THE ELECTRONIC STRUCTURE AND ACTIVITY OF SOME ORGANIC, BIO-ORGANIC AND MEDICINAL COMPOUNDS

Thesis

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By

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Dedicated to the sweet memories of my

father

Late Shri Bhanwar Singh

CERTIFICATE

This is to certify that the thesis entitled 'The Electronic Structure and Activity of Some Organic, Bio-organic and Medicinal Compounds' submitted by Shri Prithvi Singh, ID NO. 74S83001, for award of Ph.D. degree of the Birla Institute of Technology and Science, Pilani, embodies original work done by him under my supervision.

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PREFACE:

It is apparent from a survey of the literature of the past decade that a growing number of Scientists are employing theoretical chemistry to probe the chemical and biochemical events at the molecular level. Of the many theoretical methods employed, the molecular orbital method has been found very successful for such type of study. The molecular orbital investigation of molecular structure leads to what we call electronic structure. The present dissertation is aimed, consequently, at presenting an account of electronic structure-activity relationship of some organic, bio-organic and medicinal compounds.

The first chapter in the thesis mentions some important indices of electronic structure and discusses the properties related to them. The second chapter describes some molecular orbital methods that have been used to calculate the electronic indices and points out how to calculate the different electronic indices. The third chapter actually discusses the activities of different types of the chemicals of interest as a function of their electronic structure. At last the fourth chapter introduces a new structural parameter known as molecular connectivity and discusses its relationship with electronic indices and biological activity of chemicals.

All the work mentioned in the thesis has been done under the able guidance of Dr. S.P. Gupta, Assistant Professor in Chemistry at Birla Institute of Technology and Science. The author therefore expresses his sincere gratefulness to him.

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C O N T E N T S

LIST OF PUBLICATIONS:

1. SCF-MO Calculation of the Ground state Properties of the base components of Nucleic Acids

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2. π-Electron Characteristics of Some Important Carboxylic Acids

   S.P. Gupta and P. Singh
   Indian J. Biochem. Biophys. 14, 89 (1977).

3. Electronic Structure and Anthelmintic Activity of Some Organophosphorus Anthelmintics

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   Indian J. Chem. (B) in press

4. The Electronic Structure and Intermolecular Interaction of Nitrogen Heterocyclics with Nucleotide Bases

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   Indian J. Chem (B) in press

5. Electronic Structure-Activity Relationship of Antibacterial Acridines

   P. Singh and S.P. Gupta
   J. Pharm. Sci. in press

6. Theoretical Approach to Design of Some Herbicides Having high Activity

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   P. Singh and S.P. Gupta
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9. Studies on Correlations between Biological Responses and Substituents Contributions to Molecular Connectivity Index in Substituted Molecules.

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CHAPTER ONE

INDICES OF ELECTRONIC STRUCTURE AND THEIR SIGNIFICANCE

1.1 Introduction:

Since long it has been recognised that the chemical or biochemical activity and other properties of organic compounds are related to their molecular structure. At the simplest level, molecular structure is viewed as a two dimensional connectivity, which, except for completely planar compounds, permits very few rational conclusions regarding relationships between structure and activity to be drawn for a family of similar molecules. This primitive picture, nonetheless, has often been useful. However, most molecules of chemical, biochemical or pharmacological interest are not completely planar and hence for nonplanar molecules the third dimension of conformation is essential for a correct view of molecular structures.

While the three dimensional atomic array per se is of definite value in the study of structure-activity relationship, the lack of unequivocal chemical information regarding conformation in most cases makes such study tentative, at best. A more complex portrayal of chemical structure is a combination of conformational information with the electronic structure of the molceules. For the conjugated systems where the molecules are generally planar the electronic structure alone furnishes sufficient information regarding the activity of the molecules. The important indices of electronic structure are mentioned below and the properties related to them discussed. These electronic indices are calculated using some molecular

orbital methods as described in Chapter 2.

1.2 Charge Density:

The charge density is one of the essential electronic indices that are used for the interpretation of the chemical reactivity. It is involved in the determination of the attack by the electrophilic and nucleophilic reagents (the positive and negative ions respectively) in a molecule. In the isolated-molecule approximation it is quite natural that an electrophilic reagent, such as NO_2^+ ion, will attack the molecule at the position carrying the largest net negative charge and a nucleophilic reagent, such as NH_2^- ion, at the position carrying the largest net positive charge. This concept, although very elementary, satisfactorily accounts for the orientation of a second substitution on a mono-substituted benzene. For example take the case of benzoic acid. As already known the carboxylic group is an ortho-para director for the nucleophilic substitution (second substitution) and a meta director for the electrophilic substituents. This fact is very well varified by the charge calculation in this acid. It has the largest positive charges at the ortho and para positions and the least positive or negative charge at the meta position.

There also exists a correlation between the net charge on a particular atom and the acidic or basic strength of the conjugated systems.

The acidic strength of aromatic alcohols and carboxylic acids would be the greater, the greater the positive charge on the oxygen atom of the —OH group, as the positive charge repels the proton. On the other hand the basic strength of the aromatic amines would be the less, . the greater the positive charge on the nitrogen atom of the $-NH_2$ group, as it will exert the repulson on an approaching proton. In case of heterocyclic amines, the basic strength would be the greater, the greater the negative charge on the nitrogen atom. However this concept holds good only for mono-substituted systems and mono-nitrogen heterocyclics. For poly-substituted acids or bases or heterocyclics containing two or more nitrogen in the ring, the electronic charge will not be the only factor to measure the acidic or basic strength.

The more important application of the charge density is made in the theoretical prediction of the dipole moment. The total dipole moment is composed of two major contributions, firstly the dipole moment resulting from the distribution of the π-electrons and secondly that due to polarization of σ-bonds. The π-component is computed on the basis of net charges on the atoms and the geometry of the molecule by standard procedures (2). The σ-component is obtained by the vector addition of the bond moments of all the σ-bonds present in the system. These bond moments are given in the literature (3).

1.3 Free Valency:

The free valency is another useful electronic index for the interpretation of chemical reactivity in the isolated-molecule approximation, whereas the charge density determines the position of attack by charged ions, the free valency determines the position of attack by neutral reagents, i.e., free radicals. This fact is very well verified (1). In the absence of preferential orientation due to electrostatic attraction, as is the case with alternate hydrocarbons, where each atom is electrically neutral, it seems quite reasonable to suppose that the charged species will also attack the carbon with the highest unsaturation index, i.e., the free valency. This hypothesis is supported by the occurance of all kinds of substitution in the naphthalene preferentially at the α-carbon which has the greatest free valency.

The index of free valency is also helpful in the discussion of physicochemical and chemical properties of the substituents located on conjugated skeleton. Such properties of the substituent depend upon the degree of their interaction with the conjugated system to which they are attached, and this degree of interaction depends upon the free valency of the carbon atom on which the substituent is attached. According to, the so called the rule of maximum conjugation(4), the greater the free valency, the greater the degree of electronic interaction. This

rule has several implications. The most significant are as follows:

1. The increase in resonance energy due to the interaction of substituent with a conjugated skeleton should be greater. the greater the free valency of the substituted atom.

2. In elimination reactions of the disubstituted hydrocarbons, of the two substituted carbon atoms, the one that has smaller free valency should be freed first.

3. In aromatic compounds the acidity of alcohols and carboxylic acids and the basicity of amines are attributed to the conjugation of their functional groups. Therefore the acidic strength of alcohols and carboxylic acids, and basic strength of amines should respectively increase and decrease with the increase of the free valency of the carbon atom carrying the functional groups.

1.4 Energies of Highest Occupied and Lowest Unoccupied Molecular Orbitals:

According to the general theorem of quantum chemistry(5), the energy of highest occupied molecular orbital (HOMO) corresponds to the first ionization potential of the molecule and similarly that of lowest unoccupied molecular orbital (LUMO) to the first electron affinity of the molecule. This has been verified by several authors (6).

The other physicochemical properties that depend upon the energies of HOMO and LUMO are the polarographic oxidation and reduction potentials of the compounds. The plots of oxidation and reduction potentials against the energies of HOMO and LUMO respectively yield the straight lines (7).

However the most important application of the energies of these two orbitals is made in determining the electron-donor and - acceptor properties of the molecules. These properties are involved in a great number of chemical and biochemical transformations including in particular the oxidation-reduction reactions, the formation of charge-transfer complexes, semi-conduction etc. In a series of related compounds, the smaller is the value of energy of HOMO, the better would be electron-donor property of the compounds, as the smaller would be the ionization potential, i.e., the energy required to remove an electron from the molecule. Similarly the higher the value of the energy of LUMO, the higher the electron affinity and hence the better electron-acceptor property of the molecule. These electron-donor and - acceptor properties of the substances play a very important role in the formation of charge-transfer complexes. They are formed by transfer of an electron from a donor to an acceptor and exist in the form of supra-molecular structure. Such charge-transfer complexes are very important in biochemistry. They are formed as intermediates in the biochemical reactions or a permanent supra-molecular structure of some highly organized

biochemical units (8).

The stability of these charge-transfer complexes depend upon both ionization potential of the donor and electron affinity of the acceptor (9). With fixed electron-acceptor, the lower the value of ionization potential or the energy of HOMO of the donor, the more stable the complex. Similarly with the fixed electron-donor the higher the value of electron affinity or the energy of LUMO of acceptor, the more stable the complex. Such correlations have been verified spectroscopically (10-15). The bonding energy as well as the excitation energy of the complex, as a matter of fact, are the function of energy required to transfer an electron from the donor to acceptor and can be expressed as (9):

$$\Delta E_{CT} = I_D - E_A + C \qquad (1.1)$$

where I_D is the ionization potential of the donor, E_A the electron affinity of the acceptor and C is stabilization term containing solvation, polarization and non-bonding contributions. For the interaction of a structurally related series of donors (acceptors) with a common acceptor (donor) C can be considered as a constant, thus making ΔE_{CT} dependent upon I_D (E_A).

1.5 Bond-Order:

The bond-order is the measure of the binding energy

of the π-electron and its double bond character, it therefore determines the position of a molecular addition to a bond, such as ozonization, in which an ozone molecule is fixed on one of the available periferal bond of the conjugated system. Since such reaction involve the interaction between the molecules to be added and π-electrons of the conjugated systems, it is quite plausible to suppose that the reactivity of the bond will be the greater, the greater their double bond character or the π-bond-order. This concept has been verified by ozonization and certain other reaction of this type (16).

The bond-orders are successfully utilized for the calculation of interatomic distances with the use of a well-established mathematical relation (17) between the two:

$$R_{rs} = A - Bp_{rs} \qquad (1.2)$$

where A and B are constants characteristic of given type of bond.

1.6 Excitation Energy:

The excitation energy is the energy required for the excitation of an electron from a filled molecular orbital to an empty molecular orbital. This energy has no direct application in the discussion of the chemical reactivity of the compound, however is useful for the discussion of their spectroscopic properties.

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CHAPTER TWO

METHODS OF CALCULATIONS

2.1 Introduction:

In the present time the quantum-chemical methods are extensively used to find the electronic structure and discuss the chemical reactivity of the organic molecules. The quantum chemistry provides us with two fundamental methods for the study of electronic structure of the molecules, the valence bond method whose simplified qualitative version frequently is referred to as the resonance theory, and molecular orbital method. Both represent approximate procedure for obtaining approximate solution of the Schrödinger equation relative to the molecule. This equation which will be mentioned latter is the basic equation of quantum theory, whose resolution provides the electronic level and the distribution of electronic cloud in the chemical species. Approximate procedures are needed because we are unable at present to solve rigorously the Schrödinger equation for any atomic or molecular system beyond the very simple ones.

Both methods have met with outstanding success in the organic chemistry. But the valence bond theory is in fact far too complex and too difficult to handle to be of any real use in the system of structure of biochemicals. On the other hand the molecular orbital method, because of the simplicity of its mathematical apparatus, has been successfully utilized in biochemistry. The molecular orbital method exists in various stages of

refinement. There are the so called Hückel LCAO (linear combination of atomic orbital) approximation, the SCF-LCAO molecular orbital approximation, the approximation of configuration mixing etc. Although based on the same general principle, these various procedures are widely different from each other in their mathematical development and precision. Consequently they also differ widely in the labour they require. Of all the approximations, the Huckel one is simple enough and a great number of fundamental biochemical structures and problems may be quite satisfactorily dealt with at least to the first approximation by it. Refinements are, of course, always welcome and always useful but in many problems the essential results, the general idea of how things are and function at the electronic level, can be obtained with the use of this simple approximation. It is only in a few particular cases that a more refined approximation obviously has been used from very beginning. In the present dissertation have been described only two approximations. First the Hückel approximation and secondly a refined approximation known as zero-differential overlape (ZDO) approximation. These two approximations are discussed in the following sections.

