Electronic Mechanisms
of
Organic Reactions

ALLAN R. DAY

ASSOCIATE PROFESSOR OF ORGANIC CHEMISTRY
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

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Preface

This book represents an attempt to systematize organic chemistry through the use of electronic mechanisms. It is not intended in any way to take the place of the several excellent books now available in the field of theoretical organic chemistry, but rather it must depend on these books for its physical background. The rapid progress of theoretical chemistry has done much to clarify the complexities of organic chemistry, but unfortunately little effort has been made to present these new developments to students in organic chemistry. It is true that students at the undergraduate level rarely have sufficient background to grasp the real significance of the contributions made to organic chemistry by kinetic studies, the quantum-mechanical concept of resonance, etc. It is possible, however, to adapt these principles to undergraduate teaching, thereby placing the emphasis on why reactions occur rather than on the mere fact that they do occur. This emphasis not only introduces a continuity of thinking into the subject of organic chemistry but stimulates the student to think for himself.

The notes on which this book is based were developed over a period of several years. Much of the material has been presented to undergraduate and graduate students and several revisions have been made as a result of these experiences. When presented to undergraduates it has been found convenient to incorporate this work with the usual descriptive material included in courses in organic chemistry. To the advanced students in organic chemistry the notes have served two useful purposes: (1) reviewed fundamental organic chemistry through the use of electronic mechanisms; and (2) stimulated an interest in the modern approach to the study of organic reactions.

It is recognized that with the accumulation of more data many changes in current electronic mechanisms will be necessary. It is hoped that future revisions of this volume will keep it abreast of the times through the inclusion of new material as it becomes available.

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CHAPTER I

Valence Bonds

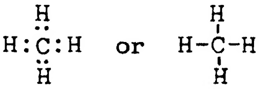
The unique ability of carbon to form stable bonds with other carbon atoms as well as with atoms of other elements accounts for the tremendous number of known carbon compounds. The huge number of carbon compounds, with their varied reactions, has made it necessary to incorporate them under a separate heading, namely, the chemistry of carbon compounds or organic chemistry. This separation from inorganic chemistry, although necessary from a practical viewpoint, has led to a very undesirable result. The belief, held by many in the past, that inorganic reactions and organic reactions are fundamentally different was due in part to this division. Other factors, such as the complex structures of many organic molecules, have also contributed to this belief. The idea that inorganic reactions are essentially ionic and organic reactions are essentially nonionic, and thus are radically different, still persists to some extent. Actually the reactions of the two types of compounds are governed by the same fundamental principles and the apparent differences tend to merge when these principles are applied. A clear understanding of the nature of valence bonds is essential for the study of organic reactions.

The Lewis formulation of valence bonds is well known to chemists (1). According to this theory, when atoms combine they do so by a mutual redistribution of their extranuclear electrons. In most cases this redistribution is such that in the compound formed each atom now has the electronic configuration of an atom of one of the inert elements, a structure expected to confer stability on the molecule.

Thus, hydrogen atoms combine

$$H\cdot \;+\; H\cdot \longrightarrow H{:}H \quad \text{or} \quad H-H$$

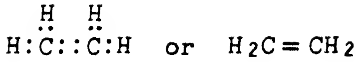
by a sharing of their respective electrons and in the resulting molecule each hydrogen atom has now the electronic structure of helium. Similarly, the valence bonds of methane



$$\begin{array}{c}H\\ H{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}{:}H\\ H\end{array} \quad \text{or} \quad \begin{array}{c}H\\ |\\ H-C-H\\ |\\ H\end{array}$$

represent shared electron pairs. The carbon atom with four electrons originally in its valence shell now has an octet and the electronic structure of neon, and since these pairs are shared, each hydrogen atom at the same time has the helium configuration.

Double and triple bonds are also due to the sharing of electrons and represent two and three pairs, respectively. Thus we write ethylene



$$\mathrm{H}:\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}::\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}:\mathrm{H} \quad \text{or} \quad \mathrm{H_2C{=}CH_2}$$

and acetylene

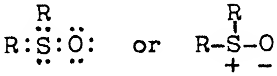
$$\mathrm{H}:\mathrm{C}:::\mathrm{C}:\mathrm{H} \quad \text{or} \quad \mathrm{HC{\equiv}CH}$$

The bonds formed by the sharing of electrons by the bound atoms are termed covalent bonds.

In addition to covalent bonds, we have the ionic bonds which result when the atoms combine by transfer of one or more electrons from one atom to another. For example, the bond in sodium chloride is due to the transfer of the single electron of the valence shell of the original sodium atom to the valence shell of the chlorine atom which originally contained seven electrons. Due to this transfer the combined sodium and chlorine atoms are now ions, being positively and negatively charged and having the electronic configurations of neon and argon, respectively. Their opposite electric charges bind the ions together in this case.

$$\mathrm{Na}\cdot + \cdot\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{Cl}}}: \longrightarrow \overset{+}{\mathrm{Na}} + :\underset{\cdot\cdot}{\overset{-}{\overset{\cdot\cdot}{\mathrm{Cl}}}}: \quad \text{or} \quad \overset{+}{\mathrm{Na}}\ \overset{-}{\mathrm{Cl}}$$

Another type of bond is frequently met and is called a semipolar bond. This bond occurs when one of the bound atoms supplies both electrons of the pair shared by the two atoms. For example, a count of the electrons in the formulation of a dialkyl sulfoxide shows that the pair of electrons forming the bond between sulfur and oxygen is supplied by the sulfur atom:



$$\mathrm{R}:\underset{\cdot\cdot}{\overset{\overset{\mathrm{R}}{\cdot\cdot}}{\mathrm{S}}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\mathrm{O}}}: \quad \text{or} \quad \mathrm{R}-\underset{+}{\overset{\overset{\mathrm{R}}{|}}{\mathrm{S}}}-\underset{-}{\mathrm{O}}$$

In acquiring a share in a pair of electrons which belong to sulfur, the oxygen atom takes on a fractional negative charge. As a result of its electron sharing, the sulfur acquires a corresponding positive charge.

In the sharing and transfer of electrons it was recognized by Lewis that the pairing of electrons is more important than the formation of octets of electrons in the valence shells of the combined atoms. It is now known that the electron acts as if it is not a point particle but possesses a spin, the angular momentum of which can be oriented by a magnetic field in either one of only two directions. Furthermore, two electrons of any atom, with their energies and motions otherwise the same, must have opposite spin orientations. For example, the two electrons in the normal helium atom are both in the lowest energy level, the K shell, and have identical behaviors except for their opposite spins. These electrons are called paired electrons.

The formation of the hydrogen molecule is due to the pairing of electrons in this sense. Each of the original hydrogen atoms has a single or unpaired electron. When these atoms join, these two electrons are paired and, if in the normal state of this molecule they are shared, each hydrogen atom has the electronic configuration of the helium atom. In the formation of sodium chloride, the original sodium atom has only one unpaired electron and the original chlorine atom only one, the other six of the chlorine atom being already paired up. Sodium chloride forms by pairing these two originally unpaired electrons.

Resonance. The Lewis theory of valence bonds has been clarified and improved in the last ten years by the use of a new concept called resonance (2, 3). An understanding of this concept may be obtained by consideration of its application to bonds of the type just discussed.

Consider the bond in the hydrogen molecule. The Lewis formula, H:H, does not imply that the electrons have a static position midway between the two nuclei. The electrons are so small and light, and are moving so rapidly that it is impossible to tell their exact positions at any time. Quantum mechanical theory (4) shows that if the electrons are paired in the sense described above, their motions are identical except for their spins, and such that they spend most of their time midway between the nuclei. There is a high probability of finding them between the nuclei at any time and this is taken as their average position.

We must realize that the net attraction holding the particles together is the result of the attractions of the positively charged nuclei for the negatively charged electrons, these attractions outweighing the repulsions between the two electrons and between the two nuclei. If the two atoms acted independently in the sense that each nucleus would attract only one electron, the one originally associated with it, the net attraction between the atoms would be so low that no stable molecule would result. The electrons, however, would be expected to exchange nuclei readily in the course of their motion because of the symmetry of the system and the identical patterns of the motion of the electrons in the separate atoms. The result of this exchange is that the electrons move about both atoms and each nucleus attracts both electrons. This is the nature of the sharing of the paired electrons and this exchange of the electrons results in a high net attraction of the particles in the molecule, so that the hydrogen atoms are bound firmly together.

Obviously, no single diagram such as the Lewis formulation can show this exchange and portray adequately the structure it confers on the molecule. The quantum mechanical theory which makes quantitative calculation of the strength of the bond does so in a complex mathematical way, yet the fundamental principle of this calculation provides a rather simple way of describing the bond.

The molecule is pictured as a hybrid of several structures which are said to be in resonance with each other. Thus, if we label the electrons and nuclei in the hydrogen molecule, the actual structure described above can be considered a resonance combination of the following structures:

$$\begin{array}{ccc} \mathrm{H}\dot{_1}\ \ \dot{_2}\mathrm{H} & \text{and} & \mathrm{H}\dot{_2}\ \ \dot{_1}\mathrm{H} \\ A \quad\ B & & A \quad\ B \\ \mathrm{I} & & \mathrm{II} \end{array}$$

Structure I pictures electron 1 associated with nucleus *A* and electron 2 associated with nucleus *B*. Structure II pictures electron 2 associated with nucleus *A* and electron 1 with nucleus *B*. These two structures are identical since the electrons are indistinguishable, but the exchange of electrons bestows a lowered energy on the system and the resultant bond is stronger than if either of the separate structures I or II persisted as the actual one for the molecule. This lowering of the energy is termed the resonance energy. It should be noted that this description does not picture the actual molecule as a mixture of molecules, some of structure I and some of structure II. There is only one kind of molecule, and its structure is a sort of average of structures I and II, but of lower energy than either of the two.

The quantum mechanical treatment reveals that more than two structures may contribute to the actual structure. We may say that the actual single structure is a hybrid of several structures. Surprisingly enough, this is the case even with hydrogen. If we recall the way in which the electrons can, by resonance or exchange, move about both atoms to form the normal molecule, then it seems possible that part of the time both electrons will be associated with only one of the two nuclei. Due to the high rapidity of electron motion, this behavior would average up to the actual structure with the electrons midway between the nuclei and with each nucleus attracting both electrons. Here the individual or separate structures in resonance would be:

$$\begin{array}{ccc} \overset{-}{\mathrm{H}}\!:\ \overset{+}{\mathrm{H}} & \text{and} & \overset{+}{\mathrm{H}}\ :\!\overset{-}{\mathrm{H}} \\ A \quad\ B & & A \quad\ B \\ \mathrm{III} & & \mathrm{IV} \end{array}$$

These separate structures do indeed have a slight stability according to the calculations of quantum mechanics, but, as expected from the instability of a negatively charged hydrogen ion, these structures are not as stable as structures I and II. For this reason, they contribute less to the actual structure of the molecule.

In general, the actual structure of the molecule will be closest that of the resonant structure which is of lowest energy. Furthermore, the resonance energy will be greatest when, of the resonant structures, two or more of the lowest energy structures are of equal or nearly equal energy. We should predict this intuitively since the electron exchange or resonance would be expected to take place most readily if the structures between which the exchange takes place have equal energies.

The higher the resonance energy, the lower the energy of the molecule and the more stable that molecule. The resonance energy is a measure of how much the actual structure of the molecule is different from, and more stable than, any of the structures of which it is a hybrid. The four resonant structures pictured for the hydrogen molecule are the only ones of any considerable stability that may be conceived for this molecule. As just explained, the first two are of equal energy and their energy is much lower than that of the last two. The contribution of the last two forms is noticeable only because these two ionic forms are equivalent. We see that the bond in this molecule, even though it is made up of two identical atoms, is partly ionic although predominantly covalent. As this suggests, no actual bond between any two atoms is purely covalent or purely ionic.

Structural requirements for resonance. Before proceeding with the application of resonance theory to the description of the bonds in more complex molecules, we must set down the two important requirements that the structures must fulfill in order to participate in resonance. First, they must have the same number of unpaired electrons. This was the case with the structures pictured for the hydrogen molecule.

Second, the relative positions of the atomic nuclei in these structures must be very nearly the same. This is to be expected, because if the nuclei are not in almost exactly the same positions these structures will differ greatly in energy. It is not possible for the dense nuclei to take part in exchange effects such as the electrons execute. The second requirement was also met by the structures proposed for the resonance in the hydrogen molecule. While the nuclei in the ionic structures are not expected to be exactly the same distance apart as in the covalent ones, still the nuclei are not at fixed distances apart. The nuclei do vibrate rapidly through small distances about their equilibrium positions and thus there would be an overlapping of the effective nuclear positions in the hypothetical purely ionic and purely covalent structures.

Where more than two atoms are present in the molecule, the requirement of a fixed nuclear arrangement becomes more evident. The triatomic

A–B–C and A–C–B

structures cannot resonate with each other to produce a single hybrid of a structure average of the two. Even if these two forms are in rapid chemical equilibrium, the system which they comprise is a mixture of two different isolable molecules, called isomers. The most rapid of these chemical equilibria are the tautomeric equilibria, but even here mixtures rather than single forms are demonstrable. Once again it should be noted that resonant structures are only imaginary ones by means of which we can describe the real and single structure of the molecule. If each of the resonant structures we use to describe the molecule were a real substance, we would not obtain the chemical and physical properties of the actual molecule by mixing these substances together. We shall meet this important difference between resonance and tautomerism many times in the discussions following.

Effect of the electronegativity of bound atoms. Since the bond joining two atoms in a molecule is never purely covalent or purely ionic, it is convenient to describe a bond which is essentially covalent by calling it a covalent bond with partial ionic character. The amount of ionic character depends upon the difference in the electronegativities of the bound atoms. The electronegativity of an element is the attraction its atom has for electrons when the atom is combined in a molecule. The most electronegative element is fluorine, the least electronegative is cesium. Of the elements most frequently found in organic compounds, hydrogen and phosphorus are the least electronegative; carbon, sulfur, and iodine are about equally electronegative; while the most electronegative are, in increasing order, bromine, nitrogen, chlorine, and oxygen.

A normal covalent bond may be defined as one between two identical or two very similar atoms. The bond in the hydrogen molecule is a normal covalent bond. The ionic character of a normal covalent bond is small, due to the instability of the ionic structures which contribute to the resonance causing the bond.

If in the molecule A—B the atoms A and B differ appreciably in electronegativity, say B is more electronegative than A, then the first of the two resonating structures, $\overset{+\,-}{\mathrm{AB}}$ and $\overset{-\,+}{\mathrm{AB}}$, will possess considerable stability and will certainly be more stable than the ionic structures, $\overset{+\,-}{\mathrm{AA}}$ and $\overset{+\,-}{\mathrm{BB}}$, which would contribute slightly to the structure of the molecules A—A and B—B. This being the case, the ionic structure $\overset{+\,-}{\mathrm{AB}}$ will contribute appreciably to the actual structure of A—B and the resonance energy will be greater than if the bond were a normal covalent bond.

As a test for this extra stability conferred on the bond by its increased ionic character, Pauling (2) has proposed a comparison of the strength of the bond with that of a normal covalent bond between the two atoms. This comparison assumes that if the bond in A—B were a normal covalent bond, its bond energy (that is, the energy required to break the bond) would be the arithmetic mean of the bond energies in the truly normal covalent molecules A—A and B—B.

In the cases for which the necessary data are available, the actual bond strength is greater than the normal covalent bond value so calculated. Furthermore, the difference depends on the relative electronegativities of the bound atoms in the manner expected. For example, the bond energies of hydrogen, H—H, and fluorine, F—F, are 103.4 and 63.5 kcal. per mole, respectively. The arithmetic mean of these is 83.5 kcal. per mole, which according to this procedure would be the bond strength for H—F if the bond were a normal covalent one. The actual bond strength is 147.5 kcal. per mole, showing an increased bond energy of 64.0 kcal. per mole due to the high difference in the electronegativities of hydrogen and fluorine, which gives the bond its high percentage of ionic character. In H—Cl the electronegativity difference of the bound atoms is less and the increase in bond energy over the normal covalent value is only 22.1 kcal. per mole. The corresponding values for H—Br and H—I are 12.5 and 1.6, respectively.

It should be pointed out that the above discussion is not restricted only to the particular bonds which were used as examples. All bonds will possess some ionic character and to some extent will behave like ionic bonds. The positive and negative charges associated with all bonds may attract negative and positive centers in other molecules and this attraction may be regarded as the initial step in many reactions. Other important factors are also involved and the mere fact that electrostatic attractions are set up does not necessarily mean that a reaction will occur, with the breaking of old bonds and the formation of new ones. The energies involved in the breaking and formation of bonds obviously must be considered in any quantitative approach to a study of reactions. Fortunately, it is possible to formulate some simple rules which are quite useful for qualitatively predicting the course of many organic reactions. These will be developed in appropriate places in the chapters on reaction mechanisms.

In addition to the large number of organic reactions which simulate ionic reactions, there is another type which follows a radical mechanism. Reactions of this type involve a pairing and unpairing of electrons rather than the sharing and unsharing of electron pairs characteristic of the "ionic" reactions. Many examples of both types will be discussed in Chapters II–XXX.

CHAPTER II

Reaction of Paraffin or Alkane Hydrocarbons

In general the paraffin hydrocarbons are stated to be relatively inert. They do, however, undergo substitution reactions under suitable conditions. Substitution occurs readily with chlorine or bromine in the presence of sunlight.

Photohalogenation is best explained on the basis of a chain mechanism. Under the influence of sunlight, the halogen molecule dissociates and the free halogen atoms then attack the hydrocarbon. There is some evidence that the mechanism involves an intermediate free radical (5):

$$:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}: \rightleftharpoons 2:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}\cdot$$

$$CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl$$

$$CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$

The chain may be terminated by the recombination of chlorine atoms or by the combination of the chlorine atom with the free methyl radical, $CH_3\cdot + Cl\cdot \longrightarrow CH_3Cl$. Continuation of the above process may lead to the formation of tetrachloromethane. Bromine reacts less readily than chlorine, and iodine does not react. Halogenation at elevated temperatures (thermal halogenation) undoubtedly follows a similar mechanism. Reactions in which the attacking reagent is an atom or a free radical are referred to as radical reactions and involve the simultaneous pairing and unpairing of electrons. Atoms and free radicals are neutral in character and owe their activity to the possession of single unshared electrons. The fact that the chlorination of ethane is accelerated by the presence of tetraethyl lead (6) also supports a radical mechanism. The formation of free ethyl radicals from the thermal decomposition of tetraethyl lead has been demonstrated by Paneth and co-workers (7).

In the above reaction, two bonds are broken, C–H and Cl–Cl, and two new bonds formed, C–Cl and H–Cl. Energy is absorbed in the breaking of the first two bonds, and energy is given up in the formation of the last two bonds. The over-all energy change may be expressed as the heat of the reaction (in calories). It has been shown that for the reaction

$$-\underset{|}{\overset{|}{C}}-H + X-X \longrightarrow -\underset{|}{\overset{|}{C}}-X + H-X$$

heat is evolved when X = Cl. Only about one-third as much heat is given off when X = Br, and if iodine were to react, heat must be absorbed. Thus there is a decrease in energy in the reactions with chlorine and bromine. Since such a decrease may be considered to be a measure of the driving force of the reaction, it is obvious that iodine would have the least tendency to react.

The paraffin hydrocarbons also undergo substitution reactions with concentrated nitric acid at elevated temperatures. Nitrations with nitric acid or fuming nitric acid have all of the characteristics of a radical type reaction, although the exact nature of the attacking radical has not been established.

$$RH + HONO_2 \longrightarrow \underset{\text{nitroparaffin}}{RNO_2} + HOH$$

$$CH_4 + HONO_2 \longrightarrow \underset{\text{nitromethane}}{CH_3NO_2} + HOH$$

In some cases the action of nitric and sulfuric acids as substituting agents requires the assumption that they are electrophilic (electron-seeking) reagents. The polarizations which correspond to the known courses of ionization

$$\underset{+}{H}-\underset{-}{O}NO_2 \quad \text{and} \quad \underset{+}{H}-\underset{-}{O}SO_2OH$$

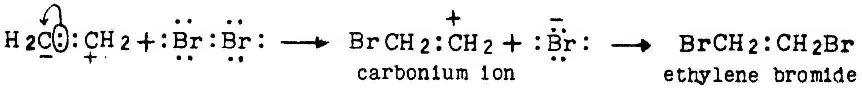
do not give rise to the required electrophilic reactants and hence could not initiate substitution reactions. These reactions will be discussed in greater detail in the section on aromatic hydrocarbons.

CHAPTER III

Reactions of Olefin or Alkene Hydrocarbons

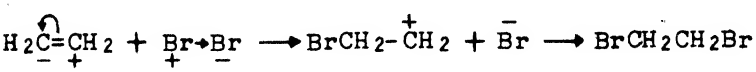
The characteristic linkage of the alkenes is a covalent bond consisting of two pairs of electrons between two carbon atoms. In the symmetrical olefins it may be assumed that the electrons are shared equally by the two unsaturated carbon atoms. The most characteristic reactions of these unsaturated compounds are of the addition type and may be explained by a common mechanism. Addition appears to be initiated by a polarization of the double bond, which may be represented by $H_2\overset{\curvearrowleft}{\underset{-}{C}}\!:\!\underset{+}{C}H_2$ or simply $H_2\overset{\curvearrowleft}{\underset{-}{C}}{=}\underset{+}{C}H_2$. Such a displacement of an electron pair is called an electromeric displacement and is facilitated by the close approach of positive ions or polarized molecules. As a result of this displacement one pair of electrons from the double bond becomes available for addition. In other words, the molecule becomes activated as a result of the electromeric shift. The shift must either precede or occur simultaneously with the addition. Multiple bonds are necessary for this effect to operate. Reactions which depend on an electromeric shift are often called "ionic reactions." The positive and negative poles resulting from the shift of an electron pair may then undergo addition with other free poles which are opposite in sign. The olefin linkage adds many electrophilic reagents, such as the halogens, hydrogen halides, sulfuric acid, and hypochlorous acid. Electrophilic or electron-seeking reagents furnish electron-poor ions (cations) which acquire electrons or a share in electrons belonging to some other atom or ion.

The addition of bromine to ethylene may be represented as follows:



$$H_2\overset{\curvearrowleft}{\underset{-}{C}}\!:\!\underset{+}{C}H_2 + :\ddot{\underset{..}{Br}}:\ddot{\underset{..}{Br}}: \longrightarrow \underset{\text{carbonium ion}}{BrCH_2:\overset{+}{C}H_2} + :\overset{-}{\ddot{\underset{..}{Br}}}: \longrightarrow \underset{\text{ethylene bromide}}{BrCH_2:CH_2Br}$$

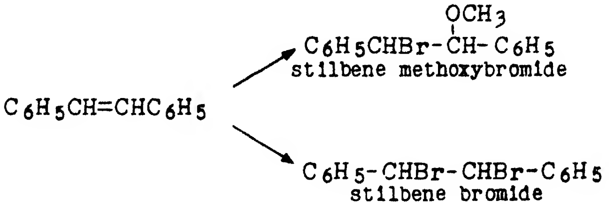
or



$$H_2\overset{\curvearrowleft}{\underset{-}{C}}{=}\underset{+}{C}H_2 + \underset{+}{Br}\rightarrow\underset{-}{Br} \longrightarrow BrCH_2{-}\overset{+}{C}H_2 + \overset{-}{Br} \longrightarrow BrCH_2CH_2Br$$

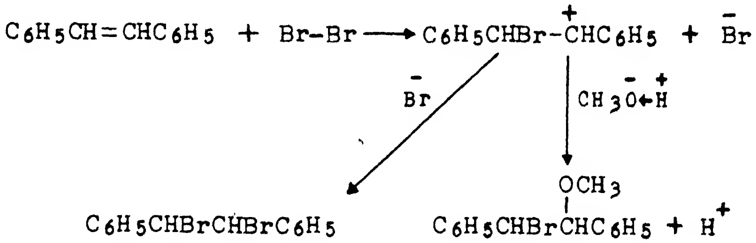
The course of the reaction involves the primary entry of a positive halogen with the formation of a carbonium ion (positive charge on carbon) which then combines with the negative bromide ion. This course is in accord with the observation that 1-chloro-2-bromoethane is formed from ethylene and bromine in neutral sodium chloride solution (8). Ethylene bromide is formed also, but no ethylene chloride. Chlorine adds most readily to the olefins, and iodine least readily.

Support for the primary entry of a positive halogen is found in a kinetic study made by Bartlett and Tarbell (9). They investigated the reaction of stilbene with a methyl alcohol solution of bromine:



$$C_6H_5CH{=}CHC_6H_5 \rightarrow C_6H_5CHBr\text{-}\overset{OCH_3}{\overset{|}{C}}H\text{-}C_6H_5 \quad ; \quad C_6H_5CH{=}CHC_6H_5 \rightarrow C_6H_5\text{-}CHBr\text{-}CHBr\text{-}C_6H_5$$

The methoxybromide is the chief product. The kinetic data obtained by these authors show that the reaction can be represented satisfactorily only as follows:



$$C_6H_5CH{=}CHC_6H_5 + Br\text{-}Br \rightarrow C_6H_5CHBr\text{-}\overset{+}{C}HC_6H_5 + \overset{-}{Br}$$

$$C_6H_5CHBr\text{-}\overset{+}{C}HC_6H_5 \xrightarrow{\overset{-}{Br}} C_6H_5CHBrCHBrC_6H_5 \qquad C_6H_5CHBr\text{-}\overset{+}{C}HC_6H_5 \xrightarrow{CH_3\overset{-}{O}\leftarrow\overset{+}{H}} C_6H_5CHBr\overset{OCH_3}{\overset{|}{C}}HC_6H_5 + H^+$$

It was concluded that methyl hypobromite was not responsible for the formation of the methoxy compound.

It is unlikely that bromine ionizes into positive and negative ions and therefore a positive bromine ion can scarcely initiate the reaction. However, the halogen molecule acts as an electrophilic reagent. The evidence for a two-step reaction with the initial addition of a positive halogen appears to be conclusive. Additional evidence for the manner in which bromine adds to olefin bonds will be found on page 265.

At high temperatures the alkenes react with chlorine or bromine to form substitution products. It is probable that these reactions are similar to the thermal halogenation of the alkanes and involve the formation of free halogen atoms:

$$CH_2{=}CH\text{-}CH_3 + Cl\cdot \rightarrow CH_2{=}CH\text{-}CH_2\cdot + HCl$$

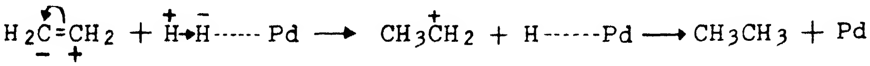
propylene

$$CH_2{=}CH\text{-}CH_2\cdot + Cl_2 \rightarrow CH_2{=}CH\text{-}CH_2Cl + Cl\cdot$$

allyl chloride

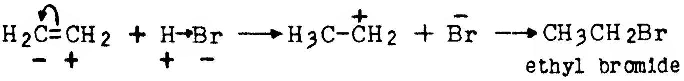
It is interesting to note that substitution occurs only above certain temperature limits and below these limits the main reaction is addition (10). This indicates that primary dissociation of the halogen molecule is necessary for substitution.

Isolated olefin bonds, in general, show little tendency to undergo hydrogenation with atomic hydrogen (H·). Molecular hydrogen is inactive also except in the presence of a catalyst such as Pt, Pd, or Ni. It is probable that the catalysts function as electrophilic reagents and thus assist in the formation of a cation, the latter serving to initiate addition to the double bond. This may be shown as follows:



$$\underset{-\ \ +}{H_2C{=}CH_2} + \overset{+\ \ -}{H{\to}H}\cdots\cdots Pd \longrightarrow CH_3\overset{+}{C}H_2 + H\cdots\cdots Pd \longrightarrow CH_3CH_3 + Pd$$

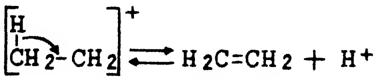
The addition of hydrogen halides to ethylene may be shown in a similar manner:



$$\underset{-\ \ +}{H_2C{=}CH_2} + \underset{+\ \ -}{H{\to}Br} \longrightarrow H_3C{-}\overset{+}{C}H_2 + \overset{-}{Br} \longrightarrow \underset{\text{ethyl bromide}}{CH_3CH_2Br}$$

The hydrogen bromide although not ionized in the absence of an ionizing solvent is a polarized molecule. Polarization effects are observed in normal covalences between atoms of unequal electronegativity. Thus bromine being more electron attracting than hydrogen pulls the bonding pair of electrons closer to itself and away from hydrogen. This inductive effect creates fractional electrical charges on the hydrogen and bromine atoms. The magnitude of the inductive effect is determined by the electron-attracting power of the atom or group in question and may be estimated from the relative positions of the elements in the periodic table. In general, atoms or groups may be divided into two classes: (1) those which attract electrons more than hydrogen does and consequently are said to be electron attracting; and (2) those which have less attraction for electrons than hydrogen does and are said to be electron-releasing atoms or groups.

In the above reaction the olefin may be regarded as a proton acceptor (base). An electron pair is made available, as the result of an electromeric shift, for the acceptance of a proton. The addition of a proton to the negative carbon atom forms a C—H bond which is less polarized in character than the H—Br bond and hence should have less tendency to regenerate a proton. It should be noted, however, that in the resulting carbonium ion the electron attraction of the electron-deficient carbon atom is powerful enough to induce ionization of an adjacent hydrogen atom:

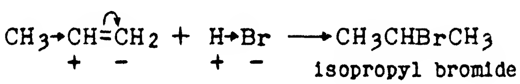


$$\left[\begin{matrix}H\\ |\\ CH_2{-}CH_2\end{matrix}\right]^{+} \rightleftarrows H_2C{=}CH_2 + H^{+}$$

The initial addition of a proton to an olefin bond is probably reversible even though it is believed that the bromide ion adds extremely rapidly to the carbonium ion.

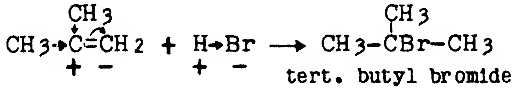
The carbonium ion mechanism is commonly accepted for the normal addition of hydrogen halides to olefins when carried out in ionizing solvents such as acetic acid. Mayo and Katz (11) have recently confirmed the fact that the course of reaction is more complex in the absence of an ionizing solvent. Their work indicates that the addition of hydrogen chloride to isobutylene in heptane as a solvent is of third order with respect to hydrogen chloride and first order with respect to isobutylene. In other words, it appears that three moles of hydrogen chloride and one mole of isobutylene are involved. In the presence of catalysts, such as traces of water or phosphoric acid, the reaction appears to be second order. Under the influence of these catalysts, the type of addition appears to be the same as that already noted for the addition when carried out in ionizing solvents. The catalysts probably function by facilitating the separation of charges. More information is necessary before the addition of hydrogen halides to olefins, under various conditions, can be adequately presented. The simple mechanism given above is to be considered as applicable only when the reactions are carried out in ionizing media.

The addition of hydrogen bromide to an unsymmetrical olefin, such as propylene, is controlled by the way in which polarization of the double bond occurs:



$$CH_3\rightarrow\underset{+}{CH}\overset{\frown}{=}\underset{-}{CH_2} + \underset{+}{H}\rightarrow\underset{-}{Br} \longrightarrow \underset{\text{isopropyl bromide}}{CH_3CHBrCH_3}$$

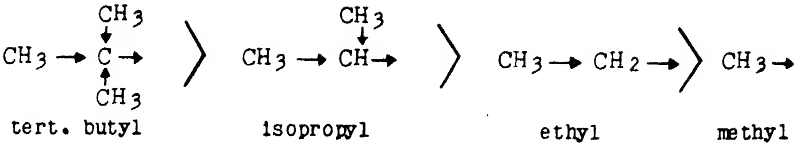
It has been stated that alkyl groups (compared to hydrogen) are electron-release groups and consequently the displacement of the electron pair should be to the right in the above example. Such a postulate would predict that the tendency would be even more pronounced in the case of isobutylene:



$$CH_3\rightarrow\underset{+}{\overset{\overset{CH_3}{\downarrow}}{C}}\overset{\frown}{=}\underset{-}{CH_2} + \underset{+}{H}\rightarrow\underset{-}{Br} \longrightarrow \underset{\text{tert. butyl bromide}}{CH_3-\overset{\overset{CH_3}{|}}{C}Br-CH_3}$$

In general these predictions are in agreement with experimental data.

A possible explanation for the electron-release characteristics of alkyl groups lies in the fact that in the carbon-to-hydrogen bond carbon is the negative end of a dipole. The effect is very small because the difference in the electronegativities of the two atoms is very small. Such an effect $(\overset{+}{H}\rightarrow\overset{-}{C})$ would tend to increase the electron density on the carbon atom of the CH group in propylene. Consequently the CH group tends to repel electrons and the electromeric displacement takes place in the direction of the CH_2 group (in the direction of lowest electron density). This explanation is in accord with the electron-release effects of various alkyl groups:



$$\underset{\text{tert. butyl}}{CH_3 \rightarrow \overset{CH_3}{\overset{\downarrow}{\underset{\underset{CH_3}{\uparrow}}{C}}} \rightarrow} \quad > \quad \underset{\text{isopropyl}}{CH_3 \rightarrow \overset{CH_3}{\overset{\downarrow}{CH}} \rightarrow} \quad > \quad \underset{\text{ethyl}}{CH_3 \rightarrow CH_2 \rightarrow} \quad > \quad \underset{\text{methyl}}{CH_3 \rightarrow}$$

The over-all effect thus is an accumulative one as would be expected.

Wheland (3) has employed the concept of hyperconjugation to explain the manner in which hydrogen halides add to propylene. Since the dipole moment of propylene is quite small, it is stated that the inductive effect must be small and cannot account for the electron-release effect of the methyl group (see page 46).

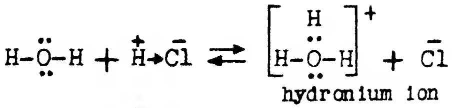
It should be noted, however, that the presence of peroxides may reverse the positions taken by the hydrogen and bromine atoms (12). For example, propylene in the presence of benzoyl peroxide reacts with hydrogen bromide to form *n*-propyl bromide. This reaction is believed to follow a radical mechanism

$$CH_3\text{-}CH::CH_2 + \cdot\underset{\cdot\cdot}{Br}: \longrightarrow CH_3\text{-}CH:CH_2Br$$

$$CH_3\text{-}CH:CH_2Br + HBr \longrightarrow CH_3CH_2CH_2Br + \cdot\overset{\cdot\cdot}{\underset{\cdot\cdot}{Br}}:$$

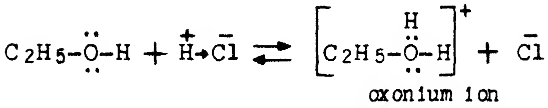
involving the formation of nascent bromine through the interaction of the peroxide and hydrogen bromide. The addition of the bromine atom to the CH_2 group rather than the CH group is not surprising in view of the electron-release effects noted above. The initial addition takes place at the position of greatest electron availability. Hydrogen chloride and hydrogen iodide always give the normal addition products. Hydrogen iodide adds most readily to the olefin bond and hydrogen chloride least readily.

There is considerable published information on the effects of solvents on the addition of hydrogen halides to olefins, but no general agreement as to the nature of these effects. More data are required before any logical order can be established. It is commonly stated that the hydrogen halides in aqueous solution add less readily to olefins. Mayo and Katz, however, have demonstrated that water in small amounts acts as a catalyst (11). It has been reported that the rate of addition increases as the basicity of the solvent decreases. For example, the rate of addition is slower in ether and dioxane solutions than in hydrocarbon solvents (13). More recently (14) it has been shown that the addition of hydrogen bromide to propylene in pentane solution, in the absence of peroxides, gives the abnormal addition product, *n*-propyl bromide. The over-all picture of the effect of solvents in these reactions is complicated and often confusing. It is clear that solvents such as water, alcohol, ether, and dioxane, which act as proton acceptors, would exert some effect on these addition reactions:



$$H-\underset{\cdot\cdot}{\ddot{O}}-H + \overset{+}{H}\rightarrow\overset{-}{Cl} \rightleftarrows \left[H-\underset{\cdot\cdot}{\overset{\overset{H}{\cdot\cdot}}{O}}-H\right]^{+} + \overset{-}{Cl}$$

hydronium ion

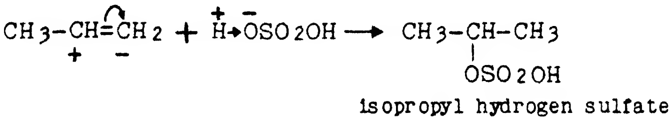


$$C_2H_5-\underset{\cdot\cdot}{\ddot{O}}-H + \overset{+}{H}\rightarrow\overset{-}{Cl} \rightleftarrows \left[C_2H_5-\underset{\cdot\cdot}{\overset{\overset{H}{\cdot\cdot}}{O}}-H\right]^{+} + \overset{-}{Cl}$$

oxonium ion

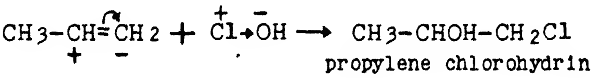
It may be said that such solvents, by facilitating the separation of charges, should aid the addition reaction. Another factor, however, must be considered. If the solvent is sufficiently basic, the oxonium ion may not act as an efficient conveyer of protons to the olefin bond and thus may actually retard the addition reaction. It is not possible at the present time accurately to predict these effects.

Other addition reactions may also be represented by "ionic" mechanisms:



$$CH_3-\underset{+}{CH}=\underset{-}{CH_2} + \overset{+}{H}\rightarrow\overset{-}{OSO_2OH} \longrightarrow CH_3-\underset{\underset{OSO_2OH}{|}}{CH}-CH_3$$

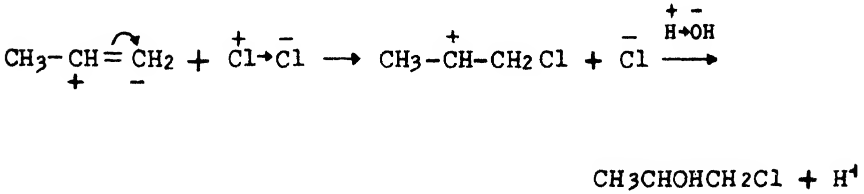
isopropyl hydrogen sulfate



$$CH_3-\underset{+}{CH}=\underset{-}{CH_2} + \overset{+}{Cl}\rightarrow\overset{-}{OH} \longrightarrow CH_3-CHOH-CH_2Cl$$

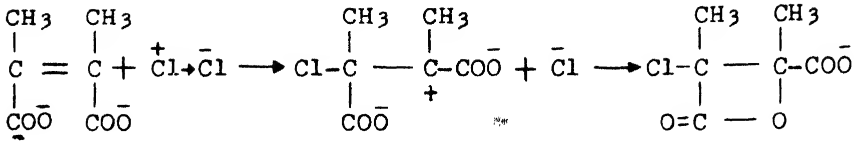
propylene chlorohydrin

It has been suggested by Tarbell and Bartlett that the formation of chlorohydrins in aqueous solution involves the following steps (15):



$$CH_3-\underset{+}{CH}=\underset{-}{CH_2} + \overset{+}{Cl}\rightarrow\overset{-}{Cl} \longrightarrow CH_3-\overset{+}{CH}-CH_2Cl + \overset{-}{Cl} \xrightarrow{\overset{+}{H}\rightarrow\overset{-}{OH}} CH_3CHOHCH_2Cl + H^{+}$$

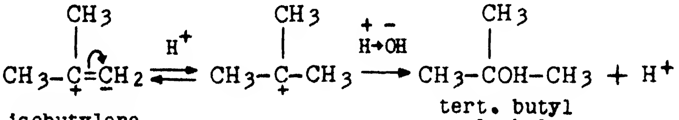
This is supported by the kinetic evidence on the bromination of stilbene in methyl alcohol solution. Further evidence for the primary entry of a positive halogen atom was obtained by treating the sodium salts of dimethyl maleic acid and dimethyl fumaric acids with chlorine water and bromine water. In both cases, halogenated β-lactones were isolated. The latter were pictured as resulting from a two-step addition process:



$$\underset{COO^-}{\overset{CH_3}{C}} = \underset{COO^-}{\overset{CH_3}{C}} + \overset{+}{Cl}\rightarrow\overset{-}{Cl} \longrightarrow Cl-\underset{COO^-}{\overset{CH_3}{C}} - \underset{+}{\overset{CH_3}{C}}-COO^- + \overset{-}{Cl} \longrightarrow Cl-\underset{O=C}{\overset{CH_3}{C}} - \underset{O}{\overset{CH_3}{C}}-COO^-$$

Since the *β*-lactones cannot be made from the halohydrins or from the corresponding dihalogen derivatives, the above course of reaction appears to be the only one that fits the experimental data.

The hydration of olefins in the presence of acid catalysts also involves the polarizable ethylene bond. It is the function of the catalyst to facilitate this polarization and to utilize it for the addition of a proton. The positive charge thus introduced into the molecule may be neutralized by the addition of a hydroxyl ion to form the corresponding alcohol. Brooks and Humphrey (16) obtained an immediate formation of alcohol by adding ice to cold solutions of alkenes in 85 per cent sulfuric acid. They further noted that the corresponding alkyl hydrogen sulfates do not undergo appreciable hydrolysis under the same conditions. It would appear from this work that the formation of alcohols is not dependent upon the formation of alkyl hydrogen sulfates. The reaction may be written as follows:



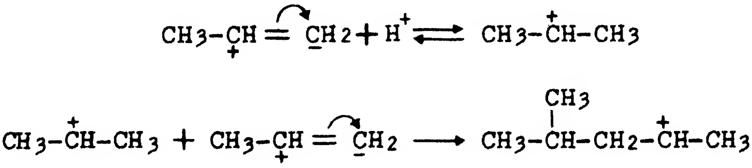
$$CH_3-\underset{+}{\overset{CH_3}{C}}=\underset{-}{C}H_2 \overset{H^+}{\rightleftharpoons} CH_3-\underset{+}{\overset{CH_3}{C}}-CH_3 \xrightarrow{\overset{+\ -}{H\rightarrow OH}} CH_3-\overset{CH_3}{C}OH-CH_3 + H^+$$

isobutylene

tert. butyl alcohol

This work does not exclude the formation of alkyl hydrogen sulfates and their subsequent hydrolysis to alcohols, for this sequence of reactions is known to occur under suitable conditions.

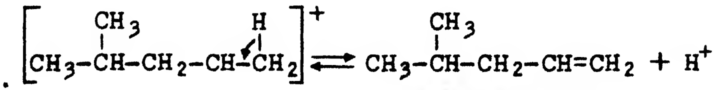
The polymerization of olefins induced by acid catalysts presents a somewhat similar problem. Again the function of the catalyst is to facilitate the polarization of the double bond:



$$CH_3-\underset{+}{C}H=\underset{-}{C}H_2 + H^+ \rightleftharpoons CH_3-\overset{+}{C}H-CH_3$$

$$CH_3-\overset{+}{C}H-CH_3 + CH_3-\underset{+}{C}H=\underset{-}{C}H_2 \longrightarrow CH_3-\overset{CH_3}{C}H-CH_2-\overset{+}{C}H-CH_3$$

The last carbonium ion shown above may serve as an activating entity for the continuation of the polymerization process or it may lose a proton and form the dimer:

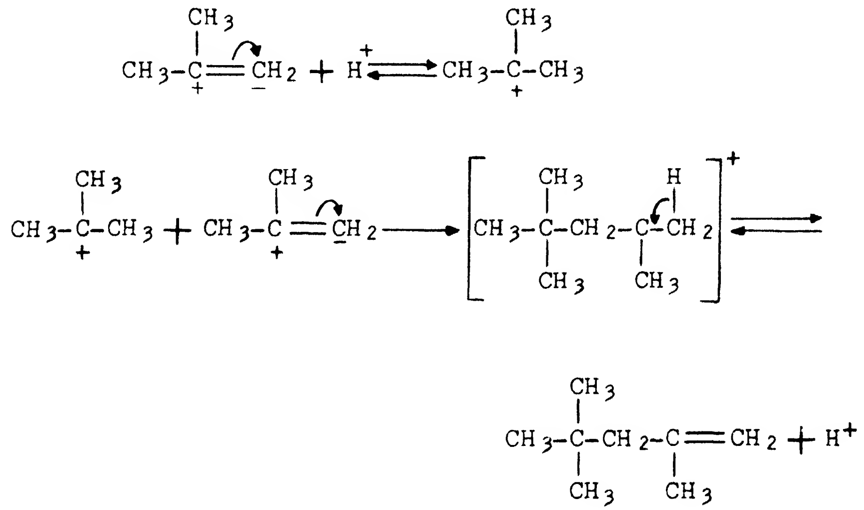


$$\left[CH_3-\overset{CH_3}{C}H-CH_2-CH-\overset{H}{C}H_2\right]^+ \rightleftharpoons CH_3-\overset{CH_3}{C}H-CH_2-CH=CH_2 + H^+$$

4-methylpentene-1

In this case the carbonium ion, CH_3CHCH_3, is not neutralized by the addition of some anion already present in the solution, but rather serves to facilitate the polarization of the double bond in another olefin molecule and subsequently adds to form a new carbonium ion. The electron-deficient carbon atom in the latter ion may recover an electron pair from an adjacent carbon-to-hydrogen bond or it may serve as an active unit for further polymerization.

The controlled polymerization of isobutylene with sulfuric acid gives good yields of 2,4,4-trimethylpentene-1 (so-called isooctene):



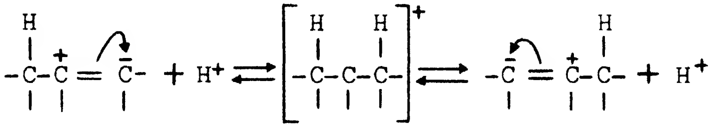
$$CH_3-\underset{+}{\overset{\overset{CH_3}{|}}{C}}=\underset{-}{CH_2} + \overset{+}{H} \rightleftarrows CH_3-\underset{+}{\overset{\overset{CH_3}{|}}{C}}-CH_3$$

$$CH_3-\underset{+}{\overset{\overset{CH_3}{|}}{C}}-CH_3 + CH_3-\underset{+}{\overset{\overset{CH_3}{|}}{C}}=\underset{-}{CH_2} \longrightarrow \left[CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-\underset{\underset{CH_3}{|}}{C}-\overset{\overset{H}{|}}{CH_2}\right]^+ \rightleftarrows$$

$$CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-\underset{\underset{CH_3}{|}}{C}=CH_2 + H^+$$

Continuation of the above process would lead to polymers of greater molecular weight.

The isomerization of olefins also appears to depend upon the polarizable bond. Drastic conditions are sometimes necessary and reagents such as aluminum chloride are effective catalysts, although ordinary acids have been used in some cases. Acid-catalyzed isomerization may be written as follows:



$$-\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{+}{C}}=\underset{|}{\overset{-}{C}}- + H^+ \rightleftarrows \left[-\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{C}-\underset{|}{\overset{\overset{H}{|}}{C}}-\right]^+ \rightleftarrows -\underset{|}{\overset{-}{C}}=\underset{|}{\overset{+}{C}}-\underset{|}{\overset{\overset{H}{|}}{C}}- + H^+$$

The catalysts which are used to promote polymerization frequently promote isomerization also, thus making it more difficult to predict the structure of the resulting polymers.

Throughout the discussion of additions to olefin bonds the electromeric shift has been symbolized as $\underset{+}{\mathrm{C}}\overset{\curvearrowright}{=}\underset{-}{\mathrm{C}}$. It should be noted that this does not mean that the bond is prepolarized. If it were significantly prepolarized, one would expect that either positive or negative ions could add first. Experimental evidence, however, definitely indicates the initial addition of a positive ion. Thus it would appear that the polarization of the double bond is the result of the close approach of a positive ion or of the positive end of a polarized molecule. The proximity of the positive part of the reagent to the polarized double bond would naturally result in its initial addition. It does not follow that any polarized reagent can promote the polarization of a double bond and subsequently add. The degree of polarization of the reagent is an important factor. Thus water alone will not add to an olefin bond although it will add in the presence of an acid catalyst, as previously noted. Finally it should be noted that ease of formation of the final addition product will depend on the relative stabilities of the bonds which are broken and the new bonds which are formed.

CHAPTER IV

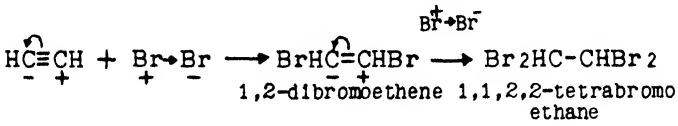
Reactions of Alkyne or Acetylene Hydrocarbons

The triple bond or acetylenic linkage is a covalent bond consisting of three pairs of electrons between two carbon atoms. For the symmetrical acetylenes the electrons may be considered to be shared equally by the two unsaturated carbon atoms. In general, additions to acetylene bonds are governed by the same factors involved in additions to olefin linkages. It is believed that the first step involves the entry of a positive ion (electron acceptor) followed by the addition of an anion or electron donor. It should be noted, however, that the double bond between two carbon atoms contains more potential energy than the single bond, and the triple bond contains more energy than the double bond. This may be observed from the following heats of formation:

C_2H_6, − 20.6 kcal.; C_2H_4, + 6.9 kcal.; C_2H_2, + 55.3 kcal

Consequently the addition reactions to a triple bond are more highly exothermic.

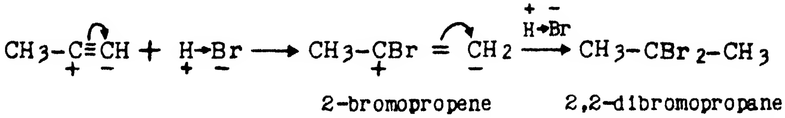
The addition of bromine to acetylene takes place in two steps, yielding first the dibromo derivative and then the tetrabromo derivative:



$$\underset{-}{HC}\equiv\underset{+}{CH} + \underset{+}{Br}\rightarrow\underset{-}{Br} \longrightarrow BrH\underset{-}{C}=\underset{+}{C}HBr \xrightarrow{\overset{+}{Br}\rightarrow\overset{-}{Br}} Br_2HC-CHBr_2$$

1,2-dibromoethene 1,1,2,2-tetrabromo ethane

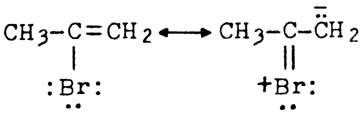
With hydrogen bromide and an unsymmetrical acetylene, the direction of the polarization determines the points of attachment of the hydrogen and bromine atoms:



$$CH_3-\underset{+}{C}\equiv\underset{-}{CH} + \underset{+}{H}\rightarrow\underset{-}{Br} \longrightarrow CH_3-\underset{+}{C}Br = \underset{-}{CH_2} \xrightarrow{\overset{+}{H}\rightarrow\overset{-}{Br}} CH_3-CBr_2-CH_3$$

2-bromopropene 2,2-dibromopropane

The direction of polarization is determined by the same factors noted for the olefin series. One new factor appears in 2-bromopropene, namely, the presence of the bromine atom. The bromine atom being an electron-attracting group might be expected to exert an inductive effect which would oppose the displacement of electrons in the opposite direction. However, when a halogen atom is attached to an unsaturated carbon atom, its inductive effect is weakened. This is caused by the unshared electrons on the halogen, which permit resonance, thus giving the carbon-halogen linkage a semi-double-bond character. This may be considered to enhance the electron-release effect of the methyl group:



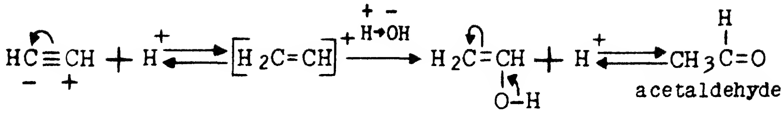
$$CH_3-\underset{\underset{\cdot\cdot}{:Br:}}{\underset{|}{C}}=CH_2 \longleftrightarrow CH_3-\underset{\underset{\cdot\cdot}{+Br:}}{\underset{\|}{C}}-\overset{-}{\ddot{C}}H_2$$

The actual state of the system is best represented as a resonance hybrid of the two resonating structures. It is convenient in writing chemical reactions to point out in a short-hand manner the resonating structures of the substances involved when the resonance has an important effect in determining the course of the reaction. To do this the resonating structures are often drawn connected by a double-headed arrow which serves as a symbol to distinguish resonance from an equilibrium of real and separate forms.

Some molecules may be assigned single structural formulas which satisfactorily describe their behavior. Others, however, cannot be so formulated but must be represented as resonance hybrids. That is, two or more resonant structures (unperturbed forms) resonate with each other and each contributes to the state of the molecule, the contribution of each resonant structure being dependent on its stability. Only in those cases where the resonating forms are nearly or completely equivalent (each having the same or about the same energy) will the forms be in complete resonance. Resonance involves modification of the electronic dispositions. The resonating structures differ only with respect to the positions of electrons, the arrangement of the atomic nuclei remaining the same. Molecules gain stability through resonance and the smaller energy of the resonance state leads to its formation in all cases where the conditions necessary for resonance are satisfied (3). The resonance energies of a large number of organic compounds have been determined from heats of hydrogenation and from heats of combustion (3).

The resonance noted in the above molecule produces a shortening of the carbon-bromine bond length. Interatomic distances may be reliably obtained from spectroscopic measurements and from X-ray and electron diffraction patterns. In general the distance between any two given covalently linked atoms is reasonably constant providing the covalence is of a definite type (single, double, or triple). In the above example, 2-bromopropene, it was stated that the carbon-to-halogen linkage possessed a semi-double-bond character. This is supported by the fact that the carbon-to-bromine bond length is shorter than the C—Br bond length in an alkyl bromide.

The hydration of acetylene and its homologs in acid solution, in the absence of mercury salts, probably follows a mechanism similar to that given for olefins:

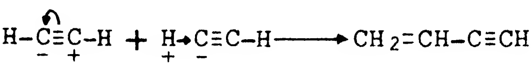


$$H\underset{-}{C}\equiv\underset{+}{C}H + \overset{+}{H} \rightleftarrows [H_2C{=}CH]^{+} \xrightarrow{\overset{+}{H}\rightarrow\overset{-}{OH}} H_2\underset{O-H}{C}{=}CH + \overset{+}{H} \rightleftarrows CH_3\overset{H}{C}{=}O$$

acetaldehyde

The last step in the reaction involves a tautomeric shift. This is discussed later under the aldehydes and ketones. The hydration of acetylene to acetaldehyde by dilute acids is greatly facilitated by the presence of mercury salts. This may be attributed to the electrophilic nature of mercuric salts.

The polymerization of the acetylene hydrocarbons as a group has not been as widely studied as the polymerization of the olefins. Two well-known examples are the dimerization of acetylene to vinylacetylene



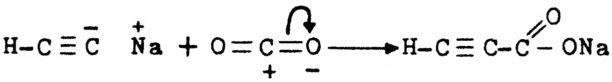
$$H-\underset{-}{C}\equiv\underset{+}{C}-H + \underset{+}{H}\rightarrow\underset{-}{C}\equiv C-H \longrightarrow CH_2{=}CH-C\equiv CH$$

and the trimerization of acetylene to benzene. The former takes place under the influence of certain copper salts. The polarization of the acetylene linkage may be induced by the close approach of a cation or possibly by complete coordination with a cation. The trimerization to benzene occurs at elevated temperatures and may involve a 1,4- addition of acetylene to vinylacetylene (see reactions of the dienes).

A distinguishing characteristic of acetylene hydrocarbons, containing the ≡CH group, is their ability to form salts (acetylides) with the alkali metals. It has been suggested that the ease with which such a hydrogen is replaced may be accounted for by the fact that the carbon atoms in acetylene lie closer together than the carbon atoms in ethylene and in ethane. The interpenetration of their fields may intensify the positive fields of each and the resulting enhancement of the kernel charge would permit the hydrogen to separate more readily. The acetylides may be regarded as the salts of very weak acids since the alkali metal acetylides are completely hydrolyzed by water:

$$H-C\equiv\overset{-}{C}\ \overset{+}{Na} + \underset{+}{H}\rightarrow\underset{-}{OH} \longrightarrow H-C\equiv C-H + NaOH$$

The alkali metal acetylides are useful reagents for the preparation of other acetylenic compounds. Thus, when sodium acetylide is heated with carbon dioxide under pressure, the sodium salt of propiolic acid is formed:



$$H-C\equiv\overset{-}{C}\ \overset{+}{Na} + O{=}\underset{+}{C}{=}\underset{-}{O} \longrightarrow H-C\equiv C-\overset{O}{\overset{\|}{C}}-ONa$$

Acetylene also reacts like an acid towards alkyl magnesium halides (Grignard reagents, see page 59) forming hydrocarbons and $HC\equiv CMgX$ or $XMgC\equiv CMgX$:

$$H-C\equiv\overset{-}{C}\leftarrow\overset{+}{H} + \overset{-}{R}\leftarrow\overset{+}{M}gX \longrightarrow RH + HC\equiv CMgX$$

This reaction simply represents the displacement of a weak acid from its salt by the action of a stronger acid. In this case acetylene is a stronger acid than the RH. The acetylenic Grignard reagents can be used in the usual Grignard syntheses.

CHAPTER V

Reactions of Conjugated Diolefins or Dienes

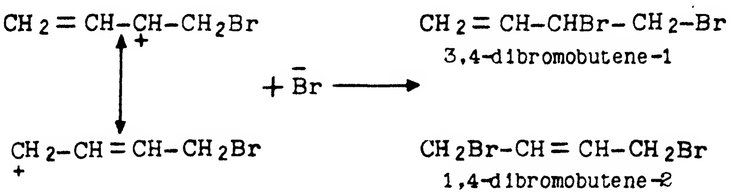
Additions to accumulated or isolated diene systems occur, in general, according to the mechanisms already given for the olefin hydrocarbons. However, many observations have indicated that addition to a conjugated diene, such as butadiene, may result in the formation of either the 1,2- or 1,4- addition product. In many cases the 1,4- derivative is the principal product. Burton and Ingold (17) suggested the following scheme for the addition of bromine to butadiene under conditions which permit ionization (in acetic acid for example):

$$CH_2=CH-\underset{+}{CH}=\underset{-}{\overset{\curvearrowleft}{CH_2}} + \underset{+}{Br}\rightarrow\underset{-}{Br} \longrightarrow CH_2=CH-\underset{+}{CH}-CH_2Br + \overset{-}{Br}$$

The first step is represented as the addition of only one bromine. The positive ion which results is a resonating structure and may be written as follows:

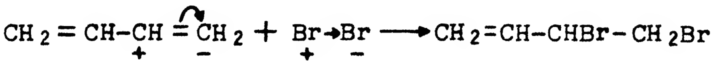
$$\left[CH_2=CH-CH-CH_2Br\right]^{+} \longleftrightarrow \left[CH_2-CH=CH-CH_2Br\right]^{+}$$

The subsequent addition of the bromide ion may then produce the 1,2- or 1,4-dibromo compound and the ratio of the isomers formed will probably depend upon their relative stabilities:



$$\begin{array}{ccc} CH_2=CH-\underset{+}{CH}-CH_2Br & & CH_2=CH-CHBr-CH_2-Br \\ & & \text{3,4-dibromobutene-1} \\ \updownarrow & +\overset{-}{Br} \longrightarrow & \\ \underset{+}{CH_2}-CH=CH-CH_2Br & & CH_2Br-CH=CH-CH_2Br \\ & & \text{1,4-dibromobutene-2} \end{array}$$

It is interesting to note that in a nonionizing solvent, such as hexane, the 1,2-dibromo derivative predominates, and it may be assumed that under these conditions addition proceeds as with a single double bond:



$$CH_2=CH-\underset{+}{CH}=\underset{-}{\overset{\curvearrowleft}{CH_2}} + \underset{+}{Br}\rightarrow\underset{-}{Br} \longrightarrow CH_2=CH-CHBr-CH_2Br$$

The addition of a second molecule of bromine to either dibromo compound yields 1,2,3,4-tetrabromobutane.

The above theory, as will be seen in later reactions, has been of value in interpreting various addition reactions to conjugated systems. There are some reactions, however, which do not appear to be explained satisfactorily by this mechanism. For example, in the absence of oxygen and peroxides and in the presence of an antioxidant, butadiene undergoes 1,2- addition with hydrogen bromide (18). Furthermore, this addition product, under the influence of hydrogen bromide and peroxides, rearranges to the 1,4- addition product.

The polymerization of butadiene and its homologs undoubtedly proceeds by way of a radical chain mechanism. In general, the reagents which promote polymerization function through their ability to form free radicals. Diene polymerization may be shown as follows (19):

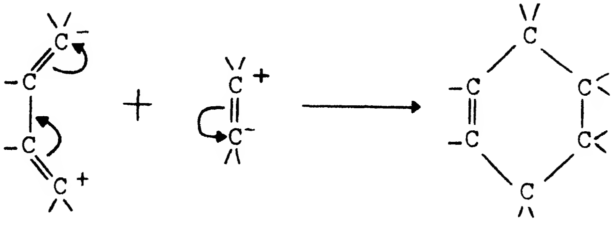
$$CH_2{=}CH{-}CH{=}CH_2 + R\cdot \longrightarrow RCH_2{-}CH{=}CH{-}CH_2\cdot$$

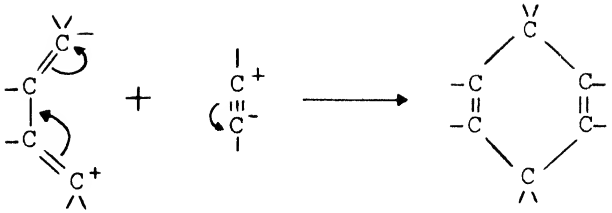
$$RCH_2{-}CH{=}CH{-}CH_2\cdot + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow$$

$$RCH_2{-}CH{=}CH{-}CH_2{-}CH_2{-}CH{=}CH{-}CH_2\cdot \text{ etc.}$$

The reagent is believed to initiate the reaction. The newly formed hydrocarbon radical can then activate another diene molecule and the chain continues to grow through a series of 1,4- additions (linear polymerization). The chain may be terminated by the combination of two free hydrocarbon radicals. It is probable that the hydrocarbon radical can transfer its activity (its unpaired electron) to other carbon atoms in the chain, thus giving rise to branched chains and cross linkages to some extent. Continuation of the above process finally leads to the formation of a high molecular weight, rubberlike polymer.

The Diels-Alder reaction is another example of 1,4- addition. The essential reaction is the addition of two unsaturated molecules, one of which contains an active double or triple bond and the other a conjugate system of double bonds, the first uniting with the second by 1,4- addition to the conjugated system:

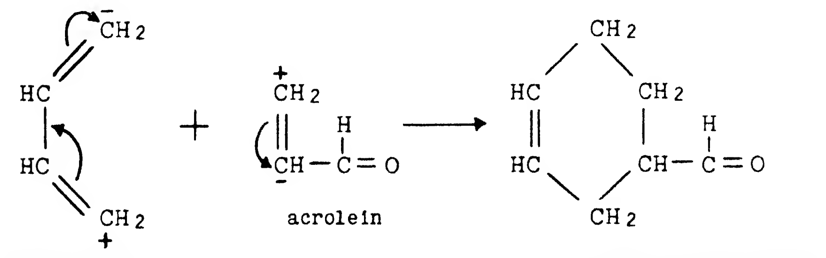


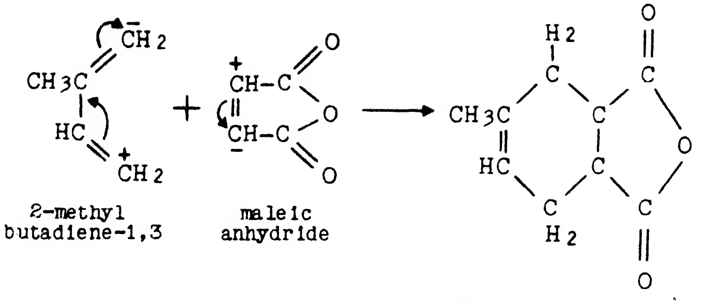


The result of such an addition is a cyclization yielding a partially hydrogenated 6-atom ring. The reaction requires that the double or triple bond be activated, as by the presence of an electron-attracting group in the adjacent or α- position. The carbonyl group, —C=O, and cyanide group, —C≡N, are examples of electron-attracting groups. In the absence of such activation, reaction may not occur or will take place much less readily.

In some cases the reactions are spontaneous, rapid, and exothermic. In general they are carried out at 25°–150° C., the time varying from several hours to several days. Solvents are not always needed, but may be ether, benzene, toluene, xylene, or ethyl alcohol.

It may be assumed that it is the activated double bond which initiates the reactions in most cases, since when it is not activated the additions occur less readily or not at all. The reactions apparently take place most readily when the double bond is most highly activated. This activation (polarization) would assist the electromeric shifts in the diene which are necessary for the addition:

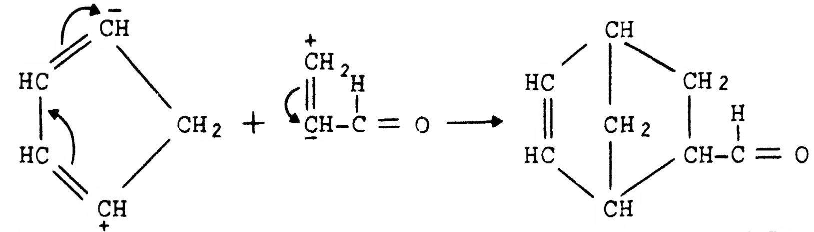




2-methyl butadiene-1,3

maleic anhydride

4-methyl-1,2,3,6-tetrahydrophthalic anhydride

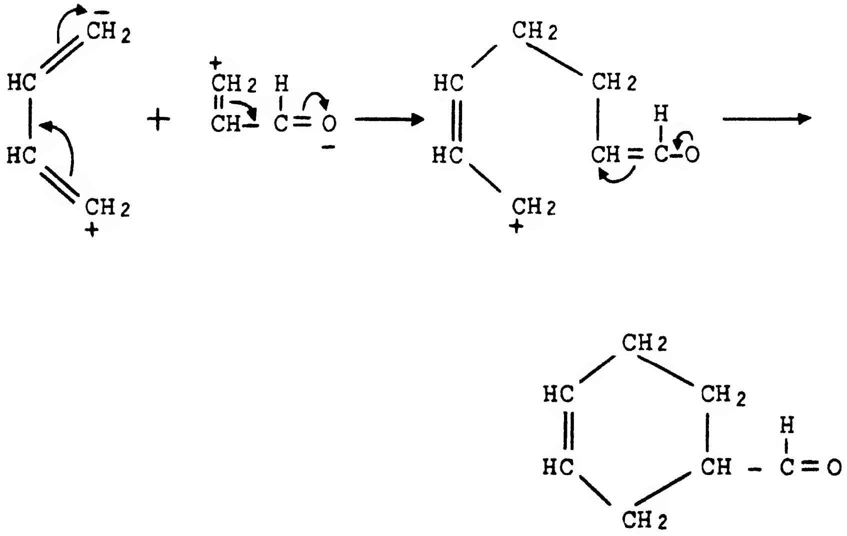


cyclopentadiene

3,6-endomethylene-1,2,3,6-tetrahydrobenzaldehyde

These reactions have been used to detect the presence of a conjugated system. The reaction is of value for such purposes only when positive results are obtained, for in some cases it has been found that conjugated systems failed to react.

The above mechanisms suggest that the reaction takes place in one step. There actually is no basis for such an assumption and it could proceed stepwise without fundamentally changing the mechanism:

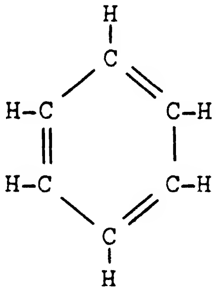


The two-step mechanism shown above is a reasonable one and it gives a clearer picture of the nature of the activating effect of the electron-attracting carbonyl group on the α,β-olefin bond. This effect is discussed in greater detail in Chapter XV.

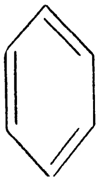
CHAPTER VI

Reactions of Aromatic Hydrocarbons

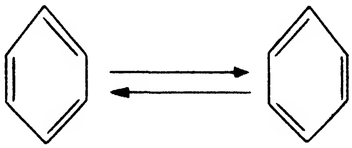
Benzene presents a type of resonance which is especially important in organic chemistry. No single structure, using conventional valence bonds, provides a satisfactory representation of this molecule. The structure



or

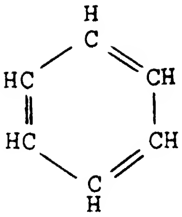


for example, would not be consistent with the lack of chemical unsaturation shown by this molecule or with the lack of ortho isomers. The Kekulé picture of a rapid equilibrium between two such forms

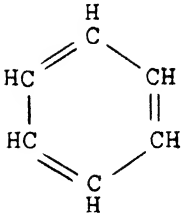


fails because it views the substance as a mixture of two forms, and we should expect each to have the chemical and physical properties of a ring of carbon atoms with alternate double and single bonds.

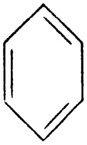
The quantum mechanical resonance theory provides a solution which is much more satisfactory than all of the others proposed for this problem. The treatment, based on the sound principles of quantum mechanics, presents a consistent and striking correlation of the chemical and physical properties of benzene and related molecules. In this treatment the actual molecule is considered to be the resonance hybrid of several structures. Two of these structures are predominant in the resonance. These are the most stable conventional structures we can picture for benzene



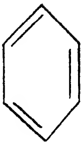
and



which we may symbolize in a shorthand way as



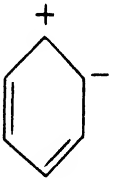
and



and call the Kekulé structures.

These structures meet the requirements for resonance. They are exactly equivalent in energy and are in complete resonance. Because of this, the actual structure is quite different from and much more stable than either of these two Kekulé structures. It is just this resonance which prevents these hypothetical structures from being real substances. They serve merely as a convenient set of symbols to describe the real structure and, to point this out, they are often called canonical or unperturbed structures.

These principal resonating structures differ not in the type of bonds they possess but in the distribution of these bonds. These covalent single and double bonds of the Kekulé structures will have a small amount of ionic character. They are, however, normal covalent bonds, since they connect identical atoms, and the contribution of ionic structures such as the following will be small:



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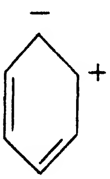


It will be noted that each ionic structure has a compensating one of opposite polarity, so that the contribution of these ionic structures does not upset the symmetric distribution of the electrons expected in the actual structure. Since these higher energy structures contribute only a relatively small amount to the actual structure, it is allowable and convenient to consider only the Kekulé structures, without explicit mention of the ionic character of the bonds, in discussing the resonance of benzene.

Let us examine the molecule we should expect from the resonance between the Kekulé structures. The bonds joining the carbon atoms should be neither single nor double bonds, but all the same and intermediate in nature between single and double bonds although stronger than the average of a single and a double bond. In accord with this is the fact that the heats of combustion and hydrogenation are both nearly 40 kcal. per mole less than would be predicted for the Kekulé structures with three single and three double bonds. This amount of energy is the resonance energy of benzene. The actual bonds are thus 40 kcal. per mole stronger than those of a Kekulé structure and we have thereby an explanation of the lack of unsaturation of benzene.

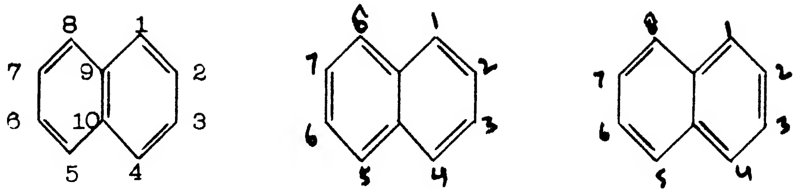
The statement that the bonds of benzene have "one-half double bond character" refers to the fact that in the two Kekulé structures which contribute equally to the resonance, any two adjacent carbon atoms are connected by a single bond in one structure and by a double bond in the other. This statement does not mean that the bonds in the actual benzene molecule have a nature exactly intermediate between a single and a double bond. Actually, the bond is considerably stronger than the average of a double and single bond.

The effect of resonance on bond length is especially striking. The separation of the carbon atoms in benzene is 1.39 Å, which is less than the single bond length in ethane, 1.55 Å, and greater than the double bond length in ethylene, 1.33 Å. Again we note how different the bond is from an exact intermediate between a normal single bond and a normal double bond. The bond length is intermediate in value, but, as expected, closer to the double bond value because of the resonance strengthening.

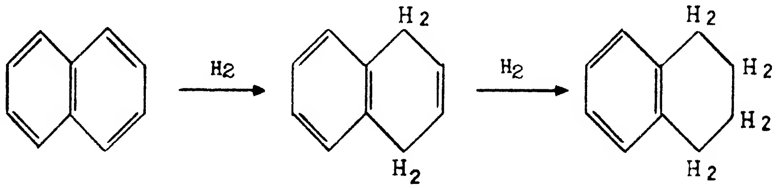
The resonance theory provides a very illuminating explanation of many complex chemical behaviors. Many examples of the chemical effects caused by resonance, of the type encountered with benzene, will be discussed in detail later in this chapter and in subsequent chapters.

The addition of two hydrogen atoms to benzene destroys the resonance of the closed conjugated system and the addition occurs only if energy is supplied. The amount of heat liberated when one mole of hydrogen is added to an olefin varies from 28 to 30 kcal. The addition of one mole of hydrogen to benzene requires the absorption of about 6 kcal., thus raising the energy of the molecule. The additions of a second and a third mole of hydrogen proceed with the liberation of heat (about 28 kcal. in each step).

The same effects have been noted for the di- and polycyclic benzene hydrocarbons. Naphthalene, for example, may be regarded as a hybrid of three unperturbed forms:

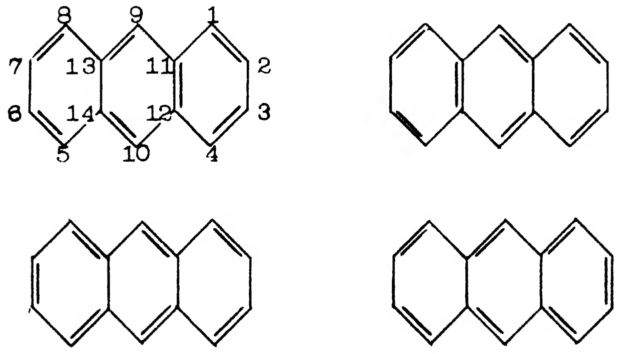


Double bonds occur between carbon atoms 1-2, 3-4, 5-6, and 7-8 in two of the three unperturbed forms. If all three forms are given equal value, the 1-2, 3-4, 5-6, and 7-8 bonds will possess two-thirds of a true double bond character, while the remaining bonds have only one-third double bond character (20). Heat is liberated in the addition of one mole of hydrogen to naphthalene, although the amount is considerably less than that for an olefin bond. The first mole of hydrogen gives 1,4-dihydronapthalene, which may be converted into 1,2,3,4-tetrahydronaphthalene by addition of a second mole of hydrogen. This is the typical behavior of a conjugated butadiene structure:

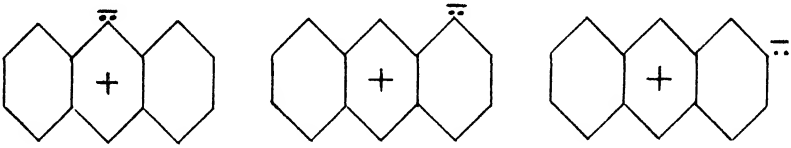


The latter compound contains one true benzenoid ring. The addition of two moles of hydrogen eliminates resonance in one ring only, and to hydrogenate the remaining benzene ring, energy equivalent to the resonance energy must be absorbed.

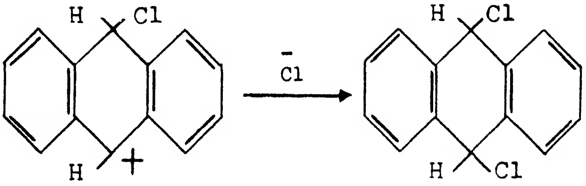
Anthracene may be regarded as a hybrid of four unperturbed forms:



Examination of the four forms shows that double bonds occur between carbon atoms 1-2, 3-4, 5-6, and 7-8 in three of the forms. Each of these bonds approximates three-fourths double bond character. The bonds 9-13, 10-14, 9-11, and 10-12 have one-half double bond character and the remaining bonds have one-fourth double bond character. Chlorine reacts with anthracene in the cold to form 9,10-anthracene dichloride. This ease of addition at the 9,10- positions could not be predicted from a consideration of the Kekulé forms alone. It has been suggested that the polarization of the molecule brought about by the attacking reagent also must be considered (2). If it be assumed that the initial step in the addition involves an intermediate similar to that noted for addition to the olefins, a probable explanation for 9,10- addition may be obtained. There are sixteen possible ionic structures for the carbonium ion formed when the reagent attacks the 9 position, twelve ionic structures when the attack is at position 1, and ten for position 2:

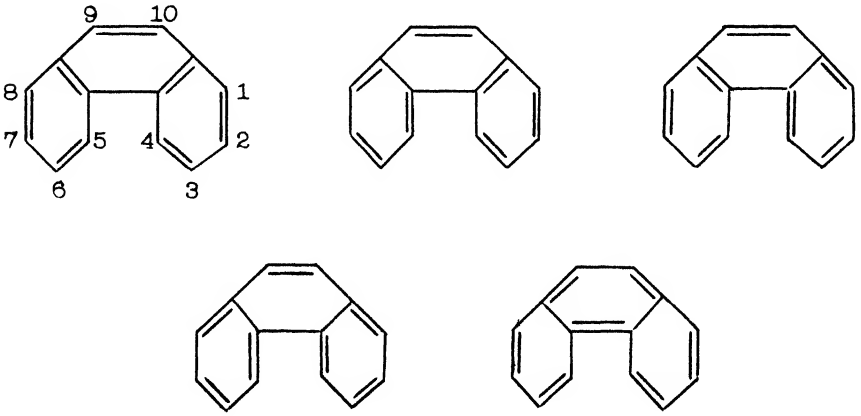


Resonance would then favor reaction at carbon atom 9. The form shown below accounts for 9,10- addition of chlorine:



In some cases it would appear that the resonance effect of the carbonium ion may be the most important factor.

Similar reasoning may be applied to phenanthrene, which may have five unperturbed forms:

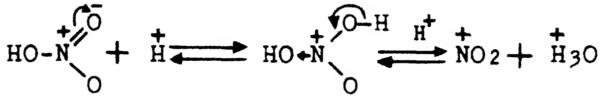


A double bond occurs between carbon atoms 9 and 10 in four of the forms, giving the 9,10- bond four-fifths double bond character, which is considerably higher than the values for the remaining bonds. The 9,10-bond is essentially olefinic in character. The ease with which additions occur to aromatic ring systems varies over a wide range, as seen from the examples given above.

Substitution reactions are characteristic of aromatic compounds in general. The term substitution is used here to mean the replacement of hydrogen. It is probable that such reactions involve the initial formation of a carbonium ion followed by the elimination of hydrogen. The common substitution reactions involve the use of electrophilic reagents such as nitric acid, sulfuric acid, and the halogens. The approach of the substituting group assists in the polarization of the ring which is necessary for the initial attack. The nitration of aromatic hydrocarbons is facilitated by the presence of concentrated sulfuric acid. Cryoscopic studies (21*a*) have shown that nitric acid ionizes in sulfuric acid solution and the number of particles formed for each molecule of nitric acid approaches four. The nitric acid behaves as a base towards sulfuric acid and the manner in which ionization occurs has been shown to be as follows (21*b*):

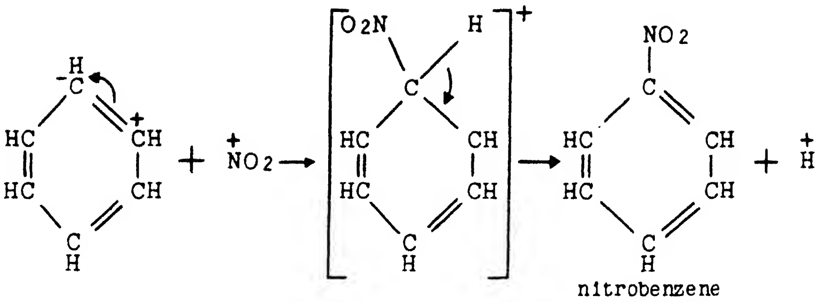
$$HNO_3 + 2H_2SO_4 \longrightarrow \overset{+}{H_3O} + \overset{+}{NO_2} + 2HSO_4^-$$

For discussion purposes it is better to write this equation in the following manner:

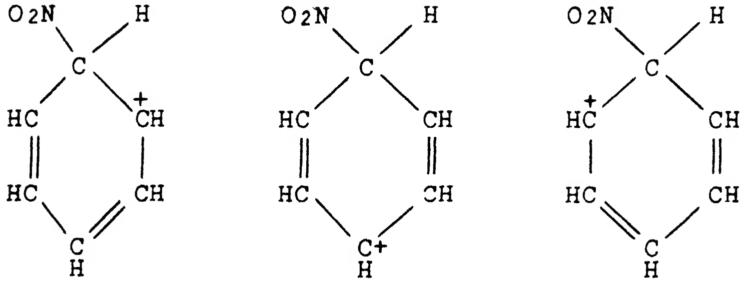


I II

From kinetic studies of the nitration of aromatic compounds in sulfuric acid solution (21*b*), it has been concluded that the active nitrating agent under these conditions is the electrophilic ion $\overset{+}{NO_2}$. The reactions are second order and have maximum rates in approximately 90 per cent sulfuric acid. The rate is not altered by small amounts of nitrous acid. From the above data, a reasonable mechanism for the nitration of benzene may be written:

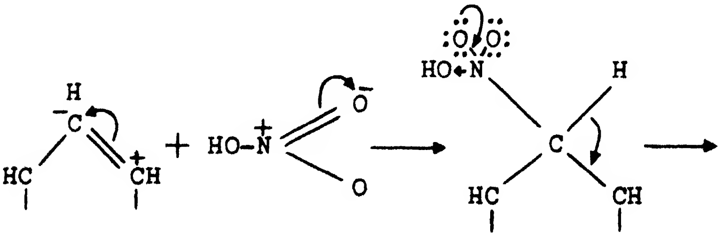


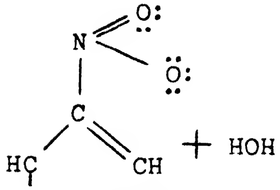
Actually the carbonium shown above is a hybrid of three ionic structures:



Neutralization of the positive charge is effected by the formation of a proton, and the chief driving force is the restoration of the resonance of the benzene ring.

It should be noted that in the ionization of nitric acid in sulfuric acid solution, two electrophilic ions are formed, I and II. There is no evidence at present to indicate that I is an active nitrating agent in the presence of sulfuric acid. In the absence of sulfuric acid, nitration proceeds readily, in general, only in those cases where the aromatic ring system is more nucleophilic in character. For example, the presence of ortho and para directing groups increases electron availability at the *o-* and *p-* positions and electrophilic agents will add more readily. Under these circumstances it is possible that the nitric acid molecule is sufficiently electrophilic to account for the initial addition reaction. The nitrogen atom in nitric acid possesses a fractional positive charge as a result of its attachments to the more electron-attracting oxygen atoms:

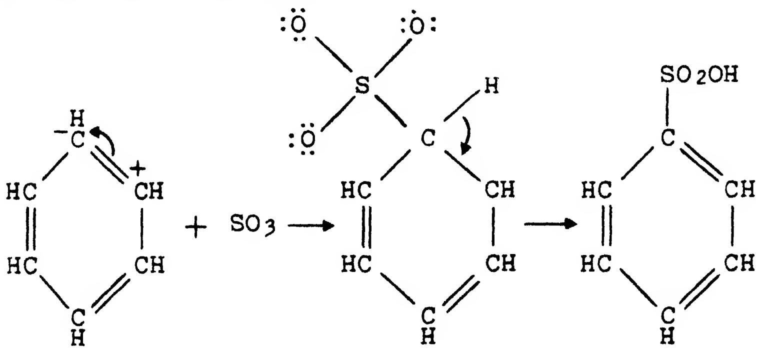




Unfortunately, nitration in the absence of sulfuric acid is complicated by other factors. For example, the nitration of phenol and anisole depends on the presence of small amounts of nitrous acid (see Chap. X). Until more information becomes available it is not possible to present a clear picture of the various nitration processes.

Reactions of this type are frequently referred to as substitution reactions. Actually they are similar to the addition reactions noted previously for the olefins. The first step involves the addition of a positive ion to a polarizable double bond. This initial addition would be expected to take place less readily with benzene because of its resonance energy. Energy equal to the resonance energy must be supplied for addition to occur. Consequently, addition to the benzene ring may be said to occur less readily than to a simple olefin bond. The second step in the reaction, splitting off of a proton and restoration of the aromatic ring, is different from that usually observed for olefin addition reactions. It must be remembered, however, that the smaller energy of the resonance state leads to its formation in all cases where the conditions for resonance are satisfied. It is probable that in all so-called aromatic substitution reactions, the second step involves the loss of a proton. The attraction of the electron-deficient carbon atom in the carbonium ion may be considered to be the initiating cause of proton formation and this takes place with loss of energy.

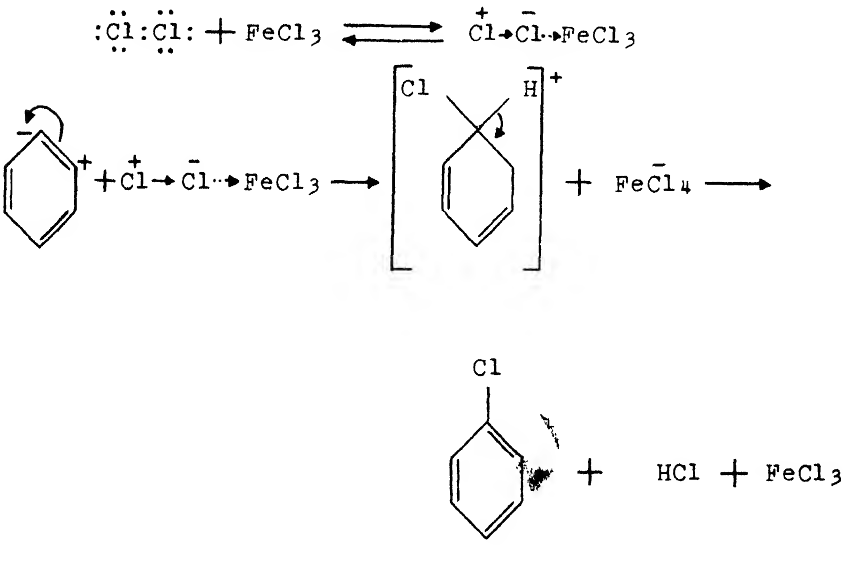
Sulfonation similarly involves the addition of an electrophilic agent to the ring. In general, rates of sulfonation increase with increasing concentration of the sulfuric acid and with increasing concentration of sulfur trioxide in fuming sulfuric acid. Where sulfur trioxide is known to be present, it is probably responsible for the formation of a sulfonic acid by direct electrophilic attack (22):



benzene sulfonic acid

Whether or not sulfuric acid is sufficiently electrophilic to react directly with the aromatic ring cannot be answered at present. The sulfur atom in the acid does possess a fractional positive charge and theoretically might add to the ring. Such an addition would involve a temporary expansion of the sulfur atom's valence shell. There is considerable evidence that sulfur can increase its valence shell in some cases, but there is no evidence available at present to indicate such a change is involved in sulfonation.

Substitution of chlorine or bromine in the benzene ring is greatly aided by the presence of catalysts such as Fe, $FeCl_3$, and $AlCl_3$. Such catalysts are electrophilic reagents and by attracting the unused electrons on one of the atoms in the halogen molecule assist in the formation of a positive halogen atom. The latter is capable of polarizing one of the carbon-carbon bonds in benzene and subsequently adding:



chlorobenzene

It is not necessary to postulate the formation of a free positive chlorine ion. Such an ion would be very unstable and its existence as a free entity appears to be improbable. Br→Cl is a more powerful brominating agent than Br—Br because it forms the electrophilic $\overset{+}{Br}$ more readily. It does not act as a chlorinating agent. Similarly I→Cl is a stronger iodinating agent than iodine (23). I→Br is an exception since it has been reported to promote nuclear bromination. Electrolysis experiments, however, indicate the following:

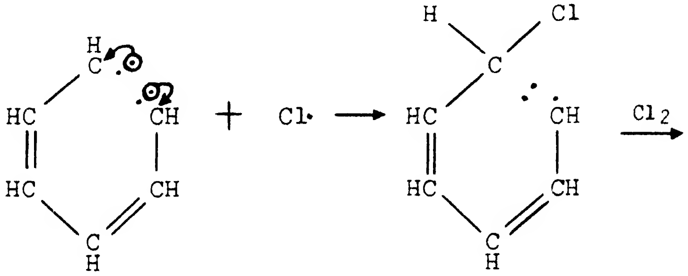
$$I{-}Br \rightleftharpoons \overset{+}{I} + \overset{-}{Br}$$

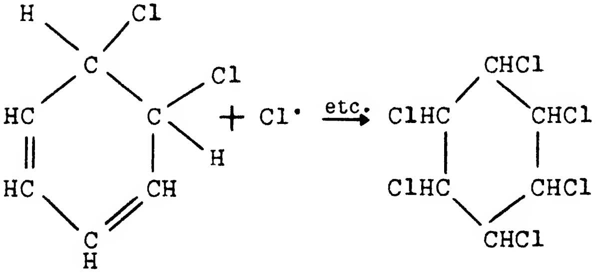
There is no explanation for this apparent anomaly at the present time.

In the absence of a catalyst which promotes the formation of X^+, but in the presence of sunlight, benzene forms true addition products with chlorine or bromine. For example, under these conditions benzene and chlorine react to form benzene hexachloride. The chlorine molecule is known to dissociate under the activating influence of sunlight

$$Cl_2 \rightleftarrows 2\colon\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}\cdot$$

consequently the addition reaction undoubtedly involves a radical mechanism:

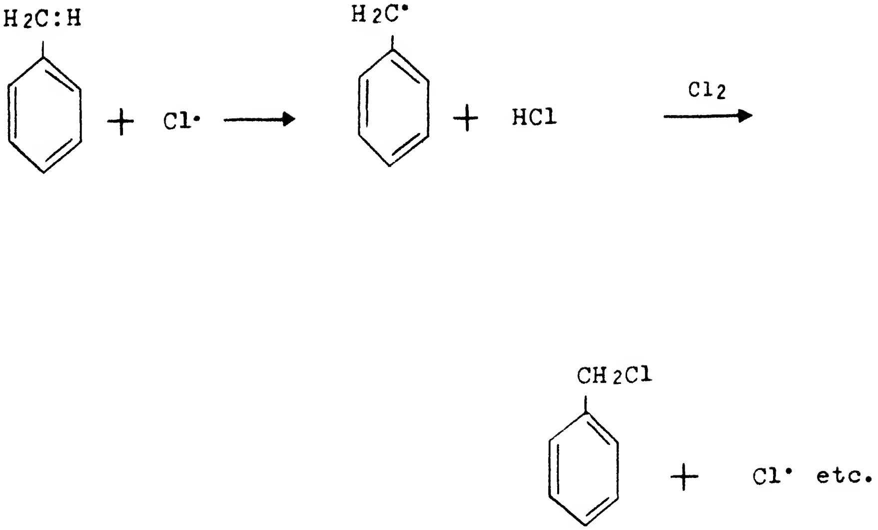




benzene hexachloride

Addition of chlorine to naphthalene to form a di- or tetrachloride takes place more readily as would be expected.

With alkyl benzenes halogenation usually occurs on the carbon atom adjacent to the ring. The photohalogenation of toluene, for example, must proceed through a mechanism similar to that already outlined for the chlorination of methane:



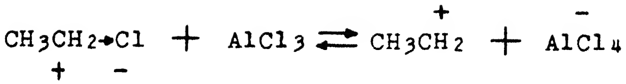
Continuation of the reaction leads to the formation of benzal chloride and benzotrichloride.

It has been reported that the halogenation of isopropylbenzene under similar conditions leads to substitution in the ring. Apparently if electron availability is increased sufficiently in the ring the electrophilic activity of the halogen molecule, $\overset{+}{Cl}\rightarrow\overset{-}{Cl}$, may compete with the radical mechanism and may even predominate if the increase in electron availability is great enough.

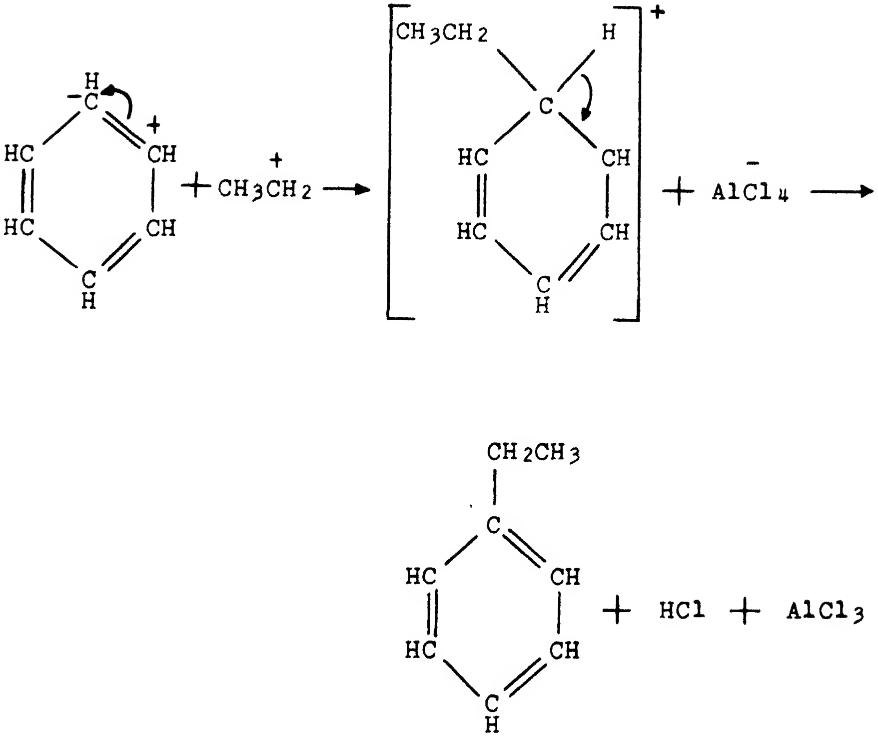
The Friedel-Crafts reactions may properly be called substitution reactions and involve an attack on the aromatic ring by a carbonium ion. Aluminum chloride when dissolved in ethyl chloride gives a conducting solution and furthermore the aluminum is found in the anion. Aluminum chloride is an active electrophilic reagent and its tendency to acquire an octet of electrons by attracting the unused electrons on the halogen atom is the initiating force of the Friedel-Crafts reactions:

$$\underset{+}{R}\rightarrow\underset{-}{Cl} + AlCl_3 \rightleftarrows \overset{+}{R} + \overset{-}{AlCl_4}$$

Boron trifluoride behaves similarly. The electrophilic carbonium ion formed in the above reaction may now attack the aromatic nucleus:

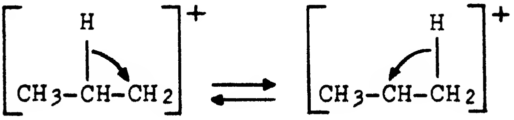


$$\overset{+}{C}H_3\overset{-}{C}H_2\rightarrow Cl + AlCl_3 \rightleftharpoons CH_3\overset{+}{C}H_2 + Al\overset{-}{C}l_4$$



ethylbenzene

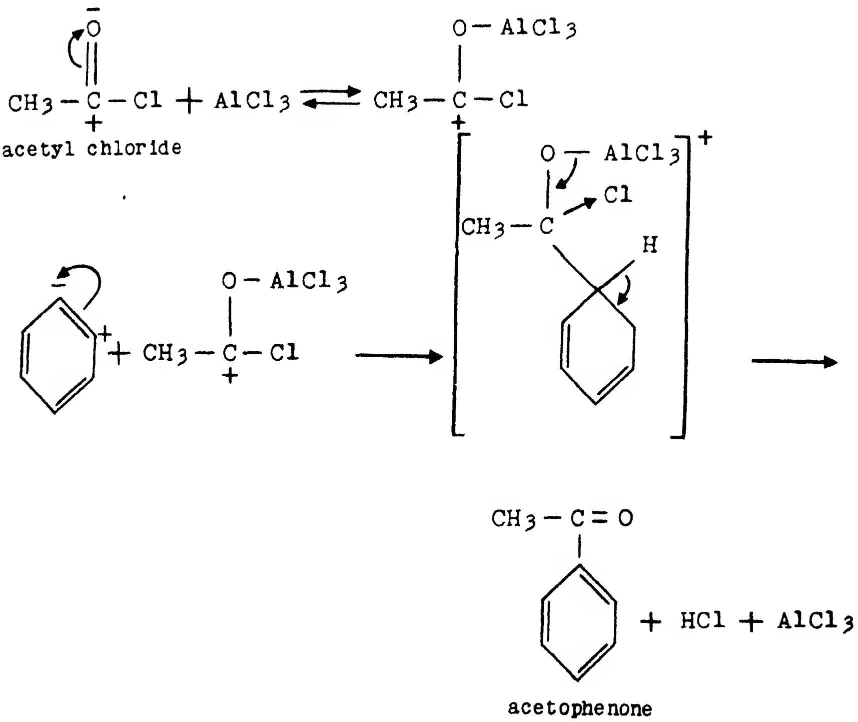
The fact that an active carbonium ion (or its equivalent $CH_3CH_2 \rightarrow Cl \rightarrow AlCl_3$) is an intermediate for this reaction also explains the tendency of many alkyl halides to undergo isomerization during the course of a Friedel-Crafts reaction. Thus benzene and *n*-propyl chloride, in the presence of aluminum chloride, yield isopropylbenzene. Highly reactive carbonium ions would be expected to undergo isomerization:



The ratio of the isomeric forms would be determined by their relative stabilities. Qualitatively the isopropyl carbonium ion may be predicted to be more stable than the *n*-propyl carbonium ion since it is more symmetrical. That is, the electron-attracting power of the electron-poor carbon atom in $CH_3-\overset{+}{C}H-CH_3$ is somewhat weakened by the fact that it is exerted in two directions, whereas the electron-poor carbon in $CH_3-CH_2-\overset{+}{C}H_2$ exerts all of its pull in one direction. Although carbonium ions have been used in formulating the above reactions, it is not necessary to consider them as free entities. The coordination complex, $\underset{+}{R}\rightarrow\underset{-}{X}\rightarrow AlX_3$, would serve the same purpose.

The above mechanism for the Friedel-Crafts reaction does not explain all of the phenomena associated with this reaction. For example, there is no adequate explanation for the fact that the introduction of a second alkyl group leads to the formation of considerable meta dialkyl benzene in spite of the fact that alkyl groups are predominantly ortho and para directing (see below).

The reactions of acyl halides with aromatic hydrocarbons, in the presence of aluminum chloride, to yield ketones may be explained in a somewhat similar manner:



In this case the aluminum chloride attaches itself to the carbonyl oxygen atom, which is more nucleophilic than the chlorine atom. Unlike the reactions with alkyl halides, these reactions require the use of at least one equivalent of aluminum chloride. Less than one equivalent would be tied up by coordination with the ketone and so would not be available for further use in the reaction.

Hydrogen fluoride may be used in place of aluminum chloride in many organic reactions. It resembles other acid condensing agents such as sulfuric acid and boron trifluoride. In general it appears to catalyze the reactions which are promoted by any or all of the above compounds and in many cases produces fewer side reactions. With aromatic hydrocarbons and alkyl halides, alkylation reactions occur. Usually only a small amount of hydrogen fluoride is necessary. The reaction proceeds in the hydrocarbon phase if some hydrogen fluoride is dissolved in it. The compound to be alkylated must be used in large excess to avoid polyalkylation. Tertiary halides react readily at 0°, secondary halides at room temperature, and primary halides at about 100°. The similarity of these reactions to the Friedel-Crafts reactions suggests a similar mechanism. Hydrogen fluoride undoubtedly acts as an electrophilic agent and serves to promote the reaction in the same manner as aluminum chloride:

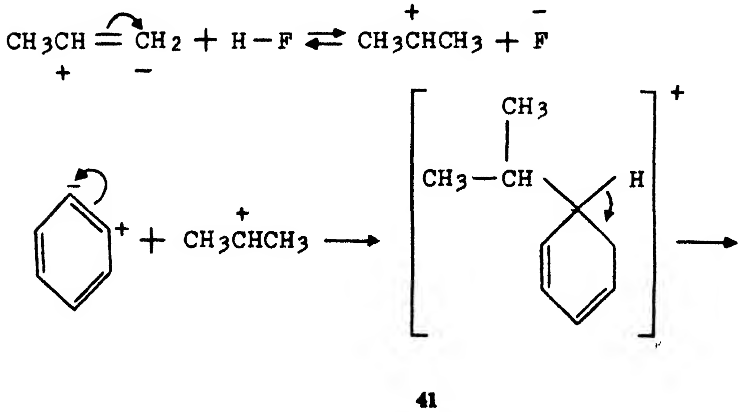
$$\overset{+}{CH_3CH_2}\rightarrow\overset{-}{Br} + H-F \rightleftharpoons [CH_3CH_2]^{+} + [Br-H-F]^{-} \qquad \text{I}$$

or

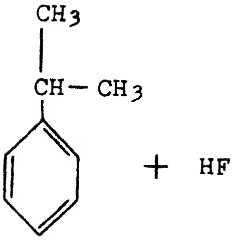
$$\overset{+}{CH_3CH_2}\rightarrow\overset{-}{Br}\cdots\cdots H-F \qquad \text{II}$$

The formation of carbonium ions does not appear to be essential for alkylation, for it will be noted that in II the polarization of the carbon-bromine bond would be enhanced through hydrogen bonding. It is possible that the fractional positive charge on the carbon atom in II is great enough to simulate ionization. Once the carbonium ion or its equivalent is formed, the reaction proceeds by the same mechanism as that shown for the Friedel-Crafts reaction. The fact that isomerization frequently occurs in these reactions may indicate that carbonium ions are formed as intermediates. For example, benzene and *n*-propyl bromide form chiefly isopropylbenzene.

