. Thus, a solution of this latter compound in toluene is colorless at room temperature, but it becomes greenish brown when heated to about 90°C. Although the color does not fade completely again if the solution is cooled, the assumption that the radical II is formed is nevertheless reasonable; at the high temperature, the hydrazine is transformed into a mixture of products, including diphenylamine, V, and 9,10-diphenyl-9,10-dihydrophenazine,

$$(C_6H_5)_2NH$$

V



VI

VI, which can be explained most simply as having resulted from a disproportionation of the radical. Further support for the belief that tetraphenylhydrazine, I, dissociates into diphenylamino, II, is provided by the fact that, in toluene solution at about 90°C, the former substance reacts with nitric oxide to give N-nitrosodiphenylamine, VII, and with

$$(C_6H_5)_2N\text{—}NO \qquad (C_6H_5)_2N\text{—}C(C_6H_5)_3 \qquad (C_6H_5)_2\overset{-}{\ddot{N}}{:}\ K^+$$

VII VIII IX

triphenylmethyl to give triphenylmethyldiphenylamine, VIII. Furthermore, the formation of the product IX (the potassium salt of diphenylamine) by the reaction with metallic potassium in ether also suggests the existence of diphenylamino radicals. (Cf. pages 703 f.)

With certain derivatives of tetraphenylhydrazine, the evidence for the dissociation into free radicals is more satisfactory than is that with tetraphenylhydrazine itself. Thus, although tetra-*p*-anisylhydrazine, X, is

$$(p\text{-}CH_3\text{—}O\text{—}C_6H_4)_2N\text{—}N(C_6H_4\text{—}O\text{—}CH_3\text{-}p)_2$$

X

colorless in the solid state, it dissolves in benzene to form a solution that is green at room temperature, and that does not obey Beer's law. The color of this solution, which becomes more intense as the temperature is raised, returns to its original intensity when the temperature is again lowered; presumably, therefore, the dissociation of this hydrazine not only increases with the temperature, but also is reversible. Moreover, an appreciable dissociation of tetra-(*p*-dimethylaminophenyl)-hydrazine, XI, has been indicated by cryoscopic determinations of the apparent

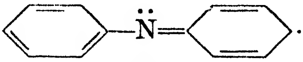
$$[p\text{-}(CH_3)_2N\text{—}C_6H_4]_2N\text{—}N[C_6H_4\text{—}N(CH_3)_2]_2$$

XI

molecular weight in both benzene and nitrobenzene.

The tendencies of the tetraarylhydrazines to dissociate into diarylamino radicals may be considered due to both steric and resonance effects. The structures which make the total resonance energy of, for example, two diphenylamino radicals greater than that of one tetraphenylhydrazine molecule include XII and XIII (in addition to many others).


XII


XIII

As with the free radicals containing "univalent oxygen," so also, with these further radicals containing "bivalent nitrogen," the identity of the element with the anomalous valence is ambiguous; in structures like XII and XIII, the unpaired electron is on a trivalent carbon atom, whereas, in such other structures as XIV (which must also take part in


XIV

the resonance), it is instead upon a bivalent nitrogen atom.

The analogy between the tetraarylhydrazines and the tetra- or hexaarylethanes is not as complete as might have been expected. Although hexa-*p*-biphenylylethane, XV, and hexa-*p*-nitrophenylethane, XVI, are

$$(p\text{-}C_6H_5\text{—}C_6H_4)_3C\text{—}C(C_6H_4\text{—}C_6H_5\text{-}p)_3$$

XV

$$(p\text{-}O_2N\text{—}C_6H_4)_3C\text{—}C(C_6H_4\text{—}NO_2\text{-}p)_3$$

XVI

much more highly dissociated than hexaphenylethane (see Table 15·2, pages 694 f.), Wieland[115] has concluded that tetra-*p*-biphenylylhydrazine, XVII, is somewhat less dissociated than tetraphenylhydra-

$$(p\text{-}C_6H_5\text{—}C_6H_4)_2N\text{—}N(C_6H_4\text{—}C_6H_5\text{-}p)_2$$

XVII

---

[115] H. Wieland, *Die Hydrazine*, Ferdinand Enke, Stuttgart, 1913, pages 71 ff.

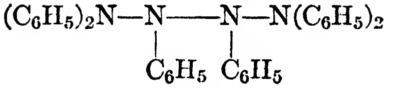
zine, and that 1,2-diphenyl-1,2-di-*p*-nitrophenylhydrazine, XVIII, is

$$p\text{-}O_2N{-}C_6H_4{-}\underset{C_6H_5}{\underset{|}{N}}{-\!-\!-}\underset{C_6H_5}{\underset{|}{N}}{-}C_6H_4{-}NO_2\text{-}p$$

XVIII

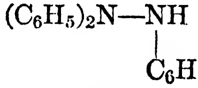
not dissociated at all. The effects of *p*-phenyl and of *p*-nitro groups in the two series are therefore in opposite directions. On the other hand, with both the ethanes (see Table 15·2) and the hydrazines,[115] methyl and methoxyl substituents increase the dissociations, and are most effective in the *ortho* positions. The reason for these inconsistencies is not known. It should be noted, however, that Wieland's estimates of the relative degrees of dissociation may not be completely reliable since, in view of the instabilities of the hydrazines, these estimates had to be based upon such data as the temperatures at which visible colors could be detected, the velocities of disproportionation and of other reactions, etc. Obviously, such estimates can have little quantitative significance; in some instances, they may even be *qualitatively* incorrect.

A group of compounds that are much more extensively dissociated into free radicals with "bivalent nitrogen" than are the tetraaryl hydrazines is illustrated by hexaphenyltetrazane, XIX. This substance, which is



$$(C_6H_5)_2N{-}\underset{C_6H_5}{\underset{|}{N}}{-\!-\!-}\underset{C_6H_5}{\underset{|}{N}}{-}N(C_6H_5)_2$$

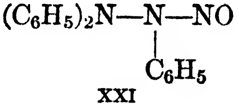
XIX



$$(C_6H_5)_2N{-}\underset{C_6H_5}{\underset{|}{NH}}$$

XX

prepared by the oxidation of triphenylhydrazine, XX, with lead dioxide at about −60°C,[116] can be obtained in "almost white" crystals, but its solutions in ether, toluene, chloroform, etc., are intensely blue. These solutions do not obey Beer's law, and their colors become more intense as the temperature is raised. At room temperature or above, the compound decomposes rapidly, whether in the solid state or in solution. Since, moreover, the tetrazane, XIX, reacts with nitric oxide and with triphenylmethyl to form the products XXI and XXII, respectively,



$$(C_6H_5)_2N{-}\underset{C_6H_5}{\underset{|}{N}}{-}NO$$

XXI

$$(C_6H_5)_2N{-}\underset{C_6H_5}{\underset{|}{N}}{-}C(C_6H_5)_3$$

XXII

the compound can be considered to dissociate spontaneously and reversibly into intensely colored triphenylhydrazyl radicals, which resonate among such structures as XXIII–XXVI, of which only the ones