2.2 Hückel Approximation:

This approximation is described in detail in several texts (1). In the orbital representation the individual

molecular orbitals of a molecule are eigen function of the corresponding one electron Hamiltonian Operator H.

$$H \psi_i = E_i \psi_i \qquad (2.1)$$

Eqn. 2.1 is known as Schrödinger equation. Instead of solving this Eqn., we approximate the molecular orbitals by using the variation method with an LCAO trial eigen function.

$$\psi_i = \sum_r C_{ir} \phi_r \qquad (2.2)$$

Here ψ_i represents a molecular orbital and ϕ an atomic orbital, while C_{ir} represent the co-efficients of the atomic orbitals. The variation principle therefore gives

$$\sum_j C_j (H_{ij} - ES_{ij}) = 0 \qquad (2.3)$$

$$|H_{ij} - ES_{ij}| = 0 \qquad (2.4)$$

where for many electron systems

$$H = \sum_i \left(- \frac{h^2}{8\pi^2 m} \nabla_i^2 \right) - \sum_i \sum_m \frac{Z_m e^2}{r_{im}} \qquad (2.5)$$

in which ∇_i^2, the Laplacian Operator, is defined as

$$\nabla_i^2 = \frac{\partial^2}{\partial x_i^2} + \frac{\partial^2}{\partial y_i^2} + \frac{\partial^2}{\partial z_i^2} \qquad (2.6)$$

The integral H_{ij} and S_{ij} may be defined as

$$H_{ij} = \int \phi_i \, H \, \phi_j \, dv \qquad (2.7)$$

$$S_{ij} = \int \phi_i \, \phi_j \, dv \qquad (2.8)$$

Instead of calculating the integrals H_{ij} we treat them as parameters. The diagonal elements H_{ii} is called coulomb integral and written as α_i. and the off diagonal element H_{ij} is called resonance integral and written as β_{ij}. These two integrals are evaluated by the following two equations respectively;

$$\alpha_i = \alpha_o + h\beta_o \qquad (2.9)$$

$$\beta_{ij} = k\beta_o \qquad (2.10)$$

where α_o and β_o are standard coulomb and resonance integrals for carbon atom and carbon-carbon bond respectively, and h and k are semi-empirical parameters under discussion. The values of the parameter h and k for different atoms and different pairs of atoms are listed in Table 2.1. For non-bonded pairs, the resonance integral β_{ij} is always taken zero. If there are some hetero-atoms adjacent to a carbon atom, the h parameter for that carbon atom is taken as calculated by

$$h_c = 0.1 \sum_{i}^{\text{adj.atom}} h_i \qquad (2.11)$$

Table 2.1

Values of h and k parameters**

ATOM	h	Bonding	k
$\dot{N}$	0.5	C=N	1.0
$\ddot{N}$	1.5	C-N	0.8
N^+	2.0	$C=N^+$	1.0
		N-O	0.7
$\dot{O}$	1.0	C=O	1.0
$\ddot{O}$	2.0	$C-O^-$	0.8
F	3.0	C-F	0.7
Cl	2.0	C-Cl	0.4
Br	1.5	C-Br	0.3
I	0.4	C-I	0.53
Hyperconjugation	$-C'-C''-H_3^*$ (H_2^*)		
C'C''	-0.1	C'-C''	0.8
H_3^*, H_2^*	-0.5	$C-H_3^*$	3.0
		$C-H_2^*$	3.0
P	-0.6	P-O	0.6
O(P)	2.0	P=O	0.6
(C) $\ddot{O}$ (P)	2.0		
(H) $\ddot{O}$ (P)	0.5		
O^-	0.5		
$\dot{S}$(P)	0.8	P=S	0.85

**These parameters are taken as given by:

1. A. Streitwieser (Jr) 'Molecular orbital theory for organic chemists (John Wiley and Sons Inc., New York - London) 1961.
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where the summation extends over all the hetero-atoms bonded to the carbon atom, otherwise it is zero. Eqn.2.11 takes into account the inductive effect produced on the carbon atom by the adjacent hetero-atoms.

The overlap integral S_{ij} is assumed to be unity, if $i = j$, otherwise zero.

The ground state of a closed-shell molecule is supposed to be a situation where 2N electrons are placed in pairs in the N molecular orbitals of the lowest energy. The total binding energy E_π of the molecule is then equated, in this approximation, to the total orbital energy of the electrons, i.e.,

$$E_\pi = 2 \sum_{i}^{occ.} E_i \qquad (2.12)$$

2.3 ZDO Approximation:

In atoms, minimization of the energy in a variation procedure with self-consistent field orbital leads to a series of simultaneous non-linear equations called the Hatree-Fock equations. Applied to LCAO molecular orbitals these equations were shown by Roothaan(2) to reduce to the form

$$\sum_{s} F_{rs} C_{is} = E_i C_{ir} \qquad (2.13)$$

in which the index i refers to molecular orbital and F_{rs} is defined as

$$F_{rs} = H^{c}_{rs} + \sum_{t}\sum_{u} p_{tu} \left[(rs/tu) - \frac{1}{2} (rt/su) \right] \quad (2.14)$$

where

$$H^{c}_{rs} = \int \phi_r H^{c} \phi_s \, dv \quad (2.15)$$

$$p_{tu} = 2 \sum_{i}^{occ.} C_{it} C_{iu} \quad (2.16)$$

and

$$(rs/tu) = \int \phi_r(1) \phi_s(1) \frac{e^2}{r_{12}} \phi_t(2) \phi_u(2) dv \quad (2.17)$$

In HMO theory the p_{tu} is known as the bond-order but defined only for the bonded atoms, here it is defined for all pairs of atomic orbitals. The term (rs/tu) is known as the electron repulson integral and interpreted as a classical electro-static repulson between the two charge distributions $\phi_r \phi_s$ and $\phi_t \phi_u$. The core Hamiltonian H^c is equivalent to the Huckel Operator H defined by eqn. 2.5.

As the F_{rs} are the functions of the co-efficients, Eqn. 2.13 is non-linear and is solved in practice by successive iterations. Starting with an assumed set of molecular orbitals and corresponding co-efficients. we may evaluate the F_{rs} quantities. We derive, in turn, a new set of molecular orbital that may be used to calculate a corresponding set of new F_{rs} values. When the derived molecular orbitals do not differ significantly from the old ones, it is said that the self consistency has reached.

Pople (3) has introduced into SCF-MO (self-consistent field molecular orbital) theory a set of simplifying approximations closely related with Pariser-Parr approximations (4). The approximations are principally the neglect of the overlap, which carries with the elimination of all coulomb repulson integrals except those of the type (rr/rr) and (rr/ss), and the use of empirical quantities for the integrals. With this simplifications Roothaan F_{rs} terms become

$$F_{rr} = I_r + \frac{1}{2} q_r \gamma_{rr} + \sum_{s \neq r} (q_s - n_s) \gamma_{rs} \qquad (2.18)$$

$$F_{rs} = \beta_{rs} - \frac{1}{2} p_{rs} \gamma_{rs} \qquad (2.19)$$

in which I_r is the valence state ionization potential for the atom r, n_s the number of π-electrons contributed by the atom s and γ_{rr} and γ_{rs} symbols for (rr/rr) and (rr/ss) respectively. The q_r is the diagonal element of the bond-order matrix, known as electron density at atom r. Eqns. 2.18 and 2.19 are known as ZDO approximation. The different parameters of ZDO approximation are evaluated as follows:

A. Coulomb Repulson Integral:

The one-centre coulomb repulson integral γ_{rr} is usually estimated as the difference between the valence state ionization potential, I_r, and the electron affinity, A_r, of the atom r. The values of I and A are found

by the method of Hinze and Jaffe (5). The values of γ_{rr} and I_r used in the present work have been taken from the paper of Dewar and Gleicher (6). These values are listed in Table 2.2.

For the evaluation of two centre coulomb integrals, various methods have been proposed (4,7-9). However, in the present work Motaga-Nishimoto (7) formula has been used to evaluate the same.

$$\gamma_{rs} = \frac{14.4}{(R_{rs} + \rho_{rs})} \qquad (2.20)$$

where R_{rs} is the distance between two atoms r and s and

$$\rho_{rs} = \frac{28.8}{(\gamma_{rr} + \gamma_{ss})} \qquad (2.21)$$

The value of γ_{rs} as obtained from Eqn. 2.20 is in electron-volts.

B. The Core Resonance Integral:

The core resonance integral β_{rs} is treated as a disposal parameter. Dewar and Gleicher have described the thermo-cyclic procedure for its evaluation using thermochemical data. Unfortunately very few thermochemical data have been reported for the conjugated systems containing nitrogen and oxygen. Therefore, the following relationship has been used to evaluate this integral.

Table 2.2

Values of Parameters

Atom	I(e.V.)	γ(e.V.)
C	-11.16	10.980
N(pyridine)	-14.12	12.341
N(pyrrole)	-28.53	16.574
O(quinone)	-17.70	13.827
O(furan)	-33.90	18.603

$$\beta_{rs} = K S_{rs} (I_r + I_s) \qquad (2.22)$$

where the overlap integral S_{rs} is calculated using the Slater type of atomic orbitals and the value of constant K is fixed empirically with reference to some experiment. The value of K = 0.31 reproduces the experimental value of ionization potential of the benzene very well.

Both the MO approximations discussed here are applicable only to π-electron systems. Since all the compounds treated in the thesis belong to conjugated systems whose chemical or biological activity and other properties mainly depend upon the delocalization of their mobile or π-electrons, only π-electrons have been considered in finding the electronic structure of these compounds. Both the methods have been used in our problems. Attempt has been made to use the refined method, i.e. ZDO approximation as far as possible, but if any technical difficulty arose in using the same for a particular series of molecules, the HMO method was adopted to solve the problem.

2.4 Calculation of Electronic Indices:

A. <u>Charge Density, Bond-Order and Free Valency:</u>

The probability of finding any electron in a small volume element, dv, is given by $|\psi|^2 dv$. In the LCAO Hückel approximation, the wave function ϕ_i for each atomic orbital in any MO has been assumed to be the same

and its contribution to a MO wave function, Ψ, is weighted by its co-efficient, C_i. The probability of finding the electron in the region of space associated with atomic orbital ϕ_i is then C_i^2. The probability can be expressed in terms of a fractional charge or electron density, q at atom r based upon our charge cloud concept of electron distribution in its domain. Since there are two electrons in a filled MO, the electron density at atom r in the ith MO is $q_r^i = 2\, C_r^2$. The total density at atom r is then a sum of the electron densities at atom r for all occupied MO's

$$q_r = 2 \sum_i^{occ.} C_{ir}^2 \qquad (2.23)$$

The net charge density, Q_r, at atom r is then given by

$$Q_r = n_r - q_r \qquad (2.24)$$

where n_r is the number of π-electrons contributed by atom r.

The bond-order is already defined by Eqn. 2.16.

The concept of free valency, F was proposed by Coulson(10) as being a residual bonding affinity of a π-electron on an atom. It is the difference between the maximum bond orders around an atom, N_{max}, and the calculated bond orders around that atom, N_r

$$F = N_{max} - N_r \qquad (2.25)$$

The maximum bond-orders around C, N, and O are taken to $\sqrt{3}$, $\sqrt{2}$ and 1 respectively (1).

B. Energies of HOMO and LUMO and Excitation Energy:

Solving the secular determinant. Eqn. 2.4, gives rise to a series of energy values corresponding to particular molecular orbitals which are solutions of the wave equation. These energy values are of the form

$$E_i = \alpha + m_i \beta \qquad (2.26)$$

where i refers to an MO.

The positive m values correspond to occupied (bonding) orbitals and negative ones to unoccupied (antibonding) orbitals. The lowest positive m value gives the energy of HOMO and the lowest (in magnitude) negative one that of LUMO. It is customary to express the energy values only by m.

The excitation energy is taken as the difference between the energies of HOMO and LUMO.

C. Frontier Electron Theory and Reactivity:

A different approach to reactivity using the isolated-molecule approximation was proposed by Fukui et. el. (11). The theory presumes that the least tightly bound electron would react preferentially with an electrophilic reagent. The π-electrons in HOMO would thus be important in the reaction. The position in the molecule

with the greatest density in these MO's would presumably be the most reactive. These orbitals are known as frontier orbitals and the electrons as frontier electrons.

Nucleophilic reactivity would be predicted to occur at a position in the molecule having the highest density of two ghost electrons in LUMO. The symbol $f_r^{(E)}$ and $f_r^{(N)}$ are used for the electron density, C_{ir}^2, at atom r for the frontier orbital, f , for electrophilic or nucleophilic attack. The index permits only a comparison of relative reactivities within the same molecule.

The concept was extended to permit the comparison of reactivities of positions in different molecules (2). The index called superdelocalizibility, S_r, is defined as

$$S_r = 2 \sum_{i}^{\text{occ./unocc.}} C_{ir}^2/m_i \qquad (2.27)$$

where the summation extends over all occupied orbitals for electrophilic substitution and over all unoccupied orbitals for nucleophilic substitution. For radical attack the superdelocalizibility index is defined as

$$S_r^{(R)} = \sum_{i}^{\text{occ.}} C_{ir}^2 / m_i + \sum_{j}^{\text{unocc.}} C_{jr}^2 / m_j \qquad (2.28)$$

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CHAPTER THREE

ELECTRONIC STRUCTURE-ACTIVITY RELATIONSHIP

3.1 Chemical Reactivity of Azanaphthalenes with Nucleophiles and Electrophiles:

In isolated-molecule approximation the static electronic indices, such as charge density, free valency, bond-order, have been found to be very useful in the discussion of chemical reactivity of the conjugated system. The properties related to these indices have already been discussed in Chapter 1. The relative reactivity of different positions in azanaphthalenes towards nucleophiles and electrophiles has been an interesting problem, yet not much work has been done in this direction. Whatever work in this direction has been done that is mainly related to nucleophilic substitution reactions, and very few kinetic data are available in connection to electrophilic substitution reactions. Therefore an exhaustive study is made on the relative reactivity on different positions in azanaphthalenes towards nucleophiles and electrophiles on the theoretical basis and arrived at and interpreted the fundamental reactivity pattern of such molecules.