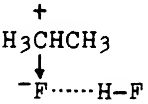
Olefins may also be used as alkylating agents under the influence of acid catalysts. Where hydrogen fluoride is used, the reaction is carried out at a low temperature and the olefin is added slowly, to prevent polymerization of the olefin. Benzene and ethylene react to form ethylbenzene. With propylene, however, the chief product is isopropylbenzene.



$$\underset{+}{CH_3CH}=\underset{-}{CH_2} + H-F \rightleftharpoons CH_3\overset{+}{C}HCH_3 + \overset{-}{F}$$

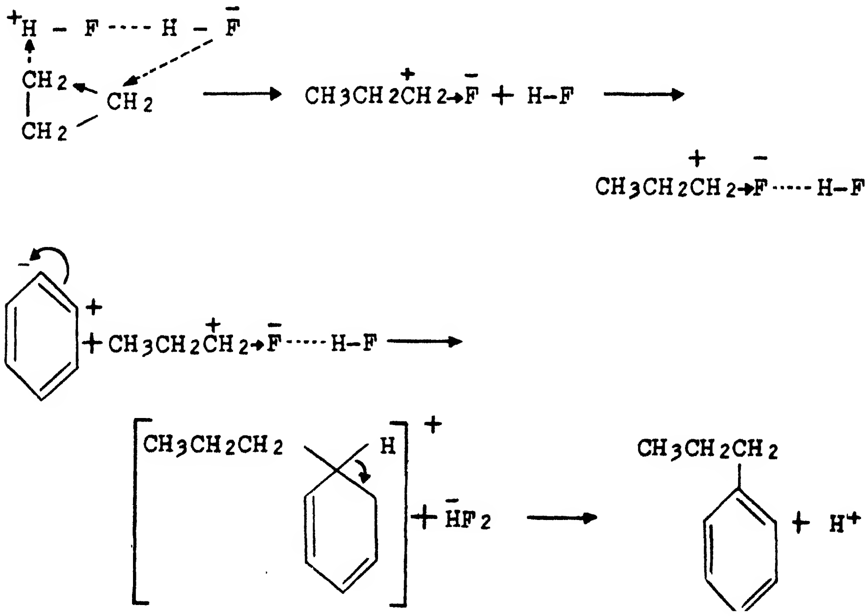


Here again the intermediate formation of carbonium ions has not been established with certainty and it would seem that a hydrogen-bonded intermediate would serve the same purpose:



$$\overset{+}{CH_3CHCH_3}\downarrow{}^{-}F\cdots\cdots H-F$$

It is interesting to note that cyclopropane is an effective alkylating agent under the influence of hydrogen fluoride and forms *n*-propyl derivatives. If the *n*-propyl carbonium ion is assumed to be an intermediate, it is not clear why it shows so little tendency to isomerize. If one assumes that *n*-propyl fluoride is the first intermediate, a possible explanation would be available:



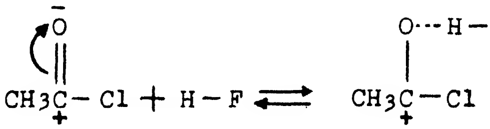
The first step in this mechanism is supported by the fact that the cleavage of cyclopropane with hydrogen bromide results in the formation of *n*-propyl bromide.

The fact that the other hydrogen halides are not effective catalysts for alkylation reactions, under the conditions used for hydrogen fluoride, suggests that the latter possesses some special characteristic. Hydrogen fluoride is highly associated, unlike the other hydrogen halides. This association is due to the extreme electronegativity of fluorine. As a result of the pronounced electron-attracting power of the fluorine atom, the hydrogen attached to it acquires a relatively high positive charge and is able to attract negative ions or atoms with fractional negative charges:

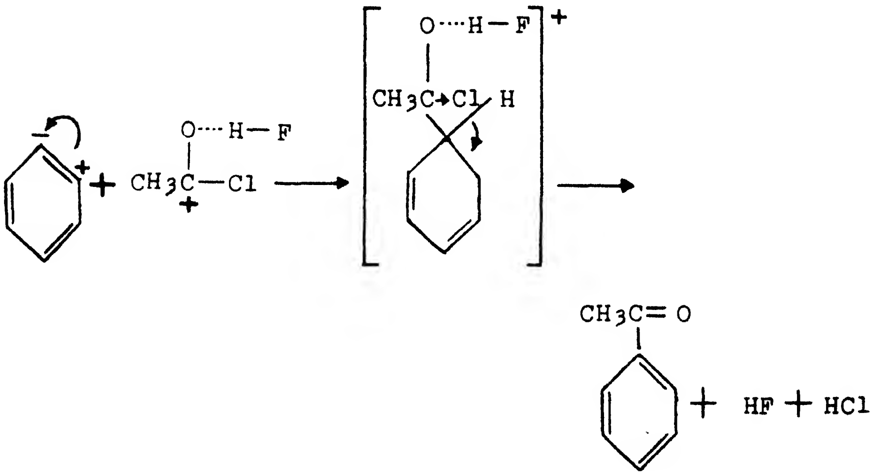
$$H{-}F \cdots H{-}F$$

The extreme tendency on the part of the hydrogen atom in hydrogen fluoride to form hydrogen bonds undoubtedly is the basis for its catalytic effect in the above reactions.

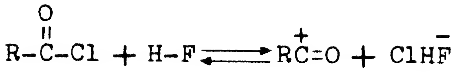
The formation of ketones from acyl halides and aromatic hydrocarbons may also be carried out under the influence of hydrogen fluoride:



$$CH_3\underset{+}{\overset{\overset{\bar{O}}{\|}}{C}}{-}Cl + H{-}F \rightleftarrows CH_3\underset{+}{\overset{\overset{O\cdots H-F}{|}}{C}}{-}Cl$$



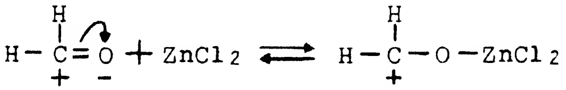
Some workers have shown preference for a mechanism involving the formation of a free acyl carbonium ion:



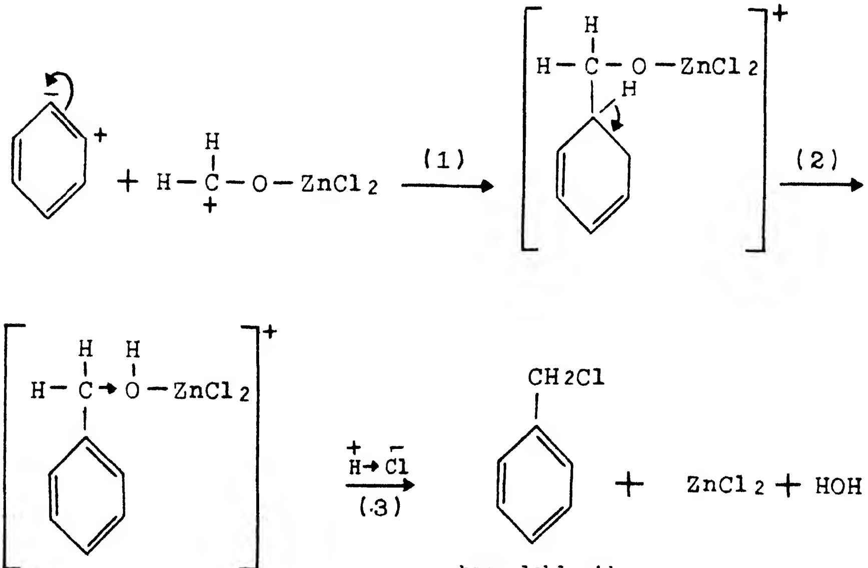
$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}Cl} + \mathrm{H{-}F} \rightleftharpoons \mathrm{R\overset{+}{C}{=}O} + \mathrm{ClH\overset{-}{F}}$$

There is no evidence available at present that can be used to determine which of the two mechanisms prevails. In view of the fact that the chlorine atom is attached to the electron-attracting carbonyl group one would not expect it could be removed so readily. It seems more probable that the hydrogen would become attached to the more electronegative oxygen atom.

Chloromethylation. This reaction represents another example of an acid-catalyzed alkylation and is frequently used to introduce chloromethyl groups into aromatic hydrocarbons (24). In general the hydrocarbon is mixed with formaldehyde (formalin or paraformaldehyde), a catalyst such as $ZnCl_2$ or H_2SO_4, and the mixture heated while a stream of hydrogen chloride is passed into the reaction mixture. In some cases where the ring is activated by the presence of *o*- and *p*-directing substituents, a catalyst is not required. The chloromethylation of benzene may be represented as follows:



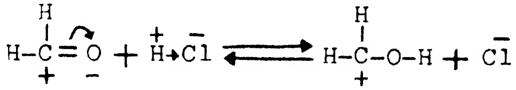
$$\mathrm{H{-}\underset{+}{\overset{\overset{H}{|}}{C}}{=}\underset{-}{O}} + \mathrm{ZnCl_2} \rightleftharpoons \mathrm{H{-}\underset{+}{\overset{\overset{H}{|}}{C}}{-}O{-}ZnCl_2}$$



benzylchloride

A small amount of the *p*-di (chloromethyl) benzene is also formed, even when excess benzene is used. The addition of zinc chloride to the carbonyl oxygen atom furnishes a carbonium ion which is capable of polarizing one of the bonds in the benzene ring and subsequently adding. The energy of formation of the new carbon-carbon bond is sufficient to overcome the resonance energy of the benzene ring. In the second step a hydrogen is split off as a proton through the attraction of the electron-deficient carbon atom in the ortho position. This takes place with loss of energy and restoration of the resonant state of the benzene ring. The last step which involves the cleavage of a carbon-to-oxygen bond is discussed under reactions of the alcohols (Chap. IX).

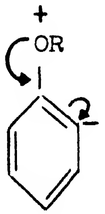
p-Xylene can be chloromethylated without the aid of a catalyst. In this case the necessary carbonium ion is formed from formaldehyde and hydrogen chloride:

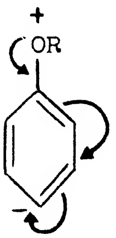


$$\mathrm{H-\overset{\displaystyle H}{\underset{+}{C}}=\underset{-}{O} + \overset{+}{H}\rightarrow\overset{-}{Cl} \rightleftharpoons H-\overset{\displaystyle H}{\underset{+}{C}}-O-H + \overset{-}{Cl}}$$

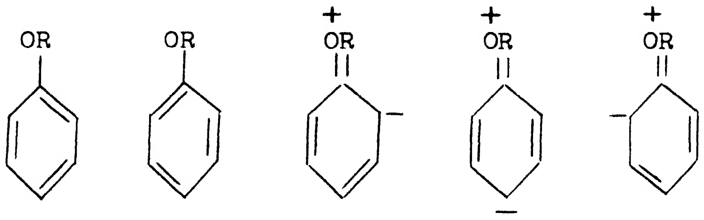
Chloroalkylation can be carried out with some other aldehydes. α-Chloroethyl derivatives may be obtained through the use of acetaldehyde for example. More side reactions are possible when aldehydes other than formaldehyde are employed and consequently they have not been so widely used.

The presence of an electron-release substituent (*o*- and *p*- directing) in the benzene ring usually makes substitution easier, while an electron-attracting substituent (*m*- directing) retards further substitution. In general, ortho and para substitution is associated with activation of the benzene ring and meta substitution with deactivation. The common ortho and para directing groups include: OH, OR, NH_2, NHR, NR_2, Ar, R, Cl, Br, and I. It is believed that such groups increase electron availability at the ortho and para positions and thus facilitate the attack of electrophilic reagents at these points. The first five of the above groups function principally through a resonance effect. In these five groups the atom which is attached to the ring possesses unshared electrons which participate in resonance with the ring. The resulting activation at the ortho and para positions may be shown as follows:



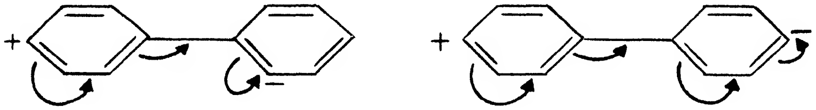


For a clearer picture of this effect it is necessary to consider all the important forms which contribute to the net structure:



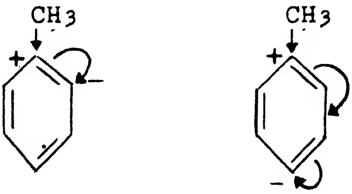
The first two forms (Kekulé forms) are the more stable structures, but all five participate in the resonance. The contribution of the ionic or quinoid structures causes an enhanced electron availability at the *o*- and *p*- positions. This contribution and its *o*- and *p*-directing effect will be increased by the presence of an electrophilic agent.

Aryl groups in general are ortho and para directing. This is not adequately explained by assuming only an inductive electron-release effect on the part of the aryl radical. A possible explanation for the increased availability of electrons in the ortho and para positions may be based upon the following unperturbed ionic structures:

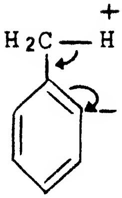


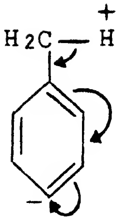
Such displacements would be aided by electrophilic agents.

Alkyl groups originally were thought to exert their directive influence through an inductive electron-release effect:



It is doubtful if the inductive effect alone is strong enough to account for the observed directive influence of these groups. Baker and Nathan (25) suggested that an electron pair uniting the carbon to hydrogen in the alkyl group may come under the influence of the adjacent aromatic ring and thus become a contributor to the resonance state of the molecule:





It will be noted that this effect (hyperconjugation) is in the same direction as the inductive effect and the result would be the strengthening of the ortho and para directing influence.

It has been pointed out by Baker and Nathan that the electron-release effects of alkyl groups when attached to aromatic rings are in the reverse order

$$CH_3 > C_2H_5 > \text{iso } C_3H_7 > \text{tert. } C_4H_9 \qquad (A)$$

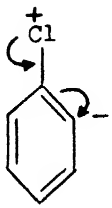
to that previously observed (where inductive effects only are operating):

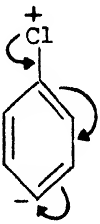
$$\text{tert. } C_4H_9 > \text{iso } C_3H_7 > C_2H_5 > CH_3 \qquad (B)$$

If it be assumed that alkyl groups may participate in resonance with the ring, providing the carbon atom attached to the ring has at least one attached hydrogen atom, a logical explanation for the reverse order is available.

It is not an easy matter to predict whether the inductive electron-release effect (*B*) or the resonance effect (*A*) will be predominant in any given case. Ingold and Taher (26) have investigated one case where the resonant effects were predcminant. They have shown that the rates of hydrolysis of *p*-alkylbenzhydryl chlorides, $(RC_6H_4)_2CHCl$, vary in the order $CH_3 > C_2H_5 > \text{iso } C_3H_7 > \text{tert. } C_4H_9$.

The halogens exert a directive influence chiefly through a resonance effect:

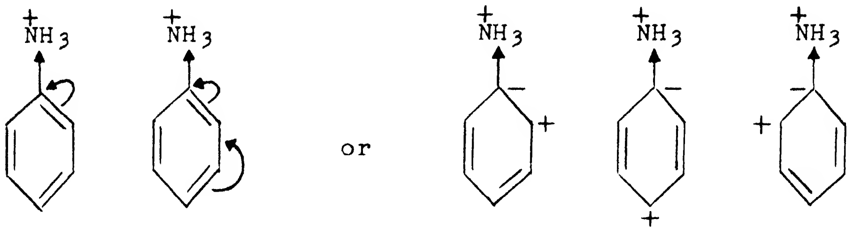




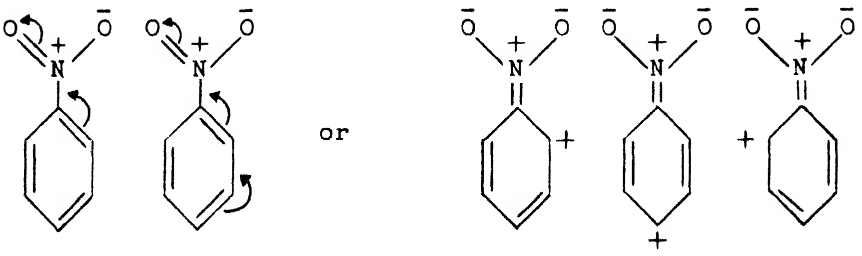
As pointed out earlier in the case of vinyl bromide, the electron-attracting properties of the halogens are less effective when they are attached to unsaturated carbon atoms. This is indicated by the fact that the C—Cl bond length is shorter than the C—Cl bond length in a saturated chloride such as ethyl chloride. Actually the inductive effect of the halogens would tend to decrease electron availability on all of the ring carbon atoms. The resonance effect, however, tends to lower the deactivation at the *o*- and *p*-positions. Thus the halogens direct predominantly to these positions.

The common meta directing groups include: $\overset{+}{\mathrm{N}}\mathrm{H}_3$, NO_2, COOH, SO_2OH, CHO, COR, and CN. These groups are electron attracting and tend to decrease electron availability on all of the ring carbon atoms through an inductive effect, resonance effect, or both. The decrease is less on the meta carbon atoms, so that substitution takes place most readily at these positions. As expected, meta substitution is normally much less rapid than ortho and para substitution.

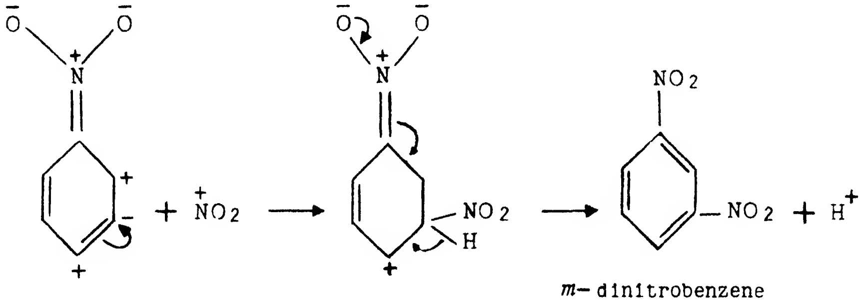
The most powerful of the meta directing groups, $\overset{+}{\mathrm{N}}\mathrm{H}_3$, $\overset{+}{\mathrm{N}}\mathrm{H}_2\mathrm{R}$, and $\overset{+}{\mathrm{N}}\mathrm{HR}_2$, direct almost exclusively to the meta position. Here it is impossible for the atom attached to the ring to increase its covalence. In this case it is the strong inductive power of the positive pole which causes the decrease in electron availability:



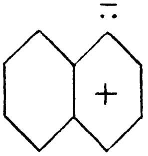
The remaining meta directing groups function chiefly through a resonance effect, similar to that produced by OH and NH_2 but in the opposite direction. In the case of the nitro group, the nitrogen atom is the positive end of a dipole and its effect on the ring may be shown as follows:

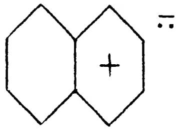


Examination of the above structures shows that the decrease in electron availability is smallest on the meta carbon atoms. Electrophilic agents would therefore be expected to add to the meta positions where electron availability has been least altered. The introduction of a second nitro group into nitrobenzene may be shown as follows:

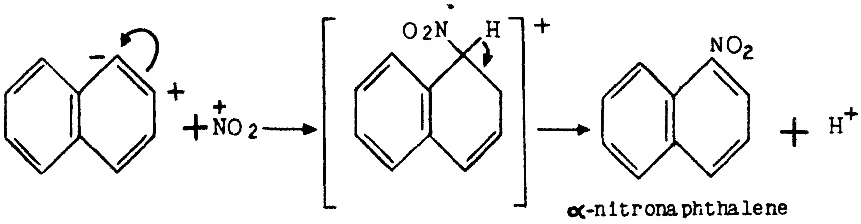


The generalizations noted above for substitution in the benzene ring may be applied to some extent to the polycyclic condensed benzene ring hydrocarbons. Chlorination, nitration, and sulfonation of naphthalene yield chiefly α-substituted derivatives. Since the various positions in naphthalene are not equivalent, as they are in benzene, it is necessary to consider the polarization of the molecule produced by the attacking reagent. There are seven possible ionic structures for the carbonium ion which is formed when the reagent attacks position 1, and six forms when the reaction occurs at position 2:





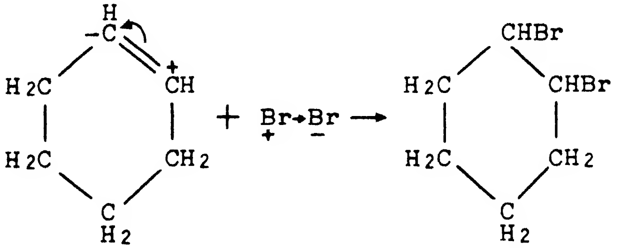
Substitution at position 1 should therefore take place more readily than at 2. Substitution at the 1 position, showing only one of the resonance forms, may be pictured as follows:



CHAPTER VII

Reactions of Alicyclic Hydrocarbons

These compounds, with the exception of the three and four carbon atom ring systems, behave chemically much like the alkanes and alkenes. Cyclohexane, for example, is somewhat similar to the alkanes in chemical behavior, while cyclohexene undergoes the usual addition reactions characteristic of the alkenes:



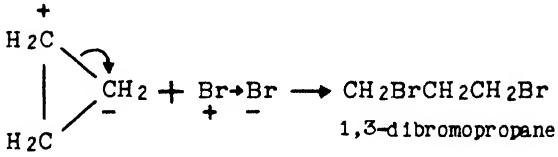
1,2-dibromocyclohexane

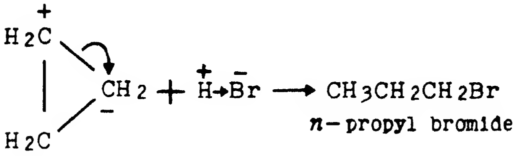
The mechanisms discussed previously for additions to the olefins are applicable to the above type of reaction also.

The three and four carbon atom ring compounds, such as cyclopropane and cyclobutane, have strained ring systems. The strain theory was first suggested in 1885 by Baeyer. The four valence bonds of carbon are equivalent and are directed towards the corners of a regular tetrahedron, so that the angle between any two of these bonds is the same and is 109° 28′. Baeyer assumed that any deviation from this normal value created a strain with a resulting decrease in stability. According to this theory, the acetylene bond and olefin bond represent strained bonds and so may be regarded as unstable or reactive centers. The ease with which they react by addition may be considered as a measure of their stability. Assuming that the valence forces lie in a straight line, the valence distortion or displacement is much greater in the case of cyclopropane than with cyclobutane and is very small for cyclopentane.

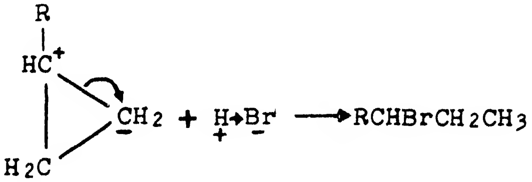
The formation of alicyclic ring systems containing more than five carbon atoms would involve a widening of the valence angles if the carbon atoms were in one plane, and for very large rings would involve an unbelievable stretching. Actually, the carbon rings above five carbon atoms are not monoplanar, and it is believed that there is little valence strain in these rings (27).

The addition reactions of the olefins involve the cleavage of one of the bonds between the unsaturated carbon atoms. In view of the fact that the strain in the cyclopropane ring is similar to (although smaller than) that in the olefin bond, it is not surprising that cyclopropane undergoes cleavage and addition with certain reagents such as bromine and hydrogen bromide. The latent tendency to cleave may be considered to become active under the influence of an electrophilic reagent:

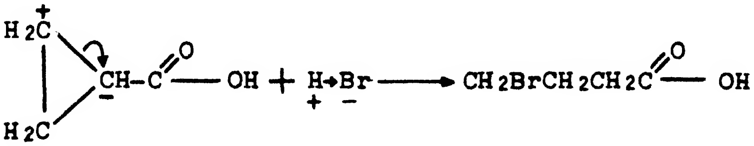




For alkyl cyclopropanes, the reaction with hydrogen bromide takes place as follows:



The bromine adds chiefly to the carbon atom attached to the alkyl group (28). In other words, the position of cleavage is largely determined by the electron-release effect of the alkyl group. The same effect was previously noted as determining the direction of polarization in propylene. The addition of hydrogen bromide to cyclopropane carboxylic acid yields 4-bromobutanoic acid:



This result too would be expected since the carboxyl group is electron attracting.

Cyclobutane undergoes similar reactions but less readily, while cyclopentane fails to undergo cleavage and addition.

CHAPTER VIII

Reactions of Halogen Compounds

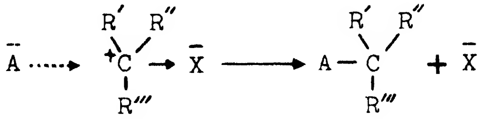
Aliphatic Halogen Compounds

Alkyl halides, RX. The alkyl halides may be regarded as monohalogenated alkane hydrocarbons. It is important to note that the alkyl halides, due to the electron attraction (inductive effect) of the halogen atom, are polarized molecules, $\overset{+}{R}\rightarrow X$. They may be compared to metal halides such as NaCl where polarization is extreme so that the salt is ionized completely, being comprised entirely of $\overset{+}{Na}$ and $\overset{-}{Cl}$ ions. Although the polarization of the alkyl halides is not so great, it is not surprising that their reactions often appear to be similar to those of sodium chloride. Their reactions may be classed as displacement reactions of one type or another:

$$R\text{-}X + C \longrightarrow R\text{-}C + X$$

In this general equation, C may represent either charged or uncharged atoms or groups. The energy of formation of the new linkage contributes in some measure to the cleavage of the old linkage. The energy necessary for such reactions is often less than that necessary to dissociate RX into R and X. Considerable evidence points to the fact that the formation of RC may begin before the dissociation of R—X is completed. The ease with which such reactions take place is related to the bond energies in compounds R—X and R—C, and in general the smaller the bond energy in R—X the greater the tendency to react. The activity of the alkyl halides decreases in the order RI $>$ RBr $>$ RCl $>$ RF. This is consistent with the known bond energies C—F $>$ C—Cl $>$ C—Br $>$ C—I. It has been suggested that in addition to the inductive effect (permanent polarization) there is an additional effect called the inductomeric effect which operates through an inductive mechanism. The latter is produced only on the demand of polarized attacking reagents. It has been further suggested (29) that in the case of the halogens, fluorine, the smallest atom, will have the greatest control over its valence electrons and iodine, the largest atom, will have the least control. Hence it may be concluded that the following order would result from the inductomeric effect, I $>$ Br $>$ Cl $>$ F. In general then, the larger iodine atom being less tightly bound to carbon should exhibit the largest inductomeric effect and the fluorine the least.

Nucleophilic displacements. These reactions involve replacement of the halogen atom by a nucleophilic atom or group. Nucleophilic reagents furnish electron-rich ions (anions) which may share an electron pair with an electron-deficient center (cation) and thus form a new bond. Such displacements cause the inversion of the configuration of the carbon atom on which they occur. This applies to all nucleophilic displacements on carbon. Accumulated evidence indicates that the displacement attack is from the back side of the molecule. In other words, the attacking anion approaches the center of the tetrahedral face which is opposite to the vertex of the tetrahedron occupied by the halogen atom. This may be shown as follows:



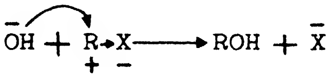
Because of the mutual repelling actions of the $\bar{X}$ and $\bar{A}$, the latter might be expected to approach the carbon atom on the side opposite to the halogen atom.

The action of water on alkyl halides is greatly facilitated by the presence of bases. The attacking reagent is the hydroxyl ion. The mechanisms for this type have been studied by Ingold, Hughes, and co-workers (30), who suggested two possible mechanisms:

I $$\overset{+}{R}\rightarrow\overset{-}{X} \xrightarrow{\text{slow}} \overset{+}{R} + \overset{-}{X} \qquad \text{unimolecular}$$

$$\overset{+}{R} + \overset{-}{O}H \longrightarrow ROH$$

II



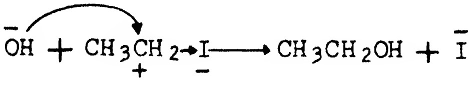
$$\overset{-}{O}H + \underset{+}{R}\rightarrow\underset{-}{X} \longrightarrow ROH + \overset{-}{X} \qquad \text{bimolecular}$$

It has been demonstrated that water molecules enter into the unimolecular ionization. In other words, it is a solvolytic ionization. The unimolecular reaction in this case is actually polymolecular. The unimolecular mechanism would be favored by a large electron-release effect on the part of R. Tertiary halides undergo hydrolysis more readily than primary or secondary halides. The hydrolysis of a tertiary halide would be expected to follow mechanism I because of the electron-release effects of the three alkyl groups, $R_3 \rightarrow C \rightarrow X$. It has been demonstrated that the rate of hydrolysis of tertiary butyl chloride in aqueous acetone or aqueous alcohol is the same in acid, neutral, or dilute alkali solutions and is independent of the hydroxyl ion concentration:

$$(CH_3)_3C\rightarrow Cl \longrightarrow (CH_3)_3\overset{+}{C} + \overset{-}{Cl}$$

$$(CH_3)_3\overset{+}{C} + \overset{-}{OH} \longrightarrow \underset{\text{tertiary butyl alcohol}}{(CH_3)_3COH}$$

The hydrolysis of isopropyl halides proceeds simultaneously by the unimolecular and bimolecular mechanisms, while the hydrolysis of primary halides, such as ethyl iodide, occurs by the bimolecular mechanism. In the latter case the velocity is proportional to the concentrations of both the alkyl halide and the hydroxyl ion:

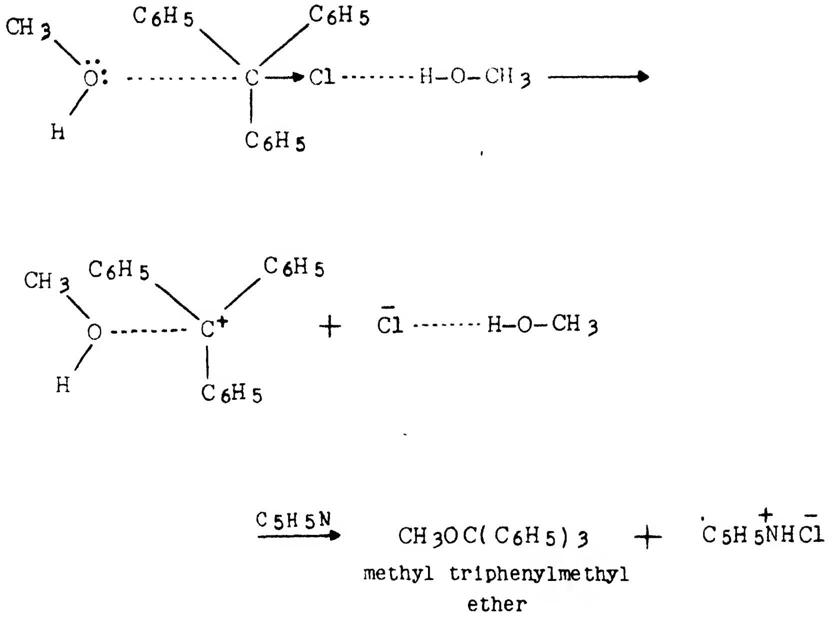


$$\overset{-}{OH} + CH_3\underset{+}{C}H_2\rightarrow\underset{-}{I} \longrightarrow CH_3CH_2OH + \overset{-}{I}$$

Here the hydroxyl ion is attracted to the fractionally charged carbon atom of the $\overset{+}{C}\rightarrow\overset{-}{I}$ bond and the formation of the C—OH bond begins before the ionization of the alkyl halide is completed. The greater nucleophilic activity of the hydroxyl ion thus leads to the cleavage of the carbon-to-iodine bond. In the alkaline hydrolysis of tertiary, secondary, and primary alkyl halides, the electron-release effects as well as the ease with which hydrolysis occurs decrease in the order $R_3\rightarrow CX > R_2\rightarrow CHX > R\rightarrow CH_2X$.

The aryl-substituted methyl halides behave in a somewhat similar manner. Triphenyl chloromethane, $(C_6H_5)_3CCl$, and diphenyl chloromethane, $(C_6H_5)_2CHCl$, follow the unimolecular mechanism, while benzyl chloride proceeds simultaneously by the unimolecular and bimolecular mechanisms.

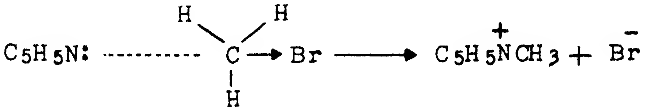
The unimolecular displacement reactions, as mentioned previously, are not as simple as the equations shown above would indicate. It has been demonstrated recently (30*b*) that the reaction between triphenyl-methyl chloride and methanol, in benzene solution, is actually a termolecular reaction, first order with respect to the halide and second order with respect to the methanol. It was concluded that the ionization step is the result of simultaneous solvating attacks on the carbon and halogen atoms of the C—X bond. Pyridine was used in the reaction to absorb the hydrogen halide and make the reaction irreversible. The mechanism was shown as follows:



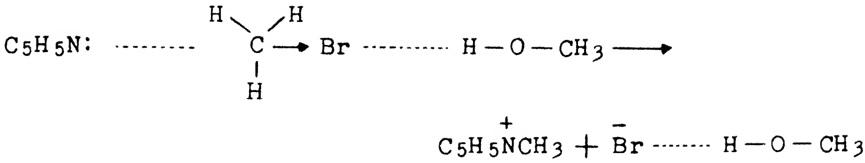
The reaction is the result of a push-pull attack on the part of the methanol. The solvating attack on the halogen atom may be regarded as an example of the so-called inductomeric effect. This effect undoubtedly contributes to the rates of both unimolecular and bimolecular displacement reactions.

In a more recent paper (30*c*), it has been shown that methyl bromide, which has been considered to undergo displacement reactions by the bimolecular (direct) mechanism, also undergoes termolecular displacements in benzene solution.

Methyl bromide reacts with pyridine, in benzene solution, to form methylpyridinium bromide. At 100° the reaction is second order:



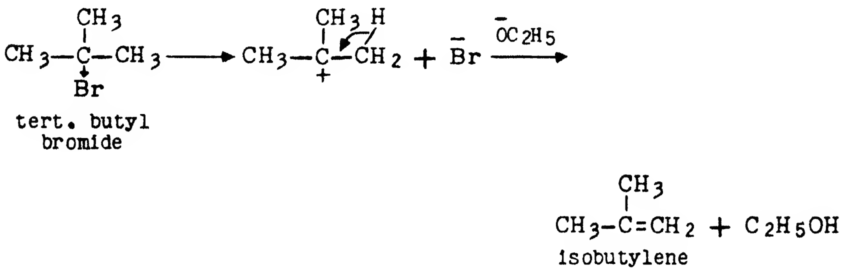
In this case, apparently there are no substances present which are capable of effectively solvating the bromide ion. In the presence of compounds which readily solvate halide ions, such as methanol, phenol, or mercuric bromide, the rate of reaction is increased and the reactions have been shown to be third order. The mechanism was illustrated as follows:



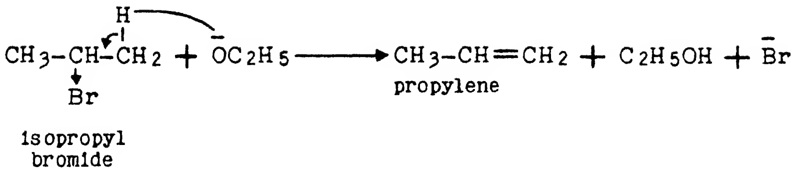
Swain (30*b* and *c*) believes that nucleophilic displacements from saturated carbon atoms require a push-pull attack and so are never unimolecular or bimolecular. Even benzene is believed to exert a polarization solvation for the halide ion.

From this work it can be seen that the so-called unimolecular and bimolecular displacements show only a quantitative difference. This difference is due to the relative rates of formation of the new covalent bonds on the carbon atom in the carbon-halogen bond in primary and tertiary halides. It is believed to occur most rapidly in the case of primary halides. Consequently, the intermediates, in nucleophilic displacements with tertiary halides, may be considered to possess more of a carbonium ion character than those from primary halide displacements. It is suggested that the unimolecular mechanism be called the carbonium ion mechanism and the bimolecular path, the direct mechanism.

The alkyl halides when treated with alcoholic solutions of potassium hydroxide give quite different results. Primary halides yield mixtures of ethers and olefins, secondary halides yield mostly olefins, and tertiary halides give olefins only. For example, *n*-propyl bromide yields *n*-propyl ethyl ether and smaller amounts of propylene, isopropyl bromide gives mostly propylene, and only isobutylene is obtained from tertiary butyl halides. The strongly nucleophilic ethoxide ion is the active agent in these reactions. The formation of an olefin by the elimination of a molecule of hydrogen halide may proceed either through a unimolecular mechanism



or by a bimolecular mechanism:

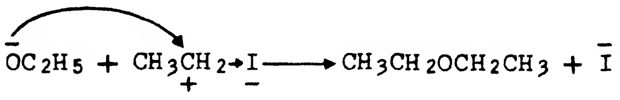


$$CH_3-\underset{\underset{Br}{\downarrow}}{CH}-\overset{H}{CH_2} + \bar{O}C_2H_5 \longrightarrow CH_3-CH{=}CH_2 + C_2H_5OH + \bar{Br}$$

The unimolecular mechanism will be favored by the strong electron-release effects of three alkyl groups attached to $\overset{\searrow}{\underset{\nearrow}{\rightarrow}}C{-}X$ in the case of the tertiary halides. The elimination of hydrogen halide from primary and secondary halides is believed, by some chemists, to occur mainly by the bimolecular mechanism.

Since olefins only are obtained from the interaction of tertiary butyl halides and alcoholic potassium hydroxide, it may be assumed that the unimolecular mechanism promotes olefin formation. In this case the attraction of the positive carbon atom for electrons from the adjacent carbon-to-hydrogen bonds is amplified by the presence of a base ($\bar{O}C_2H_5$) which itself would facilitate the formation of a proton. With primary halides, where the bimolecular mechanism prevails, the driving force for olefin formation is less (decreased tendency for proton formation). Consequently, considerable quantities of ether are formed by the replacement of the halogen atom with the ethoxy group.

The interaction of alkyl halides and sodium ethoxide in dry alcohol (Williamson reaction) to form ethers involves a nucleophilic displacement on carbon:



$$\bar{O}C_2H_5 + CH_3\underset{+}{C}H_2\rightarrow\underset{-}{I} \longrightarrow CH_3CH_2OCH_2CH_3 + \bar{I}$$

The reaction is of no value for tertiary halides, for the latter yield olefins. Nucleophilic displacements with alkyl halides are frequently accompanied by olefin formation. This is particularly true for the tertiary halides which often form olefins exclusively. This is attributed to the greater tendency of the halogen attached to the tertiary carbon atom to ionize, with the consequently greater tendency for the ionization of a β-hydrogen atom.

Other common nucleophilic displacements are those which occur between alkyl halides and potassium hydrogen sulfide, ammonia, and potassium cyanide respectively:

$$CH_3\overset{+}{C}H_2\rightarrow\overset{-}{I} + \overset{-}{S}H \longrightarrow CH_3CH_2SH + \overset{-}{I}$$

thyl thioalcohol

$$CH_3\overset{+}{C}H_2\rightarrow\overset{-}{I} + \overset{-}{N}H_2 \longrightarrow CH_3CH_2NH_2 + \overset{-}{I}$$

ethylamine

$$CH_3\overset{+}{C}H_2\rightarrow\overset{-}{I} + \overset{-}{C}N \longrightarrow CH_3CH_2CN + \overset{-}{I}$$

ethyl cyanide

Nucleophilic activity of anions is often approximated by comparing the ionization constants of the corresponding acids. Thus, $\overset{-}{O}H$, $\overset{-}{S}H$, $\overset{-}{C}N$, and $\overset{-}{N}H_2$ are more nucleophilic than the halogens. Similarly, it would be expected that $\overset{-}{O}C_2H_5$ would be more nucleophilic than $\overset{-}{O}H$.

Atom or radical displacements. These reactions may be brought about by atoms or radicals which possess a single unshared electron. The Wurtz reaction may be illustrated as follows:

$$2\ CH_3CH_2:\overset{\cdot\cdot}{\underset{\cdot\cdot}{I}}: + 2\ Na\cdot \longrightarrow 2\ CH_3CH_2\cdot + 2:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Na}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{I}}:$$

$$2\ CH_3CH_2\cdot \longrightarrow CH_3CH_2CH_2CH_3$$

n-butane

There is no doubt that free radicals are formed as intermediates in these reactions when carried out in the gas phase (31). There is some evidence available which indicates that the radical mechanism also holds when the Wurtz reaction is carried out in solution (32). Another mechanism, involving the preliminary formation of free radicals, may be written for the reaction:

$$CH_3CH_2:\overset{\cdot\cdot}{\underset{\cdot\cdot}{I}}: + Na\cdot \longrightarrow CH_3CH_2\cdot + Na:\overset{\cdot\cdot}{\underset{\cdot\cdot}{I}}:$$

$$CH_3CH_2\cdot + Na\cdot \longrightarrow CH_3CH_2:Na$$

$$CH_3\overset{-}{C}H_2\leftarrow\overset{+}{N}a + CH_3\overset{+}{C}H_2\rightarrow\overset{-}{I} \longrightarrow CH_3CH_2CH_2CH_3 + NaI$$

The last step consists of a nucleophilic displacement. This mechanism represents a definite possibility since sodium alkyls may be formed from sodium and alkyl halides. The sodium alkyls are saltlike in character and could furnish the $\overset{-}{R}$ necessary for the displacement.

The formation of alkyl magnesium halides (Grignard compounds) involves a similar mechanism. Grignard reagents as commonly used are equilibrium mixtures of an alkyl magnesium halide and a dialkyl magnesium:

$$2\ R{-}Mg{-}X \rightleftharpoons R{-}Mg{-}R + MgX_2$$

Since both of the organomagnesium compounds undergo the same type reactions, the formula RMgX is sufficient to represent the Grignard compound. The interaction of an alkyl halide and magnesium may be shown as follows:

$$CH_3CH_2\!:\!\underset{..}{\ddot{I}}\!: + \cdot Mg\cdot \longrightarrow CH_3CH_2\cdot + \cdot Mg\!:\!\underset{..}{\ddot{I}}\!: \longrightarrow \underset{\text{ethyl magnesium iodide}}{CH_3CH_2MgI}$$

The extent to which a Wurtz reaction may occur

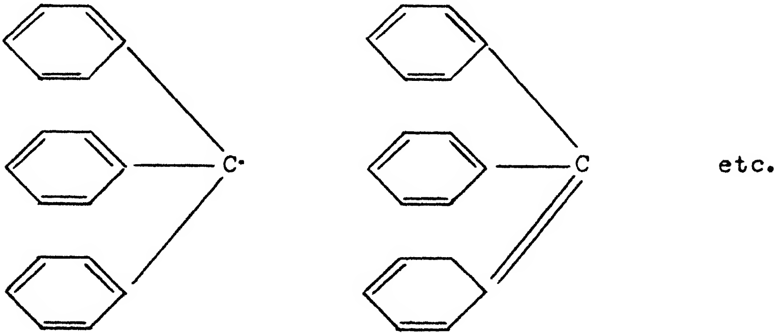
$$2R\cdot \longrightarrow R{-}R$$

is usually small.

The existence of free radicals was indicated first by Gomberg's observation that hexaphenylethane dissociates in nonpolar solvents to form free radicals:

$$(C_6H_5)_3C\!:\!C(C_6H_5)_3 \rightleftharpoons 2(C_6H_5)_3C\cdot$$

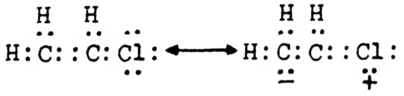
All such radicals possess an unpaired electron and are electrically neutral. In the free methyl radical the unpaired electron is concentrated on the carbon atom and is available at all times to form the ethane bond. The greater stability of the free triphenylmethyl radical (reduced tendency to form the ethane bond) is attributed to resonance (33). This resonance distributes the unpaired electron over the whole molecule thus decreasing the availability of the odd electron for bond formation:



The odd electron resonates among ten positions with the result that there are six equivalent forms with the unpaired electron on an ortho carbon atom and three in which it is on a para carbon atom. The degree of stabilization of the free radical depends, to some extent, on the number of unperturbed forms (34).

Di- and polyhalogen derivatives. The mechanisms discussed for the alkyl halides are applicable in general to the di- and polyhalogen derivatives of the saturated hydrocarbons. However, it should be noted that when two or more halogen atoms are attached to the same carbon atom, there results a marked decrease in the activity of the halogens. It is probable, in the case of compounds such as 1,1-dichloroethane, that the inductive effects of the two halogen atoms oppose each other to some extent and thus actually cause a decrease in their individual effects.

Monohalogen derivatives of the olefins. The reactivity of the halogen atom in this type of compound is often greatly altered by the presence of the double bond. For example, when the halogen is directly attached to an unsaturated carbon atom, it is characterized by a reduced tendency to undergo the usual alkyl halide reactions. The relative inertness of the chlorine atom in vinyl chloride is due to resonance between two unperturbed structures:

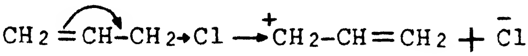


$$\mathrm{H:\overset{\overset{H}{\cdot\cdot}}{C}::\overset{\overset{H}{\cdot\cdot}}{C}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:} \longleftrightarrow \mathrm{H:\underset{\underset{-}{\cdot\cdot}}{\overset{\overset{H}{\cdot\cdot}}{C}}:\overset{\overset{H}{\cdot\cdot}}{C}::\underset{\underset{+}{\cdot\cdot}}{Cl}:}$$

This theory is supported by the fact that the carbon-to-chlorine bond length in vinyl chloride is shorter than the C—Cl bond length in an alkyl chloride. The chlorine atom is more firmly bound to the carbon atom and consequently is less reactive. The corresponding iodide is somewhat more reactive since the iodine atom is less firmly bound. The electromeric effects of the halogens decrease in the order F$\rangle$ Cl$\rangle$ Br$\rangle$ I.

It has been stated that the resonance hypothesis need not be used to explain the shortened carbon-to-chlorine bond in vinyl chloride (35). In this case it is necessary to assume that the alpha carbon atom acquires an added positive charge as a result of an electromeric shift, $\overset{\curvearrowleft}{\underset{-}{\mathrm{C}}=\underset{+}{\mathrm{C}}}\mathrm{—Cl}$, and as a consequence the carbon atom would have increased attraction for the chlorine atom and a shortening of the bond would be expected. It is difficult to understand why the electromeric shift would take place as indicated above. If the chlorine atom is exerting only an electron-attracting effect, the shift would occur in the opposite direction. For the present there appears to be a much firmer basis for the resonance explanation.

When the halogen is attached to a saturated carbon atom adjacent to the unsaturated carbon as in allyl chloride, the halogen is characterized by enhanced activity. The halogen has a greater tendency to separate as an anion than the halogen in *n*-propyl halides. This increased tendency is a result of the greater electron-release effect of the allyl group:



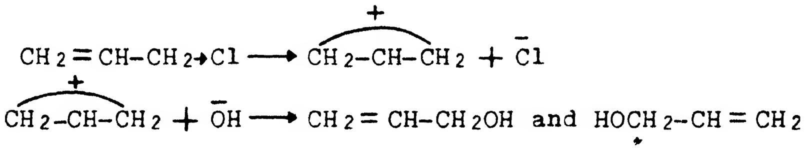
$$\mathrm{CH_2{=}CH{-}CH_2{\rightarrow}Cl \longrightarrow \overset{+}{C}H_2{-}CH{=}CH_2 + \overset{-}{Cl}}$$

The cation with its electron-deficient carbon atom resonates between two structures

$$\mathrm{CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH_2}$$

and is best represented as a resonance hybrid, $\overset{+}{\overbrace{\mathrm{CH_2{-}CH{-}CH_2}}}$. The resonance stabilizes the cation, decreasing its tendency to recombine with the anion which itself is quite stable. We see that the resonance effect thus reinforces the normal inductive effect of the halogen, the separation of the halogen atom as an anion being promoted.

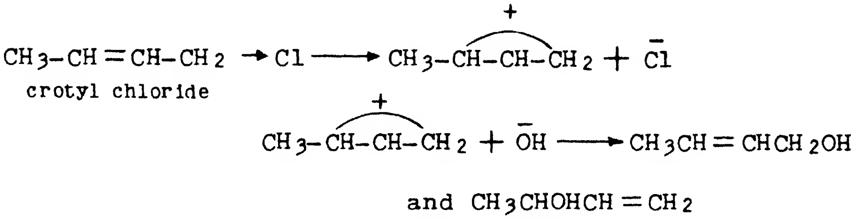
It will be noted that in any nucleophilic displacement with allyl chloride, the anion of the reagent may become attached to either end of the allylic system, providing the unimolecular mechanism is followed:



$$\mathrm{CH_2{=}CH{-}CH_2{\rightarrow}Cl \longrightarrow \overset{+}{\overbrace{CH_2{-}CH{-}CH_2}} + \overset{-}{Cl}}$$

$$\mathrm{\overset{+}{\overbrace{CH_2{-}CH{-}CH_2}} + \overset{-}{O}H \longrightarrow CH_2{=}CH{-}CH_2OH \text{ and } HOCH_2{-}CH{=}CH_2}$$

The two possible structures are identical in this case. In other cases two products are often obtained:



$$\mathrm{CH_3{-}CH{=}CH{-}CH_2 \rightarrow Cl \longrightarrow CH_3{-}\overset{+}{\overbrace{CH{-}CH{-}CH_2}} + \overset{-}{Cl}}$$

crotyl chloride

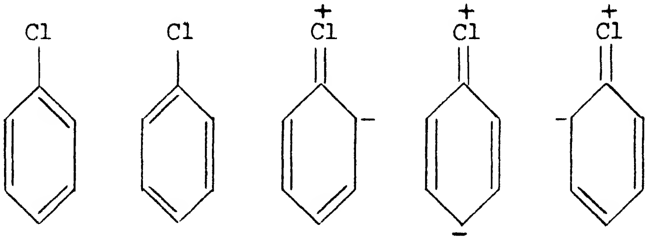
$$\mathrm{CH_3{-}\overset{+}{\overbrace{CH{-}CH{-}CH_2}} + \overset{-}{O}H \longrightarrow CH_3CH{=}CHCH_2OH}$$

$$\mathrm{\text{and } CH_3CHOHCH{=}CH_2}$$

In the above example, a mixture of crotyl alcohol and methyl vinyl carbinol is obtained. Allylic rearrangements are quite common for compounds which contain the grouping —CH=CH—CH_2—.

In olefin halides of the type $RCH{=}(CH_2)_nCH_2X$, the resonance effects noted above are not possible, and in general the halogen atom and double bond act independently.

Aromatic or aryl halides. The aryl halides resemble the vinyl halides in that both contain the group, $-\overset{|}{C}=\overset{|}{C}-X$. The reactivity of halogen directly attached to an aromatic ring is greatly reduced for the same reasons noted for the vinyl halides. The unshared electrons on the halogen atom permit resonance among the following structures (for chlorobenzene):



This effect is revealed by the shortening of the C–Cl bond length. The contribution of the ionic forms is small but it is intensified by the presence of electrophilic reagents.

The aryl halides, in general, react with sodium, although not as readily as the alkyl halides and the yields are low. Reactions of the aryl halides with magnesium yield the corresponding aryl magnesium halides. In general the latter reactions take place more slowly than with the alkyl halides:

$$\underset{\text{bromobenzene}}{2C_6H_5Br} + 2Na \longrightarrow \underset{\text{diphenyl}}{C_6H_5C_6H_5} + 2NaBr$$

$$C_6H_5Br + Mg \longrightarrow \underset{\substack{\text{phenyl magnesium}\\ \text{bromide}}}{C_6H_5MgBr}$$

An interesting method for the preparation of diphenyls has been reported by Kharasch and Fields (36). An aryl Grignard reagent is treated with an organic halide in the presence of anhydrous cobalt chloride. For example, when one mole of phenyl bromide is added to a mixture containing one mole of phenyl magnesium bromide and three mole per cent of cobalt chloride, an exothermic reaction takes place and good yields of diphenyl are formed. The diphenyl is obtained exclusively from the phenyl magnesium bromide since replacement of the phenyl bromide with *p*-tolyl bromide or ethyl bromide did not appreciably alter the yields. The phenyl bromide, however, is responsible for the formation of small amounts of terphenyl and other high-boiling compounds, since they are not formed in the presence of ethyl bromide.

The following radical (chain) mechanism was suggested to account for the observed facts:

$$\mathrm{C_6\overset{-}{H}_5 \leftarrow \overset{+}{M}gBr + CoCl_2 \rightleftarrows C_6H_5CoCl + \overset{Br}{Mg}\!-\!Cl}$$

$$\mathrm{2C_6H_5CoCl \longrightarrow C_6H_5\!-\!C_6H_5 + 2CoCl}$$

$$\mathrm{CoCl + C_6H_5Br \longrightarrow C_6H_5\cdot + \overset{Br}{Co}\!-\!Cl}$$

$$\mathrm{X\ C_6H_5\cdot \longrightarrow (C_6H_5)_2C_6H_4, C_6H_6,\ etc.}$$

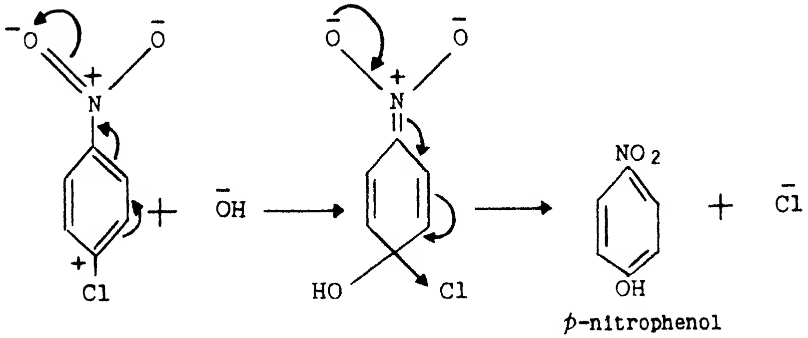
In this picture the cobalt chloride is reduced by the Grignard reagent and is oxidized back to its stable state by the organic halide. This mechanism appears reasonable in view of the following facts: (1) ArMgX does not react with ArX; (2) $CoCl_2$, $NiCl_2$, and $FeCl_3$ do not react with ArX; and (3) ArMgX reacts with the above salts to form diaryls.

The aryl halides do not react with potassium cyanide, sodium hydroxide, or ammonia under the usual laboratory conditions. Reactions with the last two reagents may be carried out by heating under pressure in the presence of copper or cuprous derivatives:

$$\mathrm{2C_6H_5Cl + 2NH_3 + Cu_2O \longrightarrow \underset{aniline}{2C_6H_5NH_2} + Cu_2Cl_2 + HOH}$$

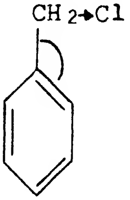
The effect of the copper or cuprous ion is probably due to their electrophilic activity. Due to this latter tendency an inductomeric effect is superimposed on the normal inductive effect, $\overset{+}{C}\rightarrow\overset{-}{Cl}$, with the resulting weakening of the carbon-to-chlorine bond.

Although it is difficult as a rule to replace a halogen atom which is directly attached to the benzene ring, there are certain exceptions. For example, the chlorine in *o*- and *p*-nitrochlorobenzene may be replaced by heating with sodium or potassium hydroxide solutions. The electron-attracting nitro group, by reducing electron availability at the ortho and para positions, opens the way for the attack of a nucleophilic agent at those positions. The reactions may be shown as follows:

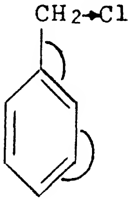


In this case the halogen atom has been replaced by an anion of greater nucleophilic activity. The halogen atom in 2,4-dinitrochlorobenzene is more readily replaced, and the chlorine in 2,4,6-trinitrochlorobenzene (picryl chloride) may be replaced by the action of water alone. The so-called activating influence of the nitro group on the halogen atom is not transmitted to the meta position, for electron availability is not appreciably decreased at this position.

When a halogen atom is attached to a carbon atom adjacent to an aromatic ring, its reactivity is comparable to the halogen in the allyl halides. This is to be expected since benzyl chloride possesses the allyl structure. The electron-release behavior of the phenyl group in benzyl chloride can be pictured as resonant:



and



CHAPTER IX

Reactions of Alcohols

The characteristic reactions of the alcohols are largely determined by the hydroxyl group. The properties of the latter are markedly modified by the nature of the carbon atom to which it is attached. The oxygen atom of the hydroxyl group because of its two unshared electron pairs may act as a proton acceptor and in this sense the alcohols are regarded as bases. However, it must be noted that the alcohols may also be regarded as weak acids. The tendency for ionization

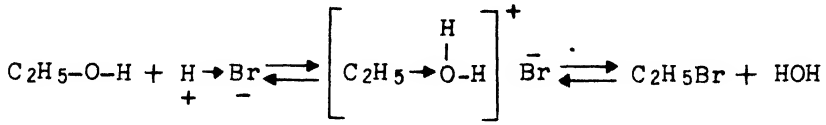
$$R-\ddot{\underset{\cdot\cdot}{O}}\leftarrow H \rightleftharpoons R-\overset{-}{\underset{\cdot\cdot}{\ddot{O}}}: + \overset{+}{H}$$

is very slight, but that it is an inherent tendency is shown by the interaction of alcohols and alkali metals:

$$2C_2H_5OH + 2Na \rightarrow \underset{\text{sodium ethoxide}}{2C_2H_5ONa} + H_2$$

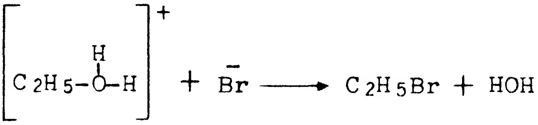
This reaction takes place least readily with tertiary alcohols. The electron-release effect of the three alkyl groups attached to the $\rightarrow\overset{\downarrow}{\underset{\uparrow}{C}}-OH$ group acts to retard the electron transfer from hydrogen to oxygen. The fact that the sodium alkoxides are rapidly hydrolyzed by water indicates that the alcohols are very weak acids.

Many of the alcohol reactions appear to depend upon the ability of alcohols to act as proton acceptors. For example, the reaction with hydrogen halides may be written as follows:



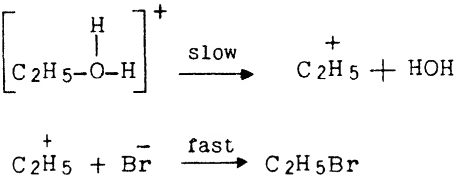
$$C_2H_5-O-H + \underset{+}{H}\rightarrow\underset{-}{Br} \rightleftharpoons \left[C_2H_5\rightarrow\overset{\overset{H}{|}}{O}-H\right]^{+}\overset{-}{Br}^{\cdot} \rightleftharpoons C_2H_5Br + HOH$$

The addition of the proton, by displacing the electron system, would facilitate cleavage between carbon and oxygen with the formation of a highly reactive carbonium ion which is neutralized by the bromide ion to form ethyl bromide. It does not seem necessary to postulate the formation of a free carbonium ion, for it is probable that the bromide ion is attracted to the carbon atom before the separation of the carbon-to-oxygen bond is completed. The kinetics of the reaction of hydrogen bromide with ethanol has been investigated by Grunwald and Winstein. Their data indicate that it is a second-order reaction, first order with respect to both $C_2H_5OH_2^+$ and $\overset{-}{Br}$ (37):



$$\left[C_2H_5-\overset{H}{\overset{|}{O}}-H\right]^+ + \overset{-}{Br} \longrightarrow C_2H_5Br + HOH$$

In this case it can be stated that the unimolecular reaction

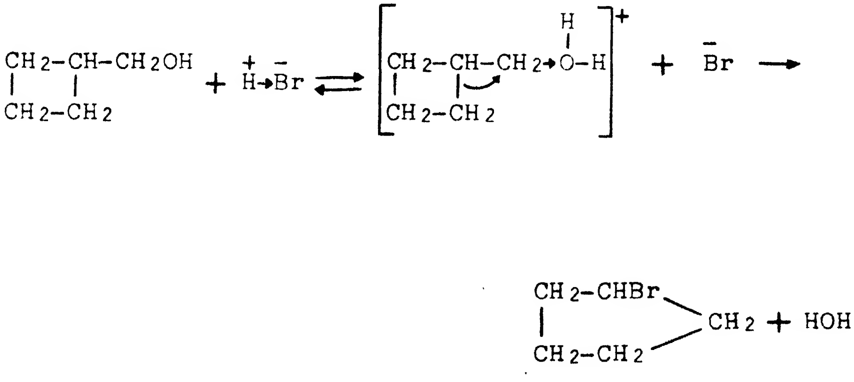


$$\left[C_2H_5-\overset{H}{\overset{|}{O}}-H\right]^+ \xrightarrow{\text{slow}} \overset{+}{C_2H_5} + HOH$$

$$\overset{+}{C_2H_5} + \overset{-}{Br} \xrightarrow{\text{fast}} C_2H_5Br$$

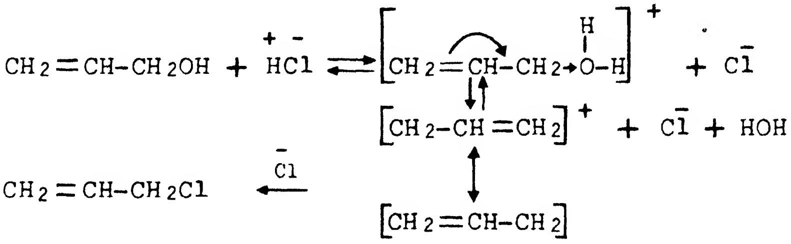
is followed to a very small extent if it occurs at all. The reaction takes place most readily with tertiary alcohols as would be expected. The electron-release effects of three alkyl groups favor both the addition of a proton and subsequent cleavage. The attraction of the unshared oxygen electrons for a proton may be considered to be the force which initiates this type of reaction.

Cyclobutyl carbinol reacts with hydrogen bromide to form largely cyclopentyl bromide. The mechanism given above appears to be applicable to this reaction and offers a logical explanation for the ring enlargement:

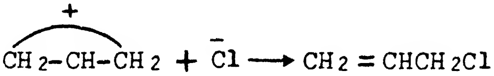


The reaction is initiated by the formation of an oxonium ion. The electron displacements, caused by the attachment of a proton, favor the splitting out of water and the opening of the strained cyclobutane ring with the subsequent formation of the more stable cyclopentane ring.

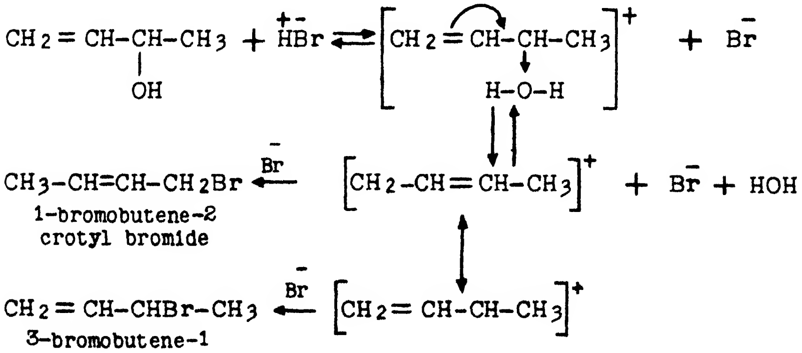
Allyl alcohol resembles the tertiary alcohols in that its hydroxyl group is more readily replaced than would be expected for a primary alcohol. For example, when heated with hydrochloric acid it is readily converted into allyl chloride. The ease of this reaction may be attributed to the electron-release effect of the olefin bond:



The electron displacement, caused by the attachment of a proton, is reinforced by an electromeric effect on the part of the double bond and the carbon-to-oxygen bond is more readily cleaved. The carbonium ion resonates between two structures and thus is stabilized. The addition of the chloride ion to either structure leads to the formation of only one end product. This can be seen more clearly by using the symmetrical resonance hybrid:

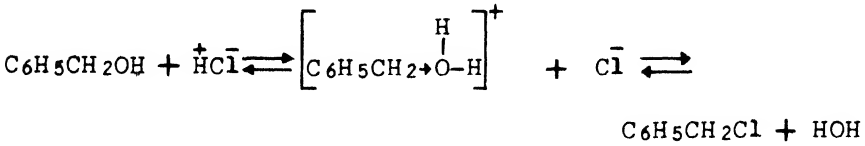


Two products may be obtained from other alcohols of the allyl type, such as buten-1-ol-3:



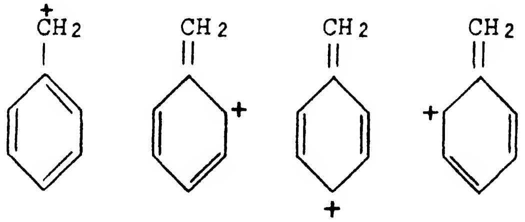
Crotyl bromide is the main product. The resonance hybrid in this case is not symmetrical, $\overset{+}{\overparen{CH_3-CH-CH}}-CH_2$, and the reaction with the bromide ion can form two addition products.

The aromatic alcohols, in which the aryl group is directly attached to the carbon atom holding the hydroxyl group, resemble allyl alcohol in some respects. For example, benzyl alcohol reacts readily with hydrochloric acid to form benzyl chloride:



$$C_6H_5CH_2OH + \overset{+}{H}\overset{-}{Cl} \rightleftharpoons \left[C_6H_5CH_2\rightarrow\overset{\overset{H}{|}}{O}-H\right]^+ + \overset{-}{Cl} \rightleftharpoons C_6H_5CH_2Cl + HOH$$

As in the case of allyl alcohol, the electron displacement caused by the attachment of the proton is reinforced by the electron-release effect of the benzene ring with the consequent cleavage of the carbon-oxygen bond. The resulting carbonium ion is stabilized through resonance:

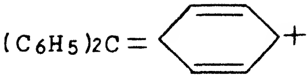


Triaryl carbinols dissolve in concentrated mineral acids with the formation of highly colored salts. With triphenyl carbinol, concentrated sulfuric acid is necessary to effect conversion to the salt. Tri- (*p*-methoxyphenyl) carbinol, however, forms a halochromic salt with concentrated hydrochloric acid. The electron-release effects of the methoxy groups facilitate the reaction:

$$(p\text{-}CH_3OC_6H_4)_3COH + \overset{+}{H}\overset{-}{Cl} \rightleftharpoons \left[(p\text{-}CH_3OC_6H_4)_3C\right]^+ \overset{-}{Cl} + HOH$$

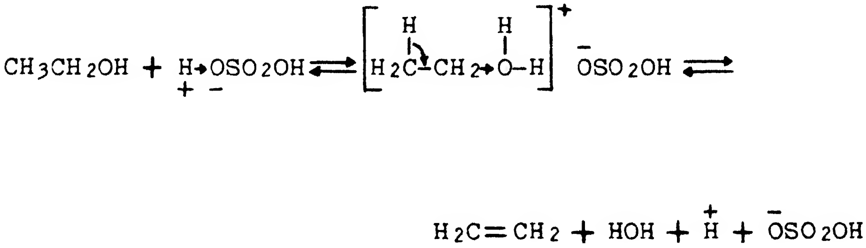
These salts may be isolated in some cases as highly colored crystalline compounds. The perchlorates are especially readily obtained. The formation of such salts is made possible because the carbonium ion is a resonance hybrid and is stabilized by considerable resonance energy. In the unperturbed structures the positive charge may be located on the ortho or para carbon atoms in the benzene rings or on the methane carbon atom. Two of the structures for the cation from triphenylcarbinol may be written as follows:

$(C_6H_5)_3\overset{+}{C}$



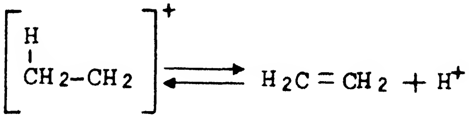
There would be ten possible structures, nine of which would contain an ortho or para benzoquinoid unit.

The so-called dehydration of alcohols to form either olefins or ethers involves similar mechanisms. The conversion of alcohols into olefins by the catalytic action of acids, such as sulfuric or phosphoric acid, does not depend upon the catalyst's affinity for water, for the reaction may often be effected with dilute acids. These catalysts function through their proton-donating properties:



$$CH_3CH_2OH + \underset{+}{H}\rightarrow\underset{-}{OSO_2OH} \rightleftarrows \left[H_2\overset{H}{C}-CH_2\rightarrow\overset{H}{O}-H\right]^{+} \overset{-}{O}SO_2OH \rightleftarrows$$
$$H_2C{=}CH_2 + HOH + \overset{+}{H} + \overset{-}{O}SO_2OH$$

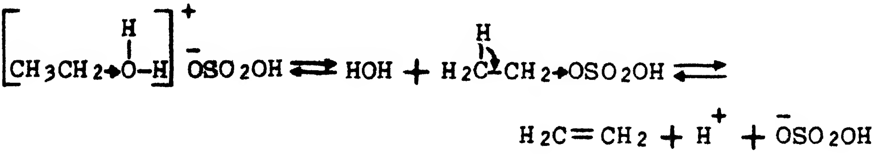
It is not known whether the cleavage of the carbon-oxygen bond and the elimination of a proton occur simultaneously or whether an intermediate carbonium ion is formed which then loses a proton to give an olefin:



$$\left[\overset{H}{C}H_2-CH_2\right]^{+} \rightleftarrows H_2C{=}CH_2 + H^{+}$$

The latter mechanism would be more apt to prevail in the case of tertiary alcohols. In either event the driving force for the elimination of the proton would be the same, namely, the adjacency of a positively charged carbon atom with its attraction for the electron pair in the carbon-hydrogen bond. Olefin formation is facilitated by increase in temperature.

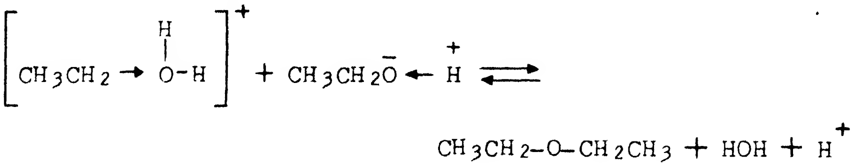
The reaction in certain cases may proceed through the formation of an alkyl hydrogen sulfate:



$$\left[CH_3CH_2\rightarrow\overset{H}{O}-H\right]^{+} \overset{-}{O}SO_2OH \rightleftarrows HOH + H_2\overset{H}{C}-CH_2\rightarrow OSO_2OH \rightleftarrows$$
$$H_2C{=}CH_2 + \overset{+}{H} + \overset{-}{O}SO_2OH$$

Here the stability of the anion, $\bar{O}SO_2OH$, may favor the elimination of this ion with subsequent elimination of a β-hydrogen and formation of the olefin. Dehydration occurs most readily with the tertiary alcohols for the reasons noted previously.

The preparation of ethers from alcohols, by the sulfuric-acid process, must be carried out in the presence of excess alcohol for ether formation to be favored over olefin formation. In the case of tertiary alcohols, only olefins result regardless of conditions. This is in accord with the facts noted above. The same oxonium cations are involved in the preparation of ethers as those which are formed in the course of olefin formation. The reaction may be shown as follows:

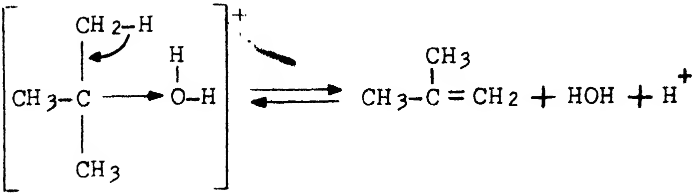


$$\left[CH_3CH_2 \rightarrow \overset{\overset{H}{|}}{O}-H\right]^+ + CH_3CH_2\overset{-}{O} \leftarrow \overset{+}{H} \rightleftharpoons CH_3CH_2-O-CH_2CH_3 + HOH + \overset{+}{H}$$

Here again it is not necessary to assume the formation of an intermediate carbonium ion, for the various steps may occur simultaneously, that is, the ethoxide group may start to add before the cleavage of the carbon-oxygen bond is completed. It is possible, however, that ether formation does take place to some extent through the formation of an intermediate carbonium ion.

$$\overset{+}{CH_3CH_2} + CH_3CH_2\overset{-}{O} \leftarrow \overset{+}{H} \rightleftharpoons CH_3CH_2OCH_2CH_3 + \overset{+}{H}$$

The formation of some olefin is observed in these reactions even when primary alcohols are used. Only olefin formation is observed when tertiary alcohols are employed. A possible explanation for the behavior of tertiary alcohols lies in the fact that the hydrogen atom in the hydroxyl group is relatively inactive. The reaction between $\left[R_3C \rightarrow \overset{\overset{H}{|}}{O}-H\right]^+$ and $R_3\overset{-}{C}O \leftarrow \overset{+}{H}$ might be expected to be retarded or prevented and olefin formation would be favored:

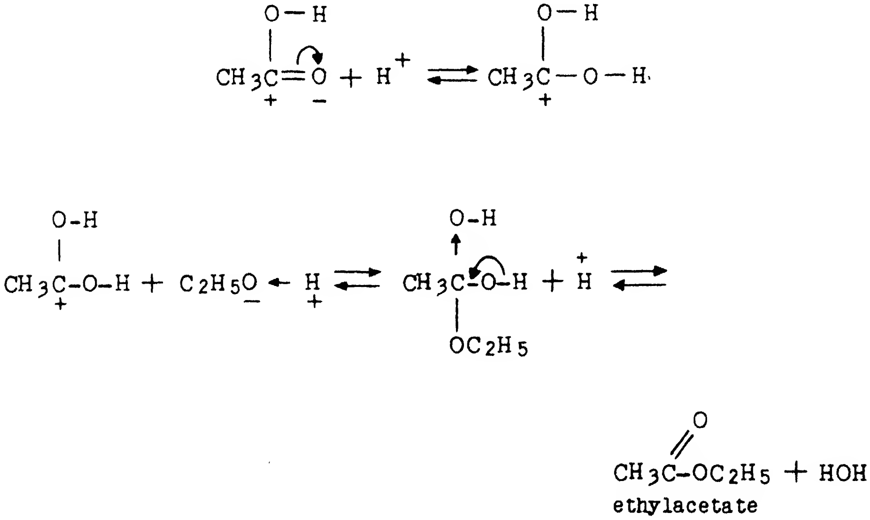


Alkyl hydrogen sulfates are not essential intermediates for ether formation, although they may serve as intermediates in some cases. Van

Alpen (38) has shown that hydrochloric acid is an excellent catalyst for ether formation at 150°–160°. He further noted that ethyl alcohol and ethyl chloride do not react to form ether under these conditions. In this case an alkyl salt is definitely eliminated as an intermediate and the above mechanism must prevail.

The vapor phase dehydration of alcohols, accomplished by passing the vapor of the alcohol over a heated catalyst such as aluminum oxide, probably follows a similar course. Here the same series of reactions may be initiated by the formation of a coordinate linkage between the aluminum atom and the oxygen atom of the alcohol group.

The reactions between alcohols and carboxylic acids to form esters are reversible, acid-catalyzed reactions. They are somewhat more complicated than those noted above. Any mechanism to be of value must account for the fact that primary alcohols are most readily esterified and tertiary alcohols least readily; and for the fact that the hydroxyl group from the acid and the hydrogen from the alcohol group unite to form water. The mechanism suggested by Lowry appears to be in accord with these known facts (39):



$$CH_3\overset{\overset{O-H}{|}}{\underset{+}{C}}=\underset{-}{O} + H^+ \rightleftharpoons CH_3\overset{\overset{O-H}{|}}{\underset{+}{C}}-O-H$$

$$CH_3\overset{\overset{O-H}{|}}{\underset{+}{C}}-O-H + C_2H_5\underset{-}{O} \leftarrow \underset{+}{H} \rightleftharpoons CH_3\overset{\overset{O-H}{\uparrow}}{\underset{\underset{OC_2H_5}{|}}{C}}-O-H + \overset{+}{H} \rightleftharpoons$$

$$CH_3\overset{\overset{O}{/\!/}}{C}-OC_2H_5 + HOH$$

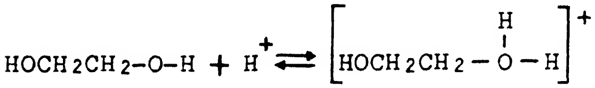
ethylacetate

The ionization of a carboxylic acid would be repressed in the presence of an acid catalyst such as sulfuric acid or hydrogen chloride, and it may be assumed that its ketonic character might be enhanced. The addition of a proton to the carbonyl group of the acid creates the necessary polarization for the reaction with C_2H_5OH with the resulting formation of the mono ethyl ester of orthoacetic acid. The latter then loses water to form the normal ester. If this mechanism were applicable to tertiary alcohols, one would expect a greatly retarded rate of reaction. As stated previously the electron-release effects of the three alkyl groups in aliphatic tertiary alcohols act to retard the electron transfer from hydrogen to oxygen.

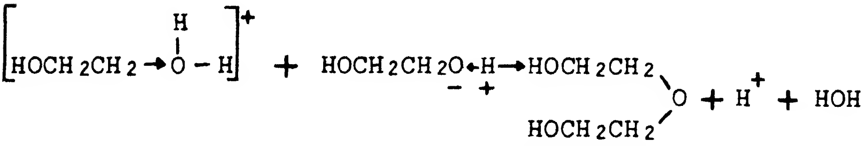
There is evidence available which indicates that in the esterification of tertiary alcohols the hydroxyl group from the alcohol and the hydrogen from the carboxylic acid split out to form water (40). This suggests a mechanism for this particular type similar to that given for the action of hydrogen halides on alcohols. It should be noted that the conditions necessary for direct esterification often are suitable for the formation of olefins and ethers and hence these products may also be formed.

The oxidation of primary and secondary alcohols appears to involve radical mechanisms. The reactions are complicated and mechanism studies in general have not been very successful. Recent papers by Waters (41) have reviewed the older experimental work and added much that is new. It is not possible at the present time to formulate mechanisms for these reactions.

In general, the mechanisms outlined above may be applied to the di- and polyhydric alcohols, although the reactions may be complicated by the presence of more than one hydroxyl group. The formation of 1,4-dioxane from ethylene glycol by heating with sulfuric acid is a familiar example. Dioxane may be regarded as a cyclic ether and its formation may be explained by the ether mechanism:



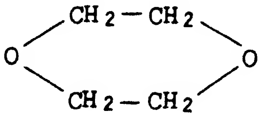
$$HOCH_2CH_2{-}O{-}H + \overset{+}{H} \rightleftarrows \left[HOCH_2CH_2 - \overset{\overset{H}{|}}{O} - H\right]^{+}$$



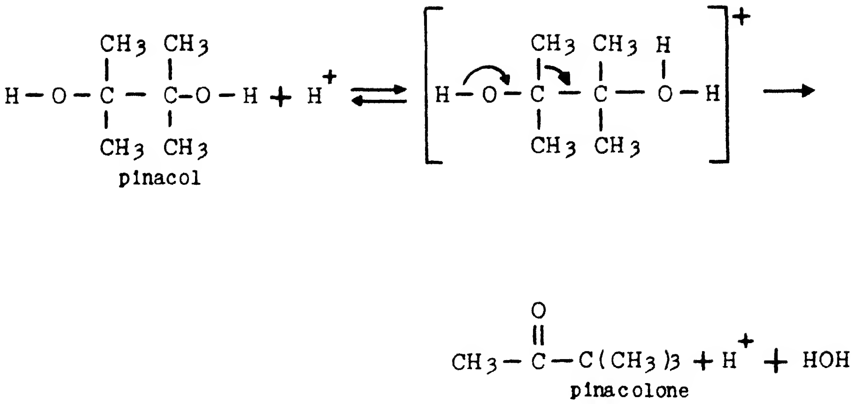
$$\left[HOCH_2CH_2 \rightarrow \overset{\overset{H}{|}}{O} - H\right]^{+} + HOCH_2CH_2\underset{-}{O} \leftarrow \underset{+}{H} \rightarrow \begin{matrix} HOCH_2CH_2\diagdown \\ \qquad O \\ HOCH_2CH_2\diagup \end{matrix} + \overset{+}{H} + HOH$$

di(β-hydroxyethyl)ether

Continuation of this process would yield dioxane:



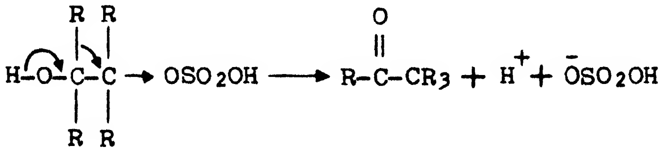
An interesting rearrangement occurs when the tetra alkyl substituted ethylene glycols (pinacols) are heated with acids. In the true pinacol rearrangement both hydroxyl groups are tertiary. Where a dilute acid such as dilute sulfuric acid is used, the effective catalyst is the hydrogen ion:



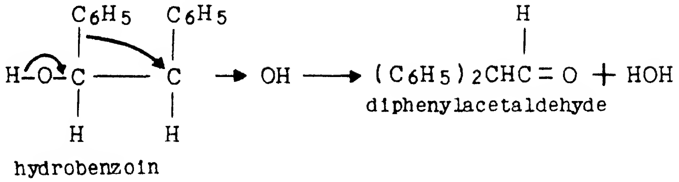
The displacement of the electron system induced by the addition of a proton facilitates cleavage of the carbon-oxygen bond. Whether a carbonium ion is formed as an intermediate or whether the migration of a methyl group with its bond electrons and the expulsion of a proton from the beta hydroxyl group occur simultaneously with the cleavage is not known. In either case the fundamental cause of the rearrangement remains the same. After the addition of the proton, the electron displacement away from the alpha carbon leaves it with a fractional positive charge or with a free positive charge if cleavage occurs. The positively charged carbon atom then may be considered to be the primary cause for the migration of the methyl group and the formation of a proton. It is not necessary to assume that the methyl group migrates as a free ion, for it is probably attracted to the alpha carbon atom before its cleavage from the beta carbon atom is completed.

It is obvious from the scheme given above that the group migration might proceed in either of two directions. It is possible that either hydroxyl group might be eliminated. In the case of tetramethyl ethylene glycol the end product would be the same regardless of the direction of the change. With unsymmetrical pinacols, the separation of the hydroxyl group will occur from that carbon atom which is attached to groups having the greatest electron-release tendencies. The relative ease with which various groups can migrate is also an important factor in determining the nature of the end product.

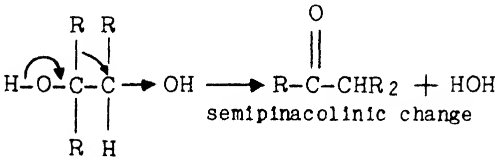
In cases where concentrated sulfuric acid is used to promote the rearrangement, it is possible that the corresponding hydrogen sulfate may be an intermediate, although this does not change the fundamental mechanism:

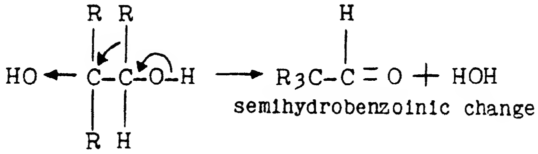


Secondary glycols under similar conditions are converted to aldehydes (hydrobenzoinic change):



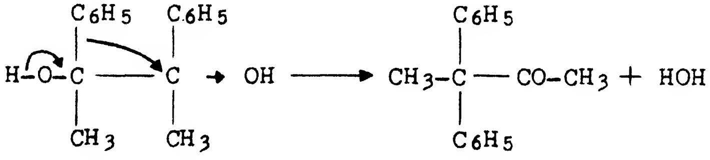
When the glycol contains one secondary and one tertiary alcohol group, two types of rearrangement are possible, although the second reaction shown below is more likely to occur:



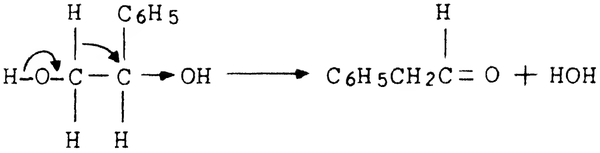


These changes are dependent upon the same factors noted for the pinacolinic change.

The vapor-phase rearrangement of pinacol to pinacolone in high yields has been reported by Emerson (42). The pinacol together with steam was passed over a silica-gel–phosphoric-acid catalyst at 275°–300° and 170 mm. Using sodium bisulfate instead of phosphoric acid, 2,3-diphenylbutandiol-2,3 was rearranged to 3,3-diphenylbutanone:



In an earlier paper Emerson and Agnew (43) converted styrene glycol to phenylacetaldehyde, using the same technique:

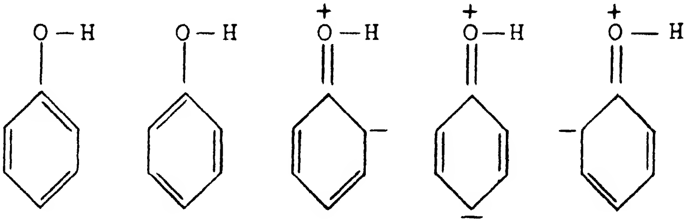


These vapor-phase reactions are acid catalyzed and probably are best represented by the mechanisms given above.

CHAPTER X

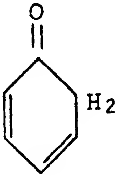
Reactions of Phenols: The Fries Rearrangement and Claisen Rearrangement

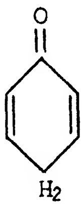
The phenols are aromatic compounds in which the hydroxyl group is directly attached to the aromatic ring. There are some striking differences between the phenols and alcohols. For example, the phenols are more acidic and usually dissolve in aqueous sodium hydroxide. This increase in acidity is attributed to a resonance which involves the unshared electrons of the oxygen atom. The following are the important forms which contribute to the net structure:



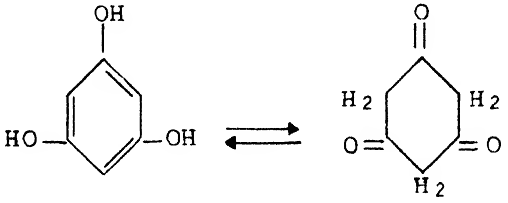
Such a condition might reasonably be expected to facilitate the liberation of a proton from the hydroxyl group. In other words, the electron displacements away from oxygen favor the ionization of the hydrogen atom. The contribution of the ionic structures causes an enhanced electron availability at the ortho and para positions. The hydroxyl group is a powerful ortho and para directing group, that is, it exhibits a marked electron-release effect.

It will be noted that the two Kekulé structures shown above contain an enol group, $-\overset{|}{C}=\overset{|}{C}-O-H$. Unlike the simple aldehydes and ketones which exist predominantly as the keto forms (p. 112), phenol exists essentially as an enol form. The stability of the latter is due to resonance. Examination of the two possible keto forms

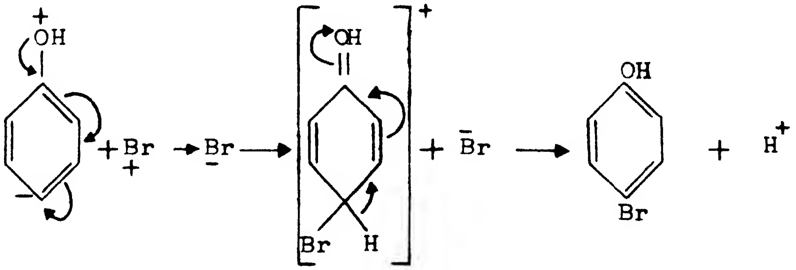




discloses the fact that they would be only slightly stabilized by the resonance of the contained conjugated systems. The enol form would be more highly stabilized by the resonance energy of the benzene ring (3). The monohydric and dihydric phenols, in general, do not give the simple reactions characteristic of keto forms. Phloro-glucinol (1,3,5-trihydroxybenzene) behaves more like a tautomeric substance. With acetylating reagents it forms a triacetate and with hydroxylamine a trioxime is formed. These facts suggest that the equilibrium does not favor the enol form to the extent noted for phenol:



Ease of substitution is one of the distinguishing characteristics of the phenols. The rapid reaction of phenol with bromine in the absence of a catalyst to form 2,4,6-tribromophenol is an excellent illustration of the ready electron availability at the ortho and para positions. The bromination proceeds in steps and the first step may be shown as follows:



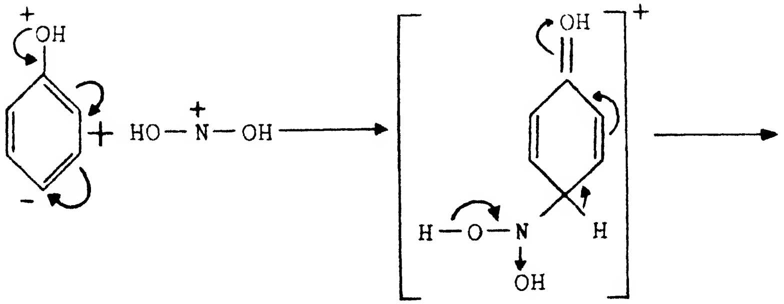
The first bromine atom may attach itself either to an ortho or para carbon atom. The above electron displacements illustrate para substitution only. Continuation of the reaction leads to the formation of the tribromo derivative. The presence of one bromine atom in the ring might be expected to decrease the directive influence of the hydroxyl group and thus retard further bromination. Actually, however, the electron-release effect of the OH group is much more powerful than that of the bromine atom with the result that the reaction proceeds rapidly to tribromophenol.

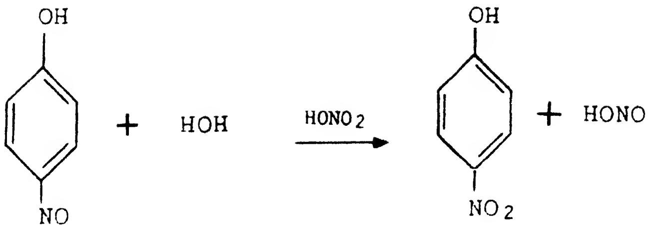
Dilute nitric acid alone readily reacts with phenol to form a mixture of ortho and para nitrophenols. The nitration of phenol is catalyzed by the presence of nitrous acid (44). More recently it has been shown that under certain conditions, nitrosophenols are intermediates in the nitration of phenols to nitrophenols (45). Schramm and Westheimer (46) in 1948 reported their data on the mechanism of the nitration of anisole. Their work supports and extends the observations of the previous workers. They found that anisole reacts rapidly with 40–50 per cent nitric acid containing a little nitrous acid. However, anisole failed to react with nitric acid which contains urea. The nitration of anisole with 40 per cent nitric acid containing a little nitrous acid gave mainly 2,4-dinitrophenol with a smaller amount of *p*-nitroanisole. They noted that when *p*-nitroanisole is added to a mixture which readily nitrates anisole, it could be recovered quantitatively. *p*-Nitroanisole, therefore, is not an intermediate in the nitrous acid-catalyzed nitration of anisole to dinitrophenol. It was further established that *p*-nitrosoanisole reacts readily with the nitrating mixture and forms the same products as those obtained from anisole under similar conditions. It should also be noted that when anisole was nitrated with 60 per cent nitric acid containing a little nitrous acid, nitroanisoles were the chief products with only a trace of 2,4-dinitrophenol being formed.

From the above work, it would appear that nitrosation is the first step in the nitration of phenol and anisole. The nitroso intermediate is then oxidized to the nitro compound by the nitric acid, the latter being reduced to nitrous acid. The fact that phenol and anisole react so readily with small amounts of nitrous acid in the presence of large quantities of nitric acid, suggests that nitrous acid acts as a base towards nitric acid. This would explain the apparently greater electrophilic activity of nitrous acid:

$$\mathrm{H{-}O{-}N{=}O} + \overset{+}{\mathrm{H}} \rightleftharpoons \underset{\text{I}}{\mathrm{H{-}O{-}\overset{+}{N}{-}O{-}H}} \xrightleftharpoons{\overset{+}{\mathrm{H}}} \underset{\text{II}}{\overset{+}{\mathrm{NO}} + \overset{+}{\mathrm{H_3O}}}$$

The following mechanism is based on the above assumption:



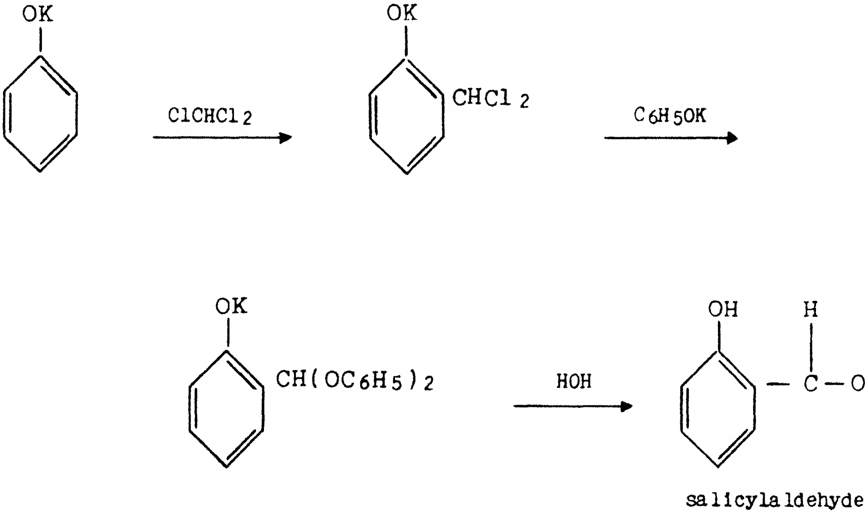


It is possible that cation II is the active agent rather than I.

Sulfuric acid reacts readily with phenol to form phenolsulfonic acids. See page 35 for the probable mechanism of aromatic sulfonation.

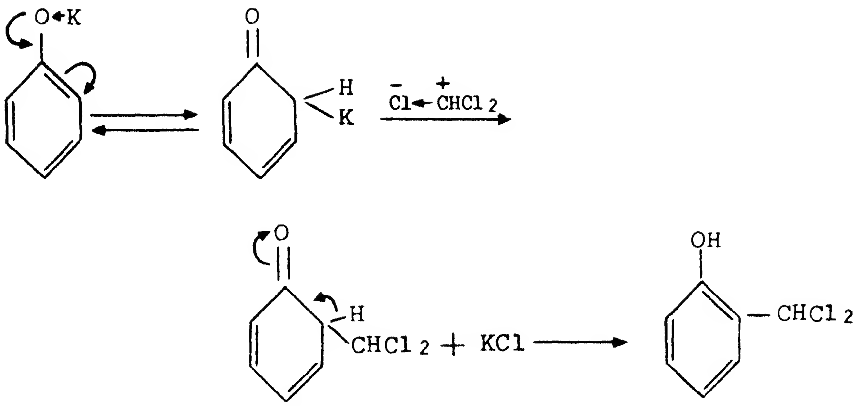
The resonance effect which explains the increased acidity of the phenols as well as their ease of substitution also explains why the hydroxyl group is more difficult to replace in phenols than in the alcohol series. The over-all result of resonance is to hold the oxygen atom more firmly bound to carbon. Thus the hydrogen halides do not react with phenols to form aryl halides. In the alcohol series these reactions depend on the preliminary formation of an oxonium cation. The possibility of the formation of such an ion from the phenols is considerably reduced because of the decreased electron availability on the oxygen atom.

The aldehyde group can be introduced into phenols by reaction with chloroform in alkaline solution (Reimer-Tiemann reaction). The following transformations appear to be reasonably well established (47):

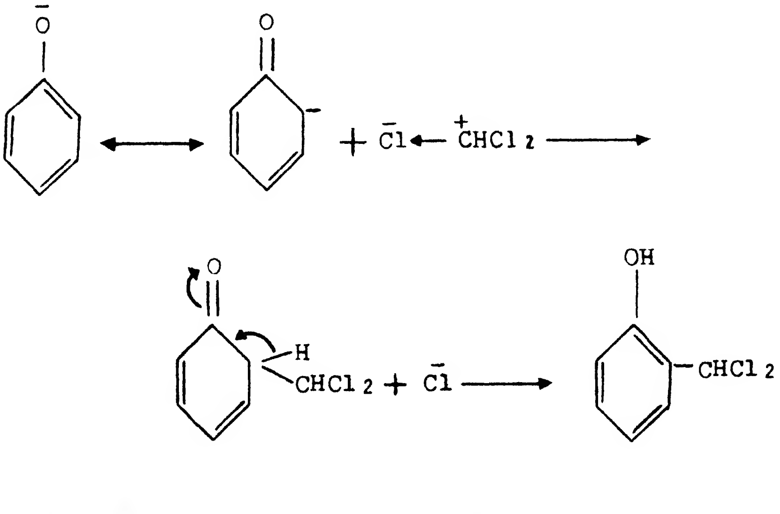


Smaller amounts of *p*-hydroxybenzaldehyde are formed also.

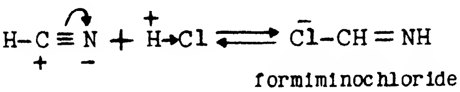
It has been suggested more recently (48) that the intermediate postulated above may owe its formation to the following mechanism:



In this case it is assumed that the potassium phenolate takes on, in part, the character of an organometallic compound. It is simpler, however, to assume that the reaction consists of an electrophilic attack by the chloroform molecule at those carbon atoms in the phenolate anion where electron availability has been increased through resonance:

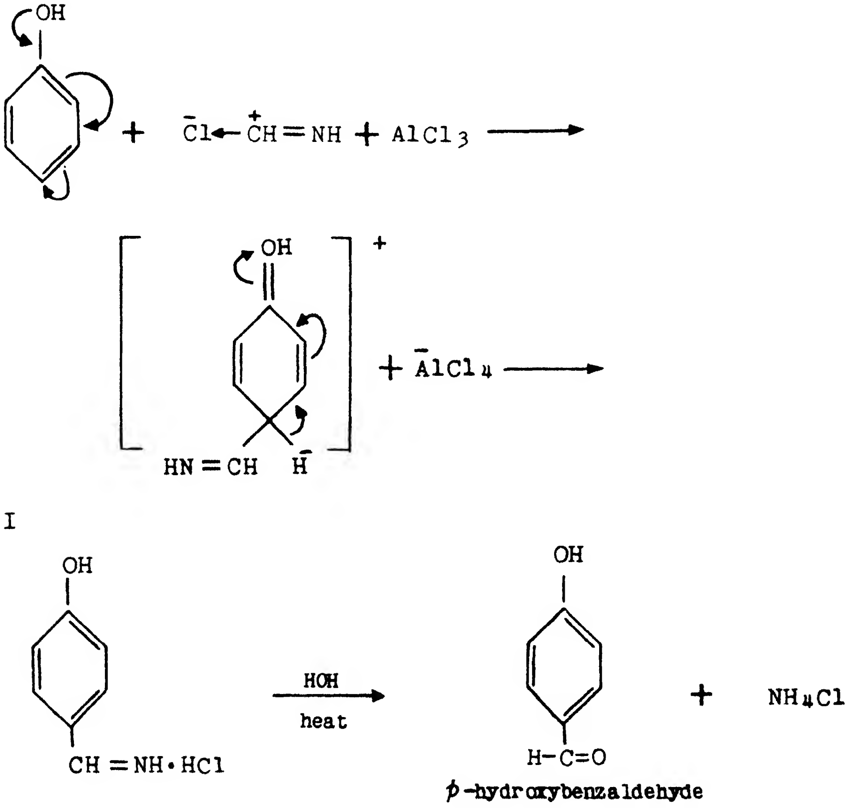


The aldehyde group may also be introduced into phenols through the use of the Gattermann synthesis. In this reaction the phenol is treated with anhydrous hydrogen cyanide and hydrogen chloride, usually in the presence of zinc chloride or aluminum chloride. The hydrogen cyanide may be replaced by sodium cyanide or zinc cyanide. With the latter the passage of hydrogen chloride not only liberates hydrogen cyanide but also forms zinc chloride, which acts as a catalyst. Various solvents have been used, such as ether, benzene, chlorobenzene, and tetrachloroethane. The reaction undoubtedly involves the formation of an electrophilic intermediate which attaches itself to the nucleophilic phenolic ring. It has been assumed by some that the intermediate is an addition product of hydrogen chloride and hydrogen cyanide:

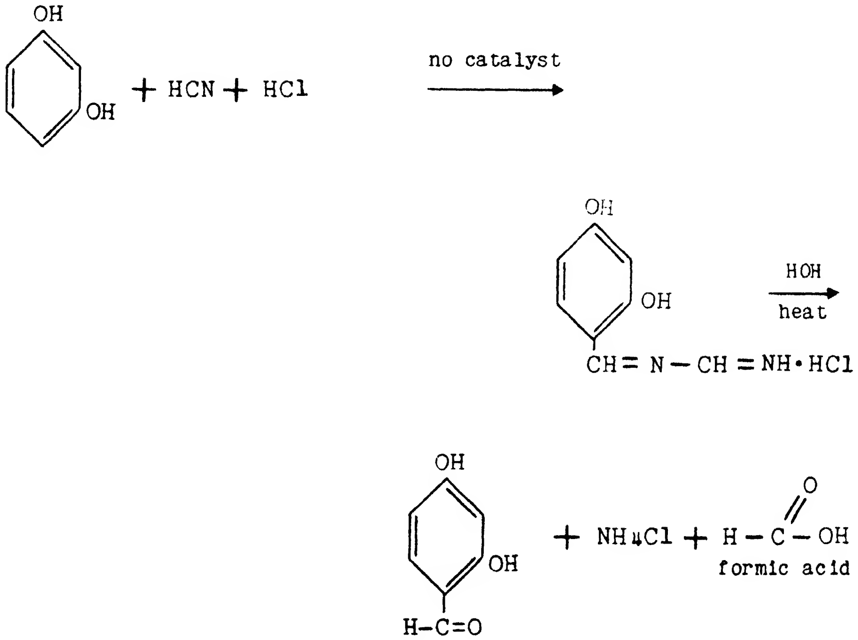


$$\mathrm{H{-}\underset{+}{C}\equiv\underset{-}{N}} + \overset{+}{\mathrm{H}}\rightarrow\mathrm{Cl} \rightleftharpoons \underset{\text{formiminochloride}}{\overset{-}{\mathrm{Cl}}\mathrm{{-}CH{=}NH}}$$

Such an intermediate, under the influence of the catalyst, could furnish the necessary electrophilic ion:



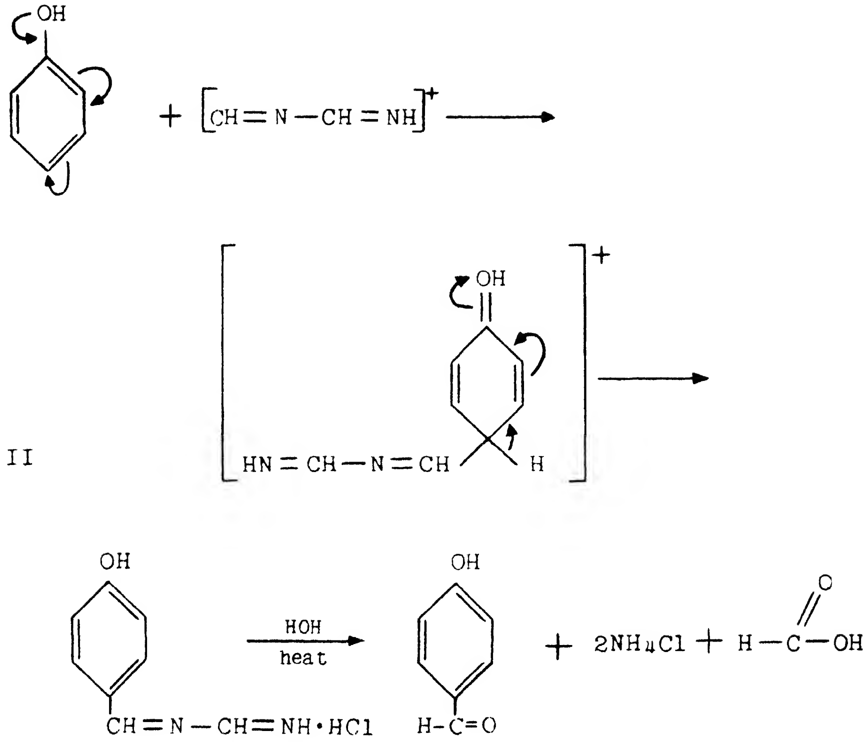
This mechanism, however, fails to explain why the hydrogen cyanide must generally be used in excess. It has been suggested that the necessary intermediate is chloromethylene formamidine and not formiminochloride. This could result from the addition of formiminochloride to hydrogen cyanide. When resorcinol is used in the Gattermann reaction, resorcylmethylene formamidine separates from the mixture as its hydrochloride. The latter is then hydrolyzed to resorcylaldehyde:



Isolation of the formamidine intermediate, in some cases, indicates the initial formation of chloromethylene formamidine. The latter could then furnish the necessary electrophilic ions for the reaction. There appears to be little doubt that this mechanism prevails in those cases where aluminum chloride is used as a catalyst. It is known that aluminum chloride, hydrogen cyanide, and hydrogen chloride react to form an aluminum chloride addition product of chloromethylene formamidine, $AlCl_3 \cdot ClCH{=}N{-}CH{=}NH$. It may be assumed that the latter then reacts with the aromatic compound by the normal Friedel-Crafts mechanism:

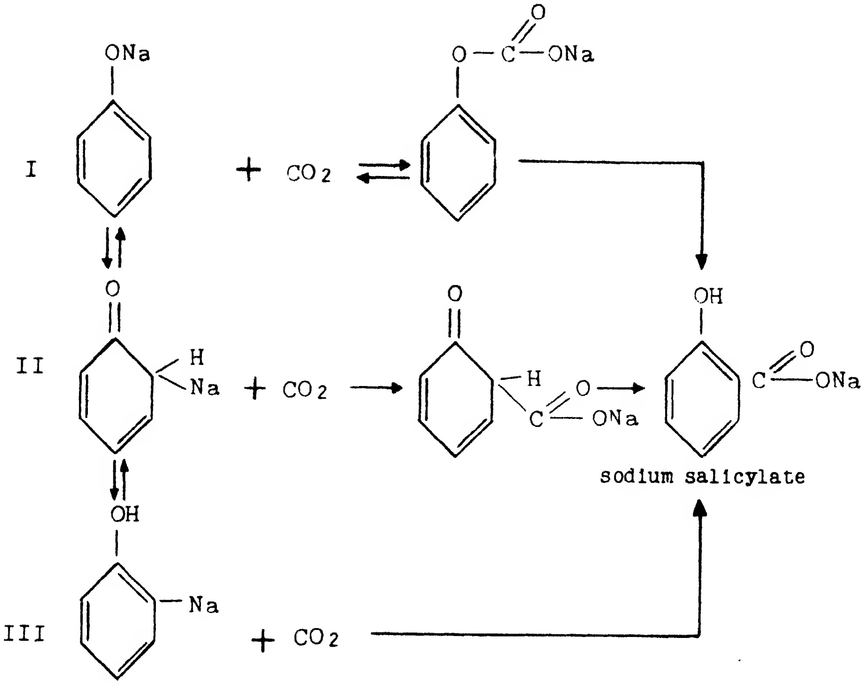
$$\overset{-}{Cl}\leftarrow\overset{+}{C}H=N-CH=NH+AlCl_3\rightleftarrows\left[CH=N-CH=NH\right]^{+}\quad\overset{-}{AlCl_4}$$

$$\text{or } Cl_3Al\leftarrow\cdots\overset{-}{Cl}-\overset{+}{C}H=N-CH=NH$$

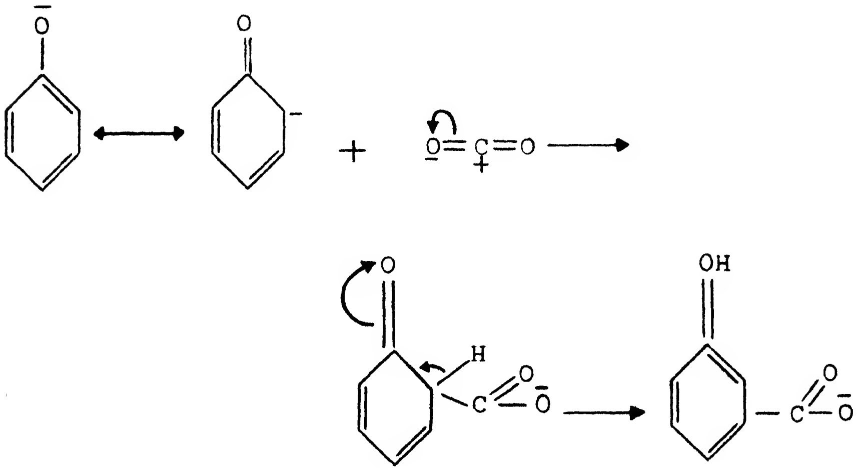


Mechanism II undoubtedly prevails for most Gattermann reactions but mechanism I cannot be ruled out entirely. For example, with polyhydric phenols it is reported that the intermediates are aldimine hydrochlorides and not substituted methylene formamidines. It should be noted that the two mechanisms are very similar as far as fundamental principles are concerned. Both may be regarded as special examples of the Friedel-Crafts reaction type. The fact that the reaction with polyhydric phenols does not require a catalyst is simply explained. The presence of two or more hydroxyl groups would be expected to increase the nucleophilic activity of the ring and thus the reaction with an electrophilic agent should occur more readily. This discussion of the Gattermann reaction has been based largely on the experimental work of Hinkel and his associates (49).