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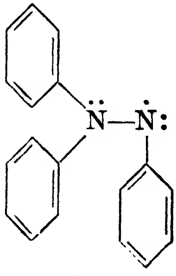
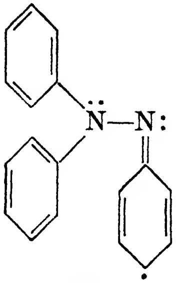
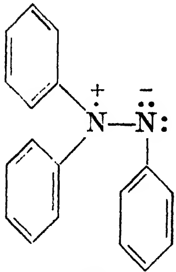
[116] S. Goldschmidt, *Ber.* **53**, 44 (1920).



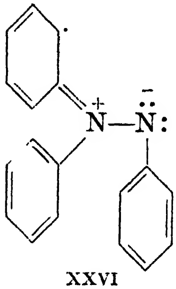
XXIII



XXIV



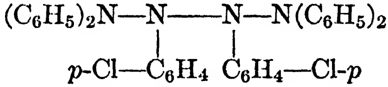
XXV



XXVI

like XXIII have analogs in the undissociated tetrazane.

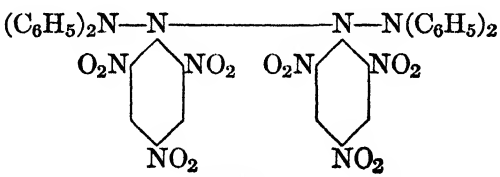
The dissociation of the tetraphenyldi-*p*-chlorophenyltetrazane, XXVII,



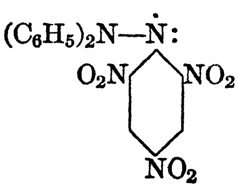
$$\begin{array}{c} (C_6H_5)_2N\text{—}N\text{——}N\text{—}N(C_6H_5)_2 \\ \quad | \qquad\quad | \\ p\text{-Cl—}C_6H_4 \;\; C_6H_4\text{—Cl-}p \end{array}$$

XXVII

seems to be even more extensive than is that of the unsubstituted compound, XIX.[117] In fact, solutions of the former substance obey Beer's law at −20°C (although they disobey this law at −70°C); evidently, therefore, the dissociation of the tetrazane XXVII must be practically complete at the higher temperature, since it then does not increase appreciably as the solution is diluted. On the other hand, the dissociation must be incomplete at the lower temperature. That the further tetrazane XXVIII dissociates completely into 2,2-diphenyl-1-picryl-



XXVIII



XXIX

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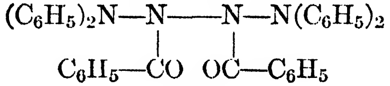
[117] S. Goldschmidt, A. Wolf, E. Wolffhardt, I. Drimmer, and S. Nathan, *Ann.* **437**, 194 (1924).

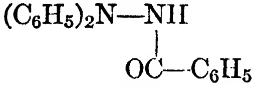
hydrazyl radicals, XXIX, was suggested originally by a cryoscopic determination of the apparent molecular weight in nitrobenzene;[118] this conclusion was later confirmed by magnetic measurements on the crystalline solid.[119,120,121] It is surprising, and not at present explainable, that nitro groups *in*crease the dissociation of this tetrazane, although they *de*crease that of the apparently analogous hydrazine XVIII.

Tetrazanes with both acyl and aryl groups have been studied somewhat more thoroughly than have the ones with only aryl groups.[117,122] With respect to methods of preparation and properties, however, the two classes of tetrazane are closely similar. Tetraphenyldibenzoyltetrazane, XXX, for example, is made by the oxidation of diphenylbenzoylhydrazine, XXXI; in solution at low temperatures, it dissociates appreciably into diphenylbenzoylhydrazyl radicals, XXXII; and at room temperature or above, it rapidly decomposes. The evidence for the dissociation into free radicals is obtained partly from a cryoscopic determination of the apparent molecular weight of the tetrazane in benzene, partly from the failures of the solutions in benzene, toluene, and chloroform to obey Beer's law, and partly from direct analysis. The analytical method employed was made possible by the fact that the hydrazyl radical, XXXII, is rapidly reduced to the corresponding hydrazine XXXI by hydroquinone XXXIII (which is oxidized in the



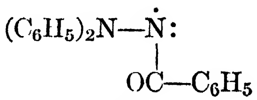
$$(C_6H_5)_2N-\underset{\substack{|\\ C_6H_5-CO}}{N}-\underset{\substack{|\\ OC-C_6H_5}}{N}-N(C_6H_5)_2$$

XXX



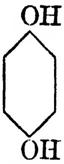
$$(C_6H_5)_2N-\underset{\substack{|\\ OC-C_6H_5}}{NH}$$

XXXI

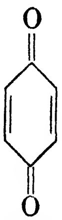


$$(C_6H_5)_2N-\underset{\substack{|\\ OC-C_6H_5}}{\dot{N}:}$$

XXXII



XXXIII



XXXIV

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[118] S. Goldschmidt and K. Renn, *Ber.* **55,** 628 (1922).

[119] H. Katz, *Z. Physik* **87,** 238 (1933).

[120] E. Müller, I. Müller-Rodloff, and W. Bunge, *Ann.* **520,** 235 (1935).

[121] J. Turkevich and P. W. Selwood, *J. Am. Chem. Soc.* **63,** 1077 (1941).

[122] S. Goldschmidt and K. Euler, *Ber.* **55,** 616 (1922); S. Goldschmidt and J. Bader, *Ann.* **473,** 137 (1929).

process to quinone XXXIV), but that the equilibrium between the hydrazyl and the tetrazane XXX (which is not reduced directly by hydroquinone) is established only slowly; consequently, the amount of radical present at equilibrium is equivalent to the amount of hydroquinone that is oxidized immediately; whereas the total amount of hydrazyl plus tetrazane is equivalent to the amount of hydroquinone that is oxidized finally after sufficient time has been allowed for the reaction to go to completion. In this way, the position of the equilibrium, and hence the value of the equilibrium constant at any desired (sufficiently low) temperature can be determined; moreover, from the temperature coefficient of the equilibrium constant, the heat of dissociation can be calculated. These data for tetraphenyldibenzoyltetrazane, XXX, are listed in Table 15·5.