(A). Results and Discussion:

The calculated net charges at the different positions in azanaphthalenes are listed in Table 3.1. The charges at the nitrogen atom have not been mentioned as they have no use in our discussion, rather a cross (X) has been put in their place just to indicate the position of nitrogen. The largest net positive charge in molecules

Table 3.1

The Calculated net charges at different positions in azanaphthalenes

Azanaphthalene	Position							
	1	2	3	4	5	6	7	8
1-	X	+0.167**	-0.030†	+0.071*	-0.033	-0.006	+0.011	+0.033
2-	+ 0.145**	X	+0.100*	+0.013†	-0.011	+0.014	-0.004	+0.011
1,2-di-	X	X	+0.100**	+0.048*	-0.005†	+0.012	+0.014	+0.033
1,3-di-	X	+0.254**	X	+0.213*	+0.016	-0.015	+0.023	-0.016†
1,4-di-	X	+0.124**	+0.134	X	-0.006†	+0.004*	+0.002	-0.006
1,5-di-	X	+0.161**	-0.022	+0.077*	X	+0.141	-0.004†	+0.033
1,6-di-	X	+0.157**	-0.021	+0.056	+0.143*	X	+0.105	-0.020†
1,7-di-	X	+0.164**	-0.011	+0.069	-0.005†	+0.033	X	+0.101*
1,8-di-	X	+0.163**	-0.034	+0.071*	+0.071	-0.034†	+0.103	X
2,6-di-	+0.166**	X	+0.077*	-0.025†	+0.166	X	+0.077	-0.025
2,7-di-	+0.173**	X	+0.065*	-0.045†	+0.046	+0.075	X	+0.173
1,2,3-tri-	X	X	X	+0.101**	+0.003	+0.011	+0.020	+0.006
1,2,4-tri-	X	X	+0.253**	X	-0.012†	+0.013	+0.103	+0.013

(contd.)

(Table-3.1 contd.)

1,3,5-tri-	X	+0.246**	X	+0.213*	X	+0.141	−0.201†	+0.069
1,3,6-tri-	X	+0.271**	X	+0.136*	+0.163	X	+0.111	−0.044†
1,3,7-tri-	X	+0.751**	X	+0.236*	−0.021†	+0.061	X	+0.116
1,3,8-tri-	X	+0.265**	X	−0.224*	+0.081	−0.041†	+0.110	X
1,4,5-tri-	X	+0.110	+0.133*	X	X	+0.159**	−0.2[illegible]†	+0.[illegible]
1,4,6-tri-	X	+0.155**	+0.125	X	+0.143*	X	+0.[illegible]	−0.[illegible]†
1,6,7-tri-	X	+0.188**	−0.011†	+0.079	+0.142	X	X	+0.151*
2,6,7-tri-	+0.157**	X	+0.169	−0.030†	+0.142	X	X	+0.151*
1,2,3,5-tetra-	X	X	X	+0.161*	X	+0.170**	−0.[illegible]†	+0.[illegible]
1,2,3,6-tetra-	X	X	X	+0.216**	+0.160*	X	+0.117	−0.08††
1,2,4,5-tetra-	X	X	+0.218**	X	X	+0.[illegible]*	−0.[illegible]†	+0.[illegible]
1,2,6,8-tetra-	X	X	+0.076	+0.069	+0.238*	X	+0.[illegible]**	X
1,3,5,7-tetra-	X	+0.[illegible]**	X	+0.[illegible]*	X	+0.[illegible]	X	+0.[illegible]
1,3,5,8-tetra-	X	+0.263**	X	+0.216*	X	+0.113	+0.[illegible]	X
1,3,6,7-tetra-	X	+0.261**	X	+0.237*	+0.154	X	X	+0.[illegible]
1,3,6,8-tetra-	X	+0.277**	X	+0.[illegible]*	+0.[illegible]	X	−0.[illegible]	X

(contd.)

(Table-3.1 contd.)

1,4,5,8-tetra-	X	+0.131**	+0.134	X	X	+0.134	+0.171	X
1,4,6,7-tetra-	X	+0.155**	+0.155	X	+0.117*	X	X	+0.117
2,3,6,7-tetra-	+0.152**	X	X	+0.152	+0.152	X	X	+0.152
1,2,3,5,7-penta-	X	X	X	+0.202	X	+0.269**	X	+0.217*
1,2,4,5,7-penta-	X	X	+0.260	X	X	+0.289**	X	+0.261*
1,2,4,6,8-penta-	X	X	+0.230	X	+0.234*	X	+0.266**	X

≠ For alternative chemical names of azanaphthalenes see ref. 3.

† ,**,* See the text; X indicates the position of nitrogen in the naphthalene ring (Fig.II).

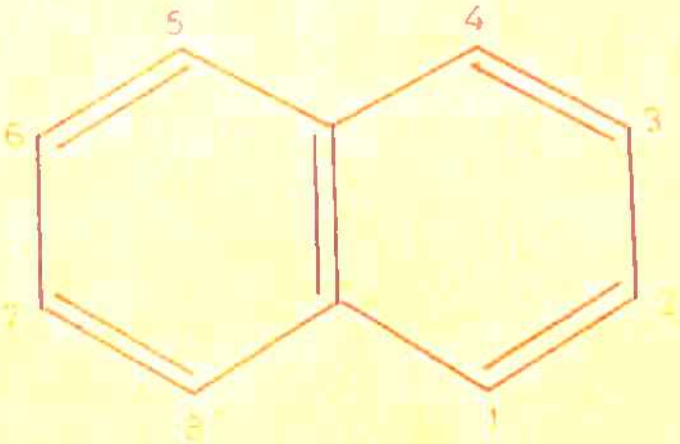
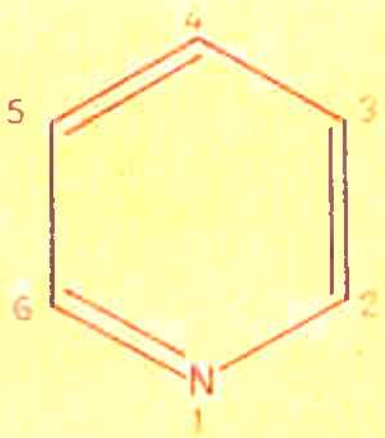
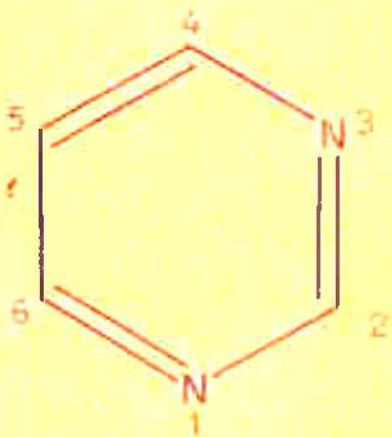


Fig. 3.1. Numbering system in naphthalene ring



(I)



(II)

is doubly starred and the next largest is singly, while a dagger (+) has been put over the largest net negative charge (many molecules have, in fact, only one negative centre). If there has been some kind of symmetry in a molecule and thus several identical positions in it, the charge of only one of such identical positions has been marked in each case. As already discussed in Chapter 1 the largest positive charge will indicate the position of nucleophilic attack and the largest negative charge that of electrophilic attack. From the table the following observations are made regarding the nucleophilic substitution reactions.

1. In all those azanaphthalenes in which one nitrogen is at position 1 of the ring and no one at position 2, ortho to N-1, the position 2, irrespective of the positions of other nitrogens (in polyazanaphthales) has the largest net positive charge, and the next largest net positive charge is possessed by position 4, para to N-1, if there is no nitrogen at this position otherwise by the position ortho to N-4 as in 1,4,5-triazanaphthalene (in this case the largest positive charge is not at position 2, but at 6, ortho to N-5 - the two positions 1 and 5 in naphthalene ring are identical), or ortho to some other nitrogen as in 1,4,6-triazanaphthalene. Compounds 1,4-di-and 1,4,5,8-and 1,4,6,7-tetraazanaphthalenes

represent the identical centres in them under discussions.

2. If the nitrogen is at position 2 and no nitrogen at 1, then largest positive charge is found to reside at position 1 irrespective of the positions of other nitrogens. The second largest net positive charge is found mostly at position 3, if it has no nitrogen or at ortho position to some other nitrogen as for example, in 2,6,7-triazanaphthalene.

3. In other compounds where position 1 and 2 both are occupied by nitrogens, the largest positive charge is found at a position which falls between two nitrogens and the second largest positive charge is at the position adjacent to one and opposite to other. If such situation does not exist, as in 1,2, 3,5-and 1,2,3,6-tetraazanaphthalenes, the position adjacent to the nitrogen singly present in a ring shows the largest positive charge.

The general pattern of the reactivity therefore will be as follows. In all azanaphthalenes, whether mono- or poly-, in which there is a nitrogen at position 1 of the ring, the most reactive centres towards nucleophilic substitution reaction would be positions2 and 4, if they are free (no nitrogen at them), and 2 > 4. In those azanaphthalenes where

position 2 is occupied by a nitrogen and position 1 is free, the most reactive centre would be position 1 and the next would be position 3, if it is free. In other azanaphthalenes the position between two nitrogens would be the most reactive and the next would be the position adjacent to one nitrogen and opposite to other.

Such general reactivity pattern of azanaphthalenes towards nucleophilic substitution reaction is consistent with the experimental observations available. For example, with the exception of 1,7-naphthyridine (1,7-diazanaphthalene) which formed the 8-amino compound exclusively all of the other 1, X-naphthyridines (1,5-, 1,6- and 1,8-diazanaphthalenes) were found (1) to be aminated at [illegible]. Besides, the experimental evaluation of the ground state electron deficiency made in some cases has led to similar results as obtained presently. By means of chemical shifts of the hydrogen atoms in pyrimidine (II) and 4- and 5-substituted pyrimidines, it has been shown that the electron deficiency at the position 2 is greater than at 4 or 6 regardless of the nature of the substituent (2). Several other methods have shown that in pyridine (I), pyrimidine and other azines the position 2 is most deficient in the ground state (3). The greater reactivity of position 1 of isoquinoline

(2-azanaphthalene) has been proved by 70-85 percent yields of the product of 1-amination of isoquinoline with amide ion (4-6) and 70-90 percent yields of 1-alkylation and -arylation products with Grignard reagents (7-8). Such kinetic data regarding the reactivity of unsubstituted polyazanaphthalenes are however scarced though much has been discussed of the nucleophilic reactivity of substituted ones (3).

Extensive theoretical calculations done in the past on azines have shown (1,9-11) the greater electron deficiency at either position 2 or 4, usually position 2 being more electron deficient than 4 in mono- and bi-cyclic azines. However. the greater electron deficiency for position 4 than for 2 has been found (12), and the greater chemical reactivity towards nucleophile at position 4 has been often observed in synthesis and supported by kinetic studies.

There are thus conflicting generalization in the heterocyclic literature as to the relative reactivity of positions 2 and 4 in azines towards nucleophiles. However, an exhaustive theoretical survey as the present one, leads, in general, position 2 to be more reactive than 4 in such type of compounds towards nucleophiles.

Regarding the electrophilic substitution reaction the following facts are noted from the Table 3.1.

1. In the two rings of azanaphthalenes, only that ring

contain the negative centre which has either no or only one nitrogen. The ring having more than one nitrogen has no negative centre. That is why there is no negative position in any of the pentazanaphthalenes.

2. In tetraazanaphthalenes, only those molecules have a negative centre - the only negative centre - where the three of the four nitrogens are in one ring and only one in the other. In these molecules the negative centre is meta to nitrogen singly present in the other ring. Similarly in triazanaphthalenes if the two nitrogens are in one ring and one in other the negative centre (the only negative centre) is essentially meta to the nitrogen singly present in the other ring. However, if all the three nitrogen atoms in triazanaphthalenes are in one ring - such cases are only two 1,2,3 - and 1,2,4 - triazanaphthalenes - then there is either no negative centre or if there is any, it is position 5.

3. In diazanaphthalenes too the negative centre is meta to X, the position of nitrogen present in second ring in 1-X type of azanaphthalenes. However, if this type of azanaphthalenes represents some kind of symmetry, then there are two identical negative centres each meta to one nitrogen. Similarly there are two identical negative centres meta to each nitrogen in two 2-X type of diazanaphthalenes (X being in second ring), as both of them represent a kind of symmetry.

But in case both the nitrogen in 1-X type of diazanaphthalenes are in the same ring, the negative centre is either position 5 or 8.

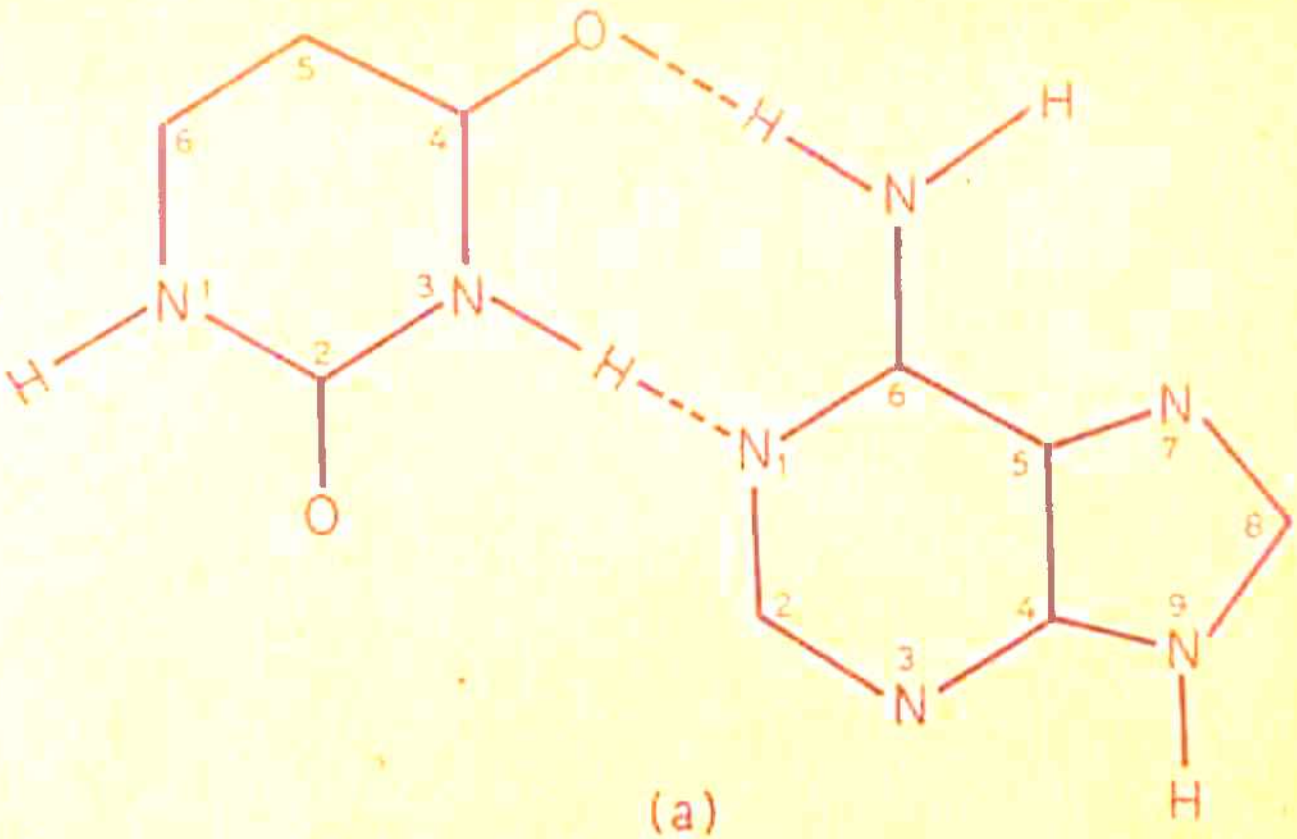
4. In monoazanaphthalenes also the most negative centre is essentially meta to the nitrogen.