It has been suggested that the introduction of the carboxyl group into phenols by heating sodium or potassium phenolates with carbon dioxide (Kolbe reaction) may follow more than one course (48):



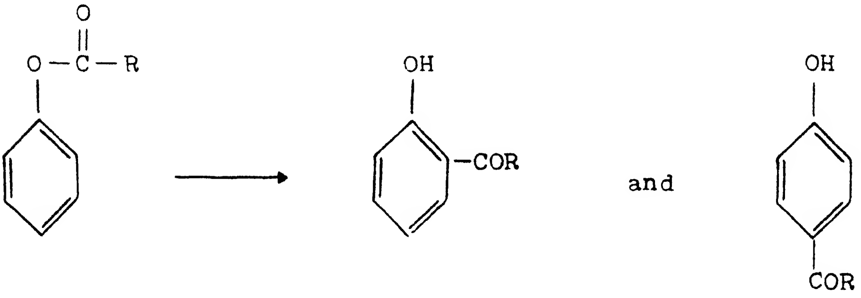
Since carbon dioxide is known to act as an electrophilic (electron-seeking) reagent, it may be assumed to attach itself to the ortho or para positions. A simple mechanism may then be shown as follows:



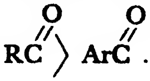
A similar mechanism may be written for para substitution. It is known that sodium phenylcarbonate may be formed in this reaction. Whether it is a necessary intermediate or whether it is simply reconverted into sodium phenolate and carbon dioxide cannot be decided definitely at present. The above mechanism agrees fairly well with the experimental data and it may be assumed that the formation of sodium phenylcarbonate is a reversible side reaction. There is no adequate explanation at present for the effect of the nature of the metal phenolate (Na or K) as well as the effect of temperature on the position of the carboxyl group in the final product.

The direct esterification of phenols proceeds with difficulty. It may be that because of resonance the nucleophilic nature of the oxygen in $Ar\bar{O}$ is much less than that of the oxygen atom in $R\bar{O}$. Such a difference would be expected to retard direct esterification.

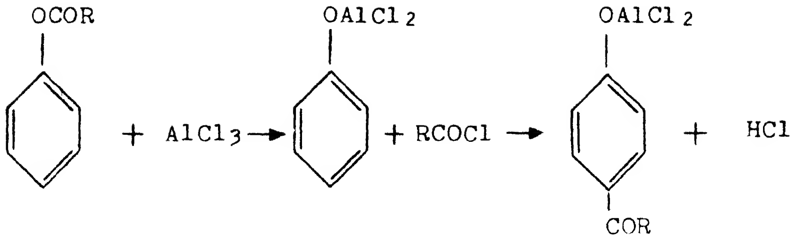
Fries rearrangement. This reaction involves the conversion of a phenol ester to an ortho or para hydroxyphenyl ketone, by treatment with anhydrous aluminum chloride (50). In general one mole of aluminum chloride is required for one mole of phenol ester:



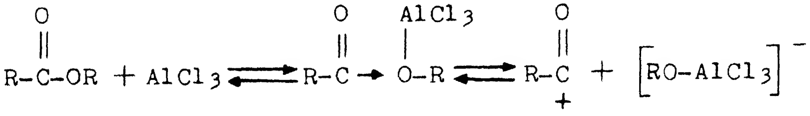
The temperature at which the reaction is carried out is an important factor. Low temperatures favor the formation of *p*-hydroxy derivatives while higher temperatures favor the formation of *o*-hydroxy compounds. It has also been shown that *p*-hydroxyphenyl ketones are converted to *o*-hydroxyphenyl ketones when heated with aluminum chloride. With certain acyl groups conversion to the *p*-isomer is possible but the temperatures for the ortho rearrangement are so high that decomposition occurs. In general, the use of nitrobenzene as a solvent reduces the temperature at which the para rearrangement takes place.

The nature of the acyl group also plays an important role and determines the ease with which the shift occurs from oxygen to a carbon atom in the ring, for example  $R\overset{O}{\overset{/\!/}{C}} > Ar\overset{O}{\overset{/\!/}{C}}$. This holds for both ortho and para shifts.

None of the mechanisms proposed to date is entirely in agreement with experimental data and with accepted mechanisms for similar reactions. One of the previously advanced mechanisms may be shown as follows:

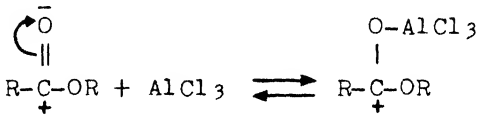


The chief weakness of this course of reaction is the attachment of the electrophilic aluminum chloride to the phenolic oxygen atom. The catalyst would be expected to be attracted to the more electronegative oxygen atom of the carbonyl group. The Fries reaction appears to be related to those reactions in which esters are used as acylating agents under the influence of aluminum chloride. In these reactions it has been assumed that a carbonium ion is a necessary intermediate:



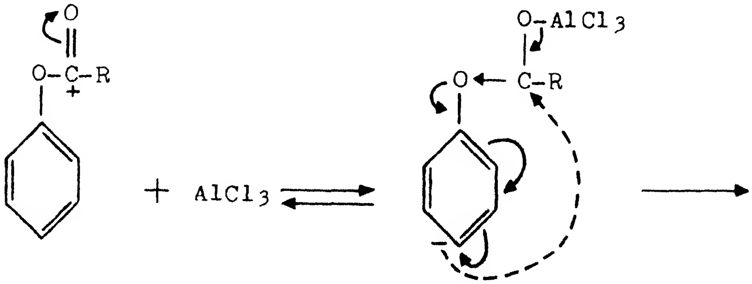
$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}OR + AlCl_3 \rightleftharpoons R{-}\overset{\overset{O}{\|}}{C} \rightarrow \overset{\overset{AlCl_3}{|}}{O}{-}R \rightleftharpoons R{-}\underset{+}{\overset{\overset{O}{\|}}{C}} + \left[RO{-}AlCl_3\right]^{-}}$$

or

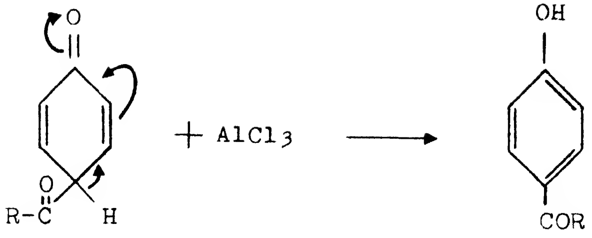


$$\mathrm{R{-}\underset{+}{\overset{\overset{\bar{O}}{\|}}{C}}{-}OR + AlCl_3 \rightleftharpoons R{-}\underset{+}{\overset{\overset{O{-}AlCl_3}{|}}{C}}{-}OR}$$

Of the two carbonium ions shown above the second appears to be more reasonable since the aluminum chloride is attached to the most electronegative oxygen atom. Either ion, however, can be used satisfactorily to explain the acylation of aromatic rings. Similar principles may be used to explain the Fries rearrangement:

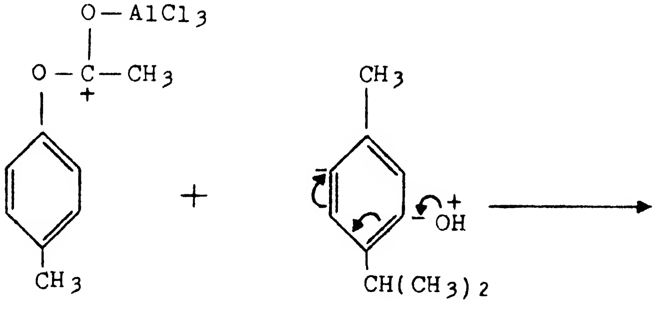


I

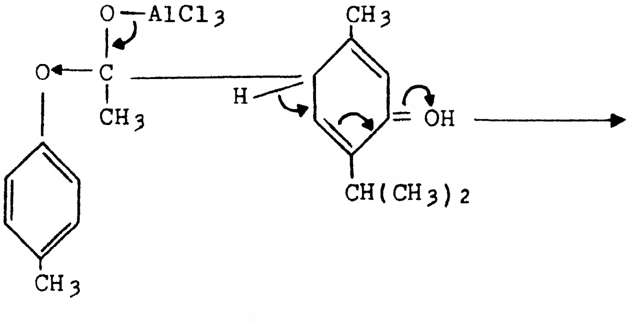


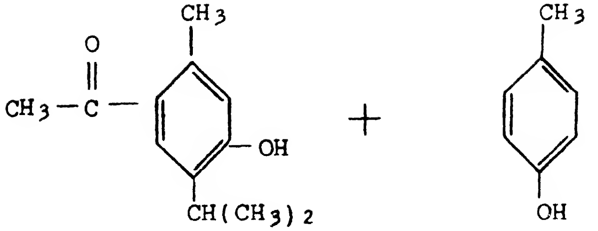
The second step represents the attack of an electrophilic agent on an aromatic ring. It is possible that the formation of the carbon-carbon bond begins before the cleavage of the carbon-oxygen bond is completed. The third step involves the conversion of a quinoid structure to a more stable benzenoid form.

It has also been suggested that the reaction may be intermolecular and the acyl group in one molecule may be utilized in the acylation of another ester molecule (51). When *p*-cresyl acetate in nitrobenzene solution is treated with aluminum chloride, no reaction occurs in 24 hours at room temperature. In the presence of one equivalent of thymol, however, a 60 per cent yield of methyl thymyl ketone was obtained:



II

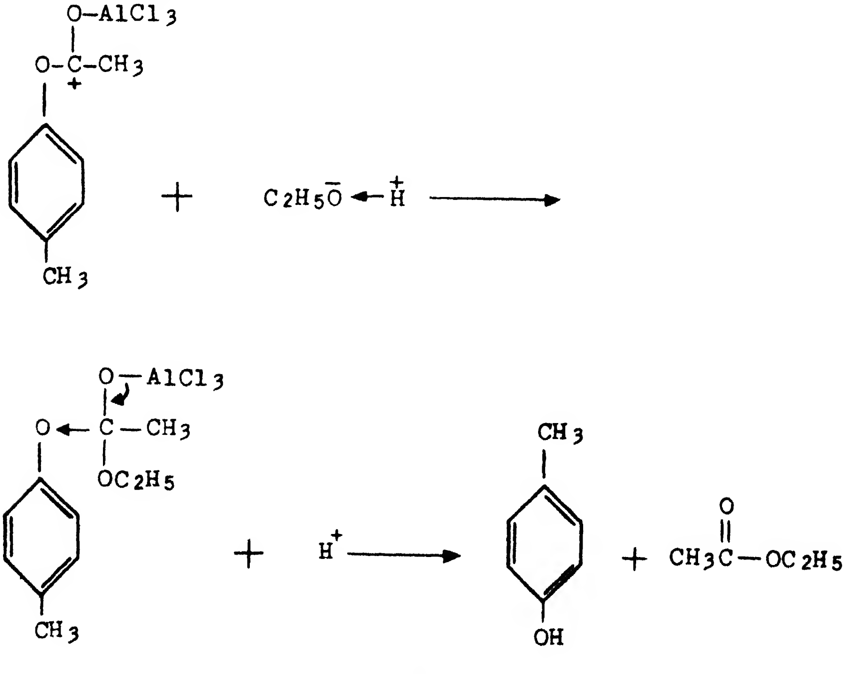




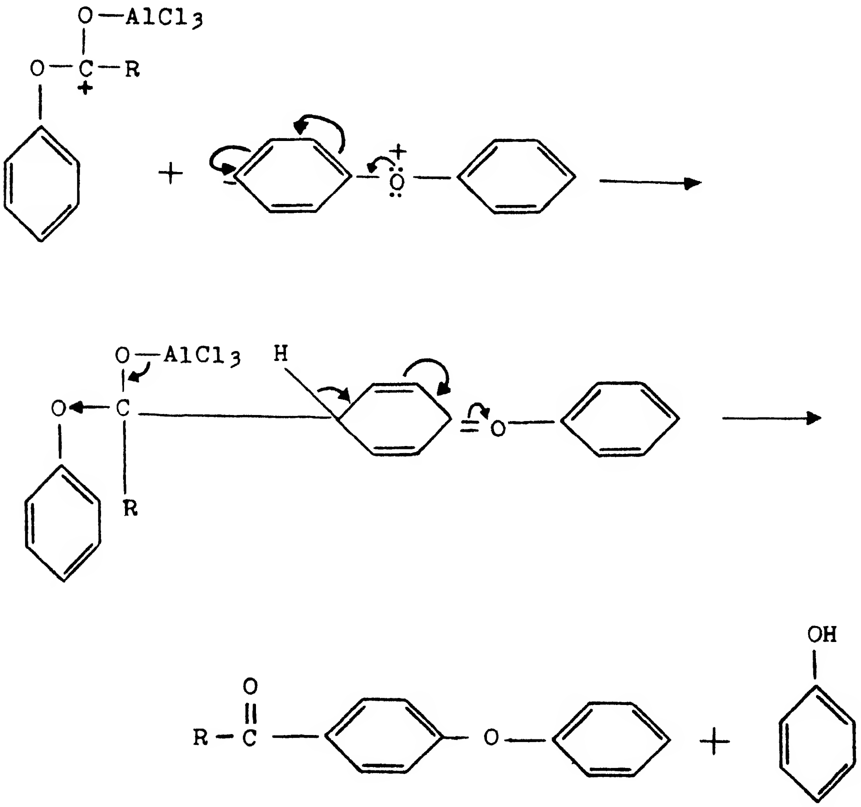
In this particular case an intermolecular acylation is indicated. Since it is known that the para rearrangements occur most readily at low temperatures, it is clear why *p*-cresyl acetate alone is not appreciably affected, for only the ortho positions are open. In the thymol ring, however, there is an open position which is para to the hydroxyl group, and the carbonium ion preferentially attacks this position.

Both mechanisms I and II are acylation reactions, catalyzed by aluminum chloride and involving the addition of an electrophilic center to a nucleophilic one. They differ in being intramolecular and intermolecular respectively. Neither course of reaction can be ruled out at the present time, but the first appears to be more probable on the basis of published evidence for the Fries rearrangement.

The mechanisms shown above appear to be in good agreement with other observations concerning the Fries reaction. For example, when the cresyl acetates are rearranged in the presence of ethanol, the formation of ethyl acetate has been noted:

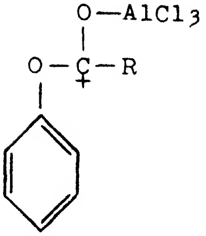


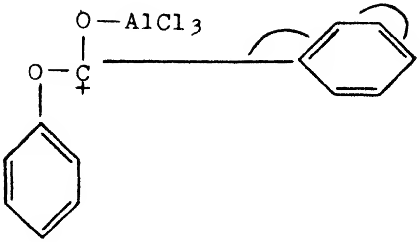
The alcohol simply furnishes another nucleophilic center which may compete for the electrophilic center in the carbonium ion. It is not surprising, therefore, that some ester exchange occurs in this case. Similarly when diphenyl ether is used as the solvent, *p*-acyldiphenyl ethers can be isolated. Here is another example of a solvent which can act as a nucleophilic agent and add to the carbonium ion:



The presence of *m*-directing groups in the *o*- or *p*- position of the phenolic ring interferes with or prevents the rearrangement. It will be recalled that *m*-directing groups tend to deactivate the ring to which they are attached. Any reduction in the nucleophilic activity of the ring would naturally retard the rearrangement.

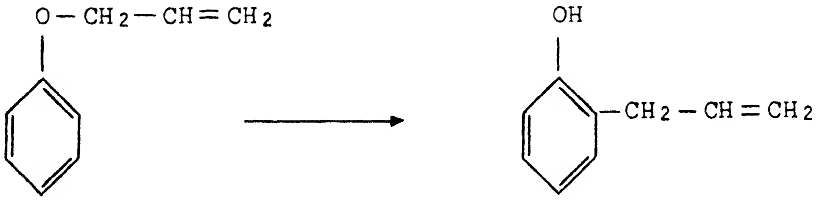
The relative ease with which various acyl groups migrate must be dependent on the electrophilic activity of the positive carbon atom [illegible] the carbonium ion. The fact that aliphatic acyl groups apparently migrate much more readily than aromatic acyl groups is well established. Examination of the aluminum chloride addition products of the phenol esters of aliphatic acids and aromatic acids discloses an important difference:





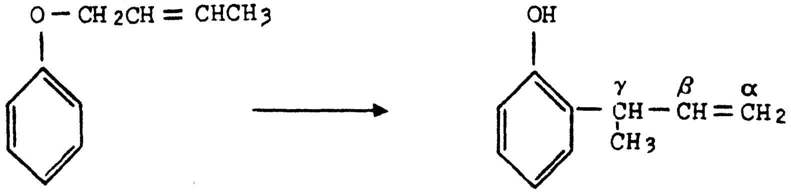
The adjacency of the carbonyl carbon atom to the aromatic ring permits resonance with the ring. The aromatic ring may be considered in this case to be an electron source. This resonance effect acts to diminish the electrophilic activity of the carbonyl carbon atom and consequently slows down the migration of the group. It is possible that steric factors may also be important but it is impossible to evaluate them at the present time.

Claisen rearrangement. This rearrangement also involves the cleavage of a carbon-oxygen bond and the formation of a new carbon-carbon bond (52). The reaction was noted originally for the allyl ethers of phenols and enols. These ethers on being heated rearrange to carbon-allyl compounds. The allyl ethers of phenol rearrange at about 200°:



allyl phenyl ether   o-allylphenol

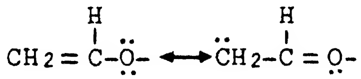
The allyl group migrates to the *o-* position if one of these positions is unsubstituted in the original ether molecule. It will be noted that, in the rearrangement of the crotyl phenyl ether, it is not the carbon atom of the carbon-oxygen bond which becomes attached to the ring but rather the carbon atom at the other end of the allyl chain. It was initially suggested by Claisen that it is the γ-carbon atom which forms the new bond with the ring. Very similar electronic mechanisms have been suggested by several workers:



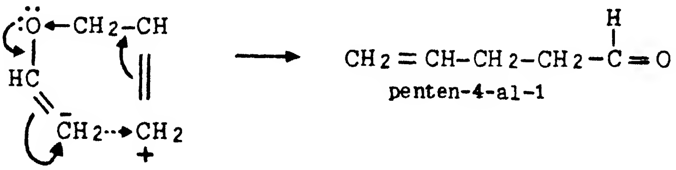
crotyl phenyl ether   o-γ-methylallylphenol

The fact that the unused electrons on the oxygen atom participate in resonance with the ring accounts for the activation of the ortho positions and the weakening of the carbon-oxygen bond. This tendency to cleave is enhanced by the fact that the allyl group acts as an electron-release group. The adjacent double bond serves as a source of electrons and, as the oxygen pulls further away from the carbon atom, the increasing positive charge on the latter acquires a greater attraction for a pair of electrons from the double bond. Finally, the electromeric shift produces a positive charge on the gamma carbon atom and this atom then adds to the electron pair available at the *o*- position. The breaking of the carbon-oxygen bond and the formation of the carbon-carbon must occur simultaneously. The ortho rearrangement has been shown to be a first-order reaction. It is an intramolecular reaction, for otherwise the rearrangement of a mixture of two allyl aryl ethers should yield more than two rearranged products. This has not been observed in the large amount of data available. The last step in the change involves the transformation of an *o*-quinoid structure to the more stable, resonant benzenoid form. The presence of substituents in the aromatic ring does not appear materially to change the ease of rearrangement. The crotyl ethers rearrange more readily than the allyl ethers (53). This fits in very well with the above mechanism, for the methyl group being an electron-release group would increase the electron-release effect of the allyl grouping.

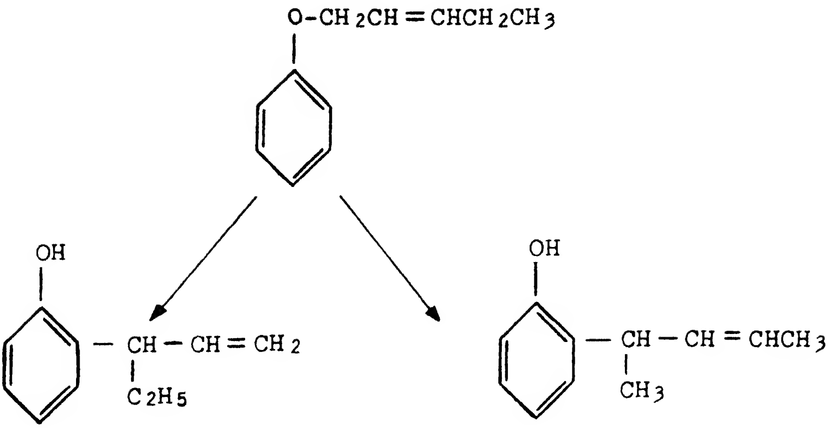
Vinyl allyl ethers also undergo the rearrangement. In this case the resonant nature of the vinoxy group serves the same purpose as the benzene ring:



$$CH_2=\overset{H}{\overset{|}{C}}-\underset{\cdot\cdot}{\ddot{O}}- \longleftrightarrow \ddot{C}H_2-\overset{H}{\overset{|}{C}}=\underset{\cdot\cdot}{O}-$$



A few ortho rearrangements have been reported which do not fit the suggested mechanism. For example, γ-ethylallyl phenyl ether on rearrangement gives a mixture which contains both the normal product and an anomalous product (54):



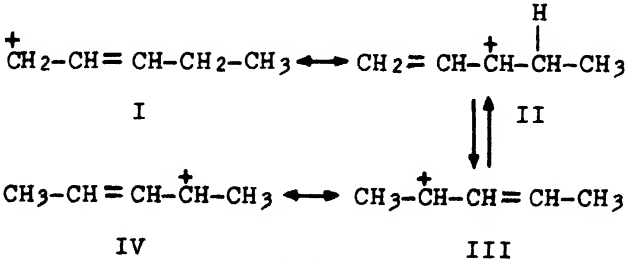
o-α-ethylallylphenol (normal)

o-α,γ-dimenthylallylphenol (anomalous)

Isomerization of the allylic side chain obviously occurs during the rearrangement. It is not possible to explain the formation of the anomalous product if the cleavage of the carbon-oxygen bond and the formation of the carbon-carbon bond are assumed to take place simultaneously. It is more probable that in some cases the allylic group separates as a carbonium ion, thus making isomerization possible (55). Allyl phenyl ether can rearrange to only one product, allylphenol. Even if the reaction proceeded in part by an ionic mechanism, only one product would be formed, since the resonant structures are equivalent:

$$\overset{+}{C}H_2-CH=CH_2 \longleftrightarrow CH_2=CH-\overset{+}{C}H_2$$

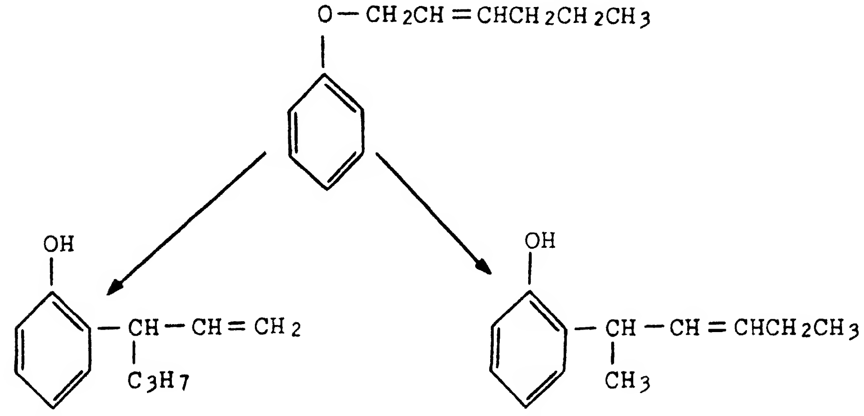
Isomerization is not possible in this case. With substituted allyl groups isomerization is possible, providing an allylic carbonium ion is an intermediate. The fact that such ions are stabilized by resonance justifies the assumption that they may be intermediates in some cases. The anomalous rearrangement of γ-ethylallyl phenyl ether may be attributed to isomerization of a carbonium ion:



$$\begin{array}{ccc}\overset{+}{C}H_2-CH=CH-CH_2-CH_3 & \longleftrightarrow & CH_2=CH-\overset{+}{C}H-\overset{H}{\overset{|}{C}H}-CH_3 \\ \text{I} & & \text{II}\ \big\updownarrow \\ CH_3-CH=CH-\overset{+}{C}H-CH_3 & \longleftrightarrow & CH_3-\overset{+}{C}H-CH=CH-CH_3 \\ \text{IV} & & \text{III}\end{array}$$

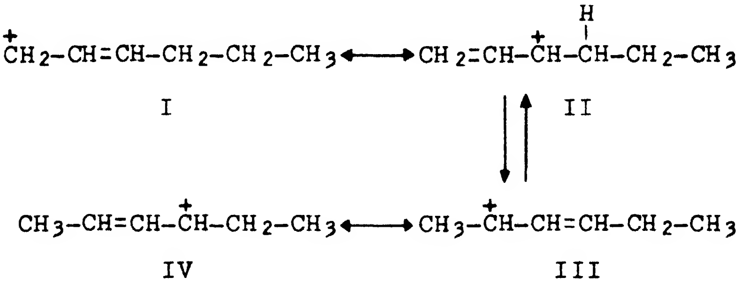
It will be noted that III and IV are completely equivalent forms and so should be stabilized to a greater degree than I and II.

While it is easy to show how isomeric carbonium ions may be formed, it is not possible in every case to determine which of the carbonium ions will preferentially add to the ring. For example, γ-*n*-propylallyl phenyl ether is reported to rearrange as follows (56):



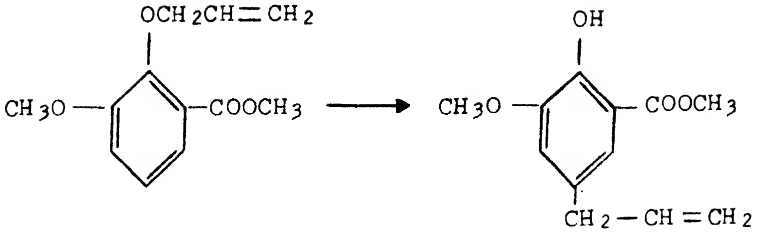
(normal) (anomalous)

Of the four carbonium ions shown below, it is not clear why III adds to form the anomalous product rather than I or IV:



$$\begin{tikzcd}
\overset{+}{C}H_2\text{-}CH{=}CH\text{-}CH_2\text{-}CH_2\text{-}CH_3 \arrow[r, leftrightarrow] & CH_2{=}CH\text{-}\overset{+}{C}H\text{-}\overset{H}{C}H\text{-}CH_2\text{-}CH_3 \arrow[d, shift right] \\
\text{I} & \text{II} \\
CH_3\text{-}CH{=}CH\text{-}\overset{+}{C}H\text{-}CH_2\text{-}CH_3 \arrow[r, leftrightarrow] & CH_3\text{-}\overset{+}{C}H\text{-}CH{=}CH\text{-}CH_2\text{-}CH_3 \arrow[u, shift right] \\
\text{IV} & \text{III}
\end{tikzcd}$$

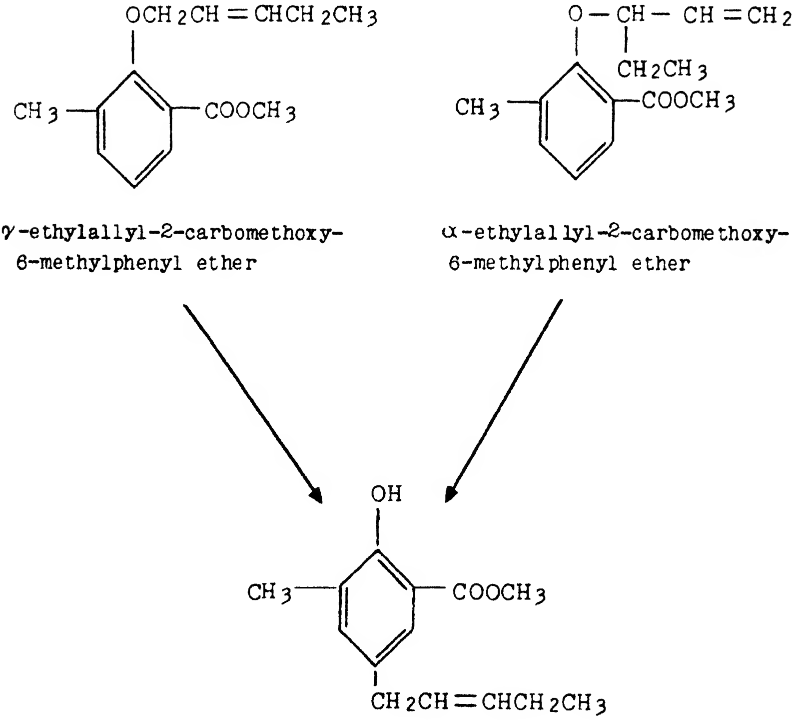
In a few cases it has been shown that there is some rearrangement to the para position even when there is an unsubstituted ortho position in the ether. Where both ortho positions are blocked, rearrangement to the para position takes place. The para rearrangement apparently occurs quite readily and efficiently:



allyl-2-carbomethoxy-6-methoxyphenyl ether

2-carbomethoxy-4-allyl-6-methoxyphenol

The para rearrangement is a first-order reaction similar to the ortho change. There appears to be little doubt that the para rearrangement involves dissociation as the first step. The fact that isomerization often occurs is in accord with the above assumption. Reported results from the para rearrangement, which involves isomerization, are not in agreement with the results for the corresponding ortho change (55):



γ-ethylallyl-2-carbomethoxy-6-methylphenyl ether

α-ethylallyl-2-carbomethoxy-6-methylphenyl ether

2-carbomethoxy-4-γ-ethylallyl-6-methylphenol

It will be noted in this case that it is the α-ethylallyl group which isomerizes and not the γ-ethylallyl group. This behavior is in sharp contrast to the behavior of the γ-ethylallyl group in the ortho rearrangement.

The Claisen rearrangement cannot be represented by a single mechanism. It is important to note, however, that the same fundamental principles are involved in every case. The ability of the unused electrons on the oxygen atom to participate in resonance with the ring accounts for the activation of the aromatic ring as well as the weakening of the carbon-oxygen bond. The tendency of the latter bond to cleave is facilitated by the fact that the allyl group acts as an electron-release group. In general, the γ-carbon atom in the allyl group starts to add to the ortho position before the cleavage of the carbon-oxygen bond is completed. The same forces, noted above, would account for dissociation as the first step in the para rearrangement. Where the γ-carbon atom is completely or partially blocked in its approach to the 2-carbon atom, it may be assumed that the tendency to dissociate will be facilitated. Isomerization probably may be associated with the formation of carbonium ions. It is not possible, however, to predict which isomeric ion will account for the final product.

CHAPTER XI

Reactions of Thioalcohols or Mercaptans

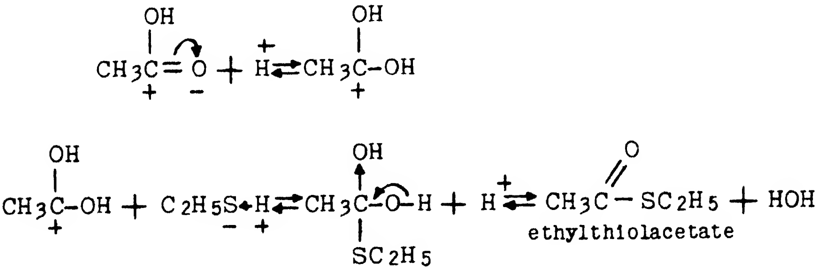
The thioalcohols are the sulfur analogs of the ordinary alcohols. The sulfur atom has two unshared pairs of electrons similar to the oxygen atom in R—$\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}$—H. However, they differ in several ways. The thioalcohols dissolve in aqueous alkalies to form thioalcoholates or mercaptides, whereas water insoluble alcohols are not soluble under these conditions. This would indicate the thioalcohols to be more acidic than alcohols. The tendency to ionize

$$R{-}S{-}H \rightleftharpoons R{-}\bar{S} + H^{+}$$

would thus be greater.

The carbon-to-sulfur linkage is more difficult to break than the carbon-to-oxygen linkage; consequently, replacement of the —S—H group is often impossible. Thus they do not react with hydrogen halides as do the alcohols.

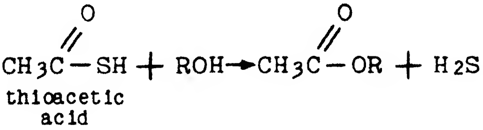
Reactions with carboxylic acids proceed normally to form thiolesters. Similar to the reactions of carboxylic acids with alcohols, these reactions are reversible and the equilibria are not favorable for the formation of good yields of thiolesters. The mechanism is probably the same as that given for the esterification of alcohols:



$$CH_3\overset{\overset{OH}{|}}{\underset{+}{C}}{=}\underset{-}{O} + \overset{+}{H} \rightleftharpoons CH_3\overset{\overset{OH}{|}}{\underset{+}{C}}{-}OH$$

$$CH_3\overset{\overset{OH}{|}}{\underset{+}{C}}{-}OH + C_2H_5\underset{-}{S}{:}\underset{+}{H} \rightleftharpoons CH_3\overset{\overset{OH}{\uparrow}}{\underset{\underset{SC_2H_5}{|}}{C}}{-}O{-}H + \overset{+}{H} \rightleftharpoons \underset{\text{ethylthiolacetate}}{CH_3\overset{\overset{O}{/\!/}}{C}{-}SC_2H_5} + HOH$$

It is interesting to note that the thioacids react with alcohols to form ordinary esters, with the elimination of hydrogen sulfide:



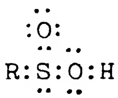
$$\underset{\substack{\text{thioacetic}\\\text{acid}}}{CH_3\overset{\overset{O}{/\!/}}{C}{-}SH} + ROH \rightarrow CH_3\overset{\overset{O}{/\!/}}{C}{-}OR + H_2S$$

Both of the above reactions are in accord with the conclusion that the alcohol carbon-to-oxygen linkage is not broken in the esterification of primary and secondary alcohols.

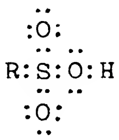
Finally the sulfur atom in these compounds can be oxidized with the formation of sulfinic and sulfonic acids:

$$\mathrm{RSH} \longrightarrow \underset{\text{alkyl sulfinic acid}}{\mathrm{RSOOH}} \longrightarrow \underset{\text{alkyl sulfonic acid}}{\mathrm{RSO_2OH}}$$

It is interesting to note that the most reasonable electronic formulas for these acids do not show double bonds between sulfur and oxygen:



$$\mathrm{R{:}\overset{:\ddot{O}:}{\underset{\cdot\cdot}{\ddot{S}}}{:}\underset{\cdot\cdot}{\ddot{O}}{:}H}$$



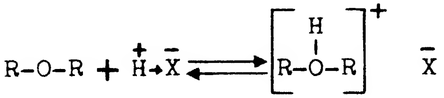
$$\mathrm{R{:}\overset{:\ddot{O}:}{\underset{:\underset{\cdot\cdot}{O}:}{\ddot{S}}}{:}\underset{\cdot\cdot}{\ddot{O}}{:}H}$$

The thiophenols (Ar—S—H) give the usual mercaptan reactions except that they are more acidic and are more difficult to esterify (see phenols).

CHAPTER XII

Reactions of Ethers

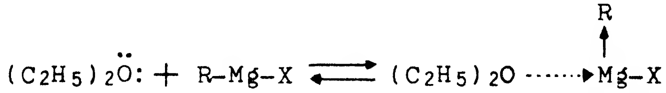
The characteristic group of the ethers, $-\overset{|}{\underset{|}{C}}-\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}-\overset{|}{\underset{|}{C}}-$, is similar to the alcohol group in that the oxygen atom has two unshared electron pairs, but it is unlike the alcohol group in lacking an ionizable hydrogen atom. Many of their reactions are initiated by the attraction of the unshared electrons for protons or for certain salts (BF_3, $AlCl_3$, $ZnCl_2$, etc.) which readily form coordinate bonds with the ether oxygen:



$$R-O-R + \overset{+}{H}\rightarrow\overset{-}{X} \rightleftharpoons \left[R-\overset{\overset{\displaystyle H}{|}}{O}-R\right]^{+} \quad \overset{-}{X}$$

As a rule the oxonium salts are not very stable, although some have been isolated. In general the formation of an oxonium ion produces an electron displacement away from carbon and towards oxygen thus weakening the carbon-to-oxygen bond. Consequently cleavage of the latter bond often occurs.

The tendency of ethers to form coordinated compounds is of practical value in carrying out certain reactions. For example, Grignard syntheses are commonly carried out in dry diethyl ether as the solvent. The ether not only acts as a solvent but apparently assists in the reaction itself through the formation of unstable addition compounds:



$$(C_2H_5)_2\ddot{O}: + R-Mg-X \rightleftharpoons (C_2H_5)_2O \cdots\cdots\rightarrow \overset{\overset{\displaystyle R}{\uparrow}}{Mg}-X$$

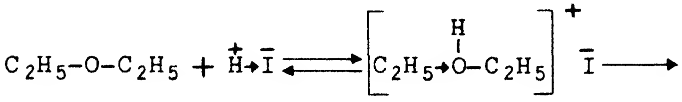
It is known that Grignard reagents form addition compounds with ether. From the structure of these salts, it is safe to assume that the presence of ether in Grignard syntheses increases the availability of the carbanion ($\overset{-}{R}$) and the cation ($\overset{+}{MgX}$). In other words these ions are more available for addition to other compounds such as aldehydes and ketones (p.116).

It has been observed that the use of ether as a solvent sometimes facilitates the addition of bromine to double bonds. Ether forms a highly unstable addition product with bromine. In view of the fact that the addition of bromine to an olefin bond involves the primary addition of positive bromine, it is reasonable to assume that ether promotes the availability of the latter through the formation of an addition compound:

$$(C_2H_5)_2\ddot{O}: + \overset{+}{Br} \rightarrow \overset{-}{Br} \rightleftharpoons \left[(C_2H_5)_2\ddot{O}:Br\right]^{+} \overset{-}{Br}$$

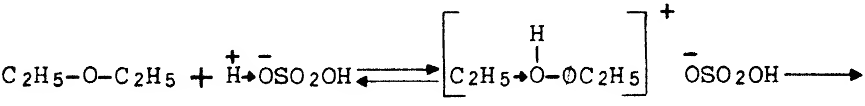
The highly unstable oxonium cation may be regarded as a ready source of positive bromine ions. The use of ether as a solvent for brominating relatively unreactive olefin bonds (as in fumaric acid) has not been widely used, possibly for two reasons: (1) The addition product is very unstable and is difficult to handle; and (2) some halogenation of the ether occurs with the formation of lacrymatory compounds.

The cleavage of ethers brought about by heating with concentrated hydriodic acid and with concentrated sulfuric acid may be written as follows:



$$C_2H_5-O-C_2H_5 + \overset{+}{H}\rightarrow\overset{-}{I} \rightleftharpoons \left[C_2H_5\rightarrow\overset{\overset{H}{|}}{O}-C_2H_5\right]^{+} \overset{-}{I} \longrightarrow$$

$$C_2H_5I + C_2H_5OH \xrightarrow{HI} 2C_2H_5I + HOH$$

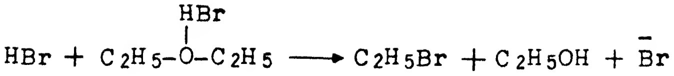


$$C_2H_5-O-C_2H_5 + \overset{+}{H}\rightarrow\overset{-}{O}SO_2OH \rightleftharpoons \left[C_2H_5\rightarrow\overset{\overset{H}{|}}{O}-0C_2H_5\right]^{+} \overset{-}{O}SO_2OH \longrightarrow$$

$$CH_3CH_2OSO_2OH + CH_3CH_2OH \xrightarrow{H_2SO_4} 2\ CH_3CH_2OSO_2OH + HOH$$

The addition of the proton, by displacing the electron system, facilitates cleavage between carbon and oxygen and may result in the formation of an alcohol and a carbonium ion. The latter is neutralized by the iodide ion or hydrogen sulfate ion to form an alkyl iodide or alkyl hydrogen sulfate. It is not known with certainty that a free carbonium ion is actually formed to any extent. It is probable that the hydrogen sulfate ion or iodide ion starts to add before the cleavage of the carbon-oxygen bond is completed. With excess reagent the liberated alcohol is also converted to the same end products.

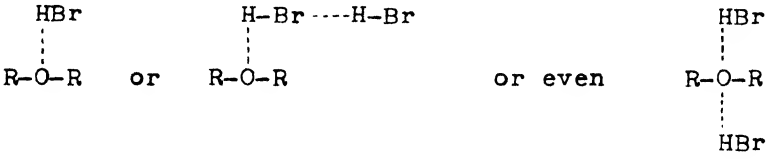
Mayo and co-workers (57) have studied the cleavage of diethyl ether with hydrogen bromide. They found that different equations are required to express the rate of cleavage in different solvents. When carried out in acetic acid, an ionizing solvent, the reaction was found to be of first order with respect to both the ether and hydrogen bromide. The mechanisms shown above undoubtedly are valid for those cases where the reactions are carried out in ionizing media. The reaction was found to be trimolecular, however, when carried out in toluene solution. In this case the effects of water were eliminated by the addition of acetyl bromide. The following equation was suggested as showing how the molecule of ether and two molecules of hydrogen bromide are involved:



$$HBr + C_2H_5-\overset{HBr}{\overset{|}{O}}-C_2H_5 \longrightarrow C_2H_5Br + C_2H_5OH + \overset{-}{Br}$$

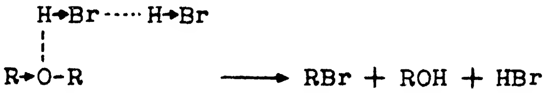
As pointed out in this paper, it is believed that the ether-acid complexes are largely of the hydrogen-bond type rather than oxonium salts (58).

While it appears to be established that the order of the reaction may be changed by change of solvents, it does not follow that the fundamental principles involved in the mechanism are altered. If it be assumed that the intermediates, in essentially nonionizing media, are of the hydrogen-bonded type



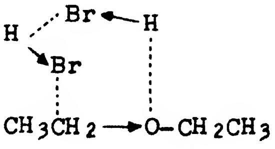
$$R-\overset{HBr}{\overset{\vdots}{O}}-R \quad \text{or} \quad R-\overset{H-Br\cdots\cdots H-Br}{\overset{\vdots}{O}}-R \quad \text{or even} \quad R-\underset{HBr}{\underset{\vdots}{\overset{HBr}{\overset{\vdots}{O}}}}-R$$

it is conceivable that the reaction might be bimolecular, trimolecular, or even polymolecular. The formation of the initial hydrogen bond, by displacing the electron system, would facilitate cleavage between carbon and oxygen:



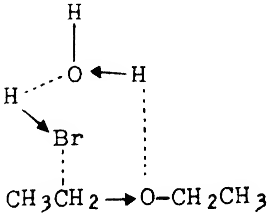
$$R\rightarrow\overset{H\rightarrow Br\cdots\cdots H\rightarrow Br}{\overset{\vdots}{O}}-R \longrightarrow RBr + ROH + HBr$$

The addition of the second molecule of hydrogen bromide, through the formation of another hydrogen bond, might be expected to further enhance the displacement and thus aid in the subsequent cleavage. The fact that no more than two molecules of hydrogen bromide are involved suggests another possibility, namely, the proximity of the alpha carbon atom, and the second bromine atom may have a marked effect on ease of cleavage (57).



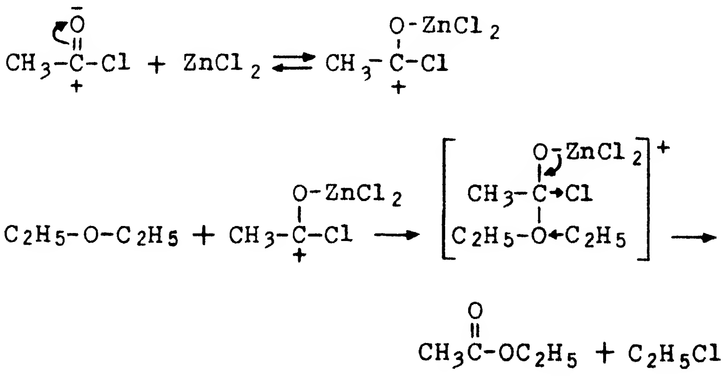
It is believed that cleavage and the attack on the alpha carbon atom occur simultaneously. This belief is based on the fact that similar reactions have been noted to proceed with inversion and with little racemization (59). This would indicate that free carbonium ions are not formed to any appreciable extent. This appears to be true for both ionizing and nonionizing media. The mechanism directly above requires no ionization, but rather the carbon-bromine bond starts to form before the carbon-oxygen is completely cleaved. The energy of formation for the new bond may therefore contribute to the breaking of the old bond. Such a scheme would be expected to have a lower activation energy than a mechanism which required ionization.

Water or alcohol accelerates the cleavage of diethyl ether in toluene. Mayo suggests a similar mechanism for this effect in which the water or alcohol replaces the second molecule of hydrogen bromide:



Such an explanation appears reasonable but it is not clear why the presence of ionizing solvents such as water or alcohol would not also promote the mechanism which involves an oxonium ion as an intermediate.

The cleavage of dialkyl ethers to form esters by treatment with anhydrous zinc chloride and acyl chlorides probably follows a somewhat similar mechanism. When diethyl ether is heated with zinc chloride alone, only small amounts of ethyl alcohol and ethylene are formed. In the presence of an acyl chloride, however, the cleavage between carbon and oxygen takes place more readily. These facts indicate that zinc chloride reacts more readily with the acyl chloride than with the ether and suggests the following mechanism:



$$CH_3-\underset{+}{\overset{\overset{-}{O}}{\overset{\|}{C}}}-Cl + ZnCl_2 \rightleftharpoons CH_3-\underset{+}{\overset{O-ZnCl_2}{\overset{|}{C}}}-Cl$$

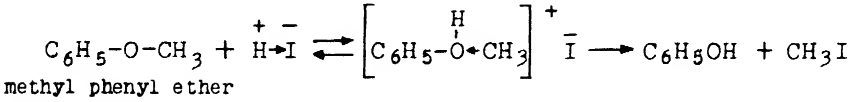
$$C_2H_5-O-C_2H_5 + CH_3-\underset{+}{\overset{O-ZnCl_2}{\overset{|}{C}}}-Cl \longrightarrow \left[\begin{array}{c} O-ZnCl_2 \\ | \\ CH_3-C\leftarrow Cl \\ | \\ C_2H_5-O\leftarrow C_2H_5 \end{array}\right]^+ \longrightarrow$$

$$\overset{O}{\overset{\|}{CH_3C}}-OC_2H_5 + C_2H_5Cl + ZnCl_2$$

The reaction is induced by the electrophilic nature of zinc chloride. The latter acquires a share in an electron pair belonging to the carbonyl oxy-

gen atom. The resulting carbonium ion then attaches itself to an electron pair on the ether oxygen atom. This addition creates the electron displacements which result in the cleavage of the oxygen-carbon bond.

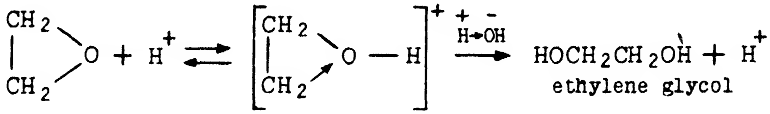
The aryl alkyl ethers are also cleaved by heating with concentrated hydriodic acid, yielding phenols and alkyl iodides. In this case the direction of the electron displacement in the oxonium ion is predominantly away from the carbon atom of the methyl group rather than the carbon atom of the phenyl group. It will be remembered that when an oxygen atom is attached to an aromatic ring it participates in resonance with the ring. Thus the oxygen is bound more tightly to the ring and as a result cleavage occurs between the oxygen atom and the alkyl radical:



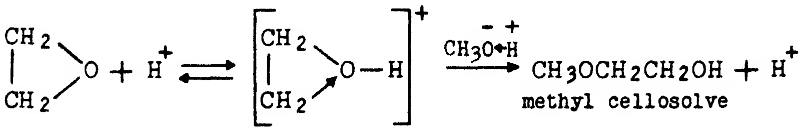
$$C_6H_5{-}O{-}CH_3 + \overset{+}{H}{\rightarrow}\overset{-}{I} \rightleftharpoons \left[C_6H_5{-}\overset{H}{\overset{|}{O}}{\leftarrow}CH_3\right]^{+} \overset{-}{I} \longrightarrow C_6H_5OH + CH_3I$$

Treatment of ethers of this type with concentrated sulfuric acid usually leads to substitution in the aromatic nucleus due to the greater electron availability at the *o*- and *p*- positions. The unsubstituted diaryl ethers are quite resistant to the cleavages noted.

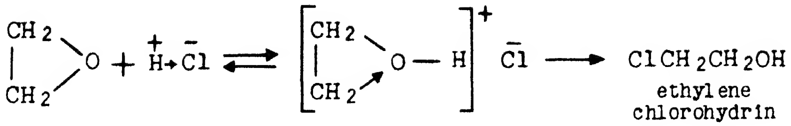
The olefin oxides, which are cyclic ethers, are particularly reactive because of the internal strain common to three-membered ring systems. Their characteristic reactions involve cleavage of the carbon-to-oxygen bond, similar to the open-chain ethers. The acid-catalyzed hydrolysis of ethylene oxide may be illustrated as follows:

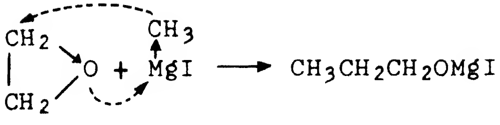


The mechanism may involve initial ring opening followed by reaction with water or the two reactions may occur simultaneously. In either case the fundamental principles would be essentially the same. Alcoholysis follows a similar scheme:



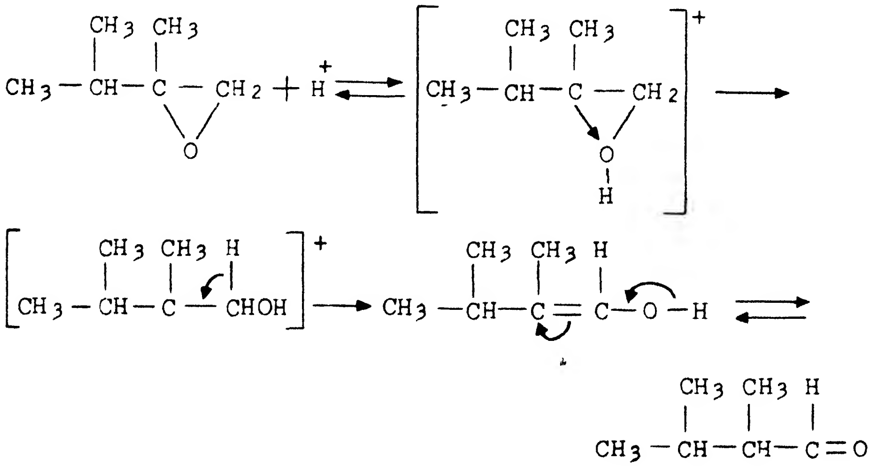
Other well-known cleavage reactions may be written in a similar manner:





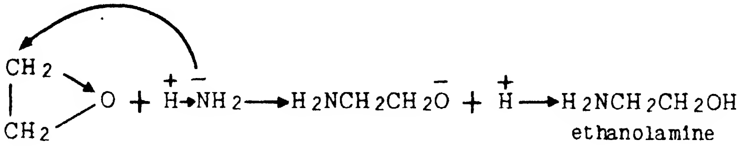
Hydrolysis of the latter yields *n*-propyl alcohol. The reaction of alkyl magnesium halides with ethylene oxide is frequently employed for the synthesis of primary alcohols.

Rearrangements have been observed in some acid-catalyzed cleavages of olefin oxides. For example, 2,3-dimethyl butene-1 oxide when heated with 10 per cent hydrochloric acid is converted to 2,3-dimethylbutanal (60). It is not necessary to assume an entirely different mechanism in this case, for it is probable that in part the reaction follows the same course as the reactions noted above:

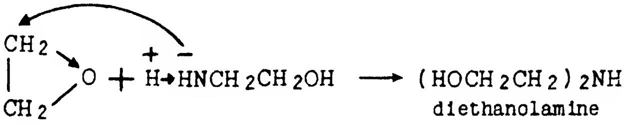


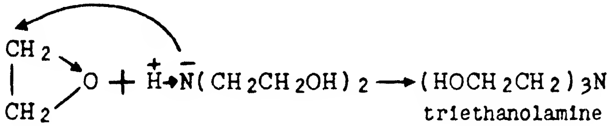
In this particular reaction, the carbonium ion is apparently more readily neutralized by attracting an electron pair from the adjacent carbon-hydrogen bond with the formation of the enol form of the aldehyde. It is possible that the cleavage and the splitting of a proton occur simultaneously. Theoretically, it is possible that the acid-catalyzed cleavage of any olefin oxide may yield either of two products depending on the conditions used. The carbonium ion may be neutralized by union with an anion or by attracting an electron pair from an adjacent carbon-hydrogen bond.

The above reactions involve as the initial step addition of an electrophilic ion (cation) to the oxygen atom. Recent work, however, has shown that under basic conditions the cleavages are of a bimolecular nucleophilic displacement type. The reaction of ethylene oxide with ammonia is an example of this type and may be shown as follows:



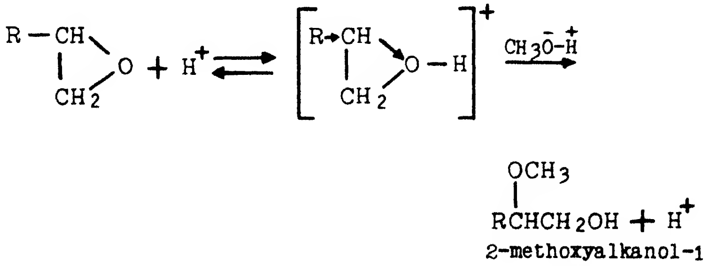
In the carbon-to-oxygen bond the oxygen, being more electron attracting, induces a fractional positive charge on the carbon atom. The nucleophilic $\overset{+}{H}\rightarrow \overset{-}{N}H_2$ is attracted to this point and the approach of this group may be considered to facilitate cleavage. In the presence of excess ethylene oxide the reaction proceeds further with the formation of diethanolamine and triethanolamine.



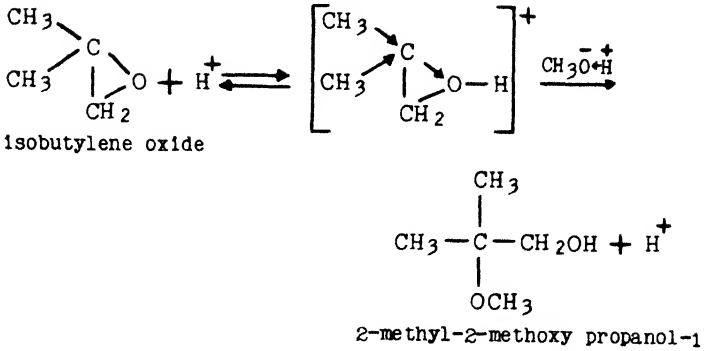


It will be noted that in all of the above reactions cleavage may occur on either side of the oxygen atom without altering the final products. This is due to the symmetry of the ethylene oxide molecule. These statements do not hold for the mono substituted olefin oxides and a consideration of the directive influences which operate in these oxides is of interest from the standpoint of mechanism (61). The following examples illustrate these influences for substituted olefin oxides:

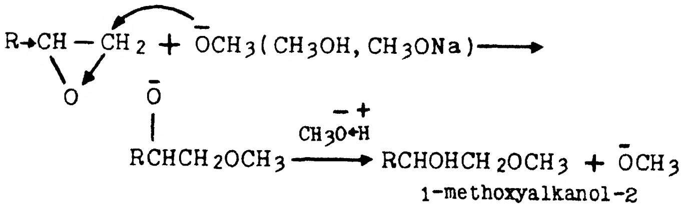
I



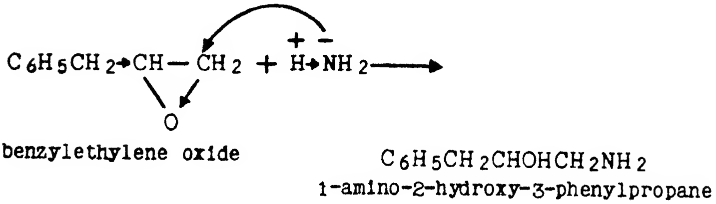
II



III

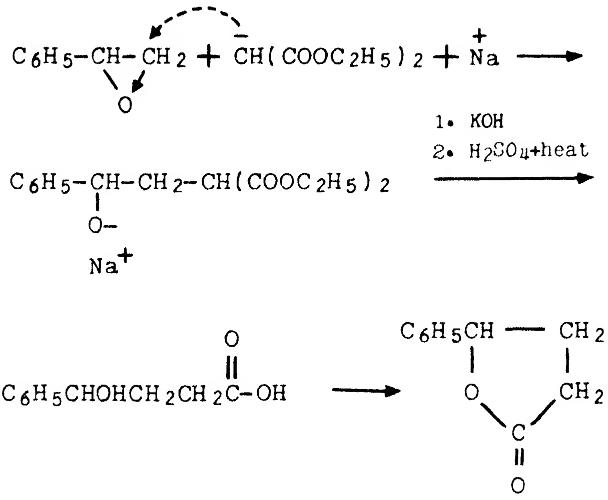


IV



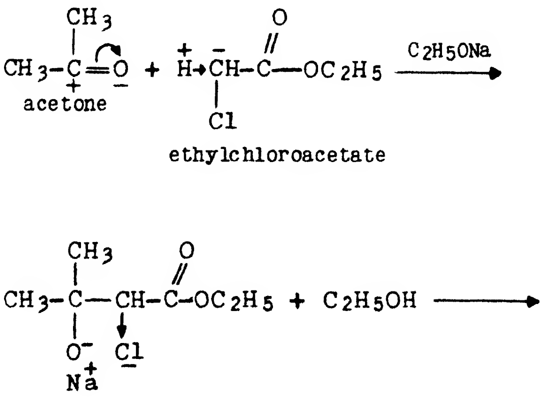
Reactions I and II are acid catalyzed and follow the unimolecular mechanism involving the ring opening of the oxonium ion. The electron-release effect of the alkyl group (or groups) is transmitted through the carbon attached to the fewest hydrogen atoms to the oxygen, rather than through the CH_2 group.

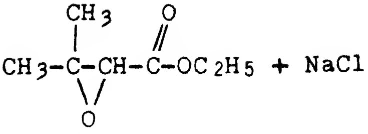
In the base-catalyzed cleavages, III and IV, the bimolecular nucleophilic mechanism prevails. Because of the electron-release effect of the alkyl group there is lower electron density (larger fractional positive charge) on the CH_2 group in the oxide ring. The approach of the methoxy anion towards the CH_2 group increases the electron-release effect of the latter and consequently weakens its carbon-to-oxygen linkage. As a result, cleavage of the $-CH_2-O-$ bond occurs. Additional evidence for the course of the cleavage reactions in basic media has been reported recently by Russell and Vander Werf (62). They condensed styrene oxide and butadiene oxide separately with sodio diethylmalonate in alcohol solution. They isolated γ-phenyl-γ-butyrolactone and γ-vinyl-γ-butyrolactone from these reactions. No other lactone could be isolated in either case. These findings definitely indicate that the attack of the nucleophilic anion takes place solely at the CH_2 group of the ethylene oxide ring. This carbon atom would have the lowest electron density and hence would be more susceptible to attack by the anion:



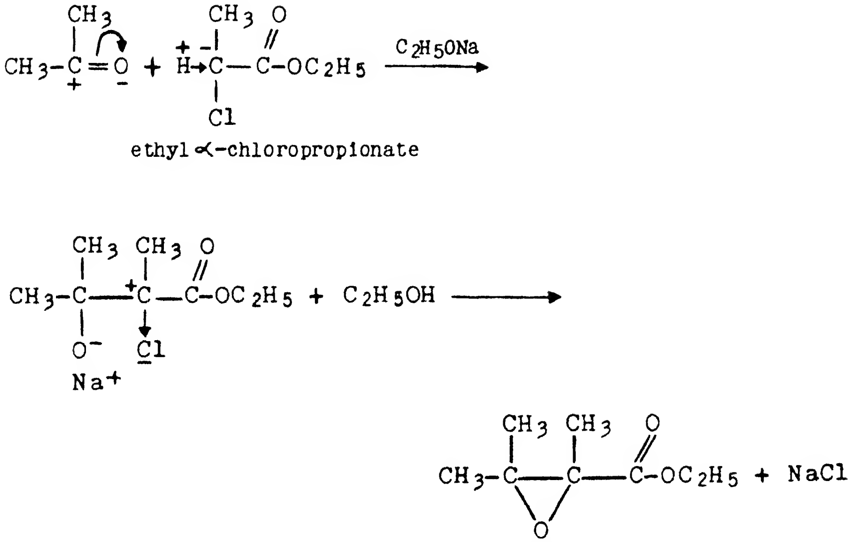
Acid-catalyzed and base-catalyzed cleavages of olefin oxides have been referred to as abnormal and normal reactions respectively. This is rather unfortunate, for as long as any mechanism is in accord with the electron requirements of the system it may be said to be normal.

The Darzen method for the preparation of aldehydes and ketones (63) also involves the cleavage of an olefin oxide. In this reaction an aldehyde or ketone is condensed with ethyl chloroacetate or ethyl α-chloropropionate under the influence of sodium ethoxide to yield a glycidic ester. The latter when saponified and heated loses a molecule of carbon dioxide and forms an aldehyde or ketone. The first step involves a Claisen condensation (see p.207):





ethyl β,β-dimethylglycidate

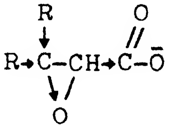


ethyl α,β,β-trimethylglycidate

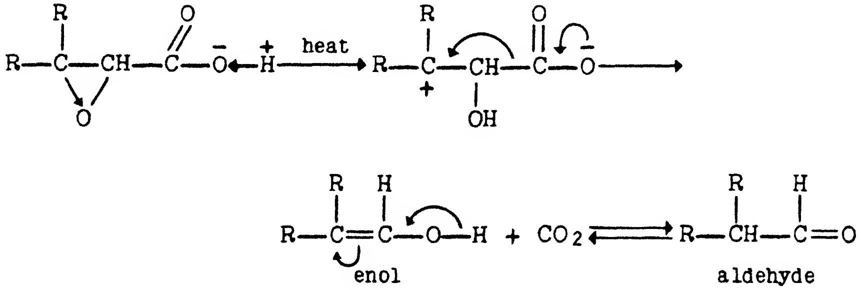
The reaction is general for aliphatic and alicyclic ketones and for aromatic ketones of the type $ArCOCH_3$. It apparently is not as general for aldehydes, although it has been used successfully in a number of cases.

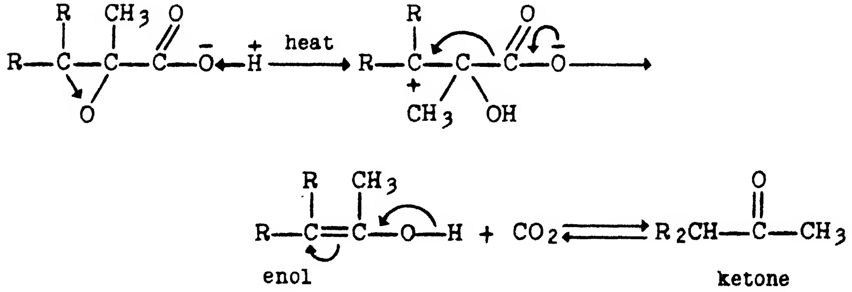
The ease of conversion of the glycidic ester to an aldehyde or ketone often varies in going from one ester to another. In general the ester is hydrolyzed and the resulting salt or free acid heated to effect the decarboxylation and cleavage. It is often possible to carry out all of the steps in one operation by simply heating the ester in alkaline solution. In other cases it may be necessary to isolate the sodium salt or free acid and subsequently apply heat to effect the change. Good yields have been obtained in some cases by heating the sodium salt with an equivalent amount of sodium hydroxide. It has also been reported that the glycidic acids decompose slowly in contact with dilute acids.

The course of the cleavage and decarboxylation reactions for the glycidic ester has not been definitely established. There is enough experimental data on hand, however, to suggest the mechanism which is followed. The decomposition of glycidic esters, whether carried out under acidic or basic conditions usually yields the same end product. The olefin oxide ring must cleave, therefore, in the same direction in every case. This can be accounted for if cleavage of the oxide ring precedes decarboxylation. The strained oxide ring, under the influence of the electron-attracting carbonyl group, would be expected to cleave very easily and in the same direction in each case:

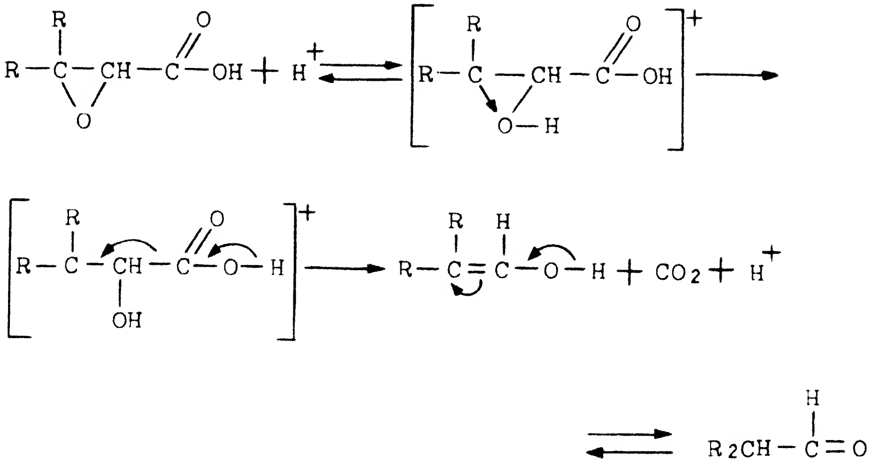


The fact that glycidic acids, when treated with hydrogen chloride, give good yields of β-chloro-α-hydroxy acids is an indication that ring opening takes place more readily than decarboxylation. With these facts in mind, the following mechanisms may be written for the decomposition of glycidic acids:

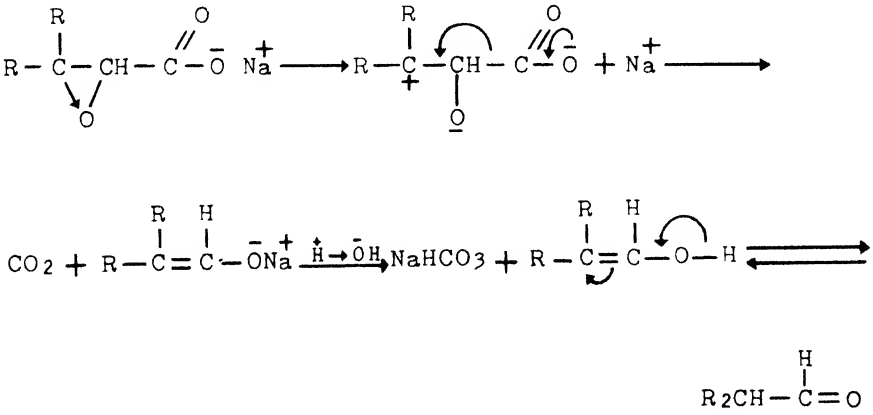




The electron-deficient carbon atom, formed by cleavage of the oxide ring, would be expected to facilitate decarboxylation as indicated above. The presence of strong inorganic acids apparently catalyzes the reaction but there is little published information on the acid-catalyzed decomposition. The acid-catalyzed reaction may be shown as follows:



In alkaline solution the salt of the glycidic acid would furnish an electron-rich anion which readily undergoes the above reaction when heated. The following mechanism is similar to those shown above:



In those cases where the dry sodium salts have been heated with solid sodium hydroxide to effect the change, the water necessary for the third step comes from the interaction of CO_2 and $\bar{O}H$ from the base:

$$\mathrm{CO_2 + \overset{-}{O}H \longrightarrow \overset{-}{H}CO_3}$$

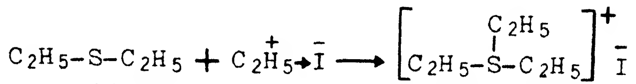
$$\mathrm{2\overset{-}{H}CO_3 \longrightarrow \overset{=}{C}O_3 + HOH + CO_2}$$

CHAPTER XIII

Reactions of Thioethers

The sulfur analogs of the ethers differ from the latter in several ways, in spite of the fact that sulfur (like oxygen) in these compounds has two unshared electron pairs. As noted previously, the carbon-to-sulfur linkage is more difficult to break than the carbon-to-oxygen bond, consequently cleavage reactions occur with greater difficulty. The utilization of the unshared electrons for the formation of coordinate bonds yields a variety of sulfonium compounds which are more stable than the corresponding oxonium compounds.

For example, the addition of alkyl halides to thioethers results in the formation of sulfonium compounds:



$$C_2H_5-S-C_2H_5 + \overset{+}{C_2H_5}\rightarrow\overset{-}{I} \longrightarrow \left[C_2H_5-\overset{\overset{C_2H_5}{|}}{S}-C_2H_5\right]^{+} \overset{-}{I}$$

diethyl thioether triethylsulfonium iodide

The sulfur atom has six valence electrons and in the thioethers two are used in pairing with the two adjacent carbon atoms, leaving two unused pairs of electrons. The addition of a carbonium ion (with an electron deficiency of one valence electron) to an unused pair of sulfur's electrons contributes a positive charge to the group because the total number of valence electrons is one less than the number belonging to the component atoms. Thus the sulfonium compounds are typical salts. Three of the bonds are predominantly covalent and the fourth is ionic.

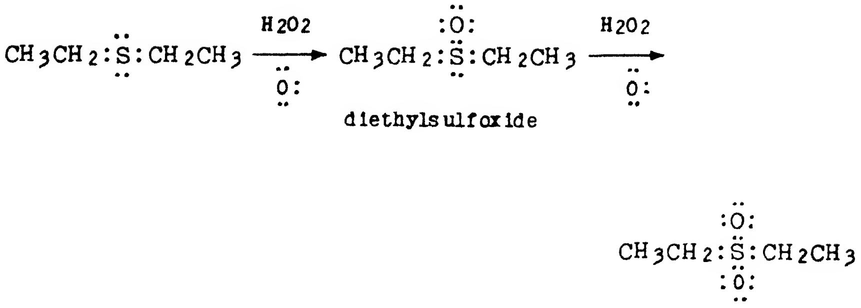
The alkyl sulfonium halides yield the corresponding sulfonium hydroxides when treated with moist silver oxide:

$$(C_2H_5)_3\overset{+\;-}{SI} + \overset{+\;-}{AgOH} \longrightarrow (C_2H_5)_3\overset{+\;-}{SOH} + AgI$$

triethylsulfonium hydroxide

The replacement of I by OH does not alter the ionic character of the bond and as might be expected, the sulfonium hydroxides are strong bases.

Similar to the thioalcohols, the sulfur atom in the thioethers is readily oxidized, yielding dialkyl sulfoxides and dialkyl sulfones. Thirty per cent hydrogen peroxide solution is frequently used for these oxidations:



$$CH_3CH_2\!:\!\ddot{\underset{\cdot\cdot}{S}}\!:\!CH_2CH_3 \xrightarrow[\ddot{\underset{\cdot\cdot}{O}}:]{H_2O_2} CH_3CH_2\!:\!\overset{:\ddot{O}:}{\ddot{\underset{\cdot\cdot}{S}}}\!:\!CH_2CH_3 \xrightarrow[\ddot{\underset{\cdot\cdot}{O}}:]{H_2O_2} CH_3CH_2\!:\!\underset{:\underset{\cdot\cdot}{\ddot{O}}:}{\overset{:\ddot{O}:}{\ddot{S}}}\!:\!CH_2CH_3$$

diethylsulfoxide

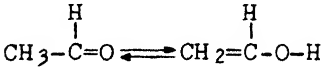
diethylsulfone

CHAPTER XIV

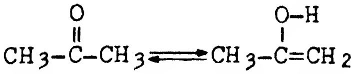
Reactions of Aldehydes and Ketones

These two classes of compounds contain the carbonyl group, $-\overset{|}{C}=O$, and their most typical reactions (common to both) are due to the reactivity of this group. The considerable dipole moments of aldehydes and ketones indicate that the carbonyl group may be written as $-\overset{|}{C}::\underset{\cdot\cdot}{O}: \longleftrightarrow -\underset{+}{\overset{|}{C}}:\underset{-}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}}:$. The aldehydes and ketones undergo addition reactions with various reagents through the functioning of an electromeric shift, $-\underset{+}{\overset{|}{C}}\overset{\curvearrowright}{=}\underset{-}{O}$. Many of these reactions are known to be catalyzed by acids or bases or both, and there are a number in which the addition occurs only in the presence of a catalyst. It is not easy to distinguish between addition reactions and so-called condensation reactions, for the primary process with either type may involve addition. Before studying these reactions, it is necessary to consider the tautomeric character of aldehydes and ketones which have one or more hydrogen atoms on the alpha carbon atom.

Compounds which behave in different reactions as if they had two or more different structures are said to exhibit tautomerism. Originally the term was used only to indicate the migration of hydrogen and with the aldehydes and ketones was shown as follows:



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

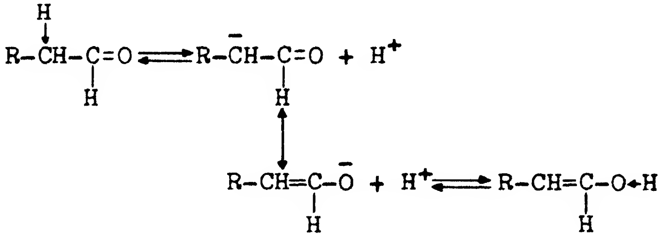


$$CH_3-\overset{\overset{O}{\|}}{C}-CH_3 \rightleftharpoons CH_3-\overset{\overset{O-H}{|}}{C}=CH_2$$

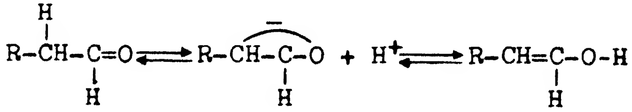
keto form enol form

This view may be extended to all types of tautomeric changes, regardless of whether the migratory group is a proton or some other cation, or whether it is an anion. All such changes involve the separation of either a cation or an anion. This separation leaves an ion (anion or cation) in which electromeric displacements occur in such a way that the eliminated ion has two possible points for recombination. The term cationotropy is used in all cases which involve the separation of a cation; the term prototropy is applied to the reversible interconversion of isomers differing only in the position of a hydrogen atom; and the term anionotropy is reserved for tautomeric changes in which the migrating group separates as an anion.

It is now generally accepted that resonance occurs between the structures which represent the ions (anions) derived from each tautomer:



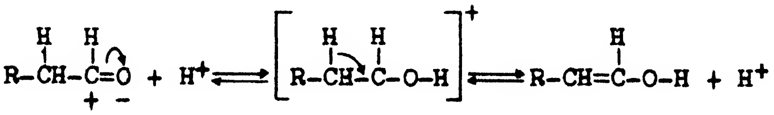
The anions are not to be regarded as separate entities but rather as resonant structures of a hybrid ion:



The driving force for the initial ionization is the electron attraction exerted by the carbonyl group, $\rightarrow \overset{|}{\underset{+}{C}}=\underset{-}{O}$. In the case of the simple aldehydes and ketones, the keto form predominates enormously over the enol form. With some carbonyl compounds, which will be discussed later, the enol form predominates. Both of the prototropic isomers shown above are acids and correspond to one and the same base, the hybrid anion.

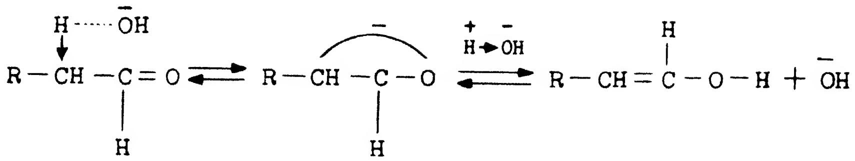
Prototropic changes may be catalyzed by both acids and bases, although the most effective catalysts are anions (bases) of high coordinating power (strong proton affinity) such as $\bar{O}H$ or $\bar{O}C_2H_5$.

Acid mechanism:



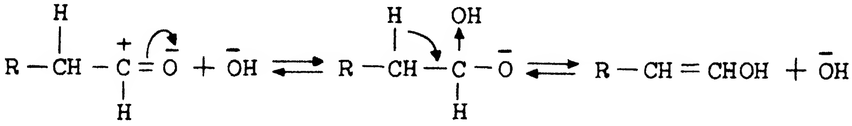
The addition of the proton by displacing the electronic system away from the α-carbon atom facilitates the separation of a proton from the α-carbon atom.

Basic mechanism:



$$R-\overset{H\cdots\bar{O}H}{CH}-\underset{H}{C}=O \rightleftharpoons R-CH-\underset{H}{C}-\bar{O} \xrightleftharpoons{\overset{+}{H}\,\overset{-}{O}H} R-CH=\overset{H}{C}-O-H+\bar{O}H$$

This represents the basic catalyst as directly assisting in the removal of a proton. A modified version was advanced by Watson, Nathan, and Laurie in 1935 (64):



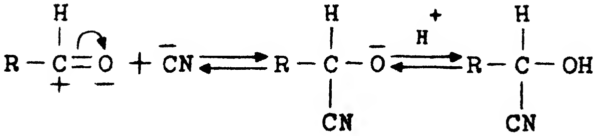
$$R-\overset{H}{CH}-\underset{H}{\overset{+}{C}}=\bar{O}+\bar{O}H \rightleftharpoons R-\overset{H}{CH}-\underset{H}{\overset{OH}{C}}-\bar{O} \rightleftharpoons R-CH=CHOH+\bar{O}H$$

This mechanism is in accord with the belief that the carbonyl group undergoes ready addition with many nucleophilic reagents.

It is convenient, for discussion purposes, to divide the various addition reactions of aldehydes and ketones into several groups even though they have much in common.

I. Simple addition reactions. These reactions depend upon the polar character of the carbonyl group. In many of these additions hydrogen becomes attached to oxygen and the anionic part of the addenda to the carbon atom. The addition of Grignard reagents similarly involves the linking of the magnesium to oxygen and the alkyl group to carbon.

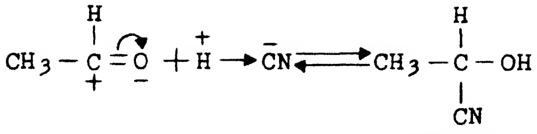
The addition of hydrogen cyanide to the carbonyl group is known to depend on the presence of cyanide ions and, as expected, bases exert a catalytic effect on the reaction by forming the essential cyanide ion. The addition of acids retards the reaction by converting cyanide ions to unreactive hydrocyanic acid. The initial step is the slow addition of the nucleophilic cyanide ion followed by the rapid addition of the hydrogen ion:



$$R-\underset{+}{\overset{H}{C}}=\underset{-}{O}+\bar{C}N \rightleftharpoons R-\underset{CN}{\overset{H}{C}}-\bar{O} \xrightleftharpoons{\overset{+}{H}} R-\underset{CN}{\overset{H}{C}}-OH$$

aldehyde cyanohydrin

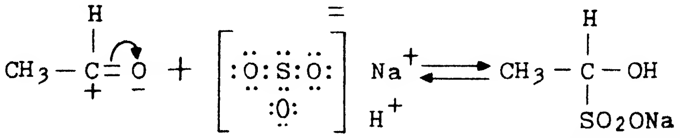
It has been stated that the olefinic linkage adds electrophilic reagents and thus differs from the carbonyl bond which may add nucleophilic or electrophilic reagents. The above reaction may be written more simply as follows:



acetaldehyde cyanohydrin

Ketones give similar addition products.

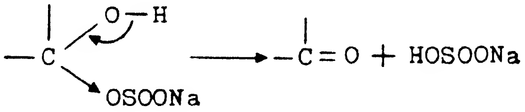
The addition of sodium bisulfite to aldehydes and methyl ketones involves the formation of a carbon-to-sulfur linkage. It appears to be commonly accepted that the bisulfite addition products are best represented as sulfonates. Their formation may be explained by assuming that the unshared electrons on the sulfur atom (rather than on the oxygen) coordinate with the carbon atom of the carbonyl group:



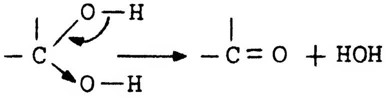
acetaldehyde bisulfite

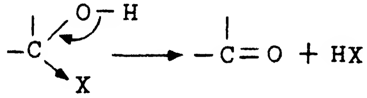
The formation of the carbon-to-sulfur linkage indicates greater stability for this bond than for the carbon-to-oxygen bond.

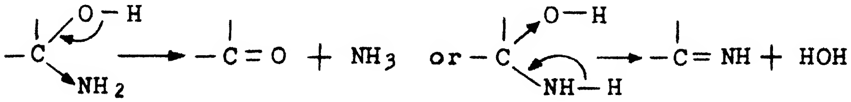
It may be said that if a C–O–S linkage were formed, the addition would be expected to exhibit a greater tendency towards reversion:



This is in accord with the instability of other similar groupings:



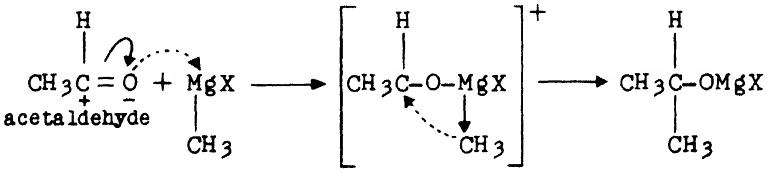


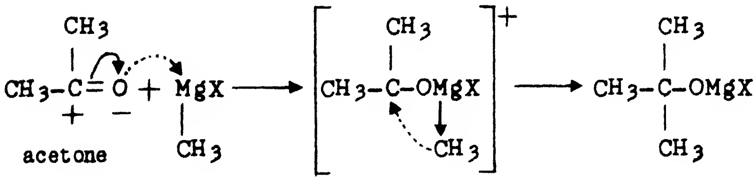


This tendency for the splitting out of component elements may be expected for the grouping $-\overset{|}{\mathrm{C}}\genfrac{}{}{0pt}{}{\diagup a}{\diagdown b}$ whenever one group is the hydroxyl group which can furnish a proton and the other is an electron-attracting group which has an atom with unshared electrons directly attached to the carbon. It is possible that the proton becomes attached to this atom before cleavage occurs. It should be noted that the grouping $-\overset{|}{\mathrm{C}}\genfrac{}{}{0pt}{}{\diagup OH}{\diagdown OH}$ can be stabilized by the presence of nearby electron-attracting groups. Thus chloral hydrate is a stable molecule, $Cl_3C{-}CH(OH)_2$, and can be easily prepared and isolated.

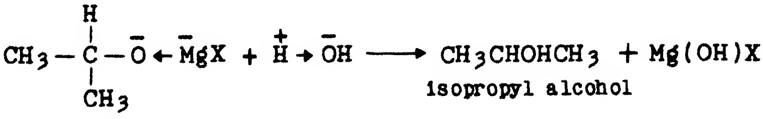
Aromatic ketones and the higher molecular weight aliphatic ketones do not form bisulfite addition products, possibly due to steric hindrance.

The addition of Grignard reagents to the carbonyl group proceeds in a similar manner:



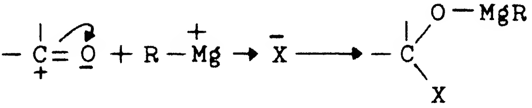


These addition compounds, which may be regarded as mixed salts (half halide and half alcoholate of magnesium) are rapidly hydrolyzed by water:

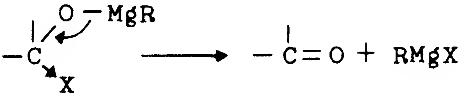


$$CH_3-\overset{H}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}-\bar{O}\leftarrow\bar{M}gX + \overset{+}{H}\rightarrow\bar{O}H \longrightarrow \underset{\text{isopropyl alcohol}}{CH_3CHOHCH_3} + Mg(OH)X$$

Theoretically the Grignard reagent might add according to the polarization $R-\overset{+}{Mg}\rightarrow\overset{-}{X}$:



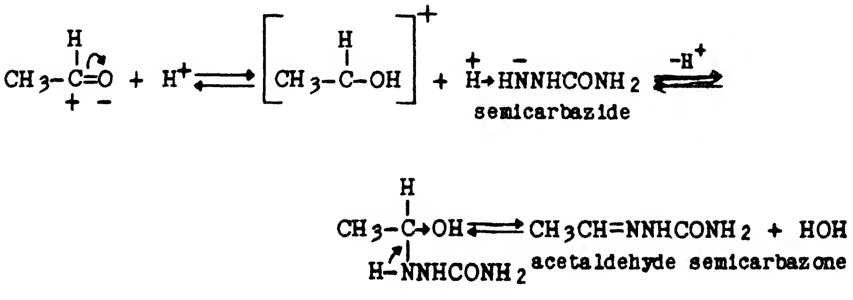
It will be noted, however, that the addition product is quite similar electronically to the $-\overset{|}{C}{<}^{a}_{b}$ grouping discussed above. Such an addition would be expected to be highly reversible



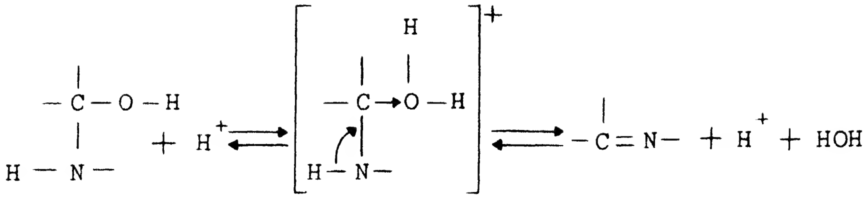
and consequently only the irreversible addition based on the polarization $\underset{-}{R}\leftarrow\underset{+}{Mg}X$ is observed.

In general aromatic aldehydes and ketones react similarly with Grignard reagents.

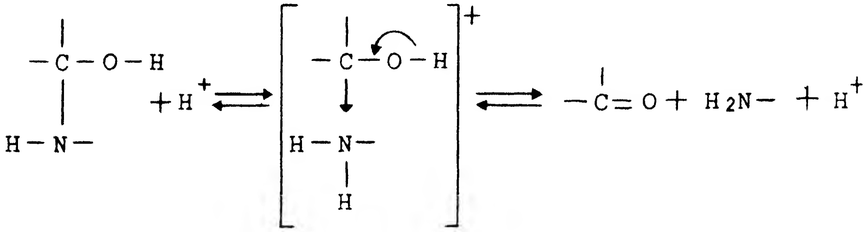
II. Addition reactions followed by the splitting out of component elements. The reactions of aldehydes and ketones with semicarbazide to yield semicarbazones are acid catalyzed:



The carbonium ion, formed in the first step, undoubtedly facilitates the ionization of the already polarized nitrogen-to-hydrogen bond in semicarbazide. The third step which involves the splitting out of water is acid catalyzed also and may be shown as follows:

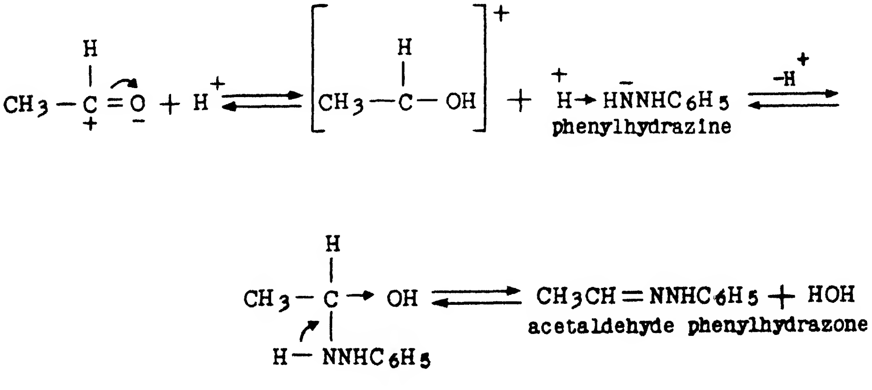


However, if the proton becomes attached to the unused electron pair on nitrogen, cleavage between carbon and nitrogen will be facilitated with the formation of the original reactants:

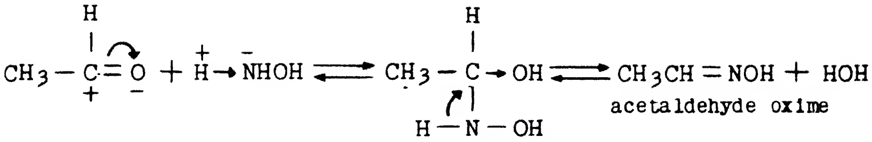


The fact that good yields of semicarbazones may be obtained indicates that the splitting out of water to form the semicarbazone is less readily reversed, at least under the conditions generally used for preparing semicarbazones.

The reactions with phenylhydrazine also show general acid catalysis:



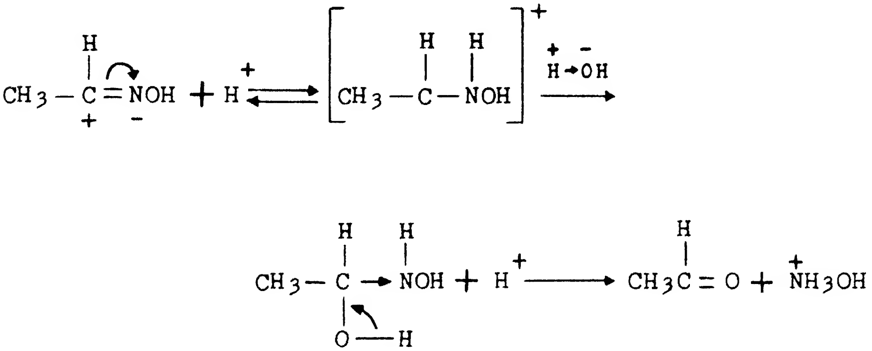
Oxime formation is more strongly accelerated by bases, probably because the nucleophilic anion, $\overset{-}{N}HOH$, is more readily formed under the influence of bases:



$$CH_3-\overset{H}{\underset{+}{C}}=\overset{-}{O}+\overset{+}{H}\rightarrow\overset{-}{N}HOH \rightleftharpoons CH_3-\overset{H}{\underset{H-N-OH}{C}}\rightarrow OH \rightleftharpoons CH_3CH=NOH+HOH$$

acetaldehyde oxime

The products formed under II may be hydrolyzed by treatment with excess acid such as hydrochloric acid. This takes place very readily with oximes:



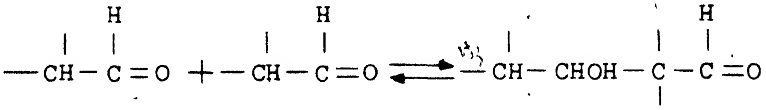
$$CH_3-\overset{H}{\underset{+}{C}}=\overset{-}{N}OH+\overset{+}{H}\rightleftharpoons\left[CH_3-\overset{H}{C}-\overset{H}{N}OH\right]^{+}\xrightarrow{\overset{+}{H}\rightarrow\overset{-}{O}H}$$

$$CH_3-\overset{H}{\underset{O-H}{C}}\rightarrow\overset{H}{N}OH+\overset{+}{H}\longrightarrow CH_3\overset{H}{C}=O+\overset{+}{N}H_3OH$$

Aromatic aldehydes and ketones behave like the aliphatic aldehydes and ketones in the above reactions.

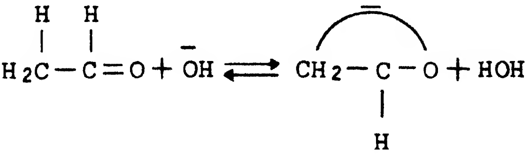
III. Reactions which involve the addition of compounds possessing α-hydrogen. These reactions are often called condensations, but it should be noted that they simply represent a special type of addition.

Aldol condensation. When aliphatic aldehydes having hydrogen on the α-carbon are treated with dilute aqueous acids or bases, a self-addition occurs with the formation of β-hydroxyaldehydes (aldols):



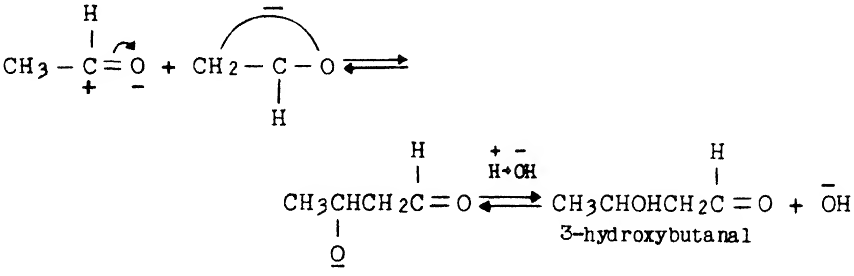
$$-\overset{|}{C}H-\overset{H}{C}=O+-\overset{|}{C}H-\overset{H}{C}=O\rightleftharpoons-\overset{|}{C}H-CHOH-\underset{|}{\overset{|}{C}}-\overset{H}{C}=O$$

The reaction is most frequently effected by basic catalysts such as sodium hydroxide. It is a reversible reaction and the real catalyst is probably the hydroxyl ion. It seems likely that the first step is the ionization of one molecule of the aldehyde followed by the reaction of the anion with a second molecule of the aldehyde. Basic catalysts would assist the ionization:

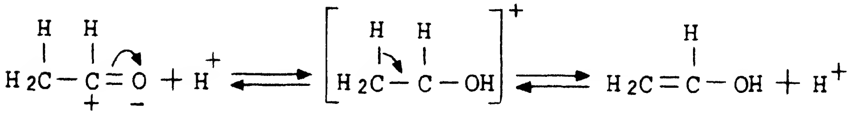


$$H_2\overset{H}{C}-\overset{H}{C}=O+\overset{-}{O}H\rightleftharpoons CH_2-\underset{H}{C}-O+HOH$$

The reaction between the hybrid anion and the second molecule of aldehyde may be shown as follows:

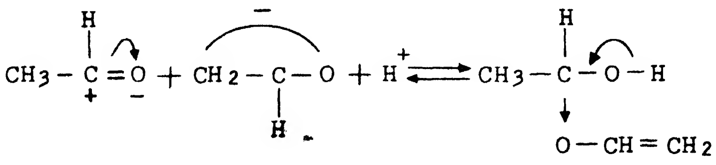


Acid catalysts probably function through oxonium ion formation:



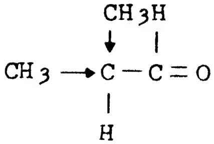
It is not known definitely whether the second molecule of aldehyde adds directly to the enol form or to the hybrid anion which the latter could provide.

It is theoretically possible that condensation might take place as follows:



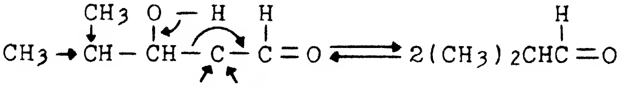
The fact that such a product has not been isolated is in accord with the high degree of reversibility noted previously for such structures. Consequently the formation of the carbon-to-carbon linkage is favored.

The presence of electron-release groups on the α-carbon atom will retard the ionization of the α-hydrogen and thus hinder aldol formation. Thus in the case of isobutyraldehyde, the electron-release effects of the methyl groups, by increasing the electron density on the α-carbon atom, tend to reduce the ease of ionization of the α-hydrogen atom:



$$\mathrm{CH_3 \rightarrow \underset{\underset{H}{|}}{\overset{\overset{CH_3}{\downarrow}}{C}} - \overset{\overset{H}{|}}{C} = O}$$

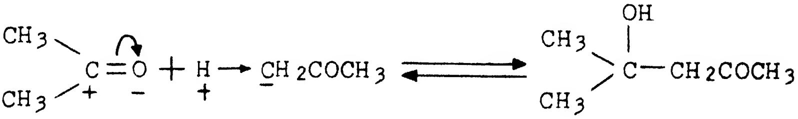
The same effect would facilitate reversal of the reaction:



$$\mathrm{CH_3 \rightarrow \overset{\overset{CH_3}{\downarrow}}{C}H - \overset{\overset{O-H}{|}}{C}H - \underset{\underset{CH_3\ \ CH_3}{\nearrow\ \nwarrow}}{C} - \overset{\overset{H}{|}}{C} = O \rightleftharpoons 2(CH_3)_2CH\overset{\overset{H}{|}}{C} = O}$$

2,2,4-trimethyl-3-hydroxypentanal

Ketones do not readily give the aldol condensation under the conditions noted above, because the equilibrium lies far to the left:



$$\mathrm{\overset{CH_3}{\underset{CH_3}{}}\!\!>\overset{+}{C} = \overset{-}{O} + \overset{+}{H} \rightarrow \overset{-}{C}H_2COCH_3 \rightleftharpoons \overset{CH_3}{\underset{CH_3}{}}\!\!>\overset{\overset{OH}{|}}{C} - CH_2COCH_3}$$

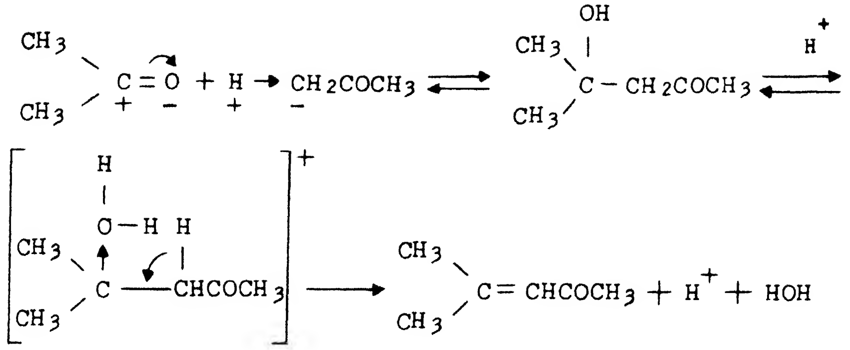
diacetone alcohol

Diacetone alcohol may be obtained in satisfactory yields, providing it is removed from the influence of the basic catalyst as it is formed. The decreased tendency on the part of ketones to undergo the aldol condensation may be attributed to the electron-release effects of the alkyl groups attached to the carbonyl carbon atom. Examination of the electron-release effects in aldehyde and ketone structures

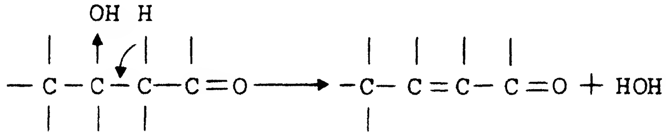
$$\mathrm{R \rightarrow \overset{\overset{H}{|}}{C} = O \quad and \quad R \rightarrow \overset{\overset{R}{\downarrow}}{C} = O}$$

reveals the fact that electron density should be greater on the carbonyl carbon atom of the ketone. In other words, the fractional positive charge on this carbon atom would be smaller than on the corresponding carbon atom in the aldehyde and would account for the fact that ketones react less readily with nucleophilic reagents than do the aldehydes.