TABLE 15·5

DISSOCIATIONS OF SOME TETRAARYLDIACYLTETRAZANES OF GENERAL STRUCTURE $ArN(Ar')N—N(CO—C_6H_5)—N(CO—C_6H_5)—N(Ar')Ar$ [a]

Ar	*Ar'*	*Solvent*	*K × 10⁵ at −18.5°C in moles per liter* [b]	*ΔH of dissociation in kcal per mole* [c]
p-$O_2N—C_6H_4$	p-$O_2N—C_6H_4$	Chloroform	0.06 [d]	....
p-$O_2N—C_6H_4$	C_6H_5	Chloroform	8.3	18
p-$Br—C_6H_4$	p-$Br—C_6H_4$	Toluene	1.45	12.5
p-$Br—C_6H_4$	C_6H_5	Toluene	3.3	....
C_6H_5	C_6H_5	Toluene	11.5	10
p-$CH_3—C_6H_4$	C_6H_5	Toluene	43	9
p-$CH_3—C_6H_4$	p-$CH_3—C_6H_4$	Toluene	170	8
p-$CH_3O—C_6H_4$	C_6H_5	Acetone	350	7.5
p-$CH_3O—C_6H_4$	p-$CH_3O—C_6H_4$	Acetone	Completely dissociated [e]	....

[a] S. Goldschmidt and J. Bader, *Ann.* **473**, 137 (1929). For further data referring to some additional compounds, see S. Goldschmidt, A. Wolf, E. Wolffhardt, I. Drimmer, and S. Nathan, *ibid.* **437**, 194 (1924).

[b] As in the original paper by Goldschmidt and Bader, the equilibrium constant K is here defined by the slightly modified equation $K = \frac{(\text{hydrazyl})^2}{4(\text{tetrazane})} = \frac{\alpha^2 m}{1 - \alpha}\cdot$ The value of K is therefore exactly ¼ as great as it would have been if the more usual definition of equation 15·64 on page 690 had instead been adopted.

[c] Rounded off and averaged values.

[d] At 0°C.

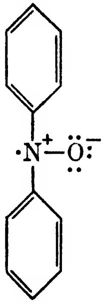
[e] At both −50°C and 0°C.

A number of further tetraaryldiacyltetrazanes, which differ from XXX in the identities of both the aryl and the acyl radicals, have been prepared and studied. The equilibrium constants and heats of dissociation of several such compounds are also given in Table 15·5. It is interesting, and perhaps again unexpected, that nitro substituents on the aryl groups joined to the terminal nitrogen atoms of the tetrazanes decrease the dissociation; in this respect, the nitro groups here resemble the ones in the dinitrotetraphenylhydrazine, XVIII, but differ from the ones in both hexa-*p*-nitrophenylethane, XVI, and tetraphenyldipicryltetrazane, XXVIII.

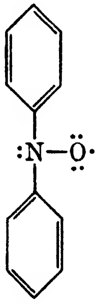
15·19 Free Radicals Containing "Quadrivalent Nitrogen." The compounds of "bivalent nitrogen" that were discussed in the preceding section can be considered related to the simple inorganic free radical, nitric oxide, NO, by the presence of two organic radicals in the place of one oxygen atom. Similarly, there exist also several compounds of "quadrivalent nitrogen" which can be considered related in the same way to a second inorganic radical, nitrogen dioxide NO_2. The simplest example of this latter class of free radicals is given by diphenylnitrogen oxide (diphenylnitroxide) which is prepared by the oxidation of N,N-diphenylhydroxylamine, I, with silver oxide, and which may be considered to resonate among structures of the various types II–V.

$(C_6H_5)_2N—OH$

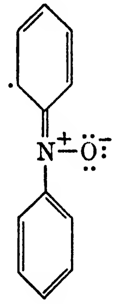
I



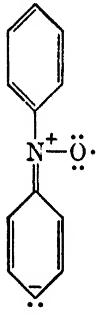
II



III



IV



V

The classification of diphenylnitrogen oxide as a compound of "quadrivalent nitrogen" is more than usually inappropriate. Although the unpaired electron is upon a nitrogen atom in structure II, it is instead upon an oxygen atom in structures III and V, and upon a carbon atom in structure IV. Moreover, in no structure does the nitrogen atom both have the unpaired electron and also form four covalent bonds. The expression "quadrivalent nitrogen" is derived from the originally used classical structure VI, the electronic analog of which (VII) places *nine* electrons in the valence shell of the nitrogen atom.

$(C_6H_5)_2N{=}O$

VI

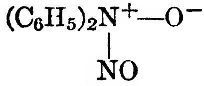
$$\begin{array}{l} C_6H_5:\overset{\cdot}{\underset{\cdot\cdot}{N}}::\overset{\cdot\cdot}{O}: \\ C_6H_5 \end{array}$$

VII

Diphenylnitrogen oxide is a red crystalline substance; it forms red solutions which do not fade noticeably at even −50°C. That the free radical does not associate to a dimer has been shown both by a cryoscopic determination of its apparent molecular weight in benzene[123] and by a magnetic measurement upon the pure solid.[124, 119, 120] The compound combines with both nitric oxide and triphenylmethyl;[125] its reactions with these two reagents are somewhat more complicated, however, than are the analogous ones of the other free radicals discussed previously. The major product obtained in the reaction with nitric oxide, for example, is *p*-nitrodiphenylamine, VIII, which Wieland and Roth assumed

$p\text{-}O_2N—C_6H_4—NH—C_6H_5$

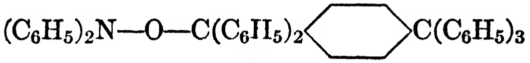
VIII



$$(C_6H_5)_2N^+—O^-\\ \quad\;|\\ \quad NO$$

IX

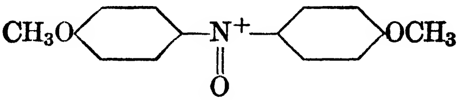
to be formed by rearrangement of the hypothetical addition compound IX. The product obtained in the reaction with triphenylmethyl was also not entirely expected, since it contained two triphenylmethyl residues for each diphenylnitrogen oxide residue; Wieland and Roth assigned to this substance structure X. (Cf. the hydrocarbon XIII



X

on page 682.)