Therefore, the general reactivity pattern of azanaphthalenes toward the electrophilic substitution reaction would be as follows. The most reactive centre toward the electrophiles in an azanaphthalene would be generally the position meta to the nitrogen singly present in one of the two rings. If all the nitrogens are present in one ring then it is the position 5 or 8 which will constitute the most reactive centre towards such substituents. This general reactivity pattern is consistent with the scanty observations made so far. For example, the bromination of 1,5-naphthyridine (1,5-diazanaphthalene) was found (1) to give the 3-bromo-and 3,7-dibromo -1, 5-naphthyridine. The 3-bromo-,8-bromo-, and 3,8-dibromo-1, 6-naphthyridine were obtained from 1,6-naphthyridine (1,6-diazanaphthalene). The 1,7-naphthyridine (1,7-diazanaphthalene) afforded the 5-bromo and 3,5-dibromo derivatives. The 3-bromo- and 3,6-dibromo-1, 8-naphthyridine were obtained from 1,8-naphthyridine (1,8-diazanaphthalene). Obviously all substituted positions in these naphthyridines are meta to their nitrogens.

..2 Intermolecular Interaction of Nitrogen heterocyclics with Nucleotide Bases:

The studies on the interaction of organic compounds with nucleotide bases are of considerable biological interest. They provide an opportunity for elucidating the molecular mechanism of the action of mutagens. If an organic compound interacts with nucleotide bases, it leads to the structural changes in DNA and RNA, for example, the addition of aminoacridine or ethidium bromide (2,7-diamino-9-phenyl-10-ethylphenanthridine bromide) to circular polyoma, DNA changes the structure from that of a superhelix to a circle (13). Thus the genetic messages that DNA and RNA bear can be destroyed. The interaction of organic compounds in general may lead to several consequences. The aminoacridines act mutagenically on bacteriophase possibly by causing the insertion or deletion of a base pair in its DNA (14-15). and ethidium bromide inhibits the synthesis of nucleic acids in a variety of organisms (16-19), while in cell-free systems it inhibits the DNA-dependent DNA polymerase and the RNA polymerase of E. Coli (20-21). Since long it has been known that the interaction of aromatic hydrocarbons with nucleic acids and their constituents leads to cancer (2[illegible]).

In view of this, recently a large number of compounds including some carboxylic acids and nitrogen heterocyclics



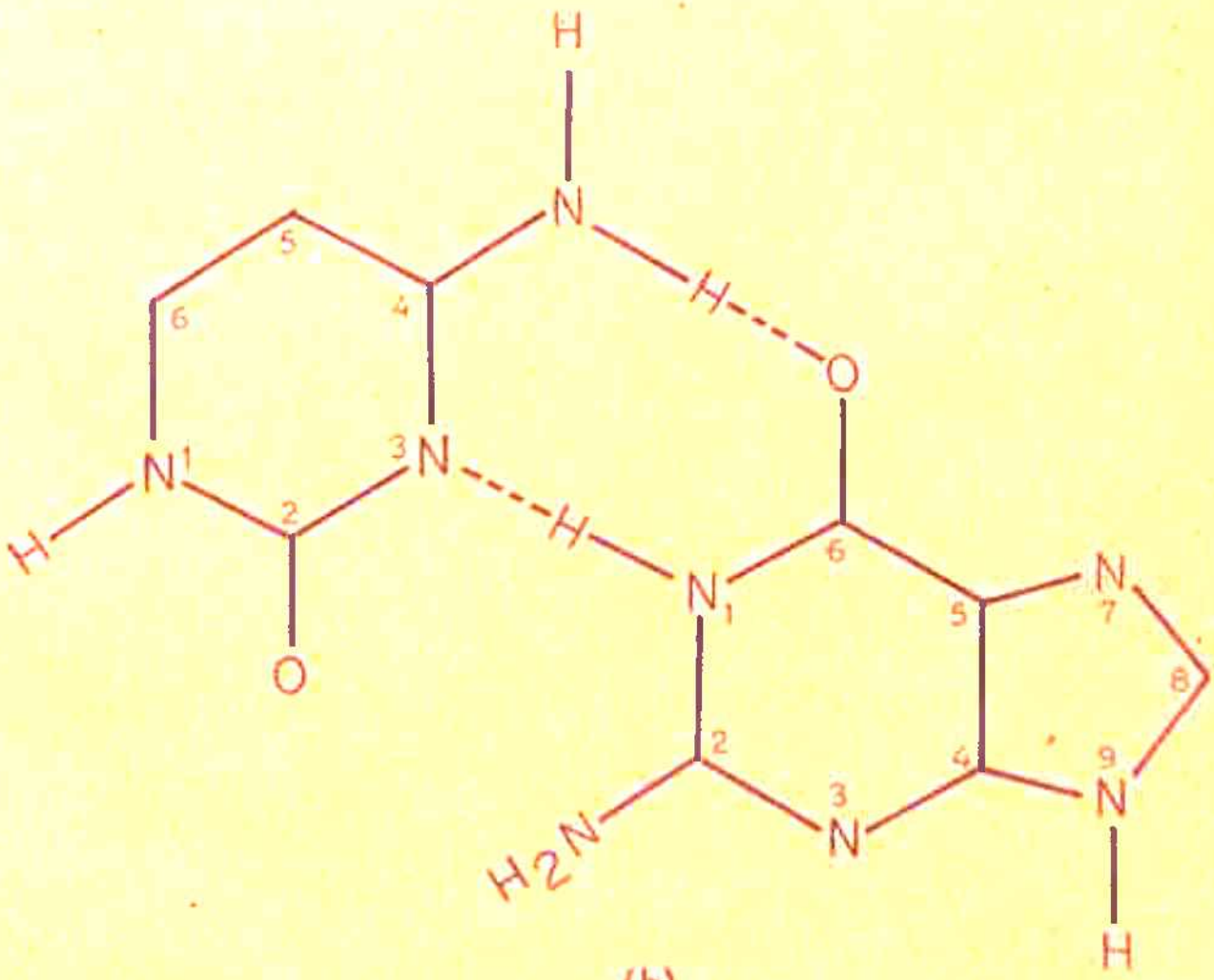


Fig. 3.2. The purine-pyrimidine pairs of nucleic acid (a) uracil-adenine pair (b) cytosine-guanine pair

were examined by X-ray powder method (23) with respect to their ability to form the intermolecular complexes with nucleotide bases. In this examination most of the carboxylic acids were found to bind with adenine and cytosine while very few of the chemicals of other type could show their affinity with any of the nucleotide bases. However it was observed that in the possible intermolecular complex formation the compounds were bonded to the nucleotide bases through the hydrogen bonding.

(A) Results and Discussion:

Of the following structures, (I) to (IV) are the nucleotide bases and (V) to (XI) the nitrogen heterocyclics. Below the structure of each heterocyclic are mentioned, within parenthesis, the names of nucleotide bases with which it interacts. A stands for adenine, G for guanine, C for cytosine and U for uracil.

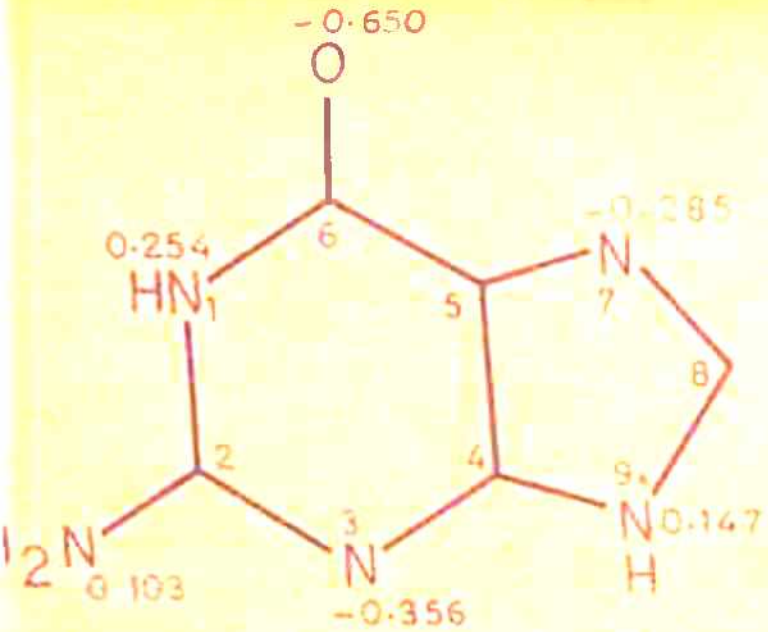
The first four heterocyclics, (V) to (VIII), are shown to have interacted with adenine (I). It is obvious from their structure that they have some analogy with the uracil (IV), the complementary base to the adenine in usual base pairing in nucleic acids. They possess, at appropriate positions, all the reactive atoms that are present in uracil and are essential for the hydrogen bonding (Fig. 3.2), and those reactive atoms in them have similar rather better electronic characteristic - more favourable to hydrogen bonding than in uracil. The negative charge density at the


0·100
NH2
6
-0·332
N
7
-0·343 N 1
5
8
2
4
9
3
N 0·149
H
N
-0·322

I


0·117
NH2
4
-0·369 N 3
5
2
6
O
1
N 0·239
H
-0·657

III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5
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8
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9
N
H
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H2N
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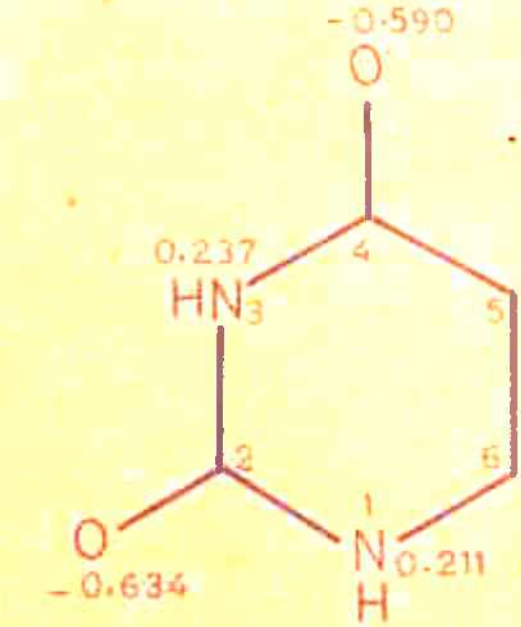
3
N
-0·356

II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H
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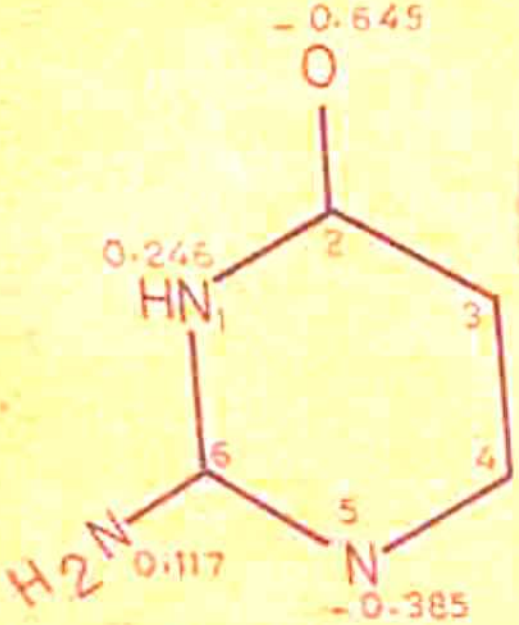
IV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HN1
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6
4
5
H2N
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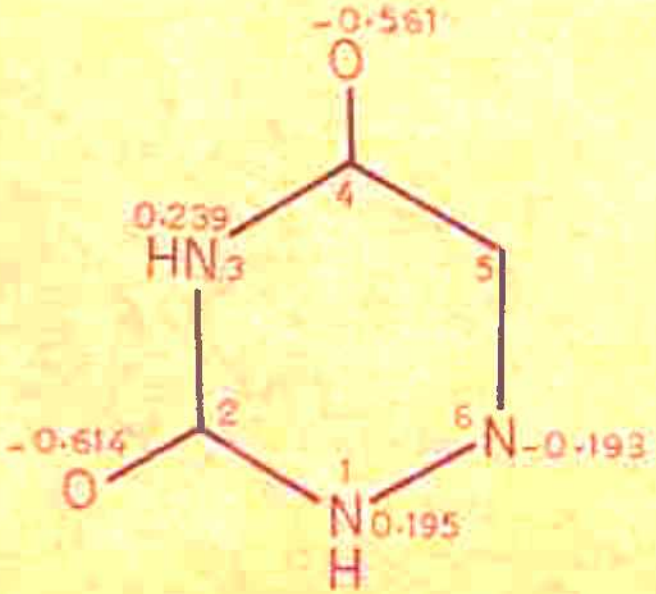
N
-0.385