It is interesting to note that acetone readily undergoes self-addition under the influence of hydrogen chloride, but in the presence of the acid catalyst, water splits out and mesityl oxide is obtained in place of diacetone alcohol:



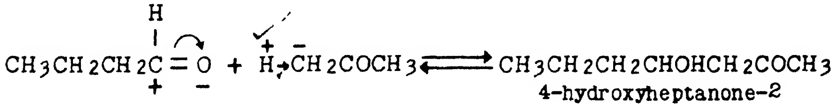
Continuation of this reaction would yield phorone. The tendency of aldols in general to lose water readily may be shown as follows:



$$-\overset{|}{\underset{|}{C}}-\overset{OH}{\underset{|}{C}}-\overset{H}{\underset{|}{C}}-C=O \longrightarrow -\overset{|}{\underset{|}{C}}-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O + HOH$$

The splitting out of water depends upon the ionization of α-hydrogen and would be catalyzed by both acids and bases.

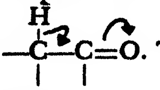
Although ketones do not readily give self-addition products under the influence of bases, they do give addition reactions with aldehydes. For example, *n*-butyraldehyde and acetone undergo an aldol-type condensation in the presence of sodium hydroxide. The acetone is used in large excess in this reaction for otherwise the self-addition of *n*-butyraldehyde would prevail:



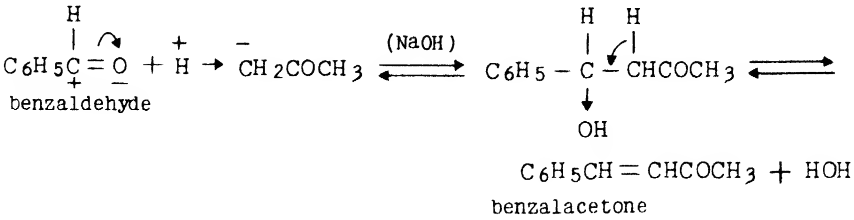
$$CH_3CH_2CH_2\overset{H}{C}=O + H\!\!-\!CH_2COCH_3 \rightleftharpoons CH_3CH_2CH_2CHOHCH_2COCH_3$$

4-hydroxyheptanone-2

It will be noted that the ketone furnishes the labile hydrogen. Theoretically the aldehyde might furnish the active hydrogen and thus add to the ketone. The resulting addition product, however, would be less stable for the reasons given above under the self-addition of ketones in the presence of basic catalysts.

In general, aldehydes will condense with suitably activated methylene groups such as are found in malonic acid, malonic esters, acetoacetic ester, and nitroparaffins. So-called active methylene groups are activated by the presence of adjacent electron-attracting groups,  These reactions are base or acid catalyzed.

Aromatic aldehydes, since they possess no alpha hydrogen, do not give the aldol condensation. They do, however, undergo aldol-type condensations with compounds which can furnish active hydrogen:



$$\underset{\text{benzaldehyde}}{C_6H_5\overset{H}{\underset{+}{C}}=\underset{-}{O}} + \overset{+}{H} \rightarrow \overset{-}{C}H_2COCH_3 \xrightleftharpoons{(NaOH)} C_6H_5-\overset{H}{\underset{OH}{C}}-\overset{H}{C}HCOCH_3 \rightleftharpoons \underset{\text{benzalacetone}}{C_6H_5CH=CHCOCH_3} + HOH$$

Dibenzalacetone may be obtained by the use of two moles of benzaldehyde.

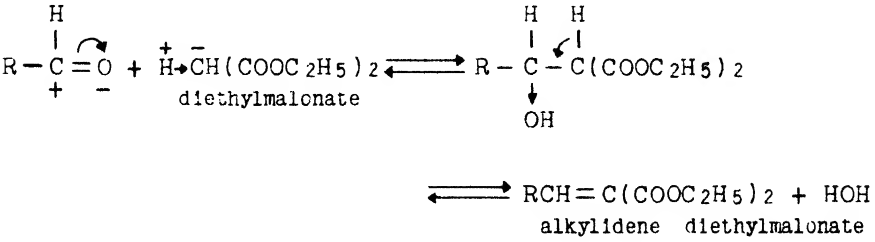
Aromatic ketones of the type ArCOR, in general, behave like the aliphatic ketones.

IV. Knoevenagel reaction. This reaction includes the condensations of carbonyl compounds (usually aldehydes) with active methylene groups in the presence of an organic base such as piperidine or triethylamine. Originally it was thought that the organic bases were the active catalysts, but it is now generally believed that the presence of some acid is necessary for the reactions to occur. It has been shown in some cases that the reaction does not proceed in the presence of piperidine alone but does so in the presence of piperidine acetate (65). This suggests general acid catalysis, but it must be remembered that this type of reaction may be induced by sodium ethoxide also. It may be that most organic bases are too weak to catalyze the reaction. The fact that the piperidinium ion, similar to the ammonium ion, acts as an acid catalyst (proton donor)

$$\overset{+}{NH_4} + B \rightleftharpoons NH_3 + \overset{+}{BH}$$

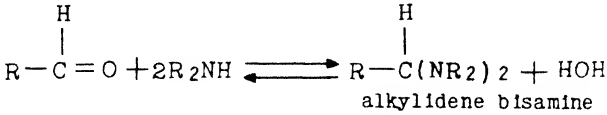
suggests that this type of reaction is more sensitive to acid catalysis.

As shown earlier, the ionization of a tautomeric compound is facilitated by both acid and base catalysts. The following general mechanism for the Knoevenagel reaction would indicate that bases would assist the ionization of α-hydrogen, and acids would act through oxonium ion formation, both assisting in the reaction:



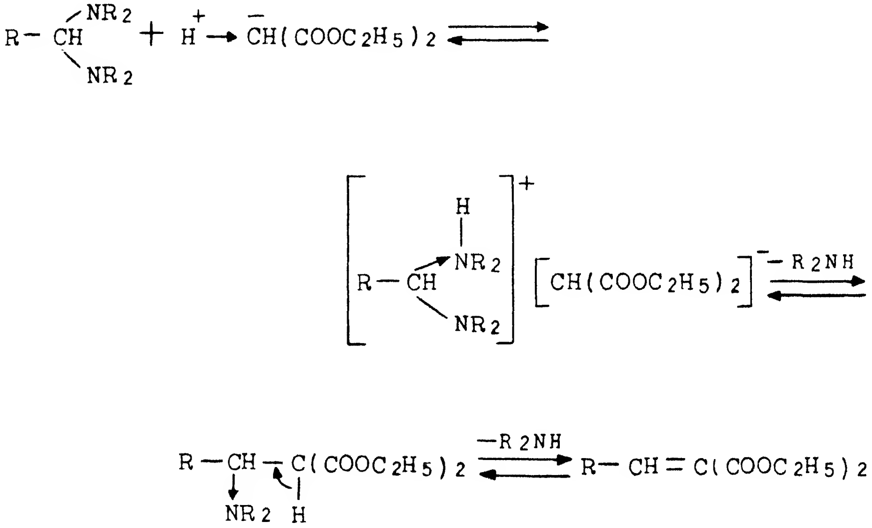
$$R-\overset{H}{\underset{+}{C}}=\underset{-}{O} + \underset{\text{diethylmalonate}}{\overset{+}{H}\rightarrow\overset{-}{C}H(COOC_2H_5)_2} \rightleftharpoons R-\overset{H}{\underset{OH}{C}}-\overset{H}{C}(COOC_2H_5)_2 \rightleftharpoons \underset{\text{alkylidene diethylmalonate}}{RCH=C(COOC_2H_5)_2} + HOH$$

Secondary amines, such as piperidine, exert a specific catalytic effect. This strongly suggests the formation of an alkylidene bisamine as an intermediate, for bisamines are known to condense with activated methylene groups:



$$R-\overset{H}{\overset{|}{C}}=O+2R_2NH \rightleftharpoons R-\overset{H}{\overset{|}{C}}(NR_2)_2+HOH$$

alkylidene bisamine

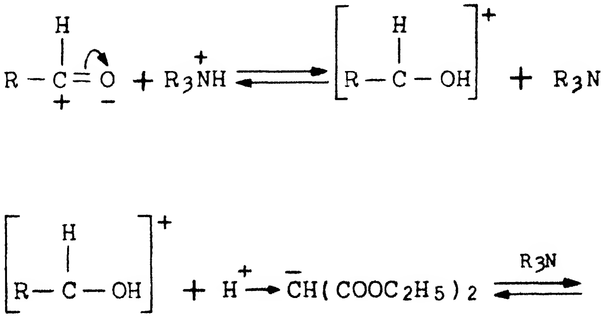


$$R-CH\begin{matrix}\diagup NR_2\\ \diagdown NR_2\end{matrix}+\overset{+}{H}\rightarrow\overset{-}{C}H(COOC_2H_5)_2 \rightleftharpoons$$

$$\left[R-CH\begin{matrix}\nearrow \overset{H}{\overset{|}{N}}R_2\\ \diagdown NR_2\end{matrix}\right]^+\left[CH(COOC_2H_5)_2\right]^- \xrightleftharpoons{-R_2NH}$$

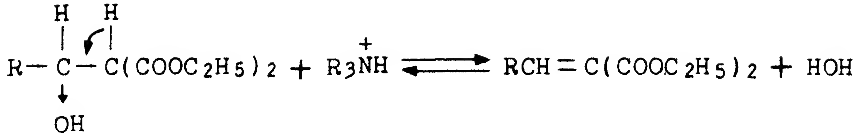
$$R-\underset{\underset{NR_2}{\downarrow}}{CH}-\underset{\underset{H}{|}}{C}(COOC_2H_5)_2 \xrightleftharpoons{-R_2NH} R-CH=C(COOC_2H_5)_2$$

Each of the four steps would be facilitated by the presence of acids. This mechanism accounts for the specific catalytic effect of secondary amines. Tertiary amines cannot yield similar intermediates, and their salts probably function only as acid catalysts:



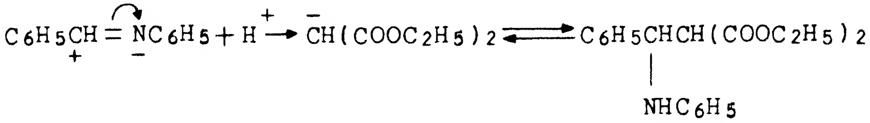
$$R-\underset{+}{\overset{H}{\overset{|}{C}}}=\underset{-}{O}+R_3\overset{+}{N}H \rightleftharpoons \left[R-\overset{H}{\overset{|}{C}}-OH\right]^+ + R_3N$$

$$\left[R-\overset{H}{\overset{|}{C}}-OH\right]^+ + \overset{+}{H}\rightarrow\overset{-}{C}H(COOC_2H_5)_2 \xrightleftharpoons{R_3N}$$



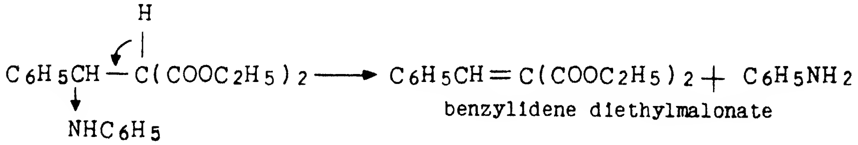
$$R-\underset{OH}{\underset{\downarrow}{\overset{H}{\overset{|}{C}}}}-\overset{H}{\overset{|}{C}}(COOC_2H_5)_2 + R_3\overset{+}{N}H \rightleftharpoons RCH=C(COOC_2H_5)_2 + HOH$$

There is little evidence for the catalytic effect of primary amines in this reaction, and apparently they are the least effective. Interaction of a primary amine and an aldehyde may yield a Schiff base (RCH=NR). This need not necessarily prevent the addition of the active hydrogen compound, for it is known that such additions occur with some Schiff bases (66). For example, ethylmalonate adds readily to benzalaniline:



$$C_6H_5\underset{+}{C}H=\underset{-}{N}C_6H_5 + \overset{+}{H}\rightarrow \overset{-}{C}H(COOC_2H_5)_2 \rightleftharpoons C_6H_5\underset{NHC_6H_5}{\underset{|}{C}}HCH(COOC_2H_5)_2$$

Furthermore, a molecule of aniline may be split out of the addition product, thus yielding the expected end product of a Knoevenagel reaction:



$$C_6H_5\underset{NHC_6H_5}{\underset{\downarrow}{CH}}-\overset{H}{\overset{|}{C}}(COOC_2H_5)_2 \longrightarrow C_6H_5CH=C(COOC_2H_5)_2 + C_6H_5NH_2$$

While no extensive studies have been reported on addition reactions to various types of Schiff bases, it appears that addition takes place most readily with the monomeric type ArCH=NAr and least readily with other types which exist normally as polymers (67). These facts fit in rather well with the knowledge that, in general, primary amines are poor catalysts for the Knoevenagel reaction.

V. Mannich reaction. This reaction usually involves the interaction of an aldehyde or ketone with formaldehyde and a primary or secondary amine. The amine is usually used as its hydrochloride. If the carbonyl compound is sufficiently acidic, it will act as an acid catalyst for the reaction and a free amine may be used in place of the hydrochloride. The reaction is least efficient with aldehydes since they compete with the formaldehyde for the amine:

$$\mathrm{C_6H_5COCH_3 + CH_2O + RNH_2 \rightleftharpoons C_6H_5COCH_2CH_2NHR + HOH}$$

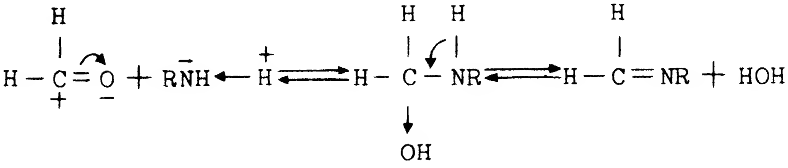
acetophenone '-alkylaminoethyl phenyl ketone

$$\mathrm{C_6H_5COCH_3 + CH_2O + R_2NH \rightleftharpoons C_6H_5COCH_2CH_2NR_2 + HOH}$$

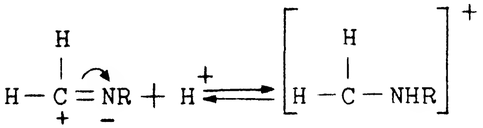
β-dialkylaminoethyl phenyl ketone

There appears to be a similarity between the Knoevenagel and Mannich reactions. While no mechanism has been established for the latter (68), the following are strongly indicated:

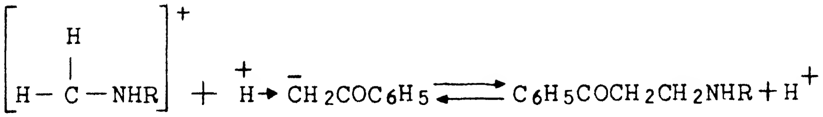
(a) With primary amines



$$\mathrm{H-\overset{H}{\underset{+}{C}}=\underset{-}{O} + R\overset{-}{N}H \leftarrow \overset{+}{H} \rightleftharpoons H-\overset{H}{\underset{OH}{C}}-\overset{H}{N}R \rightleftharpoons H-\overset{H}{C}=NR + HOH}$$



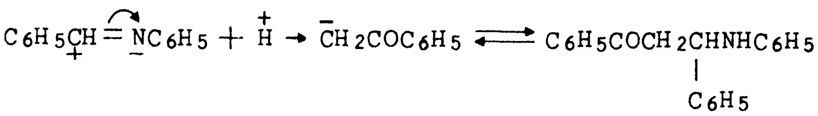
$$\mathrm{H-\overset{H}{\underset{+}{C}}=\underset{-}{N}R + \overset{+}{H} \rightleftharpoons \left[H-\overset{H}{C}-NHR\right]^{+}}$$



$$\mathrm{\left[H-\overset{H}{C}-NHR\right]^{+} + \overset{+}{H} \rightarrow \overset{-}{C}H_2COC_6H_5 \rightleftharpoons C_6H_5COCH_2CH_2NHR + H^{+}}$$

The group —C=N— is a polarized grouping similar to the carbonyl group and undergoes addition reactions through the functioning of an electromeric shift.

Mayer (66) showed that acetophenone adds to benzalaniline:

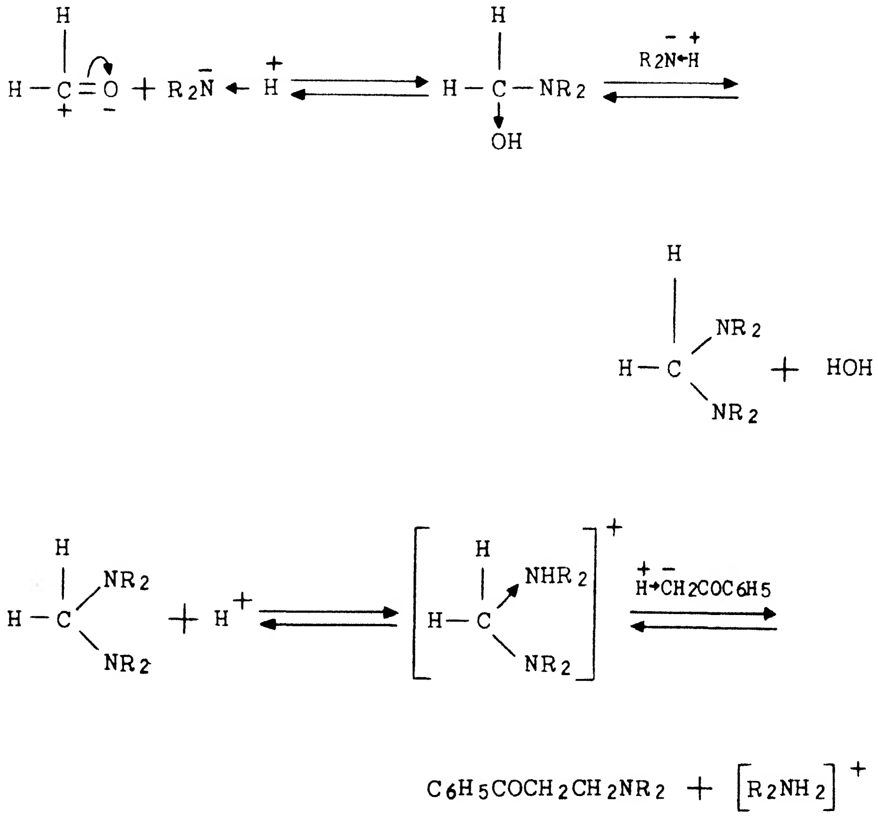


$$\mathrm{C_6H_5\underset{+}{C}H=\underset{-}{N}C_6H_5 + \overset{+}{H} \rightarrow \overset{-}{C}H_2COC_6H_5 \rightleftharpoons C_6H_5COCH_2\underset{C_6H_5}{CH}NHC_6H_5}$$

β-phenylamino-β-phenylethyl phenyl ketone

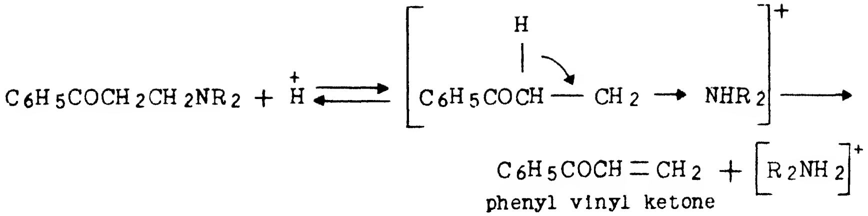
Mayer failed to note, however, that the reaction is acid catalyzed and does not take place unless a small amount of acid is present. Ethylacetoacetate and ethylmalonate add to benzalaniline without the addition of an acid catalyst. Evidently some prototropic compounds ionize sufficiently to catalyze their own additions. This work suggests that the Mannich reaction consists of the addition of an active hydrogen compound to a Schiff base, in the cases where a primary amine is used. The reaction with formaldehyde is complicated by the fact that methylene amines have a marked tendency to polymerize, but otherwise the reactions appear to agree well with other known facts.

(b) **With secondary amines**



In general, the Mannich reactions with secondary amines proceed more smoothly and are not complicated to as great an extent by the polymerization of the intermediates. There are several examples of the reaction of alkylidene bisamines with active hydrogen compounds reported in the literature (69). The above mechanism is in accord with the known facts.

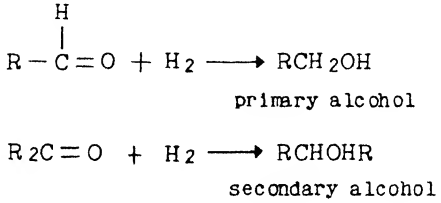
It will be noted that in both cases, *(a)* and *(b)*, the reaction products may react further since they still possess active alpha hydrogen atoms (68). The observation that the reaction products have a tendency to split out a molecule of amine also agrees with similar acid-catalyzed reactions:



$$C_6H_5COCH_2CH_2NR_2 + \overset{+}{H} \rightleftharpoons \left[C_6H_5CO\overset{\overset{H}{|}}{C}H — CH_2 \rightarrow NHR_2\right]^+ \longrightarrow C_6H_5COCH{=}CH_2 + \left[R_2NH_2\right]^+$$

phenyl vinyl ketone

VI. **Hydrogenation of aldehydes and ketones.** Hydrogenation with molecular hydrogen in the presence of a catalyst (Pt, Pd, or Ni) leads to the formation of the corresponding alcohols:



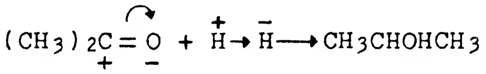
$$R-\overset{\overset{H}{|}}{C}{=}O + H_2 \longrightarrow RCH_2OH$$

primary alcohol

$$R_2C{=}O + H_2 \longrightarrow RCHOHR$$

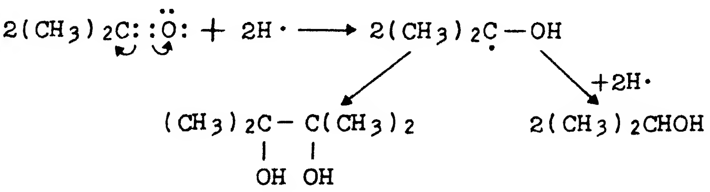
secondary alcohol

There is little evidence for the exact course followed in these reactions. Theoretically the molecular hydrogen might be expected to react in one of two ways, $\overset{+}{H}:\overset{-}{H}$ or $2H\cdot$. If atomic hydrogen is the active reagent, a radical mechanism would be involved and conditions would be favorable for pinacol formation as well as alcohol formation. Therefore it is postulated that it is the function of the catalyst, acting as an electrophilic agent, to activate the molecular hydrogen, $\overset{+}{H}\rightarrow\overset{-}{H}$——Pd:



$$(CH_3)_2\underset{+}{C}{=}\underset{-}{O} + \overset{+}{H}\rightarrow\overset{-}{H} \longrightarrow CH_3CHOHCH_3$$

When the hydrogenation is carried out with atomic hydrogen (metals + acids, sodium amalgam + water, etc.) a radical mechanism must be involved and as shown below may lead to an alcohol, a pinacol, or both:



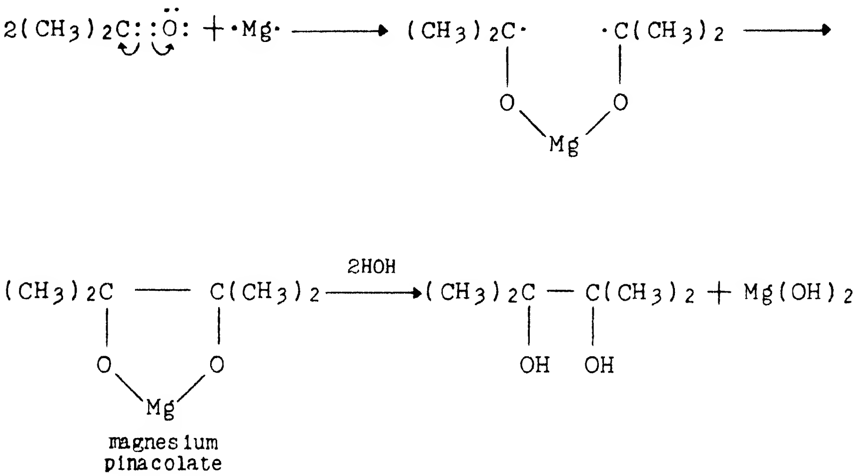
$$2(CH_3)_2C::\ddot{O}: + 2H\cdot \longrightarrow 2(CH_3)_2\dot{C}-OH$$

$$2(CH_3)_2\dot{C}-OH \longrightarrow (CH_3)_2C(OH)-C(OH)(CH_3)_2$$

$$2(CH_3)_2\dot{C}-OH \xrightarrow{+2H\cdot} 2(CH_3)_2CHOH$$

The free radical may become electronically satisfied either by combining with another free radical or with an atom of hydrogen. The relative proportions of alcohol and pinacol formed depend on the experimental conditions used and the nature of the carbonyl compound. Aliphatic aldehydes have little tendency to form pinacols. Aromatic aldehydes and ketones possess this tendency to a greater extent than their aliphatic analogs.

The conversion of ketones to pinacols by treatment with amalgamated magnesium has the advantage of eliminating alcohol formation. This reaction must also follow a radical mechanism:

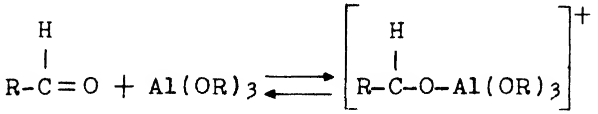


VII. Meerwein, Verley, and Ponndorf reaction. This is a very useful method for the reduction of aldehydes and ketones to the corresponding alcohols (70). The method originally consisted of treating an aldehyde with aluminum ethoxide in ethyl alcohol solution. The essential reaction may be shown as follows:

$$RCHO + CH_3CH_2OH \rightleftharpoons RCH_2OH + CH_3CHO$$

For the reduction to approach completion, the oxidation product (acetaldehyde) must be removed as formed, and this is accomplished by permitting the acetaldehyde to distil over during the reaction. Ponndorf showed that the method was more general when aluminum isopropoxide was used in place of the ethoxide. With this reagent, both aldehydes and ketones may be reduced satisfactorily. This mild reduction reaction is applicable to both the aliphatic and aromatic series. The particular value of this method lies in its specific attack on carbonyl groups, and other reducible groups which may be present in the molecule are not affected.

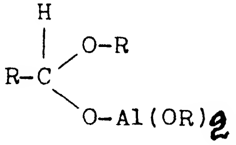
The mechanism for this reaction has not been definitely established. It is clear that the transfer of a hydrogen atom from the alkoxide or alcohol to the carbonyl compound is involved. It is probable that the electrophilic aluminum alkoxide forms a bond with the electron-rich carbonyl oxygen atom with the formation of a carbonium ion:



$$\mathrm{R{-}\overset{\overset{\displaystyle H}{|}}{C}{=}O + Al(OR)_3 \rightleftharpoons \left[R{-}\overset{\overset{\displaystyle H}{|}}{C}{-}O{-}Al(OR)_3\right]^{+}}$$

I

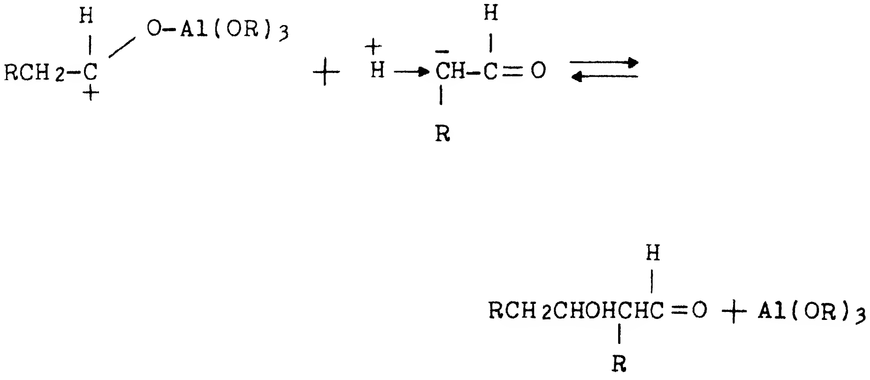
It may be further assumed that the electron-poor carbon atom in the carbonium ion is the attracting force for the transfer of a hydrion (H^-) from the reagent to the carbonium carbon atom. It has been assumed by some (70) that the aluminum derivative of a hemiacetal is an intermediate in the reaction:



II

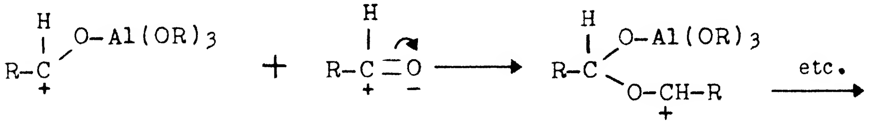
There is no doubt concerning the possibility that such a compound may be formed, but it is not likely that it is a necessary intermediate for the reaction since it does not contain an active center (or motivating force) to induce the transfer of a hydrion.

It seems more probable that the carbonium ion (I) is the necessary intermediate. The latter also explains the formation of side-reaction products which have been observed in these reductions. For example, an aldol condensation may occur between two aldehyde molecules:



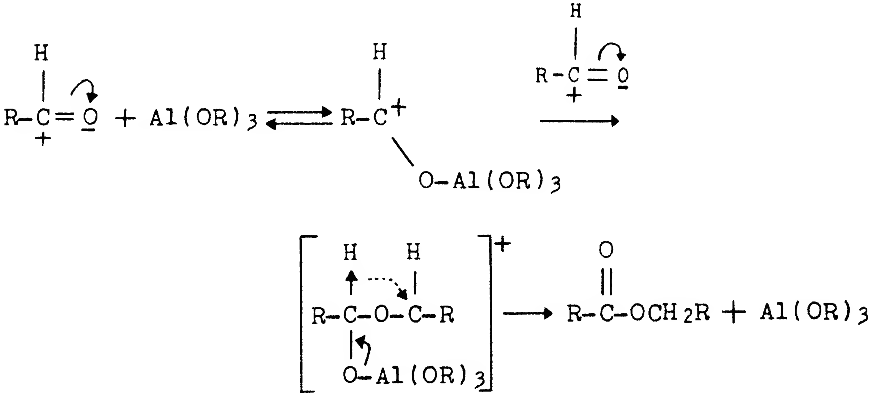
The use of one equivalent or more of the aluminum alkoxide usually results in the formation of better yields of the reduction product and less of the side-reaction products. This would be expected since the aldehyde would be more completely tied up as the aluminum-addition product.

The above intermediate also explains the polymerization of the aldehyde component which has been observed in some cases:



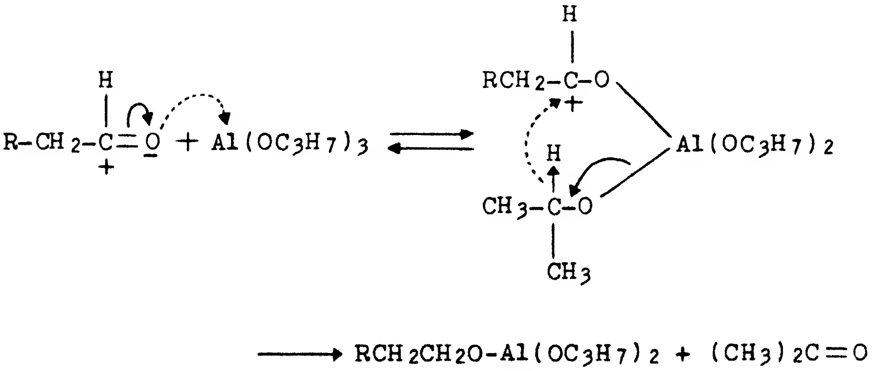
The use of excess reagent would be expected to reduce polymer formation for the same reason as noted above.

The Tischtschenko reaction may also occur to some extent (see p. 139):

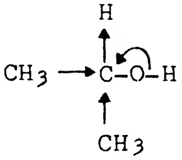


This reaction takes place best in aromatic hydrocarbon solvents. Here again an excess of the reagent might be expected to minimize this side reaction by tying up the aldehyde in the form of an addition product.

A mechanism which appears to be in accord with experimental evidence may be written as follows:



In the above mechanism it is assumed that the addition of the electrophilic aluminum alkoxide makes the carbonyl carbon atom sufficiently positive to attract a hydride ion from an isopropoxide group. This mechanism offers a plausible explanation for the fact that in general the reaction proceeds more rapidly when aluminum isopropoxide is used, and better yields are usually obtained. The abstraction of a hydride ion from isopropyl alcohol or from the isopropoxide group would be facilitated by the electron-release effects present in the molecule:

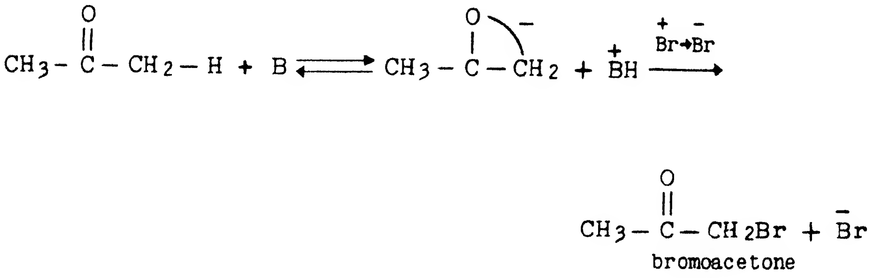


$$CH_3 \rightarrow \overset{\overset{H}{\uparrow}}{\underset{\underset{CH_3}{\uparrow}}{C}}-O-H$$

The Oppenauer oxidation of a secondary alcohol to the corresponding ketone (71) is simply the reversal of the aluminum alkoxide–ketone reaction. A large excess of ketone, usually acetone or cyclohexanone, is used to effect the reversal.

VIII. Halogenation of aldehydes and ketones. The direct action of a halogen on an aldehyde or ketone results in the replacement of one or more hydrogen atoms attached to an alpha carbon atom. The reactions are catalyzed by both acids and bases and the observed velocity is that of the ionization of hydrogen. The chief function of the catalyst is to increase the rate of the initial ionization.

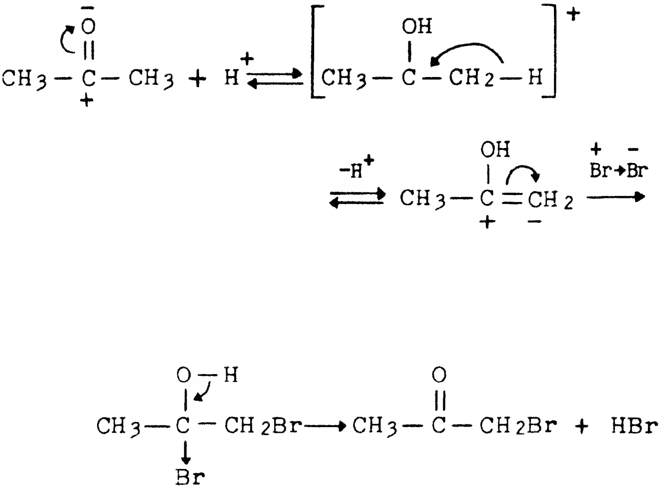
The base-catalyzed bromination of acetone may be shown as follows:



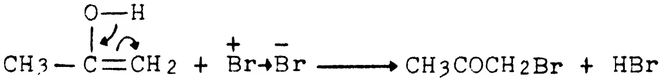
$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-H + B \rightleftharpoons CH_3-\overset{\overset{O^-}{|}}{C}-CH_2 + \overset{+}{B}H \xrightarrow{\overset{+}{Br}\rightarrow\overset{-}{Br}} CH_3-\overset{\overset{O}{\|}}{C}-CH_2Br + \overset{-}{Br}$$

It is not necessary to postulate the formation of a neutral enol form as an intermediate in base-catalyzed halogenation. The formation of di- and tribromo derivatives subsequently proceeds along similar lines.

In acid-catalyzed halogenation, the enol form may be the intermediate:

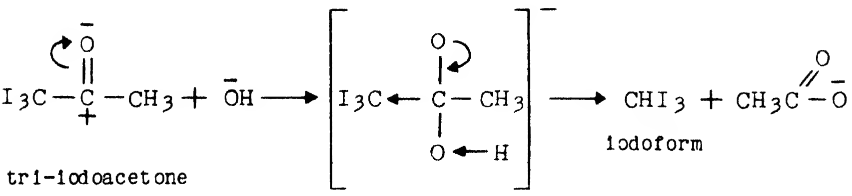


In this case the monobromo derivative may be readily isolated. It does not seem necessary that both bromine atoms add to the enol form. The last step may well take place as follows:

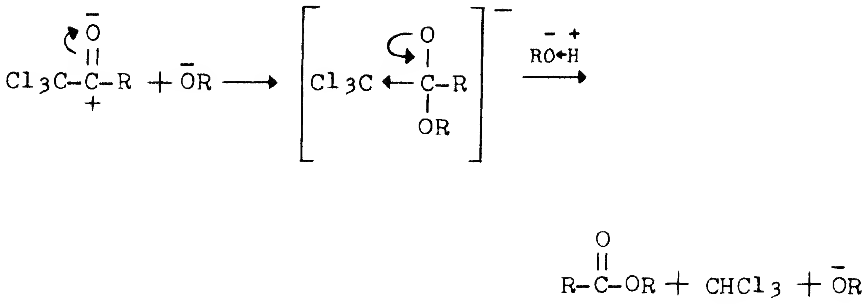


This would involve the initial addition of a positive bromine, similar to the addition of bromine to an olefin bond. Aromatic ketones of the type ArCOR behave similarly.

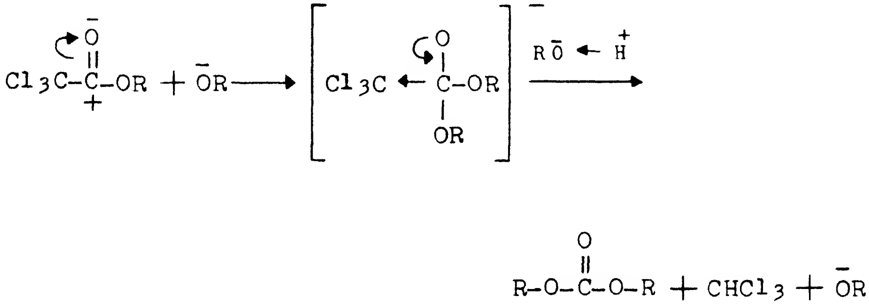
The haloform reaction is an important application of base-catalyzed halogenation. In the case of acetone, a trihalogen derivative is formed, which under the influence of the base cleaves to give a haloform and an acetate:



That the combined electron-attracting effects of the three halogen atoms facilitates the splitting off of the $-CX_3$ group has been demonstrated by Houben and Fischer (72) who converted trichloromethyl ketones to esters by treatment with alcohols in the presence of basic catalysts:



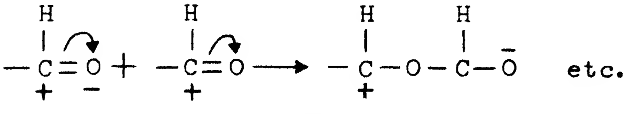
This tendency is shown also in the conversion of esters of trichloroacetic acid into carbonates by reaction with alcohols (73):



It has been shown more recently (74) that methyl esters may be obtained in the haloform reaction, when carried out in methanol solution.

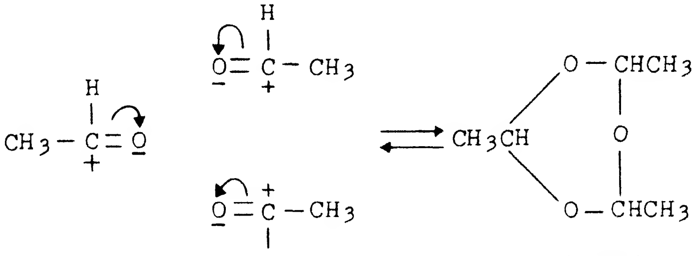
The cleavage of the Cl_3C group is brought about by its electron-attracting effect. It is important to note, however, that it is facilitated by the addition of the anion to the carbonyl carbon atom. Cleavage can take place after this addition without leaving an electron deficiency on this carbon, for the latter can acquire a share in a pair of electrons from the electron-rich oxygen atom. In other words the electromeric shift from oxygen acts to reinforce the inductive effect of the Cl_3C group and cleavage results.

IX. Reactions characteristic of aldehydes. Polymerization. Polymerization of aliphatic aldehydes undoubtedly is initiated by the dipole character of the carbonyl group. This provides the necessary positive and negative centers for the formation of carbon-oxygen linkages:



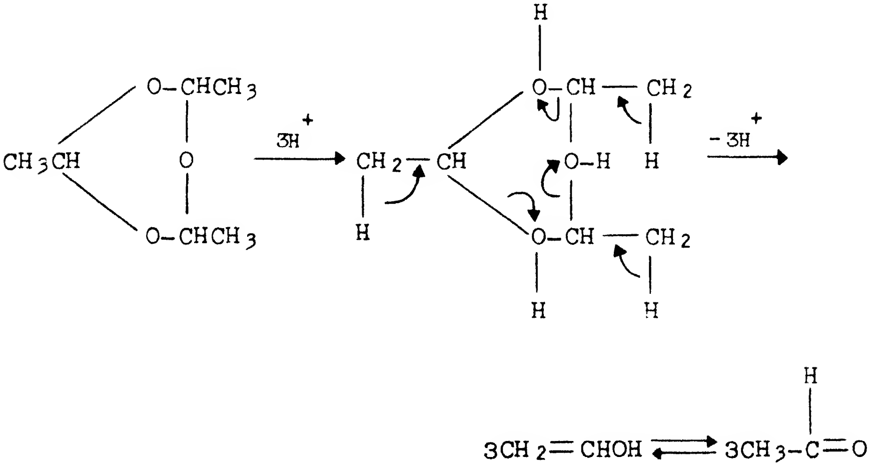
This process may result in the formation of a large linear polymer or a smaller cyclic polymer. A variety of reagents will induce polymerization. Small amounts of strong acids such as hydrogen chloride or sulfuric acid are effective catalysts. It is probable that these reagents facilitate the necessary polarization of the carbonyl group but lack the ability to form stable addition products. The extent of polymerization appears to be greatly affected by the temperature at which the reaction is carried out.

The mechanism is probably not as simple in all cases as indicated. It has been suggested (75) that the primary reaction is the hydration of the aldehyde, when carried out in aqueous solution. However, the following example appears to present the essential features of the reaction:



paraldehyde

Aldehyde polymerizations are reversible reactions, but under the conditions noted above the equilibria are usually greatly in favor of polymer formation. Such polymers may be kept for a long time in the absence of a catalyst. When paraldehyde is heated with dilute acids and the liberated aldehyde permitted to escape, depolymerization is complete. The following mechanism (76) illustrates depolymerization:

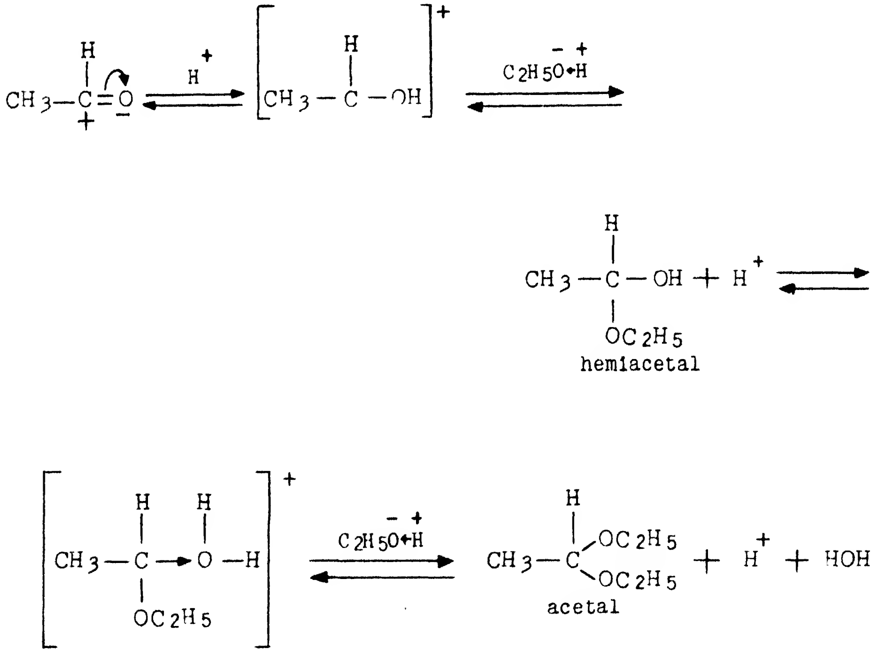


$$3CH_2{=}CHOH \rightleftarrows 3CH_3{-}\overset{\overset{\displaystyle H}{|}}{C}{=}O$$

The oxygen atoms are the points of attack for the protons. The course of reaction may proceed through three consecutive attacks of a single proton, or three protons may react simultaneously as shown above. The attachment of the protons produces an electron displacement away from carbon and thus weakens the carbon-to-oxygen bonds.

Ketones do not polymerize under the conditions noted above. This may be attributed to the fact that the electron-release effects of the two alkyl groups attached to the carbonyl carbon atom, while assisting the polarization of the carbonyl group, would actually hinder the approach of the nucleophilic reagent to the carbon.

Acetal formation. The reaction of an aldehyde with an alcohol to form an acetal is catalyzed by acids and may be effected by hydrogen chloride or by certain salts such as lithium chloride, calcium chloride, and ferric chloride (77). The reactions are reversible and the yields may be increased by the use of excess alcohol. A hemiacetal is thought to be formed first and further reaction with the alcohol then yields the acetal. It seems logical to assume that the mechanism must be similar to that involved in other acid-catalyzed etherifications:

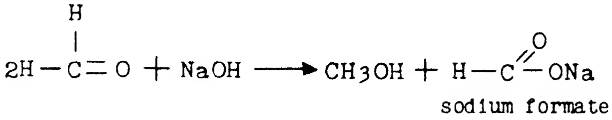


The hemiacetals, with few exceptions, cannot be isolated.

The hydrolysis of acetals by dilute acids has been studied by several workers. It is believed that the hydrolysis proceeds through initial oxonium ion formation and carbonium ions are formed as intermediates (76). The above mechanism is in accord with these conclusions.

Ketones do not give acetals under the conditions noted above.

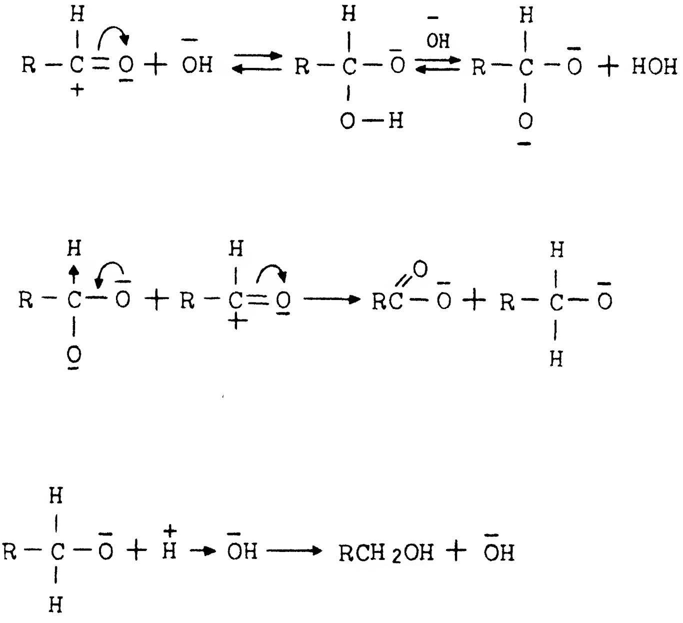
X. Reactions of aldehydes which have no alpha hydrogen atoms. Aldehydes of this type in general give the characteristic aldehyde reactions which do not involve ionizable hydrogen. This lack of alpha hydrogen often makes unusual reactions possible. For example, such aldehydes when treated with strong solutions of sodium or potassium hydroxide give rise to an oxidation and reduction known as the Cannizzaro reaction:



$$2H{-}\overset{\overset{\displaystyle H}{|}}{C}{=}O + NaOH \longrightarrow CH_3OH + H{-}\overset{\overset{\displaystyle O}{/\!/}}{C}{-}ONa$$

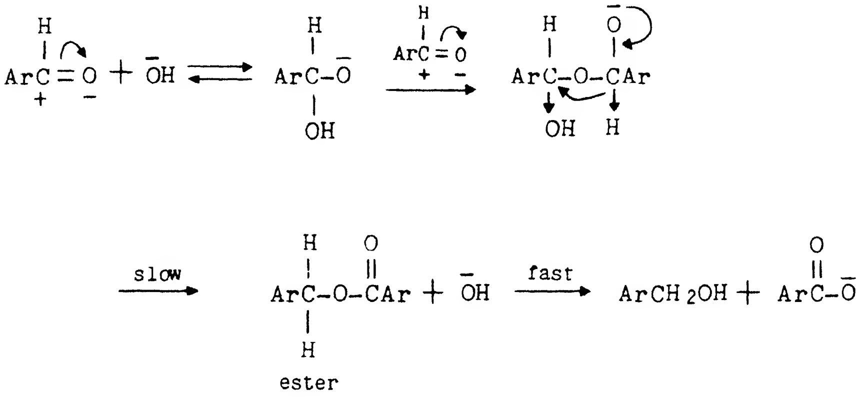
sodium formate

The reaction is known to involve the direct transfer of a hydrogen atom from one aldehyde molecule to another (78). It is the function of the base to furnish the nucleophilic hydroxyl ion for addition to the carbon atom of the carbonyl group. A mechanism which is consistent with the above data as well as with kinetic data has been given by Hammett (22) for formaldehyde:



It is stated that the release of the negative hydrogen ion (hydride ion) is due to the high concentration of negative charge on the anion formed in the second step.

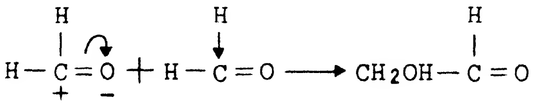
A recent paper by Alexander (79) has shed considerable light on the mechanism of the Cannizzaro reaction as applied to aromatic aldehydes. Tommila (80) had previously shown that with benzaldehyde and substituted benzaldehydes the reactions are third-order reactions and the reaction rate is given by the equation, $\text{rate} = k\ (\text{ArCHO})^{2}\,{}^{-}\text{OH}$. Lachman at an earlier date isolated benzyl benzoate from the Cannizzaro reaction with benzaldehyde by avoiding the use of excess alkali. Alexander has further shown, contrary to common belief, that the hydrolysis of benzyl benzoate proceeds under the same conditions at a faster rate than the Cannizzaro reaction. He concludes therefore that any mechanism must at least permit the formation of benzyl benzoate. The following mechanism was proposed as being in accord with much of the data:



It is theoretically possible that the hydrogen transfer might occur through an intermolecular shift rather than an intramolecular shift as shown above. However, the data in this paper indicate that an intramolecular shift is more probable.

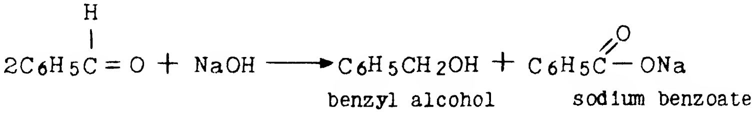
Aldehydes which have two hydrogen atoms on the alpha carbon atom tend to give only the aldol type of condensation, those with no alpha hydrogen give the Cannizzaro reaction, while the aldehydes possessing only one alpha hydrogen may give both reactions.

It is interesting to note that formaldehyde when treated with dilute bases such as calcium hydroxide solution yields isolable quantities of hexoses. Obviously, a different mechanism must be involved here:



A continuation of this process could yield a hexose, $CH_2OH(CHOH)_4\overset{\text{H}}{\text{C}}{=}O$. This resembles an aldol condensation except that the mobile hydrogen atom comes from an aldehyde group rather than from an alpha carbon atom.

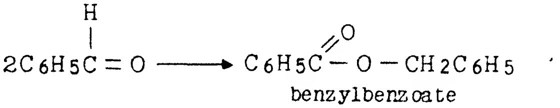
XI. Reactions of aromatic aldehydes. In general they behave like the aliphatic aldehydes which have no alpha hydrogen, although there are a few outstanding differences. They undergo the Cannizzaro reaction



$$2C_6H_5\overset{\overset{H}{|}}{C}=O + NaOH \longrightarrow \underset{\text{benzyl alcohol}}{C_6H_5CH_2OH} + \underset{\text{sodium benzoate}}{C_6H_5C\overset{O}{\not{}}-ONa}$$

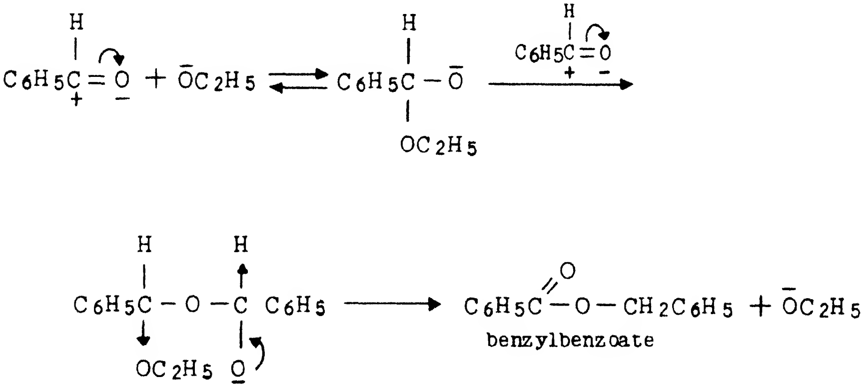
but they show little tendency to polymerize.

Aromatic aldehydes are converted into esters by the action of sodium alkoxides:



$$2C_6H_5\overset{\overset{H}{|}}{C}=O \longrightarrow \underset{\text{benzylbenzoate}}{C_6H_5C\overset{O}{\not{}}-O-CH_2C_6H_5}$$

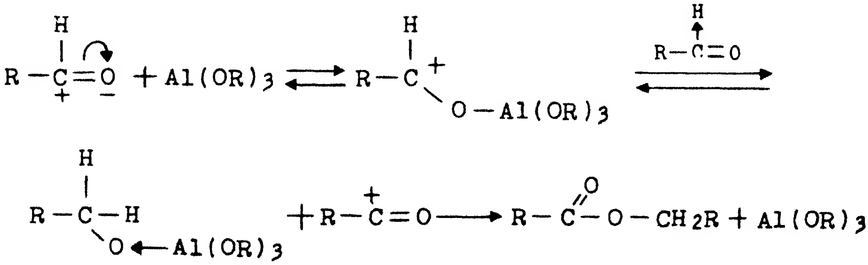
The reaction is probably closely related to the Cannizzaro reaction and may be illustrated as follows:



$$C_6H_5\underset{+}{\overset{\overset{H}{|}}{C}}=\underset{-}{O} + \bar{O}C_2H_5 \rightleftarrows C_6H_5\underset{\underset{OC_2H_5}{|}}{\overset{\overset{H}{|}}{C}}-\bar{O} \xrightarrow{C_6H_5\underset{+}{\overset{\overset{H}{|}}{C}}=\underset{-}{O}}$$

$$C_6H_5\underset{\underset{OC_2H_5}{\downarrow}}{\overset{\overset{H}{|}}{C}}-O-\underset{\underset{\underline{O}}{|}}{\overset{\overset{H}{\uparrow}}{C}}\ C_6H_5 \longrightarrow \underset{\text{benzylbenzoate}}{C_6H_5C\overset{O}{\not{}}-O-CH_2C_6H_5} + \bar{O}C_2H_5$$

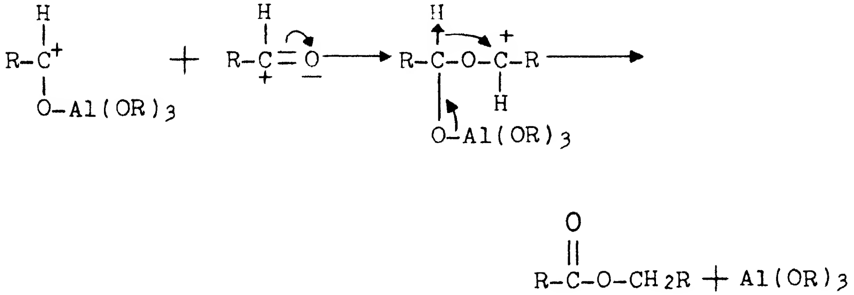
The Tischtschenko reaction is the best method for converting aliphatic aldehydes to esters. This consists of treating the aldehyde with aluminum ethoxide in an inert solvent such as xylene. It is believed by some that this reaction follows a different course than the one described above:



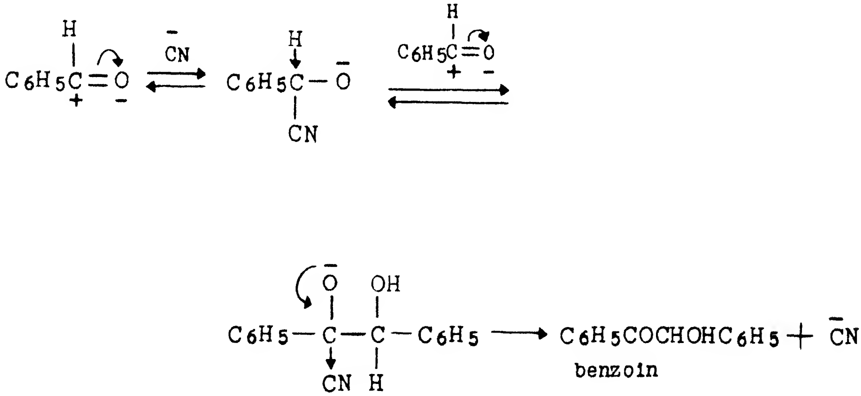
$$R-\underset{+}{\overset{\overset{H}{|}}{C}}=\underset{-}{O} + Al(OR)_3 \rightleftarrows R-\overset{\overset{H}{|}}{C}^{+}\diagdown O-Al(OR)_3 \underset{\longleftarrow}{\xrightarrow{R-\overset{\overset{H}{\uparrow}}{C}=O}}$$

$$R-\overset{\overset{H}{|}}{C}-H \diagdown O \leftarrow Al(OR)_3 \quad + R-\overset{+}{C}=O \longrightarrow R-C\overset{O}{\not{}}-O-CH_2R + Al(OR)_3$$

Here it is assumed that the addition of the electrophilic aluminum ethoxide to the carbonyl oxygen makes the carbonyl carbon atom sufficiently positive to attract a hydride ion from another molecule of aldehyde (22). It is probable that this reaction also involves an intramolecular transfer of hydrogen rather than an intermolecular transfer (81):



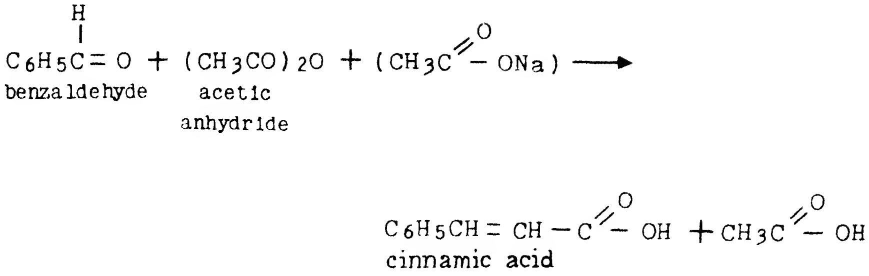
The Benzoin and Perkin reactions are highly characteristic for aromatic aldehydes. The benzoin condensation is catalyzed by potassium cyanide. Furthermore, the cyanide ion is known to be a specific catalyst for the reaction. The reaction is initiated by the nucleophilic attack of the cyanide ion and the transfer of hydrogen from one molecule of the aldehyde to another is also involved. The course of the reaction has been formulated as follows:



Unlike the Cannizzaro reaction, the benzoin condensation involves the transfer of a proton and the formation of a carbon-to-carbon bond. The electron-attracting cyanide group would facilitate the formation of a proton from the alpha position (2d step) as well as its own elimination in the final step.

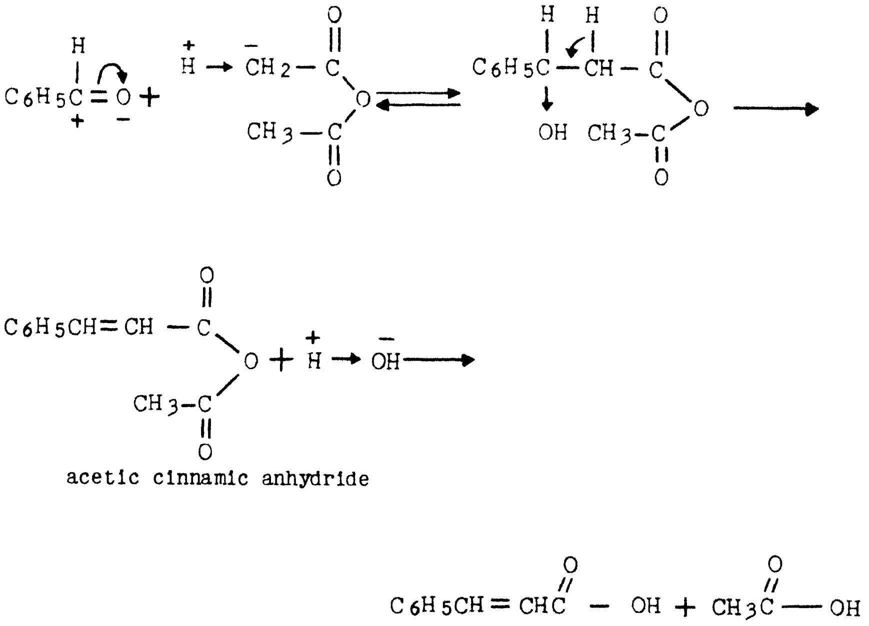
The Perkin condensation involves the interaction of an aromatic aldehyde, an acid anhydride, and the sodium salt of the corresponding acid

(82). Perkin thought that the reaction takes place between the aldehyde and the anhydride:



$$C_6H_5\overset{\overset{H}{|}}{C}=O + (CH_3CO)_2O + (CH_3C\overset{O}{\diagup\!\!\diagup}-ONa) \longrightarrow C_6H_5CH=CH-C\overset{O}{\diagup\!\!\diagup}-OH + CH_3C\overset{O}{\diagup\!\!\diagup}-OH$$

His early views have been confirmed and it is known that the sodium acetate functions as a basic catalyst. The real catalyst is the anion, and it may be replaced by the anions of other weak acids. The efficiency of the catalyst is related to its basic strength and when sodium acetate is replaced by potassium carbonate, the necessary time of heating is greatly reduced. The reaction consists of an aldol-type addition of the anhydride to the carbonyl group of the aldehyde, and the catalyst assists the ionization of the alpha hydrogen as well as the polarization of the carbonyl group:

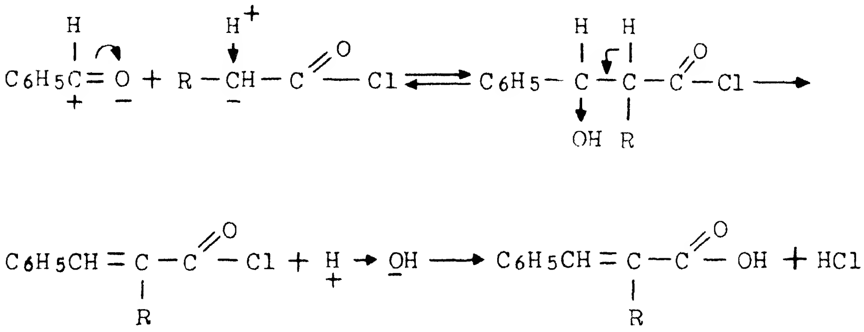


$$C_6H_5\overset{\overset{H}{|}}{\underset{+}{C}}=\underset{-}{O} + \overset{+}{H}\rightarrow\overset{-}{C}H_2-C(=O)-O-C(=O)-CH_3 \rightleftharpoons C_6H_5\overset{H}{C}(OH)-\overset{H}{C}H-C(=O)-O-C(=O)-CH_3 \longrightarrow$$

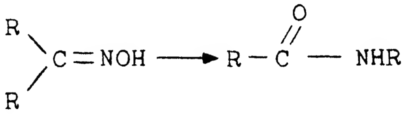
$$C_6H_5CH=CH-C(=O)-O-C(=O)-CH_3 + \overset{+}{H}\rightarrow\overset{-}{OH} \longrightarrow C_6H_5CH=CHC\overset{O}{/\!/}-OH + CH_3C\overset{O}{/\!/}-OH$$

The splitting out of water in the second step is typical of compounds containing the hydroxyl group in a β- position to a carbonyl group. The last step is the hydrolysis of a mixed anhydride.

This mechanism may also be applied to other known reactions which are similar to the Perkin reaction. For example, Kato (83) observed that acid chlorides of the type RCH_2COCl react with benzaldehyde in the presence of triethylamine to yield substituted cinnamic acids:



XII. **Beckmann rearrangement.** The conversion of aliphatic or aromatic ketoximes into isomeric acid amides

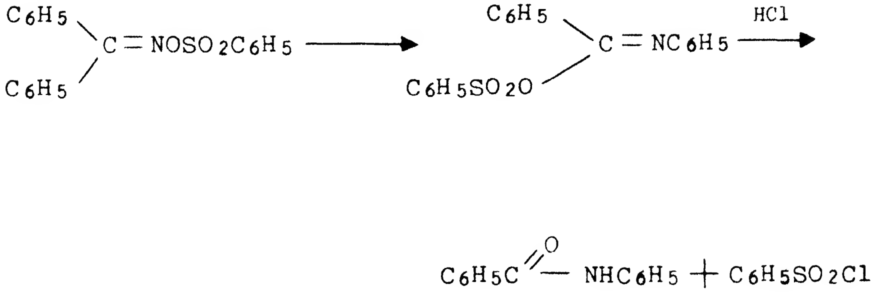


is caused by a variety of reagents: phosphorus pentachloride, phosphorus oxychloride, acetyl chloride, benzenesulfonyl chloride, sulfuric acid, hydrochloric acid, etc. In general the reagents used are acidic in character. The change is commonly carried out in dry ether under the influence of phosphorus pentachloride. Isomeric ketoximes (syn and anti) rearrange to give different amides. For a time it was assumed that the radical nearest to the hydroxyl group would change places with the hydroxyl (cis interchange). Since 1921, a large amount of evidence has been accumulated which definitely points to a trans interchange of groups.

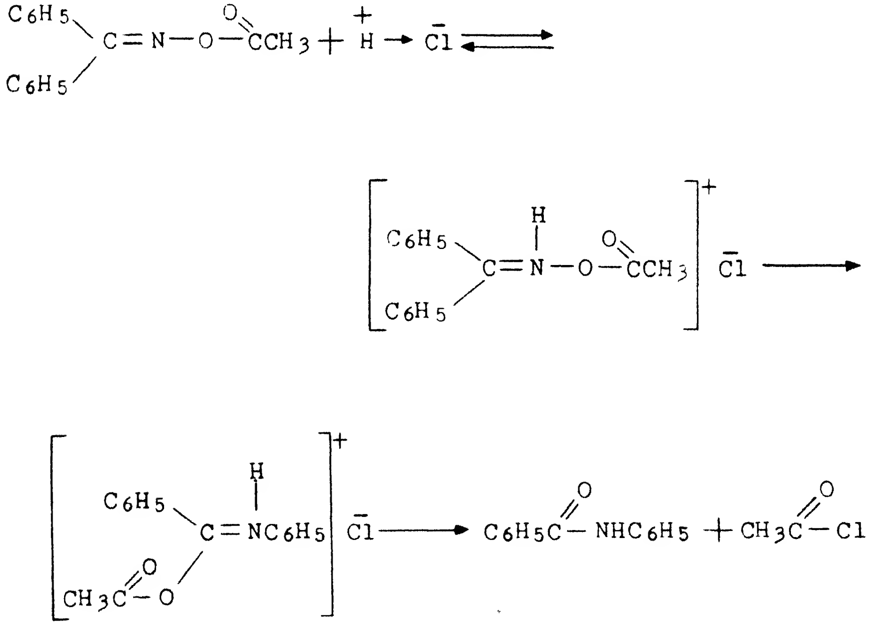
The initial function of the catalyst is to convert the oxime into an ester, a salt, or both. Kuhara (84) has shown that the acyl derivatives of the oximes undergo the change and the velocity of the rearrangement increases as the anionic stability of the acyloxy group increases. He further noted that in the rearrangement of benzophenone oxime, effected by acyl chlorides, the velocity increased as the electron-attracting character of the acyl group increased (as shown by the dissociation constants of the corresponding acids):

$$C_6H_5SO_2Cl > CH_2ClCOCl > CH_3COCl$$

The benzenesulfonate rearranges on heating or even on standing to an oil which may then be hydrolyzed to benzanilide:

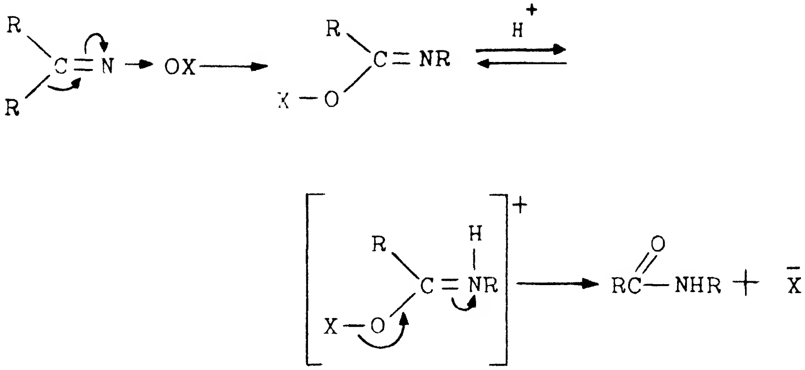


The acetate, however, rearranges only in the presence of hydrogen chloride. This indicates that the esters of weak acids rearrange only when in the form of a cation:

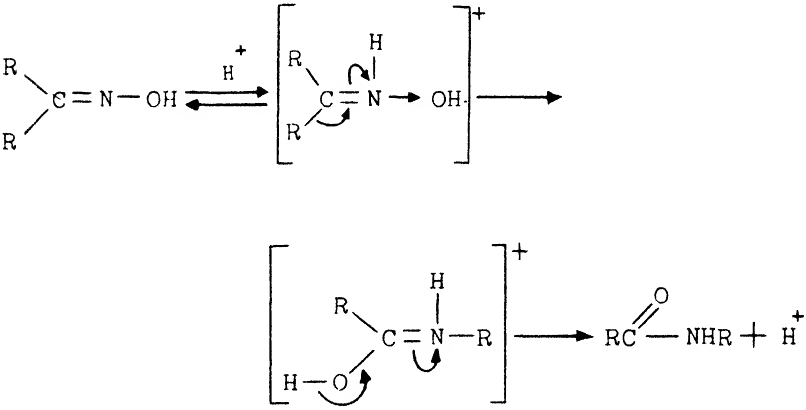


Chapman (85) has confirmed and extended the above findings. He noted that the picryl ethers of oximes, $R_2C{=}N{-}OC_6H_2(NO_2)_3$, rearrange on heating. It is probable that the rearrangement is initiated by the tendency of the OX group ($R_2C{=}NOX$) to dissociate as an anion. It has been shown (86) that the rearrangement of an optically active ketoxime does not result in the disappearance of optical activity and hence there is no reason to believe that the migrating groups are free at any time. Watson (87) has written an electronic mechanism for the rearrangement which is in accord with the experimental facts:

I



II



In the rearrangement of the oxime ester type (I), the electron attraction of the OX group initiates the electron displacements necessary for the rearrangement. In some cases, as with the esters of weak acids, the electron attraction of the OX group is not great enough to cause the change except in the presence of an acid such as hydrogen chloride which contributes a proton to the nitrogen atom. The electron attraction of the coordinated proton then initiates the electronic changes just as it does in the rearrangement of oximes with acids alone (II).

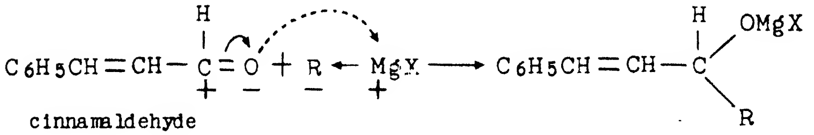
This mechanism not only agrées with the experimental facts but gives a basis for the functions of the various catalysts which may be used to produce the change. The N-ethers of aldoximes give the rearrangement and a few aldoximes have been reported to give the change.

CHAPTER XV

Reactions of α, β-Unsaturated Aldehydes and Ketones

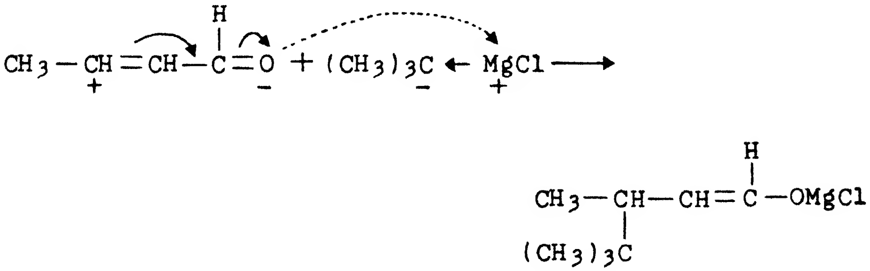
These compounds possess an olefin linkage and a carbonyl group so situated that they form a conjugated system, $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$. Their chief reactions are addition reactions which are complicated by the fact that some reagents add to the carbonyl group, some add to the olefin linkage, and others add 1,4 to the conjugated system. These reactions are best approached by considering the electronic systems of the unsaturated carbonyl compounds and the nature of the reagents which undergo addition to such systems. The dipolar carbonyl group, while also retaining its normal tendency to undergo addition reactions in some cases, exerts an electron-attracting effect on the rest of the molecule. Most of the reactions of these compounds may be explained on the basis of these two effects which are induced or enhanced by the approach of a suitable reagent. Whether 1,2- or 1,4- addition occurs appears to be largely determined by the nature of the reagent and the structure of the carbonyl compound.

Grignard reagents usually add 1,2- to α, β-unsaturated aldehydes.



$$C_6H_5CH=CH-\underset{+}{\overset{\overset{H}{|}}{C}}=\underset{-}{O} + \underset{-}{R} \leftarrow \underset{+}{MgX} \longrightarrow C_6H_5CH=CH-\overset{\overset{H}{|}}{C}\begin{matrix}\diagup OMgX \\ \diagdown R\end{matrix}$$

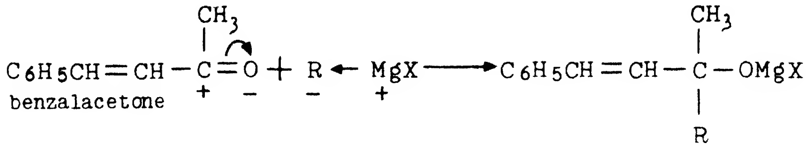
Hydrolysis of the addition product yields an unsaturated alcohol. An exception to this mode of addition is the 1,4- addition of tertiary butyl magnesium chloride or tertiary amyl magnesium chloride to crotonaldehyde (88):



$$CH_3-\underset{+}{CH}=CH-\overset{\overset{H}{|}}{C}=\underset{-}{O} + \underset{-}{(CH_3)_3C} \leftarrow \underset{+}{MgCl} \longrightarrow CH_3-\underset{\underset{(CH_3)_3C}{|}}{CH}-CH=\overset{\overset{H}{|}}{C}-OMgCl$$

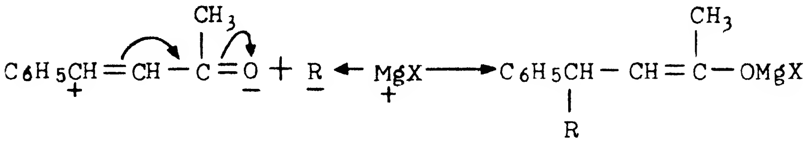
It will be noted that Grignard reagents of the type R_3CMgX would be less reactive than R_2CHMgX and RCH_2MgX. Because of the greater electron-release effect of the three alkyl groups, the tendency to produce the necessary polarization for the reaction would be greatly reduced.

α,β-Unsaturated ketones react with Grignard reagents to form unsaturated alcohols (1,2- addition), saturated ketones (1,4- addition), or both:



$$C_6H_5CH{=}CH-\underset{+}{\overset{CH_3}{\overset{|}{C}}}{=}\underset{-}{O} + \underset{-}{R} \leftarrow \underset{+}{MgX} \longrightarrow C_6H_5CH{=}CH-\underset{\underset{R}{|}}{\overset{\overset{CH_3}{|}}{C}}-OMgX$$

benzalacetone



$$\underset{+}{C_6H_5CH}{=}CH-\overset{CH_3}{\overset{|}{C}}{=}\underset{-}{O} + \underset{-}{R} \leftarrow \underset{+}{MgX} \longrightarrow \underset{\underset{R}{|}}{C_6H_5CH}-CH{=}\overset{\overset{CH_3}{|}}{C}-OMgX$$

It is easy to see how either 1,2- or 1,4- addition might occur, but it is more difficult to understand the difference in behavior of the α,β-unsaturated aldehydes and ketones. It is probable that this difference is due to the nature of the groups which are attached to the carbonyl carbon atom. There is evidence for this in the following examples (89):

		% 1,4-addition
$C_6H_5CH{=}CHCOCH_3$	$\xrightarrow{C_6H_5MgBr}$	12
	$\xrightarrow{C_2H_5MgBr}$	60
$C_6H_5CH{=}CHCOCH_2CH_3$	$\xrightarrow{C_6H_5MgBr}$	40
	$\xrightarrow{C_2H_5MgBr}$	71
$C_6H_5CH{=}CHCOCH(CH_3)_2$	$\xrightarrow{C_6H_5MgBr}$	88
	$\xrightarrow{C_2H_5MgBr}$	100
$C_6H_5CH{=}CHCOC(CH_3)_3$	$\xrightarrow{C_6H_5MgBr}$	100
	$\xrightarrow{C_2H_5MgBr}$	100

$$C_6H_5CH{=}CHCOC_6H_5 \quad \xrightarrow{C_6H_5MgBr} \quad 94$$

$$\xrightarrow{C_2H_5MgBr} \quad 99$$

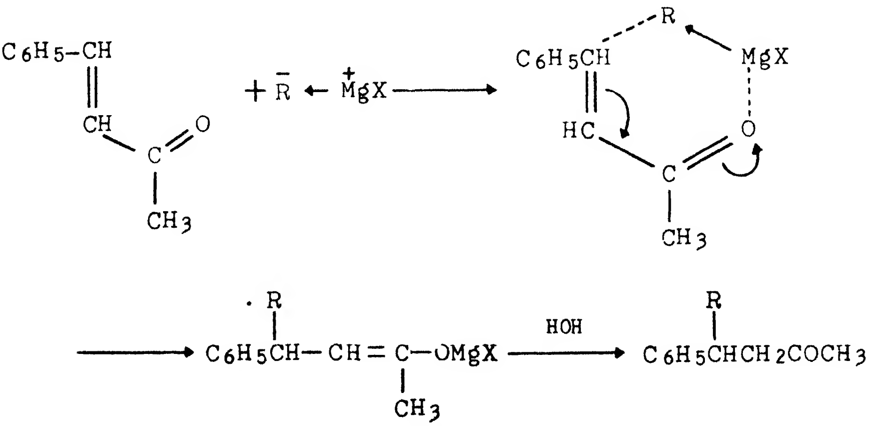
$$(C_6H_5)_2C{=}CHCOC_6H_5 \quad \xrightarrow{C_6H_5MgBr} \quad 0$$

$$\xrightarrow{C_2H_5MgBr} \quad 18$$

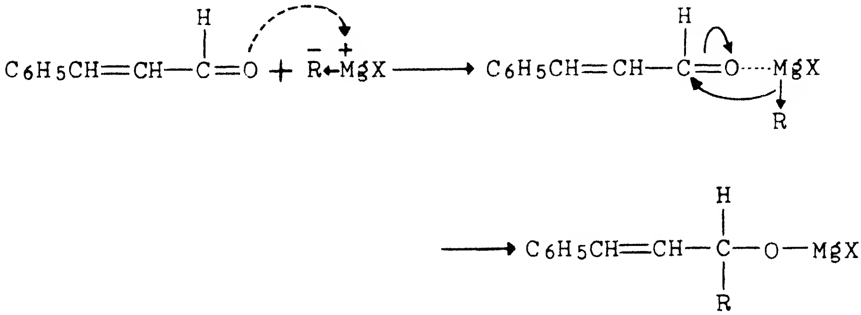
Steric hindrance appears to offer a possible explanation of the results shown above. It might be assumed that with increasing steric hindrance around the carbonyl group, 1,2- addition is retarded or prevented, and as a result 1,4- addition is facilitated. However, there is little evidence to support the contention that the rate of addition to the carbonyl group is regulated entirely by steric hindrance.

The fact that the α,β-unsaturated ketones exhibit the greatest tendency to undergo 1,4- addition with RMgX suggests another possible factor. The electron-release effects of the two radicals attached to the carbonyl group in a ketone while assisting the polarization of the carbonyl group might actually lower the attraction between the carbonyl carbon atom and the approaching carbanion ion, thus serving to slow down 1,2- addition and favoring 1,4- addition. Gilman and Kirby (90) have studied the reactions of benzalacetophenone with several phenylmetallic compounds and noted that the extent of 1,4- addition increased as the reactivity of the metallo compound decreased. It was found that only 1,2- addition resulted with the very active compounds, diphenylcalcium and phenylpotassium. This evidence appears to support the second effect rather than steric hindrance. It is possible that both effects may be involved.

A "cyclic" mechanism may also be used to explain 1,4- additions to α,β-unsaturated ketones. This mechanism involves the assumption that an unstable or ephemeral ring structure is a necessary intermediate for the reaction (91). Its structure is such that the electromeric shifts, necessary for the formation of the 1,4- addition product, should readily occur:



This mechanism is an attractive one but more evidence is required before it can be stated definitely that it is the only mechanism involved in the 1,4- addition of Grignard reagents and other reagents to α,β-unsaturated ketones. In many cases 1,4- addition is accompanied by 1,2- addition. The latter obviously cannot proceed by way of the "cyclic" mechanism. It may involve an "ionic" mechanism as shown earlier in the chapter or a coordination complex may be the initial intermediate in the reaction (91):



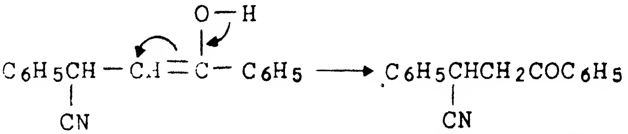
The formation of such a complex would facilitate the electromeric shift in the carbonyl group, which in turn might be expected to promote the α,γ-shift of the alkyl group from magnesium to carbon.

It is possible to write "cyclic" mechanisms for many other reactions, but the mere fact that they may appear to be reasonable is not sufficient reason for their general adoption at the present time. It is interesting to note that regardless of the mechanism used the same fundamental principle is involved, namely, the union of positive centers with negative ones. The forces which initiate the reaction may be fractional charges but under certain conditions may be essentially ionic charges. The over-all result is the cleavage of some bonds and the formation of new ones. These may be predicted qualitatively by applying the principles discussed on pages 12 and 58.

Hydrogen cyanide adds normally (1,2) to α,β-unsaturated aldehydes but adds 1,4 to α,β-unsaturated ketones:

$C_6H_5CH{=}CHCOC_6H_5 + HCN \longrightarrow$

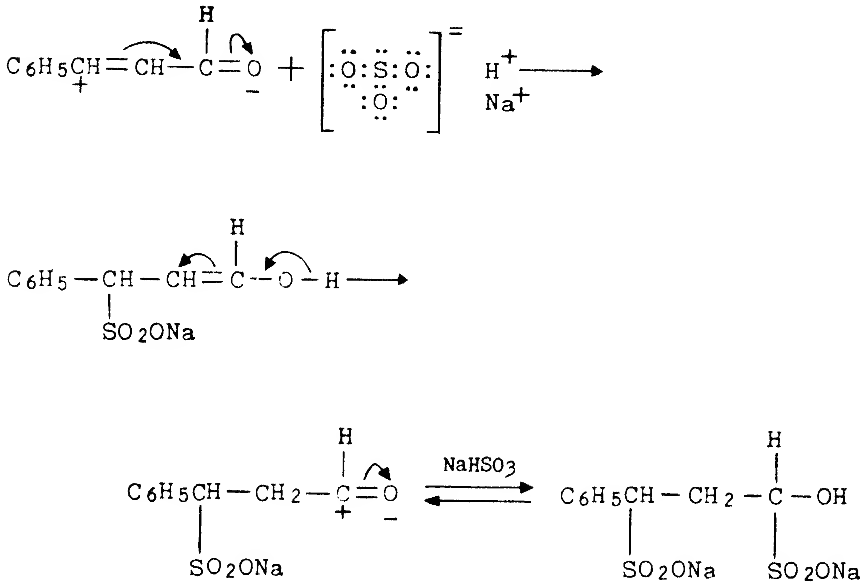
benzalacetophenone

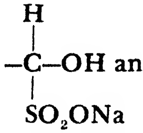


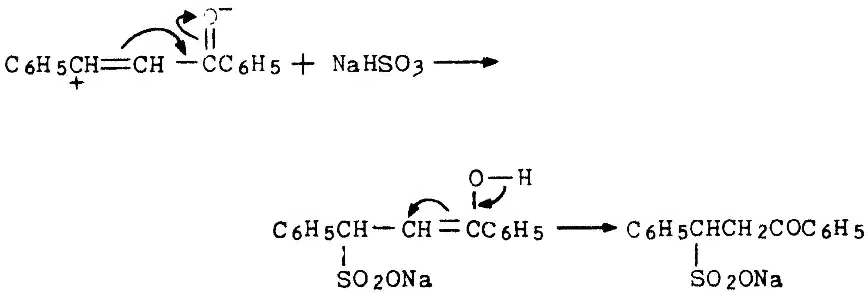
1-cyano-1-phenyl-2-benzoylethane

Here, again, the approach of the cyanide ion to the carbonyl carbon atom is retarded either because of steric hindrance or by the electron-release effect of the two radicals attached to the carbonyl carbon atom. The latter effect seems more probable in this case.

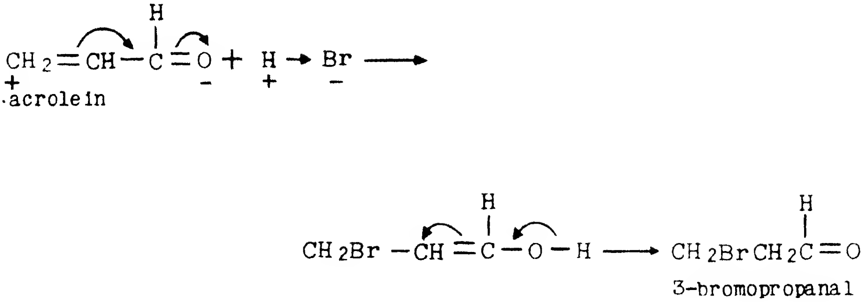
α,β-Unsaturated aldehydes react with excess sodium bisulfite to form the sodium salts of disulfonic acids:

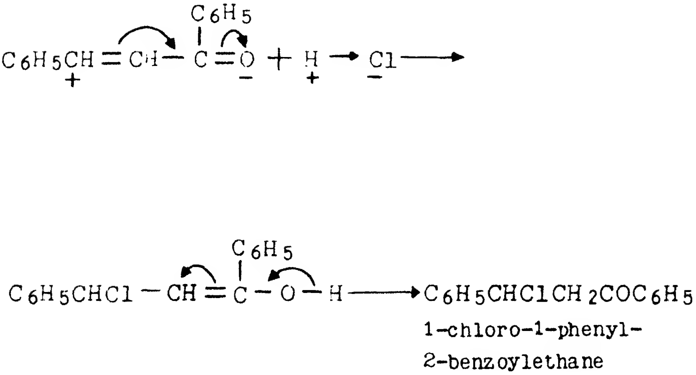


The $-\overset{|}{C}H-SO_2ONa$ bond is relatively stable compared with  $-\underset{SO_2ONa}{\overset{H}{C}}-OH$ and consequently would be expected to be formed. The reaction then involves a 1,4- addition followed by tautomerization of the enol to the keto form and subsequent addition of a second molecule of sodium bisulfite to the carbonyl group. Although sodium bisulfite usually adds (1,2) only to saturated methyl ketones, it adds (1,4) to many α,β-unsaturated ketones:



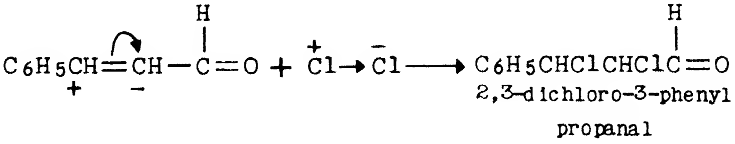
The hydrogen halides add 1,4 to many α,β-unsaturated aldehydes and ketones:





The 1,2- addition of HX would scarcely be expected because of the instability of such an addition product.

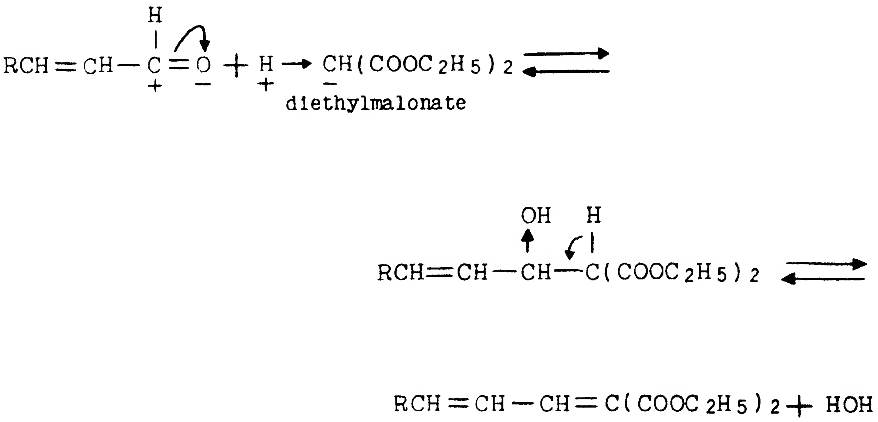
Halogens add to the olefin bond (3,4) in the normal manner:



The reactions of the α,β-unsaturated aldehydes and ketones with the common carbonyl reagents, hydroxylamine, phenylhydrazine, and semicarbazone usually give the expected oximes, phenylhydrazones, and semicarbazones, when carried out in acid solution. In neutral or alkaline solution, all of the possible addition reactions may occur.

Michael reaction. A large number of compounds containing active hydrogen of the type $-\overset{\overset{\textstyle H}{|}}{C}-X$, where X = COOR, COR, CN, NO_2, etc., will add to α,β-unsaturated carbonyl compounds in the presence of basic catalysts. There must be at least one hydrogen attached to the α-carbon atom and the X group must be an electron-attracting group. The catalyst is often sodium ethoxide either in dry alcohol or suspended in dry ether or benzene. Organic bases such as piperidine or diethylamine are also used.

With α,β-unsaturated aldehydes, the normal aldol type of condensation occurs:

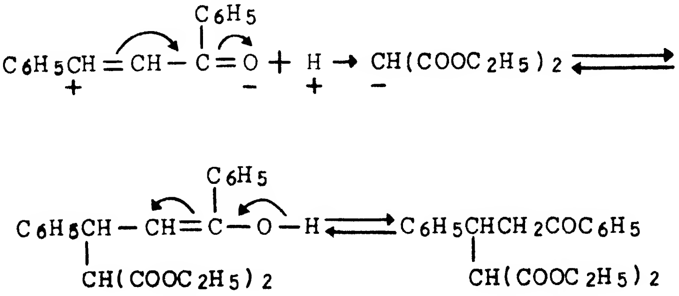


$$RCH{=}CH{-}\overset{\overset{H}{|}}{\underset{+}{C}}{=}\underset{-}{O} + \underset{+}{H}\rightarrow \underset{-}{CH}(COOC_2H_5)_2 \rightleftharpoons$$

$$RCH{=}CH{-}\overset{OH}{CH}{-}\overset{H}{C}(COOC_2H_5)_2 \rightleftharpoons$$

$$RCH{=}CH{-}CH{=}C(COOC_2H_5)_2 + HOH$$

However, these reagents add 1,4 to α,β-unsaturated ketones. It is the function of the basic catalyst to facilitate the ionization of the proton from the reagent and to facilitate the electron displacements in the unsaturated ketone (92) :



$$\underset{+}{C_6H_5CH}{=}CH{-}\overset{\overset{C_6H_5}{|}}{C}{=}\underset{-}{O} + \underset{+}{H}\rightarrow \underset{-}{CH}(COOC_2H_5)_2 \rightleftharpoons$$

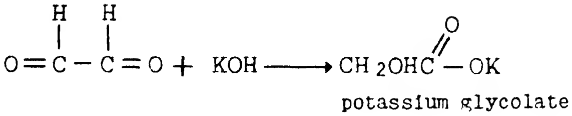
$$C_6H_5\underset{\underset{CH(COOC_2H_5)_2}{|}}{CH}{-}CH{=}\overset{\overset{C_6H_5}{|}}{C}{-}O{-}H \rightleftharpoons C_6H_5\underset{\underset{CH(COOC_2H_5)_2}{|}}{CH}CH_2COC_6H_5$$

The reversibility of this reaction has been definitely established. Usually the reaction proceeds as shown above when only a small amount of catalyst is used. When an equivalent of sodium ethoxide is used, however, secondary reactions have been observed (93).

CHAPTER XVI

Reactions of Dialdehydes and Diketones

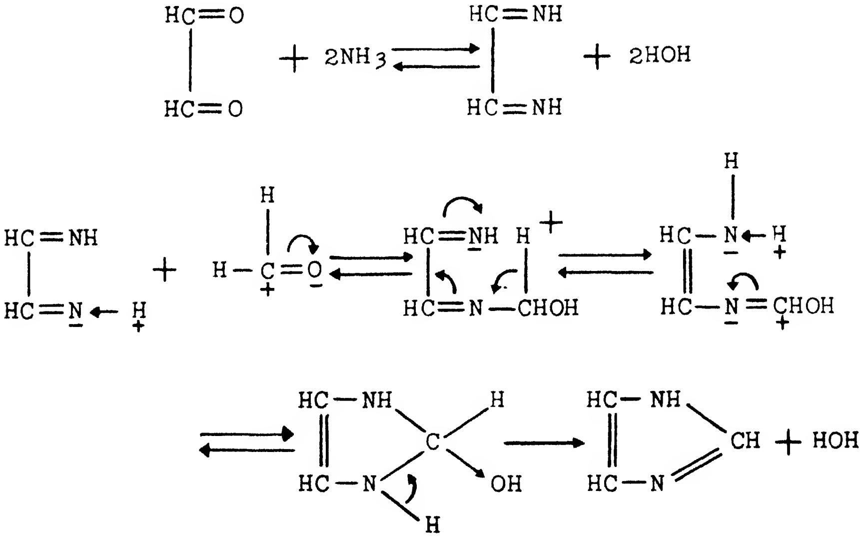
Glyoxal, the simplest dialdehyde, normally exists as a polymer. The monomeric form may be obtained from the polymer by distillation. Glyoxal gives many of the usual aldehyde reactions, that is, it reacts with two moles of sodium bisulfite, forms a dioxime and a diphenylhydrazone, reduces ammoniacal silver solution, and undergoes the Cannizzaro reaction:



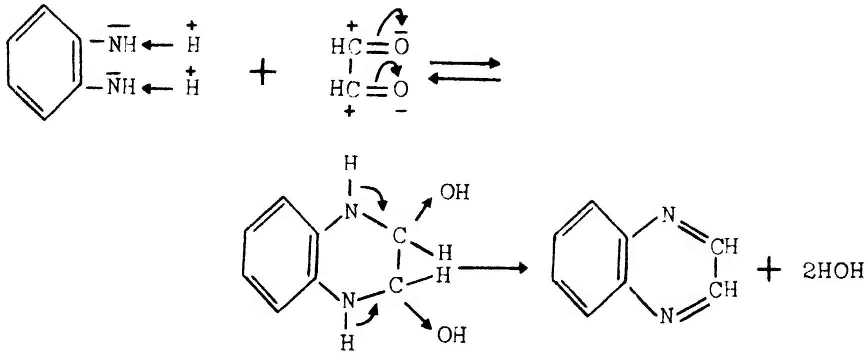
$$O=\overset{H}{\overset{|}{C}}-\overset{H}{\overset{|}{C}}=O + KOH \longrightarrow \underset{\text{potassium glycolate}}{CH_2OHC(=O)-OK}$$

The mechanisms involved in these reactions are similar to those noted previously for the simple aldehydes.

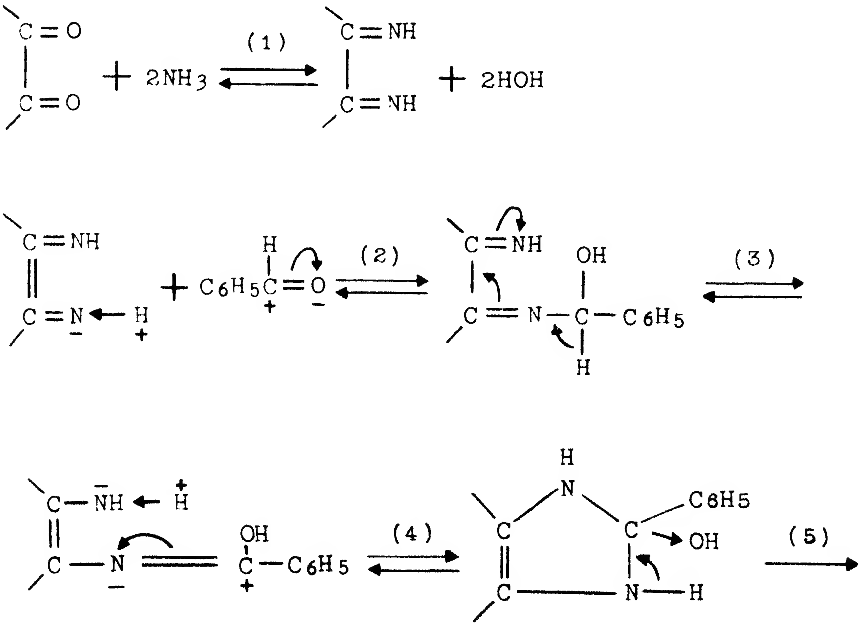
Glyoxal often undergoes chemical reactions with the formation of heterocyclic compounds. For example, with ammonia and formaldehyde, it yields imidazole (glyoxaline). The mechanism may be shown as follows:

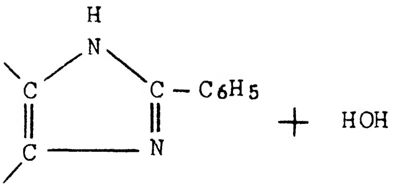


With *o*-phenylenediamine, glyoxal forms quinoxaline:

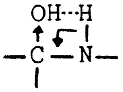


The above courses of reaction are strongly indicated since they are quite similar to other ortho condensations which lead to the formation of heterocyclic compounds (94) by such paths. For example, phenanthraquinone reacts with ammonia and aldehydes to form 2-substituted phenanthrimidazoles. It has been shown that phenanthraquinone di-imine is an intermediate in these reactions (95). The di-imine can be isolated as its acetate, and the latter when treated with aldehydes gives excellent yields of phenanthrimidazoles. For these reactions the following mechanism appears to be well established:



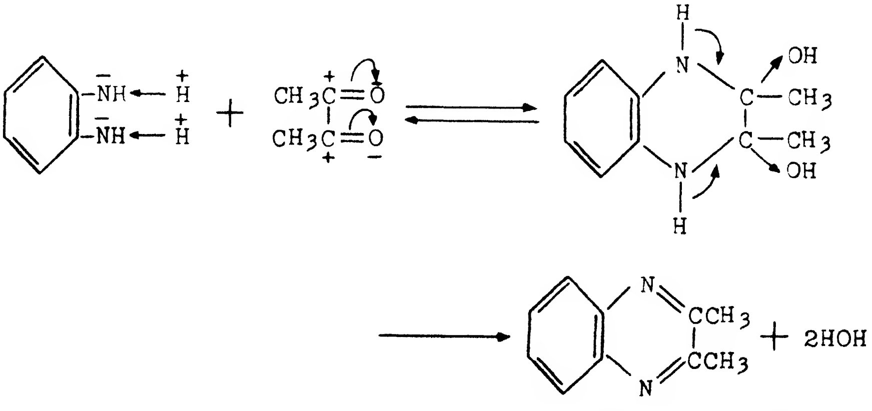


The first step represents the usual aldol-type addition of ammonia to carbonyl groups. The second step consists of an aldol-type addition of the di-imine to the aldehyde. The resulting product contains a highly active system and step three indicates its prototropic nature. The process of cyclization shown in the fourth step involves the addition of an amino group across the double bond between carbon and nitrogen and results in the temporary formation of a dihydro phenanthrimidazole. The latter then loses a molecule of water to form the phenanthrimidazole. The instability of the dihydro compound is not surprising in view of the fact that the grouping



is known from many other reactions to exhibit a marked tendency to lose water. This tendency is due to the inherent electronegative nature of the hydroxyl group and the electropositive nature of hydrogen when attached to nitrogen.