Several derivatives of diphenylnitrogen oxide have been prepared, both by suitable modifications of the procedure outlined above and also by other essentially different reactions. For example, if anisole $C_6H_5—OCH_3$ is nitrated in a mixture of acetic and sulfuric acids, and if the nitration mixture is then treated with perchloric acid, there is obtained a small amount of a perchlorate salt,[126] the cation of which may be considered to resonate among such structures as XI–XIII. If this



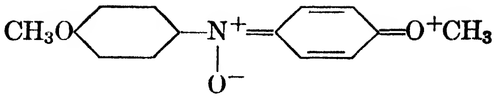
XI

[123] H. Wieland and M. Offenbächer, *Ber.* **47,** 2111 (1914).

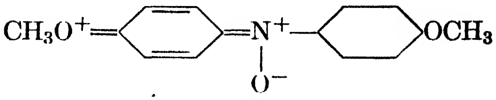
[124] L. Cambi, *Gazz. chim. ital.* **63,** 579 (1933).

[125] H. Wieland and K. Roth, *Ber.* **53,** 210 (1920).

[126] K. H. Meyer and H. Gottlieb-Billroth, *Ber.* **52,** 1476 (1919).



XII



XIII

salt is now reduced, di-*p*-anisylnitrogen oxide, XIV, is obtained.[126] This

$(p\text{-}CH_3O—C_6H_4)_2NO$ XIV

$(p\text{-}CH_3O—C_6H_4)_2N—N(C_6H_4—OCH_3\text{-}p)_2$ XV

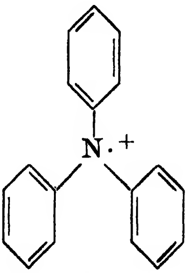
same free radical results also from the reaction between diphenylnitrogen oxide and tetra-*p*-anisylhydrazine, XV.[127]

Diphenylnitrogen oxide is a very unstable compound which cannot be kept without decomposition for more than about a day at room temperature. Some of its derivatives, however, are more stable. Di-*p*-anisylnitrogen oxide, XIV, for example, remains essentially unchanged for a year or more.

A different class of free radicals, which is commonly (but again inappropriately) said to contain quadrivalent nitrogen, consists of the so-called *aminium* cations. Although triphenylamine, XVI, for example, has almost no basic character at all, it can be transformed, in the presence of an oxidizing agent, into a peculiar and characteristic type of salt. Thus, by the action of bromine, there is formed the blue triphenylaminium tribromide, XVII, the cation of which doubtless resonates among such structures as XVIII–XX. Since this compound is

$(C_6H_5)_3N$ XVI

$[(C_6H_5)_3N]^+Br_3^-$ XVII



XVIII

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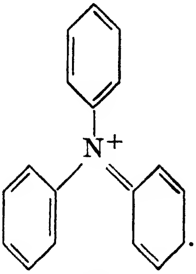
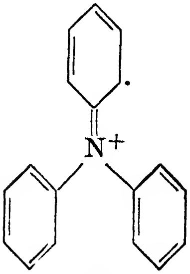
[127] H. Wieland and F. Kögl, *Ber.* **55**, 1798 (1922).



XIX



XX

extremely unstable, however, it has not been extensively studied. The best-known free radicals of this type are tri-*p*-tolylaminium picrate, XXI, tri-*p*-tolylaminium perchlorate, XXII, and tetra-*p*-tolylhydrazinium perchlorate, XXIII.[128] The picrate is prepared by the reaction of the corresponding tertiary amine, XXIV, with lead dioxide in the presence of picric acid; the two perchlorates are prepared by the reaction of the amine XXIV and the hydrazine XXV, respectively, with chlorine tetroxide $(ClO_4)_x$, which is itself made by the action of iodine upon silver perchlorate.[128] (Cf. also footnote *m* of Table 1·1, page 4.)

$$[(p\text{-}CH_3\text{—}C_6H_4)_3N]^+\ 2,4,6\text{-}(NO_2)_3C_6H_2\text{—}O^-$$

XXI

$$[(p\text{-}CH_3\text{—}C_6H_4)_3N]^+\ ClO_4^-$$

XXII

$$[(p\text{-}CH_3\text{—}C_6H_4)_2N\text{—}N(C_6H_4\text{—}CH_3\text{-}p)_2]^+\ ClO_4^-$$

XXIII

$$(p\text{-}CH_3\text{—}C_6H_4)_3N$$

XXIV

$$(p\text{-}CH_3\text{—}C_6H_4)_2N\text{—}N(C_6H_4\text{—}CH_3\text{-}p)_2$$

XXV

The above aminium cations do not associate appreciably to dimers, presumably because the monomeric forms are specially stabilized by resonance with structures like XIX and XX, no analogs of which can be written for the hypothetical dimer; and also because the steric repulsions of the bulky phenyl groups prevent the formation of a strong nitrogen-nitrogen bond; and finally because the positive charges lead to strong repulsions between the cations. The experimental evidence that dimerization does not occur is derived partly from the intense colors

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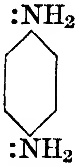
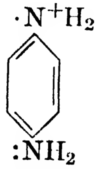
[128] E. Weitz and H. W. Schwechten, *Ber.* **59**, 2307 (1926), **60**, 1203 (1927).

of the salts, but most conclusively from magnetic measurements on tri-*p*-tolylaminium perchlorate, XXII.[119, 129]

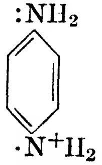
The semiquinones (Wurster's salts) related to *p*-phenylene diamine, XXVI, and its derivatives (cf. Section 2·7) are somewhat analogous to the aminium cations. Thus, the semiquinone cation obtained from the parent diamine, XXVI, can resonate among several structures like XXVII–XXIX. The reason why such semiquinones are most stable in acidic solution should now be apparent; for, in neutral or basic solution, the semiquinone would be electrically neutral, and so the resonance would then have to occur among such structures as XXX–XXXII,



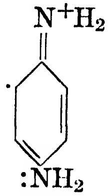
XXVI



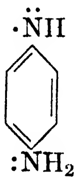
XXVII



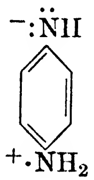
XXVIII



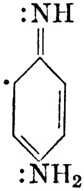
XXIX



XXX



XXXI



XXXII

some of which are relatively very unstable on account of their wide separations of charge. (Cf. Section 10·9.) That these semiquinones are really free radicals, like the ones containing oxygen in place of nitrogen, has been shown by both the potentiometric[113] and magnetic[119, 129, 130] methods.