V.(A)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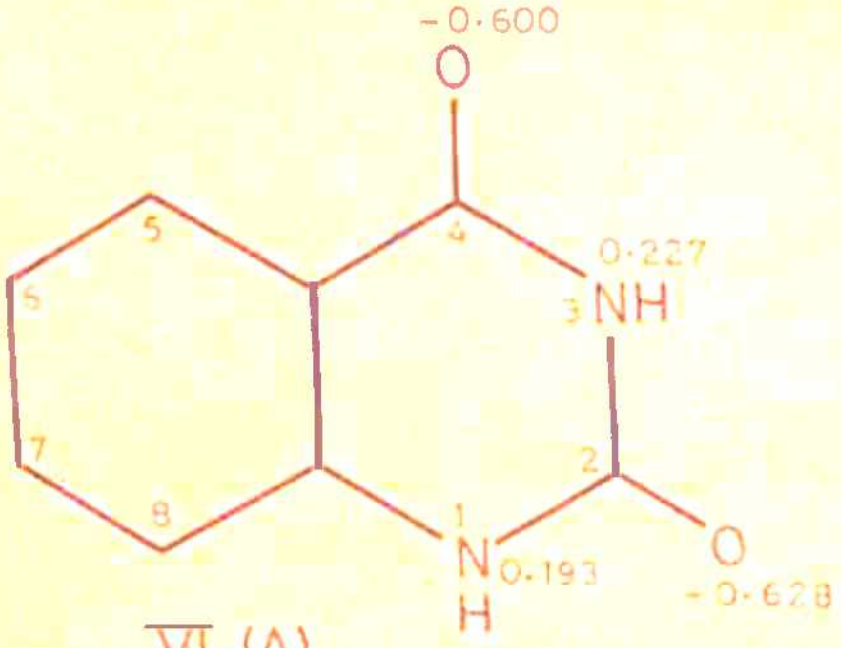
O
4
0.239
HN3
5
2
6
-0.614
O
N-0.193
1
N
0.195
H

VII. (A)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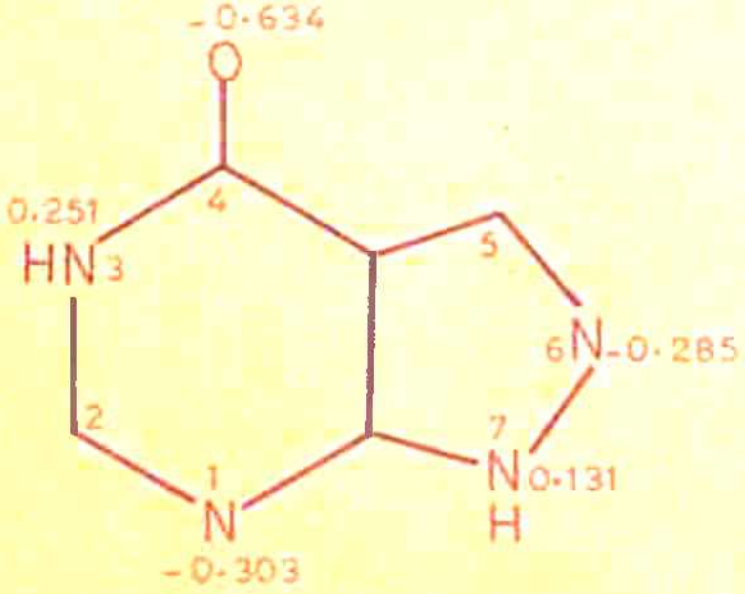
O
5
4
0·227
6
3NH
7
2
8
1
N
0·193
H
O
-0·628

VI.(A)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O
0·251
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HN3
5
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2
7
1
N
N
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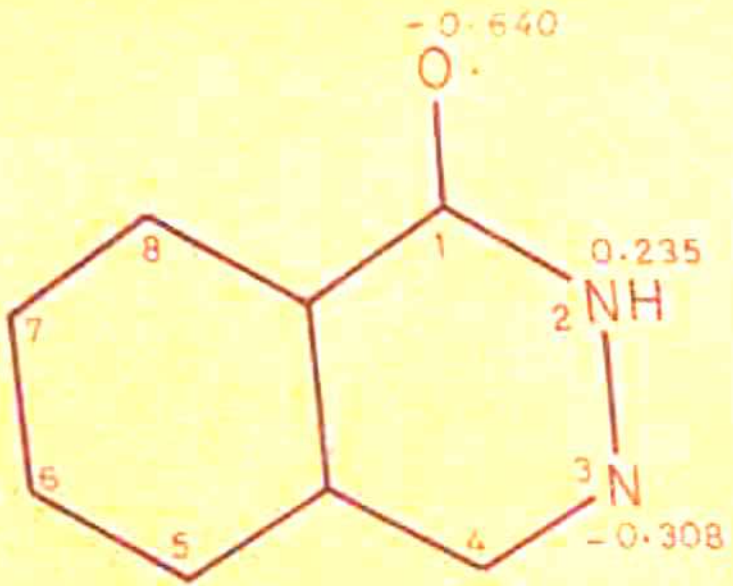
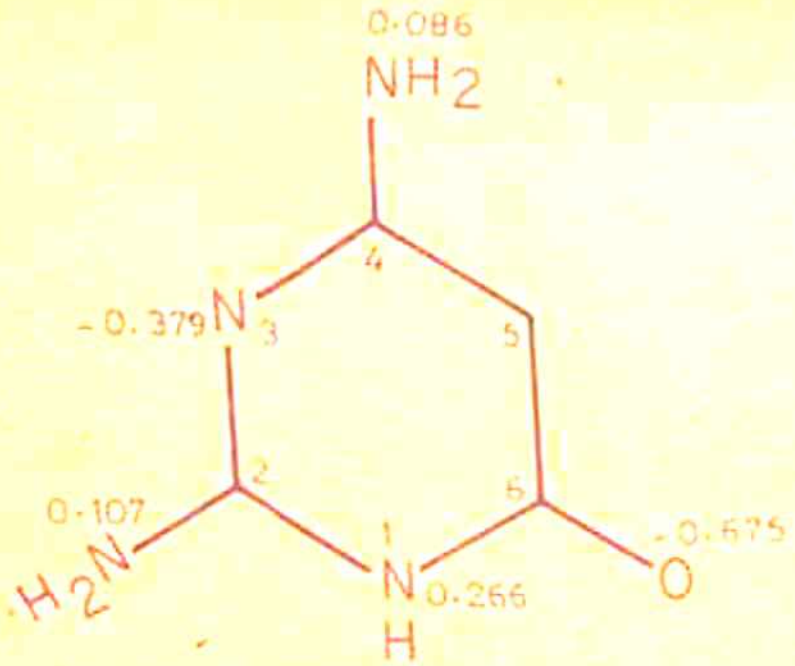
H
-0·303

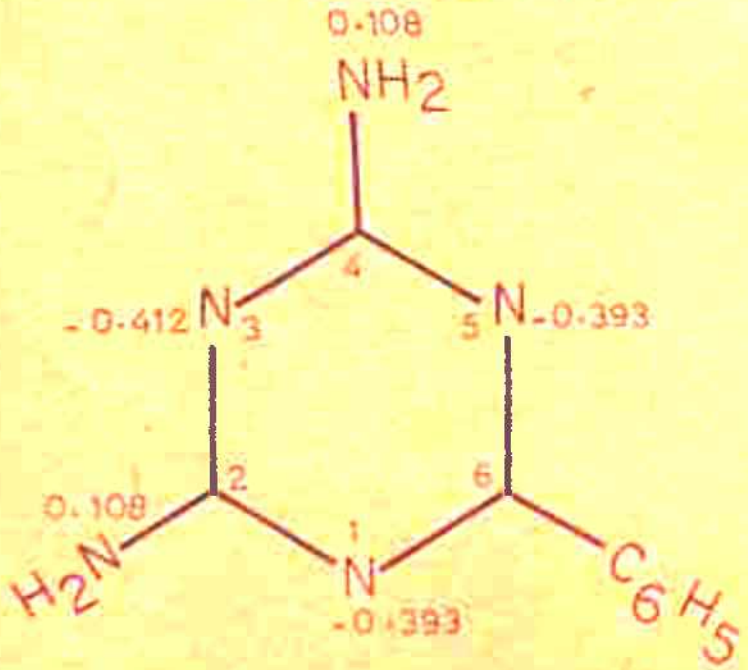
VII.(A)



IX.(A,C)



X.(C,T,U)



XI.(A,C,T)

concerned oxygen atom, in the three of the four heterocyclics. O-2 (oxygen bonded to carbon 2 of the ring) in isocytosine (V), O-4 in benzoylene urea (VI) and 4-hydroxy pyrazolo [3,4-d] pyrimidine (VIII), is greater than that at O-4 in uracil, and the greater is the negative charge density at an atom, the more strongly it will attract the proton. The charge density at O-4 in 6-azauracil (VII) is slightly less than that in uracil but not too less to attract the proton. Similarly the positive charge density at the concerned nitrogen atom (N1 in isocytosine (V) and N3 in other three heterocyclics) in each of the four heterocyclics is comparable to that of N3 in uracil. Therefore the capability of their nitrogen to donate the proton to an acceptor is almost same as that of N3 of uracil.

1-2(H)-phthalazinone (IX) is found to interact with adenine and cytosine (III). As a matter of fact it must, as. though structurally not too much similar with the complements of adenine and cytosine, the uracil and guanine (II) respectively, it has their nitrogen and oxygen participating in the hydrogen bonding in usual base pair (Fig. 3.2). at the corresponding identical positions in its benzenoid ring, and the electronic characteristics of these atoms in it as compared to that in uracil and guanine seem quite satisfactory for hydrogen bonding with adenine and cytosine. Likewise the compound, 2,4-diamino-6-hydroxypyrimidine (X) which is found to interact with three nucleotide bases, cytosine, thymine (not shown) and uracil, shows the structural and

electronic similarity with the complements of these three
and adenine of thymine and uracil).
its N3 is even greater than that
N1 of adenine, though the net positive charge at its
N4 (nitrogen attached to carbon 4) is just comparable to that
at N6 of latter. Similarly the net positive charge at its
N1 and the net negative charge at its O6 are little higher
and O6 of guanine respectively.

However the compound, 2,4-diamino-6-phenyl-s-triazine (XI), though bind with three nucleotide bases, adenine, cytosine and thymine, shows some structural similarity with the complement of thymine, the adenine only. Its N3 seems to be better proton-acceptor than N1 of adenine and similarly its N4 better proton-donor than N6 of latter. It is expected that these two nitrogens of this heterocyclic would be acting as proton-acceptor and-donor respectively in the hydrogen bonding with adenine and cytosine also, while the complements of these two bases bind with them as shown in Fig. 3.2.

From the above discussion it can be inferred that if there is any structural similarity between a nitrogen heterocyclic and a nucleotide base, and all the electronegative elements, that are present in the latter and form the hydrogen bond in the complementary base pair, are also present in the former at appropriate positions with appropriate electronic charge density, there may occur the intermolecular interaction through hydrogen bonding between the heterocyclic and the base complementary to the first one.

Interaction of Carbonylic acids with Adenine:

Recently some carbonylic acids were also found to interact with the nucleotide bases particularly with adenine [illegible] attempt has been made to explain the interaction of these acids with adenine through the charge-transfer mechanism. As a matter of fact these acids have been found to be bonded to adenine through the hydrogen bonding (23). But it is assumed that the hydrogen bonding involves the charge-transfer process. The involvement of charge-transfer process in the hydrogen bonding is not uncommon; there has been the experimental and theoretical evidences (24-26) to verify the charge transfer mechanism of hydrogen bonding. The charge-transfer mechanism of hydrogen bonding can be explained as follows. Suppose A-H and B molecules are joined together through hydrogen bonding. Now if the proton-donor (A-H) can be regarded as electron-acceptor, and the proton-acceptor (B) as the electron-donor, the bonding energy may be interpreted as the stabilization energy mainly caused by the resonance between the following two structures.

$$A\text{-}H.....B \longleftrightarrow A^{-}.....H\text{-}B^{+} \qquad (3.1)$$

I II

This charge-transfer mechanism is analogous to Mulliken's theory (27) of molecular complex formation and the structure I corresponds to 'no bond' and II to charge-transfer structure.

(A) Results and Discussion:

In this light the energies of HOMO's and LUMO's of carboxylic acids seems to be of great significance. As already discussed in Chapter 1, the energy of HOMO determines the electron-donor property and that of LUMO the electron-acceptor property of the compound. The energy value of HOMO of adenine is 8.571 eV. This value is much less than that of any acid mentioned in Table 1.1. This indicates that adenine can easily donate an electron to the acids, provided the acids have high electron affinity. Our calculation, however, shows that the acids do possess the same. The energy value of their LUMO's are much greater than that of adenine (2.038 eV only). Thus theoretically also it appears that these carboxylic acids are bonded to adenine through the charge-transfer process. It is quite likely, though not very sure, that the experimental study may also prove the involvement of charge-transfer in the formation of the complexes. It can be mentioned that purine and pyrimidine bases have the strong tendency to form the molecular complexes with organic compounds (28) and this tendency depends upon their electron-donor capacities. The electron-donor capacities of these bases have also been found to increase the stability of polynuclear aromatic hydrocarbons in aqueous systems (29-30). This effect is claimed to be of importance for the carcinogenic activity of the hydrocarbons (31).