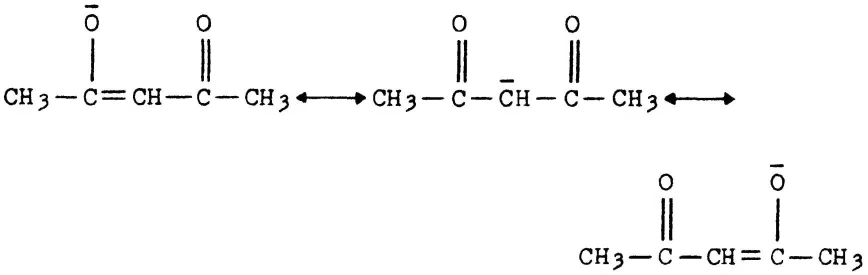
The 1,2-diketones behave normally towards many ketone reagents, forming dioximes, disemicarbazones, adding two moles of hydrogen cyanide, etc. They also react with *o*-phenylenediamine to form substituted quinoxalines:



2,3-dimethylquinoxaline

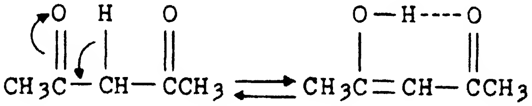
Benzil, $C_6H_5COCOC_6H_5$, reacts similarly with *o*-phenylenediamine to give 2,3-diphenylquinoxaline.

Acetylacetone, an example of a 1,3-diketone, under ordinary conditions consists largely of the enol form. The hydrogen atoms on an alpha carbon atom have an increased tendency to ionize when there are two strongly electron-attracting groups attached to the carbon.. This is due to the increased possibilities for resonance that exist in the resulting anion:



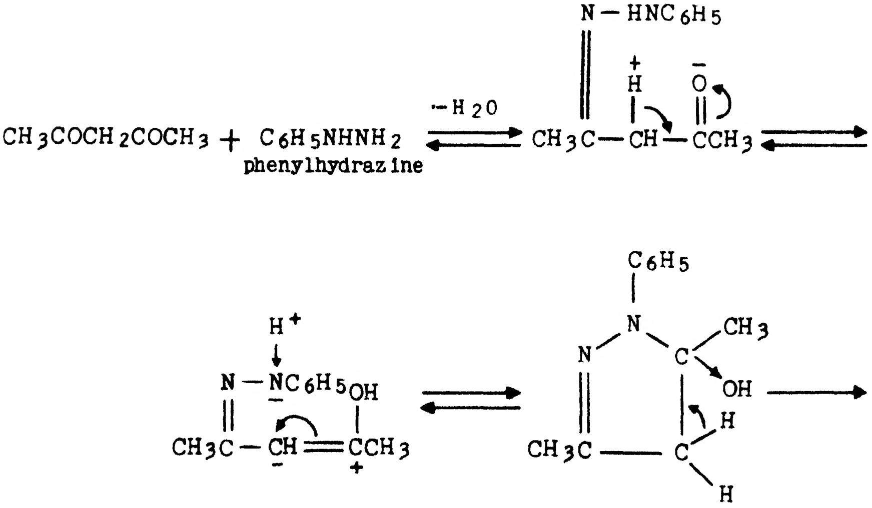
$$CH_3-\overset{\overset{\bar{O}}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\overset{\overset{O}{\|}}{C}-\bar{C}H-\overset{\overset{O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\overset{\overset{O}{\|}}{C}-CH=\overset{\overset{\bar{O}}{|}}{C}-CH_3$$

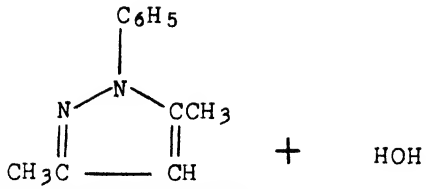
It may be said also that in the molecular form the enol would be stabilized through hydrogen bonding. Infrared examination[9] has demonstrated the existence of the chelate ring which is caused by hydrogen bond formation in the enol form:



$$CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{C}H-\overset{\overset{O}{\|}}{C}CH_3 \rightleftarrows CH_3\overset{\overset{O-H\cdots}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}CH_3$$

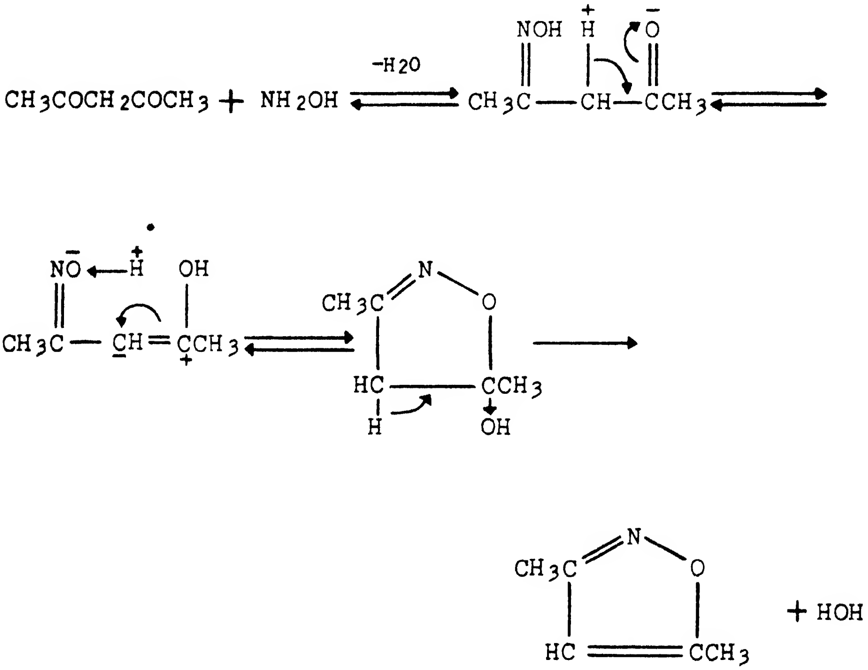
Acetylacetone reacts with a variety of reagents to form heterocyclic compounds:





1-phenyl-3,5-dimethylpyrazole

With hydroxylamine, acetylacetone yields 3,5-dimethylisoxazole:



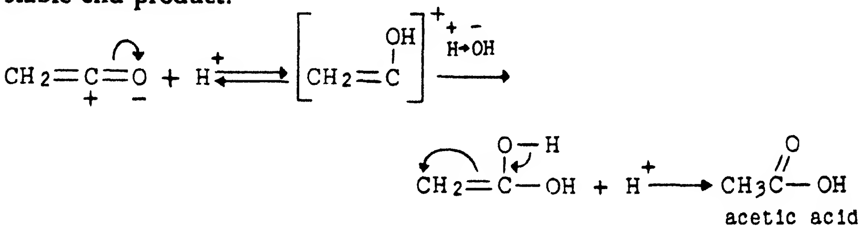
The above mechanisms are not to be regarded as established, but it is reasonable to assume that ring closure is effected by addition to an unsaturated linkage followed by aromatization (94).

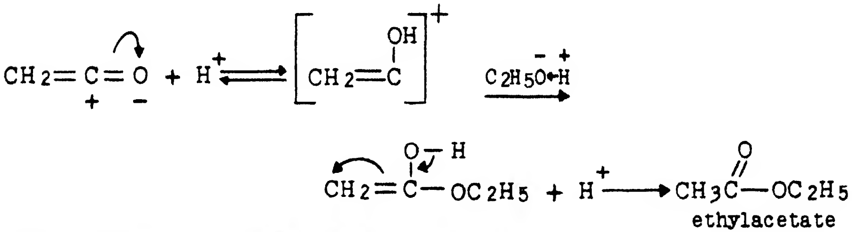
CHAPTER XVII

Reactions of Ketenes

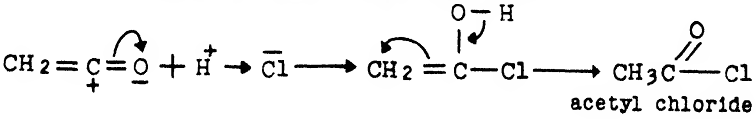
Two types are known, the aldoketenes, RCH=C=O, and the ketoketenes, $R_2C=C=O$. Ketene, $CH_2=C=O$, may be regarded as the parent compound of both types. The ketenes are among the most reactive of all unsaturated compounds and at one time it was thought that their reactivity was concentrated in the olefin linkage. However, it is known now that addition usually occurs to the carbonyl group followed by the tautomerization of the addition product.

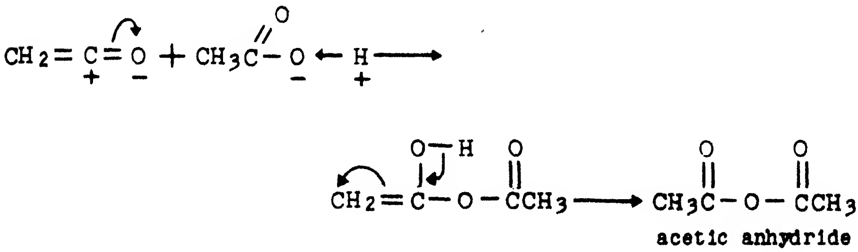
Many of these reactions are catalyzed by acids. The addition of a proton to the carbonyl oxygen atom yields a carbonium ion. The electron-deficient carbon atom of this ion attracts an anion from the reagent present and the enolic addition product then tautomerizes to the more stable end product:





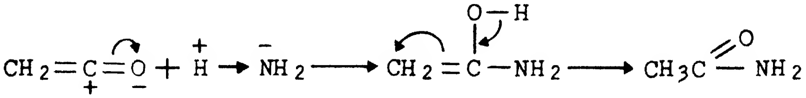
Other reactions may be written in a similar manner:



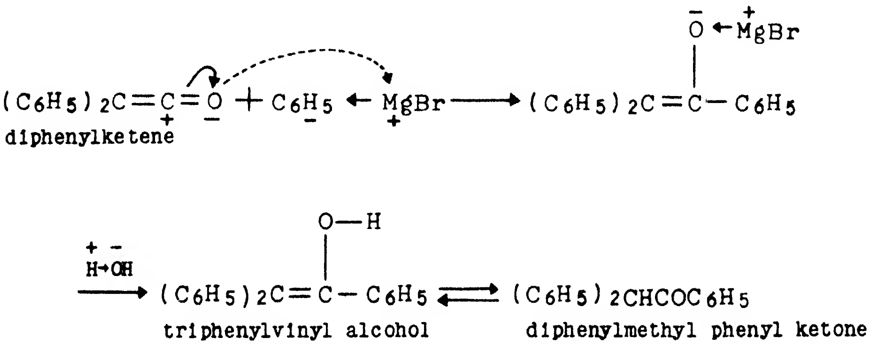


In these two examples the reagents used are acidic and the reactions do not require the presence of an additional acid catalyst.

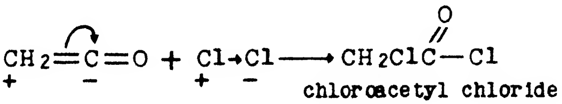
Ketene reacts with ammonia to form acetamide and with primary and secondary amines to give mono- and disubstituted acetamides. It is probable in these cases that the initial step is the addition of the nucleophilic reagent to the carbonyl carbon atom:



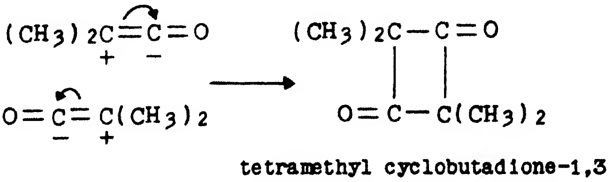
Ketenes also undergo addition with Grignard reagents. The course of the following reaction has been established by Gilman and Heckert (96):



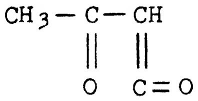
Reagents, such as chlorine or bromine, which are characteristic of the olefin linkage, add to this linkage only in the ketenes:



Ketene and aldoketenes polymerize rapidly even at low temperatures and in dilute solution. Many of the ketoketenes also polymerize readily, although some, such as diphenylketene, are fairly stable at ordinary temperatures. The ketoketenes dimerize to cyclic structures, the process involving self-addition to the olefin linkage:

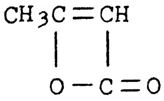


The nature of the structure of the dimer of ketene has been investigated by several workers. Originally, because of the formation of pyruvic aldehyde on ozonolysis of the dimer, it was formulated as $CH_3COCH{=}C{=}O$ (acetylketene). Later (97) it was suggested that it consists of an equilibrium mixture of acetylketene and β-crotonolactone:



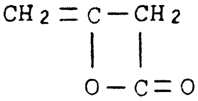
I

and



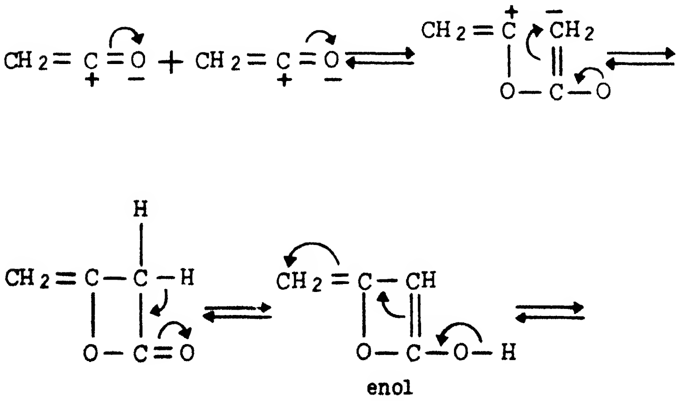
II

More recently (98) it has been suggested that its reactions are best accounted for by the following vinylaceto-β-lactone structure:

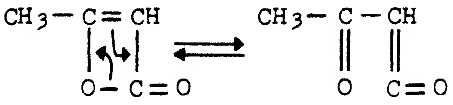


III

On the basis of present data, diketene is best regarded as an equilibrium mixture of two or three forms. Structure I best accounts for the formation of pyruvic aldehyde on ozonolysis, while only III can account for the formation of γ-chloroacetoacetyl chloride reported by Boese (98). The formation of the cyclic structures may take place as follows:

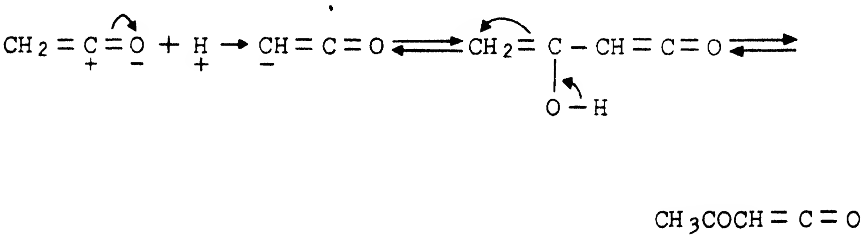


III

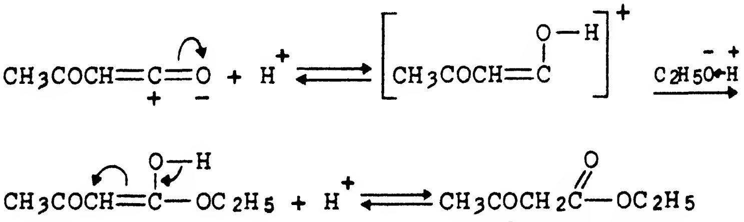


II I

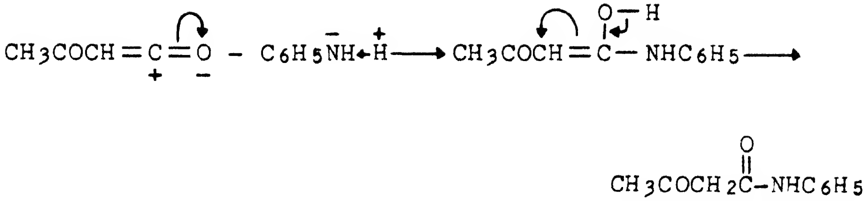
The various equilibria postulated above are based on electron displacements which are generally accepted as being characteristic of carbonyl compounds. The above picture is intended to show only general relationships, hence it does not necessarily follow that III is formed first and I last. Presumably, it is possible that I may be formed first from ketene:



Actually, any one of the three structures may be used to illustrate most of the reactions of the diketene. It is simpler, however, to use the acetylketene structure (I). For example, the diketene reacts with alcohols, in the presence of acid catalysts such as benzenesulfonic acid, to form esters of acetoacetic acid:



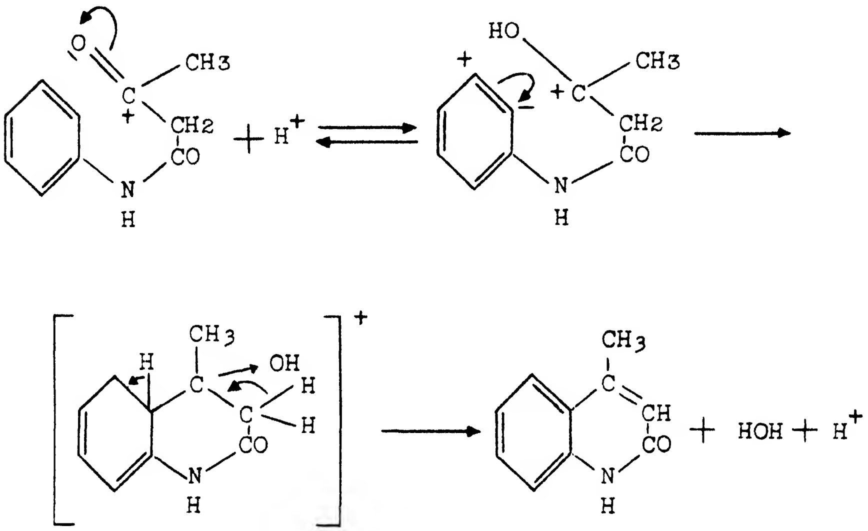
Many other useful products may be made from diketene (98). For example, diketene reacts with aliphatic and aromatic primary amines to form N-substituted acetoacetamides:



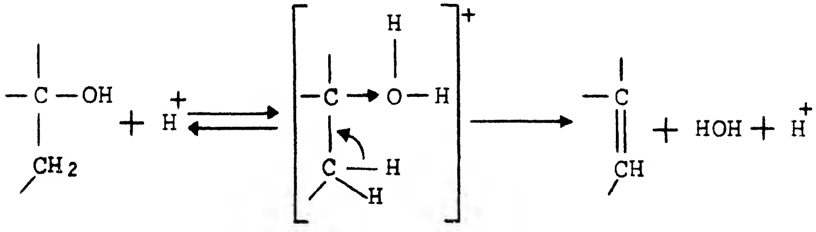
$$CH_3COCH=C=O + C_6H_5NH-H \longrightarrow CH_3COCH=C(OH)-NHC_6H_5 \longrightarrow CH_3COCH_2C(=O)-NHC_6H_5$$

acetoacetanilide

Acetoacetanilide when dissolved in concentrated sulfuric acid followed by precipitation with water gives an almost quantitative yield of 4-methylcarbostyril. The course of this acid-catalyzed ring closure is undoubtedly represented by the following mechanism:

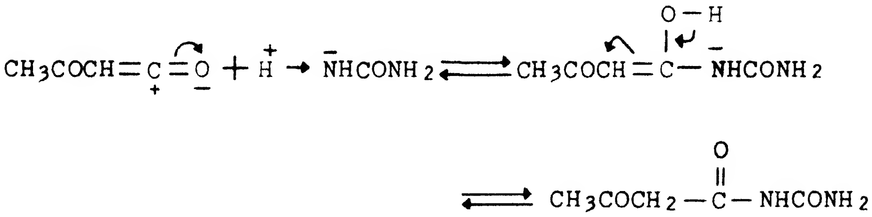


The first step is the addition of a proton to the carbonyl oxygen atom. The resulting carbonium ion then induces polarization of one of the bonds in the benzene ring and subsequently adds. A proton is then eliminated with the restoration of the resonating benzene ring. This addition of a carbonium ion followed by the loss of a proton is identical with the mechanism accepted for the Friedel-Crafts reactions. The splitting out of water from the heterocyclic ring, in the last step, has been observed in many other reactions and would be catalyzed by acids:



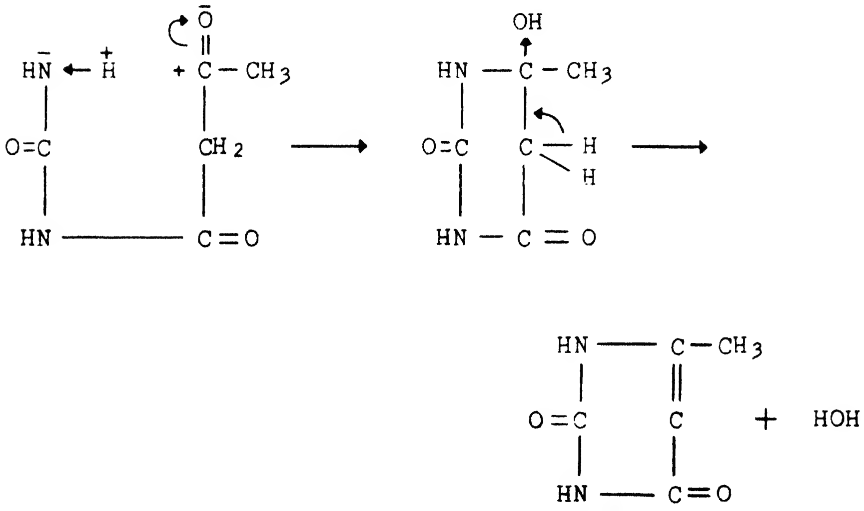
This step involves the same mechanism as that given for the dehydration of tertiary alcohols (Chap. IX).

Diketene reacts with urea in an inert solvent to form 4-methyl uracil. The following mechanism is indicated:



$$CH_3COCH{=}\underset{+}{C}{=}\underset{-}{O} + \overset{+}{H} \rightarrow \overset{-}{N}HCONH_2 \rightleftharpoons CH_3COCH{=}\overset{\overset{\displaystyle O-H}{|}}{C}-\overset{-}{N}HCONH_2$$

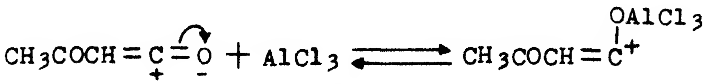
$$\rightleftharpoons CH_3COCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-NHCONH_2$$



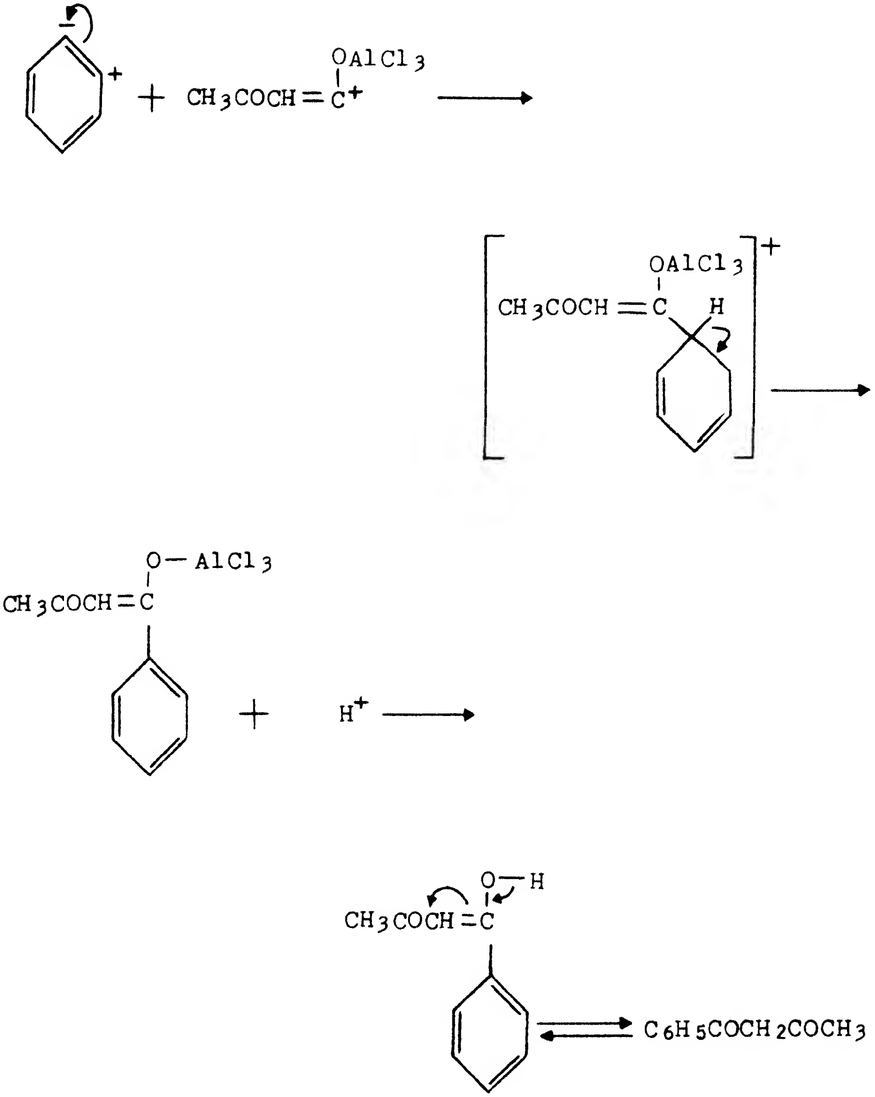
4-methyl uracil

The reaction consists of two aldol-type additions followed by the splitting out of water.

Diketene reacts with benzene in the presence of aluminum chloride to form benzoyl acetone in good yields. Assuming that a carbonium ion is a necessary intermediate, the following mechanism appears probable:



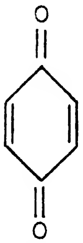
$$CH_3COCH{=}\underset{+}{C}{=}\underset{-}{O} + AlCl_3 \rightleftharpoons CH_3COCH{=}\overset{\overset{\displaystyle OAlCl_3}{|}}{C^+}$$


+
OAlCl3
CH3COCH=C+
OAlCl3
CH3COCH=C
H
+
O—AlCl3
CH3COCH=C
+
H+
O—H
CH3COCH=C
C6H5COCH2COCH3

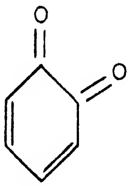
CHAPTER XVIII

Reactions of Quinones

The quinones are not aromatic compounds but rather are unsaturated alicyclic diketones and in many ways they react like unsaturated diketones. Two forms of benzoquinone are known, *p*-benzoquinone and *o*-benzoquinone. The para isomer is the more stable and hence more readily obtainable:

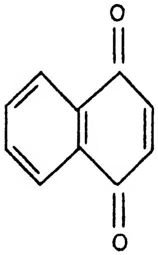


(1,4) *p*-benzoquinone

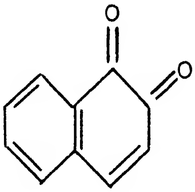


(1,2) *o*-benzoquinone

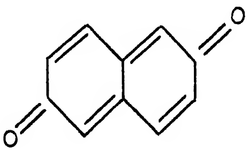
Of the three known naphthoquinones, the 1,4- or α-naphthoquinone is most readily obtained:



(1,4)
α-naphthoquinone

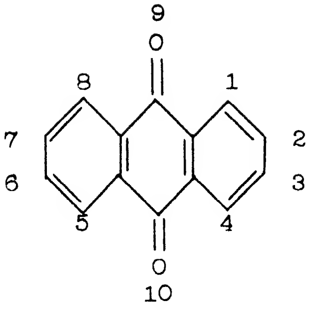


(1,2)
β-naphthoquinone

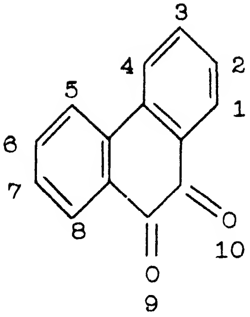


(2,6)
amphi naphthoquinone

The well-known quinones of anthracene and phenanthrene are 1,4- and 1,2-quinones respectively:



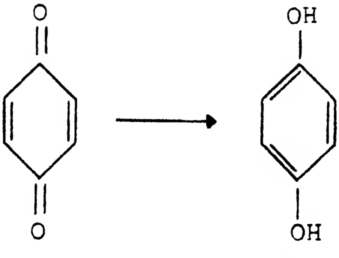
anthraquinone



phenanthraquinone

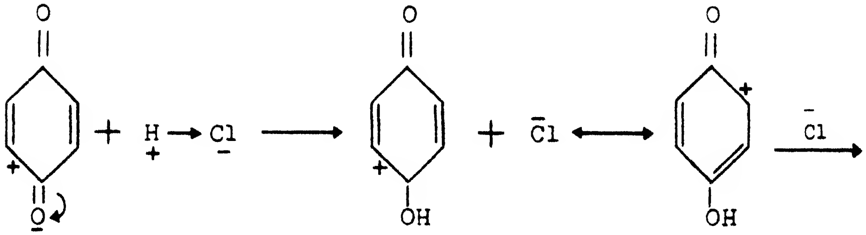
Unlike the ortho quinones of benzene and naphthalene, anthraquinone and phenanthraquinone are stable and readily prepared.

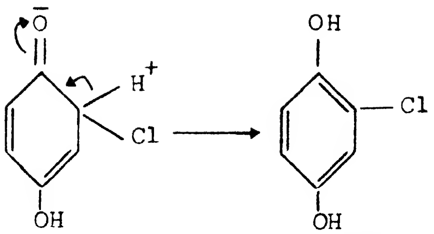
The quinones are reduced by various reagents, such as sulfurous acid, stannous chloride, and sodium hydrosulfite, to the corresponding aromatic compounds, the hydroquinones. Regardless of the positions of the carbonyl groups, the two hydrogen atoms always add to the conjugated system terminated by the oxygen atoms:



hydroquinone

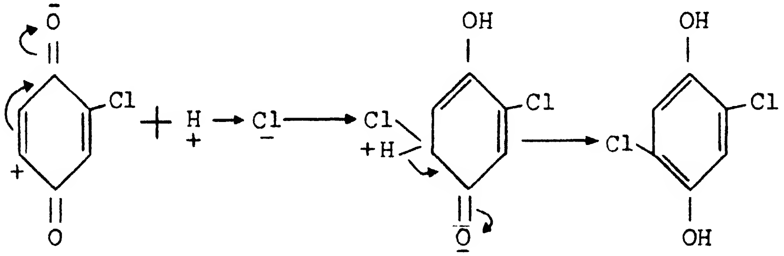
The hydrogen halides add to the quinones with the formation of halogen-substituted hydroquinones:





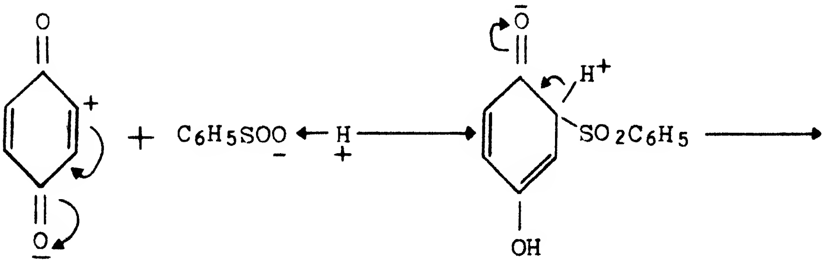
2-chlorohydroquinone

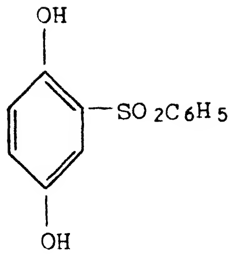
This mechanism involves a 1,4- addition, followed by enolization of the addition product (99). The course of the reaction is similar to that noted for the addition of hydrogen halides to α,β-unsaturated aldehydes and ketones. If the chlorohydroquinone is oxidized to the corresponding quinone, as it frequently is by the unchanged quinone present, a second molecule of hydrogen chloride adds to form 2,5-dichlorohydroquinone:



Theoretically the second molecule of hydrogen chloride might add in more than one way, but actually it adds in such a way as to form only the 2,5- derivative.

Benzene sulfinic acid adds in a similar manner to quinones:



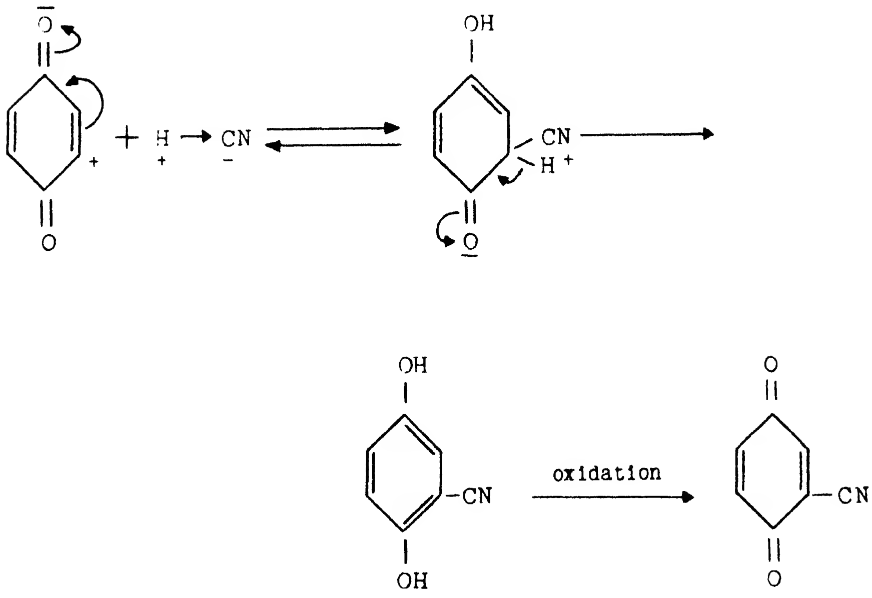


phenyl-2,5-dihydroxyphenyl
sulfone

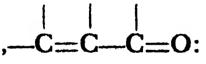
It will be noted that the sulfinate ion adds in such a way that a carbon-to-sulfur linkage is formed (see addition of sodium bisulfite to aldehydes and ketones).

Alcohols and amines, particularly aromatic amines, also undergo addition to yield either 2- or 2,5- substituted derivatives.

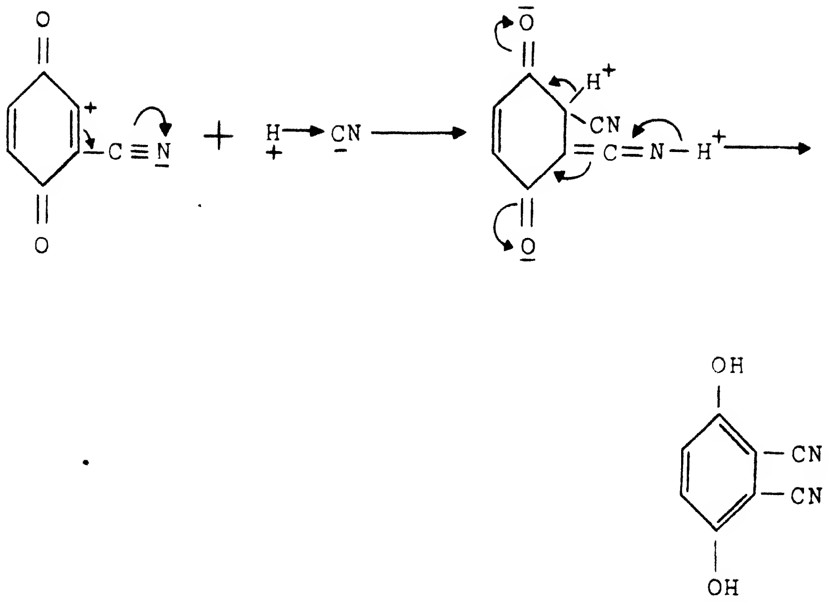
Hydrogen cyanide adds to *p*-benzoquinone in an interesting manner (100). The first step takes place according to the mechanism outlined above:



It has been suggested that the second molecule of hydrogen cyanide adds 1,4 to the conjugated system which includes the cyanide group rather than to the system,

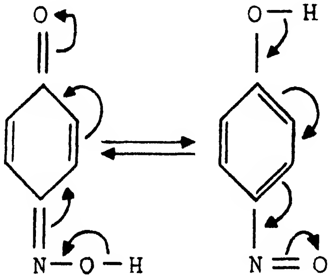


$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O:$$



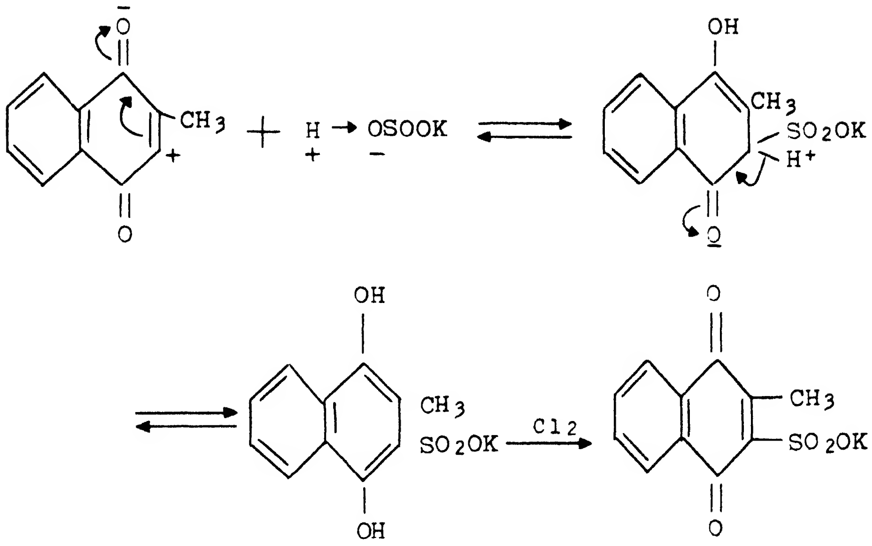
2,3-dicyanohydroquinone

Oximes of the quinones usually result when the quinones are heated in aqueous alcohol with hydroxylamine hydrochloride. Anthraquinone reacts least readily with hydroxylamine hydrochloride. Both the monoximes and dioximes are known for most of the quinones. The monoxime of *p*-benzoquinone is identical with the product obtained by the action of nitrous acid on phenol (*p*-nitrosophenol) and is best represented as a tautomeric substance:

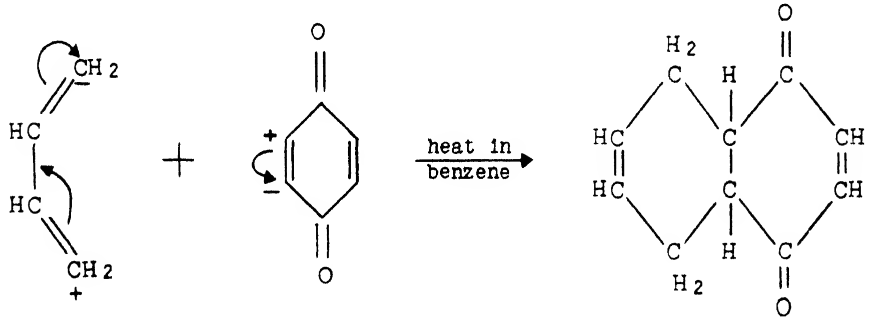


The same holds true for the monoximes of α- and β-naphthoquinones.

Phenanthraquinone forms a bisulfite addition product from which it may be recovered by the addition of acid. The other quinones react with sodium or potassium bisulfite to form hydroquinone sulfonic acids. 2-Methyl-1,4-naphthoquinone when heated with potassium bisulfite yields potassium 2-methyl-1,4-dihydroxynaphthalene-3-sulfonate. The latter by oxidation with chlorine gives the corresponding quinone (101):



The 1,4-quinones undergo addition with conjugated dienes (Diels-Alder reaction):



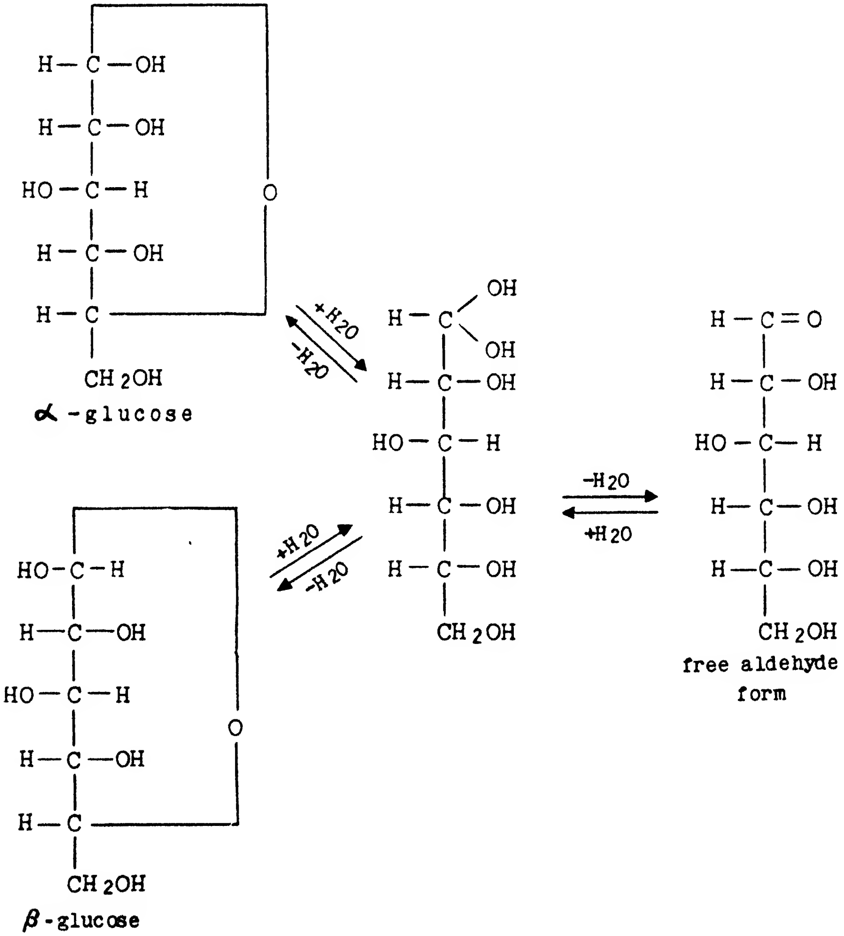
The end product still has an activated olefin linkage and can add a second molecule of the diene.

CHAPTER XIX

Reactions of Sugars

The sugars may be defined as mono aldo or mono keto polyhydric alcohols or anhydrides of two such molecules. The reactions of the carbonyl group and of the alcohol groups follow in general the mechanisms previously discussed for the reactions of the aldehydes, ketones, and alcohols.

The hexoses exist in the solid state as delta lactones. In aqueous solution the lactones are in equilibrium with the free aldehyde or ketone forms. In the case of *d* (+)-glucose this may be shown as follows:

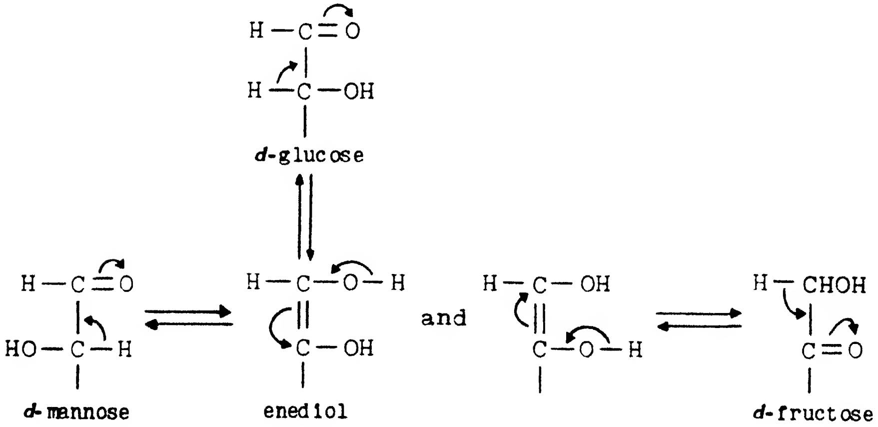


Similar equilibria may be formulated for *d* (+)-mannose, *d* (−)-fructose, and *d* (+)-galactose.

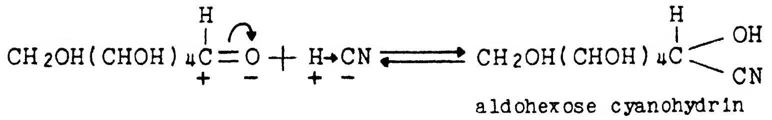
Mutarotation, which essentially consists of a change in optical rotation in aqueous solution to an equilibrium value, is exhibited by all hexoses which reduce Fehling's solution with the exception of certain ketoses. Two forms of glucose (α and β) can readily be obtained. When a sugar crystallizes from solution, it separates almost entirely in that form which is least soluble under the conditions used, the solution equilibrium then shifting to produce more of this isomer. The α-form of *d*-glucose is obtained as a monohydrate from a cold saturated aqueous solution and as anhydrous crystals from boiling ethyl alcohol. The β-form is obtained from a pyridine solution in the cold or from hot acetic acid solution. The specific rotations for the α- and β-forms in aqueous solution are +113° and +19° respectively. Each solution gradually changes to the equilibrium value of 52.5°. The conditions at equilibrium may be represented by the reversible interconversions shown above.

The delta lactones represent the most stable ring structures for the hexoses, and while gamma lactones may be formed under suitable conditions, they are not involved in the reaction mechanisms to be discussed.

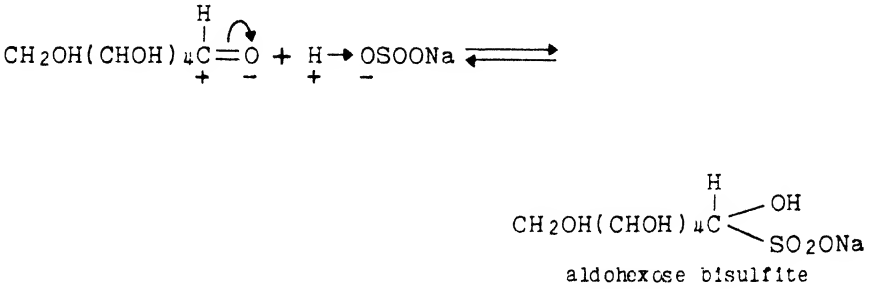
d-Glucose, *d*-mannose, or *d*-fructose, when treated with dilute sodium or potassium hydroxide solutions or pyridine, yield an equilibrium mixture of all three hexoses. This is made possible by the fact that they may form the same enediol forms and the fact that these sugars possess identical configurations around carbon atoms 3, 4, 5, and 6. This may be shown as follows:



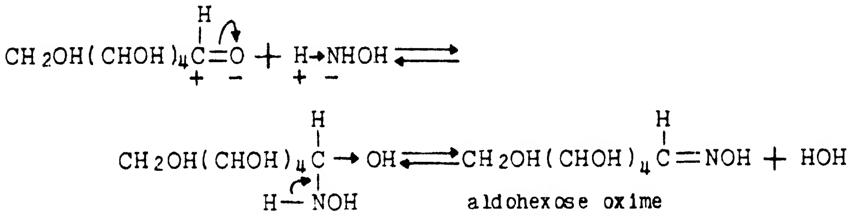
In aqueous solution the hexoses give many of the characteristic aldehyde and ketone reactions. For example, the addition of hydrogen cyanide yields cyanohydrins:



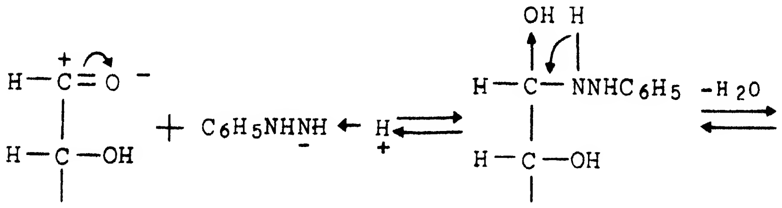
Sodium bisulfite adds slowly to the aldohexoses but not to the ketohexoses (102):

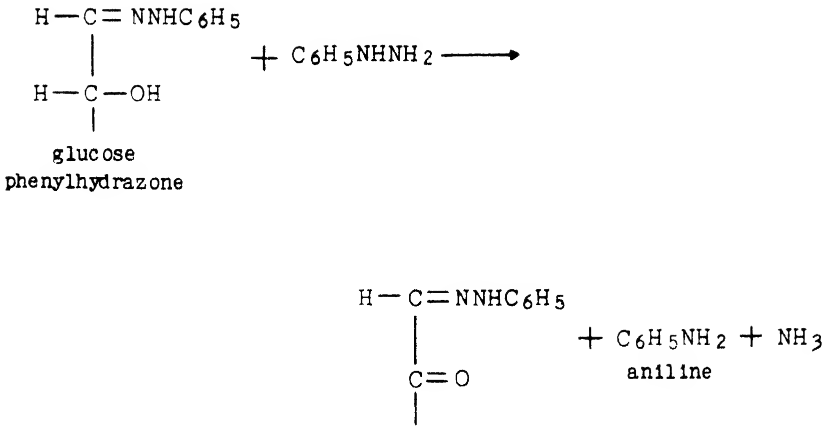


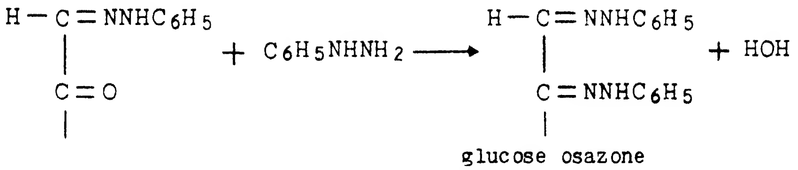
Hydroxylamine reacts with the hexoses to form oximes:



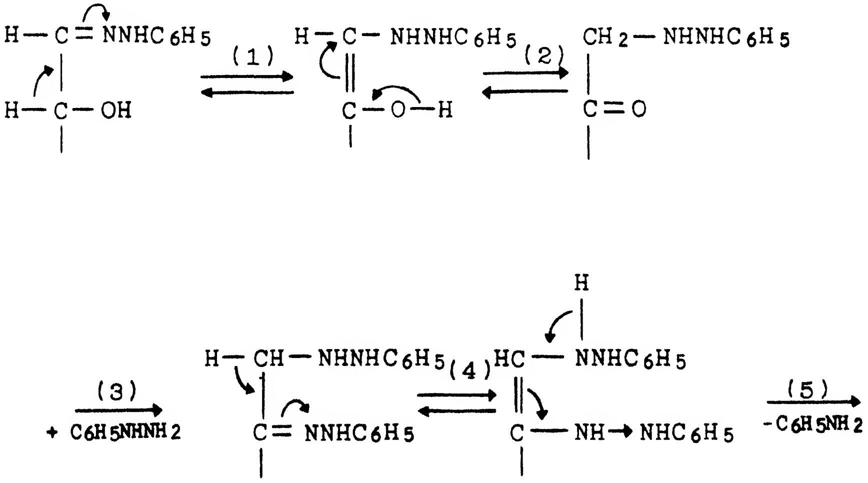
The aldoses react with one molecule of phenylhydrazine to form phenylhydrazones, but with excess phenylhydrazine (3 moles) the reaction takes an unusual course with the formation of osazones:

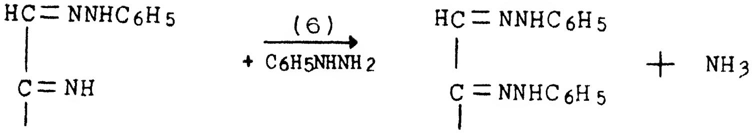




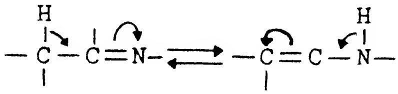


The first step consists of the usual reaction of phenylhydrazine with an aldehyde group. The second step involves the conversion of an alcohol group to a carbonyl group. The fact that the secondary alcohol group affected is the one adjacent to the original carbonyl group suggests that the initial formation of an enamine form may be necessary for the reaction to occur:





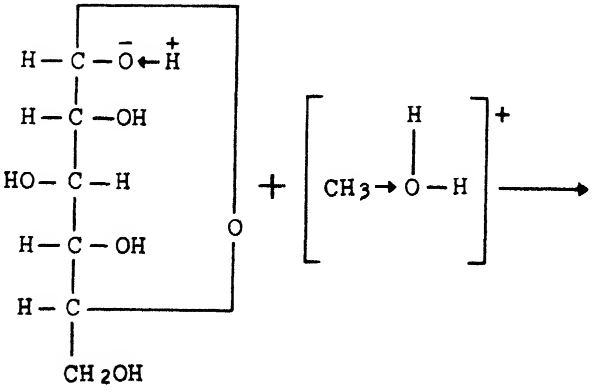
This course of reaction was originally advanced by Weygand in 1940. This mechanism may be interpreted on the basis of well-known reactions. The reversible formation of the enamine is to be expected:

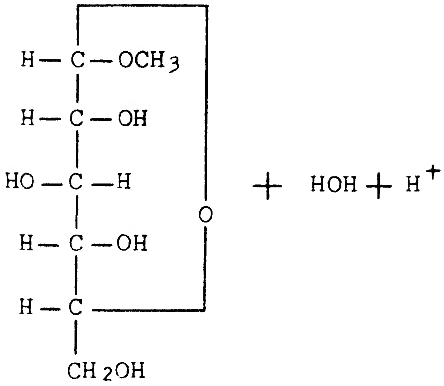


Examination of the structure of the enamine discloses the fact that an enol structure is also present. Step 2 then represents the reversible change of the enol to the keto form. Step 3 involves an aldol type of condensation of a second molecule of phenylhydrazine with the free carbonyl group. This is followed by an α,γ-shift of hydrogen in the resulting ketimine (step 4) and subsequently by the splitting out of aniline (step 5). The final step consists of an aldol type of condensation of a third molecule of phenylhydrazine with the imino grouping to form the osazone and ammonia.

d-Glucose, *d*-mannose, and *d*-fructose yield the same osazone. These hexoses possess identical configurations around carbon atoms 3, 4, 5, and 6 and during the reaction with phenylhydrazine the groups attached to carbon atoms 1 and 2 become identical, thus giving the same osazone.

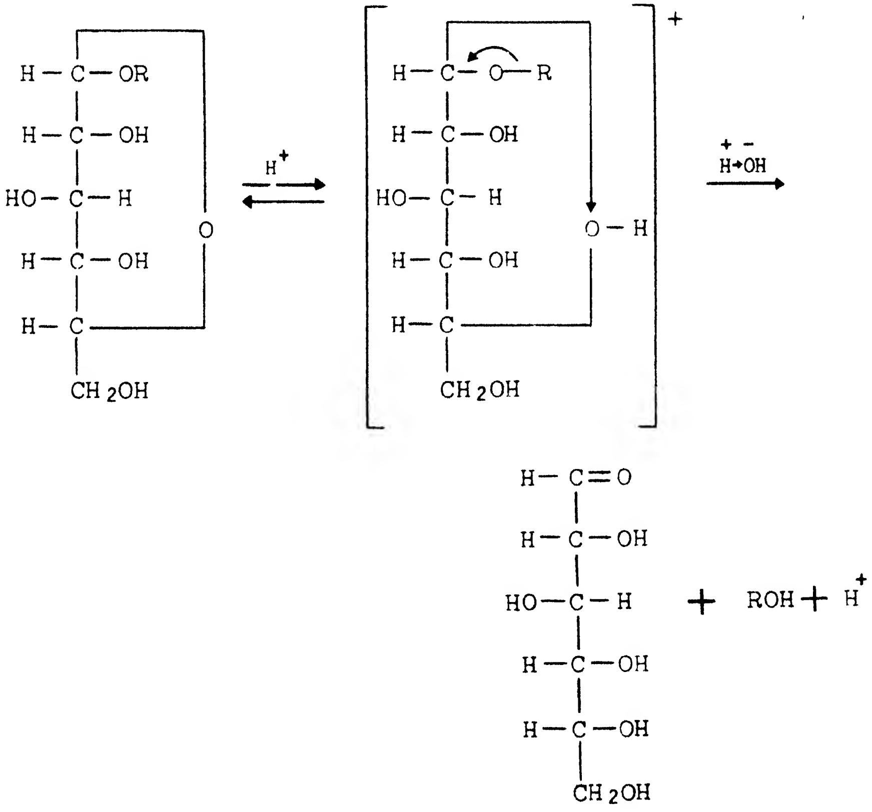
In anhydrous media, the reactions of the hexoses are characteristic of the lactone forms. Glucose, for example, when treated with methyl alcohol and hydrogen chloride yields alpha or beta methyl glucosides:





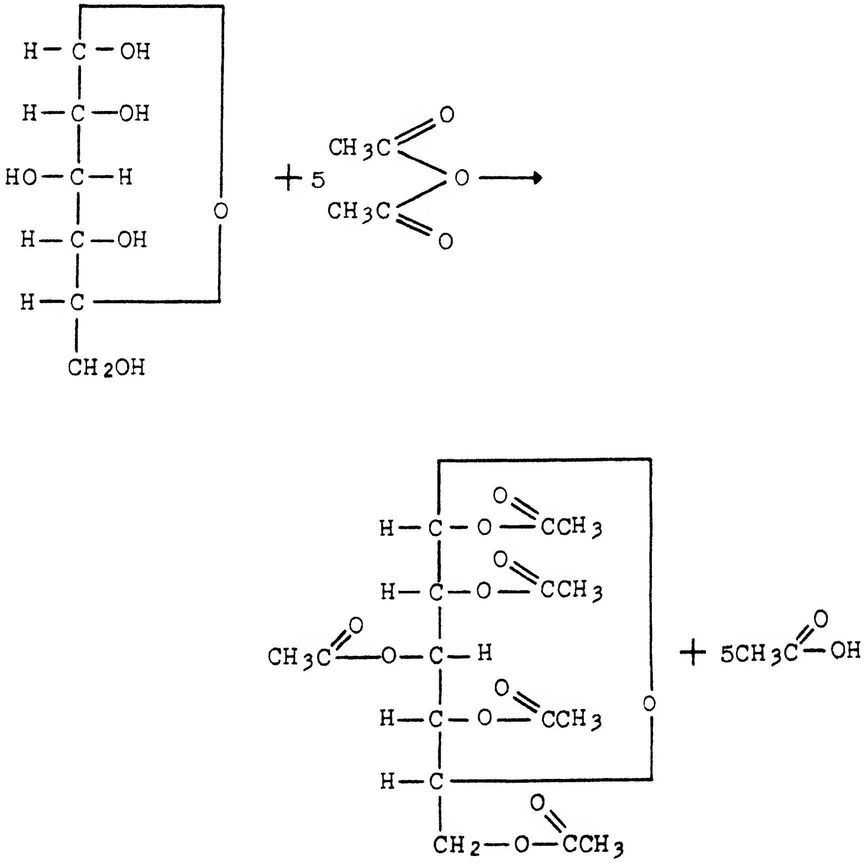
∝-methylglucoside

The other hexoses react similarly. The above mechanism is the one commonly used for the formation of ethers from alcohols. The acid-catalyzed hydrolysis of glucosides has been widely studied. It has been suggested (76) that the initial attack of the acid is not on the glucoside oxygen atom, but rather upon the lactone oxygen atom:



The acid hydrolyses of dissaccharides and polysaccharides to hexoses involve similar mechanisms since they also contain glycoside linkages.

With acetic anhydride, glucose forms a penta-acetate of the α- or β-form depending on the conditions used:

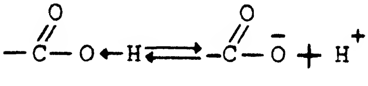


The reactions of acid anhydrides are discussed in Chapter XXI.

CHAPTER XX

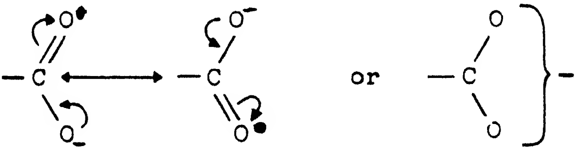
Reactions of Monobasic Acids

Saturated aliphatic acids. The carboxyl group, which is the characteristic functional group of the organic acids, is a composite group. The chief characteristic of this group is the tendency on the part of the hydrogen atom to separate as a proton:

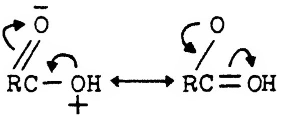


$$-\overset{O}{\overset{/\!/}{C}}-O\leftarrow H \rightleftarrows -\overset{O}{\overset{/\!/}{C}}-\bar{O} + H^{+}$$

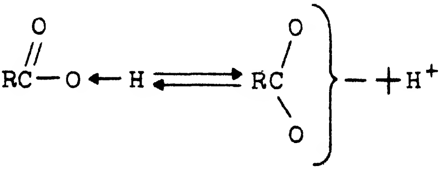
The acidic nature of the carboxyl group is due to the resonance energy of the carboxylate ion which serves to stabilize the ion. As a result of resonance, the carbonyl group of the composite carboxyl group shows little tendency to undergo the usual carbonyl reactions. Two unperturbed forms contribute to the actual state of the ion:



The undissociated carboxylic acids may also exhibit resonance but to a lesser extent, since the two unperturbed forms are not equivalent, that is, they are not of the same order of stability:

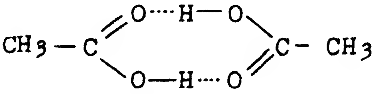


Since the ion is more stabilized through resonance than is the undissociated acid, the carboxyl group owes its acidity to this effect. Once the initial ionization has occurred

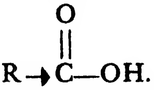


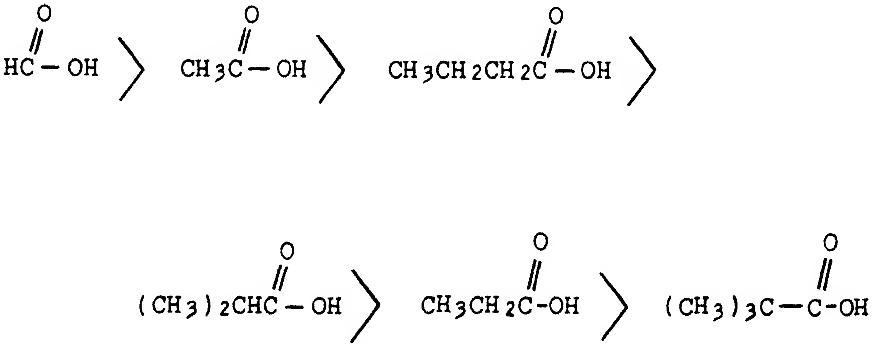
the resonance hybrid of the carboxylate ion, due to the distribution of the negative charge over both oxygen atoms, has a reduced attraction for the proton.

Acetic acid, and many of its homologs, exist as dimers in the absence of an ionizing solvent. The two molecules are held together through hydrogen bonding:



In the so-called hydrogen bond, the hydrogen atom acts to hold two other atoms together. Such bonds are strongest when the two atoms held together by the hydrogen atom are most electronegative (most electron attracting). They are always much weaker, however, than ionic or covalent bonds. It is believed that the atoms are held together by electrostatic attractions (3).

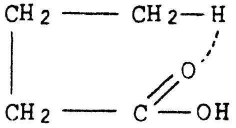
The electron-release effects of alkyl groups (as compared to hydrogen) have been referred to frequently in previous chapters. These inductive effects are noted also in the series of saturated monobasic acids. Replacement of the hydrogen atom of the H-C grouping in formic acid with an alkyl group produces a decrease in acid strength. The electron-release effect of the alkyl group opposes the resonance effect to which the acidity of the carboxyl group is ascribed,  $R\rightarrow\overset{\overset{O}{\|}}{C}—OH$. A comparison of the acid strengths of formic acid, acetic acid, propionic acid, *n*-butyric acid, isobutyric acid, and trimethylacetic acid



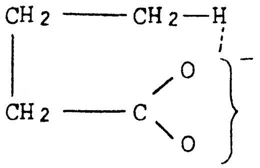
$$H\overset{\overset{O}{\|}}{C}-OH > CH_3\overset{\overset{O}{\|}}{C}-OH > CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}-OH >$$

$$(CH_3)_2CH\overset{\overset{O}{\|}}{C}-OH > CH_3CH_2\overset{\overset{O}{\|}}{C}\text{-}OH > (CH_3)_3C-\overset{\overset{O}{\|}}{C}\text{-}OH$$

discloses the fact that formic acid is the strongest and trimethylacetic acid the weakest acid in this particular group, as might be expected from a consideration of the inductive effects. It will be noted, however, that *n*-butyric acid and isobutyric acid occupy anomalous positions if inductive effects alone are operative (103). It has been suggested that the terminal methyl group of *n*-butyric acid is similar in its situation with the methyl group in *o*-methylbenzoic acid and consequently the anomalies shown by these acids have a common origin, namely, the formation of a hydrogen bond between the methyl group and the carboxyl group:

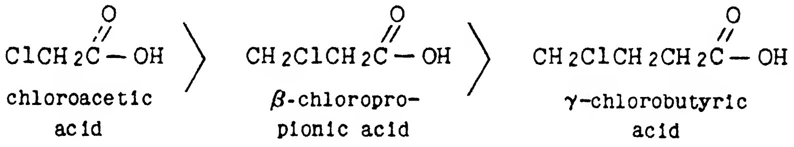


and



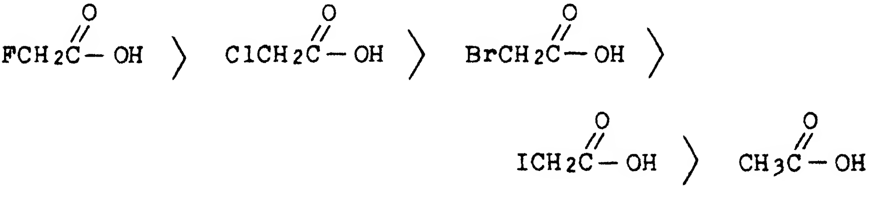
The formation of a hydrogen bond would tend to increase the electron attraction of the carbonyl group, thus assisting in the formation of the proton, and in the stabilization of the resulting anion. For the relatively high acid strength of isobutyric acid, it has been suggested that the branching of the chain permits a more frequent approach of the methyl groups to the carboxyl group and thus accounts for its position in the above series. It should be noted that the replacement of the hydrogen atom in formic acid with the methyl group produces a much greater decrease in acid strength than subsequent replacements of hydrogen atoms in acetic acid.

The presence of electron-attracting substituents such as the halogens results in increased acid strengths. The effect decreases as the distance between the halogen and carboxyl group increases:



$$\underset{\text{chloroacetic acid}}{ClCH_2\overset{\overset{O}{/\!/}}{C}-OH} > \underset{\beta\text{-chloropropionic acid}}{CH_2ClCH_2\overset{\overset{O}{/\!/}}{C}-OH} > \underset{\gamma\text{-chlorobutyric acid}}{CH_2ClCH_2CH_2\overset{\overset{O}{/\!/}}{C}-OH}$$

The inductive effect in this case, $Cl \leftarrow CH_2 \leftarrow \overset{\overset{O}{/\!/}}{C} \leftarrow O \leftarrow H$, enhances the resonance effect necessary for ionization. Fluorine exerts the most pronounced effect and iodine the least effect on the acid strength:



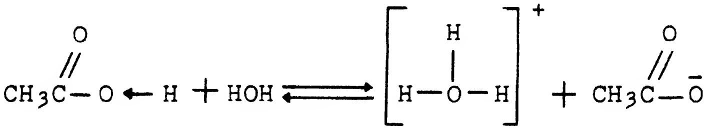
$$FCH_2\overset{\overset{O}{/\!/}}{C}-OH > ClCH_2\overset{\overset{O}{/\!/}}{C}-OH > BrCH_2\overset{\overset{O}{/\!/}}{C}-OH > ICH_2\overset{\overset{O}{/\!/}}{C}-OH > CH_3\overset{\overset{O}{/\!/}}{C}-OH$$

This is in accord with the relative electron-attracting powers of the halogens:

$$F > Cl > Br > I$$

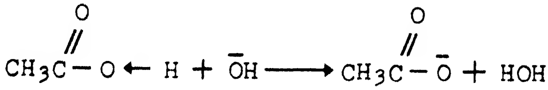
The hydroxyl group and alkoxy groups have the same general effect on the carboxy acids as the halogen substituents, but to a much smaller extent.

The ionization of acids in water and in other polar solvents involves the transfer of a proton from the carboxyl group to the solvent



$$CH_3\overset{\overset{O}{//}}{C}-O \leftarrow H + HOH \rightleftharpoons \left[\begin{array}{c} H \\ | \\ H-O-H \end{array}\right]^+ + CH_3\overset{\overset{O}{//}}{C}-\bar{O}$$

with the formation of a hydroxonium ion and a carboxylate ion. The change does not take place to any great extent, for the organic acids as a rule are weak acids. The proton transfer takes place rapidly when the acids are treated with stronger bases, and salts are formed:

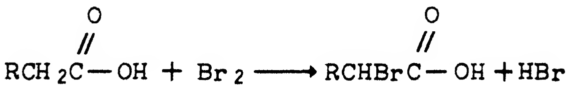


$$CH_3\overset{\overset{O}{//}}{C}-O \leftarrow H + \bar{O}H \longrightarrow CH_3\overset{\overset{O}{//}}{C}-\bar{O} + HOH$$

Since the hydroxyl ion is a much stronger base than the carboxylate ion, the reaction is practically complete.

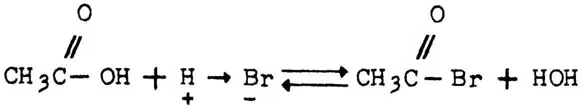
The reactions of carboxy acids with alcohols to form esters have been discussed previously under the alcohols. It is interesting to note that the hydrogen of the carboxyl group is not initially involved in the mechanism of ester formation.

The direct chlorination or bromination of the saturated monobasic aliphatic acids leads to the formation of alpha halogen substituted acids:

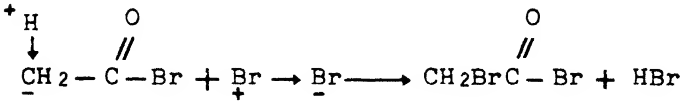


$$RCH_2\overset{\overset{O}{//}}{C}-OH + Br_2 \longrightarrow RCHBr\overset{\overset{O}{//}}{C}-OH + HBr$$

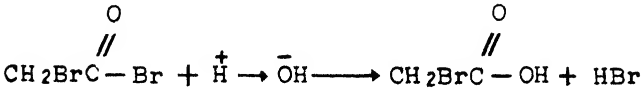
This bears a formal resemblance to the halogenation of aldehydes and ketones. However, it has been noted that, unlike the bromination of aldehydes and ketones, the bromination of acetic acid is dependent on the concentration of bromine. Furthermore, the substitution is catalyzed by the presence of a small amount of red phosphorus or by the presence of hydrogen halides. It has been shown that the effect of the hydrogen halides is specific and is not exerted by other acids (104). The catalytic order, $CH_3\overset{\overset{O}{//}}{C}-Br > HBr > HCl$, has been established for the bromination of acetic acid. This suggests that the acyl bromide is the real catalyst, and the hydrogen halides owe their effect to the formation of acyl halides. Where hydrogen bromide is used as the catalyst, the reaction may be shown as follows:



$$CH_3\overset{O}{\overset{//}{C}}-OH + \underset{+}{H} \rightarrow \underset{-}{Br} \rightleftharpoons CH_3\overset{O}{\overset{//}{C}}-Br + HOH$$



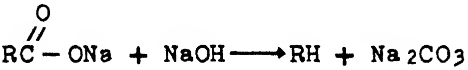
$$\overset{+H}{\overset{\downarrow}{\underset{-}{CH_2}}}-\overset{O}{\overset{//}{C}}-Br + \underset{+}{Br} \rightarrow \underset{-}{Br} \longrightarrow CH_2Br\overset{O}{\overset{//}{C}}-Br + HBr$$



$$CH_2Br\overset{O}{\overset{//}{C}}-Br + \overset{+}{H} \rightarrow \overset{-}{OH} \longrightarrow CH_2Br\overset{O}{\overset{//}{C}}-OH + HBr$$

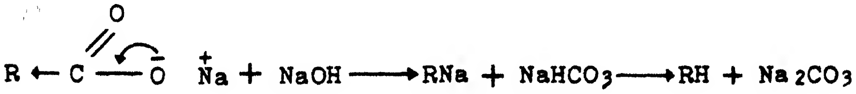
The electron attraction of the $-\overset{O}{\overset{//}{C}}-Br$ group should be greater than that of the $-\overset{O}{\overset{//}{C}}-OH$ group, thus increasing the tendency of the alpha hydrogen to ionize. Whether or not the second step involves the reaction of bromine with the enol form of the acid is not known with certainty. Red phosphorus is a more active catalyst than hydrogen bromide, since it facilitates the formation of the necessary acyl halide.

The decarboxylation of the monobasic acids may be effected by heating a dry mixture of a sodium salt with sodium hydroxide:



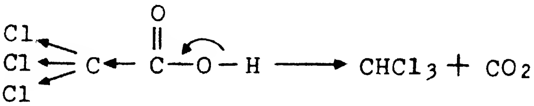
$$R\overset{O}{\overset{//}{C}}-ONa + NaOH \longrightarrow RH + Na_2CO_3$$

In this reaction the extra hydrogen atom necessary for the formation of the alkane hydrocarbon comes indirectly from the sodium hydroxide:



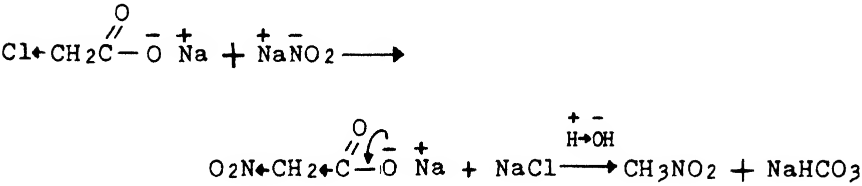
$$R \leftarrow \overset{O}{\overset{//}{C}} \overset{\curvearrowleft}{-} \overset{-}{O}\ \overset{+}{Na} + NaOH \longrightarrow RNa + NaHCO_3 \longrightarrow RH + Na_2CO_3$$

The salt would furnish the electron-rich anion in which the electron shifts shown above may occur. A carbanion or a sodium alkyl may be formed as an intermediate. The latter would then react with the sodium bicarbonate to form the alkane and sodium carbonate. Although there is no direct evidence for this course of reaction, the above mechanism is supported by the fact that the presence of electron-attracting groups on the alpha carbon atom facilitates decarboxylation. Thus trichloroacetic acid when refluxed in water solution undergoes decarboxylation:



$$\mathrm{Cl_3C{\leftarrow}C(=O){-}O{-}H \longrightarrow CHCl_3 + CO_2}$$

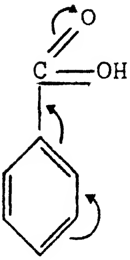
A similar mechanism accounts for the Kolbe method for preparing nitromethane from chloroacetic acid. An aqueous solution of sodium chloroacetate is treated with sodium nitrite and the mixture warmed to start the reaction. The reaction is exothermic and once started needs no further external heating:



$$\mathrm{Cl{\leftarrow}CH_2C(=O){-}\overset{-}{O}\,\overset{+}{Na} + \overset{+}{Na}\overset{-}{NO_2} \longrightarrow O_2N{\leftarrow}CH_2{\leftarrow}C(=O){-}\overset{-}{O}\,\overset{+}{Na} + NaCl \xrightarrow{\overset{+}{H}\to\overset{-}{OH}} CH_3NO_2 + NaHCO_3}$$

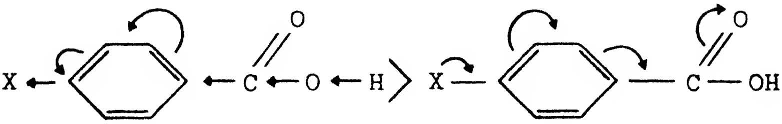
In general, the α-nitroacids decarboxylate so readily that they cannot be isolated. Their esters, however, may be prepared. The β-nitroacids are more stable than the α-isomers as would be expected since the inductive electron-attracting effect of the nitro group is weakened by its greater distance from the carboxyl group. The fact that ethyl nitroacetate is relatively stable compared to the free acid appears to support the "ionic" mechanism shown above.

Aromatic acids. The resonance mechanism, used to explain the acid nature of the aliphatic acids, may be applied here also. Benzoic acid ionizes to a greater extent than acetic acid, indicating a greater electron-release effect for the methyl group than for the phenyl group. Both acids are much weaker than formic acid. The effect of the phenyl group is not explained entirely on the basis of a weak inductive effect. It has been suggested that the phenyl group may exert an electron-release or an electron-attracting action, depending upon the electron demands of the particular system attached to the phenyl group. In the case of benzoic acid, electron displacements take place in the direction of the carboxyl group which contains the electron-attracting carbonyl group:



This opposes the resonance effect necessary for ionization, thus stabilizing the molecule rather than the ion.

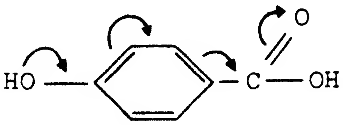
The relative strengths of the substituted aliphatic acids are dependent upon the inductive effects of the substituents. In the case of the substituted aromatic acids where the substituents are attached to the aromatic ring, the resonance effect must be considered also. It has been noted above that the halogens are strongly electron-attracting and as a result the halogen-substituted acetic acids are stronger than acetic acid, and the acid strengths decrease in the order of decreasing inductive effects, F > Cl > Br > I. The strengths of the halogen-substituted benzoic acids, however, are not of the order which would be expected on the basis of inductive effects alone. It will be remembered that the halogens are *o,p*-directing, and this property is not dependent upon their inductive effects, but rather on the resonance of their unshared electrons with the aromatic ring. While the halogen-substituted benzoic acids are stronger than benzoic acid, the differences are somewhat smaller than those noted with the corresponding halogen-substituted acetic acids. This again indicates opposition to the inductive effect by a resonance effect, and thus the increase in acid strength is less than expected.



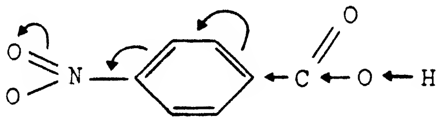
The ortho halogen-substituted benzoic acids are considerably more acidic than the meta and para isomers. This agrees with the fact that the inductive influence of a substituent is greater the closer it is to the carboxyl group. The fact that the fluorobenzoic acids are less acidic than the other halogen-substituted benzoic acids (103) is in agreement with the belief that the electromeric effects of the halogens decrease in the order, F > Cl > Br > I.

Hydroxyl and alkoxy groups in the ortho and meta positions increase the acid strength of benzoic acid and cause a decrease when in the para position. The ortho derivatives are more acidic than the meta compounds.

In these two types the inductive effects appear to predominate, resulting in an increase in acid strength. The resonance effect predominates in the para acids and here a decrease in acid strength is noted:



The nitro group always increases the acid strength of benzoic acid regardless of its position, the increase being greatest for *o*-nitrobenzoic acid. In the case of the nitrobenzoic acids, the inductive and resonance effects operate in the same direction. Since the resonance effect has no influence on the meta position, the para acid is stronger than the meta acid:

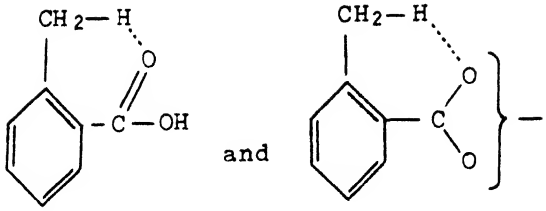


Other electron-attracting substituents such as —COR and —COOR behave similarly.

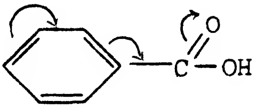
As previously noted, the replacement of the hydrogen atom in formic acid with various alkyl groups results in decreased acid strength. The decreases noted are related to the relative electron-release (inductive) effects of the alkyl groups used. The effects of alkyl groups in alkyl-substituted benzoic acids, on acid strength, are more difficult to predict. They exhibit two effects, both of which are electron releasing, the inductive and resonance (hyperconjugation) effects.

The *p*-alkyl-substituted benzoic acids are somewhat weaker acids than the parent acid, as might be expected. The relative electron-release effects of the alkyl groups used, however, follow a different order than that noted for the alkyl-substituted formic acids, namely, $(CH_3)_3C \rangle CH_3 \rangle CH_3CH_2 = (CH_3)_2CH$ (105). In this series both the inductive and resonance effects are operative and it is not easy to predict which one will predominate in any given case.

o-Methylbenzoic acid is reported to be a somewhat stronger acid than benzoic acid. This is an unexpected finding in view of the electron-release character of this group and indicates the presence of an additional factor. It has been suggested that the unshared electrons on a carbonyl oxygen atom may interact with a methyl group occupying the ortho position and form a hydrogen bond (see p. 179):

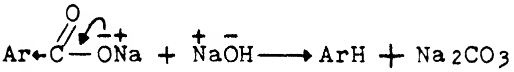


The reactions of the aromatic acids are similar to those of the aliphatic acids. The carboxyl group is a meta-directing group



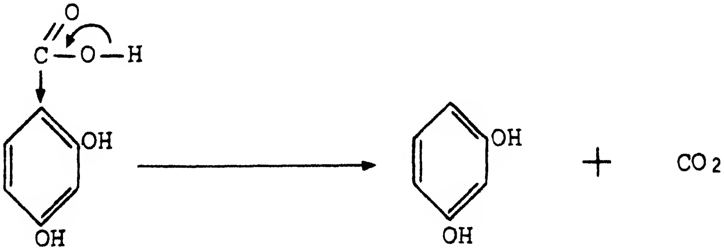
since it tends to decrease electron availability more at the ortho and para positions than at the meta positions, and electrophilic reagents therefore react at the latter positions.

The aromatic monobasic acids, similar to the aliphatic acids, may be decarboxylated by heating their sodium salts with sodium hydroxide:

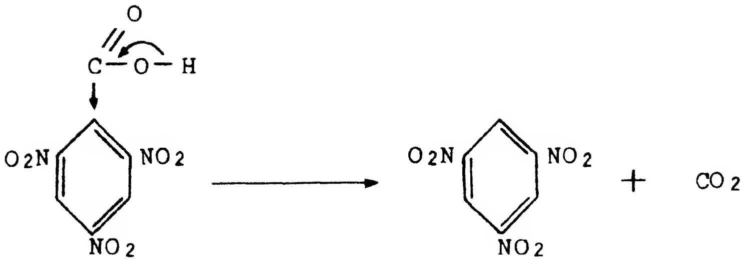


$$\mathrm{Ar}\leftarrow\overset{O}{\overset{\|}{C}}-\overset{-\,+}{\mathrm{ONa}} + \overset{+\,-}{\mathrm{NaOH}} \longrightarrow \mathrm{ArH} + \mathrm{Na_2CO_3}$$

It is probable that the same mechanism holds for both the aliphatic and aromatic series.. In general the presence of two or more electron-attracting substituents in the aromatic ring facilitates decarboxylation. Thus 2,4-dihydroxybenzoic acid is converted into resorcinol by boiling its dilute aqueous solution:



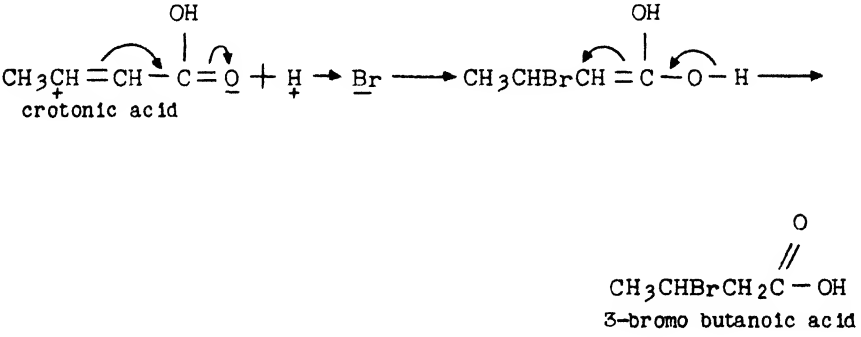
Similarly gallic acid is readily converted into pyrogallol. Another well-known example is the conversion of 2,4,6-trinitrobenzoic acid to 2,4,6-trinitrobenzene:



Aromatic acids which lose carbon dioxide relatively easily may be decarboxylated by heating with amines such as pyridine, dimethylaniline, or quinoline. The amines form salts with the acids and thus increase the availability of the anions. This again points to an "ionic" mechanism for these reactions.

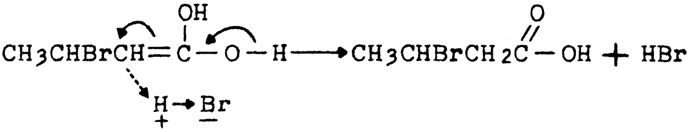
The effects of substituents in the ring on ease of decarboxylation are more difficult to predict than in the case of substituted, saturated aliphatic acids. In the latter series only inductive effects need be considered. This simple picture is complicated in the aromatic series by the resonant nature of aromatic ring systems.

Unsaturated monobasic acids. The addition reactions of the α,β-olefinic acids resemble in some ways the reactions noted for the α,β-unsaturated aldehydes and ketones. The addition of hydrogen bromide, for example, yields β-bromo acids:



$$CH_3\underset{+}{C}H=CH-\overset{OH}{\overset{|}{C}}=\underset{-}{O}+\underset{+}{H}\rightarrow\underset{-}{Br}\longrightarrow CH_3CHBrCH=\overset{OH}{\overset{|}{C}}-O-H\longrightarrow CH_3CHBrCH_2\overset{O}{\overset{//}{C}}-OH$$

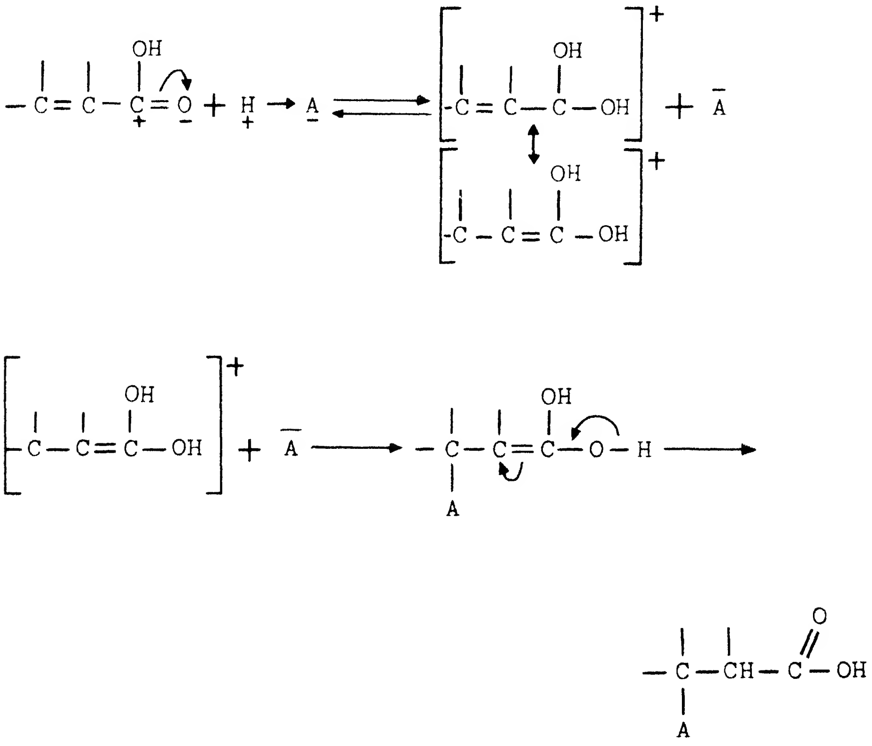
Since, in general, excess hydrogen bromide would be present, the second step would be more accurately shown as follows:



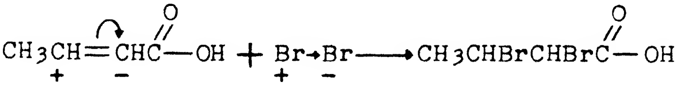
$$CH_3CHBrCH=\overset{OH}{\overset{|}{C}}-O-H\longrightarrow CH_3CHBrCH_2\overset{O}{\overset{//}{C}}-OH+HBr$$

$$\underset{+}{H}\rightarrow\underset{-}{Br}$$

The halogens, however, add more slowly to α,β-unsaturated acids than they do to isolated olefin linkages. This difference is explained by the nature of the system involved, $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$. The oxygen atom is the most electronegative atom in the molecule and would be expected to offer the greatest attraction for electrophilic reagents of the type $\overset{+}{H}\rightarrow\overset{-}{A}$:



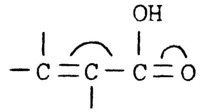
This mechanism does not exclude direct addition to the double bond, but restricts it to those electrophilic reagents which are not attracted by oxygen. The halogens belong in the latter class:



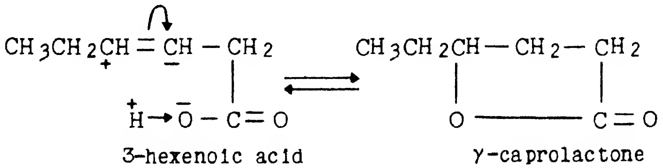
2,3-dibromobutanoic acid

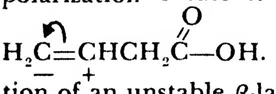
The slower addition of bromine to such an unsaturated bond is probably due to the fact that the nucleophilic character of the linkage is reduced through its conjugation with the carbonyl group.

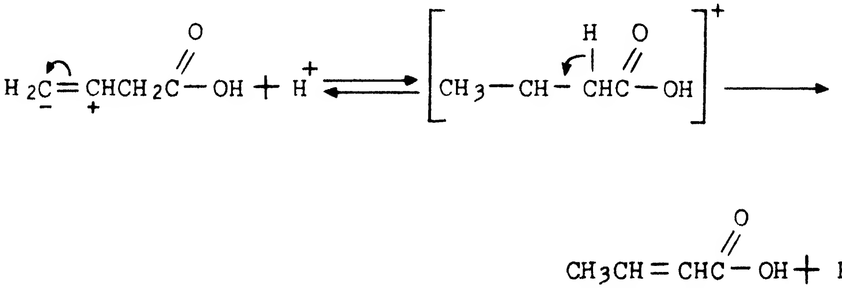
Esterification of the α,β-unsaturated acids takes place less readily than with the corresponding saturated acids or the unsaturated acids in which the double bond is further removed from the carboxyl group. This decreased activity of the carboxyl group is to be expected on the basis of the Lowry mechanism for esterification (see under alcohols) since the electrophilic character of the carbon atom of the carbonyl group would be weakened by conjugation with the olefin linkage:



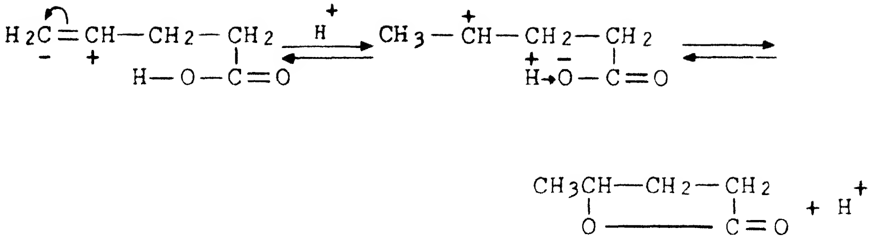
The β,γ and γ,δ-unsaturated acids are converted into lactones by sulfuric acid. This may be shown as follows (76):



The sulfuric acid serves to facilitate the necessary polarization of the olefin bond and furnishes a proton to add to the polarized bond. The important role played by electron-release effects on the polarization is shown by examination of the following examples. 3-Butenoic acid (vinylacetic acid) when heated with 50 per cent sulfuric acid is converted into crotonic acid instead of a γ-lactone. The addition of hydrogen bromide to 3-butenoic acid gives only 3-bromobutanoic acid. These reactions indicate that the β,γ double bond is no longer under the influence of the carboxyl group but rather under the influence of electron-release effects of groups on the γ-carbon atom alone. In this case, the manner in which polarization occurs is such as to make the γ-carbon atom negative,  $\overset{-}{H_2C}{=}\overset{+}{C}HCH_2C(=O){-}OH$. This polarization is that required for the formation of an unstable β-lactone, and it is not surprising that the tautomeric change to crotonic acid occurs instead:

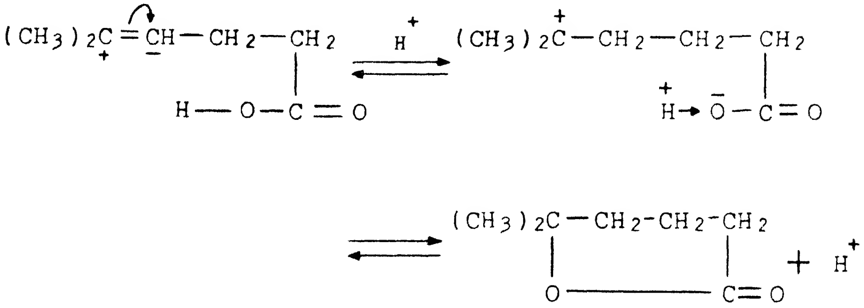


With γ,δ-acids of the type 4-pentenoic acid, the polarization is such that γ-lactones are formed:



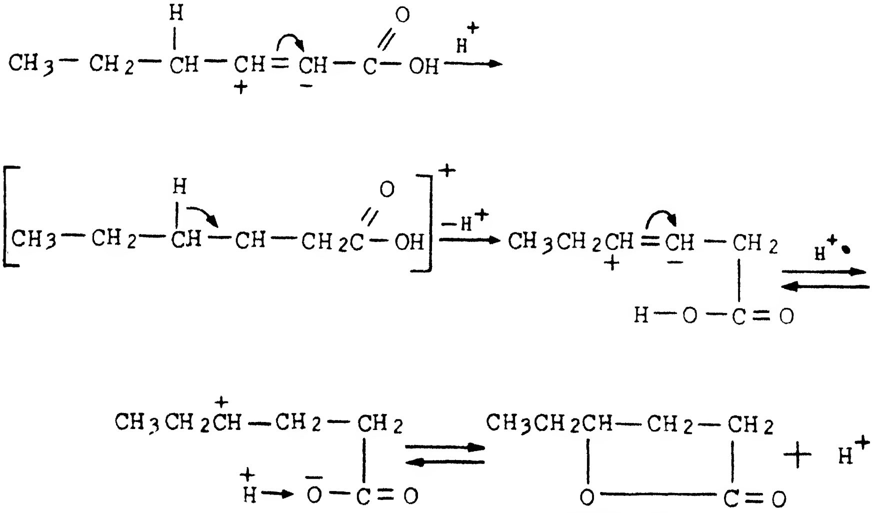
γ-valerolactone

However, with 5-methyl-4-hexenoic acid, a δ-lactone is formed:



In the latter case the electron-release effects of the two methyl groups control the polarization.

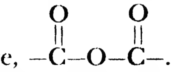
Certain of the α,β-unsaturated acids have been found to yield the same lactone as the isomeric β,γ-acid. The reaction takes place less readily since the α,β-acid must isomerize to the β,γ-acid before lactone formation occurs:



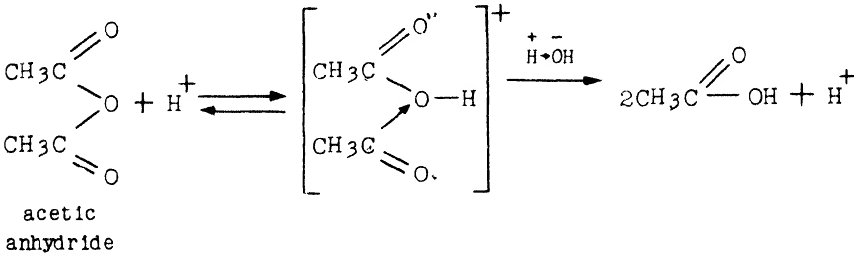
γ-caprolactone

CHAPTER XXI

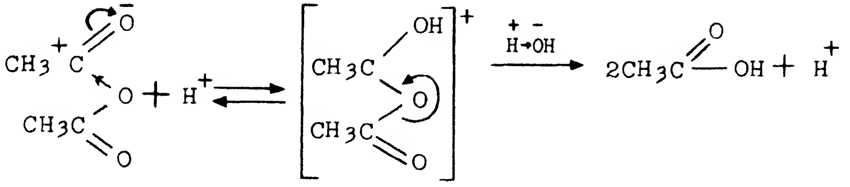
Reactions of Derivatives of the Monobasic Acids

Acid anhydrides. The anhydride group is a composite group consisting of two carbonyl groups joined through an ether linkage,  $-\overset{\overset{\displaystyle O}{\|}}{C}-O-\overset{\overset{\displaystyle O}{\|}}{C}-$. The characteristic reactions of this group are hydrolysis, alcoholysis, and ammonolysis. These reactions involve a cleavage of a carbon-to-oxygen bond, a type of reaction which was noted for the simple ethers. In the case of the anhydrides, however, the cleavage takes place much more readily than with the ethers.

It is known that the hydrolysis of anhydrides is catalyzed by acids (106). Acid hydrolysis has been represented as follows (76):

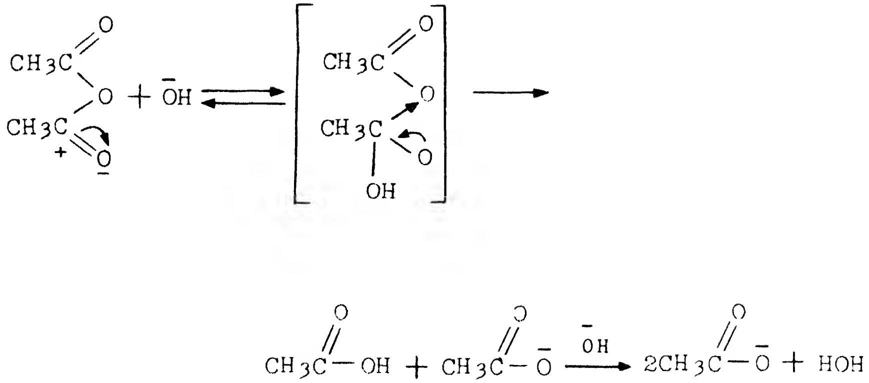


The singly linked oxygen atom in the anhydrides, because of the electron attraction of the two adjacent carbonyl groups, would be expected to have weaker basic properties than the oxygen atom of an ether and should have less attraction for a proton. The fact that the anhydrides are more readily hydrolyzed is better explained by attachment of the proton to the carbonyl oxygen atom:



The electron-deficient carbon atom in the intermediate carbonium ion is the driving force for the resulting cleavage. It is probable that the hydroxyl ion starts to add before the cleavage is completed.

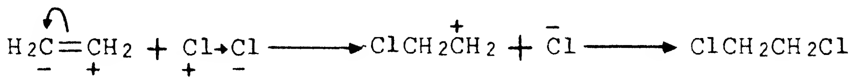
Base-catalyzed hydrolysis of the aliphatic acid anhydrides is too rapid to measure. Basic hydrolysis is believed to involve addition of the nucleophilic anion at the carbon atom of the carbonyl group:



$$CH_3\overset{O}{C}{-}OH + CH_3\overset{O}{C}{-}\bar{O} \xrightarrow{\bar{O}H} 2CH_3\overset{O}{C}{-}\bar{O} + HOH$$

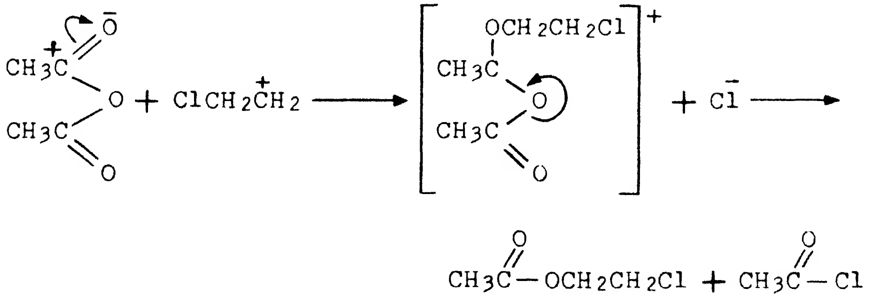
Hydrolysis by water alone probably proceeds through the basic mechanism. It will be noted that the addition of the anion to the one carbonyl carbon atom neutralizes the electron attraction of this carbonyl group. The remaining free carbonyl group retains its electron-attracting power and the unbalance thus created makes cleavage possible. This cleavage is further facilitated by the ease with which the first carbonyl carbon atom can recover a pair of electrons from the attached electronegative oxygen atom.

The addition of chlorine to ethylene, in acetic anhydride as solvent, has been reported to give β-chloroethylacetate and ethylene chloride as the chief products (107). This reaction is of interest for two reasons: (1) the results are in agreement with the two-step mechanism accepted for addition to olefins; and (2) the reaction appears to be similar to the acid-catalyzed hydrolysis of anhydrides with a carbonium ion taking the place of a proton. This may be shown as follows:



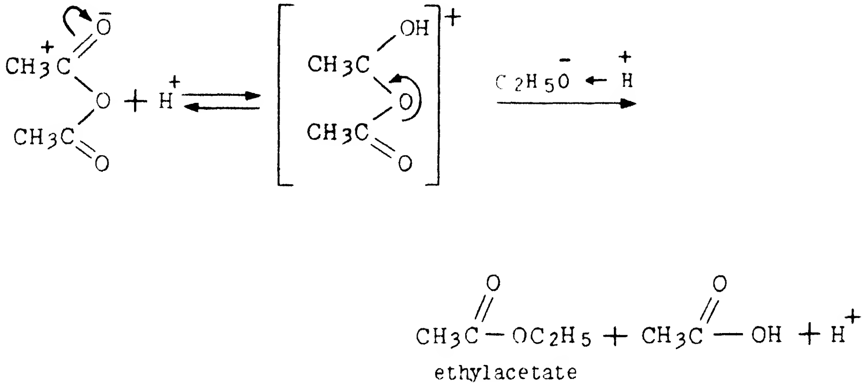
$$\underset{-}{H_2C}{=}\underset{+}{CH_2} + \underset{+}{Cl}{\rightarrow}\underset{-}{Cl} \longrightarrow ClCH_2\overset{+}{C}H_2 + \bar{Cl} \longrightarrow ClCH_2CH_2Cl$$

and

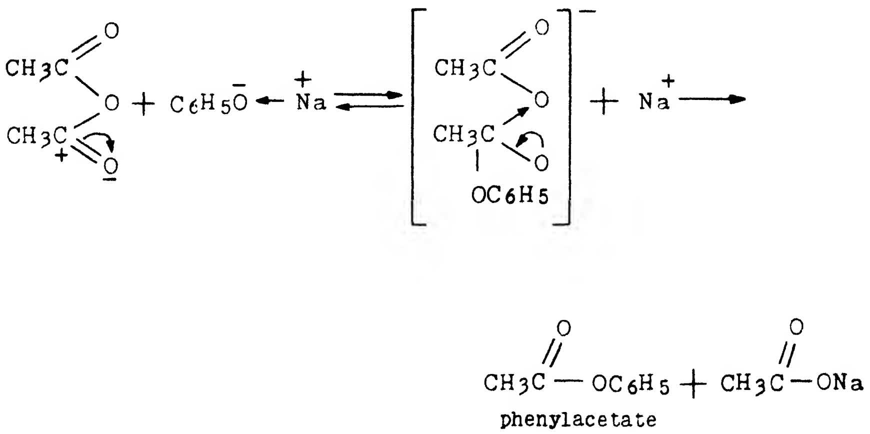


Similar results were obtained when methylacetate was used in place of the acetic anhydride except that methyl chloride was formed in the last step rather than acetyl chloride.