An essentially different type of free radical, which may with some justification be said to contain quadrivalent nitrogen, can be illustrated by the electrically neutral ammonium NH_4.[131] This substance is not known in the pure state, but it can be obtained as an amalgam by the electrolysis of an aqueous ammonium salt with a mercury cathode, or by the reaction between an alkali-metal amalgam and an ammonium

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[129] P. Rumpf and F. Trombe, *Compt. rend.* **206**, 671 (1938); *J. chim. phys.* **35**, 110 (1938).

[130] L. Pauling and J. H. Sturdivant, quoted by L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, 1st ed., 1939, page 259, 2nd ed., 1940, page 279.

[131] Cf. J. W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Longmans, Green, and Company, London, Volume IV, 1923, pages 1005 ff.

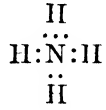
salt. Moreover, a solution of ammonium in liquid ammonia is formed at the cathode when a solution of ammonium chloride in that solvent is electrolyzed. The radical is rather unstable; it decomposes spontaneously, or whenever an attempt is made to isolate it, into ammonia and hydrogen. In its properties, it resembles an alkali metal; thus, its solution in liquid ammonia is blue (although the color rapidly fades as the ammonium decomposes), and its amalgam is an effective reducing agent that can, for example, reduce *p*-nitrophenol, XXXIII, to *p*-aminophenol, XXXIV.[132]


XXXIII


XXXIV

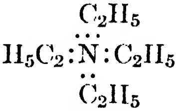
Tetraethylammonium $(C_2H_5)_4N$ also has been made in liquid ammonia solution, both by the electrolysis of tetraethylammonium iodide (or chloride) and by the action of metallic potassium upon tetraethylammonium chloride.[133] The resulting solution of this radical is again blue, but it soon becomes colorless. Schlubach and Ballauf have reported that, after the change in color has occurred, the radical can be shown (by the reaction with iodine to form tetraethylammonium iodide) to be still present in undiminished concentration. No explanation of this change in color without simultaneous decomposition can at present be given; obviously, the problem needs further investigation.

Ammonium and tetraethylammonium differ from all the other free radicals considered previously, in that each of the two ammoniums apparently contains a nitrogen atom with nine electrons in its valence shell. The exceptional electronic structures, XXXV and XXXVI, respectively, doubtless provide the explanation for the fact that the radicals can exist only in solution in a solvent like liquid ammonia or mercury.



$$\begin{array}{c} \mathrm{H} \\ \mathrm{H}:\overset{\cdots}{\underset{\cdot\cdot}{\mathrm{N}}}:\mathrm{H} \\ \mathrm{H} \end{array}$$

XXXV



$$\begin{array}{c} C_2H_5 \\ H_5C_2:\overset{\cdots}{\underset{\cdot\cdot}{\mathrm{N}}}:C_2H_5 \\ C_2H_5 \end{array}$$

XXXVI

In either of these solvents, the ammonium presumably behaves in the same way as does an alkali metal; that is to say, it dissociates into the corresponding positive ion and an electron. The positive ion is here, of course, an ammonium (rather than an alkali-metal) cation; its nitrogen atom now has only eight electrons in its valence shell

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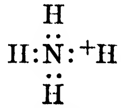
[132] S. Takagi, T. Ueda, and T. Sakaguti, *J. Pharm. Soc. Japan* **58**, 938 (1938); *C.A.* **33**, 2113 (1939).

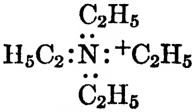
[133] H. H. Schlubach and F. Ballauf, *Ber.* **54**, 2811 (1921).

(structures XXXVII and XXXVIII). In liquid ammonia, the electron



$$\begin{array}{c}\mathrm{H}\\ \mathrm{H}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{N}}}:{}^{+}\mathrm{H}\\ \mathrm{H}\end{array}$$

XXXVII



$$\begin{array}{c}\mathrm{C_2H_5}\\ \mathrm{H_5C_2}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{N}}}:{}^{+}\mathrm{C_2H_5}\\ \mathrm{C_2H_5}\end{array}$$

XXXVIII

is solvated; it, rather than the ammonium radical or ion, is responsible for the blue color of the solution. In the amalgam, on the other hand, the electron becomes one of the so-called "conductivity electrons."

All metals are considered to consist of a more or less rigid framework, which is composed of the positively charged atomic kernels, and which is immersed in a "sea" of (almost) freely moving electrons. This picture explains, among other properties, the high electric conductivities of metals since, under an imposed electric field, the heavy kernels may remain stationary, and only the light conductivity electrons need move.[134]

15·20 Organometallic Analogs of the Hexaarylethanes.

Hexaphenyldigermanium, I, hexaphenyldilead, II, hexamethylditin, III,

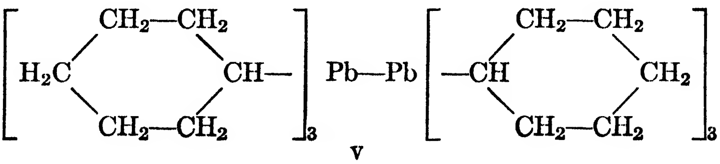
$(C_6H_5)_3Ge—Ge(C_6H_5)_3$
I

$(C_6H_5)_3Pb—Pb(C_6H_5)_3$
II

$(CH_3)_3Sn—Sn(CH_3)_3$
III

$(o\text{-}CH_3—C_6H_4)_3Sn—Sn(C_6H_4—CH_3\text{-}o)_3$
IV

hexa-*o*-tolylditin, IV, and hexacyclohexyldilead, V, have been considered



V

to dissociate into free radicals by rupture of the central metal-metal bonds. This opinion is supported by the chemical properties of the substances, and also by determinations of the apparent molecular weights in solution by both the melting-point and boiling-point methods. Some doubt is cast, however, by the fact that solutions of the compounds are colorless; completely conclusive evidence that *no* appreciable disso-

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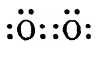
[134] Cf., for example, N. F. Mott and H. Jones, *The Theory of the Properties of Metals and Alloys*, Oxford University Press, Oxford, 1936.

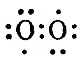
ciation occurs has been obtained by magnetic measurements.[135] The explanation of the anomalous molecular weights is not known. The properties of these compounds illustrate most forcibly the risk which is run when, merely on the basis of chemical behaviors and apparent molecular weights, conclusions are drawn regarding the existence of free radicals.

15·21 Biradicals. Ordinarily, a substance with an even number of electrons per molecule has no unpaired electrons, and hence is not a free radical. Conceivably, however, such a substance might have two unpaired electrons per molecule; it then would be a free radical or, more specifically, a *biradical.*

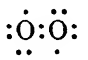
A few simple inorganic biradicals are known; the most familiar of these is oxygen O_2, which has been found spectroscopically[136] to have two unpaired electrons per molecule, and which therefore does not possess the structure, I, most commonly written for it. (Cf. pages 417 f.)