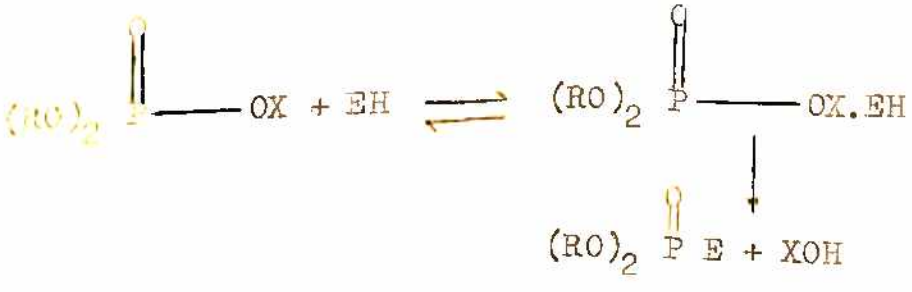
Table 3.2

Energies of HOMO and LUMO of carboxylic acids

Molecule	Energy of HOMO, LUMO	
	HOMO(e.V.)	LUMO(e.V.)
Benzoic acid	9.713	2.594
Salicylic acid	9.478	2.534
m-Hydroxybenzoic acid	9.425	2.542
p-Hydroxybenzoic acid	9.465	2.486
Anthranilic acid	9.233	2.494
m-Aminobenzoic acid	9.159	2.500
p-Aminobenzoic acid	9.206	2.421
p-Aminosalicylic acid	9.107	2.367
Picolinic acid	9.676	2.909
Nicotine acid	9.772	2.709
Pyradinic acid	9.752	3.214
Orotic acid	10.941	3.941
Cyanuric acid	12.130	3.057

3.4 Anthelmintic Activity of Organophosphorus Compounds:

In the recent three decades some of the organophosphorus compounds including vinyl phosphates have been found to be useful as anthelmintics (32). The common chemical feature of these organophosphorus materials is a pentavalent phosphorus with two of the valencies, saturated by a linkage to an oxygen (or sulfur), and the remaining three valencies each linked through an oxygen or sulfur to the aliphatic or aromatic groups. They all are believed to exert an inhibitory effect upon specific biochemical functions of the parasites (33-34). Their toxicity to the parasite or to the host is mainly related to the reaction with the cholinesterase enzyme system in the body (35-38). It is believed that they inhibit the acetylcholinesterase by phosphorylating its esteratic site (39-41). The mechanism of this is very simple (42-46).



Here the first step is just the attack of the enzyme, EH on the P—O bond of the phosphate and the second step is the rate determining step. This mechanism seems to be analogous to that of alkali hydrolysis of the phosphate (47), thus the inhibitory power of the organophosphorus

compounds will depend upon the ease of their enzymic hydrolysis.

Pullmans (48) have proposed that practically in all fundamental types of biochemical substrates undergoing such enzymic hydrolysis, the bond which is hydrolyzed carries formal positive charges on its two extremities. They called it a 'dipositive bond'. They further proposed that the enzymic hydrolysis takesplace the easier, the greater the π-electron deficiency of the hydrolyzable bond. The dipositivity of the bond measures the electron deficiency of the bond, therefore, the deficiency may be increased by increasing the formal positive charge either of the one of its constituent atoms (in which case this atom is probably in some way one of the reactive centres for the reaction) or of its two atoms.

In a subsequent paper Pullman and Valdemoro (49) have shown, by making a simple HMO calculation on some organophosphorus esterase inhibitors, that the inhibitory power of inhibitors parallel the value of the positive charges on their P atom. A further study on a series of diethyl substituted phenyl phosphates by Fukui et al (50) established a correlation between the inhibitory power of the compounds and their S_P^N (nucleophilic superdelocalizibility of P atom). These authors had found that the ease of alkali hydrolysis of these phosphates, their average molar concentration to inhibit the fly brain cholinesterase and their insecticidal

activity were well correlated with their S_p.

Now it is proposed that the ease of alkali or enzymic hydrolysis of the phosphates will also depend upon the π-bond-order of the bond. Since the π-bond-order refers to the strength of the π-bond, the less is the bond-order of the hydrolyzable bond, the easier would be the hydrolysis.

From the forgoing discussion it can be established that the enzymic inhibitory activity of an inhibitor is the function of its over all electronic structure. Now the question is whether the anthelmintic activity or the efficacy- a property separate form molecular activity (51) - of an anthelmintic drug is also related to its electronic structure or not. To prove this some organophosphorus anthelmintics have been chosen.

(A) Results and Discussion:

The two propositions of Pullmans discussed in the proceeding section indicate that the enzymic hydrolysis of a substrate undergoes a kind of nucleophilic substitution reaction. The positive centre of the substrate attracts the nucleophilic site of the enzyme and in the first stage binds with it, then the reaction proceeds as in Eq. 3.2 and the net result is the hydrolysis of the substrate. The larger are Q_p and S_p^N the easier would be the hydrolysis.

In Table 3.3 are listed the calculated values of Q_p, S_p^N, P_{PO} and P_{PO} for the organophosphates shown in

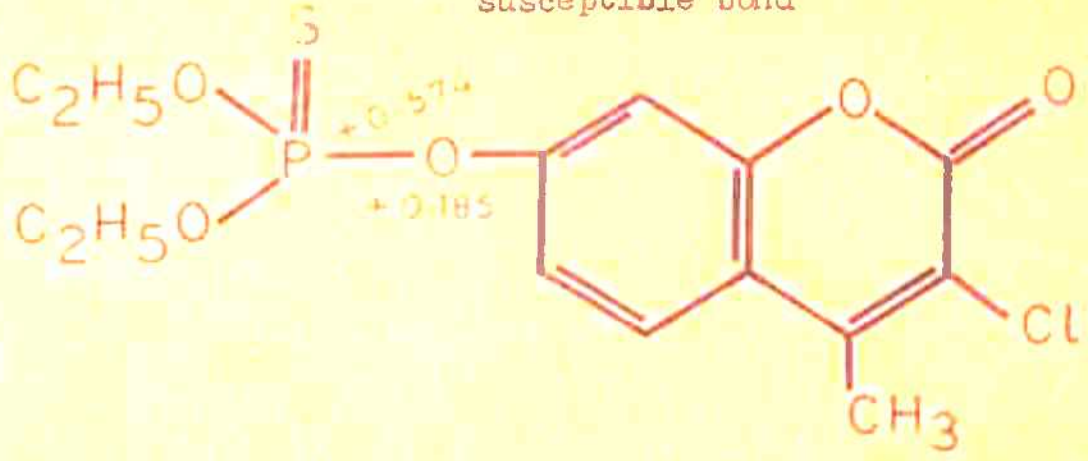
Table 3.7

The electronic indices and LD_{50} values of some organophosphorous anthelmintics.

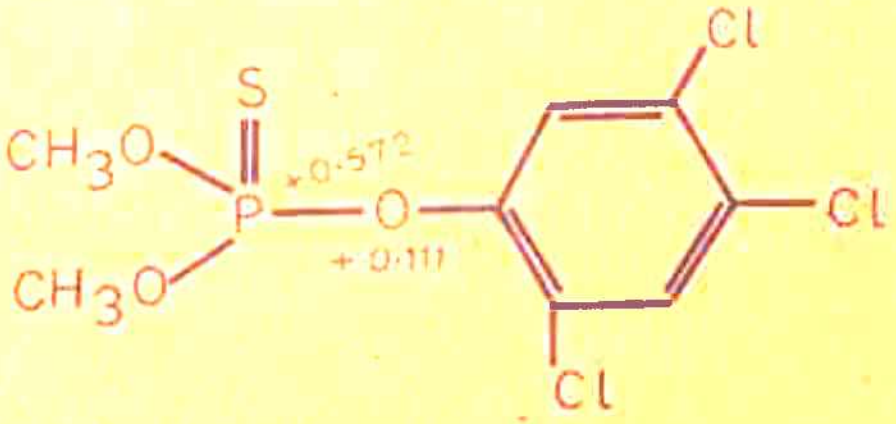
	Compound	σ_F	S^*_I	π_{PO}	I_{PO}	LD_{50} mg/kg *,32	Remarks[32]
I	Coumaphos (Co-Ral)	0.574	1.256	0.754	0.262	56	Good anthelmintic for ruminants when used in specific manner.
II	Fenchlorphos (Trolene)	0.572	1.241	0.683	0.284	1700	-- -- --
III	Malaoxon	0.728	1.643	0.854	0.331	900	A useful anthelmintic, possessing a reasonable safety factor, for treating gastrointestinal parasites.
IV	Naphthalophos (Naftalofos)	0.725	1.553	0.815	0.345	70-75	Same as coumaphos.
V	Dichlorvos (SD1750)	0.728	1.616	0.868	0.327	78	One of the most efficacious and widely used anthelmintics.
VI	Nevinphos (SD2046)	0.731	1.690	0.892	0.320	4	All three found to possess limited anthelmintic activity for parasites of sheep at tolerated doses.
VII	SD1808	0.731	1.681	0.890	0.320	22	
VIII	SD3562	0.730	1.686	0.886	0.322	22	
IX	SD7779	0.731	1.687	0.890	0.321	65	Not very toxic, effective for parasites of the abomasum and upper small intestine.
X	SD8447	0.728	1.631	0.854	0.331	4000-5000	Notably nontoxic but also inactive as an anthelmintic.

*LD_{50} values for oral administration to rats.

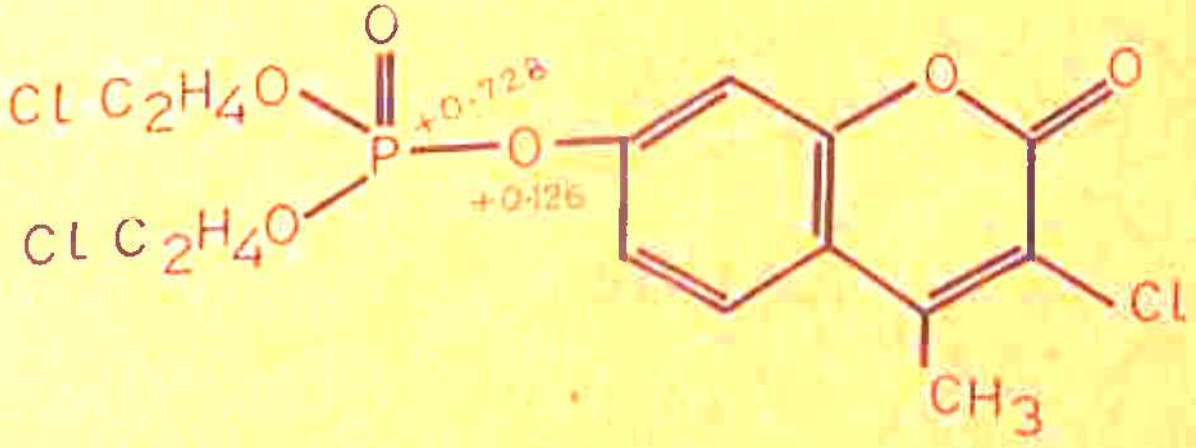
Fig. 3.3. Organophosphorus anthelmintics and their dipositive susceptible bond



(I) Coumaphos (CoRal)

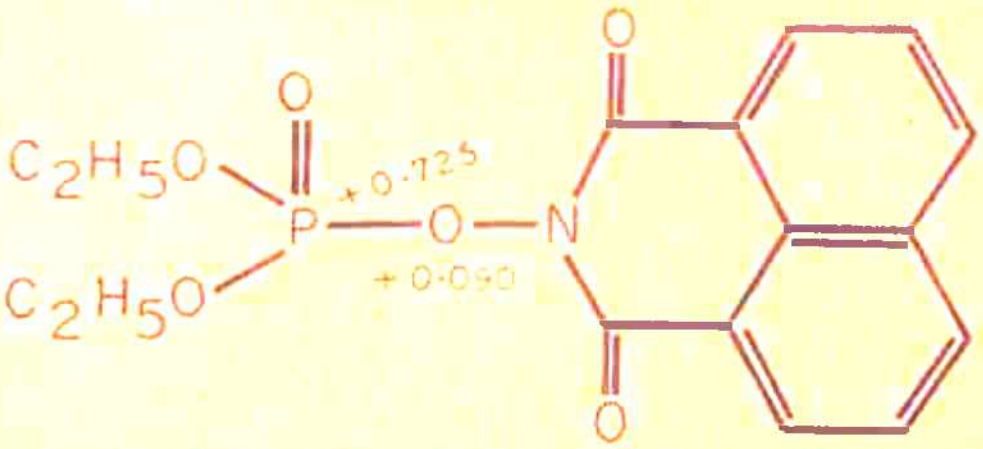


(II) Fenchlorphos (Trolene)

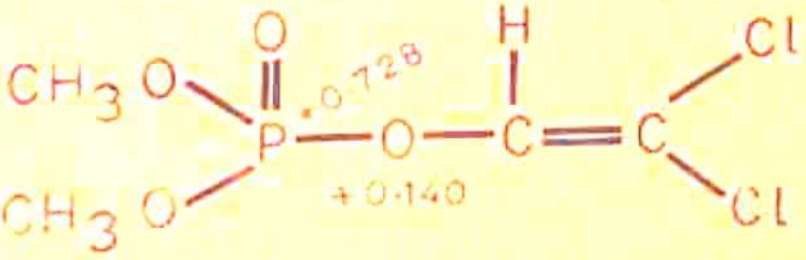


(III) Haloxon

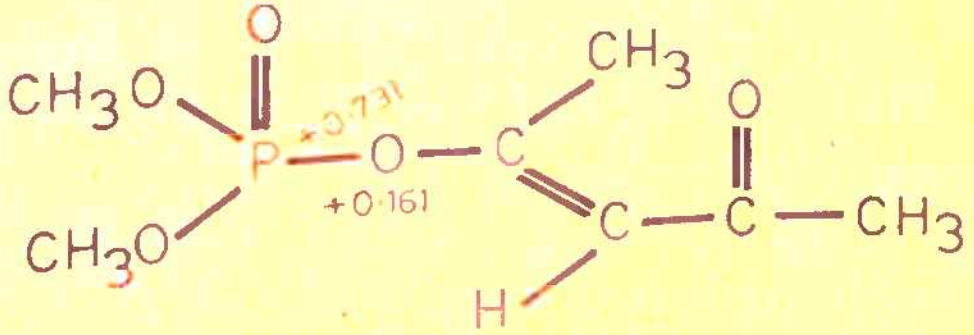
Fig. 3.3. (continued)