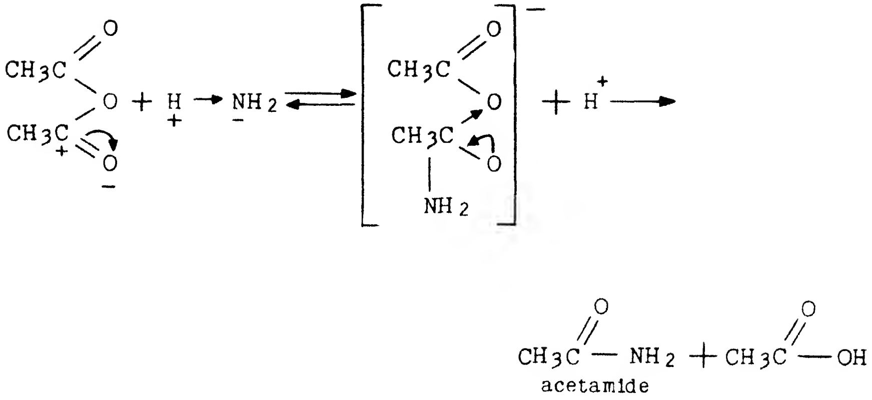
The reactions of acid anhydrides with alcohols and phenols are similar to the hydrolysis reactions noted above. They are catalyzed by acids, especially by strong acids such as sulfuric acid, and also by bases such as sodium acetate and tertiary amines. Acid-catalyzed acetylation may be shown as follows:

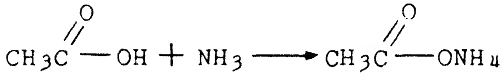


A simple method for the acetylation of phenols (108) consists in treating an aqueous solution of the sodium phenolate with acetic anhydride. The ease with which this reaction occurs may be attributed to an increase in concentration of the nucleophilic phenoxyl anion:

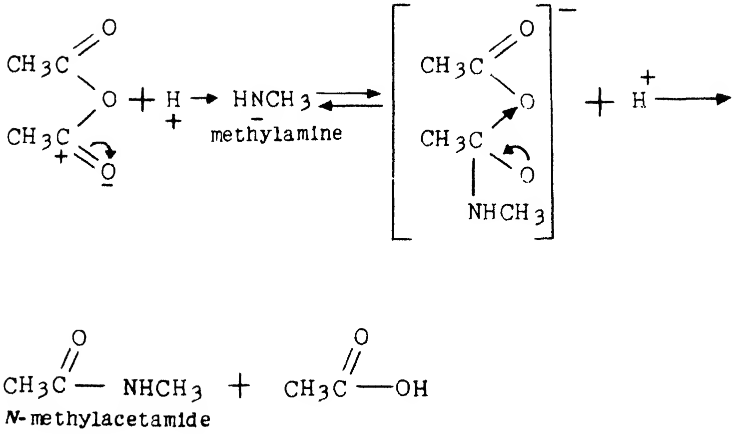


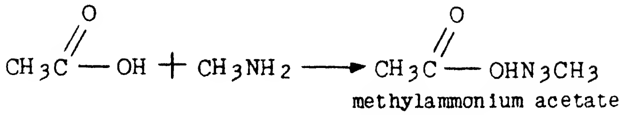
The reactions of the anhydrides with ammonia and amines are also similar to the reaction with water:





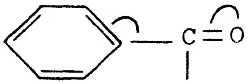
$$CH_3C(=O)—OH + NH_3 \longrightarrow CH_3C(=O)—ONH_4$$



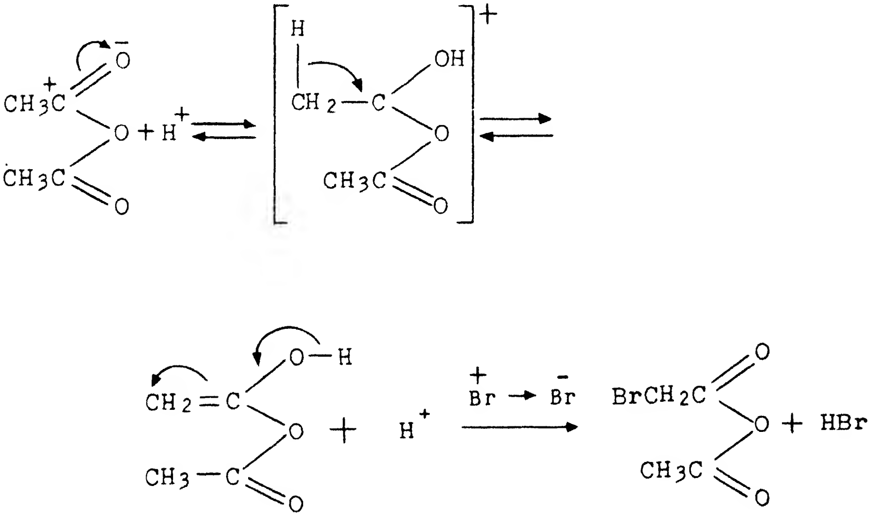


$$CH_3C(=O)—OH + CH_3NH_2 \longrightarrow CH_3C(=O)—OHN_3CH_3$$

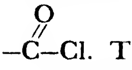
The aromatic acid anhydrides, such as benzoic anhydride, behave similarly except that they are not so reactive as the low molecular weight aliphatic anhydrides. The decreased activity of the aromatic acid anhydrides may be explained by the resonant nature of these molecules. The aromatic ring acts as an electron-release group when attached to an electron-attracting group such as a carbonyl group, thus serving to reduce the electrophilic activity of the carbonyl carbon atom:



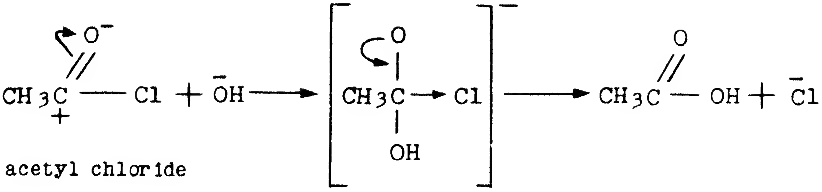
The halogenation of aliphatic acid anhydrides is catalyzed by strong acids. Kinetic studies have shown that the bromination of acetic anhydride may proceed through the enol form, similar to the mechanism established for acetone:



bromoacetic anhydride

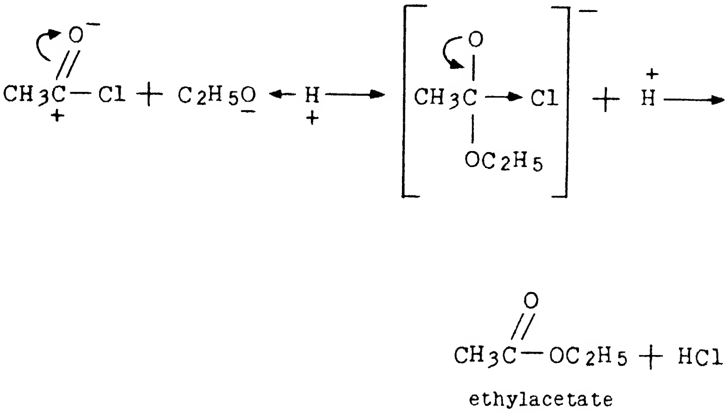
Acyl chlorides. The acid chlorides also contain a composite functional group,  $-\overset{O}{\overset{/\!/}{C}}-Cl$. They undergo the same type reactions as the anhydrides, namely, hydrolysis, alcoholysis, and ammonolysis. However, due to the strong electron attraction of the chlorine atom, the addition of nucleophilic reagents to the carbon atom of the carbonyl group takes place more readily than in the case of the anhydrides.

The hydrolysis of an acid chloride is not catalyzed by acids, and the base-catalyzed reaction occurs too rapidly for kinetic study. Hydrolysis with water alone or with bases may be written as follows:

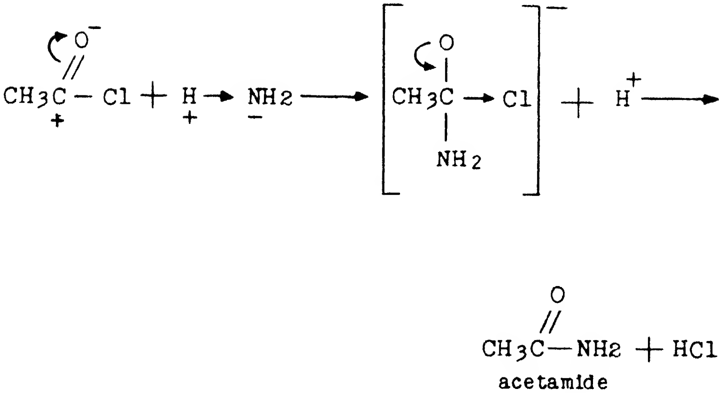


$$\underset{+}{CH_3C}(=O^-)-Cl + \overset{-}{O}H \longrightarrow \left[CH_3C(O)(OH) \rightarrow Cl \right]^- \longrightarrow CH_3C(=O)-OH + \overset{-}{Cl}$$

Alcoholysis and ammonolysis may be written in a similar manner:



$$\underset{+}{CH_3C}(=O^-)-Cl + \underset{-}{C_2H_5O} \leftarrow \underset{+}{H} \longrightarrow \left[CH_3C(O)(OC_2H_5) \rightarrow Cl \right]^- + \overset{+}{H} \longrightarrow CH_3C(=O)-OC_2H_5 + HCl$$



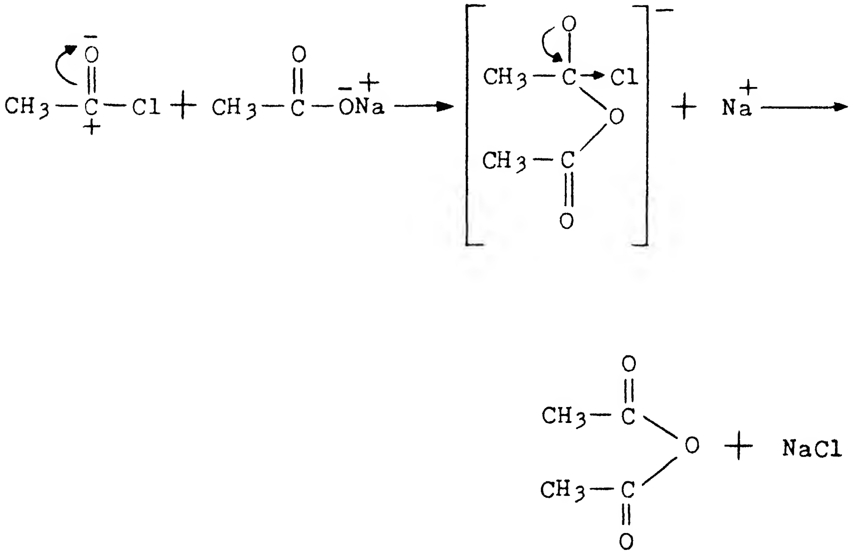
$$\underset{+}{CH_3C}(=O^-)-Cl + \underset{+}{H} \rightarrow \underset{-}{NH_2} \longrightarrow \left[CH_3C(O)(NH_2) \rightarrow Cl \right]^- + \overset{+}{H} \longrightarrow CH_3C(=O)-NH_2 + HCl$$

$$HCl + NH_3 \longrightarrow NH_4Cl$$

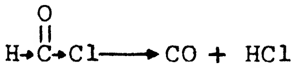
It will be noted that in the above examples the addition of an anion to the carbonyl carbon atom reduces the electron attraction of that atom. This serves, in effect, to enhance the electron attraction of the halogen. The cleavage of the carbon-halogen bond is further assisted by the ease with which the carbonyl carbon atom can recover an electron pair from the electronegative oxygen atom.

It is a well-known fact that in the alcoholysis of acyl chlorides the formation of hydrogen chloride tends to retard the rate of the reaction. This may be attributed to a decrease of the alkoxyl anion concentration as a result of the accumulation of protons. The promoting action of pyridine when used as a solvent for the alcoholysis of acyl chlorides may be associated with its ability to combine with hydrogen chloride.

The preparation of acid anhydrides from acyl halides and the corresponding sodium salts of the acids may be illustrated in a similar manner. The first step consists of the addition of an anion to the carbonyl carbon atom of the acyl chloride:

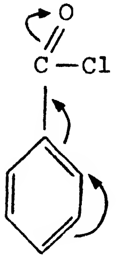


The first acyl chloride in the series, formyl chloride, has never been isolated. A possible explanation for its instability lies in the fact that the hydrogen atom is attached to a strong electron-attracting group and readily splits off as a proton:



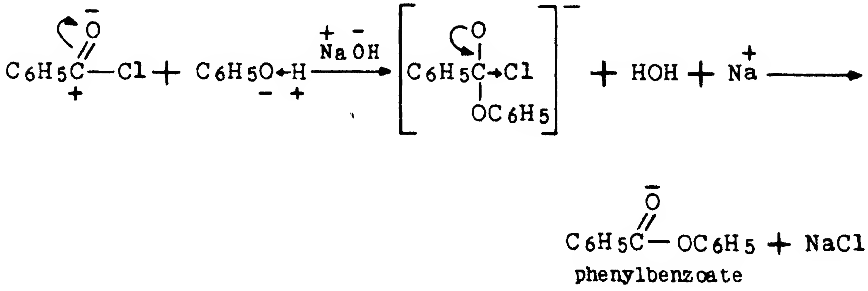
$$H\rightarrow\overset{\overset{\displaystyle O}{\|}}{C}\rightarrow Cl \longrightarrow CO + HCl$$

The aromatic acid chlorides give the same reactions, but they are less reactive. A possible explanation for the reduced activity of benzoyl chloride, for example, lies in the fact that the phenyl group acts as an electron-release group when attached to an electron-attracting group:

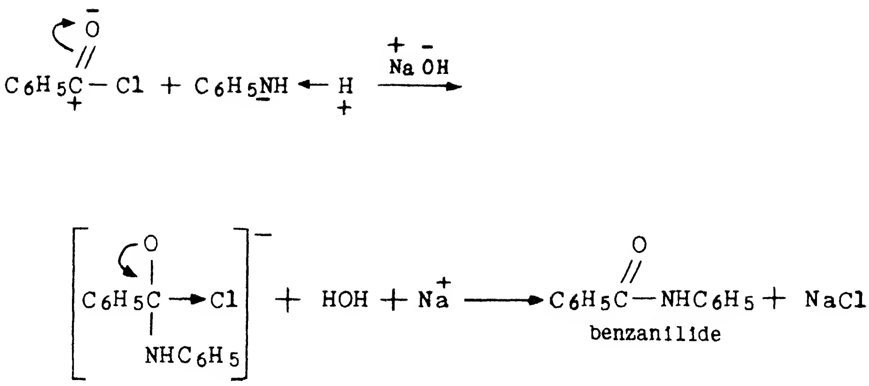


The result of such an effect would be to reduce the electrophilic activity of the carbonyl carbon atom.

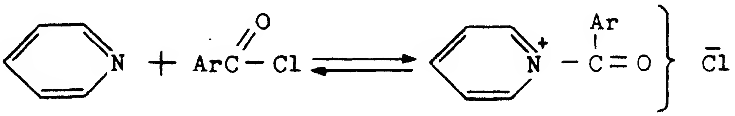
Benzoyl chloride is often used as a benzoylating reagent in the presence of sodium hydroxide solution. Under these conditions it is more reactive. The true function of the hydroxide does not appear to be established. In the benzoylation of an amine, alcohol, or phenol, obviously the nucleophilic hydroxyl ion does not attack the carbonyl carbon atom of benzoyl chloride only, for if this were the case hydrolysis would result and the desired benzoylation would not occur. Therefore, the base must cause an increase in the concentration of the desired anion. In the benzoylation of alcohols and phenols, the formation of $\bar{\text{O}}\text{R}$ and $\bar{\text{O}}\text{Ar}$ would be increased by the presence of a base. It is interesting to note that from the relative nucleophilic activity of the anions $^{-}\text{NH}_2$, ^{-}OR and ^{-}OH, the hydroxyl ion would be expected to add less readily than the amide or alkoxy ions to the carbonyl carbon atom:



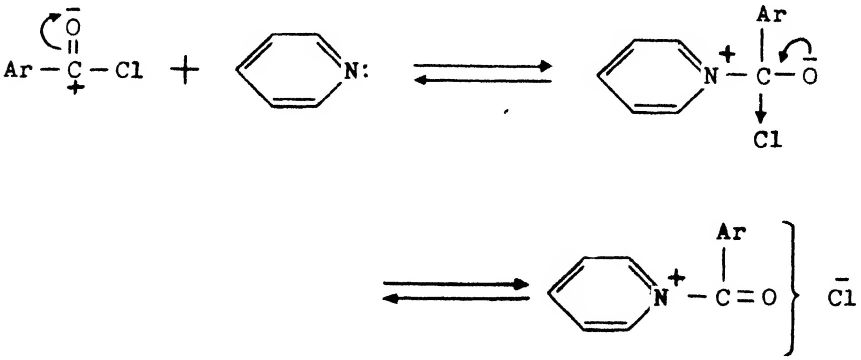
The same reasoning may be applied to the benzoylation of amines and the tendency $\overset{-}{\text{RNH}}\leftarrow\overset{+}{\text{H}}$ would be enhanced by the base:



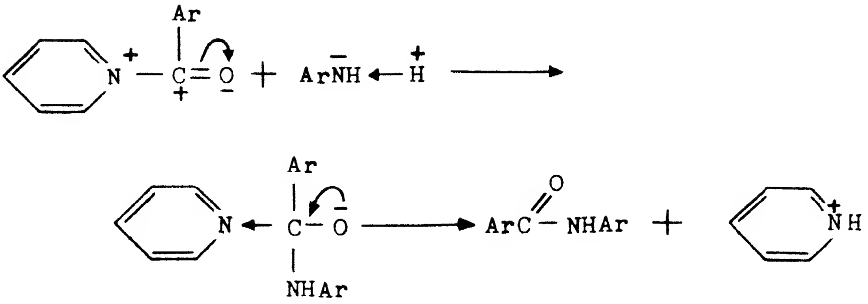
Pyridine is frequently used as a promoter and solvent for benzoylation reactions. A probable explanation for the promoting action of pyridine has been given under the aliphatic chlorides. There is another possible explanation for the effect of pyridine in these reactions. Heat is evolved when an acyl chloride is dissolved in pyridine and an addition compound is formed:



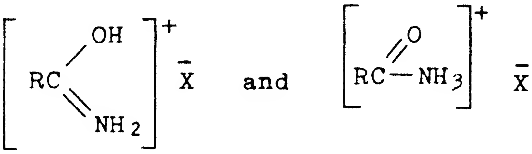
This quaternary addition compound may well be the actual acylating agent. The formation of such a compound may be shown as follows:



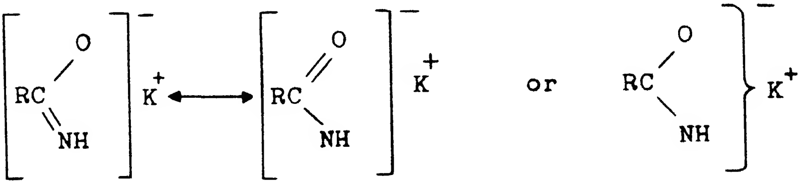
This intermediate could then act as the acylating agent:



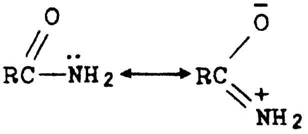
Acid amides. The composite functional group of the amides is composed of a carbonyl group and an amine group. The amides are very weak bases which form salts only with strong acids. Salts such as the hydrochlorides, $RCONH_2 \cdot HCl$, are readily hydrolyzed by water. There are two possibilities for the structure of the salts



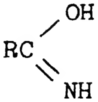
although the first is to be preferred because resonance is possible in the cation of only the first form. In other words, the first cation would be stabilized through resonance. The amides also show weak acidic properties. When acetamide is heated with potassium in benzene, potassium acetamide is formed. Such salts are rapidly decomposed by water or alcohol. The potassium salts may be formulated as follows:



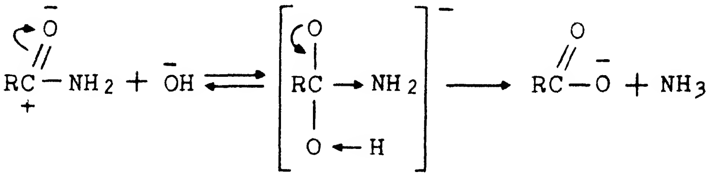
The actual structure of a neutral amide is best represented as the resonance hybrid of two structures:



It also appears possible that small amounts of another form tautomeric to this exists, namely:

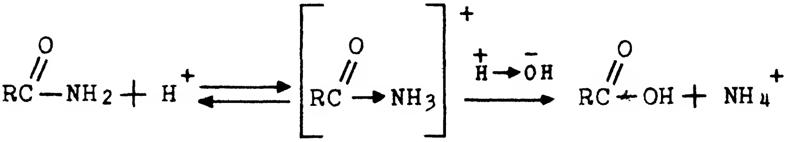


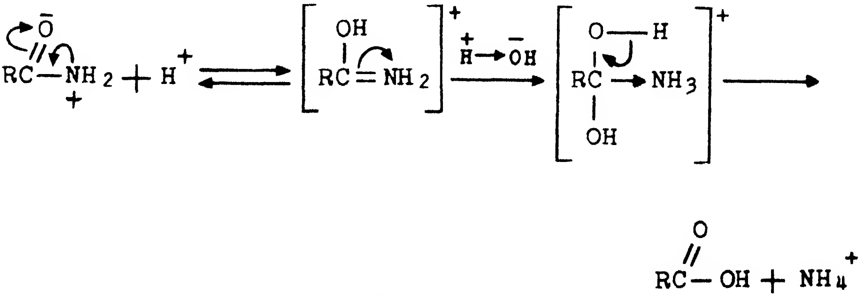
The amides, like the acid anhydrides and acyl chlorides, are readily hydrolyzed. Hydrolysis is catalyzed by both acids and bases, but more efficiently by the latter. Base-catalyzed hydrolysis involves a nucleophilic attack of the hydroxyl ion on the carbonyl carbon atom and may be shown as follows:



A salt of the acid would be the final product. Here again it will be noted that the addition of the anion to the carbonyl carbon atom tends to neutralize the electron attraction of the carbonyl group. Thus the C—N bond may be considered to have been weakened and the tendency to cleave is further aided by the ease with which the carbonyl carbon atom can recover a pair of electrons from the adjacent electronegative oxygen atom. That the NH_2 group splits off rather than the hydroxyl group is due to the fact that this leads to an irreversible reaction.

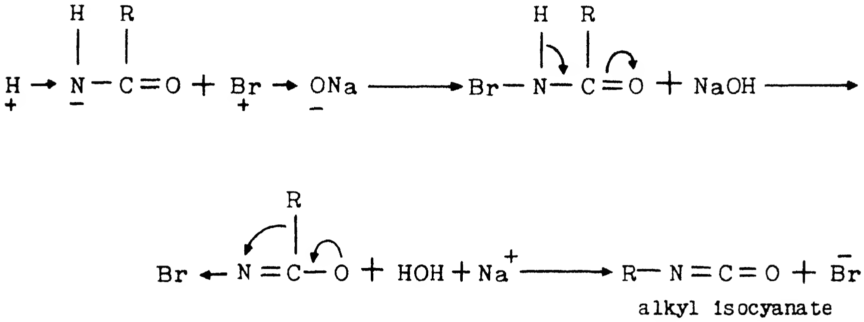
Acid-catalyzed hydrolysis involves the initial addition of a proton to the $-NH_2$ group or more probably to the carbonyl oxygen atom:

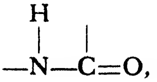
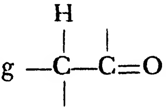


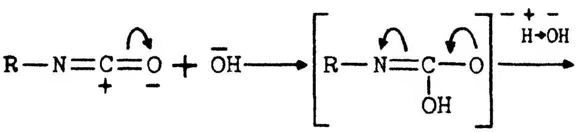


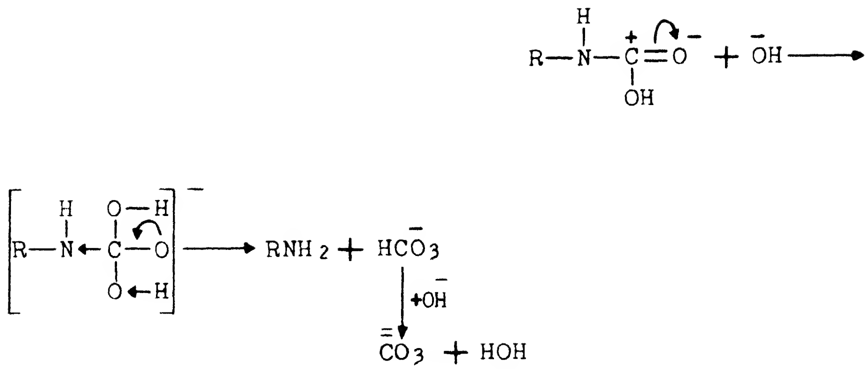
In the second course of reaction the addition of the proton gives a cation which has the necessary grouping for an electromeric shift and subsequent addition of the nucleophilic hydroxyl ion. The cleavage of the carbon-to-nitrogen bond is brought about by the strong electron attraction of the $-\overset{+}{N}H_3$ group. This tendency to pull away is undoubtedly aided by the ease with which the carbon atom can acquire a share in an electron pair from one of the adjacent oxygen atoms.

The conversion of an acid amide into a primary amine by the action of chlorine or bromine and an alkali (Hofmann reaction) involves the migration of an alkyl group from carbon to nitrogen. This reaction has been represented as follows (76):



The loss ot a proton in the second step may be attributed to the electron-attracting carbonyl group and to the presence of a base. The structure  $-\overset{H}{\overset{|}{N}}-\overset{|}{C}=O$, is similar to the grouping  $-\overset{H}{\overset{|}{\underset{|}{C}}}-\overset{|}{C}=O$ in this respect. The migration of the alkyl group as a carbanion is induced by the electron attraction of the bromine atom and the tendency of the electron-rich oxygen atom to increase its covalence with carbon through an electromeric shift. The bromoamide as well as the isocyanate can be isolated from the reaction. There is some evidence (109) which indicates that the migration is intramolecular and does not involve the existence of a free carbanion. It must be assumed from this that the attachment of the alkyl radical to nitrogen is initiated before the cleavage of the radical from carbon is complete. The final step, hydrolytic conversion of the isocyanate to a primary amine, may be shown as follows:

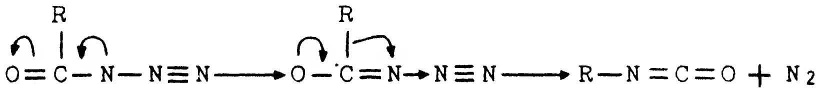




$$R-\overset{\overset{H}{|}}{N}-\underset{\underset{OH}{|}}{\overset{+}{C}}=\overset{-}{O} + \overset{-}{O}H \longrightarrow \left[R-\overset{\overset{H}{|}}{N}\leftarrow\underset{\underset{O\leftarrow H}{|}}{\overset{\overset{O-H}{|}}{C}}-O \right]^{-} \longrightarrow RNH_2 + HC\overset{-}{O}_3$$

$$HC\overset{-}{O}_3 \xrightarrow{+\overset{-}{O}H} \overset{=}{C}O_3 + HOH$$

The Curtius rearrangement of acid azides to isocyanates may be represented by a similar mechanism (76). This change does not involve catalytic action, for it occurs on heating alone or in a neutral solvent such as benzene:



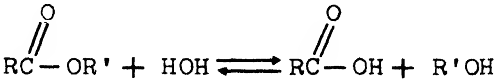
$$O=\overset{\overset{R}{|}}{C}-N-N\equiv N \longrightarrow O-\overset{\overset{R}{|}}{C}=N\rightarrow N\equiv N \longrightarrow R-N=C=O + N_2$$

The azide group actually is a resonance hybrid of two structures:

$$:\underset{\cdot\cdot}{N}::\overset{+}{N}::\underset{\cdot\cdot}{\overset{-}{N}}: \quad \text{and} \quad :\underset{\cdot\cdot}{\overset{\overset{-}{\cdot\cdot}}{N}}:\overset{+}{N}:::N: \quad \text{or} - N=N\overset{\rightarrow}{=}N \quad \text{and} \quad -N\leftarrow N\overset{\leftarrow}{\equiv}N$$

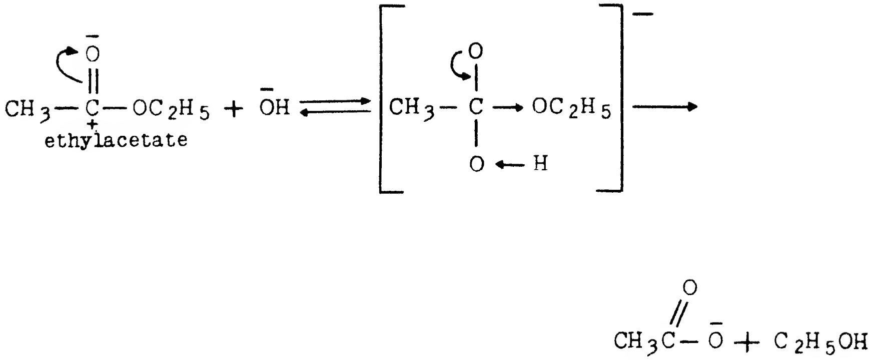
In general the aromatic acid amides give the same reactions as the aliphatic amides.

Esters. The chemistry of the composite ester group, $-\overset{\overset{O}{/\!/}}{C}-OR$, is readily explained from the fact that it consists of a carbonyl group and an ether grouping. Like the other acid derivatives, the esters may be hydrolyzed. In the presence of water alone, the rate of hydrolysis is low and equilibrium is established very slowly:



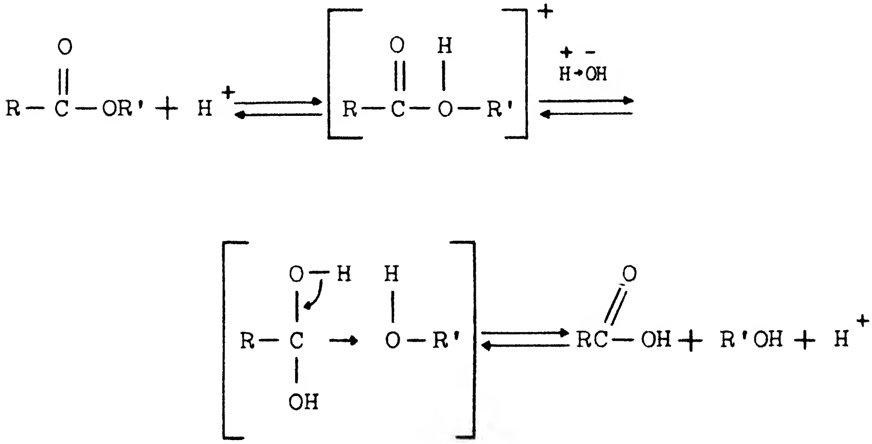
$$R\overset{\overset{O}{/\!/}}{C}-OR' + HOH \rightleftharpoons R\overset{\overset{O}{/\!/}}{C}-OH + R'OH$$

The presence of acids increases the rate at which equilibrium is reached, but the reaction does not reach completion unless one of the products is removed as it is formed. Base-catalyzed hydrolysis, however, goes to completion. The first step in basic hydrolysis is the addition of the hydroxyl ion to the carbonyl carbon atom.

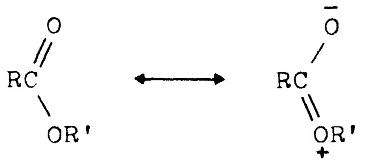


The addition of the hydroxyl group destroys the resonance of the ester grouping and weakens the C–OR bond. It may be stated more simply that the addition of the anion tends to neutralize the electron attraction of the carbonyl group and thus weakens the C–OR bond. The cleavage of this bond is facilitated by the ease with which the carbon atom can acquire a share in an electron pair from one of the adjacent electron-rich oxygen atoms. The presence of electron-attracting substituents in either R or R′ facilitates the addition of the hydroxyl ion to the carbonyl carbon, while the presence of electron-repelling substituents retards the addition of the hydroxyl ion. These effects are most pronounced when the substituents are in the R group. In general, the ease with which alkaline hydrolysis occurs increases as the strength of the parent acid of the ester increases.

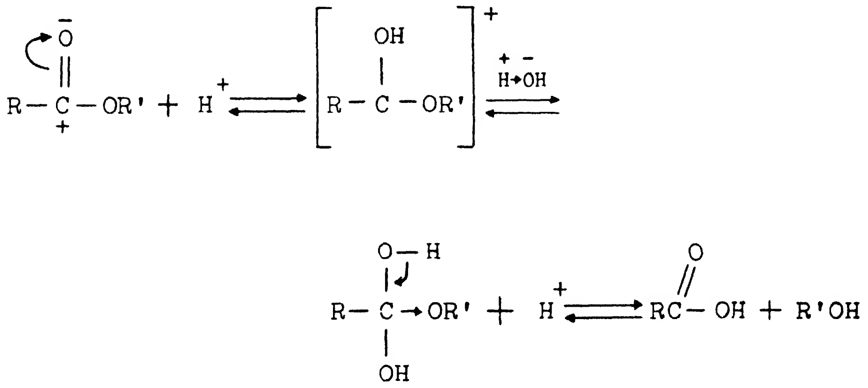
It was suggested originally that acid-catalyzed hydrolysis involved the transfer of a proton from the catalyst to the oxygen atom of the OR′ group:



It has been pointed out by later workers, however, that it is difficult to understand why in acid hydrolysis but not in esterification the proton should add at the ether oxygen rather than at the carbonyl oxygen. Resonance in the ester grouping

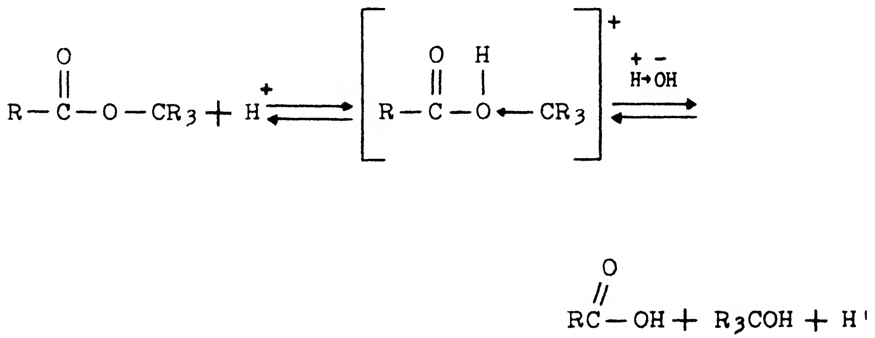


would establish a fractional negative charge on the carbonyl oxygen atom and it is reasonable to assume that the proton would add to this atom. The following mechanism for acid hydrolysis has been suggested (110) as being in better agreement with the accepted mechanism for esterification:

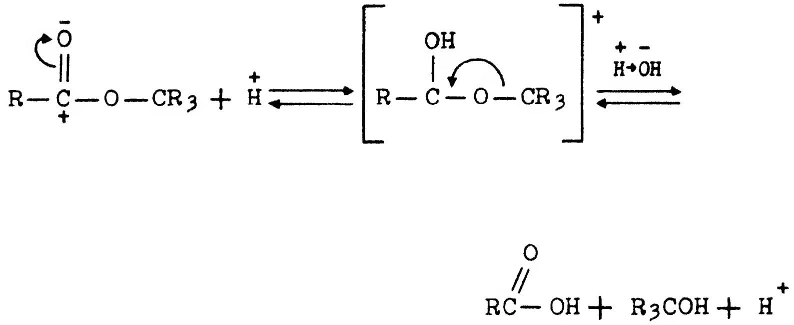


In both of these mechanisms the cleavage of the C–OR bond is made possible (in the last step) by the same factors which were noted in alkaline hydrolysis.

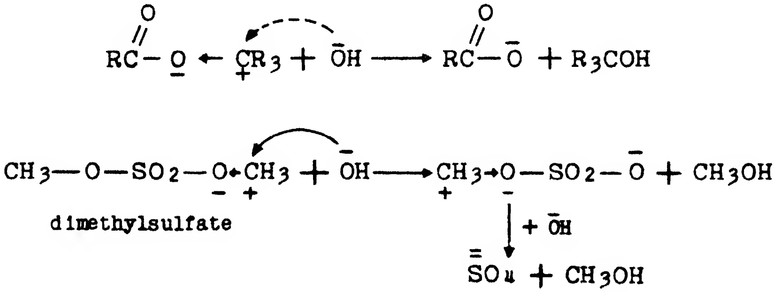
The mechanisms noted above do not include the hydrolysis of the esters of tertiary alcohols (40). The latter behave like the esters of strong acids such as sulfonic acids, in that cleavage of the alkyl-oxygen bond occurs when they are hydrolyzed:



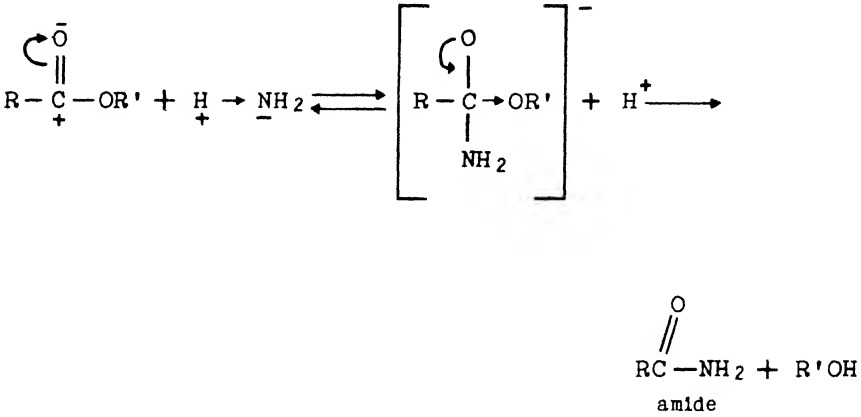
or



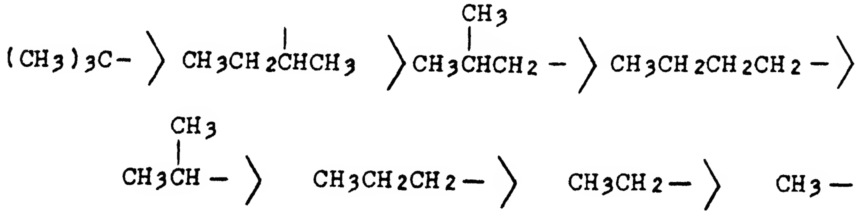
In acid media the initial step is undoubtedly the addition of a proton to the ether oxygen atom or to the carbonyl oxygen followed by cleavage. The electron-release effect of the tertiary radical is the directing influence in these reactions. It is not necessary to postulate an alkyl carbonium ion intermediate in this reaction, for it is probable that the hydroxyl ion starts to add before the cleavage is completed. The mechanism involved in base-catalyzed hydrolysis of such esters is not as obvious. It may be assumed that the hydroxyl ion attaches itself to the carbonyl carbon atom, although the electrophilic character of the carbonyl carbon should be weakened in these compounds. Furthermore, such a mechanism could scarcely be applied to the alkyl sulfonates and sulfates. For the present, these reactions will be represented as follows:



The reactions of ammonia with esters may be written in a similar manner. Ammonolysis occurs most readily with methyl esters and generally requires the presence of some water:



The rates of ammonolysis of various esters differ considerably depending on the nature of R and R′. The rates decrease as the electron-release effect of R or R′ increases. The retarding effects of various alkyl groups on ammonolysis rates of esters have been established through kinetic studies (111):

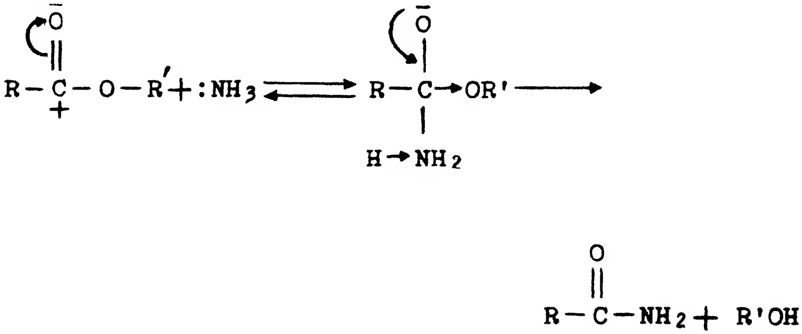


$$(CH_3)_3C- > CH_3CH_2CH(CH_3)- > (CH_3)_2CHCH_2- > CH_3CH_2CH_2CH_2- > (CH_3)_2CH- > CH_3CH_2CH_2- > CH_3CH_2- > CH_3-$$

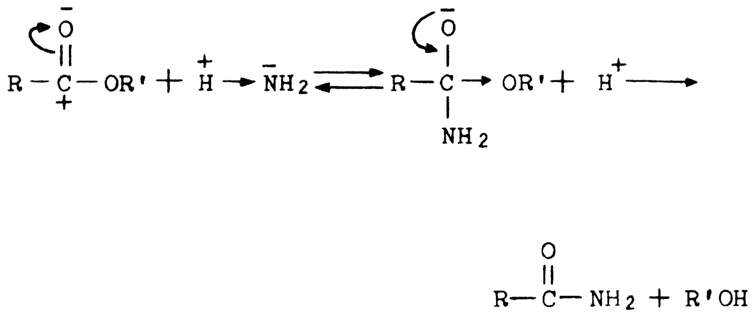
These results are in accord with the belief that the electron-release effects of R and R′ tend to reduce the electrophilic activity of the carbonyl carbon atom, the magnitude of reduction being dependent on the relative electron release of the group in question.

Actually one may consider two possible mechanisms for the ammonolysis of esters:

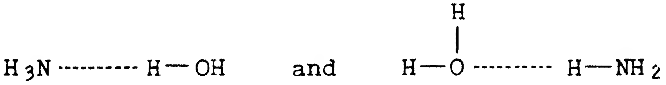
I



II



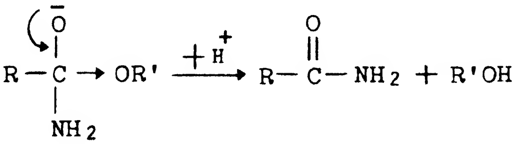
Both mechanisms involve the addition of a nucleophilic agent to the carbonyl carbon atom. The fact that the presence of a polarizing (ionizing) solvent such as water is necessary for ammonolysis to occur readily suggests that II is more probable than I. It is not necessary to postulate free amide ions ($\bar{N}H_2$), although they may exist to some extent. It is possible that through hydrogen bonding the polarization of the $\overset{+}{H}\rightarrow\overset{-}{N}H_2$ bond may be increased to the point that it simulates ionization. Hydrogen bonding may occur in two ways but only in the second case would the essential polarization be enhanced:



$$H_3N \cdots\cdots H-OH \qquad \text{and} \qquad H-\overset{\overset{\displaystyle H}{|}}{O}\cdots\cdots H-NH_2$$

That the latter type of hydrogen bonding is involved appears to be supported by the fact that the ammonolysis of esters proceeds even more readily when carried out in anhydrous ethylene glycol (112).

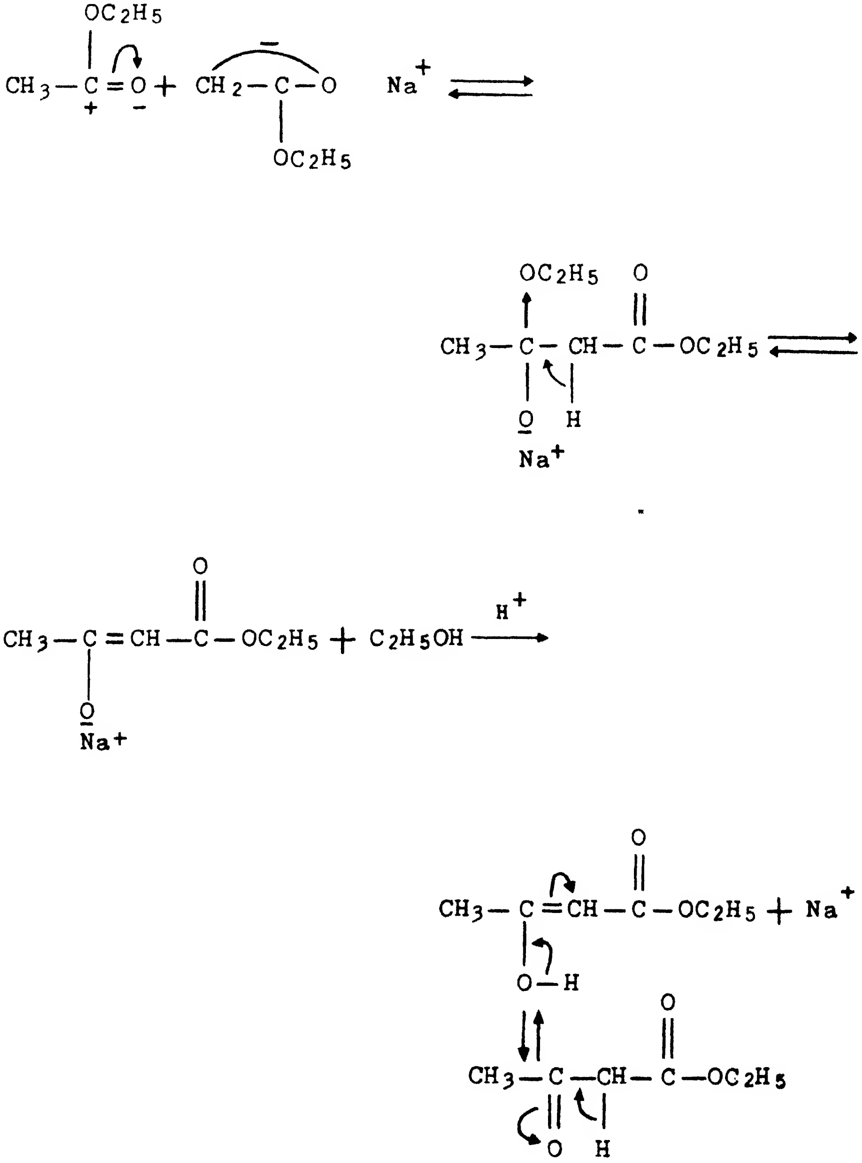
In the last step of the ammonolysis



the less nucleophilic $\bar{O}R$ group splits off more readily than the more nucleophilic NH_2 group, the cleavage being facilitated by the ease with which the carbonyl carbon atom can recover an electron pair from the adjacent oxygen atom.

Claisen condensation. Under the influence of sodium ethoxide, sodamide, mesityl magnesium bromide, and similar catalysts, the monocarboxylic esters undergo condensation with aldehydes, ketones, and carboxylic esters to form β-keto derivatives. It is probable that the real catalyst is a strong nucleophilic reagent such as $\bar{O}C_2H_5$, $\bar{N}H_2$, or

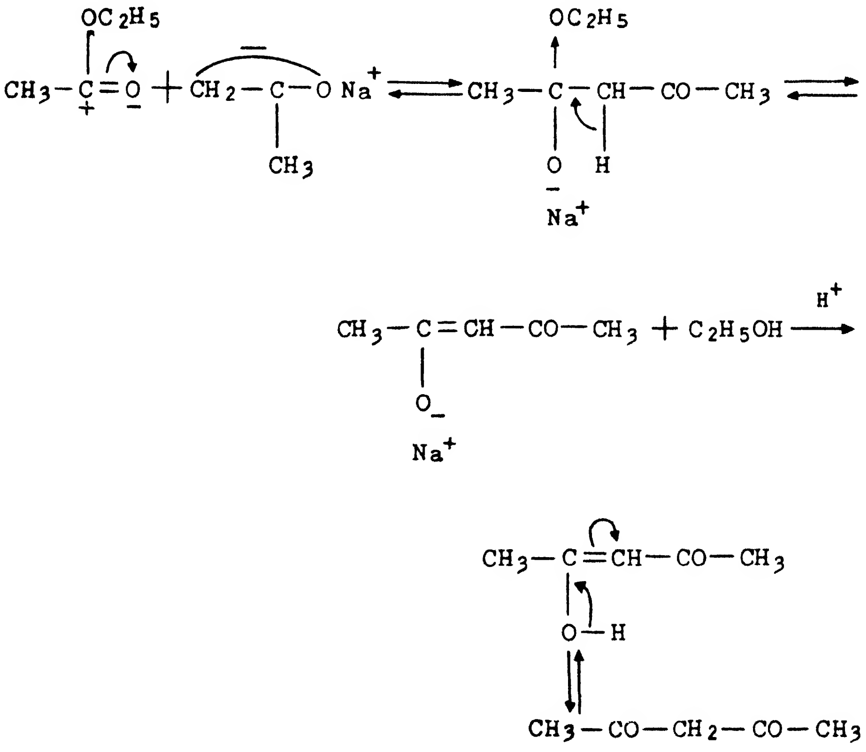
$(CH_3)_3C_6\overset{-}{H}_2$, which are anions of weak acids. The reaction essentially consists of an aldol-type addition to a carbonyl group. As noted previously under the aldol condensation, two requirements are essential: the ionization of active hydrogen in the reagent being added; and polarization of the carbonyl group to which addition occurs. Both would be facilitated by the presence of basic catalysts. The self-condensation of ethylacetate to form ethylacetoacetate is the most widely used example of the Claisen condensation. The mechanism may be shown as follows:



Since the final product is a metal enolate, the catalyst used must be the salt of a weaker acid than the parent acid of the enolate (113), for otherwise the equilibrium would lie far to the left. Continuous removal of alcohol from the reaction also shifts the equilibrium to the right. The above mechanism is based on principles which have been discussed previously.

It was formerly thought that the Claisen condensation occurred only when two hydrogen atoms were attached to the alpha carbon atom. It is known now that a salt of a weaker acid than ethyl alcohol will effect the condensation when only one alpha hydrogen is present. Ethylisobutyrate undergoes no appreciable condensation in the presence of sodium ethoxide. However, in the presence of mesityl magnesium bromide the reaction may be carried out. This is attributed to the fact that mesitylene is a much weaker acid than ethyl alcohol. The condensation product from ethylisobutyrate, $(CH_3)_2CHCOC(CH_3)_2\overset{O}{\overset{/\!/}{C}}—OC_2H_5$, is less acidic than ethylacetoacetate since its only active hydrogen is a gamma hydrogen atom.

A similar mechanism may be written for the condensation of esters with ketones, such as the reaction of ethylacetate with acetone to yield acetyl acetone:

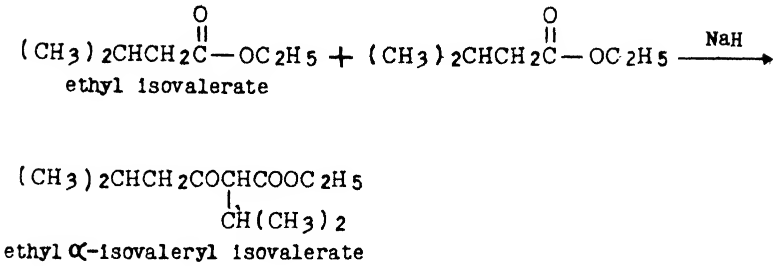


$$\underset{+}{\overset{OC_2H_5}{CH_3—C}}=\underset{-}{O} + \overline{CH_2—\underset{CH_3}{C}—O}\,Na^+ \rightleftharpoons CH_3—\overset{OC_2H_5}{\underset{\underset{Na^+}{O^-}}{C}}—\underset{H}{CH}—CO—CH_3 \rightleftharpoons$$

$$CH_3—\underset{\underset{Na^+}{O^-}}{C}=CH—CO—CH_3 + C_2H_5OH \xrightarrow{H^+}$$

$$CH_3—\underset{O—H}{C}=CH—CO—CH_3 \rightleftharpoons CH_3—CO—CH_2—CO—CH_3$$

The use of sodium hydride for effecting the condensation of certain carbonyl compounds has been reported (114):

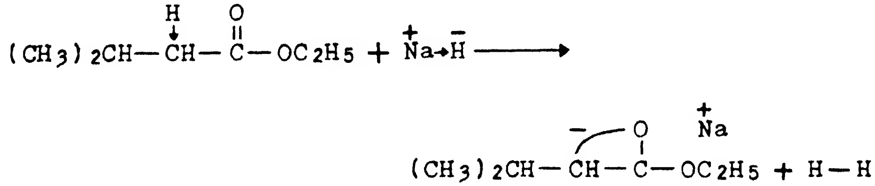


$$(CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}-OC_2H_5 + (CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow{NaH} (CH_3)_2CHCH_2CO\underset{CH(CH_3)_2}{\underset{|}{C}H}COOC_2H_5$$

ethyl isovalerate

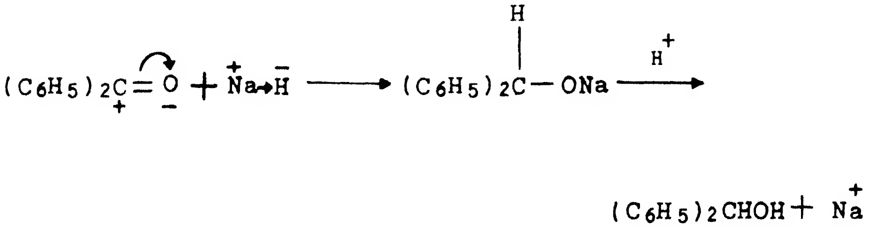
ethyl α-isovaleryl isovalerate

The chief function of sodium hydride as a condensing agent is to facilitate the formation of the anion which is necessary for the addition to occur:



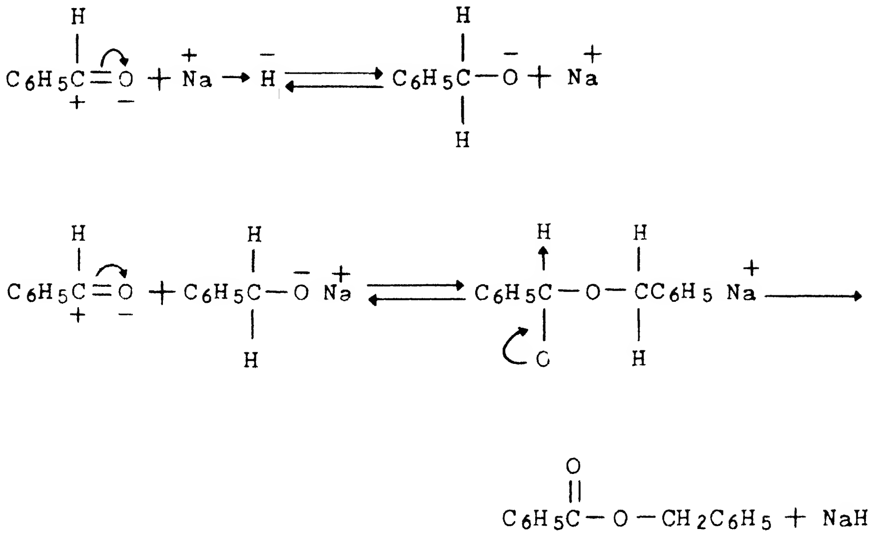
$$(CH_3)_2CH-\overset{H}{\overset{\downarrow}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + \overset{+}{Na}\rightarrow\overset{-}{H} \longrightarrow (CH_3)_2CH-\overset{-}{C}H-\overset{O}{\overset{|}{C}}-OC_2H_5 \;\overset{+}{Na} + H-H$$

Sodium hydride may also act as a reducing agent. Benzophenone, which has no alpha hydrogen, is reduced to benzhydrol (diphenylmethanol) when refluxed in xylene solution in contact with sodium hydride:



$$(C_6H_5)_2\underset{+}{C}=\underset{-}{O} + \overset{+}{Na}\rightarrow\overset{-}{H} \longrightarrow (C_6H_5)_2\overset{H}{\overset{|}{C}}-ONa \xrightarrow{\overset{+}{H}} (C_6H_5)_2CHOH + \overset{+}{Na}$$

With benzaldehyde, however, little reduction occurs but a good yield of benzylbenzoate is formed. This behavior is somewhat similar to the action of sodium alkoxides on aromatic aldehydes (page 139). The reaction mechanism may be shown as follows:



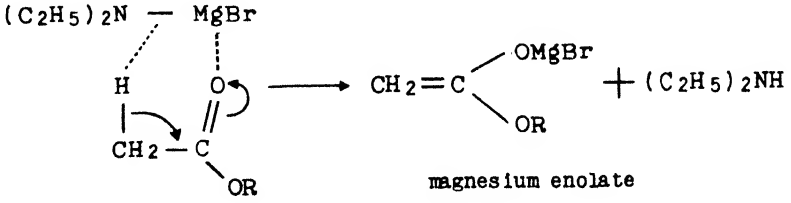
✓The use of diethylamino magnesium bromide for the condensation of certain esters has been reported also (115). These reactions are quite rapid and the yields of β-ketoesters are fairly good. In some cases amide formation was observed also:

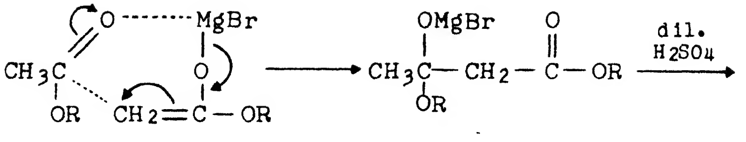
$$2\ CH_3COOR' + (C_2H_5)_2NMgBr \longrightarrow CH_3COCH_2COOR'$$

$$RCOOR' + (C_2H_5)_2NMgBr \longrightarrow RCON(C_2H_5)_2$$

The data indicate that diethylamino magnesium bromide reacts chiefly with the alpha hydrogen atoms of the alkyl acetates, ethyl propionate, *t*-butyl-*n*-butyrate, ethyl phenylacetate, and ethyl *n*-butyrate. The same reagent, however, attacks the carbonyl group of ethyl isobutyrate and ethyl isovalerate. It is interesting to note that although ethyl propionate is self-condensed by diethylamino magnesium bromide, it forms the corresponding amide with methylanilino magnesium bromide.

A cyclic mechanism has been suggested for the self-condensations noted above (115):

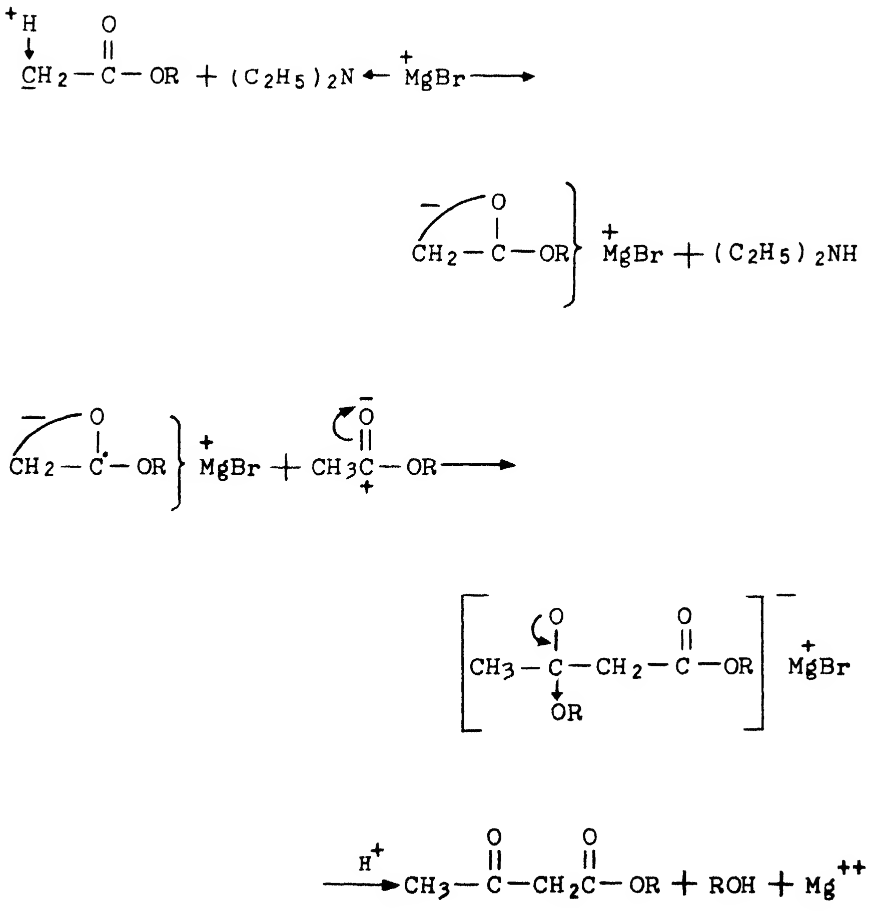




$$CH_3COCH_2COOR + ROH + Mg^{++}$$

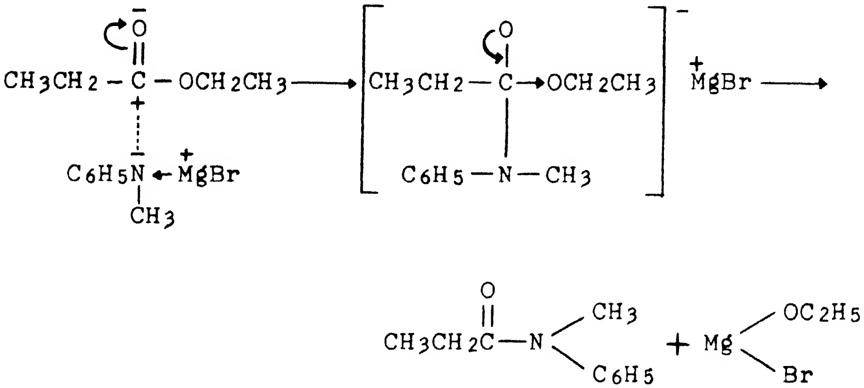
This mechanism involves the intermediate formation of ephemeral ring structures within which the necessary electron shifts occur to form the end products.

It is possible to explain the above reaction without involving a cyclic mechanism:



In this case the diethylamino magnesium bromide is pictured as facilitating the ionization of alpha hydrogen and the hybrid anion resulting from this ionization then undergoes addition with another ester molecule.

The difference in behavior between diethylamino magnesium bromide and methylanilino magnesium bromide is undoubtedly due to the fact that $C_6H_5\bar{N}CH_3$ is a weaker base than $(C_2H_5)_2\bar{N}$ and consequently would be less active in promoting the ionization of alpha hydrogen. As a result the competing reaction, aminolysis, becomes the predominant reaction.

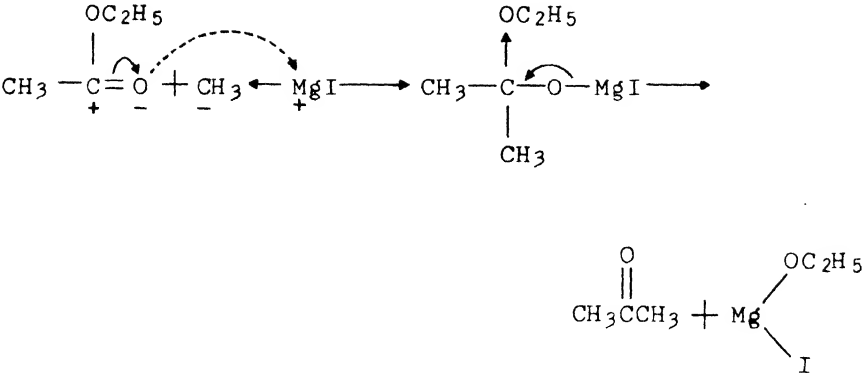


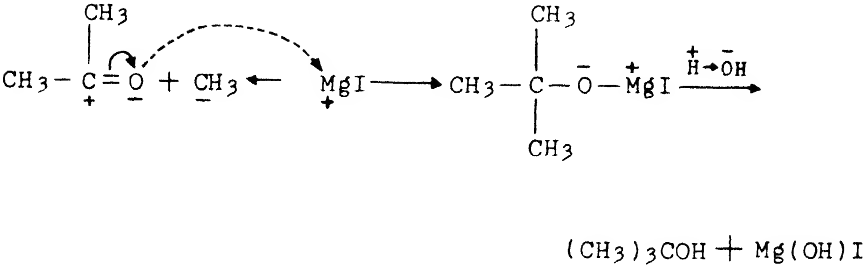
N-methyl-*N*-phenyl
propionamide

It has been noted previously that in the self-condensation of esters, the catalyst used must be the salt of an acid weaker than the parent acid of the hybrid anion for otherwise the equilibrium would lie too far to the left to be of any practical value. This same reasoning may be applied here. The fact that diethylamino magnesium bromide reacts chiefly with the alpha hydrogen atoms of ethyl-*n*-butyrate but mainly with the carbonyl group of ethyl isobutyrate is readily explained. Since ethyl isobutyrate is a weaker acid than ethyl-*n*-butyrate, the same catalyst will not necessarily promote the self-condensation of both esters unless it is a weaker acid than both.

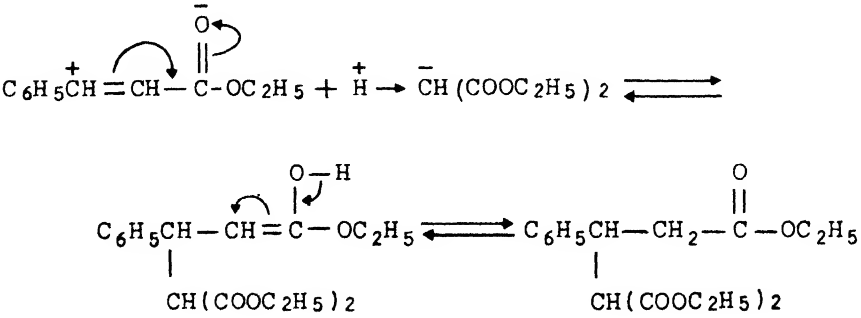
The cyclic mechanism cannot be regarded as an established one at the present time and there appears to be no very sound reasons for preferring it rather than the simpler mechanism shown above. The fact that the self-condensations noted above take place rapidly is not in itself an indication that a cyclic mechanism is involved, for the rate of ionization of alpha hydrogen would depend primarily on the basic strength of the catalyst used.

Reaction with Grignard reagents. The reaction of esters with alkyl magnesium halides also involves the ketonic character of the ester group. Addition products are formed which by further reaction may yield ketones or tertiary alcohols. In actual practice ketones are difficult to isolate in good yields, for they react too rapidly with an additional molecule of alkyl magnesium halide. The following mechanism involves principles which have been discussed previously:



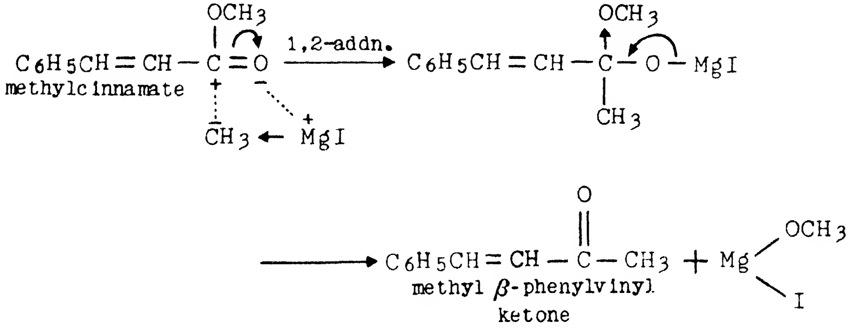


Esters of α,β-unsaturated acids. The behavior of the conjugated system in esters of this type may be compared with the reactions of other α,β-unsaturated carbonyl compounds. Both 1,2- and 1,4- additions have been observed. There is less experimental evidence available than in the case of the α,β-unsaturated aldehydes and ketones, but in general it appears to be in harmony with the mechanisms discussed for the reactions of the corresponding aldehydes and ketones. For example, the addition of malonic ester to ethyl cinnamate, under the influence of a small amount of sodium ethoxide (Michael reaction), proceeds by way of the 1,4-addition mechanism:

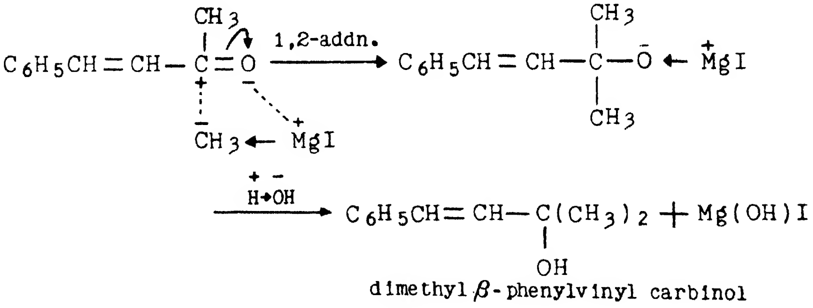


Hydrolysis and decarboxylation of this product leads to the formation of β-phenyl glutaric acid.

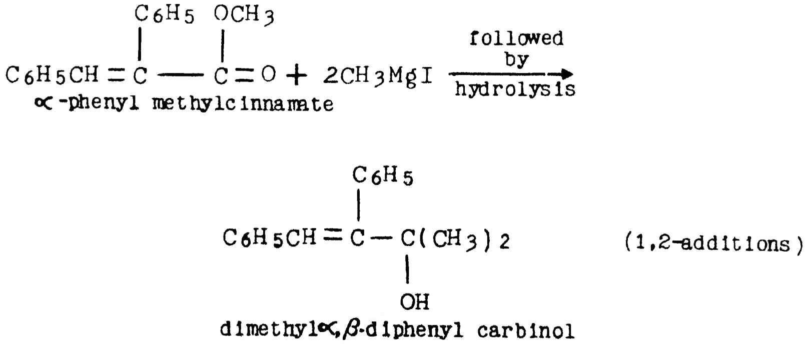
With Grignard reagents, both 1,2- and 1,4- additions have been reported. The mode of addition appears to be determined largely by the same factors previously discussed under the reactions of the α,β-unsaturated aldehydes and ketones: (1) number and magnitude of electron-releasing groups present; (2) proximity of the latter to the carbonyl group; and (3) the activity of the Grignard reagent:

I


$$C_6H_5CH{=}CH{-}\overset{OCH_3}{\overset{|}{C}}{=}O + \overset{-}{C}H_3 \leftarrow \overset{+}{M}gI \xrightarrow{\text{1,2-addn.}} C_6H_5CH{=}CH{-}\underset{CH_3}{\overset{OCH_3}{C}}{-}O{-}MgI \longrightarrow C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}CH_3 + Mg\begin{smallmatrix}OCH_3\\ I\end{smallmatrix}$$

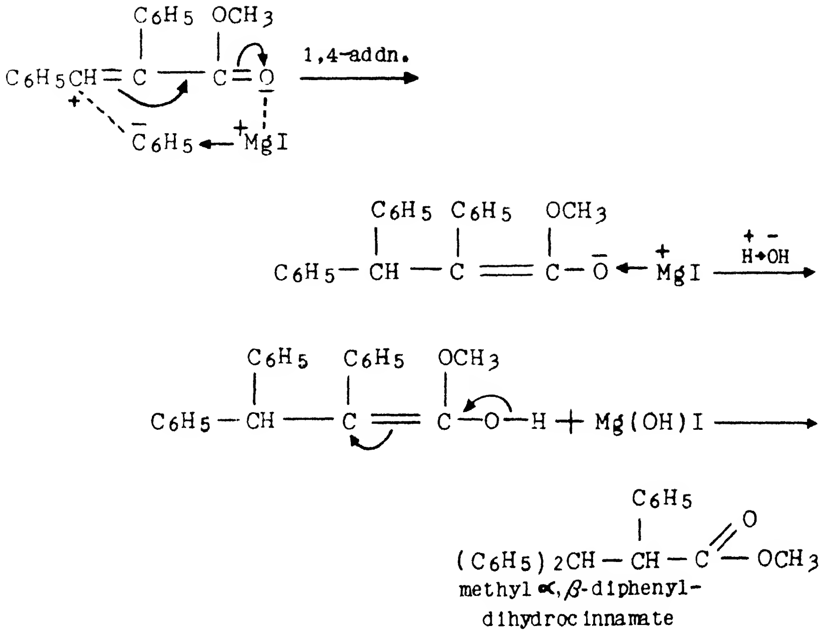
II


$$C_6H_5CH{=}CH{-}\overset{CH_3}{\overset{|}{C}}{=}O + \overset{-}{C}H_3 \leftarrow \overset{+}{M}gI \xrightarrow{\text{1,2-addn.}} C_6H_5CH{=}CH{-}\underset{CH_3}{\overset{CH_3}{C}}{-}\overset{-}{O} \leftarrow \overset{+}{M}gI \xrightarrow{\overset{+}{H}\cdot\overset{-}{OH}} C_6H_5CH{=}CH{-}\underset{OH}{C}(CH_3)_2 + Mg(OH)I$$

III


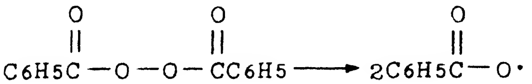
$$C_6H_5CH{=}\overset{C_6H_5}{\overset{|}{C}}{-}\overset{OCH_3}{\overset{|}{C}}{=}O + 2CH_3MgI \xrightarrow[\text{hydrolysis}]{\text{followed by}} C_6H_5CH{=}\overset{C_6H_5}{\overset{|}{C}}{-}\underset{OH}{C}(CH_3)_2$$

IV

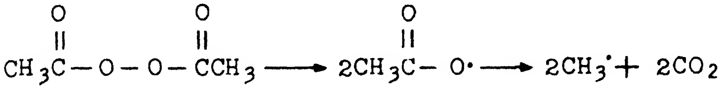


$$C_6H_5CH{=}C(C_6H_5){-}C(OCH_3){=}O + C_6H_5MgI \xrightarrow{\text{1,4-addn.}} C_6H_5{-}CH(C_6H_5){-}C(C_6H_5){=}C(OCH_3){-}\overset{-}{O} \leftarrow \overset{+}{Mg}I \xrightarrow{\overset{+}{H}\,\overset{-}{OH}} C_6H_5{-}CH(C_6H_5){-}C(C_6H_5){=}C(OCH_3){-}O{-}H + Mg(OH)I \longrightarrow (C_6H_5)_2CH{-}CH(C_6H_5){-}C(=O){-}OCH_3$$

The esters of acrylic acid and methacrylic acid are of particular interest because of the ease with which they polymerize to important thermoplastic polymers. They polymerize under the influence of heat, light, or peroxides. Small amounts of oxygen also promote the polymerization. The reaction follows a radical mechanism and apparently it is the function of the catalyst to supply a radical which initiates a chain reaction. It is known, for example, that benzoyl peroxide and acetyl peroxide slowly decompose to form free radicals:



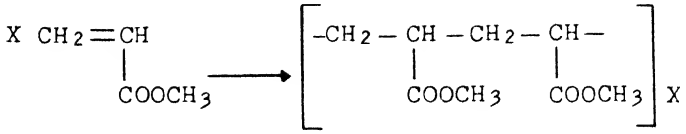
$$C_6H_5C(=O){-}O{-}O{-}C(=O)C_6H_5 \longrightarrow 2C_6H_5C(=O){-}O\cdot$$



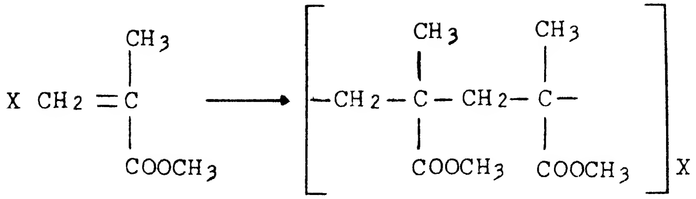
$$CH_3C(=O){-}O{-}O{-}C(=O)CH_3 \longrightarrow 2CH_3C(=O){-}O\cdot \longrightarrow 2CH_3\cdot + 2CO_2$$

In the case of the acetyl peroxide, the free acetyl radical is known to further decompose to a free methyl radical and carbon dioxide. The free benzoyl radical probably undergoes a similar decomposition.

The polymerization of the acrylates leads to the formation of long carbon chains with ester groups on alternate carbon atoms:



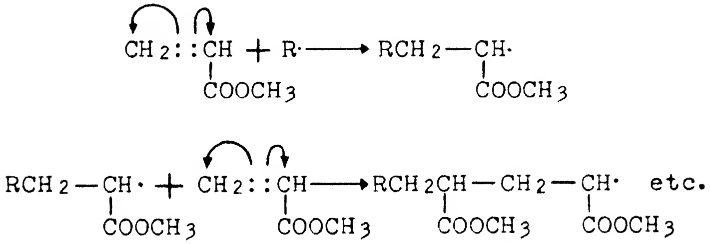
$$X\ CH_2{=}\underset{COOCH_3}{CH} \longrightarrow \left[-CH_2-\underset{COOCH_3}{CH}-CH_2-\underset{COOCH_3}{CH}-\right]_X$$



$$X\ CH_2{=}\overset{CH_3}{\underset{COOCH_3}{C}} \longrightarrow \left[-CH_2-\overset{CH_3}{\underset{COOCH_3}{C}}-CH_2-\overset{CH_3}{\underset{COOCH_3}{C}}-\right]_X$$

Electronically, this may be shown as follows:

I

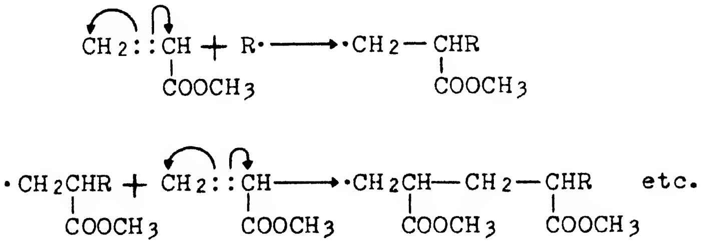


$$CH_2{:}{:}\underset{COOCH_3}{CH} + R\cdot \longrightarrow RCH_2-\underset{COOCH_3}{CH}\cdot$$

$$RCH_2-\underset{COOCH_3}{CH}\cdot + CH_2{:}{:}\underset{COOCH_3}{CH} \longrightarrow RCH_2\underset{COOCH_3}{CH}-CH_2-\underset{COOCH_3}{CH}\cdot \quad \text{etc.}$$

The free radical initiates the reaction and the first reaction product is also a free radical. The latter can then activate another acrylate molecule and the chain continues to grow. Actually the free radical from the catalyst might add to the second carbon atom rather than the third. It will be noted, however, that the same type of linear polymer would be formed:

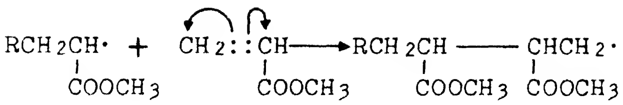
II



$$CH_2{:}{:}\underset{COOCH_3}{CH} + R\cdot \longrightarrow \cdot CH_2-\underset{COOCH_3}{CHR}$$

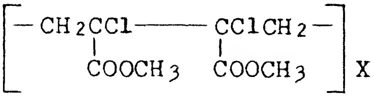
$$\cdot CH_2\underset{COOCH_3}{CHR} + CH_2{:}{:}\underset{COOCH_3}{CH} \longrightarrow \cdot CH_2\underset{COOCH_3}{CH}-CH_2-\underset{COOCH_3}{CHR} \quad \text{etc.}$$

Theoretically, a third course of reaction is possible:

III 

$$\underset{\mathrm{COOCH_3}}{\mathrm{RCH_2CH\cdot}} + \underset{\mathrm{COOCH_3}}{\mathrm{CH_2::CH}} \longrightarrow \mathrm{RCH_2}\underset{\mathrm{COOCH_3}}{\mathrm{CH}} - \underset{\mathrm{COOCH_3}}{\mathrm{CH}}\mathrm{CH_2\cdot}$$ etc.

There is no evidence available to indicate that any of the above reactions proceeds by path III. In the case of the polymer of methyl α-chloroacrylate there is experimental evidence to show that the halogen atoms are attached to adjacent carbon atoms:



$$\left[-\mathrm{CH_2}\underset{\mathrm{COOCH_3}}{\mathrm{CCl}} - \underset{\mathrm{COOCH_3}}{\mathrm{CCl}}\mathrm{CH_2}-\right]_{\mathrm{X}}$$

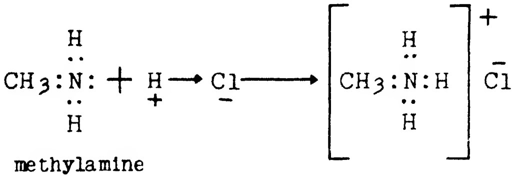
It is probable, therefore, that the polymerization of methyl α-chloroacrylate follows course III.

It is more difficult to predict the course of radical reactions than "ionic" reactions where electron pairs are involved. It is reasonable to suppose that the initial free radical will attack the acrylate at that point where it can most readily form a paired bond (point of greatest electron density). There does not appear to be sufficient evidence at present to enable one to predict with any degree of accuracy what points within the molecule should be most active.

CHAPTER XXII

Reactions of Aliphatic Amines

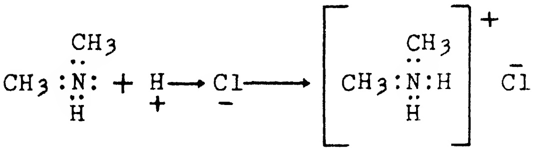
The amines may be regarded as derivatives of ammonia in which one, two, or three of the hydrogen atoms are replaced by aliphatic radicals. The three classes of amines are called primary, secondary, and tertiary amines, respectively. They are similar to ammonia in that each has an unshared electron pair on the nitrogen atom. The basic properties of the amines are dependent on this unshared pair which acts as a proton acceptor:



$$\mathrm{CH_3:}\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\underset{\underset{\mathrm{H}}{\cdot\cdot}}{\mathrm{N}}}\mathrm{:} + \underset{+}{\mathrm{H}}\rightarrow\underset{-}{\mathrm{Cl}}\longrightarrow\left[\mathrm{CH_3:}\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\underset{\underset{\mathrm{H}}{\cdot\cdot}}{\mathrm{N}}}\mathrm{:H}\right]^{+}\overset{-}{\mathrm{Cl}}$$

methylamine

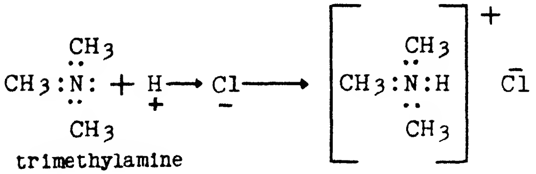
methylammonium chloride



$$\mathrm{CH_3:}\overset{\overset{\mathrm{CH_3}}{\cdot\cdot}}{\underset{\underset{\mathrm{H}}{\cdot\cdot}}{\mathrm{N}}}\mathrm{:} + \underset{+}{\mathrm{H}}\rightarrow\underset{-}{\mathrm{Cl}}\longrightarrow\left[\mathrm{CH_3:}\overset{\overset{\mathrm{CH_3}}{\cdot\cdot}}{\underset{\underset{\mathrm{H}}{\cdot\cdot}}{\mathrm{N}}}\mathrm{:H}\right]^{+}\overset{-}{\mathrm{Cl}}$$

dimethylamine

dimethylammonium chloride



$$\mathrm{CH_3:}\overset{\overset{\mathrm{CH_3}}{\cdot\cdot}}{\underset{\underset{\mathrm{CH_3}}{\cdot\cdot}}{\mathrm{N}}}\mathrm{:} + \underset{+}{\mathrm{H}}\rightarrow\underset{-}{\mathrm{Cl}}\longrightarrow\left[\mathrm{CH_3:}\overset{\overset{\mathrm{CH_3}}{\cdot\cdot}}{\underset{\underset{\mathrm{CH_3}}{\cdot\cdot}}{\mathrm{N}}}\mathrm{:H}\right]^{+}\overset{-}{\mathrm{Cl}}$$

trimethylamine

trimethylammonium chloride

Nitrogen has five valence electrons and in ammonia and the amines three are used in pairing with the electrons of hydrogen and carbon. The addition of a proton to the unshared pair of electrons contributes a positive charge to the radical because the total number of valence electrons is one less than the number belonging to the component atoms. In the ammonium and alkyl ammonium salts, four of the bonds are predominantly covalent and the fifth ionic.

The linkage of a proton to nitrogen is one which is readily formed and readily broken. The addition of sodium or potassium hydroxide solution to an alkyl ammonium salt releases the free amine:

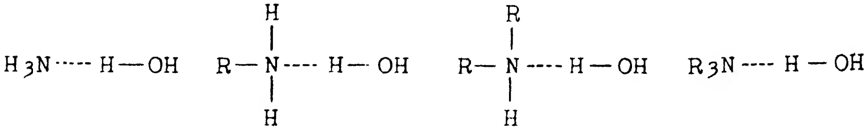
$$\left[(CH_3)_3N-H\right]^+ + \overset{-}{O}H \longrightarrow (CH_3)_3N + HOH$$

In this reaction the ammonium ion may be regarded as an acid, since it donates a proton to the hydroxyl ion.

The water-soluble amines react with water in the same manner as ammonia. In all cases, weakly basic solutions are formed:

$$(CH_3)_2NH + HOH \rightleftharpoons \left[(CH_3)_2NH_2\right]^+ + \overset{-}{O}H$$

In the forward reaction, the amine is acting as a proton acceptor and the water molecule as a proton donor. In the reverse reaction, the hydroxyl ion acts as a proton acceptor and the ammonium ion as a proton donor. The hydroxyl ion and the amine compete for the proton. The hydroxyl ion being a very strong base has a much stronger attraction for the proton than the free amine, consequently the equilibrium lies far to the left. The dissolution of ammonia, primary, secondary, or tertiary amines in water is accompanied by the formation of associated molecules as a result of hydrogen bonding. Hydrogen-bonded molecules of the following type may exist in aqueous solution:



$$H_3N\cdots H-OH \qquad R-\underset{H}{\overset{H}{N}}\cdots H-OH \qquad R-\underset{H}{\overset{R}{N}}\cdots H-OH \qquad R_3N\cdots H-OH$$

The relative basic strengths of primary, secondary, and tertiary amines are not always predictable on the basis of inductive effects alone. For example, the introduction of one or two methyl groups into the ammonia molecule increases the basic strength:

$$(CH_3)_2NH \quad > \quad CH_3NH_2 \quad > \quad NH_3$$

$$K_b = 59.9 \times 10^{-5} \qquad K_b = 42.5 \times 10^{-5} \qquad K_b = 1.79 \times 10^{-5}$$

This is to be expected since the electron-release effects of the methyl groups would tend to increase the electron density on the nitrogen atom and thus increase its tendency to act as a proton acceptor. The introduction of a third methyl group, however, produces a marked decrease in basic strength, $K_b = 6.31 \times 10^{-5}$. Trimethylamine thus lies between ammonia and methylamine.

It has been suggested that this anomaly is due to a steric factor (116). It is believed that the three bonds of a trivalent nitrogen atom should extend into space at angles of 90° to each other. In the cases which have been examined they have been found to be considerably larger. This increase or spreading was assumed to be necessary in order to accommodate the attached groups. The addition of a fourth atom or group reduces the expanded angles as a result of forcing the configuration of the nitrogen atom towards that of a tetrahedron. The crowding together of the four groups sets up a strain which decreases the stability of the addition compound. Such an effect would tend to reduce the electron-donor activity of the nitrogen atom in tertiary amines. This explanation offers a logical solution of the anomaly mentioned above. The authors of this explanation have shown that the relative affinity of methylamine, dimethylamine, and trimethylamine for trimethylboron (as determined from the dissociation constants of the addition compounds) is the same as their attraction for protons (as measured by their basic dissociation constants).

Similar results were obtained from ethylamine, diethylamine, and triethylamine when hydrogen chloride was used as the reference acid:

$$(C_2H_5)_2NH > C_2H_5NH_2 > (C_2H_5)_3N > NH_3$$

When trimethylboron was used as the reference acid, the order was altered:

$$C_2H_5NH_2 > (C_2H_5)_2NH > NH_3 > (C_2H_5)_3N$$

Replacement of methyl groups with ethyl groups would increase the steric factor. This increase does not change the relative base strengths when hydrogen chloride is the reference acid. When the more hindered acid, trimethylboron, is used the order is changed. The use of a more highly hindered reference acid, tri-*t*-butylboron, produces a further change:

$$NH_3 > C_2H_5NH_2 > (C_2H_5)_2NH > (C_2H_5)_3N$$

From this brief summary of some of Dr. Brown's work, it will be noted that the relative base strengths of amines are dependent on three factors: (1) inductive effects of the group or groups attached to nitrogen; (2) a steric effect which is dependent upon the number and size of the groups attached to nitrogen; and (3) magnitude of steric hindrance associated with the reference acid itself.

Tertiary amines react with alkyl halides to form quaternary ammonium salts:

$$(C_2H_5)_3N: + \underset{+}{C_2H_5}\rightarrow\underset{-}{I} \longrightarrow \left[(C_2H_5)_4N\right]^{+} \quad \overset{-}{I}$$

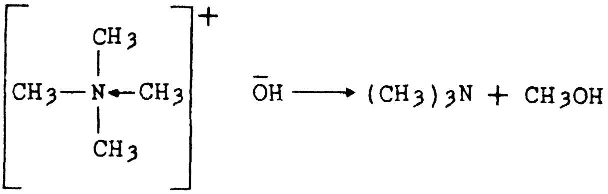
tetraethylammonium iodide

This addition usually proceeds most readily with alkyl iodides. It is probable that the formation of the new carbon-nitrogen bond proceeds simultaneously with the breaking of the carbon-iodine bond. In this case the nitrogen atom acts as an acceptor for a carbonium ion. The quaternary salts are converted to the corresponding hydroxides when treated with moist silver oxide:

$$\left[(C_2H_5)_4N\right]^{+} \overset{-}{I} + \overset{+}{Ag}\overset{-}{O}H \longrightarrow \left[(C_2H_5)_4N\right]^{+} \overset{-}{O}H + AgI$$

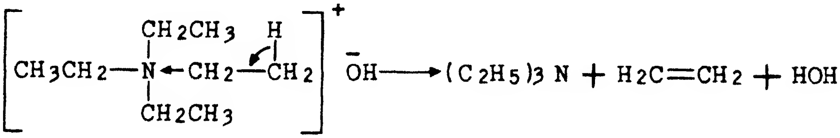
These hydroxides are strong bases and the hydroxyl group is held to the ammonium group by an ionic bond similar to the bond in sodium hydroxide.

Although the quaternary hydroxides are fairly stable, they decompose when heated. Tetramethyl ammonium hvdroxide, for example, forms trimethylamine and methyl alcohol:



$$\left[\begin{array}{c} CH_3 \\ | \\ CH_3—N\leftarrow CH_3 \\ | \\ CH_3 \end{array}\right]^{+} \overset{-}{O}H \longrightarrow (CH_3)_3N + CH_3OH$$

The quaternary bases of higher molecular weight usually give a tertiary amine, an olefin, and water:



$$\left[\begin{array}{ccccc} & CH_2CH_3 & & H & \\ & | & & | & \\ CH_3CH_2— & N & \leftarrow CH_2 & \swarrow & CH_2 \\ & | & & & \\ & CH_2CH_3 & & & \end{array}\right]^{+} \overset{-}{O}H \longrightarrow (C_2H_5)_3N + H_2C{=}CH_2 + HOH$$

The greater electron attraction of the nitrogen atom is the primary cause of the cleavage of the nitrogen-carbon bond. The simultaneous elimination of a proton would facilitate the cleavage. The formation of the proton is undoubtedly induced by the fractional positive charge on the adjacent carbon atom. The presence of the hydroxyl ion may also be considered to promote proton formation.

When trimethyl ethyl ammonium hydroxide is heated, the ethyl group is eliminated (as ethylene) in preference to a methyl group. This is in accord with the belief that the ethyl group has a somewhat greater electron-release effect.

Quaternary ammonium salts also decompose when strongly heated:

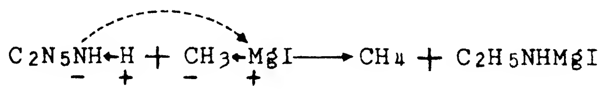
$$\left[(C_2H_5)_2N(CH_3)_2\right]^+ \bar{C}l \longrightarrow (C_2H_5)_2NCH_3 + CH_3Cl$$

The smallest alkyl group is usually eliminated as RX. This is not in agreement with the relative electron-release effects noted above. Here relative electron-release effects do not appear to be the predominant factor.

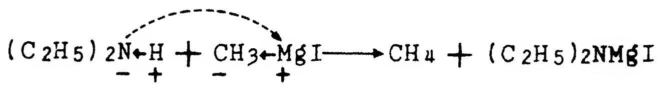
The reactions of the amines discussed above depend on the unshared electron pair on the nitrogen atom. Another group of reactions involves replacement of hydrogen atoms which are attached to the amino nitrogen atom. These reactions, of course, are limited to the primary and secondary amines. Hydrogen, when attached to nitrogen, may be regarded as active hydrogen and, under suitable conditions, is replaced by metals such as sodium:

$$2NH_3 + 2Na \longrightarrow \underset{\text{sodamide}}{2NaNH_2} + H_2$$

Primary and secondary amines react with Grignard reagents at ordinary temperatures to give compounds in which a hydrogen atom attached to nitrogen is replaced by —MgX:

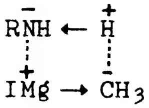


$$C_2N_5\underset{-}{NH}\leftarrow\underset{+}{H} + \underset{-}{CH_3}\leftarrow\underset{+}{Mg}I \longrightarrow CH_4 + C_2H_5NHMgI$$



$$(C_2H_5)_2\underset{-}{N}\leftarrow\underset{+}{H} + \underset{-}{CH_3}\leftarrow\underset{+}{Mg}I \longrightarrow CH_4 + (C_2H_5)_2NMgI$$

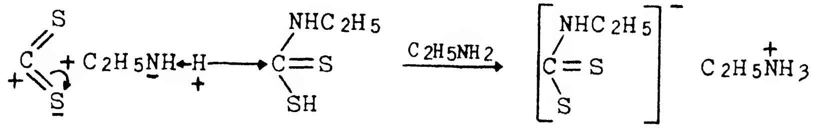
The derivative of the primary amine reacts with another molecule of methyl magnesium iodide, when heated, to form a second molecule of methane. These reactions are the basis of the Zerewitinov method for the estimation of primary and secondary amine groups. These reactions involve the displacement of a weak acid from its salt by the action of a stronger acid, the amine being the stronger acid, and the hydrocarbon methane, the weaker acid. The reactions are not to be regarded as proceeding through the formation of ions. It is more probable that the breaking of the old bonds and the formation of the new ones occur simultaneously and the energy of formation of the new bonds contributes to the cleavage of the old bonds:



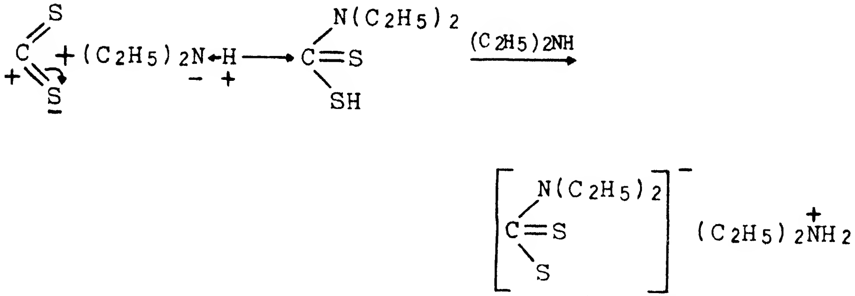
Actually the above reactions are exothermic and it may be concluded that the formation of the new linkages furnishes more than enough energy to promote the reaction.

Acylation of primary and secondary amines involves the replacement of hydrogen attached to nitrogen by an acyl radical. These reactions have been included under the reactions of the acid anhydrides and acyl chlorides.

Primary and secondary amines react characteristically with carbon disulfide in alcohol solution:



ethylammonium
ethyldithiocarbamate



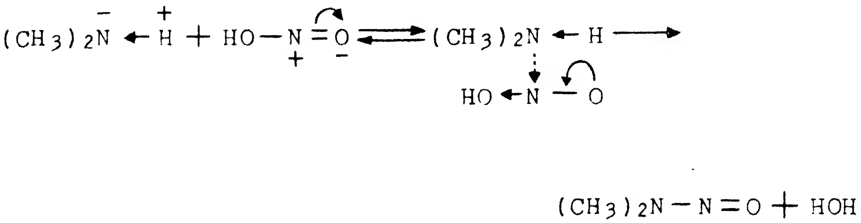
diethylammonium
diethyldithiocarbamate

The above reactions may be regarded as aldol-type additions with the $-\overset{|}{C}=S$ group acting as a carbonyl group. Carbon dioxide reacts in a similar manner.

Primary and secondary amines react in a very characteristic manner with nitrous acid ($NaNO_2 + HCl$). The reactions appear to be rather complex (117) and the mechanisms have not been definitely established. Secondary amines react with nitrous acid to form nitrosoamines and water. The reaction may be represented as follows:

$$(CH_3)_2\underset{-}{N}\leftarrow\underset{+}{H} + H\underset{-}{O}\leftarrow\underset{+}{N}=O \longrightarrow \underset{\text{nitrosodimethylamine}}{(CH_3)_2N-N=O + HOH}$$

Here, again, the reaction is not to be considered as an ionic one. The fractional charges present in polarized bonds may initiate reactions and thus serve the same purpose as if they possessed free ionic charges. In many cases it is most probable that the formation of new bonds and the cleavage of others must proceed simultaneously. The above reaction may be more accurately represented as follows:

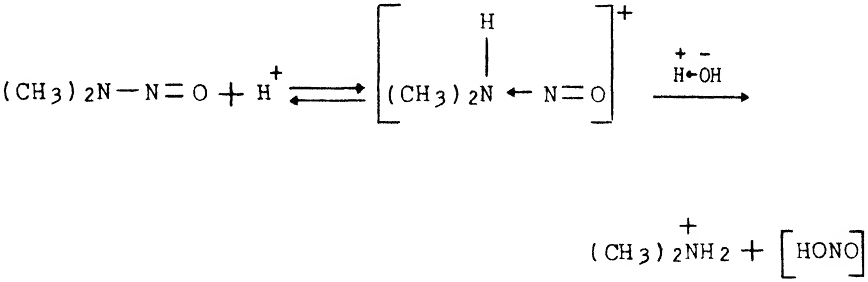


$$(CH_3)_2\overset{-}{N}\leftarrow\overset{+}{H} + HO-\underset{+}{N}=\underset{-}{O} \rightleftarrows \begin{array}{c}(CH_3)_2N\leftarrow H\\ \downarrow\\ HO\leftarrow N-O\end{array} \longrightarrow (CH_3)_2N-N=O + HOH$$

Nitrosyl chloride yields the same reaction product as that obtained with nitrous acid:

$$(CH_3)_2\underset{-}{N}\leftarrow\underset{+}{H} + \underset{-}{Cl}\leftarrow\underset{+}{N}=O \longrightarrow (CH_3)_2N-N=O + HCl$$

The aliphatic nitrosoamines are hydrolyzed by heating with hydrochloric acid with the formation of a salt of the secondary amine and nitrous acid (as its decomposition products). In some cases, nitrosyl chloride has been detected among the products. The following represents a possible course of reaction for the hydrolysis of nitrosoamines:

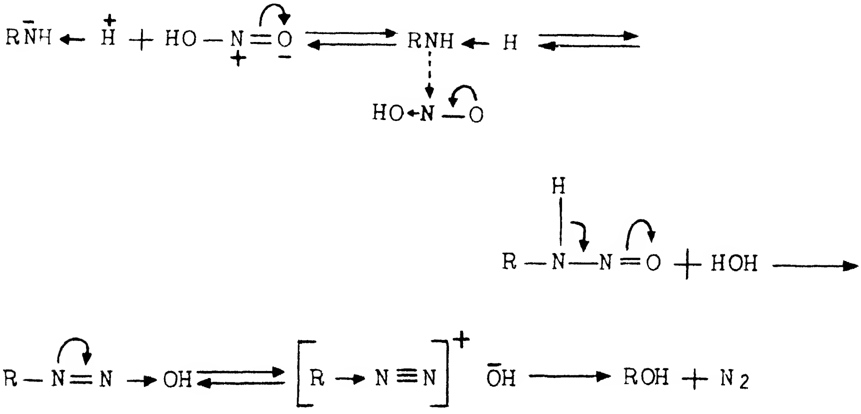


$$(CH_3)_2N-N=O + \overset{+}{H} \rightleftarrows \left[(CH_3)_2\overset{\overset{H}{|}}{N}\leftarrow N=O\right]^+ \xrightarrow{\overset{+\ -}{H\leftarrow OH}} (CH_3)_2\overset{+}{N}H_2 + \left[HONO\right]$$

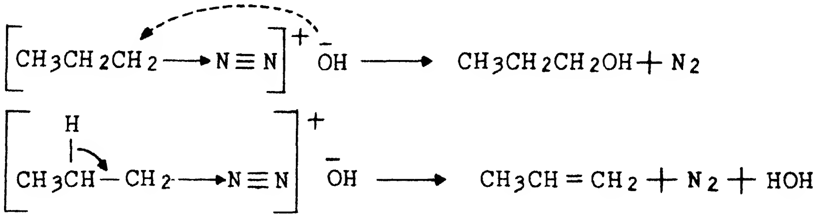
Primary amines are converted into alcohols and nitrogen by the action of nitrous acid:

$$RNH_2 + HONO \longrightarrow ROH + N_2 + HOH$$

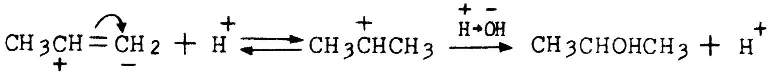
Only in the cases of methylamine and ethylamine are the reactions as simple as the above equation indicates. The higher primary amines usually give two isomeric alcohols and some olefin. Thus *n*-propylamine forms *n*-propyl alcohol, isopropyl alcohol, and propylene. The nature of the reaction products suggests that a carbonium ion is a necessary intermediate. Any postulated mechanism must not only explain the main course of reaction but the formation of isomeric alcohols and olefins as well. The intermediate formation of a diazonium compound, $\boxed{R—N\equiv N}^{+}$ $\bar{X}$, has been indicated only in a few exceptional cases. Assuming that such intermediates are formed in all cases, the following mechanism may be postulated:



The formation of an olefin and the mixture of alcohols from *n*-propylamine must be associated with the last step in the above reactions. It would seem, therefore, that the diazonium structure must account for the mixture of products. The positive charge on the nitrogen atom initiates the cleavage reaction, $\boxed{R\rightarrow N\equiv N}^{+}$. This tendency to cleave may be enhanced in either of two ways: (1) the hydroxyl ion may be attracted to the positively charged carbon and thus weaken the carbon-nitrogen bond; or (2) the elimination of a beta hydrogen would also weaken the carbon-nitrogen bond:



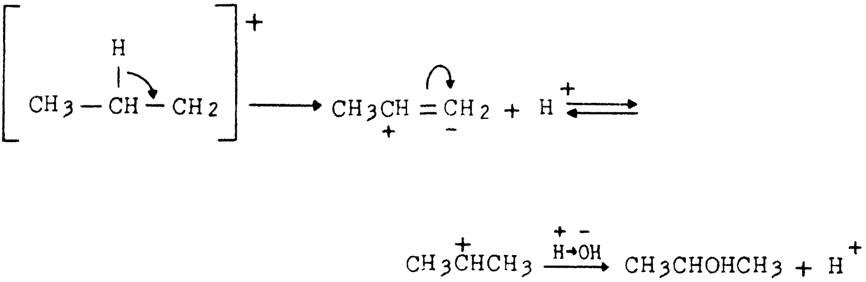
In acid solution, the propylene may be converted in part to isopropyl alcohol:



$$\mathrm{CH_3\underset{+}{C}H{=}\underset{-}{C}H_2 + \overset{+}{H} \rightleftharpoons CH_3\overset{+}{C}HCH_3 \xrightarrow{\overset{+}{H}\rightarrow\overset{-}{O}H} CH_3CHOHCH_3 + \overset{+}{H}}$$

The mixture of products obtained from *n*-propylamine could also be explained on the assumption that a free carbonium ion is formed as a transient intermediate:

$$\mathrm{CH_3CH_2\overset{+}{C}H_2 + \overset{+}{H}\rightarrow\overset{-}{O}H \longrightarrow CH_3CH_2CH_2OH + \overset{+}{H}}$$

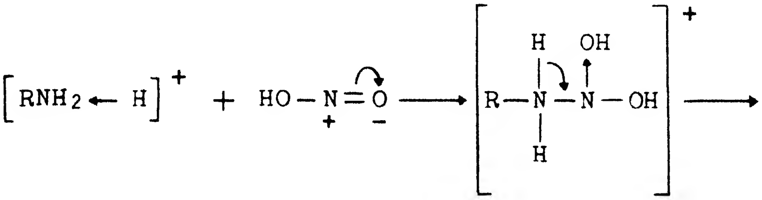


$$\left[\mathrm{CH_3-\overset{\overset{\displaystyle H}{|}}{C}H-CH_2}\right]^{+} \longrightarrow \mathrm{CH_3\underset{+}{C}H=\underset{-}{C}H_2 + \overset{+}{H} \rightleftharpoons}$$

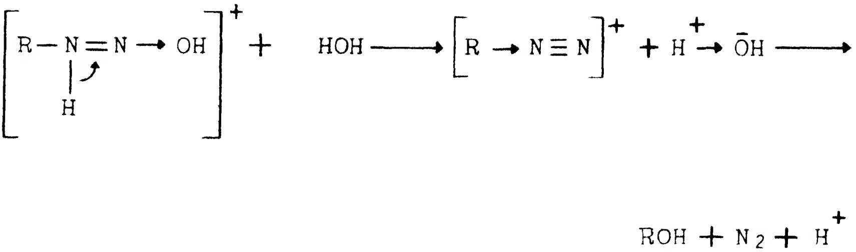
$$\mathrm{CH_3\overset{+}{C}HCH_3 \xrightarrow{\overset{+}{H}\rightarrow\overset{-}{O}H} CH_3CHOHCH_3 + \overset{+}{H}}$$

Evidence for the formation of carbonium ions, except in those cases where they are stabilized through resonance, is rather meager. Therefore, the first of the two mechanisms noted above is to be preferred. It should be noted, however, that the fundamental principles which are involved are practically the same for the two mechanisms.