$:\overset{\cdot\cdot}{O}::\overset{\cdot\cdot}{O}:$

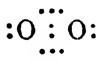
I


$:\underset{\cdot}{\overset{\cdot\cdot}{O}}:\underset{\cdot\cdot}{\overset{\cdot}{O}}:$

II


$:\underset{\cdot\cdot}{\overset{\cdot}{O}}:\underset{\cdot}{\overset{\cdot\cdot}{O}}:$

III


$:O\overset{\cdot\cdot\cdot}{\underset{\cdot\cdot\cdot}{:}}O:$

IV

Other biradicals of similar type include sulfur monoxide SO[137] and diatomic sulfur S_2.[138]

With the aid of the conventional symbols, the state of molecular oxygen can be described most conveniently as a resonance hybrid of structures II and III. The dots above and below the "oxygen atoms" are here intended to represent electrons in different "orbits" about the oxygen kernels; structures II and III are therefore not identical as they might appear to be. An alternative, but completely equivalent, description of the oxygen molecule is given by the single structure IV, in which the two oxygen atoms are linked to each other by one single covalent bond and by two *3-electron bonds.*[139] The 3-electron bonds, each of which is represented by 3 dots in a horizontal line, are in fact defined by the statement that structure IV implies resonance between structures II and III. Obviously, sulfur monoxide and diatomic sulfur can be assigned completely analogous structures.

The reason why oxygen has the biradical structure, IV, instead of the

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[135] For magnetic measurements on hexaphenyldigermanium, see P. W. Selwood, *J. Am. Chem. Soc.* **61**, 3168 (1939); hexaphenyldilead, see R. Preckel and P. W. Selwood, *ibid.* **62**, 2765 (1940); hexamethylditin and hexacyclohexyldilead, see H. Morris and P. W. Selwood, *ibid.* **63**, 2509 (1941); hexa-*o*-tolylditin, see H. Morris, W. Byerly, and P. W. Selwood, *ibid.* **64**, 1727 (1942).

[136] R. S. Mulliken, *Phys. Rev.* **32**, 880 (1928).

[137] E. V. Martin, *Phys. Rev.* **41**, 167 (1932).

[138] E. Olsson, *Z. Physik* **100**, 656 (1936).

[139] L. Pauling, *J. Am. Chem. Soc.* **53**, 3225 (1931).

expected structure, I, is now understood.[140] The mathematical complexities of the necessary quantum-mechanical treatment are, however, too great to be discussed here. With sulfur monoxide and diatomic sulfur, the theoretical explanations of the observed biradical structures are, of course, quite analogous to the one that applies to oxygen.

At the present time, it is not certain whether free methylene CH_2 is a biradical, with two unpaired electrons per molecule, or just an extremely reactive compound, with no unpaired electrons. The substance has been prepared by both the thermal[141] and the photochemical[142] decomposition of diazomethane CH_2N_2, and by the photochemical decomposition of ketene $CH_2{=}C{=}O$.[142,143] Inconclusive[144] evidence that the thermal decomposition of methane also gives free methylene has been advanced.[145]

The half-life of methylene varies with the nature of the carrier gas, and may be as long as 0.23 sec in nitrogen at about 1.5 mm pressure.[142] The compound can be detected by its ability to remove tellurium or selenium mirrors, with the production, respectively, of telluroformaldehyde $(CH_2Te)_x$ and selenoformaldehyde $(CH_2Se)_x$. Methylene also combines with iodine;[142] moreover, it attacks mirrors of antimony, but not those of zinc, cadmium, or lead.[141] At 140°–220°C, methylene dimerizes almost quantitatively to ethylene.[146] That more extensive polymerization is also possible is suggested by the fact that diazomethane is slowly converted at ordinary temperatures into a polymethylene $(CH_2)_x$. At temperatures ranging between 0°C and 50°C, methylene combines with ethylene to form unidentified products, but it does not react with nitric oxide.[143] At 400°–500°C, it combines with carbon monoxide to produce ketene.[147]

Biradicals with the general structure $\cdot CH_2(CH_2)_nCH_2\cdot$, where n ranges from 2 to 4, have been made by the reactions between polymethylene dihalides and sodium vapor.[148] These substances are very unstable, and they have relatively great tendencies to break up into

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[140] J. E. Lennard-Jones, *Trans. Faraday Soc.* **25**, 668 (1929); G. W. Wheland, *ibid.* **33**, 1499 (1937).

[141] F. O. Rice and A. L. Glasebrook, *J. Am. Chem. Soc.* **55**, 4329 (1933); **56**, 2381 (1934).

[142] T. G. Pearson, R. H. Purcell, and G. S. Saigh, *J. Chem. Soc.* **1938**, 409.

[143] M. Burton, T. W. Davis, A. Gordon, and H. A. Taylor, *J. Am. Chem. Soc.* **63**, 1956 (1941).

[144] Cf. E. W. R. Steacie, *Atomic and Free Radical Reactions*, Reinhold Publishing Corporation, New York, 1946, pages 87 f.; *Free Radical Mechanisms*, Reinhold Publishing Corporation, New York, 1946, pages 74 ff.

[145] Cf. L. S. Kassel, *J. Am. Chem. Soc.* **57**, 833 (1935).

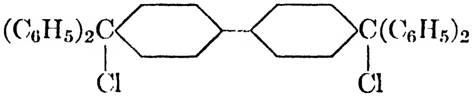
[146] E. W. R. Steacie, *J. Phys. Chem.* **35**, 1493 (1931).

[147] H. Staudinger and O. Kupfer, *Ber.* **45**, 501 (1912).

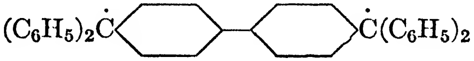
[148] C. E. H. Bawn and J. Milsted, *Trans. Faraday Soc.* **35**, 889 (1939).

smaller saturated and unsaturated fragments. They have not been extensively studied.

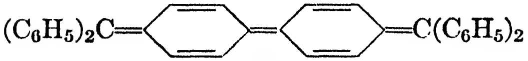
A few organic biradicals of long life have been prepared. Not all the compounds, however, which have in the past been considered biradicals actually belong to this class. For example, the hydrocarbon that is obtained by the action of zinc upon the dichloro compound, V, has a violet-red color, and it is rapidly decolorized by reaction with oxygen. Consequently, it was at one time assumed to be a biradical with structure VI. (For the sake of simplicity, the resonance with structures in which the unpaired electrons are upon carbon atoms of the rings is ignored here and throughout the remainder of this section.) A magnetic study has shown, however, that the compound is diamagnetic and hence not a biradical.[149] Its structure must therefore be written as VII.