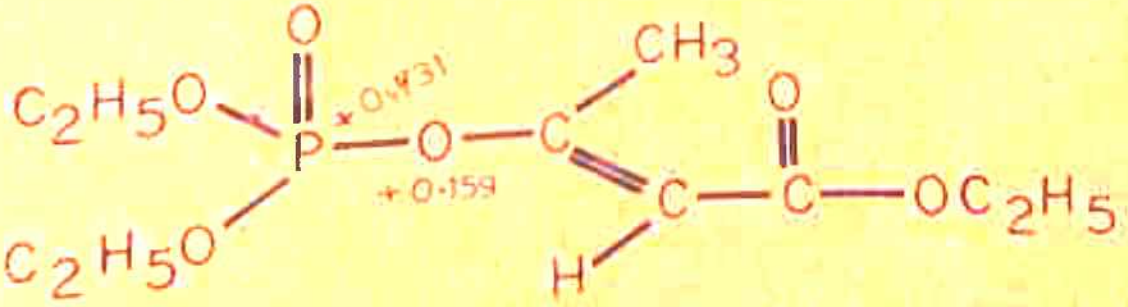
(IV) Naphthalophos (Maretin)



(V) Dichlorvos (SD 1750)

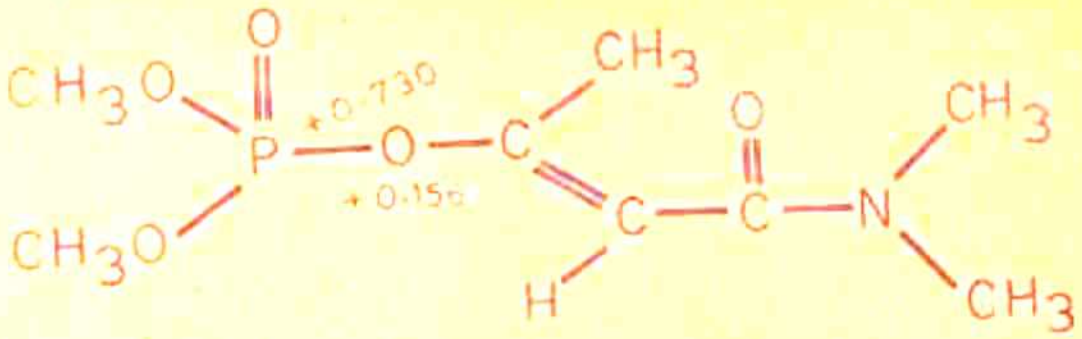


(VI) Mevinphos (SD 2046)

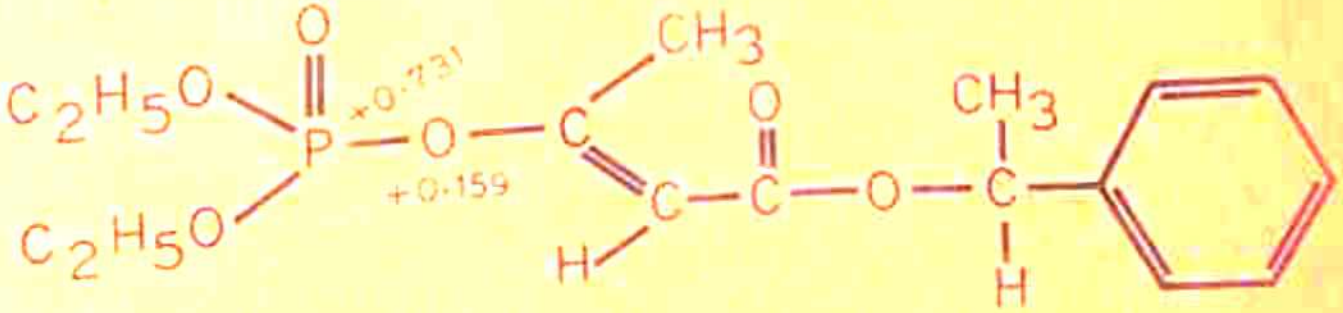


(VII) SD 1808

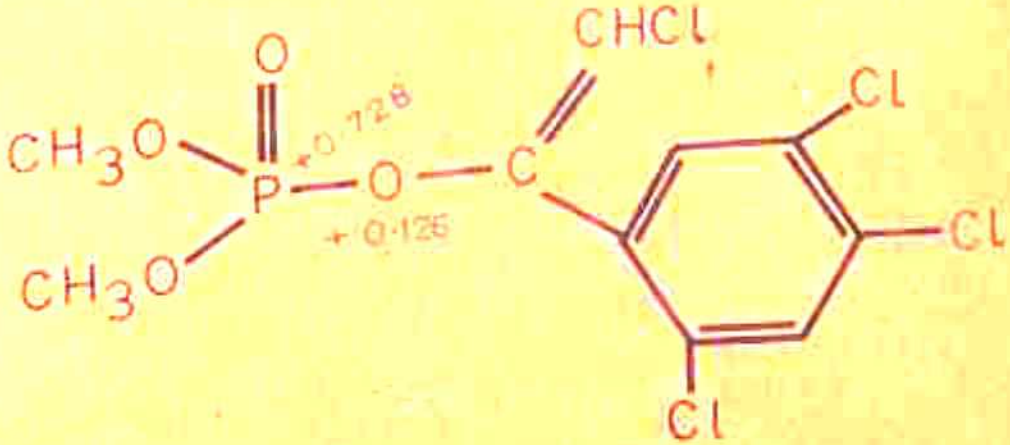
Fig. 3.3. (continued)



(VIII) SD 3562



(IX) SD 7779



(X) SD 8447

Fig. 3.3 along with their LD_{50} (lethal dose producing 50 percent effect) values and some remarks on their utility and efficacy. Q_{PO} is the sum of Q_P and Q_O and refers to the dipositive character of the labile P-O bond. The dipositive susceptible P-O bond in each compound is shown in Fig. 3.3. Compounds (V) to (X) belong to a series of some particular organophosphates namely the vinyl phosphate. Out of these six compounds, the dichlorvos (V) has been found to be most efficacious and widely used anthelmintic. Its LD_{50} is 7 mg/kg. The next three compounds of the series, namely mevinphos (VI), SD 1808 (VIII) and SD 3562 (VIII) possess very low LD_{50} as compared to that of dichlorvos. Now it can be seen from the table that this is in accordance to their high Q_P, S_P^2 and Q_{PO}, and low P_{PO} values. The highest value of the first three indices of mevinphos quite agree with its lowest LD_{50}. Thus the electronic indices and LD_{50} of these three compounds indicate that they must be very reactive, however, they have been found to possess very limited anthelmintic activity. This can be explained as they are so reactive that they are hydrolytically deactivated in their way to the effective site.

The values of the electronic indices of SD 7779 (IX) in that series indicates that this compound should be very similar in behaviour and reactivity to the above mentioned three compounds. As a matter of fact it is, it also possesses very limited anthelmintic activity effective only for parasite of abomasum and upper small intestine.. Its

little higher LD_{50} can be taken, within experimental error, reasonably in accordance to the value of its electronic indices. The S_P^N and P_{PO} values respectively 1.639 and 0.854 in case of SD 8447 (X) perhaps represent lower and 0.331 the higher limit for the series, so that the LD_{50} of this compound is as high as 4000-5000 mg/kg, and in all the compound is non-toxic and inactive as an anthelmintic.

Of the rest four compounds the first two namely coumaphos (I) and fenchlorphos (II) form exclusively a separate group, as in place of the oxygen atom doubly bonded to the phosphorus they have the sulphur atom. The remarkable point here is that the anthelmintic activity of these two compounds is exclusively related to the π-electron deficiency and the strength of the labile bond. Table 3.3 shows that although the S_P^N of fechlorphos is greater than that of coumaphos (Q_P of the two being almost same), the high LD_{50} value of the former as compared to that of the latter can be well accounted for by its lower Q_{PO} and higher P_{PO}.

The remaining two compounds, haloxon (III) and naphthalophos (IV) are found to follow no trend. The reason is obvious. They do not belong to any particular group or series and among themselves also they differ in many respects, for example, the oxygen atom of the suscetible P-O bond in one case is next attached to a ring carbon and in other to a ring nitrogen.

From above discussion it can be concluded that anthelmintic activity of the drugs is also the function of their electronic structure. In a series of related compounds if the activity of one compound is known, the electronic structure can be successfully utilized to predict the activity of other compounds. This can also be the basis of the drug design. The study of the electronic structure of a series of related compounds of known activity can always indicate what modification should be made in the structure of a compound to have the desired effect.

3.5 Electronic Structure-Activity Relationship of Antibacterial Acridines:

The antibacterial activity of acridines has been found to be proportional to the fraction ionized as cation (52-54). The simplest interpretation of the mode of action of acridine cation is that they compete with the hydrogen ions for a vitally important anionic group on the bacterium (55). The vital activity of the vulnerable anionic group (A^-) of the bacterium is supposed to be reduced by the formation of a feebly dissociated complex (ABH) with the cation (BH^+) of the drug. The more feebly is dissociated the complex in A^- and BH^+ ions the more would be the reduction in the vital activity of anion. The dissociation of the complex would be suppressed only when the cation (BH^+) is present in excess, hence the activity of the drug (B) will depend upon its degree of cationization as (BH^+).

Since the cationization of the acridines will largely depend upon the electron density of their ring nitrogen, q_N (the greater is q_N, the more would be attraction for proton), it is expected that there exists a correlation between their antibacterial activity and q_N.

(A) Results and Discussion:

In Table 3.4 are listed the calculated electron densities at the ring nitrogen and two neighboring carbon atoms 4' and 5' of the bridges, and the antibacterial activity for a series

Table 3.1

The electronic parameters for regression analysis and observed and calculated antibacterial activity of aminoacridines.

Acridine	q_r	q_r^+	q_r^-	log 1/c obsd	log 1/c calc 5.6	log 1/c calc 5.3	ΔE_{LA}	log 1/c calc 1.0
4-Amino -	1.234	0.966	0.961	5.611	5.[illegible]	[illegible]	[illegible]	[illegible]
2-Amino -	1.233	0.964	0.961	4.000	4.047	[illegible]	[illegible]	[illegible]
3-Amino -	1.256	0.957	0.958	4.398	4.4[illegible]	4.485	2.562	4.475
9-Amino -	1.234	0.959	0.957	5.204	5.216	5.301	2.604	5.328
4,5-Diamino -	1.224	0.970	0.970	<3.613	3.913	3.797	2.53[illegible]	3.846
2,7-Diamino -	1.236	0.968	0.96[illegible]	4.301	4.1[illegible]	4.055	2.542	4.069
3,7-Diamino -	1.253	0.961	0.965	5.204	5.57[illegible]	4.420	2.560	4.435
3,6-Diamino -	1.270	0.958	0.958	5.204	4.75[illegible]	4.785	2.576	4.759
3,9-Diamino -	1.305	0.960	0.960	5.204	5.441	5.537	2.615	5.551
4-Amino-5-methyl -	1.232	0.967	0.963	<3.699	3.891	3.969	2.536	3.947
2-Amino-9-methyl -	1.248	0.965	0.962	4.301	4.232	4.313	2.555	4.333
9-Amino-2-methyl -	1.293	0.960	0.960	5.204	5.204	5.279	2.603	5.308
9-Amino-3-methyl -	1.296	0.959	0.959	5.204	5.256	5.344	2.606	5.368
9-Amino-4-methyl -	1.291	0.945	0.958	5.505	5.471	5.256	2.600	5.247
9-Amino-3-Chloro -	1.289	0.960	0.959	5.204	5.085	5.193	2.599	5.226
9-Amino-2-Chloro -	1.295	0.954	0.958	5.204	5.357	5.322	2.602	5.287
9-Amino-4-Chloro -	1.297	0.943	0.958	5.204	5.589	5.365	2.602	5.287
2-Amino-6-Chloro -	1.234	0.957	0.959	<3.69[illegible]	4.055	4.012	2.538	3.988
3-Amino-9-Chloro -	1.234	0.964	0.963	<3.699	4.027	4.012	2.541	4.040
3-Amino-6-Chloro -	1.251	0.959	0.958	4.602	4.327	4.377	2.557	4.374

of aminoacridines. Similarly in Table 3.5 are listed the same for a series of fluorinated acridines. In Table 3.4 log 1/c (c is the minimal bacteriostatic concentration (54) for strept. pyogenes - 48 hours incubation in 10 percent serum broth at 37°C; pH 7.3) as expected, appears to be linearly correlated with q_N. likewise mean K.D. time, t, in Table 3.5 appears to be proportional to q_N.

A regression analysis (56) reveals the following three equations relating biological responses with q_N.

$$\log 1/c = 21.48\ q_N - 22.478 \qquad (3.3)$$

$$n = 20, r = 0.896,\ s = 0.309,\ F^1_{2,1} = 73.30$$

$$t_1 = 142.8\ q_N - 168.23 \qquad (3.4)$$

$$n = 22,\ r = 0.605,\ s = 1.419,\ F^1_{2,1} = 17.91$$

$$t_2 = 158.0\ q_N - 185.64 \qquad (3.5)$$

$$n = 35,\ r = 0.551,\ s = 1.806,\ F^1_{2,1} = 13.55$$

The statistical parameters, r(correlation coefficient) s(standard deviation) and F(F ratio between the calculated and observed activities) show that correlation between q_N and log 1/c is highly significant. In Eqn. 3.3, F is highly significant at 99 percent level ($F^1_{18}(0.01)=8.28$). In Eqn. 3.4 and 3.5 also F is significant at 99 percent level ($F^1_{2,1}(0.01) = 7.55$) but not as highly as in Eqn. 3.3. In the latter two equations the correlation coefficient is also comparatively low (the correlation between log t and

Table 3.5

The electronic parameters for regression analysis and observed antibacterial activity of fluorinated acridines.