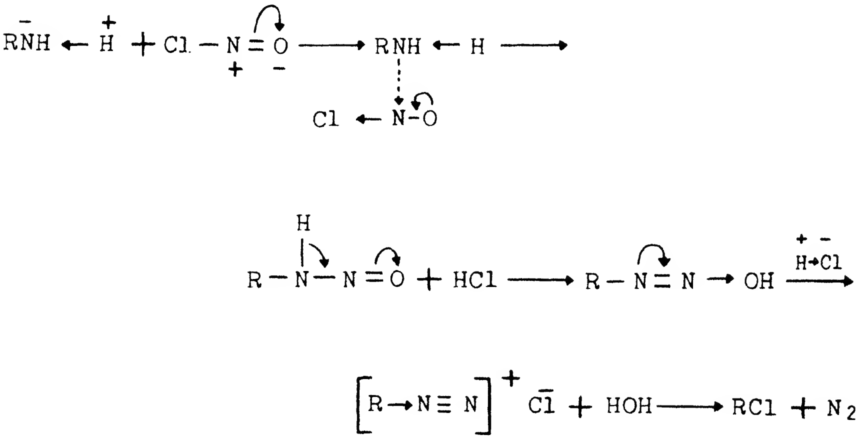
The reactions of primary amines with nitrous acid, similar to the decomposition of ammonium nitrite, are acid catalyzed and may be shown as follows:



$$\left[\mathrm{RNH_2 \leftarrow H}\right]^{+} + \mathrm{HO-\underset{+}{N}=\underset{-}{O}} \longrightarrow \left[\mathrm{R-\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{N}}-\overset{\overset{\displaystyle OH}{\uparrow}}{N}-OH}\right]^{+} \longrightarrow$$



Nitrosyl chloride reacts in a similar manner with primary amines to form nitrogen and alkyl chlorides:

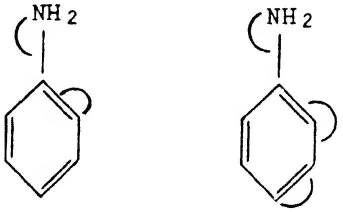


Apparently this reaction has not been extensively studied. The fact that some alkyl chloride is formed would indicate that the course of the reaction must be similar to the one suggested for primary amines and nitrous acid.

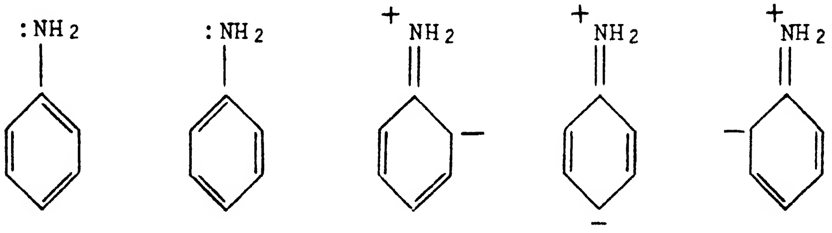
CHAPTER XXIII

Reactions of Aromatic Amines and Diazonium Compounds

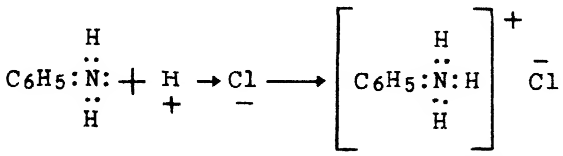
Many of the chemical properties of the aromatic amines are similar to those of the aliphatic amines. There are, however, some notable differences. For example, the aromatic primary amines are weaker bases than the aliphatic primary amines. In the chapter on the Reactions of the Aromatic Hydrocarbons, it was noted that the *o*- and *p*-directing influence of the amino group is due to the ability of the unshared electrons of the nitrogen atom to participate in resonance with the aromatic ring. The resonance may be shown as follows:



This effect is more readily understood from a consideration of all the important forms which contribute to the net structure:



The tendency of nitrogen to increase its covalency with the nuclear carbon atom serves to decrease the availability of nitrogen's unshared electron pair for accepting a proton. Aniline forms soluble salts with the common acids but its salts with weak acids are considerably hydrolyzed in water solution:



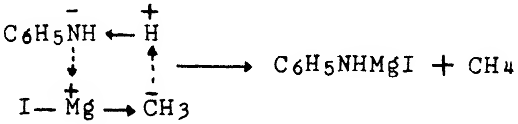
$$C_6H_5:\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}}}: + \underset{+}{H} \rightarrow \underset{-}{Cl} \longrightarrow \left[C_6H_5:\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}}}:H \right]^{+} \bar{Cl}$$

phenylammonium chloride

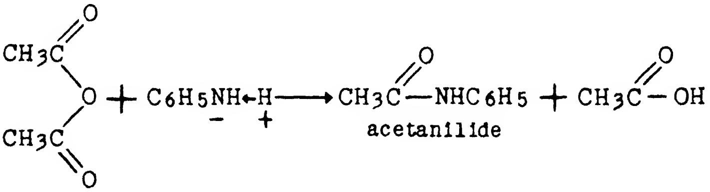
Secondary aromatic amines of the type of diphenylamine, $(C_6H_5)_2NH$, are less basic in character than the primary amines. This is to be expected, since more resonant structures in which the $-\overset{|}{C}=\overset{|}{N}-$ group occurs are possible due to the two benzene nuclei. For secondary amines of the type of methylaniline, the basicity is of the same order of magnitude as for aniline.

Aromatic tertiary amines of the type triphenylamine, $(C_6H_5)_3N$, show none of the usual basic properties. Mixed tertiary amines such as dimethylaniline, however, possess about the same basicity as aniline. The decreased availability of the nitrogen atom's unshared electron pair in triphenylamine is also evidenced by its failure to form quaternary ammonium salts. Dimethylaniline, however, reacts with alkyl halides to form quaternary salts.

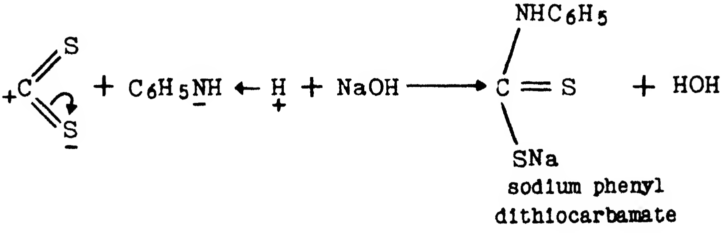
The decreased electron availability on nitrogen noted above also accounts for the fact that the tendency $\text{Ar}\underset{-}{\text{NH}}\leftarrow\underset{+}{\text{H}}$ is greater than for the aliphatic amines. In general, the aromatic primary amines and both the purely aromatic and mixed secondary amines give the reactions in which hydrogen attached to nitrogen is replaced. They decompose Grignard reagents



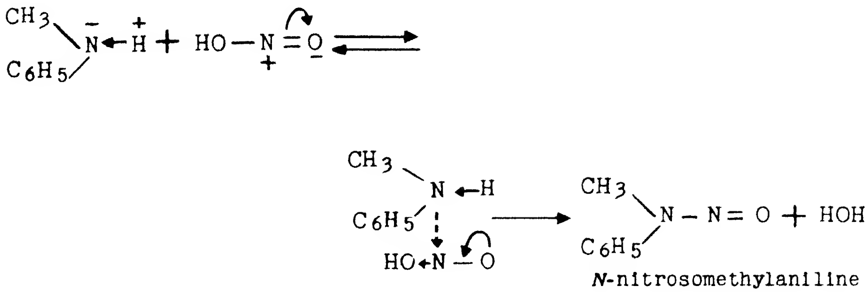
and they are readily acylated by acid anhydrides and acyl chlorides:



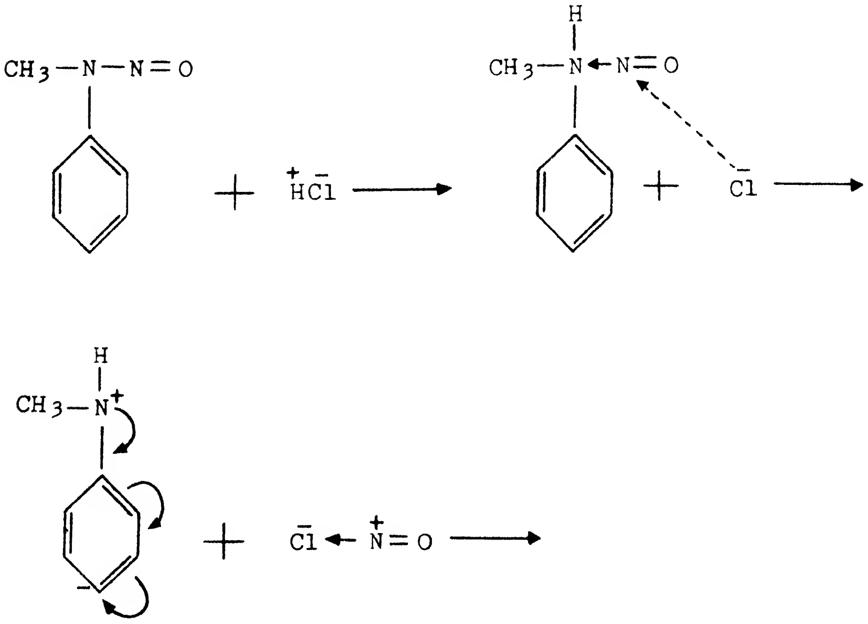
Aromatic amines do not combine with carbon disulfide at ordinary temperatures in the absence of ammonium hydroxide or an alkali such as sodium hydroxide. This difference in behavior from the aliphatic amines is due to the weakly basic nature of the aromatic amines:

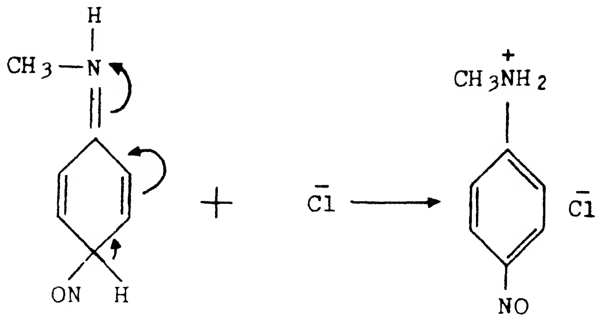


Both types of secondary amines react with nitrous acid to form N-nitrosoamines:



Acid hydrolysis of the aromatic nitrosoamines is complicated by the formation of nuclear substituted nitroso compounds. Nitrosomethylaniline may be converted completely to methylaniline by heating with hydrochloric acid in the presence of urea. The latter decomposes the nitrous acid as it is formed and thus prevents nitrosation of the aromatic nucleus. When nitrosomethylaniline is treated with a solution of hydrogen chloride in alcohol and ether and allowed to stand, it is converted to the hydrochloride of *p*-nitrosomethylaniline (Fischer-Hepp reaction). Hydrogen chloride plays a specific role in this reaction. Sulfuric acid does not cause the so-called rearrangement. The hydrogen halide by reaction with the nitrosoamine produces a nitrosyl halide which then reacts at the para position:





It is probable that the formation of an anilinium ion, through the attachment of a proton, assists in the cleavage of the nitrogen-nitrogen bond.

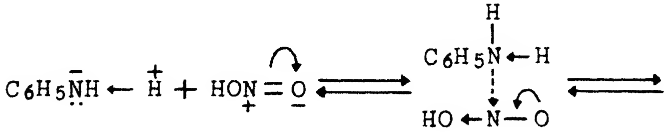
Aromatic primary amines react with nitrous acid to form diazonium salts. Because of the instability of diazonium compounds, the reactions are often carried out at 0°-10° C. Usually sodium nitrite is added to a solution of the amine in hydrochloric acid solution. The acid must be used in excess of that required for the reaction

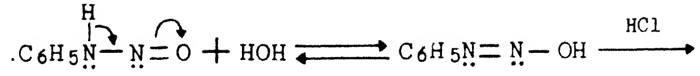
$$ArNH_2 + 2HCl + NaNO_2 \longrightarrow \left[ArN_2\right]^{+}\bar{Cl} + NaCl + 2H_2O$$

in order to retard the coupling of the diazonium compound with the amine. The diazonium cation may resonate between two unperturbed forms:

$$\underset{\text{I}}{Ar-\overset{\cdot\cdot}{N}::\overset{+}{N}:} \longleftrightarrow \underset{\text{II}}{Ar-\overset{+}{N}:::N:}$$

A kinetic study of the reaction has been reported (118) but the exact course of the diazotization reaction has not been established. The first step undoubtedly involves an electrophilic attack on the aromatic amine. The attacting reagent may be N_2O_3, NOCl, or HONO. The following postulated mechanism appears probable, although the reaction may be more complicated than represented:





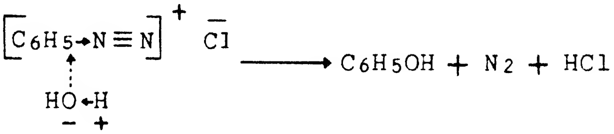
$$C_6H_5\overset{H}{\underset{..}{N}}-\underset{..}{N}=O + HOH \rightleftharpoons C_6H_5\underset{..}{N}=\underset{..}{N}-OH \xrightarrow{HCl}$$

$$\left[C_6H_5\ddot{N}=N:\right]^{+}\overset{-}{Cl} \longleftrightarrow \left[C_6H_5N\equiv N:\right]^{+}\ \overset{-}{Cl}$$

benzene diazonium chloride

Two general types of reactions are known for diazonium compounds: (1) decomposition reactions in which the two nitrogen atoms are evolved as free nitrogen; and (2) condensation or coupling reactions in which the two nitrogen atoms are retained in the reaction product. The diazonium cation can react as either of its resonant forms depending on the demand of the reagent. The first type of reaction appears to be characteristic of form II and may be regarded as a nucleophilic displacement reaction.

Phenols are formed when diazonium salts are heated with water:



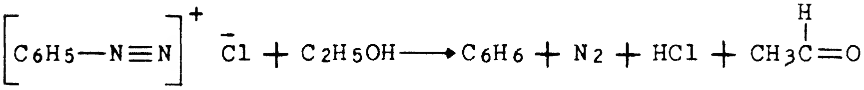
$$\left[\underset{\underset{\overset{-}{HO}\leftarrow\overset{+}{H}}{\vdots\uparrow}}{C_6H_5}\rightarrow N\equiv N\right]^{+}\ \overset{-}{Cl} \longrightarrow C_6H_5OH + N_2 + HCl$$

The formation of the new bonds probably proceeds simultaneously with the cleavage of the old bonds. The over-all result is the replacement of the $\overset{+}{-N\equiv N}$ group with the more nucleophilic hydroxyl group. The solution must be kept strongly acidic to retard the coupling reaction of the diazonium cation with the phenol.

A similar reaction takes place with methyl alcohol:

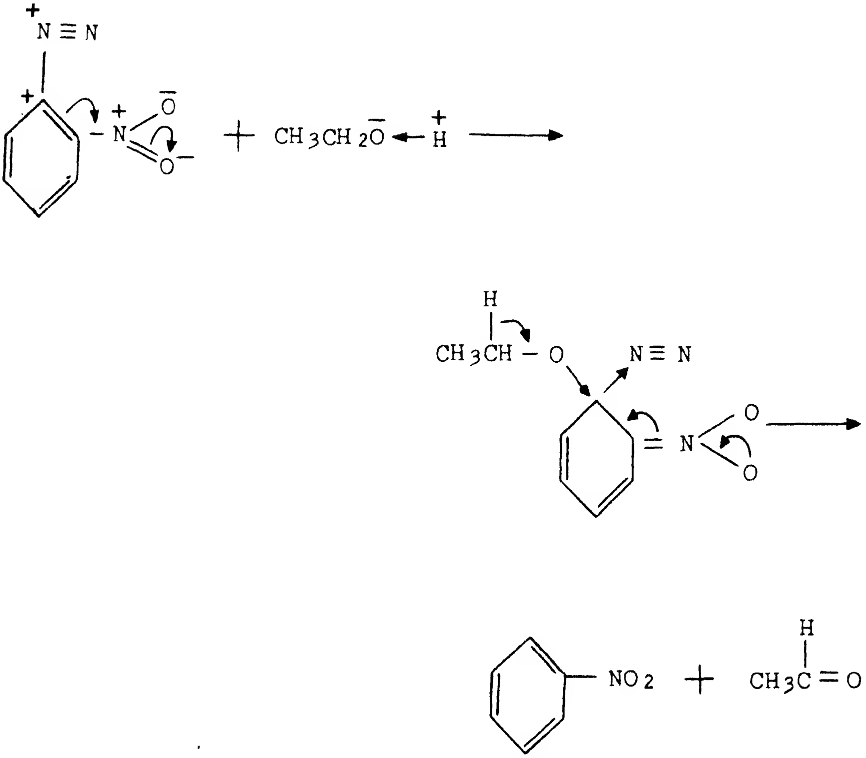
$$\left[C_6H_5\longrightarrow N\equiv N\right]^{+}\ \overset{-}{Cl} + \overset{-}{CH_3O}\leftarrow\overset{+}{H} \longrightarrow C_6H_5OCH_3 + N_2 + HCl$$

With ethyl alcohol a secondary reaction often occurs:



$$\left[C_6H_5-N\equiv N\right]^{+}\ \overset{-}{Cl} + C_2H_5OH \longrightarrow C_6H_6 + N_2 + HCl + CH_3\overset{H}{\overset{|}{C}}=O$$

This reaction predominates when an electron-attracting group is present in the aromatic nucleus, particularly if it is in the ortho position. The elimination of nitrogen from the original diazonium ion would be greatly retarded by the presence of an electron-attracting group in the ortho position. The loss of a pair of electrons from the ethoxy ion to the diazonium ion would account for the elimination of nitrogen and the formation of acetaldehyde:



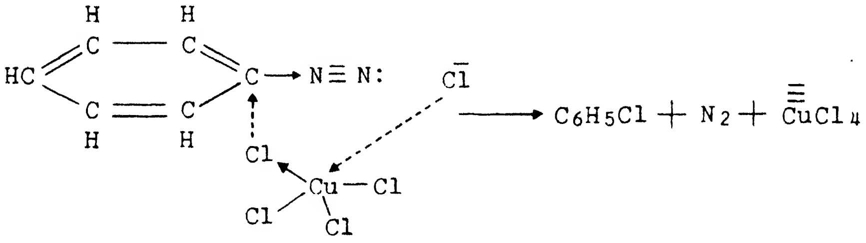
This reaction is similar to the reaction of *p*-nitrochlorobenzene with alkalies. In both cases the presence of an electron-attracting nitro group opens the way for a nucleophilic attack. It has been suggested that the above reactions may follow a radical mechanism which involves the formation of free phenyl radicals (119). This suggestion is based on the fact that rates of the reactions with methyl alcohol and ethyl alcohol are identical. Hence they must possess a common rate-determining step, which is assumed to be the formation of free phenyl radicals.

The $-N_2Cl$ group may be replaced by iodine by treating an acid solution of a diazonium salt with potassium iodide:

$$\left[C_6H_5 \rightarrow N \equiv N\right]^{+} \overset{-}{Cl} + \overset{+}{H} \rightarrow \overset{-}{I} \longrightarrow \underset{\text{Iodobenzene}}{C_6H_5I} + N_2 + HCl$$

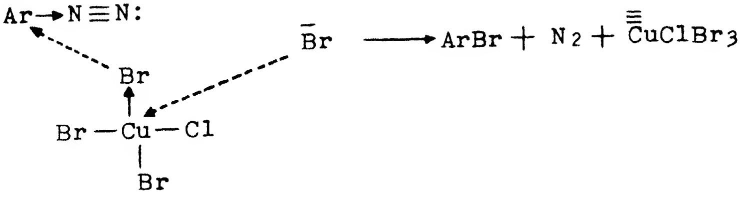
Chlorine or bromine cannot be introduced by such simple means. The diazonium compounds when heated with hydrochloric or hydrobromic acid give very poor yields of chloro- or bromobenzene. The preparation of chloro or bromo compounds in good yields requires the presence of a cuprous halide (Sandmeyer reaction). Free copper may also be used in acid solution to effect the reaction. It is possible that where copper is used the cuprous ion, formed by reaction with the acid, is the effective reagent. It has been shown that a double salt of cuprous halide and diazonium salt is formed in some cases. These complexes readily decompose with the formation of an aromatic halide, cuprous halide, and nitrogen. These results have led some chemists to suggest that in these complexes the copper atom of the cuprous halide coordinates with one of the nitrogen atoms of the diazonium compound. Such a coordination might be expected to weaken the carbon-nitrogen bond and thus facilitate the normal decomposition reaction. This explanation, however, leaves certain questions unanswered.

Hodgson (120) has recently published an excellent review of his own work and the work of others on the Sandmeyer reaction. The mechanism which he suggests is in good agreement with experimental evidence:

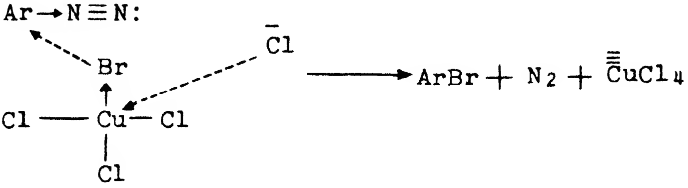


In this mechanism it is assumed that cuprous chloride dissolves in hydrochloric acid to form a complex anion. The latter is attracted to the diazonium cation and the resulting complex decomposes through the simultaneous formation of a carbon-chlorine bond and cleavage of the carbon-nitrogen bond.

This mechanism may be used also to interpret the results obtained from mixed Sandmeyer reactions (120). For example, the diazonium salt from *p*-nitroaniline was decomposed in two ways: (1) by cuprous chloride in concentrated hydrobromic acid; and (2) by cuprous bromide in concentrated hydrochloric acid. The ratio of 4-chloronitrobenzene and 4-bromonitrobenzene which resulted from (1) was 4 : 96, while for (2) the ratio was 60 : 40. The dissolution of CuCl in HBr was assumed to give the complex anion $\overset{\equiv}{\mathrm{CuClBr_3}}$, and the following mechanism was proposed:

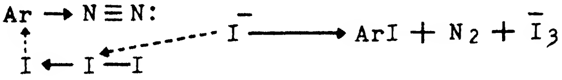


Since bromine is more reactive than chlorine, through the operation of inductomeric effects, a preponderance of the bromo compound would be expected. In (2) the attacking anion will be $\overset{\equiv}{\mathrm{Cu}}\mathrm{Cl_3Br}$:

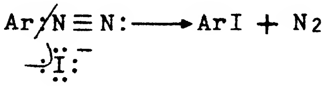


In this case the diazonium group will be replaced initially by a bromine atom. It will be noted, however, that the original anion is not reformed but $\overset{\equiv}{\mathrm{Cu}}\mathrm{Cl_4}$ is formed instead. The competition introduced by increasing concentrations of $\overset{\equiv}{\mathrm{Cu}}\mathrm{Cl_4}$ results in the formation of more of the chloro compound as would be expected.

A logical explanation for the action of iodides on acid solutions of diazonium salts is also included in the paper referred to above. It is suggested that a small amount of free iodine is formed as the result of oxidation of the iodide ion by the diazonium ion. The iodine then combines with the iodide present to form the complex anion I_3^-. The latter then acts as a halogen carrier in the same manner as that already noted for $\overset{\equiv}{\mathrm{Cu}}\mathrm{X_4}$:

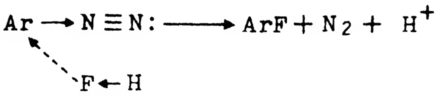


Only a very small amount of iodine could initiate the reaction since the anion, I_3^- is constantly being regenerated from the iodide which is present. This mechanism is supported by the following facts. Potassium iodide slowly decomposes a diazonium compound in acetic acid solution. If sodium bisulfite or sodium thiosulfate was added first, however, subsequent addition of potassium iodide gave no iodo compound. The addition of cupric sulfate produced an immediate precipitate of the iodo compound. Theoretically the iodo compound might result from the oxidation-reduction reaction by the direct combination of aryl radicals and free iodine:



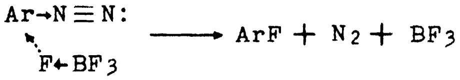
If this were the only course of reaction, diaryl formation would be expected and this is not the case. This reaction, therefore, must take place to a very slight extent and merely serves to initiate the main reaction.

An explanation for the poor yields of fluoro compounds obtained from diazonium salts and hydrofluoric acid is included in the paper referred to above. Hydrofluoric acid, in aqueous solution, consists largely of H^+ and HF_2^- and a small amount of un-ionized HF. The attraction of fluorine for hydrogen may thus retard the formation of the complex cuprous anion, $\overset{\equiv}{\mathrm{Cu}}\mathrm{F}_4$. It is stated that the small yield of fluoro compound results from the direct attack of the un-ionized HF on the diazonium cation:



$$\begin{array}{l}\mathrm{Ar}\rightarrow\mathrm{N}\equiv\mathrm{N}: \longrightarrow \mathrm{ArF}+\mathrm{N}_2+\mathrm{H}^+\\ \quad\nwarrow\\ \qquad\mathrm{F}\leftarrow\mathrm{H}\end{array}$$

The introduction of fluorine into the aromatic nucleus may be accomplished in many cases by the thermal decomposition of diazonium fluoborates $(\mathrm{Ar—N}\equiv\mathrm{N})^+\mathrm{BF}_4^-$. The latter are prepared by the addition of fluoboric acid to the diazonium solution. They are difficultly soluble and relatively stable. The decomposition of the diazonium fluoborates, presumably, is analogous to the decomposition of diazonium salts in the presence of $\overset{\equiv}{\mathrm{Cu}}\mathrm{X}_4$:



$$\begin{array}{l}\mathrm{Ar}\rightarrow\mathrm{N}\equiv\mathrm{N}:\\ \nwarrow \qquad\qquad\quad \longrightarrow \mathrm{ArF}+\mathrm{N}_2+\mathrm{BF}_3\\ \mathrm{F}\leftarrow\mathrm{BF}_3\end{array}$$

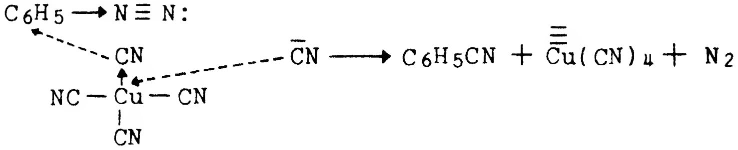
Cupric, ferric, and cobalt salts also form complex anions with halide ions which decompose diazonium cations in a manner similar to that noted for cuprous salts. It is believed that they function with comparable efficiency only when the diazonium cation is sufficiently positive (as when a nitro group is present in the aromatic ring).

Hodgson concludes that diaryl formation in the Sandmeyer reaction is best accounted for by a different mechanism from that suggested for the formation of halogen compounds. Diaryl formation is largely determined by the concentration of the complex cuprous anion. When the concentration of the latter is high, the chief attack is on the carbon atom which is attached to the diazonium group. It was noted, however, that when the concentration of the complex anion was reduced by dilution with water, diaryl formation was increased. In more dilute solution more free cuprous chloride would be present, and it is believed that the latter is oxidized to the cupric ion with the simultaneous formation of diaryl:

$$2\mathrm{Ar{:}N}\equiv\mathrm{N{:}} + 2\mathrm{Cu}^+ \longrightarrow \mathrm{Ar{:}Ar} + 2\mathrm{N}_2 + 2\mathrm{Cu}^{++}$$

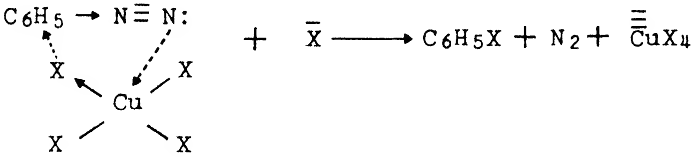
The increase in diaryl formation was accompanied by an increase in the amount of phenol formed. This would be expected because of the higher concentration of water present in the more dilute solutions.

Replacement of $-N_2Cl$ by the cyanide group may be effected by adding the diazonium solution to a warm solution of cuprous cyanide in potassium cyanide. Since potassium cyanide alone is ineffective, it is probable that the attacking agent is the complex anion $\overset{\equiv}{C}u(CN)_4$:



This mechanism is simply an adaptation of the Hodgson mechanism for the cuprous halide reactions.

Experimental data for the Sandmeyer reactions indicate that cuprous salts serve as carriers for nucleophilic halide and cyanide ions. If the above mechanisms are entirely correct, however, it is difficult to understand why the halide or cyanide ions do not directly attack the diazonium cation rather than coordinating with the cuprous salt as an intermediate step. If it be assumed that the copper atom plays an active role in the formation of the complex, a logical answer to this question may be obtained:



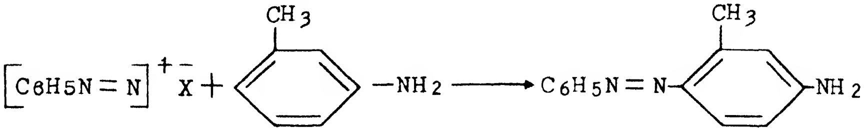
The coordinate linkages are shown as being formed simultaneously. The temporary coordination of the copper atom with nitrogen would also assist in the cleavage of the C—N bond. After the cleavage of this bond, nitrogen is liberated and the complex cuprous anion is re-formed through the recovery of a halide ion from the solution.

The condensation or coupling reactions appear to be characteristic of form I of the diazonium cation. These reactions are carried out in weakly acidic, neutral, or basic solutions. In general, diazonium compounds condense with compounds containing so-called active hydrogen, providing a stable bond may be formed. In these reactions the diazonium cation behaves as an electrophilic reagent. With certain primary aromatic amines, diazoamino derivatives are formed:

$$\left[C_6H_5N=N\right]^{+}\overset{-}{X} + \overset{+}{H} \rightarrow \overset{-}{H}NC_6H_5 \longrightarrow C_6H_5N=N-HNC_6H_5$$

benzene diazoaminobenzene

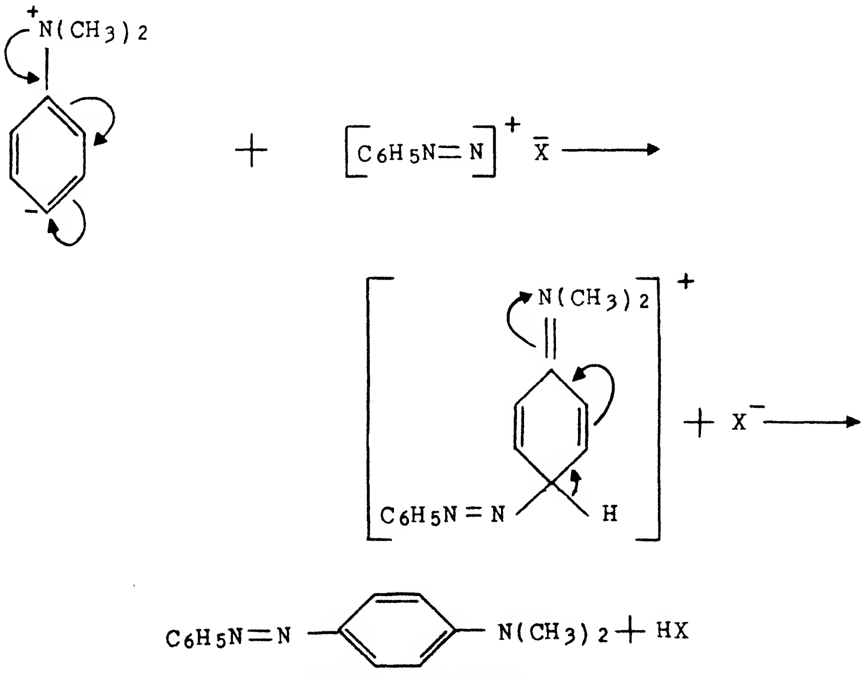
With other aromatic primary amines, nuclear substitution takes place and azo compounds are formed. The magnitude of electron availability in the ring apparently determines whether a diazoamino compound or an azo compound will be formed:



m-toluidine

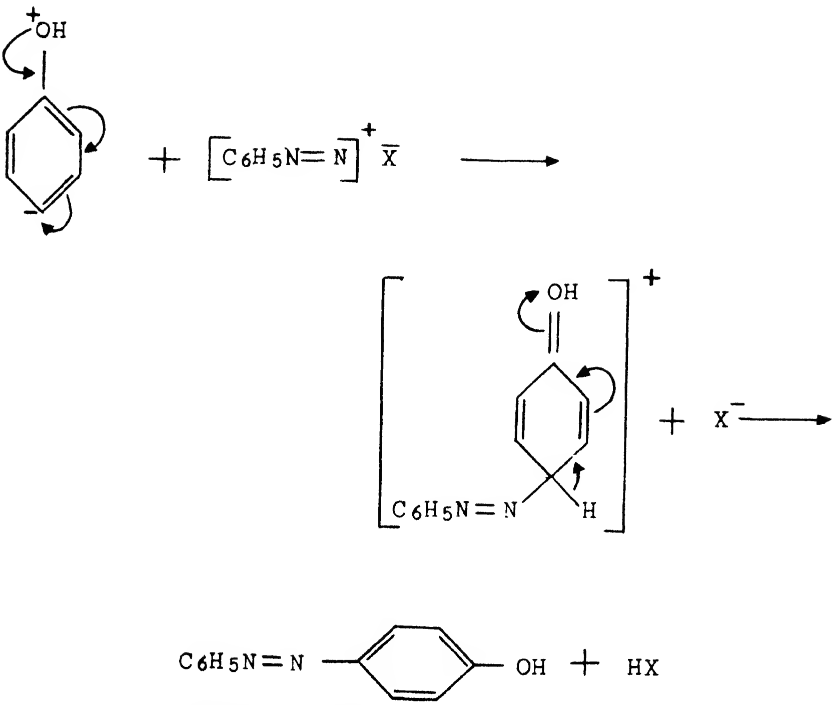
o-methyl-*p*-amino-benzene azobenzene

With tertiary aromatic amines only azo compounds may be formed, since there is no hydrogen attached to the nitrogen atom. The formation of the azo compounds is best represented as an aromatic substitution reaction:



p-dimethylaminobenzene azobenzene

A similar reaction occurs with the phenols.



p-hydroxybenzene
azobenzene

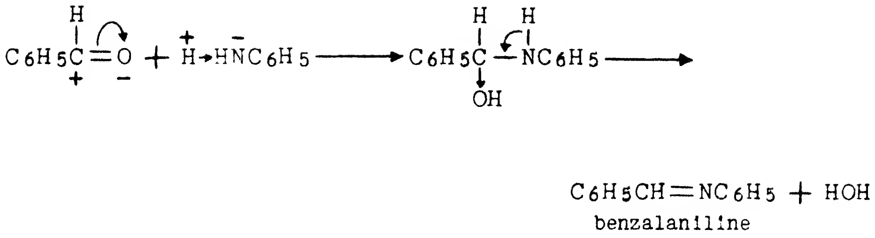
Other reactions have been reported which appear to follow radical mechanisms. For example, when an aqueous solution of a sodium aryldiazotate is stirred with a liquid organic compound of the type C_6H_5R, the following reaction occurs (121):

$$ArN{=}NOH + C_6H_5R \longrightarrow ArC_6H_4R + N_2 + HOH$$

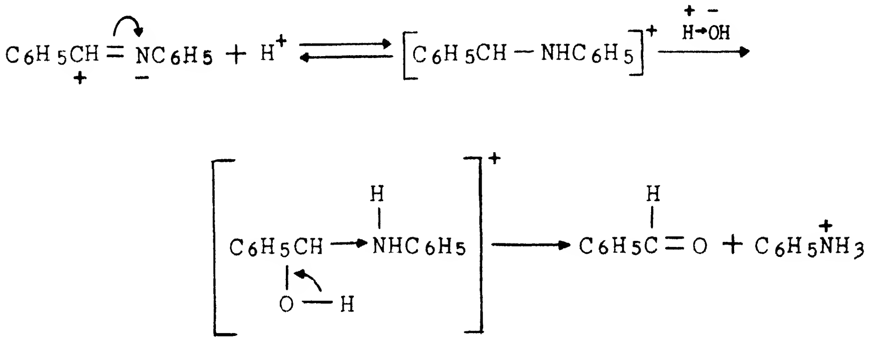
Ortho and para substituted products are formed regardless of the nature of R ($R{=}CH_3$, Br, NO_2, or CN). The fact that the entering group does not follow the directive influences noted for electrophilic and nucleophilic substitutions suggests that the free phenyl radical is the actual reactant.

At the present time it is difficult to classify all of the reactions of diazonium and diazo compounds in terms of mechanism. It may be said that in many of their reactions they appear to react as electrophilic reagents and in others they may function as a source of free aromatic radicals.

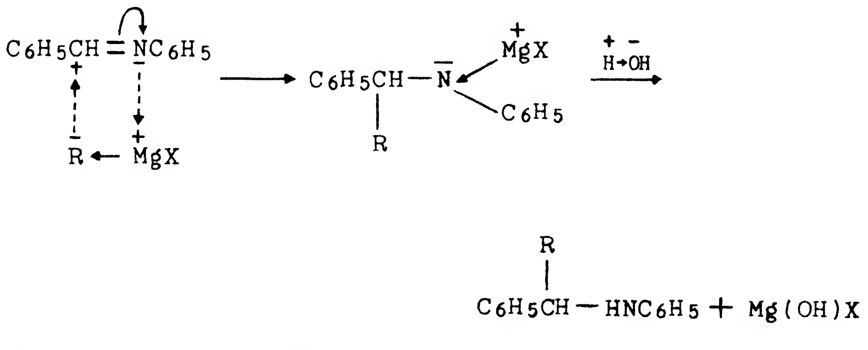
The reaction of aromatic primary amines with aldehydes leads to the formation of anils or Schiff bases:



The anils are weak bases and are readily hydrolyzed by dilute acids but not by aqueous alkalies:

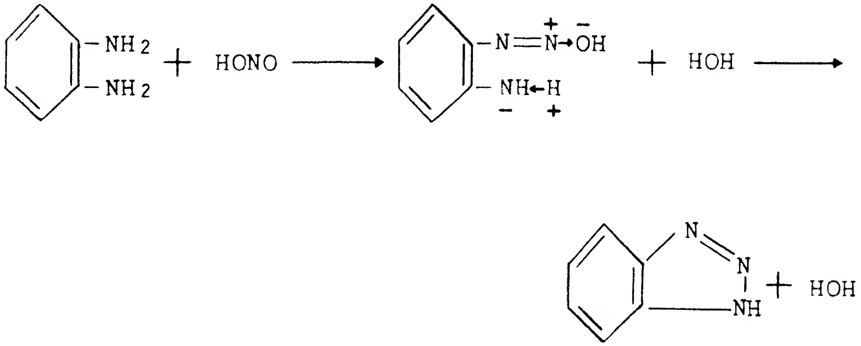


Nitrogen is more electron attracting than carbon and the functional group, $-\overset{|}{C}{=}N-$, undergoes addition reactions through the operating of an electromeric shift similar to that noted for the carbonyl group. For example, with Grignard reagents these bases form addition products which are hydrolyzed by water to give secondary amines:

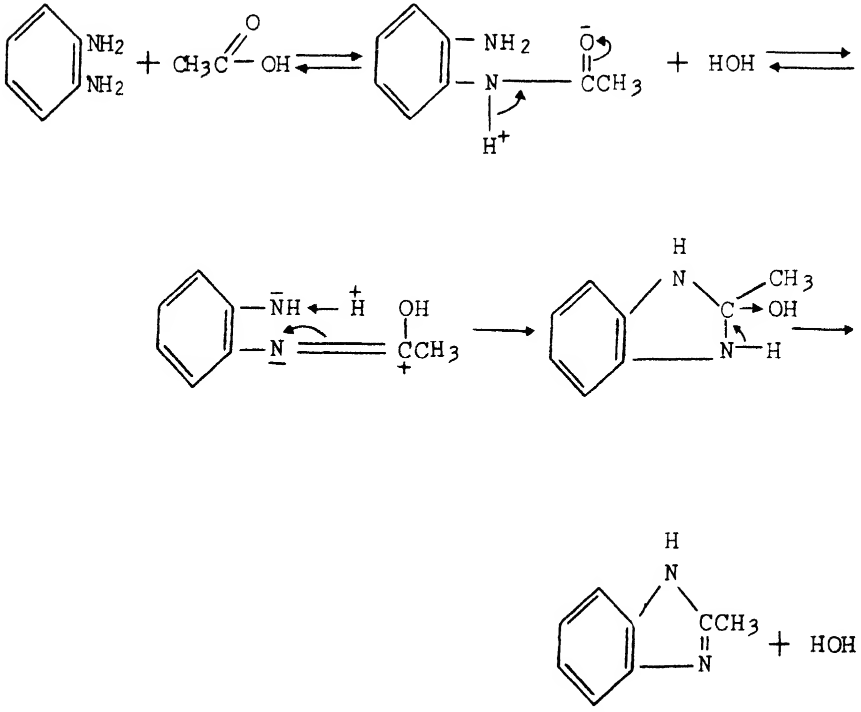


Other characteristic carbonyl reagents such as hydrogen cyanide and sodium bisulfite also have been observed to add to Schiff bases. The addition of active hydrogen compounds has been discussed previously under the Knoevenagel and Mannich reactions.

Aromatic diamines. The reactions of the meta and para diamines resemble those of the primary aromatic amines. The ortho diamines, however, are characterized by a tendency to undergo ring closures to form heterocyclic compounds. Attempted diazotization of *o*-phenylenediamine results in the formation of aziminobenzene:

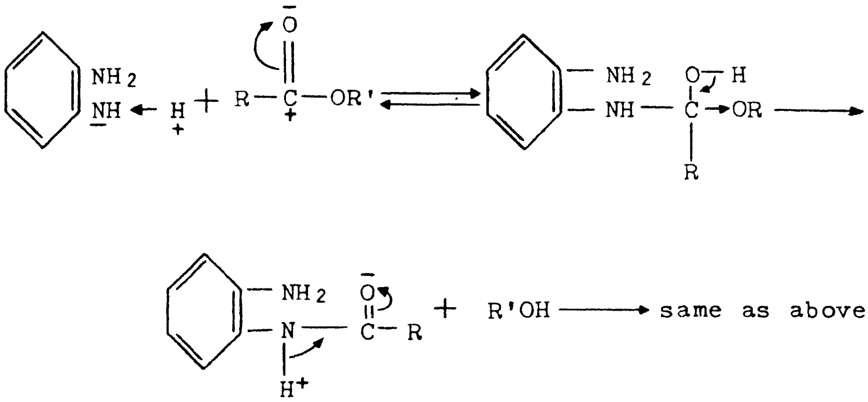


o-Phenylenediamine when heated with organic acids in the presence of hydrochloric acid yields benzimidazoles:

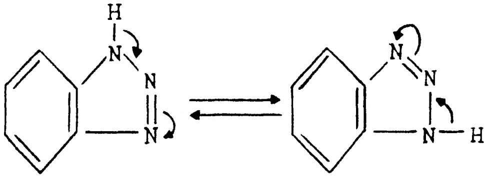


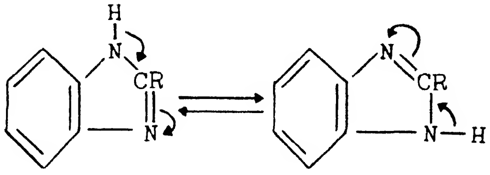
2-methylbenzimidazole

2-Alkyl benzimidazoles are also formed when *o*-phenylenediamine is heated with an amide or an ester (94) :



The aziminobenzene and benzimidazoles shown above are tautomeric compounds and are best represented as follows:

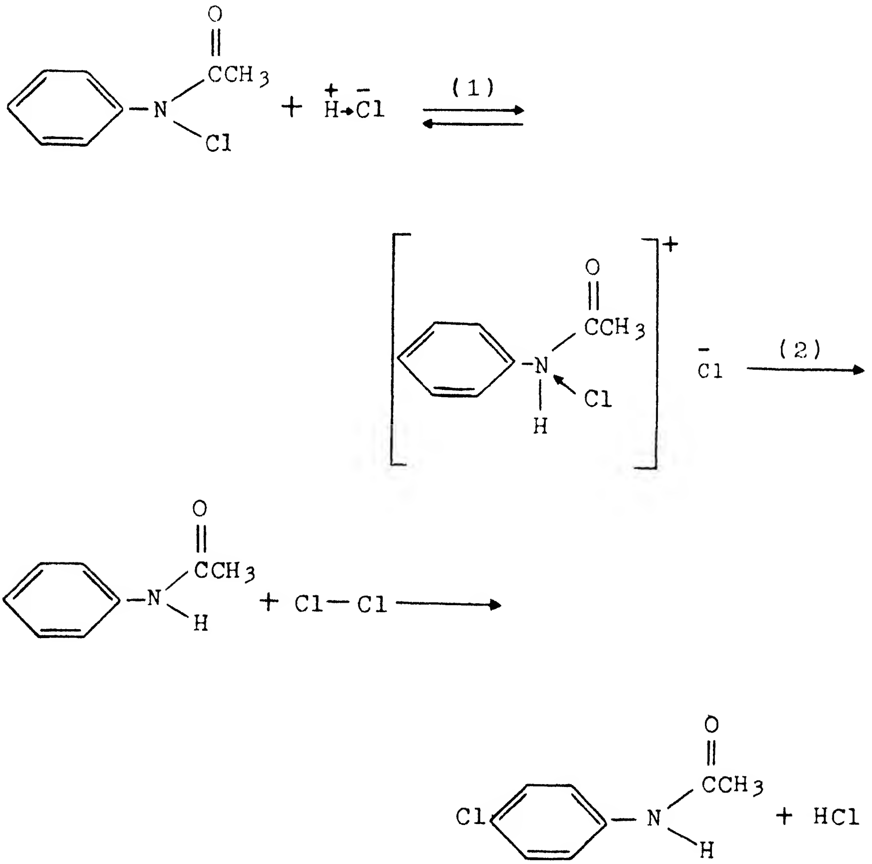




CHAPTER XXIV

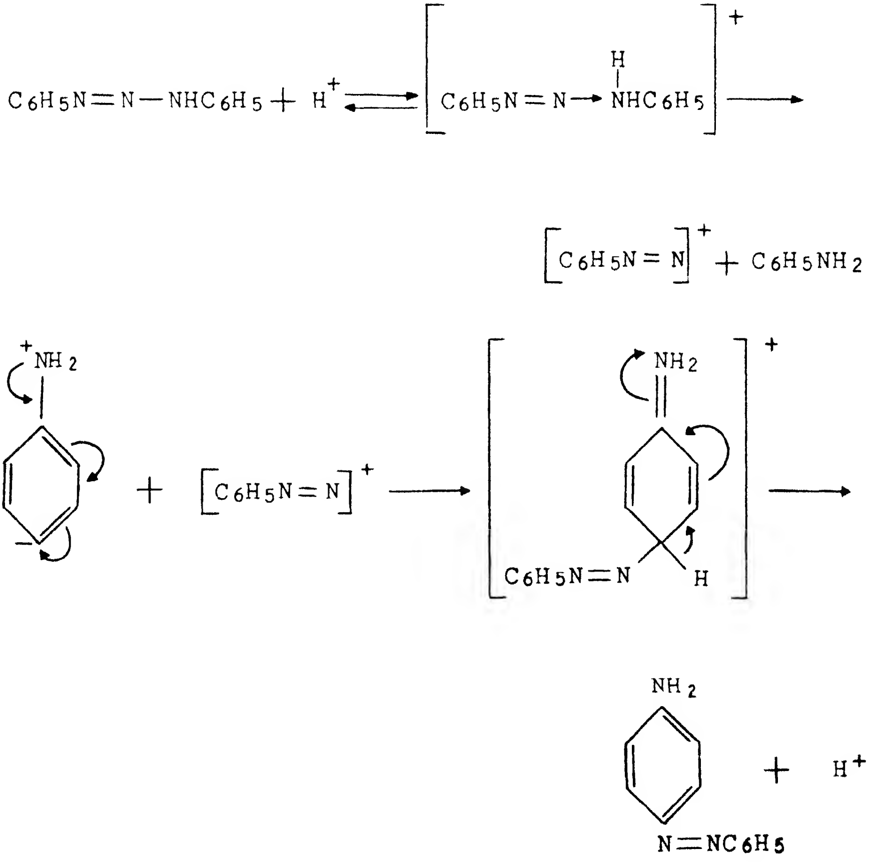
Isomerization Reactions of N-Substituted Aromatic Amines

These reactions involve the migration of a substituent from the amino nitrogen atom to the ortho or para position in the aromatic nucleus. An example which has been carefully investigated is the rearrangement of N-chloroacetanilide into *p*-chloroacetanilide. In aqueous solution the reaction is catalyzed by hydrochloric acid but not by sulfuric acid or acetic acid. The following intermolecular type of mechanism (76) accounts for the known facts:



The rate of the rearrangement is primarily dependent on the nature of the halogen atom which is attached to nitrogen. Bromine would be expected to show greater stability as a positive ion than chlorine. Consequently it is not surprising that N-bromoacetanilide rearranges, with hydrobromic acid as the catalyst, much more rapidly than does N-chloroacetanilide with hydrochloric acid. The last step in this rearrangement involves a nuclear substitution.

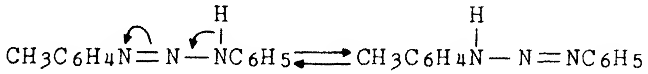
The rearrangement of diazoamino compounds into aminoazo compounds is effected by acids. The *p*-aminoazo derivative is usually obtained, although an ortho compound may be formed if the para position is blocked by the presence of a substituent. The conversion of benzenediazoaminobenzene into *p*-aminobenzeneazobenzene is a well-known example of this type of reaction. The reaction is usually carried out by heating a solution of benzenediazoaminobenzene in aniline in the presence of aniline hydrochloride. The steps in this rearrangement are well established (122). The phenylammonium ion acts as an acid catalyst or proton donor. Fission of the diazoamino compound into benzene diazonium chloride and aniline is induced by the introduction of a positive charge. The cleavage products then react to form the aminoazo compound:



When dimethylaniline is used as the solvent and its hydrochloride used as the acid catalyst, benzenediazoaminobenzene yields *p*-dimethylaminobenzeneazobenzene. This is excellent evidence for an intermolecular mechanism.

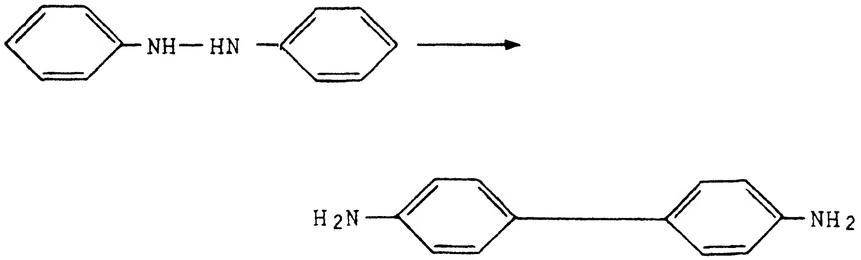
The rearrangement can also be carried out in hydrochloric acid solution, but the yield of *p*-aminobenzeneazobenzene is low due to the formation of phenol from the interaction of benzene diazonium chloride and water. When the reaction is carried out in hydrochloric acid solution in the presence of β-naphthol, it is possible to account for 91 per cent of the benzene diazonium chloride as 1-benzeneazo-2-naphthol (122). In this case the coupling reaction takes place much more rapidly than the reaction with water.

The rearrangement of an unsymmetrical diazoamino compound may give rise to two different aminoazo compounds due to the tautomeric nature of the diazoamino group:

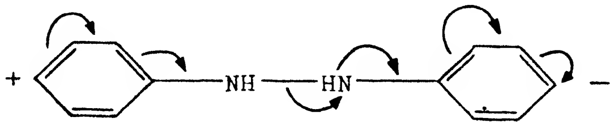


$$CH_3C_6H_4N{=}N{-}\overset{H}{N}C_6H_5 \rightleftharpoons CH_3C_6H_4\overset{H}{N}{-}N{=}NC_6H_5$$

The rearrangement of hydrazobenzene into 4,4′-diaminodiphenyl (benzidine) is another example of isomerization involving migration from side chain to nucleus:

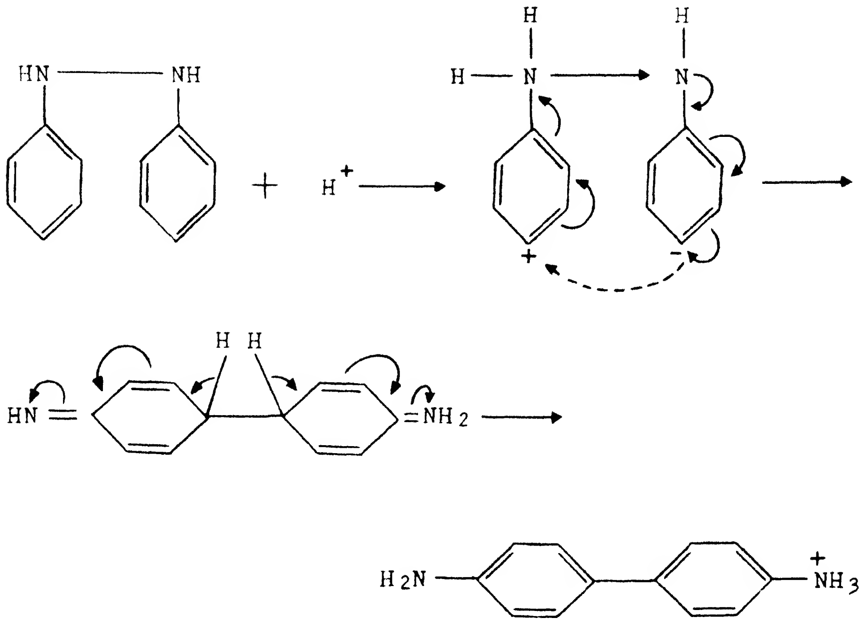


This reaction has been shown to be intramolecular (123). The change is usually carried out under the catalytic influence of acids. The fact that it is an intramolecular reaction must mean that the 4,4′ positions come within each other's sphere of influence before the nitrogen-to-nitrogen bond is cleaved. Recalling the electromerism and resonance encountered in the reactions of aniline, the electron displacements necessary for the rearrangement of benzidine may be shown as follows:

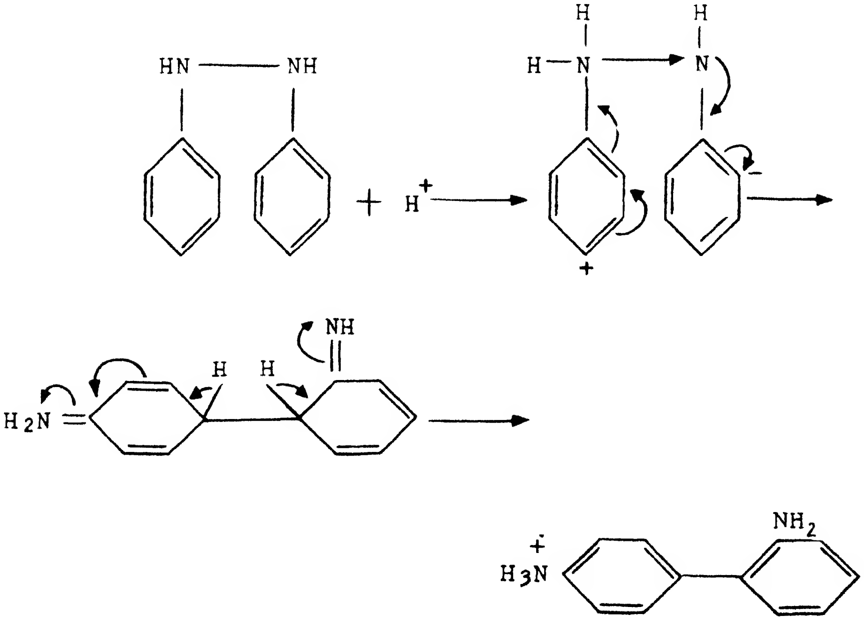


The first step in the reaction, according to Ingold, is the coordination of a proton with one of the nitrogen atoms. The positive charge introduced by the addition of a proton would be expected to assist the above displacements which lead to the cleavage of the nitrogen-to-nitrogen bond.

The following is a modification of the mechanism first suggested by Ingold:

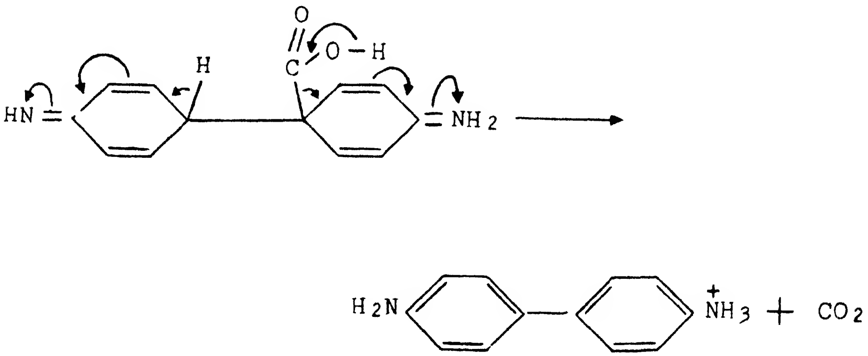


The final step consists of a prototropic change to the more stable benzenoid structure. While benzidine is the chief product, some 2,4′-diaminodiphenyl is also formed:

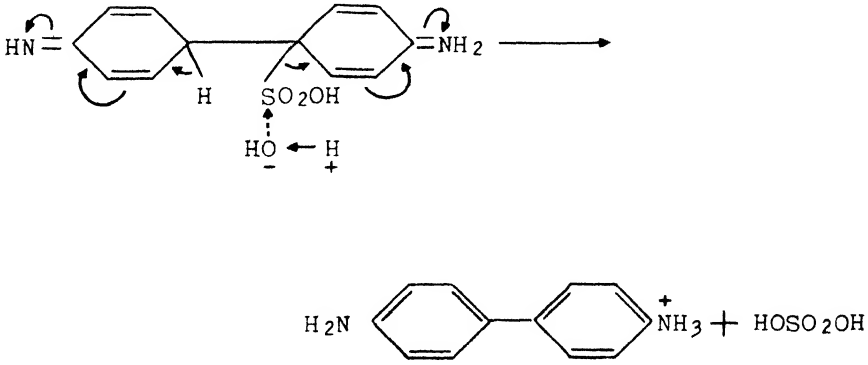


These reactions appear to be normal para or ortho substitutions of an aniline derivative by a cationoid reagent. The above mechanisms have been criticized by Robinson (124). He points out the fact that imine salts are readily hydrolyzed and therefore the intermediates shown above should give some phenol and ammonia. These two products have never been reported. Whether or not the rate of hydrolysis of the imine, with its resultant restoration of the resonant benzenoid state, can compete with the simple prototropic change shown above is difficult to answer at the present time.

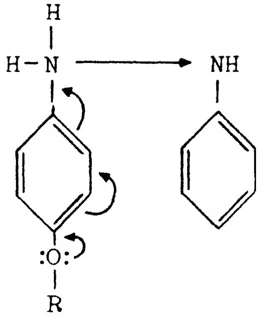
The benzidine rearrangement occurs with other hydrazo compounds in which both of the para positions are unsubstituted. When one of these positions is substituted, the rearrangement may proceed in one of three ways. 4-Carboxy-hydrazobenzene rearranges to benzidine with the elimination of the carboxyl group. The elimination of this group probably occurs in the last step of the mechanism shown above:



Loss of a para sulfonic acid group has also been observed in these reactions:

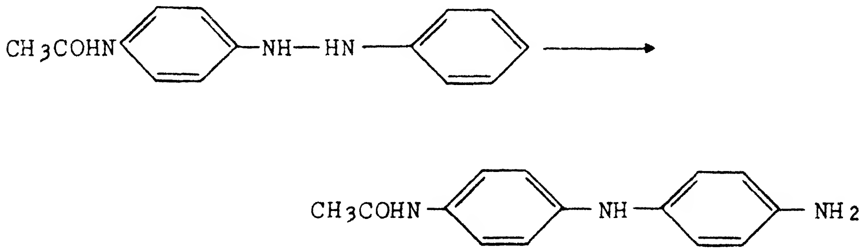


The para substituent is not eliminated when it is an electron-releasing group, that is, when it participates in resonance with the aromatic ring:

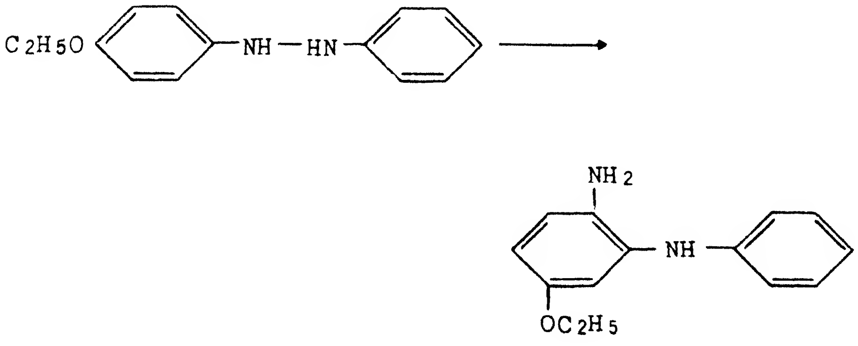


It will be noted that this participation decreases the cationoid character of the para carbon atom and so reduces its availability for substitution in the aniline ring. With examples of this type either an ortho-semidine or a para-semidine transformation takes place:

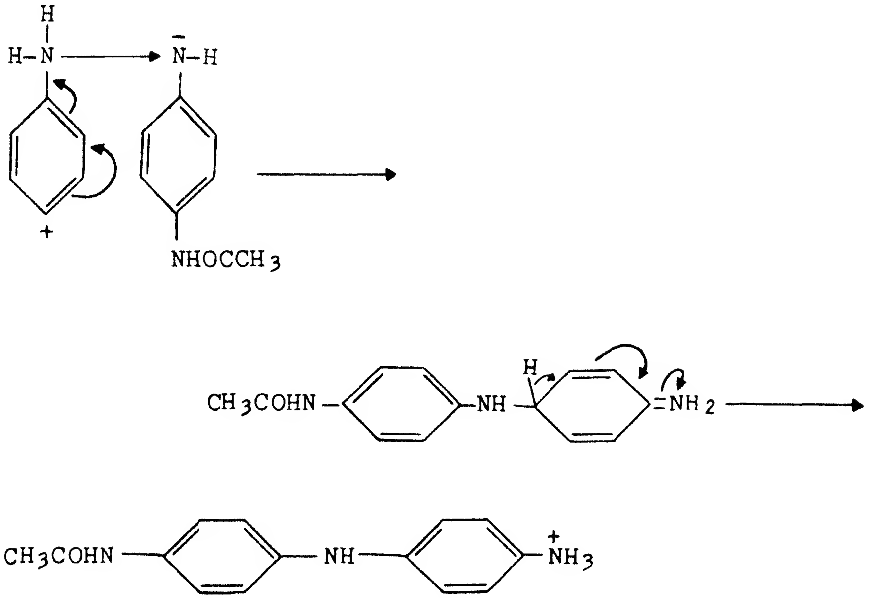
p-semidine



o-semidine



Robinson (124) states the semidine rearrangement is clearly intramolecular. If this is accepted, it must be assumed that the new carbon-nitrogen bond starts to form before the cleavage of the nitrogen-nitrogen bond is completed. This seems less probable than in the case of the benzidine rearrangement. The following mechanism appears to be in agreement with most of the known data:



When both para carbon atoms are substituted, only the *o*-semidine rearrangement may occur.

CHAPTER XXV

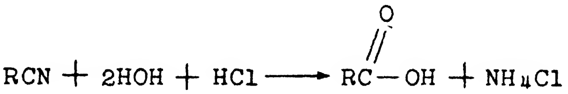
Reactions of Alkyl and Aryl Derivatives of Hydrogen Cyanide

The fact that there are two types of derivatives of hydrogen cyanide, RCN and RNC, suggests that the parent acid is a tautomeric compound.

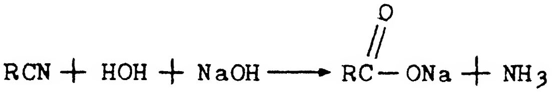
$$H:C:::N: \rightleftharpoons H\cdot N:::C:$$

Examination of the Raman spectrum of hydrogen cyanide has furnished good evidence that both forms are present in the gaseous phase (125), although the HNC isomer is present in very small amounts.

Cyanides or nitriles, R—C≡N. The most typical reactions of this class of compounds are addition reactions which are due essentially to the electromeric shift, $R{-}\underset{+}{C}\overset{\curvearrowright}{\equiv}\underset{-}{N}$. The unsaturated carbon-to-nitrogen bond may be compared with the unsaturated carbon-to-oxygen bond in carbonyl groups. Since both nitrogen and oxygen are more electron attracting than carbon, the electromeric shift occurs in the same direction for both classes of compounds. The cyanides are hydrolyzed by both acids and alkalies:

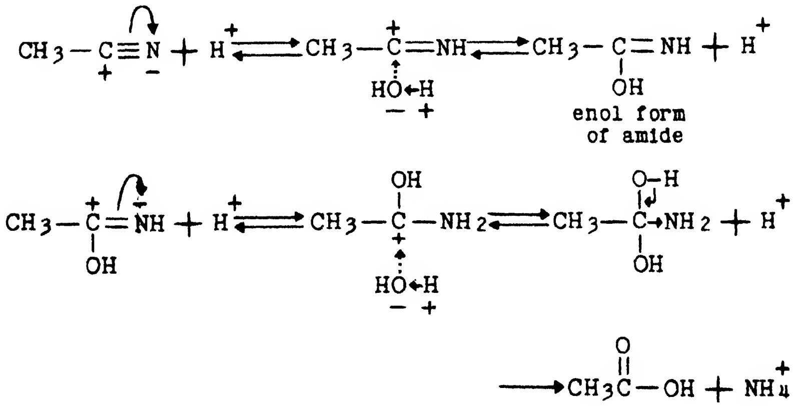


$$RCN + 2HOH + HCl \longrightarrow R\overset{O}{\overset{/\!/}{C}}{-}OH + NH_4Cl$$



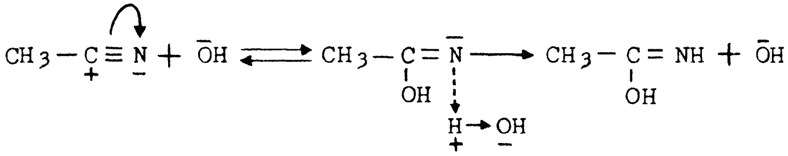
$$RCN + HOH + NaOH \longrightarrow R\overset{O}{\overset{/\!/}{C}}{-}ONa + NH_3$$

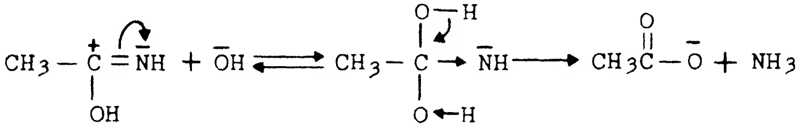
Amides are intermediates in the hydrolyses but usually can be isolated only under special conditions. Acid hydrolysis may be shown as follows:



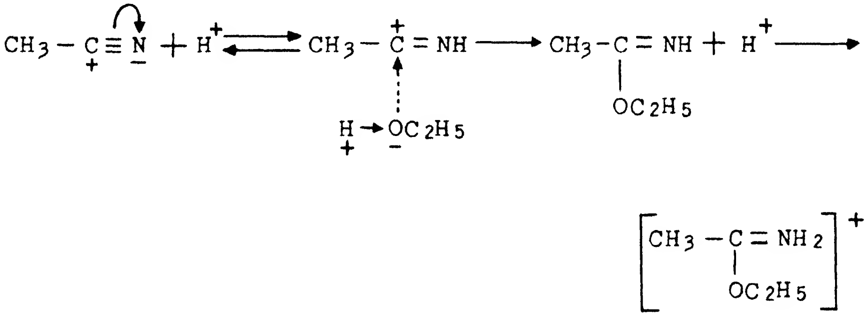
See reference (126) for an excellent kinetic study on the hydrolysis of cyanamide and nitriles.

Basic hydrolysis of cyanides probably involves the initial addition of the nucleophilic hydroxyl ion to the unsaturated carbon atom:

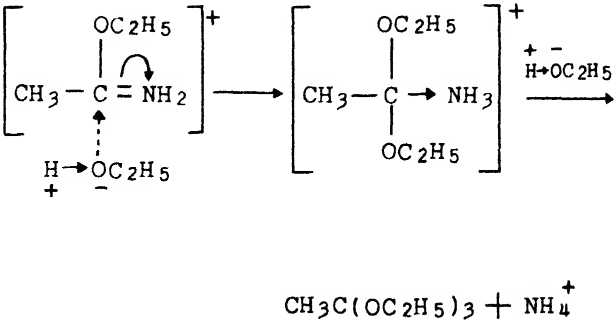




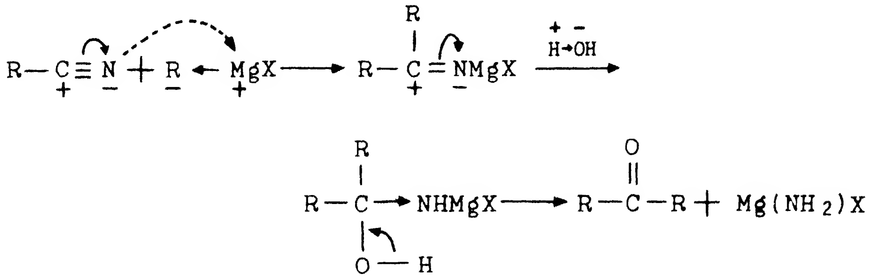
Under the influence of dry hydrogen chloride, alcohols add across the triple bond to form imino ether hydrochlorides:



On treatment with excess alcohol, the imino ether hydrochlorides are converted to the corresponding ortho esters:

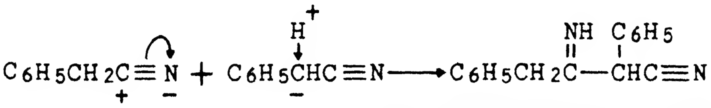


With Grignard reagents the nitriles form addition products which may be hydrolyzed to ketones:



The lower aliphatic nitriles tend to polymerize under the influence of Grignard reagents, but otherwise the method is useful for preparing ketones from aliphatic and aromatic nitriles. Nitriles such as benzyl nitrile and ethyl cyanoacetate are not suitable for the reaction, for they are sufficiently acidic to decompose the Grignard reagent.

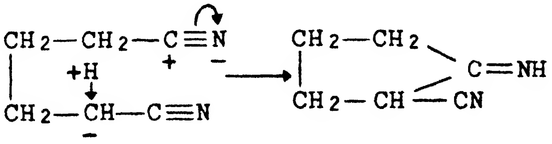
The nitriles which have hydrogen attached to the alpha carbon atom behave as very weak acids. This tendency is enhanced by the presence of a phenyl group on the alpha carbon atom. Benzyl cyanide undergoes a self-condensation (Thorpe reaction) under the influence of sodium ethoxide:



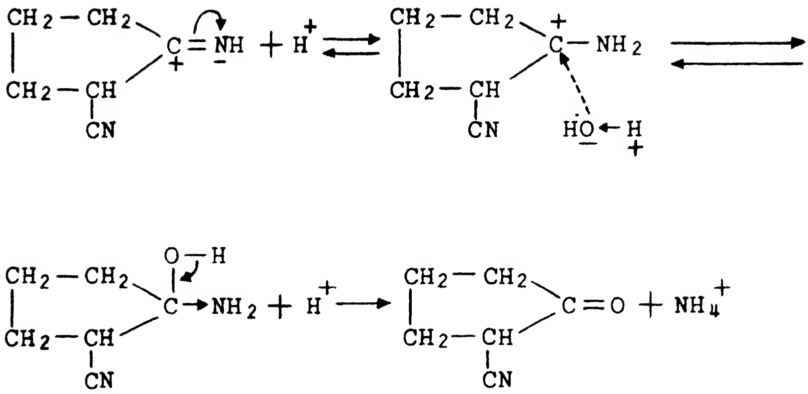
α,γ-diphenyl-β-imino-n-propyl nitrile

This reaction is similar to the aldol condensation with the dipolar cyanide group acting like a carbonyl group and the catalyst aids both the polarization of the cyanide group and the ionization of a hydrogen.

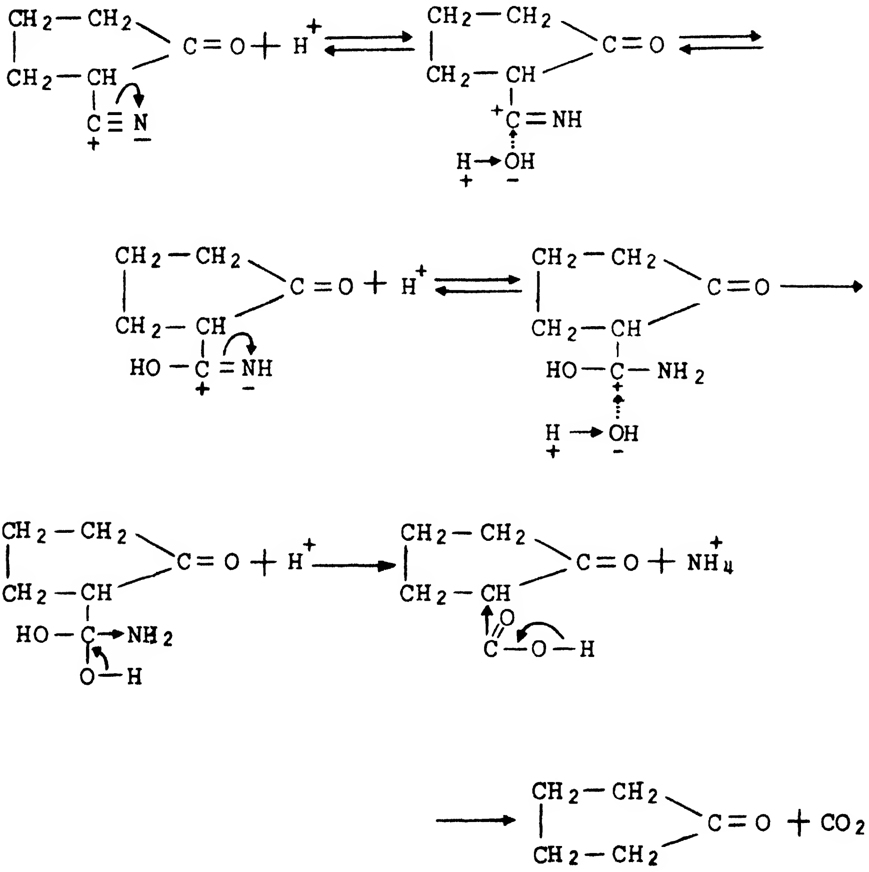
When this reaction is applied to suitable dinitriles, ring closure takes place. Adiponitrile when treated with sodium ethoxide in dry alcohol solution yields 1-imino-2-cyanocyclopentane:



The latter is hydrolyzed by dilute acids to 2-cyanocyclopentanone:



When more concentrated acid solutions are used, hydrolysis continues to the formation of a β-keto acid which loses carbon dioxide to form cyclopentanone:

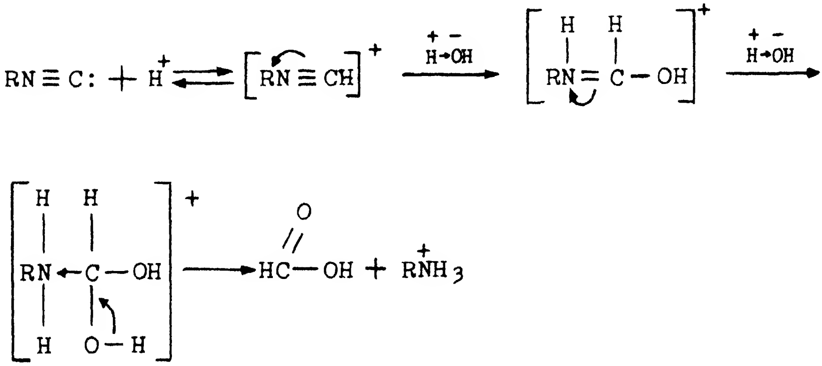


The decarboxylation in this case is facilitated by the adjacency of the electron-attracting carbonyl group.

Extension of this method to the synthesis of rings with more than six carbon atoms in the ring is more difficult since the probability of the close approach of the two ends of the molecule is greatly reduced and condensation between different molecules is more apt to occur. Successful synthesis of the larger rings has been accomplished by carrying out the reaction in very dilute solution in the presence of diethyl lithium amide as catalyst (127).

Isocyanides or isonitriles. The characteristic properties of the isonitriles are best explained by the formula proposed by Langmuir, $R{:}N{:::}C{:}$ or $R\text{—}N\overset{\rightarrow}{=}C$. In this type of compound the carbon atom possesses an unshared electron pair.

They are very readily hydrolyzed by acids but are unaffected by sodium or potassium hydroxide solutions:

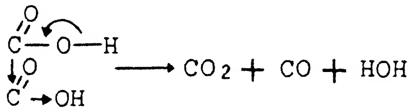


The fact that a N-substituted formamide is an intermediate suggests the above course of reaction as the probable one.

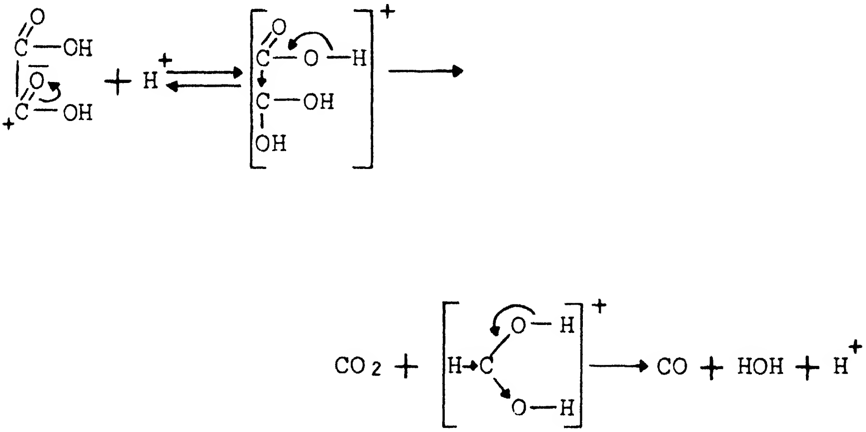
CHAPTER XXVI

Reactions of Dicarboxylic Acids and Their Derivatives

The dicarboxylic acids resemble in many ways the monocarboxylic acids and similar mechanisms may be formulated for their reactions with bases, alcohols, and the halogens. In addition to these reactions, certain others are noted in this series as a result of the presence of two carboxyl groups. For example, oxalic acid when heated decomposes into carbon dioxide, carbon monoxide, and water. Formic acid may be formed as an intermediate in this reaction. While there is no direct evidence available as to the mechanism, one may arrive at a mechanism with reasonable certainty by applying the principles noted in the previous chapters:

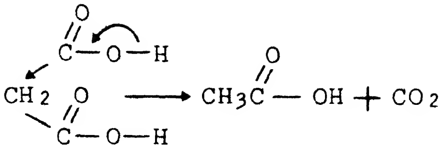


The dehydration of oxalic acid by means of concentrated sulfuric acid may be shown in a similar manner:

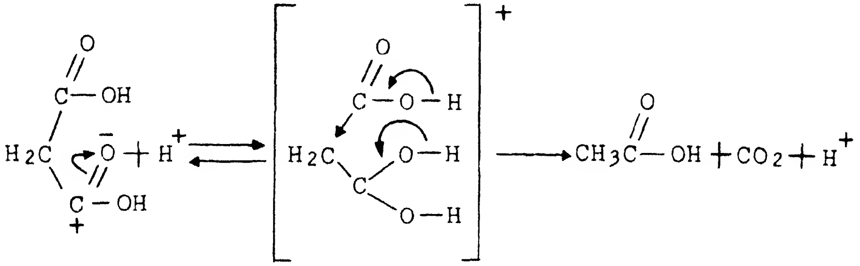


In this case the addition of a proton from the acid catalyst to the carbonyl oxygen atom initiates the electron displacements which result in the cleavages shown above.

When malonic acid is heated, decarboxylation results with the elimination of only one carboxyl group:

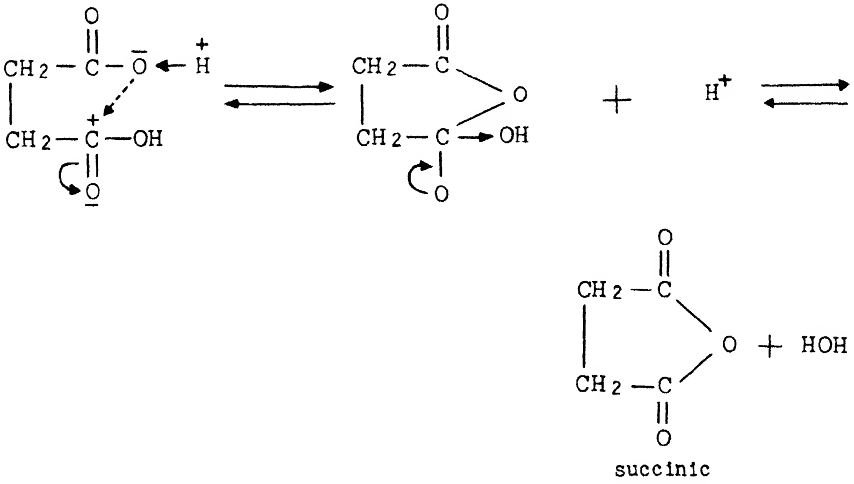


This is characteristic of compounds in which two carboxyl groups are attached to the same carbon atom. The electron-attracting carbonyl group is the initial driving force for the reaction. This decarboxylation is catalyzed by strong acids. For example, malonic acid is readily decarboxylated when its solution in dilute hydrochloric acid or dilute sulfuric acid is heated at the boiling point:



Here again it must be the function of the catalyst to donate a proton to the oxygen of the carbonyl group. Such an addition would facilitate the decarboxylation of the malonic acid as shown above.

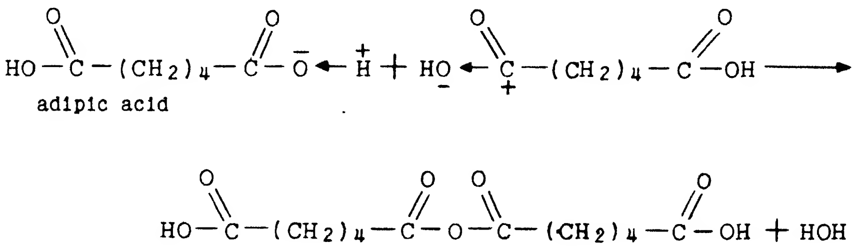
Succinic and glutaric acids under similar conditions undergo dehydration to yield cyclic anhydrides. These reactions proceed more readily in the presence of acetyl chloride or some similar reagent which will react with the water liberated:



succinic anhydride

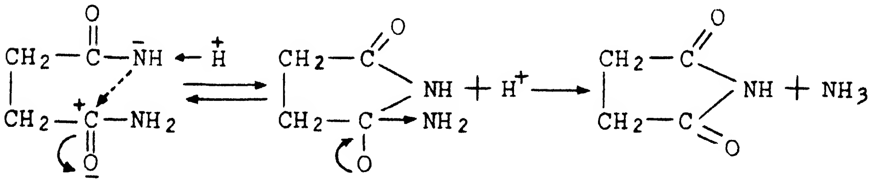
In this case, neutralization of the positive and negative centers is most readily effected by ring closure. In the cases of oxalic acid and malonic acid, where stable ring formation is not possible, neutralization is effected through cleavage.

The acids above glutaric acid tend to form linear polyanhydrides when heated:

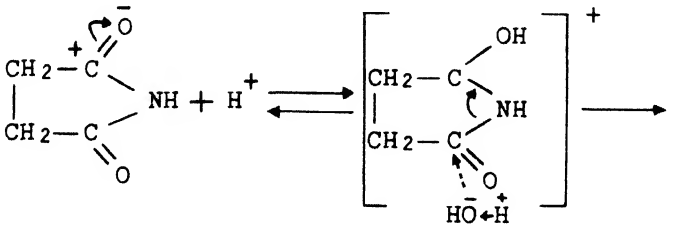


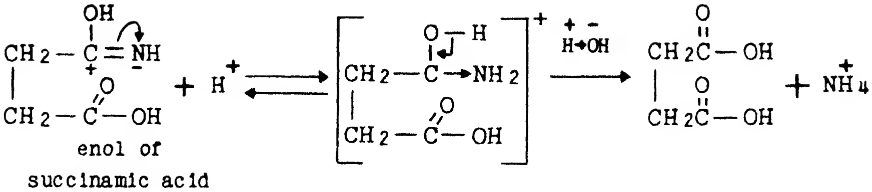
Continuation of this process would lead to the formation of a polyanhydride.

Derivatives of the dibasic acids, anhydrides, acyl chlorides, and esters, behave in general like the corresponding derivatives of the monobasic acids. Certain additional reactions are encountered which are of considerable interest. For example, succinamide when heated loses ammonia and forms succinimide:

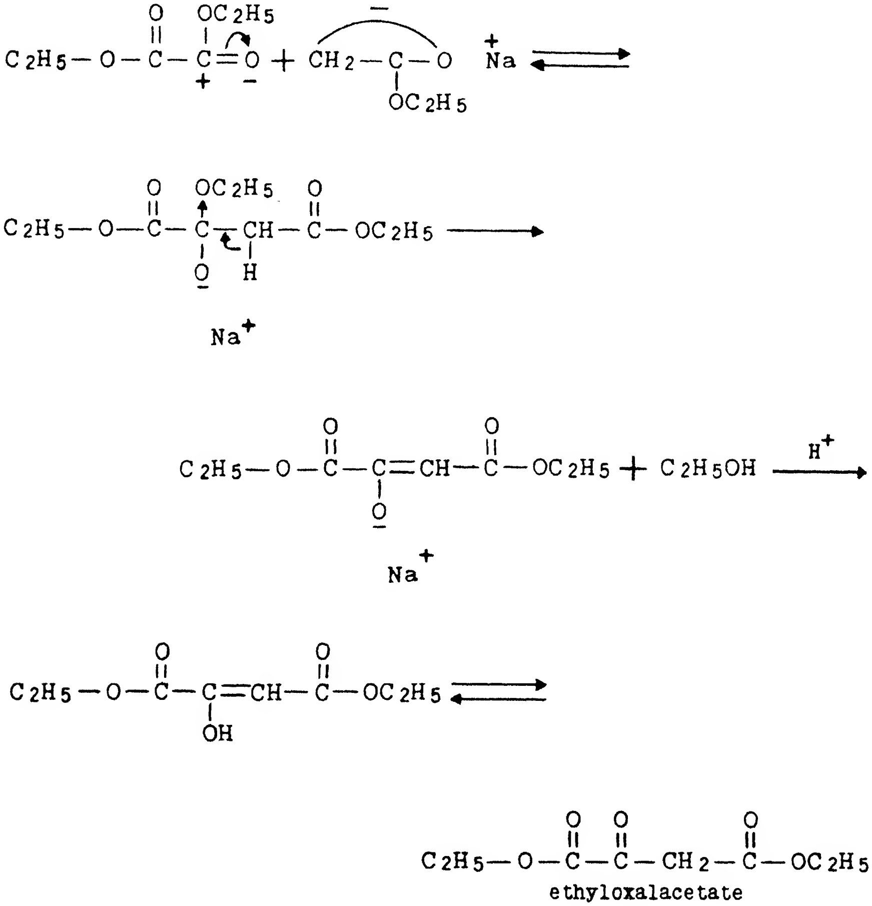


It will be noted that this reaction is very similar to the formation of succinic anhydride from succinic acid. The structural systems in succinic acid and succinamide are electronically equivalent as far as the above reactions are concerned. Succinimide resembles the amides of the monocarboxylic acids in many ways. It is hydrolyzed when heated with acids or bases:



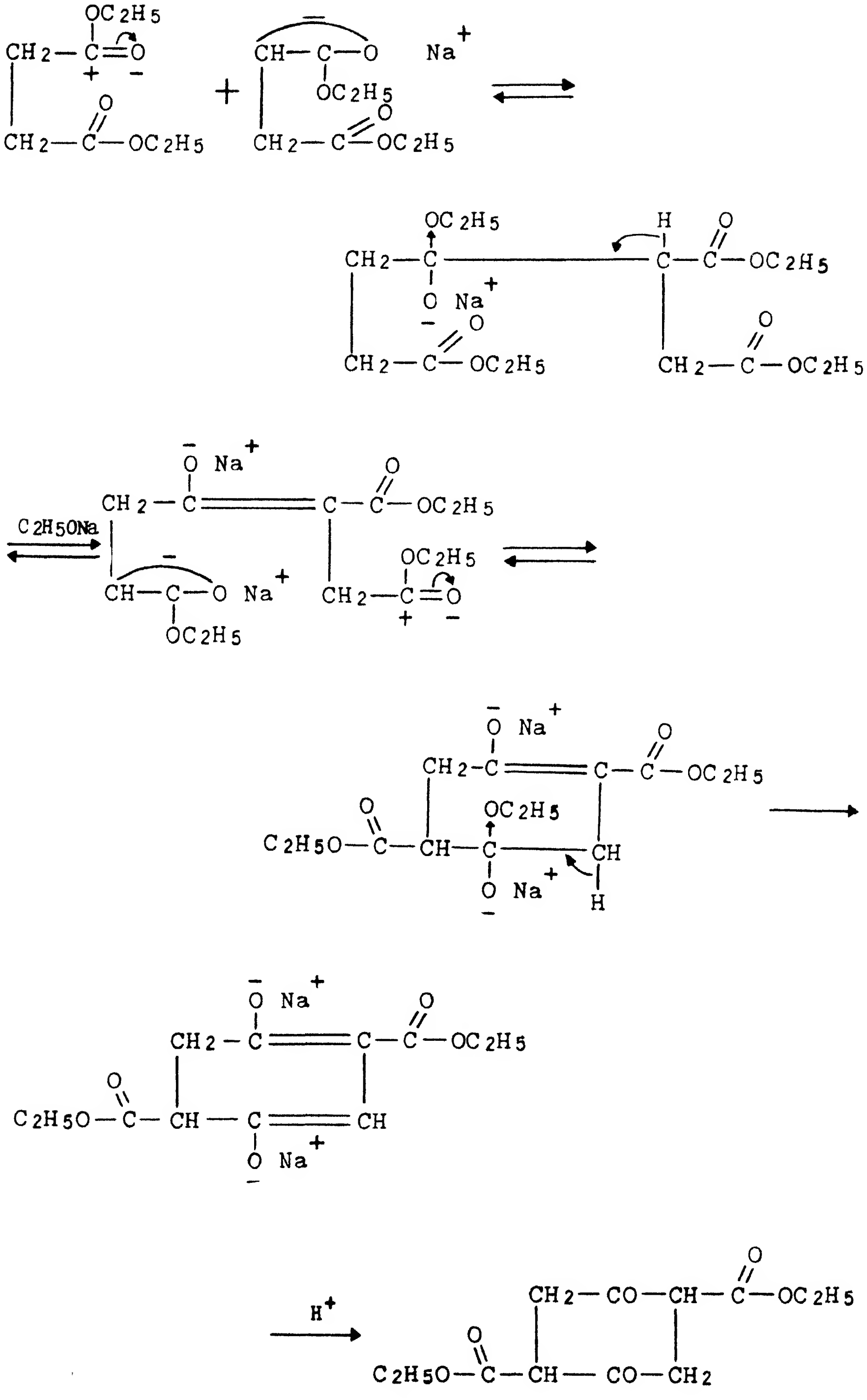


Esters of the dibasic acids also undergo the Claisen type of condensation. Those with no alpha hydrogen, such as ethyloxalate, cannot undergo self-condensation but they can condense with other esters or ketones which possess alpha hydrogen atoms:

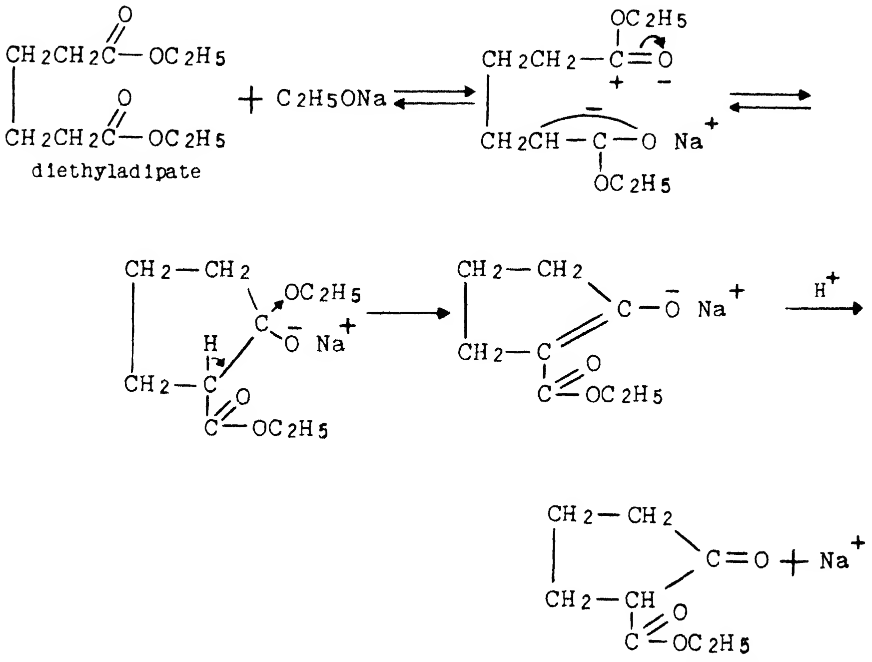


Ethyloxalate can also condense with two molecules of ethylacetate to form ethyl ketopinate.

Diethylsuccinate, under similar conditions, yields a cyclic diketo ester, diethyl succinylsuccinate:

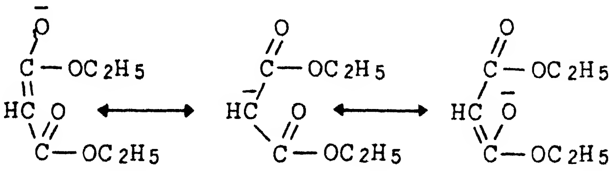

C2H5ONa
H+

The ethyl esters of certain of the higher homologs of succinic acid undergo intramolecular condensation to form cyclic keto esters (Dieckmann condensation). This takes place most readily in those cases where five- or six-membered rings are formed:

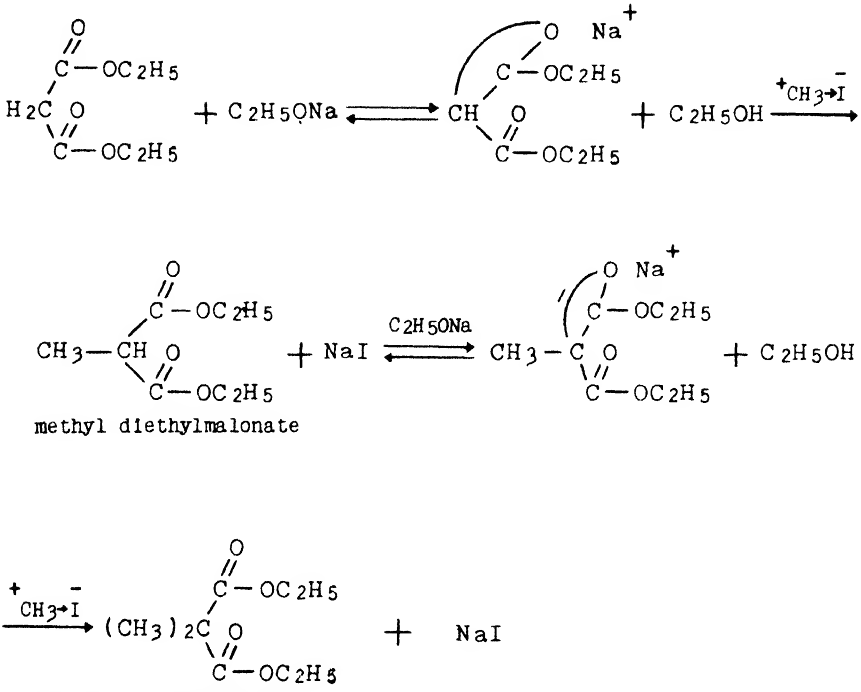

diethyladipate

α-carbethoxycyclopentanone

The important "malonic ester syntheses" depend on the fact that diethylmalonate is more acidic than esters of the ethylacetate type as well as the esters of the higher dibasic acids, that is, the hydrogen atoms in the methylene group have a greater tendency to ionize. This is attributed to the increased possibilities for resonance in the anion, which is due to the adjacency of two carbonyl groups:



The use of the ester in malonic ester syntheses may be shown as follows:

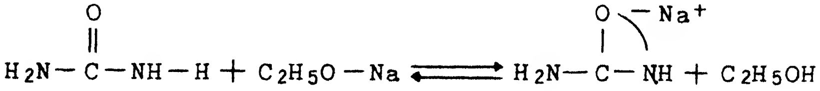


methyl diethylmalonate

dimethyl diethylmalonate

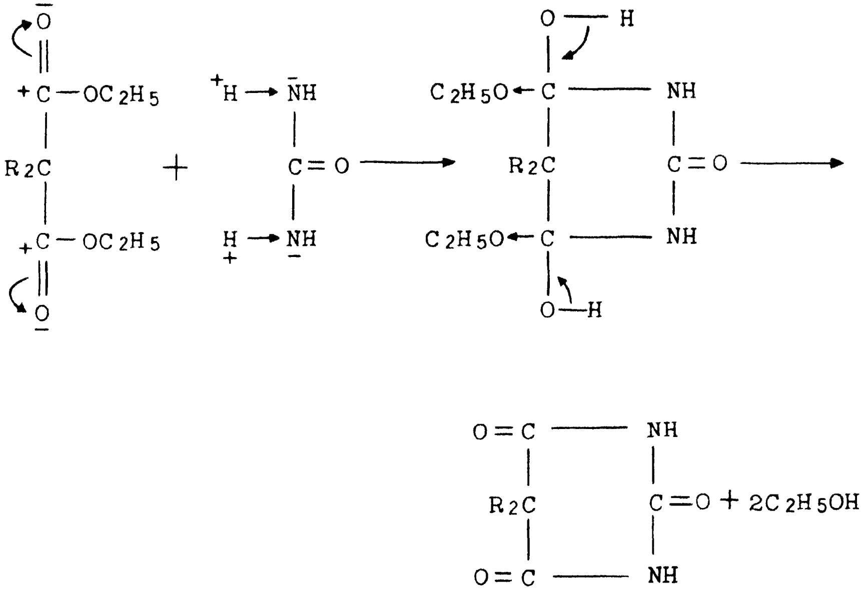
Hydrolysis of the methyl and dimethyl derivatives followed by decarboxylation yields propionic acid and isobutyric acid respectively. It is theoretically possible for the methyl group to add to either the carbonyl oxygen atom or to the carbon atom. If addition to oxygen does occur, rearrangement must result, for only the carbon-to-carbon product is isolated.