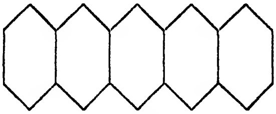
V



VI

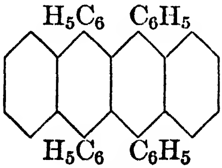


VII



VIII

Similarly, the blue pentacene, VIII, and the red 5,6,11,12-tetraphenylnaphthacene (rubrene), IX, which can be readily oxidized by the air in the presence of light, are diamagnetic and hence are not free radicals.[149] These substances must therefore be resonance hybrids of structures like X and XI, respectively, without unpaired electrons.



IX

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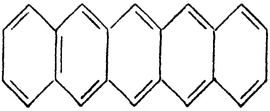
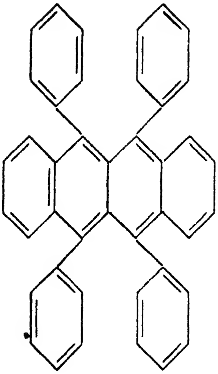
[149] E. Müller and I. Müller-Rodloff, *Ann.* **517**, 134 (1935).

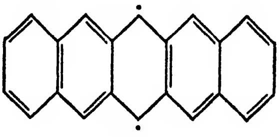


X

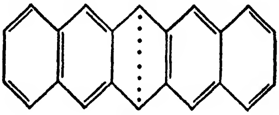


XI

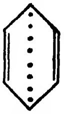
Not infrequently, the statement is made that the diamagnetic substances of the above types are really biradicals, but that the two unpaired electrons in each molecule have opposite spins. Such a statement is, however, theoretically unsound. If, for example, the two electrons represented by the dots in structure XII have oppo-



XII



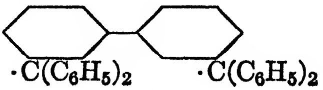
XIII



XIV

site spins, then by definition they are paired, and the structure in question is identical with XIII, with a formal bond. (See Section 10·8.) Since structure XIII can resonate with the doubtless much more stable ones like X, without formal bonds, the former structure, therefore, cannot represent the molecule of pentacene any better than the analogous Dewar structure, XIV, represents that of benzene.

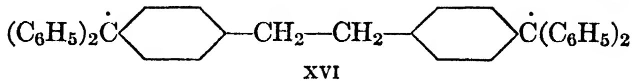
In summarizing the results of their magnetic measurements upon a number of both true and alleged biradicals, Müller and Müller-Rodloff stated [149] as a general rule that a substance is a biradical if, and only if, no structure with all electrons paired (but without formal bonds) can be written for it. Thus, the hydrocarbon with structure VII is not a biradical because this structure itself has no unpaired electrons (or formal bonds). Similarly, pentacene and rubrene are not biradicals, because structures X and XI, respectively, likewise have no unpaired electrons (or formal bonds). On the other hand, the hydrocarbon XV



XV

is a biradical because, for it, no *meta* quinoid structure without either unpaired electrons or formal bonds (or both) is possible; the compound apparently associates, however, either to a dimer or to some still higher polymer, since the observed paramagnetism is only a few per cent of that calculated for the biradical.[149]

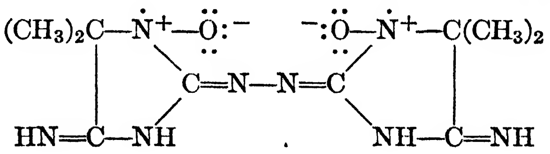
The biradicals oxygen, sulfur monoxide, and diatomic sulfur (discussed above) violate the rule just stated In addition to these definitely established exceptions to this rule, a few other exceptions, which may be only apparent, have also been reported. Thus, the hydrocarbon XVI



XVI

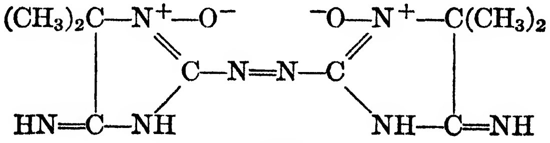
should be a biradical since for it, just as for the hydrocarbon XV, no quinoid structure is possible. Although Wittig and Leo reported[150] that the apparent molecular weight of the substance in benzene indicates only a slight dimerization (or polymerization), Müller and Bunge subsequently found[151] that the material is diamagnetic both in the solid state and in benzene solution, and hence that it is not a biradical. Presumably, therefore, the measured molecular weights are again unreliable (cf. pages 685 f. and Section 15·20), or else the biradical XVI rapidly decomposes or disproportionates in some way to more stable diamagnetic products with comparatively low molecular weights. Although the situation is thus not entirely clear, there is no need here to assume that the rule of Müller and Müller-Rodloff is violated.

A different type of exception can be illustrated with porphyrindine. Since this substance is paramagnetic, it apparently must be assigned the biradical structure XVII (cf. structures II and III, page 734), even



XVII

though the alternative structure, XVIII, without unpaired electrons, can



XVIII

also be drawn.[152] The paramagnetism increases, however, as the tem-

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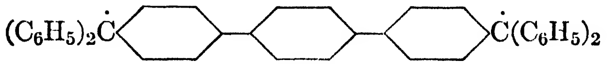
[150] G. Wittig and M. Leo, *Ber.* **61**, 854 (1928).

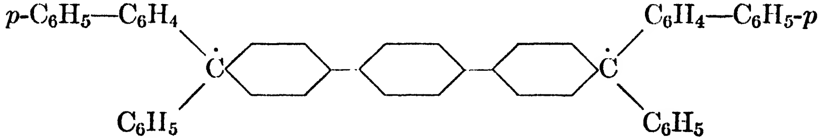
[151] E. Müller and W. Bunge, *Ber.* **69**, 2164 (1936).

[152] E. Müller and I. Müller-Rodloff, *Ann.* **521**, 81 (1936).

perature is raised. Presumably, therefore, an equilibrium exists between the two forms XVII and XVIII, with the latter the more stable. The *ground state* of the molecule is therefore diamagnetic, as predicted. From the temperature coefficient of the paramagnetism, the form XVIII has been calculated to be more stable than the biradical form, XVII, by about 0.56 kcal per mole.[152] Moreover, the two terphenyl derivatives, for which the biradical structures, XIX and XX (cf. structure VI), and

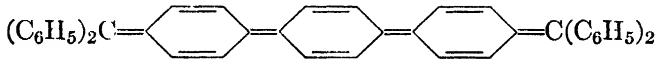


XIX

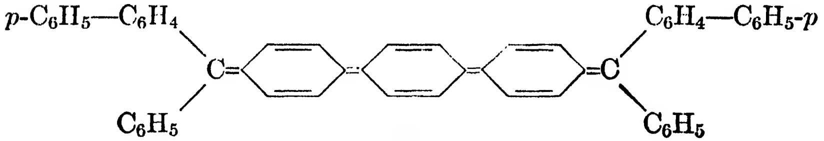


XX

the respective quinoid structures, XXI and XXII (cf. structure VII),



XXI



XXII

must be considered, are apparently analogous to porphyrindine. Each of these compounds is paramagnetic both in the solid state and in benzene solution; in solution, the relative amount of each compound that is in the biradical form increases as the temperature is raised.[153] These variations with the temperature may be due to changes in the positions of the equilibria between the monomeric biradicals (XIX and XX) and diamagnetic dimers or polymers; or they may be due instead to changes in the positions of the equilibria between the biradicals (XIX and XX) and the monomeric quinoid forms (XXI and XXII, respectively). If the latter interpretation is the correct one, then the direction in which the equilibria change with the temperature shows that, just as with porphyrindine, the diamagnetic forms have lower energies than do the biradical forms. The rule of Müller and Müller-Rodloff is therefore not necessarily violated.

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[153] E. Müller and H. Pfanz, *Ber.* **74**, 1051 (1941).

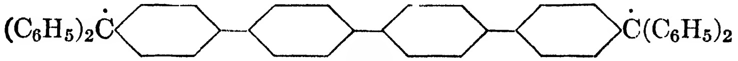
The further terphenyl derivative, with structure XXIII or XXIV,

XXIII

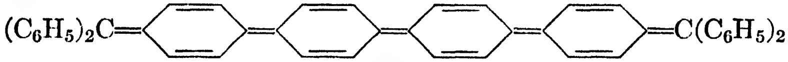
XXIV

like the two preceding hydrocarbons, is paramagnetic both in the solid state and in benzene solution.[153] With this compound, however, the fraction of the material which is in the biradical form is practically independent of the temperature; here, therefore, if there is an equilibrium between the biradical form, XXIII, and the quinoid form, XXIV, the two forms must have practically the same energy. The data are not sufficiently precise to show which form is the more stable; hence it is not certain whether this terphenyl derivative is a real, or only an apparent, exception to the rule of Müller and Müller-Rodloff.

In the quaterphenyl series, the hydrocarbon with structure XXV or XXVI has also been studied.[154] This compound, like its terphenyl analog (XIX or XXI), is paramagnetic both in the solid state and in benzene solution. Since the fraction of the material which is in the biradical form, XXV, increases with the temperature, it is once more possible that the quinoid structure, XXVI, is more stable than is the biradical structure, XXV.

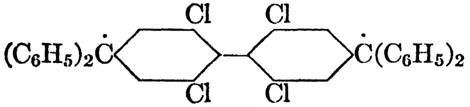


XXV

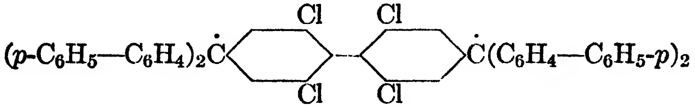


XXVI

Some clearly only apparent exceptions to the rule of Müller and Müller-Rodloff are represented by the compounds XXVII and XXVIII,



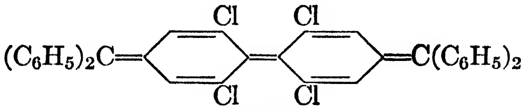
XXVII



XXVIII

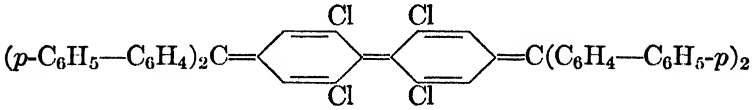
[154] E. Müller and H. Pfanz, *Ber.* 74, 1075 (1941).

which are biradicals,[155] even though the alternative structures, XXIX



XXIX

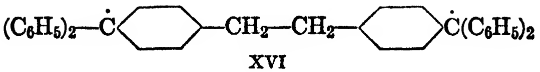
and XXX, respectively, can also be written. (These biradicals associate



XXX

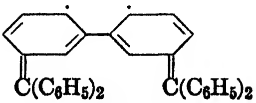
to diamagnetic dimers or polymers.) Here, however, the quinoid structures, XXIX and XXX, require the two central rings to be coplanar; since such coplanarity is made impossible by the four chlorine atoms (see Section 6·12), these structures are doubtless greatly strained by the thus-required rotation about the central carbon-carbon double bond. Consequently, although diagrams XXIX and XXX can be written on paper, they cannot represent stable structures of the respective molecules. The observed paramagnetisms are therefore not really in conflict with the rule of Müller and Müller-Rodloff.

In the calculations of the relative amounts of paramagnetic biradical and diamagnetic isomer, dimer, or polymer, the assumption has usually been made that the contribution of a biradical to the paramagnetic susceptibility is just twice that of a free radical with only one unpaired electron. This assumption, however, is doubtless incorrect with many of the compounds to which it has been applied; it is, in fact, valid only when the two unpaired electrons are completely independent of each other, as they are when they are in different molecules, or when they are "insulated" from each other by a chain of saturated atoms, as in structure XVI. (For discussion



XVI

of this compound, however, see above.) In the biradicals XV, XVII, XIX, etc., however, the two unpaired electrons are able to interact strongly, as can be seen most easily if the possibilities for resonance are taken explicitly into account. The compound represented above by structure XV, for example, must actually be a resonance hybrid of a great many structures; one of these structures is XXXI, in



XXXI

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[155] E. Müller and H. Neuhoff, *Ber.* **72**, 2063 (1939); E. Müller and E. Tietz, *ibid.* **74**, 807 (1941).

which the two unpaired electrons are upon fairly close carbon atoms. Consequently, the electrons can interact fairly strongly with each other. Under these circumstances, the paramagnetic susceptibility of the biradical is not twice, but $\frac{8}{3}$, as great as is that of a radical with only one unpaired electron. (Cf. page 693.) Consequently, the reported concentrations of biradical should be multiplied by the constant factor $\frac{3}{4}$. (In quantum-mechanical terminology, such a biradical does not consist of two independent parts, each of which is in the *doublet* state characteristic of a free radical with one unpaired electron, but it is instead a single unified system in the *triplet* state characteristic of a molecule with two unpaired electrons.)

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