The condensations of dialkyl diethylmalonates with urea to form the medicinally important barbiturates are base-catalyzed reactions. Apparently it is the function of the catalyst to assist the ionization of hydrogen from the urea molecule and the polarization of the carbonyl groups of the ester:



$$H_2N-\overset{\overset{\displaystyle O}{\|}}{C}-NH-H + C_2H_5O-Na \rightleftharpoons H_2N-\overset{\overset{\displaystyle O^{-}Na^{+}}{|}}{C}-NH + C_2H_5OH$$

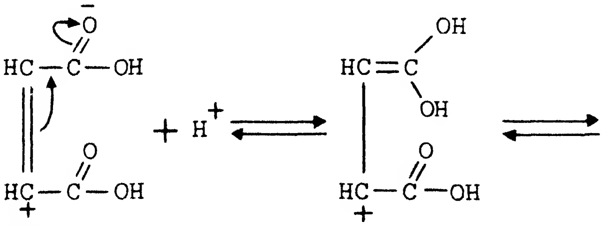
The condensation may be represented as follows:



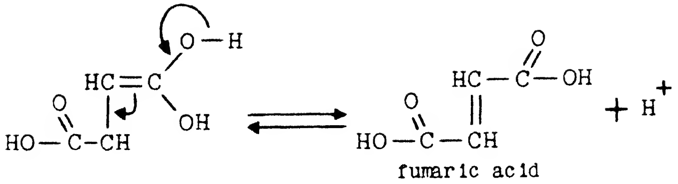
5,5-dialkylbarbiturate

The reaction probably takes place in two steps and the product is obtained as a sodium salt which, upon acidification, yields the free dialkyl barbiturate. There is a formal resemblance between this reaction and the ammonolysis of esters.

The unsaturated dibasic acids, maleic and fumaric acids, are interesting examples of geometric isomers. The interconversion of cis and trans isomers has been accomplished by a variety of reagents. In cases where one form is more stable than the other, conversion of the more labile form to the stable form may be readily effected. In cases where the stability of the two isomers is approximately the same, mixtures of the two isomers are obtained. In a large number of examples studied, the trans form is the stable form. When maleic acid is heated with dilute hydrochloric acid, it is converted into fumaric acid. In this rearrangement, the double bond must take on the character of a single bond, so that rotation to the stable form occurs:



maleic acid

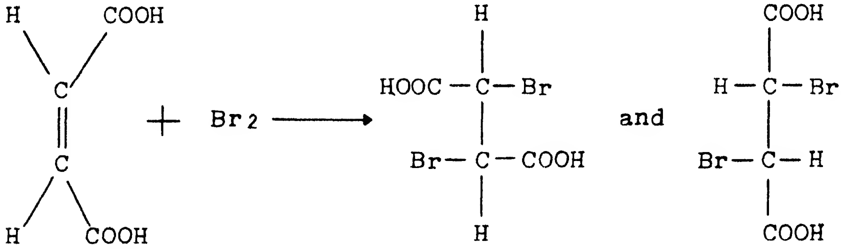


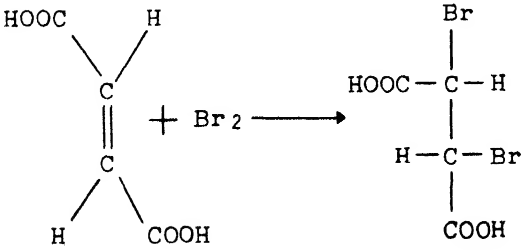
Methyl maleate in dry ether solution is converted into methyl fumarate by the action of potassium. With other catalysts, the mechanisms are probably similar.

The conversion of fumaric acid into maleic acid calls for the absorption of energy. This may be effected by irradiation with ultraviolet light. Although less obvious, it is probable that this change also depends upon the activation of the double bond.

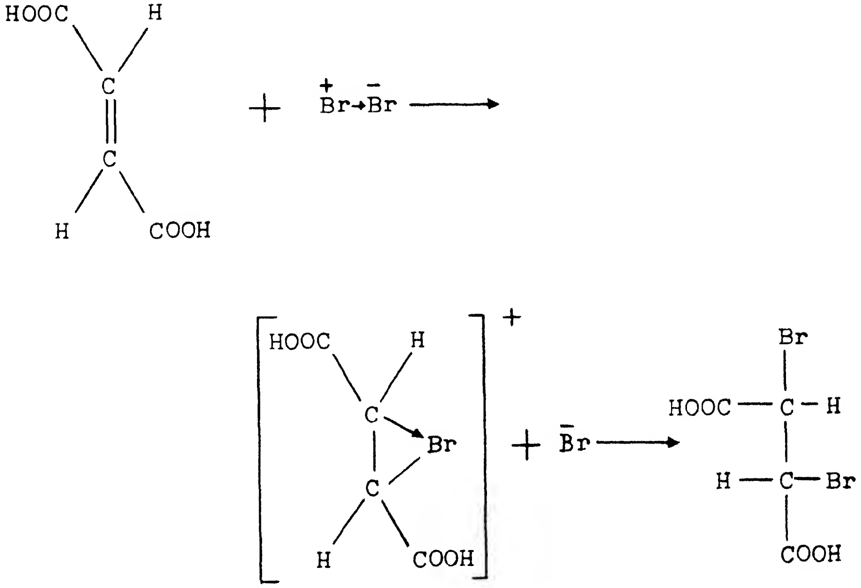
In general, the reactions of the carboxyl groups resemble those of the corresponding saturated acid, and the double bond has many of the characteristics of a simple olefin bond. However, there are some significant differences. Maleic acid forms an anhydride when heated. This is to be expected, since in the cis form the two carboxyl groups are so situated that a five-membered ring may readily be formed. The carboxyl groups in fumaric acid occupy trans positions and ring formation is impossible. Fumaric acid may be converted into maleic anhydride at higher temperatures. In this case the isomerization to maleic acid is a necessary intermediate step.

The addition of bromine to maleic acid yields chiefly racemic dibromosuccinic acid, while fumaric acid gives mostly meso dibromosuccinic acid. Examination of the known configurations of these acids leaves no doubt that the reactions involve the trans addition of bromine:



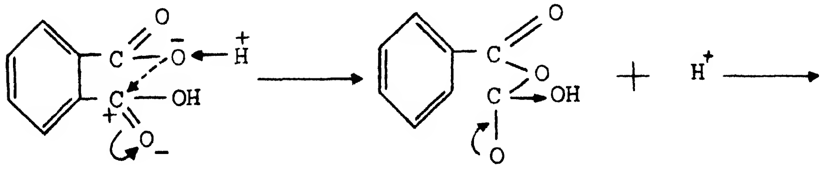


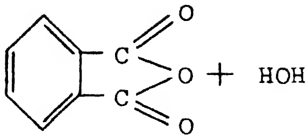
Evidence has already been presented, under the addition of halogens to the olefins, that such an addition must take place in two steps which involve intermediate ions when carried out in polar solvents. The addition of bromine to maleic and fumaric acids cannot involve simultaneous addition of both bromine atoms of the bromine molecule, for if this were true cis addition would surely occur. In order to account for the fact that rotation does not occur around the carbon-to-carbon linkage, an intermediate three-membered ring similar to the ethylene oxide ring has been postulated (128). If free rotation were possible, maleic acid and fumaric acid should yield the same mixture of dibromo derivatives:



This hypothesis accounts for the known facts, and the trans addition of halogens to olefin bonds is commonly accepted.

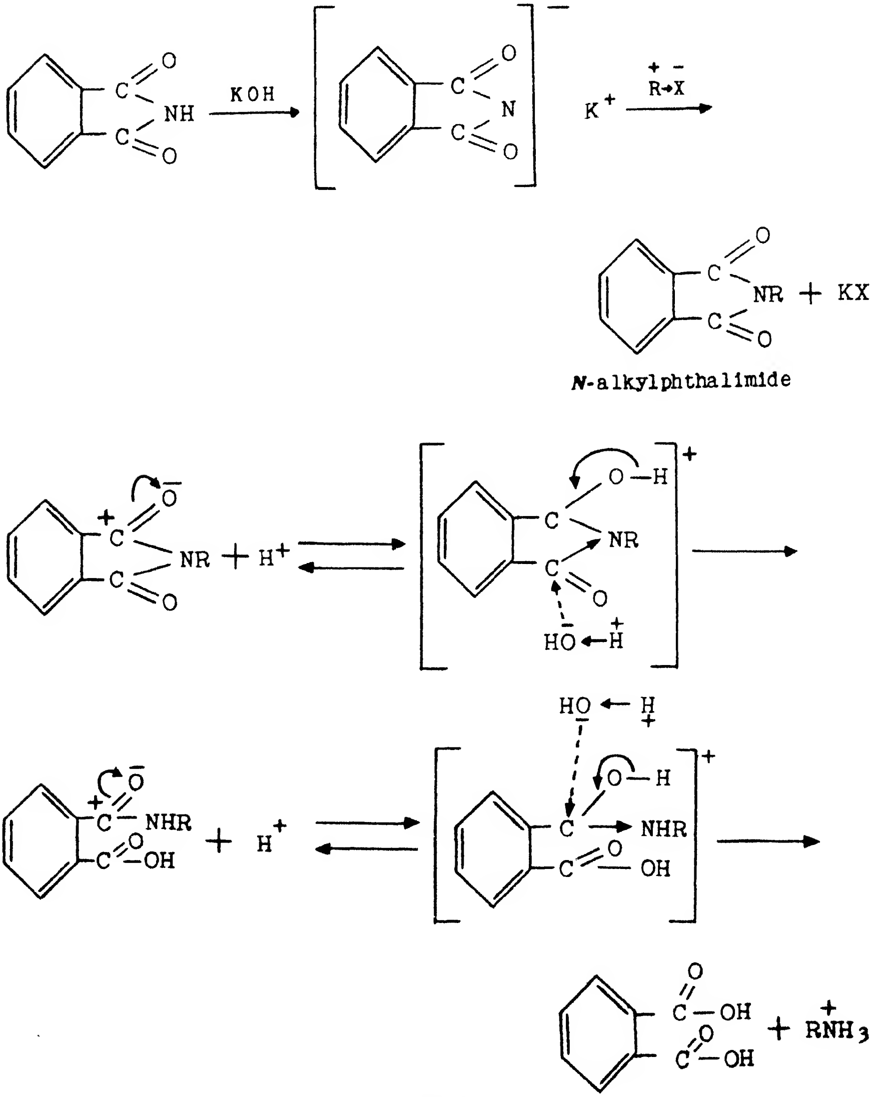
The aromatic dibasic acids in which the two carboxyl groups occupy ortho positions resemble succinic and maleic acids in some respects. Phthalic acid, for example, when heated yields a five-membered cyclic anhydride:





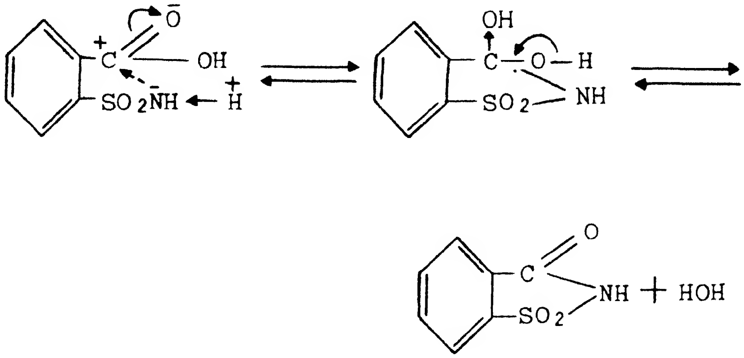
phthalic anhydride

The corresponding imide, phthalimide, is used in the Gabriel reaction for the preparation of primary amines and amino acids:

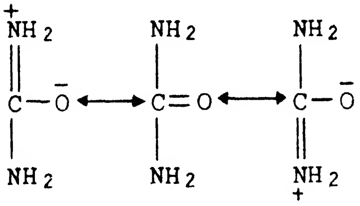


N-alkylphthalimide

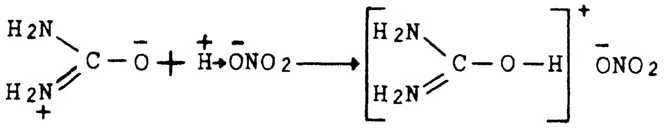
The imide of the mixed sulfonic-carboxylic acid, *o*-sulfobenzoic acid, is known as saccharin. It may be prepared by the oxidation of *o*-toluenesulfonamide. The intermediate *o*-sulfonamide of benzoic acid then forms the imide:



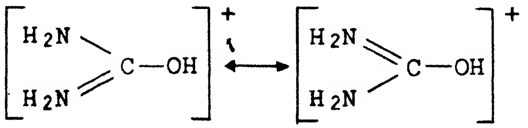
Derivatives of carbonic acid. Carbonic acid, $HO{-}\overset{\overset{O}{\|}}{C}{-}OH$, may be regarded as the simplest dibasic organic acid. Although the acid itself is unstable, many of its derivatives are known. Urea or carbamide is the diamide of carbonic acid. It is best represented as a resonance hybrid:



Although its aqueous solution is neutral, urea acts as a weak monoacid base. It is assumed that in salt formation the proton becomes attached to the oxygen atom rather than to nitrogen. The formation of urea nitrate may be shown as follows:

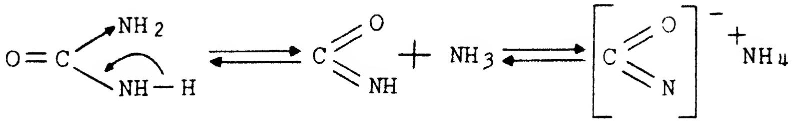


As pictured, the cation is stabilized by resonance:

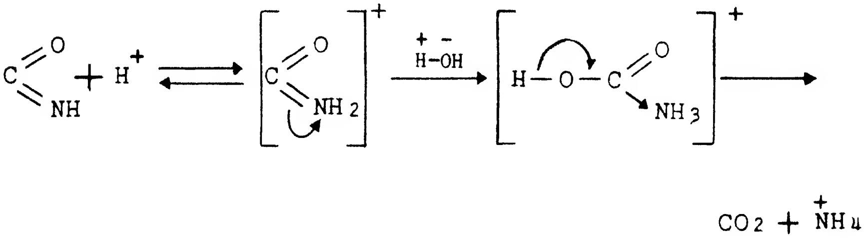


The addition of the proton to oxygen has not been deduced from direct evidence, but rather by analogy to the salts of thiourea. Thiourea is readily oxidized in acid solution to a disulfide (129). Therefore it appears probable that in this case the proton adds to the sulfur atom, for this reaction is known to be a characteristic reaction of the –SH group.

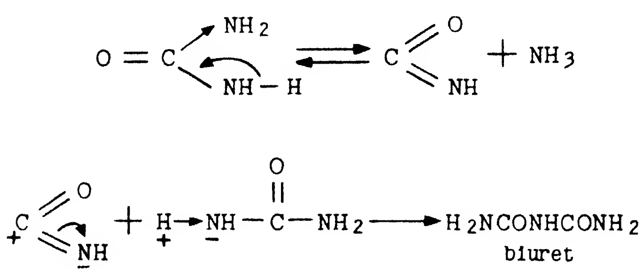
Urea is hydrolyzed by both alkalies and acids, but unlike the aliphatic acid amides, the hydrolysis of urea is more rapid with acids. The rate of acid hydrolysis, within wide limits, is independent of the hydrogen ion concentration (130). This unusual behavior has been stated to be due to the intermediate formation of ammonium cyanate. It has been assumed that the speed of acid hydrolysis is determined by the rate of change of urea into ammonium cyanate and is independent of the hydrogen ion concentration:



The acid catalyst apparently enters into a rapid reaction with the isocyanic acid formed:



When urea is heated just above its melting point, it is partially converted into biuret. Part of the urea dissociates into ammonia and cyanic acid and the latter then reacts with unchanged urea to form biuret:

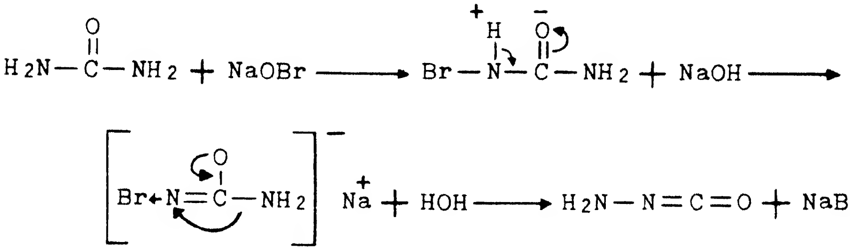


At higher temperatures the cyanic acid polymerizes to a mixture of cyanuric acid and cyamelide.

Sodium hypohalites react with urea in a manner somewhat similar to that noted for the amides of the acetamide series:

$$CO(NH_2)_2 + 3NaOBr + 2NaOH \longrightarrow Na_2CO_3 + N_2 + 3NaBr + 3H_2O$$

There is little evidence available for establishing a mechanism for the reaction, although hydrazine is known to be an intermediate in this reaction. Under the usual conditions the hydrazine is quickly converted to nitrogen. If it is assumed that an amino group migrates from carbon to nitrogen instead of an alkyl group, a mechanism similar to that written for the Hofmann reaction may be used:



$$H_2N-\overset{\overset{O}{\|}}{C}-NH_2 + NaOBr \longrightarrow Br-\overset{\overset{+}{H}}{\underset{}{N}}-\overset{\overset{\bar{O}}{\|}}{C}-NH_2 + NaOH \longrightarrow$$

$$\left[Br\leftarrow N=\overset{\overset{O}{|}}{C}-NH_2\right]^- \overset{+}{Na} + HOH \longrightarrow H_2N-N=C=O + NaBr$$

The hypothetical amino isocyanate would then be hydrolyzed to hydrazine:

$$H_2N-N=C=O + 2NaOH \longrightarrow H_2N-NH_2 + Na_2CO_3$$

The final step probably consists of the usual reaction between hydrazine and sodium hypobromite followed by the splitting out of hydrogen bromide:

$$H_2N-NH_2 + 2NaOBr \longrightarrow N_2 + 2NaBr + 2H_2O$$

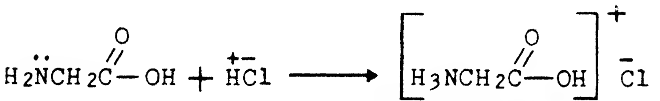
CHAPTER XXVII

Reactions of Amino Acids

The amino acids contain amino and carboxyl groups, and as a result are both basic and acidic in character. The aliphatic alpha amino acids are of particular importance, for they are the chief building units of the proteins. When the latter are hydrolyzed, they are converted largely into mixtures of α-amino acids.

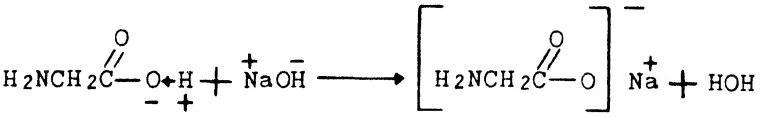
In general, the aliphatic amino acids are soluble in water and difficultly soluble or insoluble in organic solvents. They do not have true melting points but decompose at high temperatures, aminoacetic acid or glycine, for example, decomposing above 200° C. These properties are similar to those of a true salt. Since an amino acid contains an amino and an acidic group, salt formation may take place within the molecule. It is known that the amino acids exist in the solid state as internal salts of dipolar ions (zwitterions). Glycine is best represented as $H_3\overset{+}{N}CH_2CO\overset{-}{O}$.

In aqueous solution, glycine behaves as an amphoteric electrolyte and can form salts with both acids and bases:



$$H_2\ddot{N}CH_2\overset{O}{\overset{/\!/}{C}}-OH + \overset{+}{H}\overset{-}{Cl} \longrightarrow \left[H_3NCH_2\overset{O}{\overset{/\!/}{C}}-OH\right]^{+}\overset{-}{Cl}$$

carboxymethylammonium chloride



$$H_2NCH_2\overset{O}{\overset{/\!/}{C}}-\underset{-}{O}\!\cdot\!\underset{+}{H} + \overset{+}{Na}\overset{-}{OH} \longrightarrow \left[H_2NCH_2\overset{O}{\overset{/\!/}{C}}-O\right]^{-}\overset{+}{Na} + HOH$$

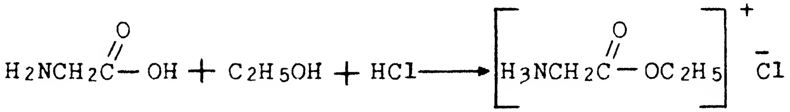
sodium aminoacetate

There is considerable evidence to show that even in aqueous solution glycine exists predominantly as a dipolar ion. The reactions with bases and acids are more accurately formulated as follows:

$$H_2NCH_2CO\overset{-}{O} \underset{H^+}{\overset{\overset{-}{OH}}{\rightleftarrows}} H_3\overset{+}{N}CH_2CO\overset{-}{O} \underset{\overset{-}{OH}}{\overset{\overset{+}{H}}{\rightleftarrows}} H_3\overset{+}{N}CH_2COOH$$

It should be noted that a dipolar ion does not migrate in an electric field. In acid solution, however, it migrates to the cathode and in basic solution to the anode.

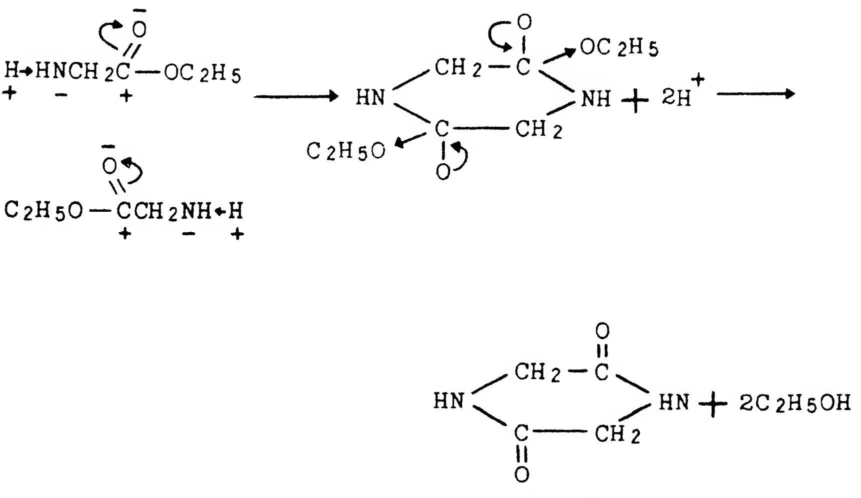
The amino acids give many of the reactions characteristic of the monocarboxylic acids and of the primary aliphatic amines. When they are heated with dry ethyl alcohol containing hydrogen chloride, the hydrochlorides of the ethyl esters are formed:



$$H_2NCH_2\overset{\overset{O}{/\!/}}{C}-OH + C_2H_5OH + HCl \longrightarrow \left[H_3NCH_2\overset{\overset{O}{/\!/}}{C}-OC_2H_5\right]^{+} \overset{-}{Cl}$$

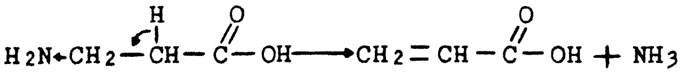
This reaction follows the same course as that previously discussed for the esterification of the monobasic acids.

The free esters in most cases can be distilled under reduced pressure. When heated at atmospheric pressure, however, aminolysis occurs with the formation of cyclic diamides better known as diketo piperazines:



Diketopiperazine, together with a linear polyamide, is also formed when glycine is heated. Both types are readily hydrolyzed by acids and bases, similar to the simple amides.

The β-amino acids behave differently at high temperatures, losing a molecule of ammonia to form the corresponding α,β-unsaturated acids:

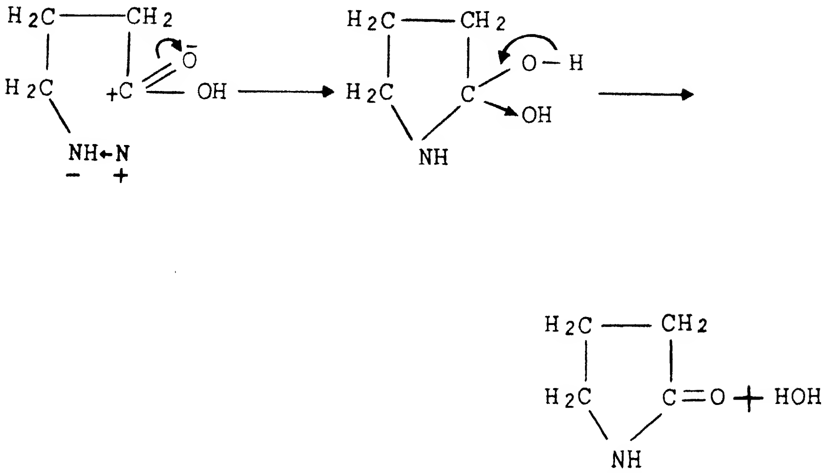


$$H_2N\leftarrow CH_2-\overset{H}{CH}-\overset{\overset{O}{/\!/}}{C}-OH \longrightarrow CH_2=CH-\overset{\overset{O}{/\!/}}{C}-OH + NH_3$$

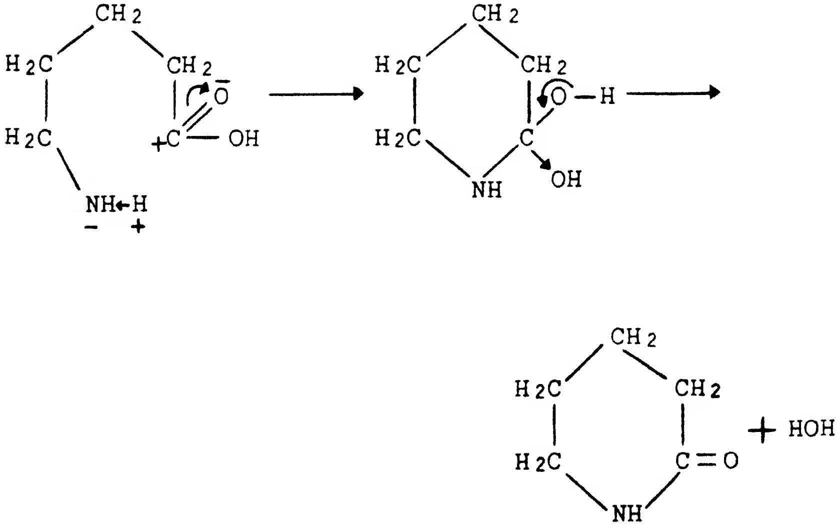
β-aminopropionic acid   acrylic acid

This reaction depends on the lability of alpha hydrogen and the ability of nitrogen to accept a proton.

The gamma and delta amino acids are converted into cyclic amides (lactams) when heated:

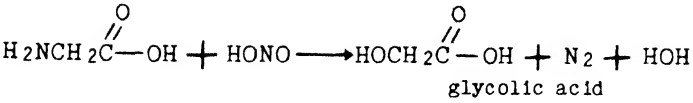


γ-butyrolactam or α-pyrrolidone



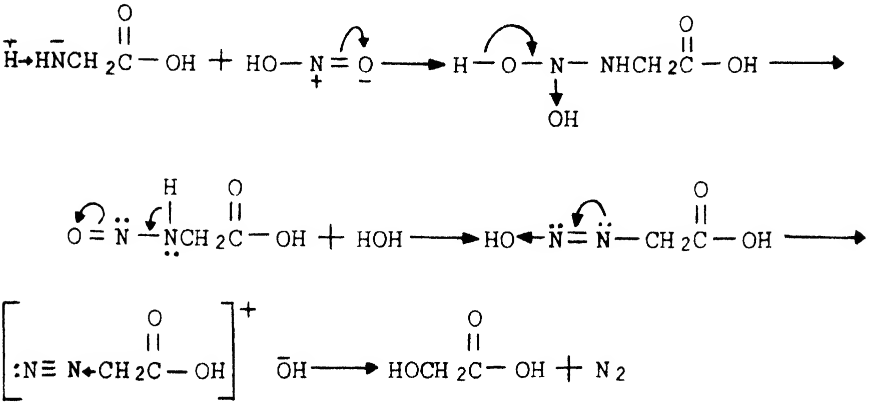
δ-valerolactam or α-piperidone

The amino acids react like aliphatic primary amines towards nitrous acid, being converted into hydroxy acids:



$$H_2NCH_2\overset{\overset{O}{/\!/}}{C}-OH + HONO \longrightarrow \underset{\text{glycolic acid}}{HOCH_2\overset{\overset{O}{/\!/}}{C}-OH} + N_2 + HOH$$

The course of the reaction probably is the same as that postulated for the reaction of aliphatic primary amines with nitrous acid:

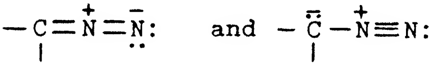


$$\overset{+}{H}\rightarrow\overset{-}{H}NCH_2\overset{\overset{O}{\parallel}}{C}-OH + HO-\underset{+}{N}=\underset{-}{O} \longrightarrow H-O-\underset{\underset{OH}{\downarrow}}{N}-NHCH_2\overset{\overset{O}{\parallel}}{C}-OH \longrightarrow$$

$$O=\ddot{N}-\underset{\cdot\cdot}{\overset{\overset{H}{|}}{N}}CH_2\overset{\overset{O}{\parallel}}{C}-OH + HOH \longrightarrow HO\leftarrow\ddot{N}=\ddot{N}-CH_2\overset{\overset{O}{\parallel}}{C}-OH \longrightarrow$$

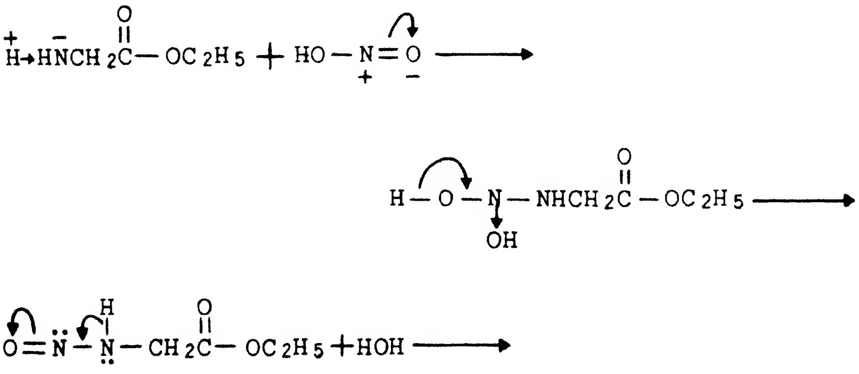
$$\left[:N\equiv N\leftarrow CH_2\overset{\overset{O}{\parallel}}{C}-OH\right]^{+}\ \bar{O}H \longrightarrow HOCH_2\overset{\overset{O}{\parallel}}{C}-OH + N_2$$

When glycine ethyl ester hydrochloride is treated with nitrous acid, diazoacetic ester is formed. The latter is an example of an aliphatic diazo compound. It must be extracted as it is formed, for otherwise it would be decomposed by the acid present in the aqueous solution. The aliphatic diazo group is best represented as a resonance hybrid of two structures:



$$-\underset{|}{C}=\overset{+}{N}=\underset{\cdot\cdot}{\overset{-}{N}}: \quad \text{and} \quad -\underset{|}{\overset{\overline{\cdot\cdot}}{C}}-\overset{+}{N}\equiv N:$$

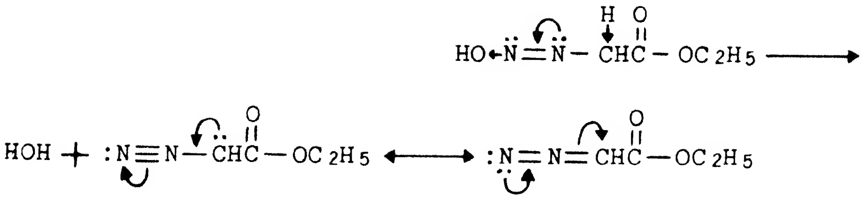
The formation of diazoacetic ester may be formulated as follows:



$$\overset{+}{H}\rightarrow\overset{-}{H}NCH_2\overset{\overset{O}{\parallel}}{C}-OC_2H_5 + HO-\underset{+}{N}=\underset{-}{O} \longrightarrow$$

$$H-O-\underset{\underset{OH}{\downarrow}}{N}-NHCH_2\overset{\overset{O}{\parallel}}{C}-OC_2H_5 \longrightarrow$$

$$O=\ddot{N}-\underset{\cdot\cdot}{\overset{\overset{H}{|}}{N}}-CH_2\overset{\overset{O}{\parallel}}{C}-OC_2H_5 + HOH \longrightarrow$$

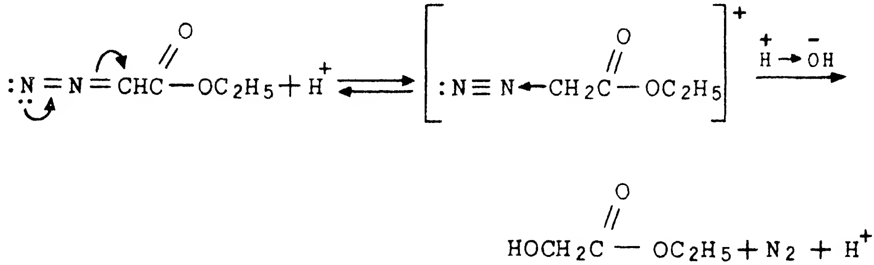


$$HO\leftarrow\ddot{N}=\ddot{N}-\overset{H}{\overset{\downarrow}{C}}H\overset{O}{\overset{\|}{C}}-OC_2H_5 \longrightarrow$$

$$HOH + :N\equiv N-\ddot{C}H\overset{O}{\overset{\|}{C}}-OC_2H_5 \longleftrightarrow :\ddot{N}=N=CH\overset{O}{\overset{\|}{C}}-OC_2H_5$$

In this case the electron-attracting positive nitrogen, instead of cleaving from carbon, becomes neutralized by causing an alpha hydrogen to ionize. This behavior is not unexpected since alpha hydrogen in an ester is more active than alpha hydrogen in the corresponding acid.

When diazoacetic ester is treated with dilute hydrochloric acid, ethyl glycollate is formed. This reaction is similar to the decomposition of aromatic diazonium compounds to give phenols, and probably follows a similar mechanism:

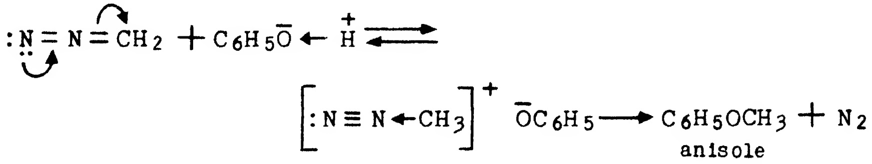


$$:\ddot{N}=N=CH\overset{O}{\overset{/\!/}{C}}-OC_2H_5+\overset{+}{H} \rightleftharpoons \left[:N\equiv N\leftarrow CH_2\overset{O}{\overset{/\!/}{C}}-OC_2H_5\right]^+ \xrightarrow{\overset{+}{H}\rightarrow\overset{-}{OH}}$$

$$HOCH_2\overset{O}{\overset{/\!/}{C}}-OC_2H_5+N_2+H^+$$

In the presence of strong hydrochloric acid, ethyl chloroacetate is also formed.

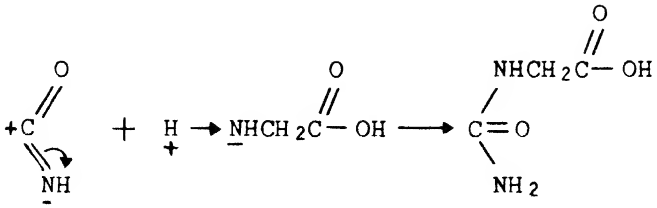
Similar reactions occur between aliphatic diazo compounds and other compounds which contain hydroxyl or amino groups. The use of diazomethane with such derivatives provides a valuable method of methylation. Phenols and enol forms of compounds such as ethylacetoacetate react readily with diazomethane but alcohols which are weaker acids require the presence of an acid catalyst:



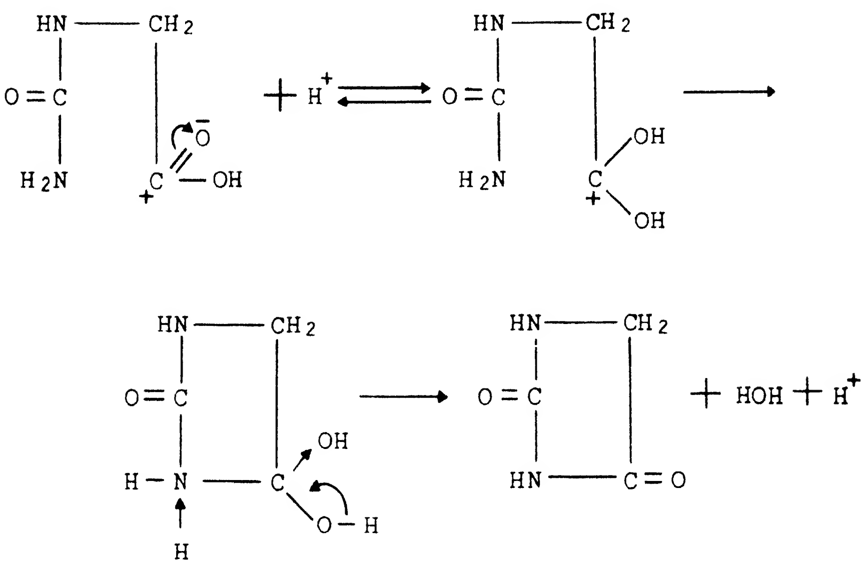
$$:\ddot{N}=N=CH_2+C_6H_5\bar{O}\leftarrow\overset{+}{H} \rightleftharpoons$$

$$\left[:N\equiv N\leftarrow CH_3\right]^+\ \bar{O}C_6H_5 \longrightarrow \underset{\text{anisole}}{C_6H_5OCH_3}+N_2$$

The amino acids undergo other reactions which are characteristic of aliphatic primary amines. They may be acylated by treatment with acid anhydrides or acyl chlorides with the formation of N-acyl derivatives. The primary amines react with isocyanic acid to form alkyl ureas. The amino acids react similarly, glycine, for example, giving hydantoic acid:



The latter when heated with hydrochloric acid is converted into hydantoin:

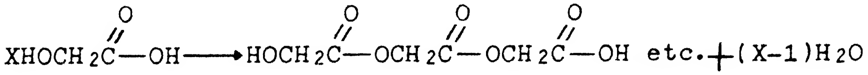


The aromatic amino acids, such as the *o*-, *m*-, and *p*-aminobenzoic acids, apparently do not exist in the solid state as zwitterions. In aqueous solution, both zwitterions and uncharged molecules may be present.

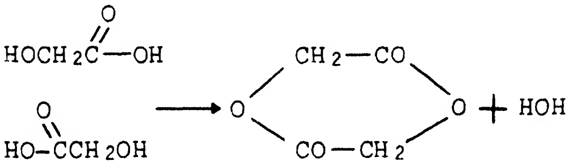
CHAPTER XXVIII

Reactions of Aliphatic Hydroxy Acids

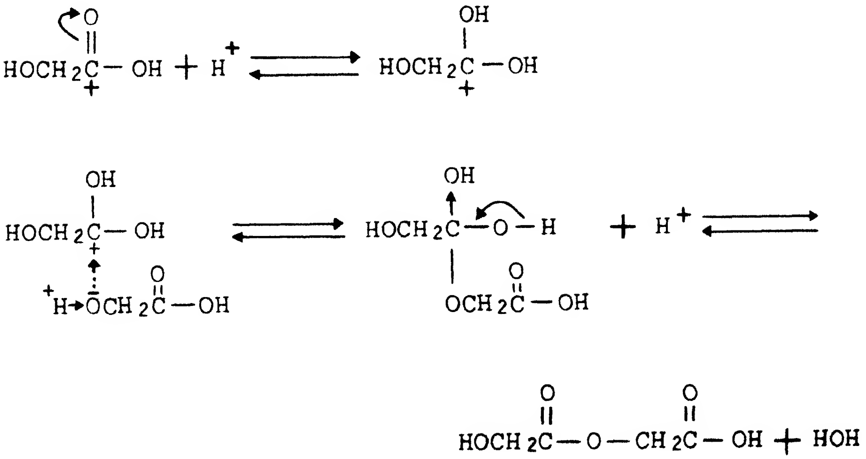
The hydroxy acids are similar in many of their properties and reactions to the alcohols and acids. The mechanisms for most of these reactions have been discussed previously. The presence of the hydroxyl and carboxyl groups in the same molecule, however, makes certain additional reactions possible. For example, under the influence of an acid catalyst or of heat alone, the hydroxy acids are converted into esters or unsaturated acids. The nature of the end product is determined by the relative positions of the hydroxyl and carboxyl groups in the hydroxy acid. α-Hydroxy acids may form either linear polyesters or cyclic diesters:



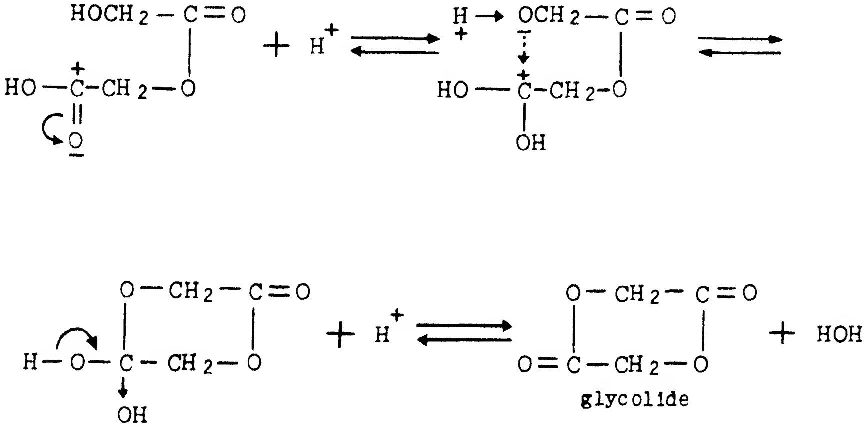
$$\mathrm{XHOCH_2\overset{O}{\overset{/\!/}{C}}{-}OH \longrightarrow HOCH_2\overset{O}{\overset{/\!/}{C}}{-}OCH_2\overset{O}{\overset{/\!/}{C}}{-}OCH_2\overset{O}{\overset{/\!/}{C}}{-}OH\ \ etc. + (X{-}1)H_2O}$$



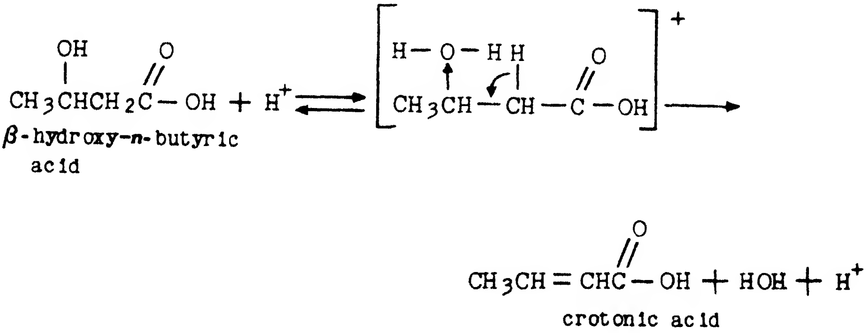
In the presence of acid catalysts these reactions probably follow the Lowry mechanism for esterification:



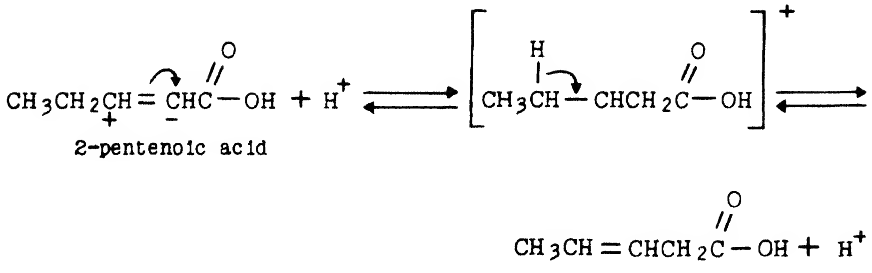
Continuation of this process leads to the formation of a polyester. If the next step, however, involves the alcohol group and carboxyl group within the same molecule, a cyclic diester is formed:



Under similar conditions, action of heat alone or in the presence of acids, the β-hydroxy acids are converted into unsaturated acids. α,β-Unsaturated acids are formed first, but in some cases isomerization of the latter to β,γ-acids has been reported:



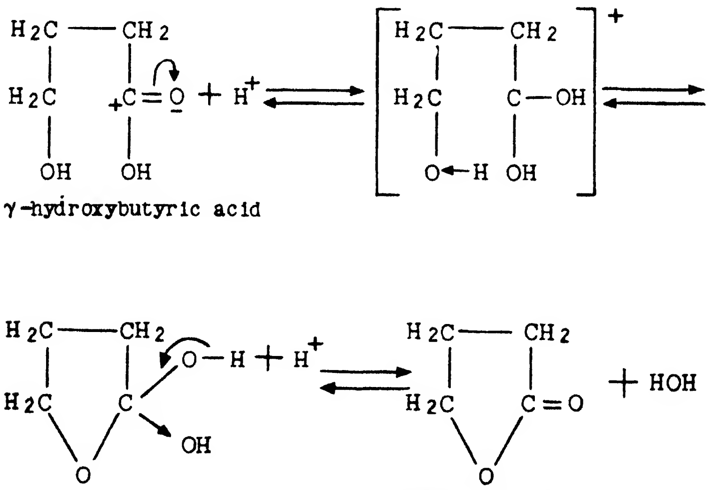
The course of this reaction is dependent upon the potentially ionizable hydrogen on the alpha carbon atom. The tendency of this hydrogen to ionize is aided by the formation of an oxonium ion. β-Hydroxy-*n*-valeric acid under similar conditions has been reported to form both α,β- and β,γ-unsaturated acids. The isomerization of the α,β-acid may be shown as follows:



2-pentenoic acid

3-pentenoic acid

γ-Hydroxy acids lose water with the greatest ease to form cyclic esters (lactones). The ease with which the lactones are formed makes it difficult and sometimes impossible to isolate the free γ-hydroxy acids. Acidification of solutions containing the sodium salts of γ-hydroxy acids liberates the free acids which tend to change into lactones. The conversion into lactones is accelerated by heat and by acids:

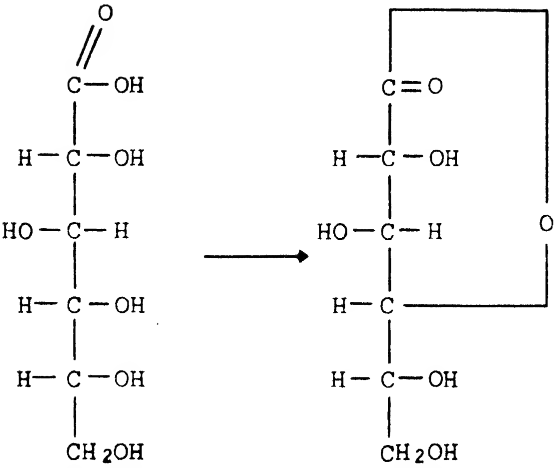


γ-hydroxybutyric acid

γ-butyrolactone

Lactones usually are readily hydrolyzed by treatment with alkalies.

Delta hydroxy acids may be converted into the corresponding lactones, although apparently not as readily as the γ-hydroxy acids. The greater ease of formation of γ-lactones is illustrated by the behavior of gluconic acid. In the latter acid there are hydroxyl groups on the α, β, γ, δ, and ε carbon atoms, but only the γ-lactone is formed:



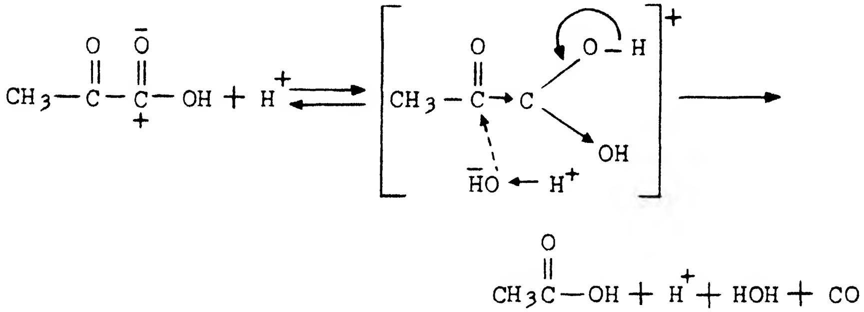
gluconic acid γ-gluconolactone

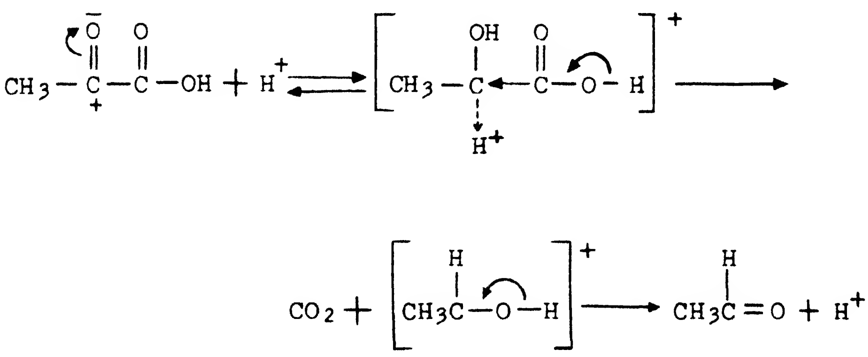
CHAPTER XXIX

Reactions of Aliphatic Keto Acids

Pyruvic acid (pyroracemic acid), the simplest example of an α-keto acid, is a stronger acid than the corresponding fatty acid, propionic acid. This may be attributed to the electron attraction of the carbonyl group adjacent to the carboxyl group. Pyruvic acid reacts normally with some acid and ketone reagents. For example, it forms salts and esters and reacts with hydroxylamine, phenylhydrazine, and hydrogen cyanide.

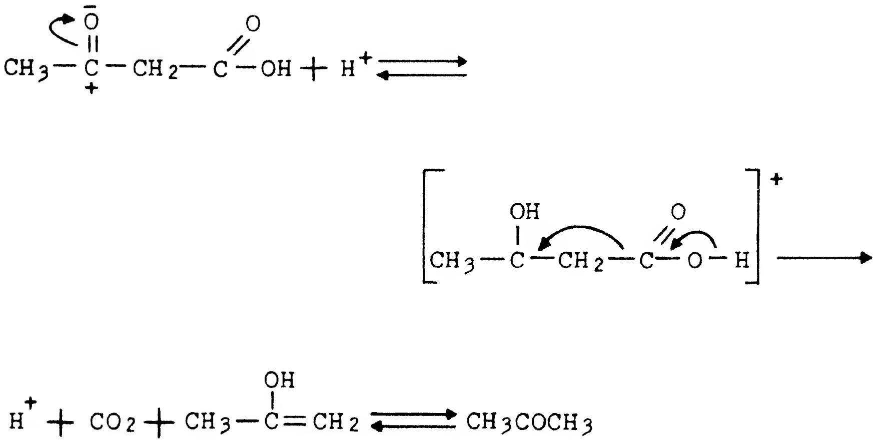
When warmed with concentrated sulfuric acid, pyruvic acid is converted into acetic acid and carbon monoxide. When heated with dilute sulfuric acid, however, it is converted chiefly into acetaldehyde and carbon dioxide. Mechanisms have not been established for these reactions. Since both are catalyzed by acids, it is reasonable to assume that oxonium ion formation is the initial step in each case:



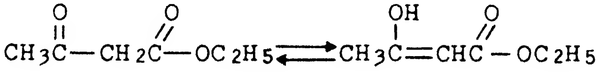


Concentrated sulfuric acid by greatly reducing the ionization of pyruvic acid would increase the ketonic character of the carboxyl carbonyl group and thus increase the attraction of this carbonyl oxygen atom for a proton. Dilute sulfuric acid would not have such a marked effect on the ionization of pyruvic acid, and consequently the proton would tend to add to the oxygen atom of the free ketone group in the α- position.

Acetoacetic acid, a β-keto acid, is less stable than pyruvic acid and decomposes readily into acetone and carbon dioxide. This tendency is accelerated by heat or acids:

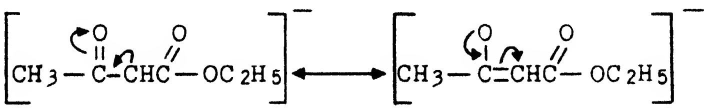


The ethyl ester of acetoacetic acid is widely cited as an example of a tautomeric compound. It is a typical ketone in its reactions with hydrogen cyanide, sodium bisulfite, and hydroxylamine. With other reagents it may act as an unsaturated alcohol. For example, it is converted into ethyl β-chlorocrotonate by phosphorus pentachloride and into a sodium salt by sodium. It decolorizes bromine solution and gives a violet color with ferric chloride. The following established equilibrium is in accord with these properties:

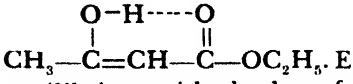


$$CH_3\overset{\overset{O}{\|}}{C}-CH_2\overset{\overset{O}{/\!/}}{C}-OC_2H_5 \rightleftarrows CH_3\overset{\overset{OH}{|}}{C}{=}CH\overset{\overset{O}{/\!/}}{C}-OC_2H_5$$

As in other cases of prototropy, the initial step is the separation of a proton. The resulting anion resonates between two structures and thus is stabilized:



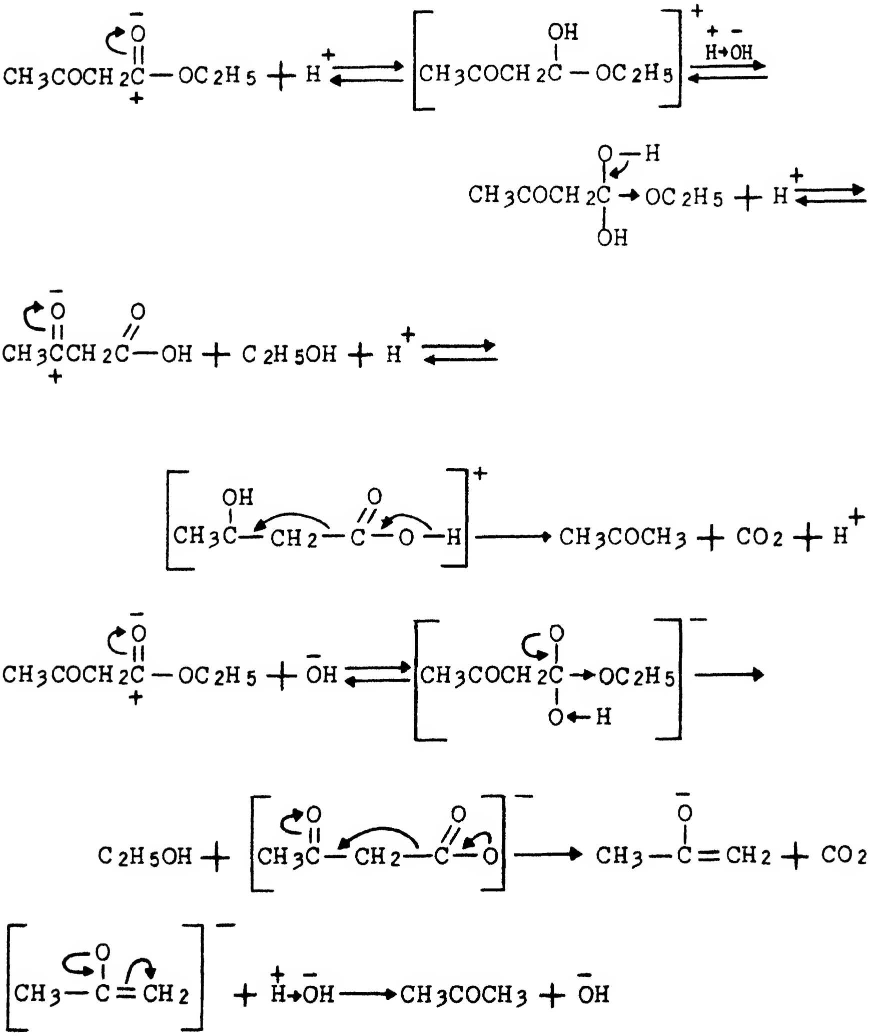
In the molecular form the enol is stabilized through hydrogen bonding,



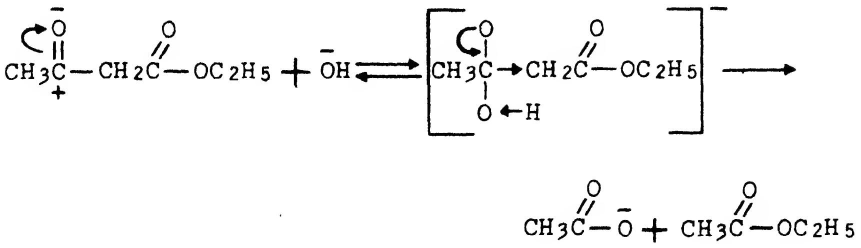
$CH_3{-}\overset{\overset{O-H\cdots\cdots O}{|\qquad\quad\|}}{C{=}CH{-}C}{-}OC_2H_5$. Ethylacetoacetate contains more enol form in equilibrium with the keto form than is the case with a simple ketone such as acetone but less than acetylactone. As mentioned previously, the anion from acetylacetone resonates among three structures and the molecular form of the enol is stabilized through hydrogen bonding.

Ethylacetoacetate and its substituted derivatives undergo "ketonic cleavages" when hydrolyzed by dilute acids or dilute bases and "acid cleavages" when hydrolyzed by strong alkali solutions. The reactions are not mutually exclusive but proceed simultaneously, the one predominating in dilute acid solution or weakly alkaline solution, and the other in strongly alkaline solution.

The ketonic cleavage appears to involve acid- or base-catalyzed hydrolysis of the ester to acetoacetic acid followed by decarboxylation to a ketone:



The "acid cleavage" involves an attack by the base at the ketone group rather than at the carbethoxy group:



$$CH_3\overset{\overset{\bar{O}}{\|}}{\underset{+}{C}}-CH_2\overset{\overset{O}{/\!/}}{C}-OC_2H_5 + \bar{O}H \rightleftharpoons \left[CH_3\overset{\overset{O}{|}}{\underset{\underset{O \leftarrow H}{|}}{C}}\rightarrow CH_2\overset{\overset{O}{/\!/}}{C}-OC_2H_5\right]^- \longrightarrow CH_3\overset{\overset{O}{/\!/}}{C}-\bar{O} + CH_3\overset{\overset{O}{/\!/}}{C}-OC_2H_5$$

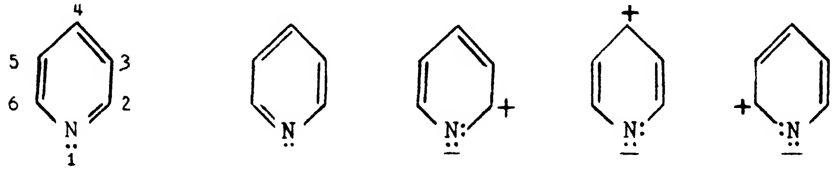
The ethylacetate shown in the last step would be hydrolyzed to ethyl alcohol and acetate ion.

CHAPTER XXX

Reactions of Heterocyclic Compounds

Electronic mechanisms have not been applied so widely to the reactions of the heterocyclic compounds as to the aliphatic and aromatic series. This is probably due to the greater complexity of heterocyclic compounds. Although it is beyond the scope of this book to discuss heterocyclic reactions in general, it is important to note that the same fundamental principles may be applied in this series.

Pyridine, for example, has a somewhat higher resonance energy than benzene (39 kcal. for C_6H_6, 43 kcal. for C_5H_5N). The following structures contribute to the net structure of the molecule:

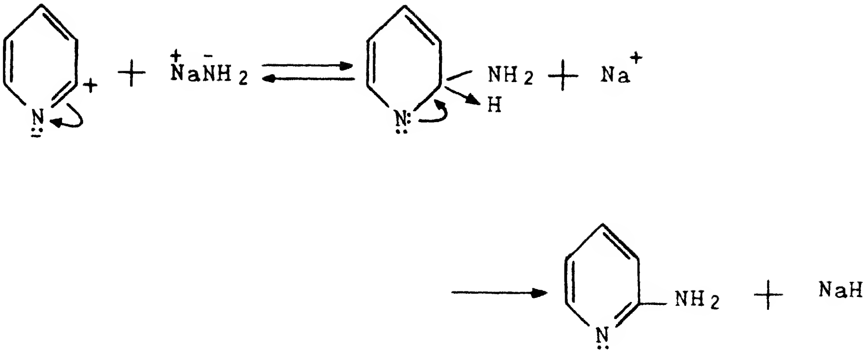


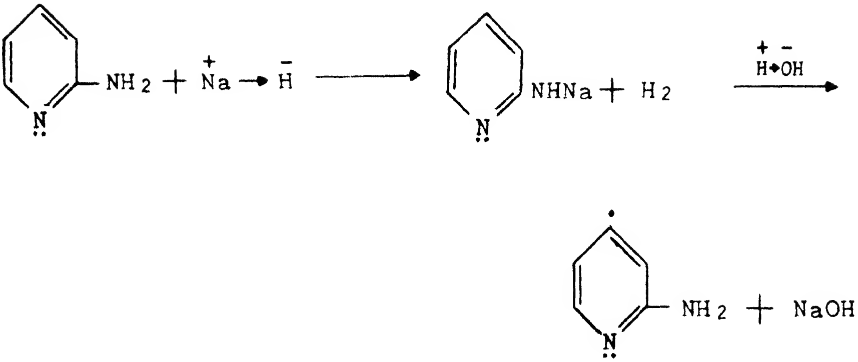
The ionic structures make an appreciable contribution to the net structure and cause a decrease in electron availability at all positions. This decrease, however, is smallest at the β(3)- position. Sulfonation and nitration of pyridine occur with great difficulty and lead to the formation of β-substituted derivatives. These reactions are carried out in strongly acidic media, and, consequently, the pyridinium ion, $C_5H_5NH^+$ and not free pyridine would be present. The positive charge on the nitrogen atom in the ion would aid the electron displacements toward nitrogen and hence increase the tendency towards β-substitution.

Halogenation of pyridine also occurs with great difficulty. Bromination may be effected in the vapor phase at high temperatures. At 300° C. bromination leads largely to the formation of β-bromopyridine, as would be expected. At 500° C., however, α-bromopyridine is formed. Since it is known that the bromine molecule dissociates at this temperature, it seems probable that the attacking agent would be the bromine atom rather than the electrophilic bromine molecule and thus involve a radical mechanism.

The unsubstituted pyridine nucleus is also quite resistant to acylation or alkylation in Friedel-Crafts reactions.

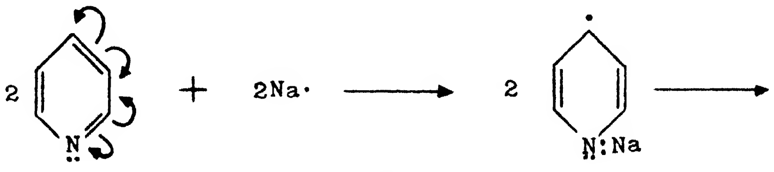
In sharp contrast to the difficulty with which substitution takes place with electrophilic reagents, the reaction with sodamide takes place with comparative ease to form 2-aminopyridine. This behavior is in accord with the resonant nature of the pyridine molecule and the strongly nucleophilic character of sodamide:

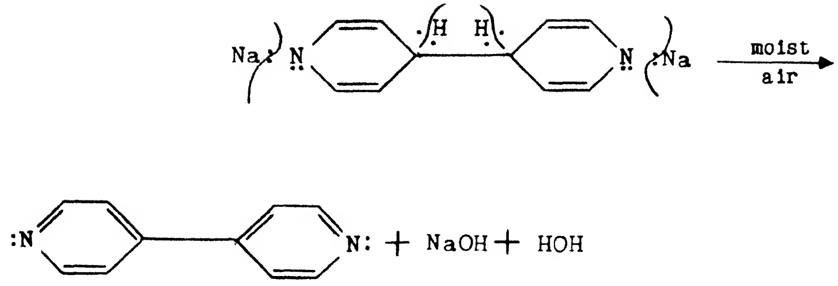




With two equivalents of sodamide it is possible to prepare 2,6-diaminopyridine. Apparently there is little tendency for substitution to occur at the 4- position.

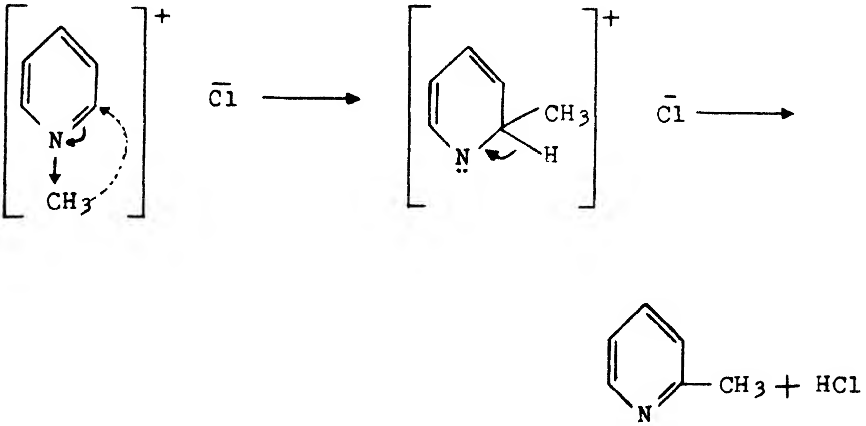
Pyridine undergoes an interesting reaction with sodium. Sodium becomes attached to nitrogen and two rings are united to form a tetrahydrodipyridyl. The latter is oxidized with moist air to a dipyridyl. If the reaction is carried out at room temperature and allowed to stand for several days before treating with moist air, γ,γ′-dipyridyl is the main product:





A radical mechanism is definitely indicated. The odd electron in the pyridyl radical may resonate among several positions. In the formation of γ,γ′-dipyridyl, the unsaturated pyridine system behaves essentially like a conjugated diene. By varying the conditions other dipyridyls can be obtained, such as α,α′-, β,β′-, α,β-, and β,γ-dipyridyls (131).

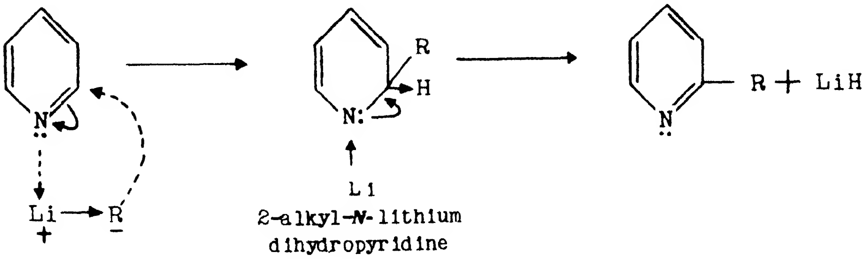
Alkylation of pyridine may be effected by heating the alkyl pyridinium salts at 300°. The alkyl group enters the 2- or 4- position:



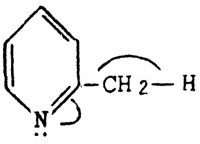
2-methylpyridine
or
α-picoline

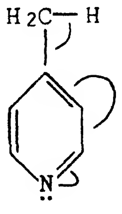
The electron-attracting nitrogen atom may be considered to be the initiating force for the reaction. The electron shifts produce a positive charge on the alpha and gamma carbon atoms, making them receptive for the addition of a carbanion. Whether or not a free carbanion is an actual intermediate is not known. It is more probable that this reaction is just another example of new bonds being formed simultaneously with the breaking of old ones. It has been reported that isomerization of the alkyl group also occurs in some cases. The *n*-propyl group undergoes partial isomerization to the isopropyl group during the reaction.

A similar reaction takes place when the addition compounds between pyridine and Grignard reagents are heated at 150°–160° under pressure (132). Apparently Grignard reagents add quantitatively to pyridine (133) and under the conditions noted above give 2-alkyl or 2-aryl pyridines. Similarly alkyl lithium compounds add to pyridine, and the addition compounds when heated to 100° split out lithium hydride and form 2-alkyl substituted pyridines (134). Lithium alkyls and Grignard reagents would readily furnish the necessary nucleophilic alkyl groups for these reactions:

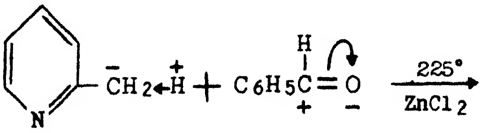


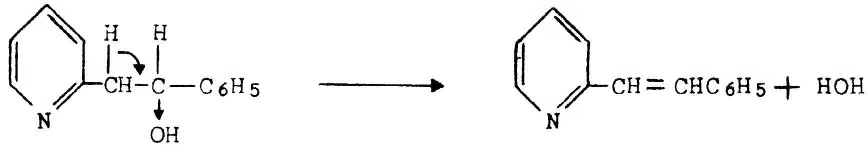
The reactivity of the methyl groups in 2-methyl and 4-methyl pyridines is another interesting example of the effect of the electron-attracting ring nitrogen atom on the rest of the molecule. The methyl group when in the 2- or 4- position behaves more or less like an activated methylene group:





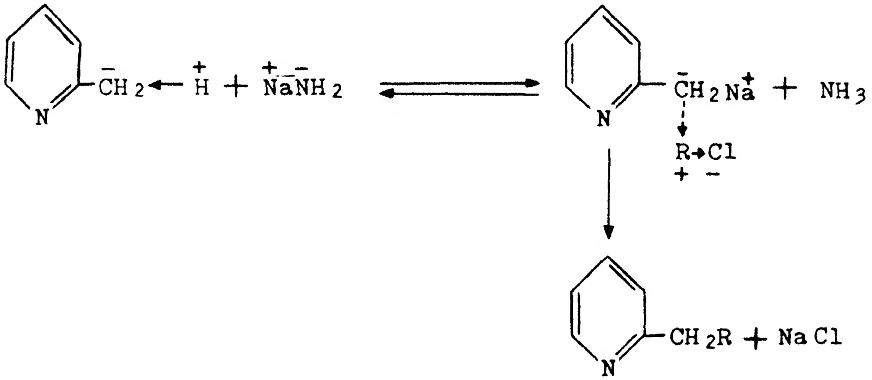
An aldol type addition occurs when 2-methyl pyridine is heated with an aldehyde alone or in the presence of zinc chloride:





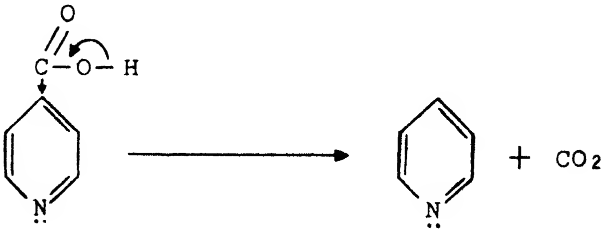
2-styrryl pyridine

2-Methyl and 4-methyl pyridine may be alkylated by alkyl chlorides in the presence of sodamide (135). These reactions may be carried out at room temperature or slightly above:

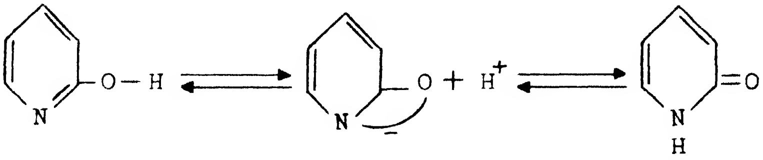


Some dialkylated product is also formed. When a ketone is used in place of the halide, a tertiary alcohol is formed.

This activating effect on the part of the ring nitrogen is shown also by the fact that the 2- and 4-carboxylic acids are more readily decarboxylated by heat than is the β-acid:

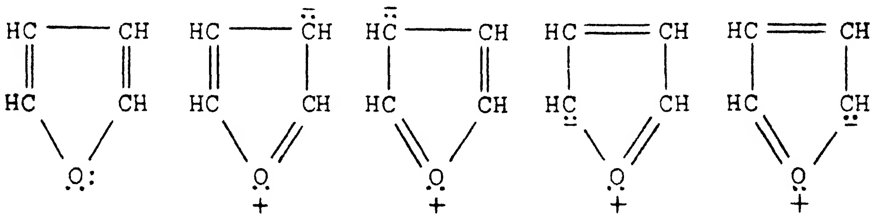


The character of the hydroxy pyridines also appears to be adequately explained by the effect of the ring nitrogen atom. Those with the hydroxyl group in the beta position behave as true phenols, as would be expected, since the nitrogen does not appreciably affect the β- position. When the hydroxyl group occupies the α- or γ- position, however, it is under the influence of the nitrogen and behaves as a tautomeric substance. They give many of the reactions of the corresponding pyridones:


α-pyridone

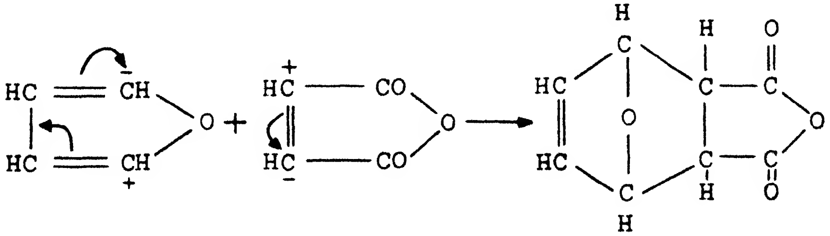
Similarly, β-aminopyridine exhibits the behavior of an aromatic amine. When the amino group occupies the α- or γ- position the compounds behave more like the imino analogs of the pyridones.

Furan. Furan is a five-membered heterocyclic compound. Its resonance energy (23 kcal.) is considerably less than that of benzene (39 kcal.). The following structures contribute to the net structure of the molecule:

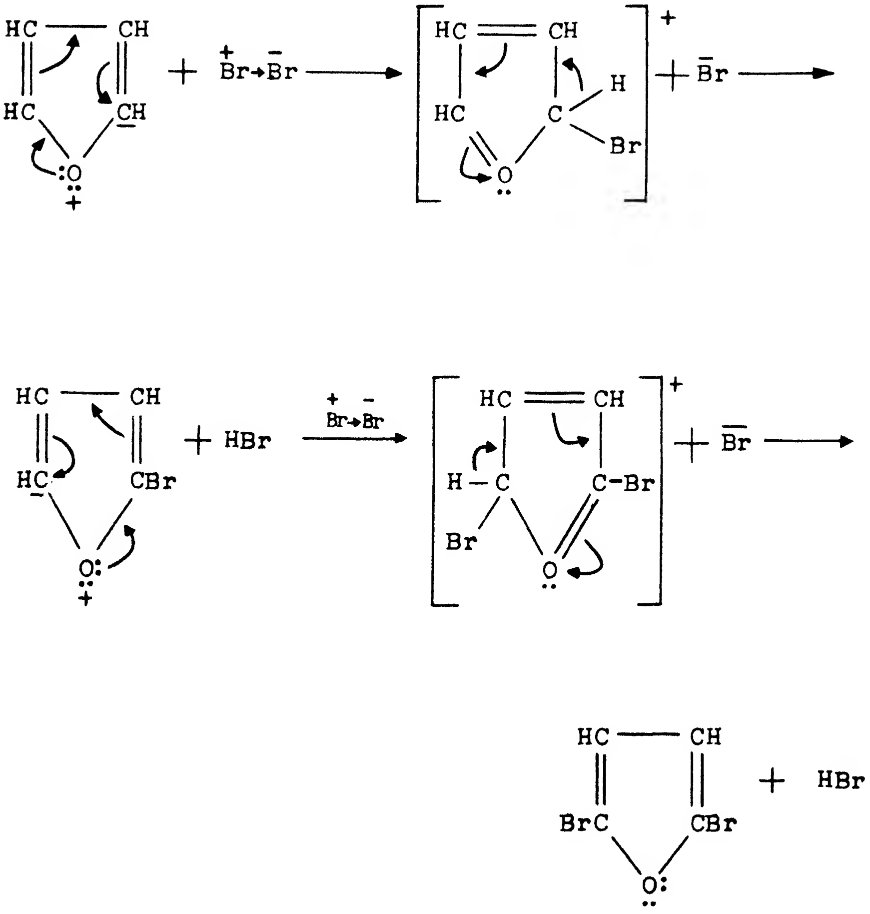


The observed carbon-to-oxygen bond length is less than that expected for a single link between the two atoms.

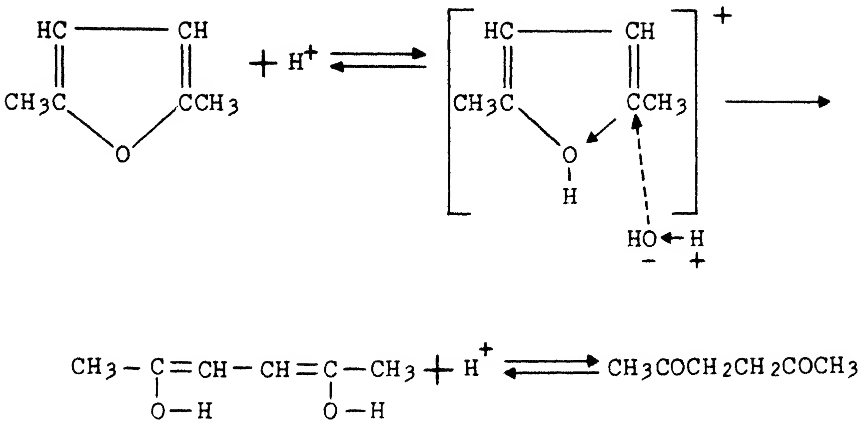
Furan is much more reactive than pyridine towards electrophilic reagents, as would be expected. Its conjugated dienic character is shown by the addition of maleic anhydride (136):



In general all substituting groups enter an alpha position if one is open. Many of the substitution reactions are complicated by the fact that cleavage of the ring occurs quite readily in the presence of acids and consequently large amounts of polymeric material are often obtained. Bromination gives 2,5-dibromofuran as the chief product:

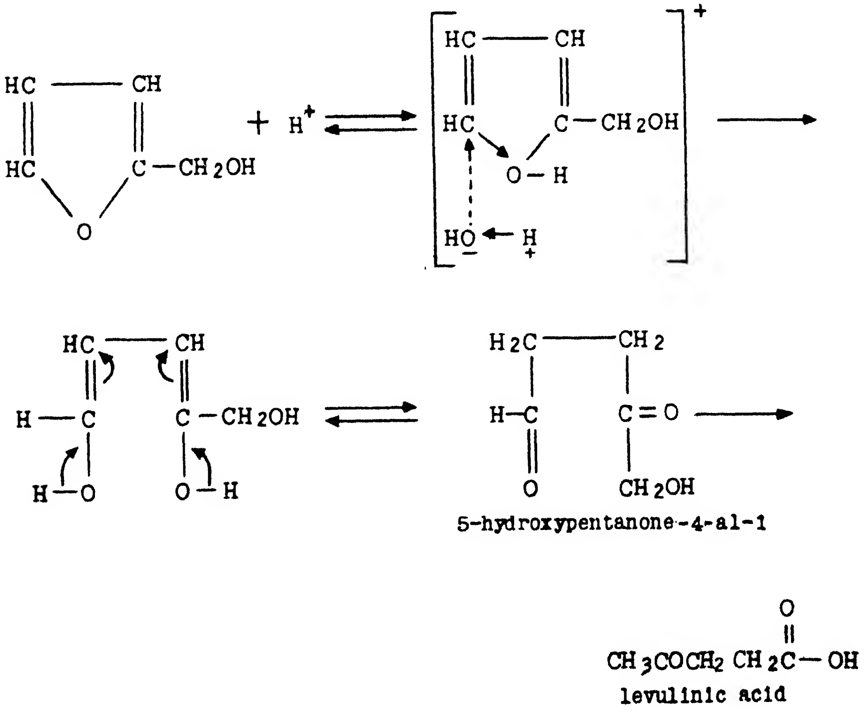


Cleavage of the furan ring occurs violently in the presence of concentrated acids but takes place moderately under the influence of dilute acids. The ring, however, is resistant to alkalies. The cleavage reactions appear to be quite complicated and little is known concerning the mechanisms which are involved. It may be assumed that the first step in the reaction is the addition of a proton to the ether oxygen atom and the resulting electron displacements promote cleavage. It is believed that dicarbonyl compounds are the first hydrolysis products (137). Conversion of 2,5-dimethyl furan to acetonylacetone by heating with dilute hydrochloric acid has been reported. In this case the following mechanism seems probable:



The reverse of this reaction has also been realized. 2,5-Dimethyl furan may be obtained from acetonylacetone by heating with phosphorus pentoxide or anhydrous zinc chloride.

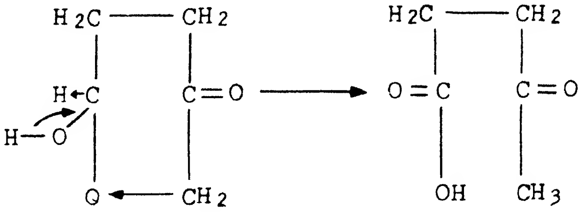
The above mechanism probably applies to other furan compounds, although many of them are more complicated. Furfuryl alcohol is a good example of a more complicated case. It reacts violently with concentrated hydrochloric acid but yields levulinic acid when treated with dilute hydrochloric acid:



5-hydroxypentanone-4-al-1

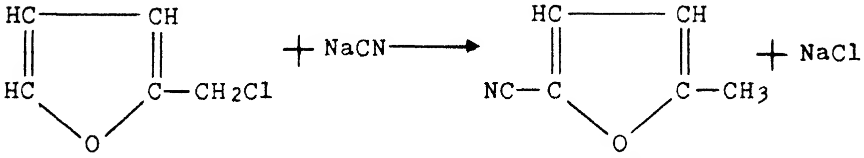
levulinic acid

This reaction appears to follow the expected course as far as the formation of a dicarbonyl compound is concerned. The conversion of the latter to levulinic acid is more difficult to interpret. It has been assumed that this intramolecular oxidation and reduction involves the intermediate formation of a six-membered ring (138).



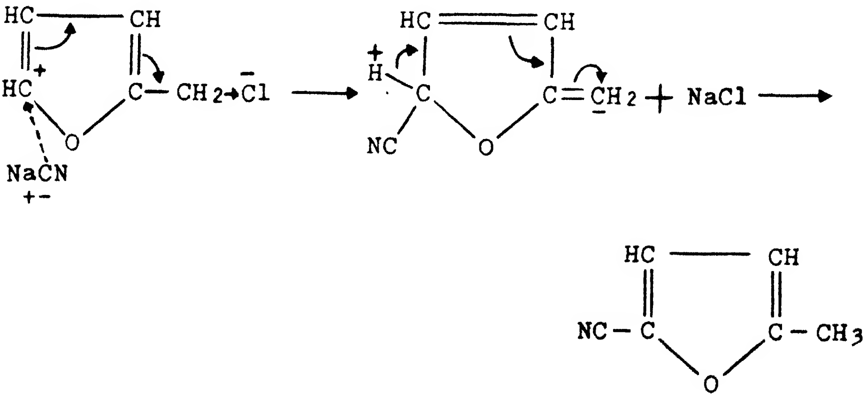
If a cyclic hemiacetal is the necessary intermediate, the last step must involve a mechanism similar to that established for the Cannizzaro reaction. It should be noted that the above mechanism cannot be regarded as established. Secondary alcohols, prepared from furfural and Grignard reagents, have also been used to prepare γ-ketonic acids (139).

An interesting rearrangement, which does not involve cleavage, takes place when furfuryl chloride is treated with sodium cyanide (140):

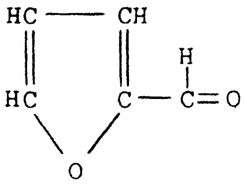


2-cyano-5-methylfuran

It is doubtful if this reaction represents a true rearrangement. It is more probable that the first step is the addition of the nucleophilic cyanide ion to the alpha carbon atom followed by a prototropic change to a more stable product:

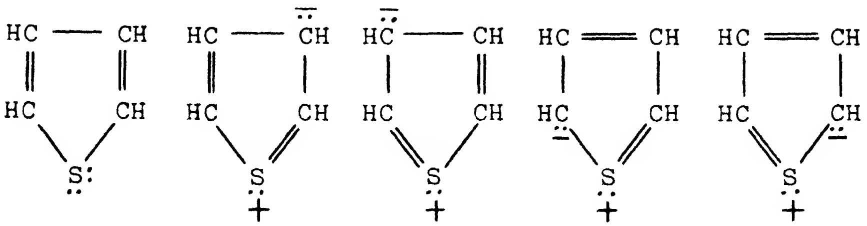


Furfural, one of the important furan derivatives



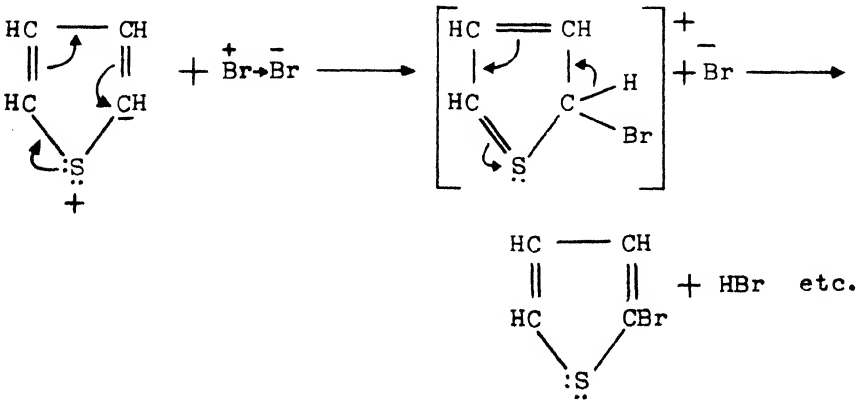
behaves chemically like the aromatic aldehydes. It is readily oxidized to furoic acid and reduced to furfuryl alcohol. It gives the simple addition reactions and undergoes the Cannizzaro reaction and the benzoin (furoin) condensation.

Thiophene. Thiophene is the thio analog of furan and may be considered as a hybrid of five resonant structures:

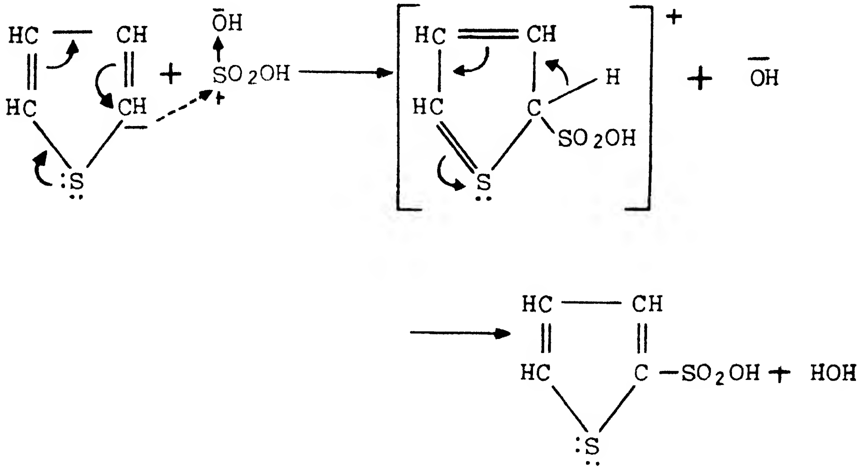


The carbon-sulfur bond length is less than that expected for a single bond between the two atoms. The resonance energy of thiophene (31 kcal.) indicates that it is stabilized to a greater degree than is furan but to a smaller extent than benzene or pyridine. The chemical reactivity of thiophene, in general, is in good agreement with this fact.

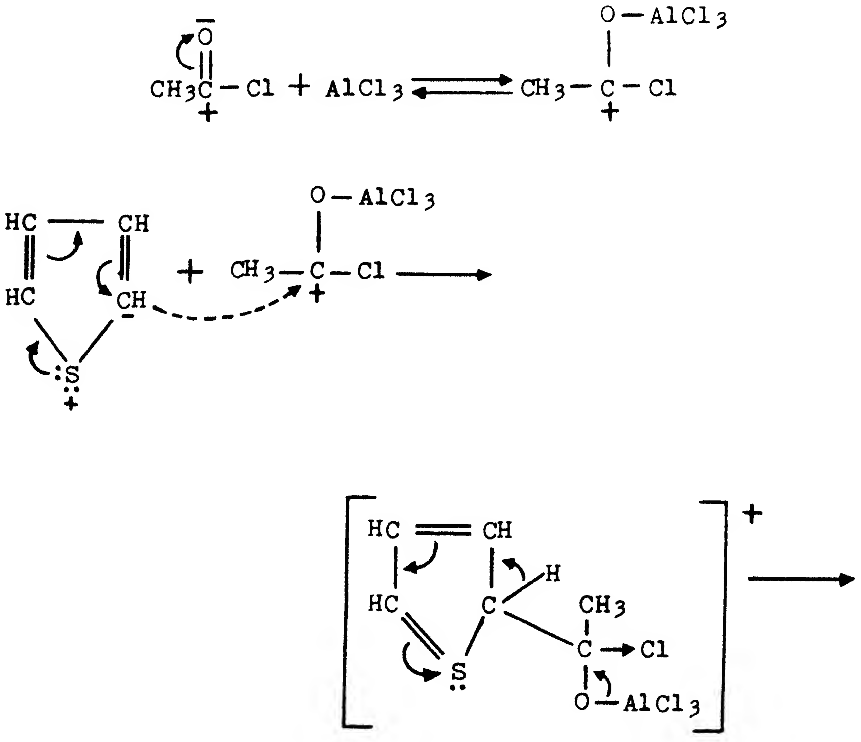
Thiophene does not give an addition product with maleic anhydride. Substituting groups usually enter the alpha positions but alpha orientation is not so exclusive as in the case of furan. Bromination gives 2-bromo and 2,5-dibromothiophene and with excess bromine tri- and tetrabromo derivatives may be formed:

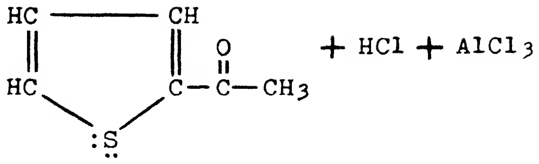


Nitration and sulfonation occur under mild conditions. For example, α-thiophene sulfonic acid may be prepared from thiophene and concentrated sulfuric acid at a relatively low temperature:



Acyl chlorides react readily with thiophene in the presence of aluminum chloride and a solvent such as carbon disulfide. The thiophene is added with the acyl chloride to minimize tar formation:

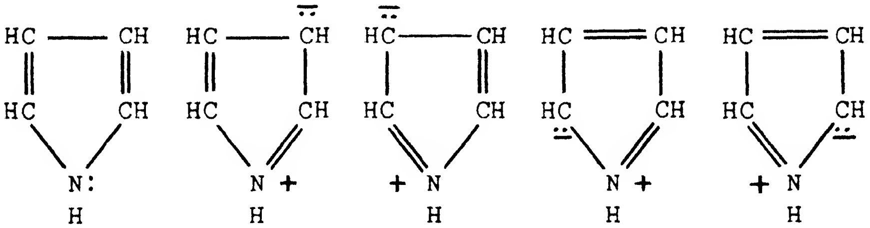




methyl α-thienyl ketone

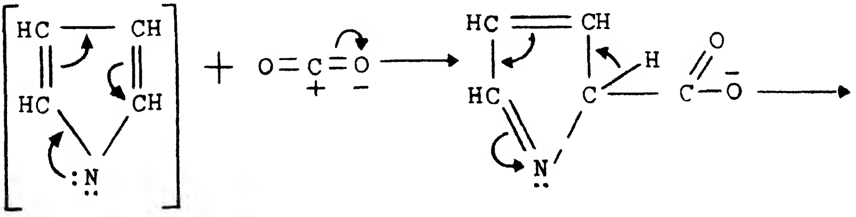
The thiophene ring is more stable than the furan ring and is not cleaved by treatment with dilute acids. This is not surprising in view of the fact that the carbon-sulfur bond, in general, is more difficult to cleave than the carbon-oxygen bond.

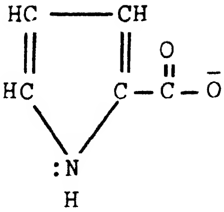
Pyrrole. Pyrrole is another example of a five-membered heterocyclic compound. Its resonance energy has been reported to be 31 kcal. (same as for thiophene). The following structures contribute to its net structure:



The carbon-nitrogen bond length is less than that expected for a single bond between the two atoms. The electron displacements away from the nitrogen atom account for its weakly basic character as well as for the weakly acidic nature of the hydrogen which is attached to the nitrogen atom.

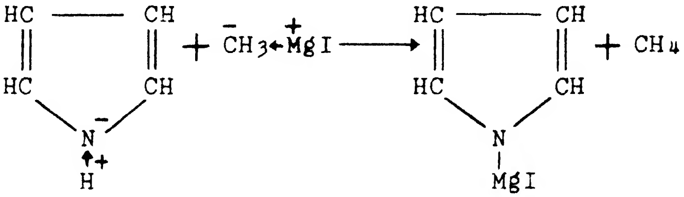
Potassium reacts with pyrrole, in a petroleum ether, to form pyrrylpotassium. A more general method for preparing metallic derivatives consists in carrying out the reaction between pyrrole and certain metals in liquid ammonia (141). Pyrrole carboxylic acids are obtained when pyrrylpotassium is heated with carbon dioxide. At 200°–220° the 2- and 3-pyrrole carboxylic acids are formed. This reaction undoubtedly follows the same course as the Kolbe syntheses of hydroxy-substituted aromatic carboxylic acids (page 83):



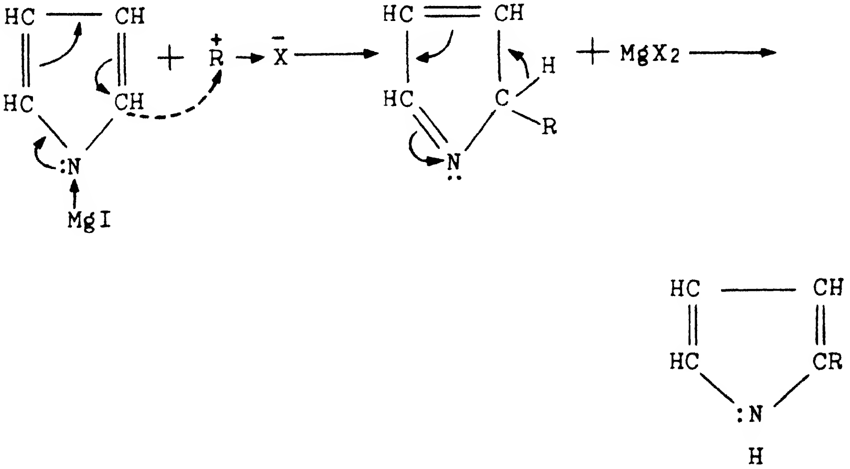


The formation of the 3-carboxylic acid follows a similar mechanism. It is not clear at present what determines whether the electrophilic reagent attacks the 2- position or the 3- position.

Pyrrole decomposes methyl magnesium iodide with the evolution of methane (142):

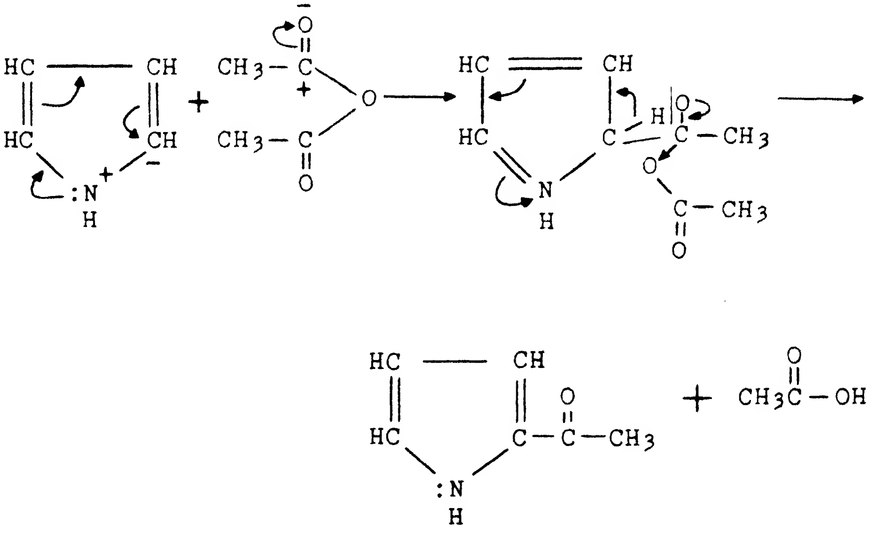


When N-pyrrylmagnesium halides are heated with alkyl halides or carbon dioxide, substituted pyrroles are formed. In general, with alkyl halides, 2-alkyl pyrroles are obtained. An exception to this generalization is noted, however, when methyl iodide is used as the alkyl halide. In this case the alkyl group enters the 3- position predominantly:



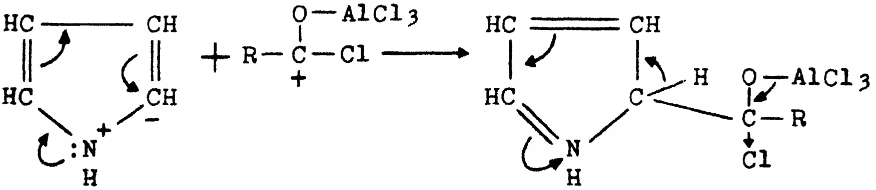
In general, substitution occurs readily in the pyrrole ring. Substituting groups usually enter the alpha positions if the latter are not occupied. Halogenation proceeds very readily. Even iodine, in potassium iodide solution, reacts easily to form tetraiodopyrrole. Nitration and sulfonation cannot be carried out successfully with pyrrole because the latter is rapidly resinified by treatment with concentrated acids. Some of the substituted pyrroles, which contain meta directing groups, may be nitrated or sulfonated.

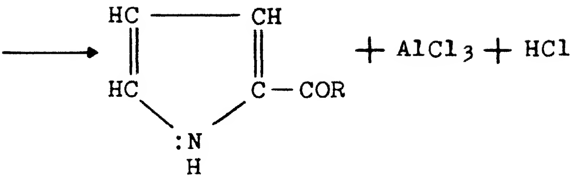
When pyrrole is heated at 240° with acetic anhydride, 2-acetylpyrrole and 2,5-diacetylpyrrole are formed. It is possible that a N-acyl compound is an intermediate and is subsequently rearranged to a C-acyl derivative. It is not necessary, however, to assume such an intermediate. The following mechanism represents the reaction as a simple anionic attack at the carbonyl carbon atom of the anhydride:



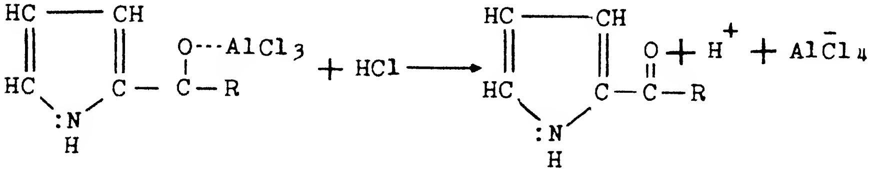
methyl α-pyrryl ketone

This reaction is similar to the Friedel-Crafts acylations except that it is carried out without the activating influence of aluminum chloride. Actually a more general method for the acylation of pyrroles consists of treating the latter with an acyl halide and aluminum chloride. In the presence of the catalyst, the acyl group will enter a β- position if the α-positions are blocked. The aluminum chloride serves to increase the electrophilic nature of the carbonyl carbon atom, otherwise the mechanism is similar to the one shown above:

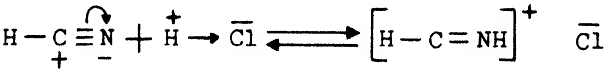


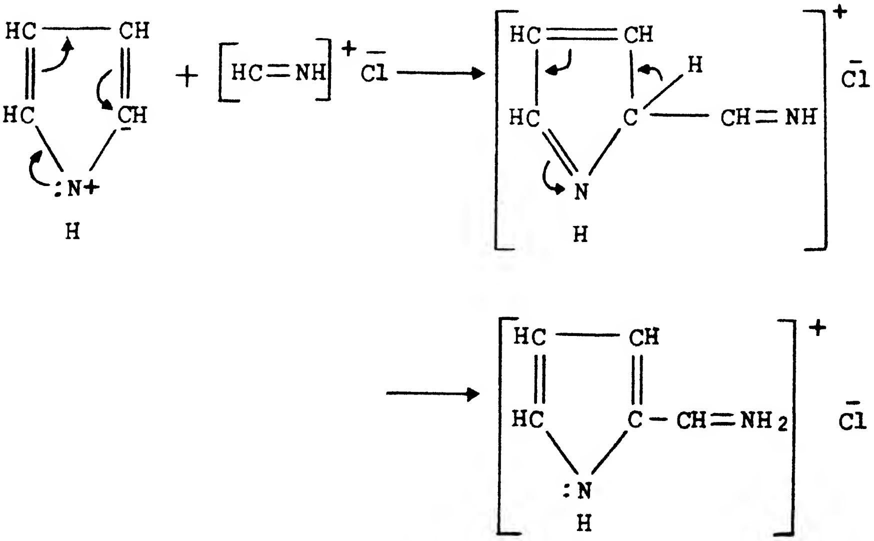


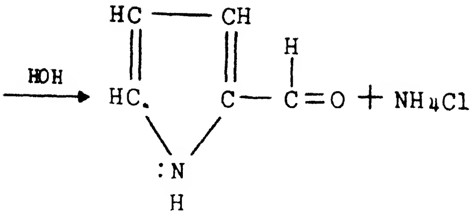
In reactions of this type, it is necessary to hydrolyze the reaction product in order to obtain the free ketone. This may be shown as follows:



α-Pyrrole aldehydes may be prepared by the application of the Gattermann synthesis for hydroxy aldehydes. The aldehyde group enters an alpha position unless the latter is blocked by a substituent. It has been reported (143) that α-pyrrole aldimine hydrochloride precipitates when pyrrole is dissolved in dry ether and treated with anhydrous hydrogen cyanide and hydrogen chloride. The aldimine hydrochloride is hydrolyzed to the aldehyde by warming with water:







α-Pyrrole aldehyde may be prepared also by the Reimer-Tiemann reaction.

Cleavage of the pyrrole ring with acids is not usually possible. Acids, in general, promote polymerization rather than cleavage.

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