Acridine	σ_m	$\sigma_{4'}$	$\sigma_{5'}$	obsd.	calcd. Eq.4	calcd. Eq.7	obsd.	calcd. Eq.7	calcd. Eq.8
				obsd. K.D. time, t (hr) for 0.5 percent phenol.			obsd. MIC in mcg./ml.		
5-Chloro-3-fluoro -	1.240	0.957	0.946	11.00	8.75	8.81	13.00	10.13	10.2
5-Chloro-8-fluoro -	1.242	0.956	0.946	10.50	9.03	9.17	12.50	10.15	10.43
5-Chloro-6-fluoro -	1.241	0.955	0.947	10.00	8.81	9.06	12.00	10.21	10.51
5-Chloro-3,6-difluoro -	1.234	0.956	0.947	9.50	7.81	8.05	10.50	9.18	9.36
5-Chloro-3,8-difluoro -	1.236	0.957	0.946	10.00	8.17	8.25	12.50	9.50	9.64
5-Amino-3-fluoro -	1.227	0.963	0.966	9.50	6.81	7.03	10.75	8.08	8.20
5-Amino-8-fluoro -	1.228	0.962	0.965	9.00	7.03	7.20	10.50	8.21	8.39
5-Amino-6-fluoro -	1.227	0.961	0.965	8.50	6.81	7.03	9.50	8.08	8.25
5-Amino-3,6-difluoro -	1.220	0.963	0.966	7.00	5.81	6.00	9.00	6.97	7.08
5-Amino-3,8-difluoro -	1.222	0.963	0.965	7.50	6.18	6.28	9.50	7.21	7.39
3-Fluoro-5-phenoxy -	1.232	0.960	0.958	8.00	7.60	7.74	9.00	8.87	9.02
8-Fluoro-5-phenoxy -	1.234	0.960	0.958	8.00	7.81	8.04	9.50	9.18	9.34
6-Fluoro-5-phenoxy -	1.232	0.959	0.959	7.00	7.60	7.79	8.00	8.87	9.06
3,6-Difluoro-5-phenoxy -	1.226	0.959	0.958	7.00	6.75	6.84	8.50	7.92	8.00
3,8-Difluoro-5-phenoxy -	1.227	0.961	0.958	6.50	6.89	6.97	8.00	8.08	8.19
3-Fluoro-5-p-fluorophenoxy -	1.232	0.960	0.958	7.00	7.60	7.74	8.50	8.87	9.02
8-Fluoro-5-p-fluorophenoxy -	1.230	1.050	1.031	6.50	7.32	5.79	7.50	8.55	6.51
6-Fluoro-5-p-fluorophenoxy -	1.232	0.959	0.959	6.00	7.60	7.79	6.50	8.87	9.06
3,6-Difluoro-5-p-fluorophenoxy -	1.226	0.960	0.959	6.50	6.75	6.87	8.50	7.92	8.07

(Contd.)

(Table 3.5 contd.)

3-Fluoro-5-phenylamino -	1.228	0.363	0.363	5.70	7.03	7.13	8.00	8.24	8.33
8-Fluoro-5-phenylamino -	1.229	0.362	0.363	7.00	7.17	7.31	8.00	8.34	8.53
6-Fluoro-5-phenylamino -	1.227	0.975	0.943	8.90	9.41	8.97	8.99	8.98	7.69
3,6-Difluoro-5-phenylamino -	1.222	0.977	0.952	6.90	6.11	6.07	8.00	8.24	6.81
3,8-Difluoro-5-phenylamino -	1.223	0.363	0.363	6.00	6.52	6.49	6.25	8.13	7.53
3-Fluoro-5-p-fluorophenyl-amino -	1.228	0.363	0.363	5.00	5.05	5.13	5.00	8.24	8.33
8-Fluoro-5-p-fluorophenyl-amino -	1.229	0.362	0.363	4.90	7.17	7.31	8.00	8.34	8.52
6-Fluoro-5-p-fluorophenyl-amino -	1.228	0.361	0.364	8.00	8.05	8.21	8.00	8.24	8.11
3,6-Difluoro-5-p-fluoro-phenylamino -	1.221	0.363	0.364	5.50	6.03	6.11	8.13	8.13	7.22
3,8-Difluoro-5-p-fluoro-phenylamino -	1.204	0.363	0.361	5.00	5.60	5.56	6.00	6.41	6.47
3-Fluoro-5-α-naphthylamino -	1.228	0.363	0.363	6.00	7.05	7.13	8.00	8.34	8.33
8-Fluoro-5-α-naphthylamino -	1.229	0.362	0.363	7.00	7.17	7.31	8.00	8.34	8.52
6-Fluoro-5-α-naphthylamino -	1.245	0.976	0.943	8.90	9.41	8.97	8.99	10.13	10.11
3,6-Difluoro-5-α-naphthylamino-	1.228	0.975	0.943	6.90	7.05	6.89	8.00	8.21	7.15

and ... was found still less significant). The calculated activity from these equations are listed in respective tables. There is good agreement between the calculated and observed values.

In case of acridines q_4 appears to be most important. The inclusion of q_4' and q_5'', the electron densities at the nearest neighbors of nitrogen, which might effect the degree of cationization, in the regression analysis makes no significant improvement in the correlation in any case (compare the statistical parameters of Eqns. 3.6 - 3.8 with those of Eqns. 3.3 - 3.5 respectively, and results obtained by them).

$$\log t_1 = 19.77\, q_N - 32.109\, q_4' + 39.42\, q_5' - 27.34 \qquad (3.6)$$

$$n = 20,\ r = 0.910,\ s = 0.305,\ F^3_{16} = 24.34$$

$$t_1 = 147.5\, q_N - 29.96\, q_4' + 14.25\, q_5' - 158.72 \qquad (3.7)$$

$$n = 33,\ r = 0.638,\ s = 1.42,\ F^3_{29} = 6.11$$

$$t_2 = 159.9\, q_N - 32.20\, q_4' + 9.66\, q_5' - 166.10 \qquad (3.8)$$

$$n = 33,\ r = 0.585,\ s = 1.82,\ F^3_{29} = 4.69$$

In case of aminoacridines, one more independent electronic index can be correlated with the activity, and that is the delocalization energy. Since the aminoacridines cations exhibit the resonance phenomenon as shown in Fig. 3.4, the degree of cationizations of aminoacridines will depend (57) upon the extra stabilization the cations gained by this resonance (delocalization). Hence the difference in the

Acridine

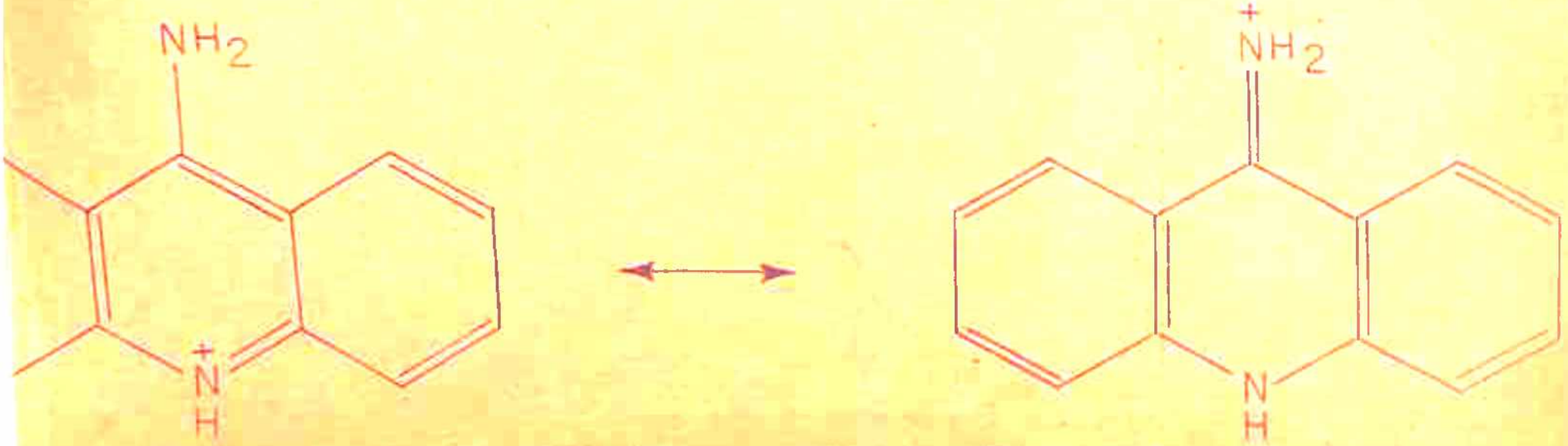


Fig. 3.4. Cationic resonance in aminoacridine

the ionized and unionized forms

. ΔDE, should be proportional to their

. In case of aminoacridines listed in Table 3.4.

Δ replaced by $\Delta E_{\pi b}$, the difference in the π-bond

of their ionized and unionized forms, as all these

compounds have the same number of delocalized bonds of

ing in either form.

A regression analysis reveals the following equation correlating log 1/c with $\Delta E_{\pi b}$.

$$\log 1/c = 20.52\ \Delta E_{\pi b} - 43.08 \qquad (3.9)$$

$$= 20.\ r = 0.897,\ s = 0.307,\ F^1_{1,} - 71.$$

The statistical parameters of Eqn. 3.9 are almost equal to those of Eqn. 3.3 and also the results obtained by the two equationsvery nearly tally with each other. The reason is that there exists nearly a perfect correlation between q_N and $\Delta E_{\pi b}$ (in Eqn. 3.10, $r \approx 1$ and $s \approx 0.0$).

$$\Delta E_{\pi b} = 1.057\ q_N + 1.$$

$$- 20,\ r = 0.998,\ s = 0.001,\ F^1_{18} = 6299 \qquad (3.10)$$

This also shows that from antibacterial activity point of view q_N is more important for acridines than the charge at any other atom, and this electronic index can be successfully utilized to predict the antibacterial activity of any acridine before its synthesis.

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CHAPTER FOUR

MOLECULAR [illegible] AND BIOLOGICAL ACTIVITY

4.1 Introduction:

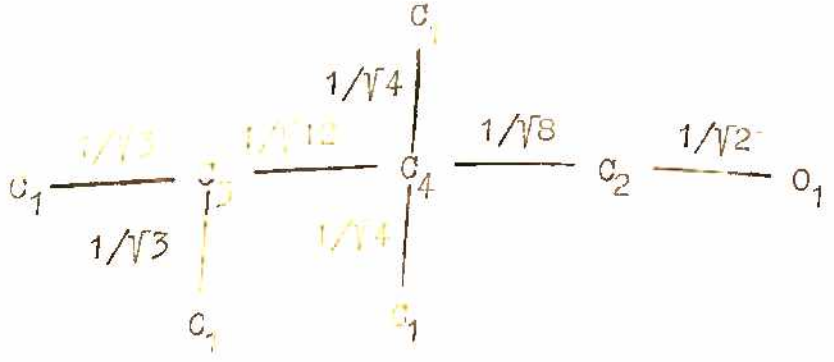
[illegible] a new parameter known as molecular connectivity has been devised by Randić (1). The molecular connectivity index, χ, signifies the degree of branching or connectivity in a molecule and is derived from the numerical extent of branching or connectivity in the molecular skeleton.

It has long been known that branched-and straight-chain organic molecules differ in their properties. For example, branched-chain alcohols and hydrocarbons generally have lower boiling points and higher solubilities than the corresponding straight-chain isomers. However, until the recent suggestion by Randić, there was no simple computed quantitative scheme for correlating physicochemical data with such topological characteristics as branching. The earlier ideas of Hosoyea (2) and Smolenski (3) have not received acceptance as means for correlating properties. The Hosoyea index shows only a qualitative correlation and the Smolenski aditivity function becomes complex to apply.

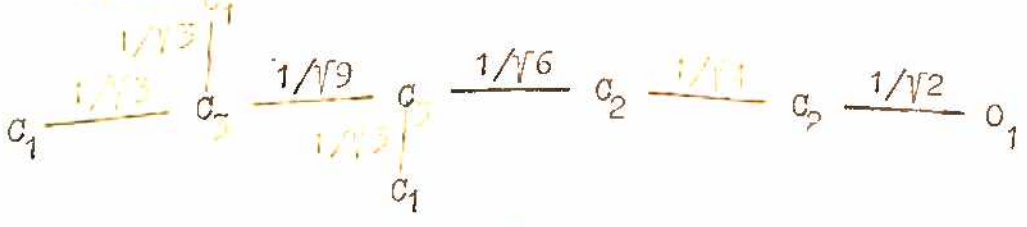
Since the manner in which the organic groups are combined to form a molecule appearsto influence molecular properties, the relationship between connectivity index and physicochemical and biological properties was studied (4-7). In all cases a good correlation was found.

· Calculation of Molecular [illegible]:

The method of calculation of connectivity index, χ, has been described by Randić (1) and by Kier et. al. (4-5). To calculate it, the structure of molecule is drawn out in skeleton form [illegible] hydrogen atoms, and [illegible] assigned a number corresponding to the number of atoms attached to it, [illegible] 1, 2, 3 or 4 in case of a carbon atom. Hydrogen atoms are not included in the count and the first [illegible] the [illegible] dealt with in an identical manner. A number is derived for each bond by calculating the product of two number associated with the two atoms of the bond. The reciprocal of the square root of this number is called the bond value and the sum of bond values becomes the connectivity index, χ. Two [illegible] of this process are illustrated below:



2,2,3-trimethylbutanol, χ = 3.304



3,3-dimethylpentanol, χ = 3.621

Calculation of connectivity [illegible] for two isomers of heptanol.

Scheme I –

Cyclic [illegible] one additional bond for each ring chain isomer; therefore, the value of one bond must be subtracted for each ring. For example, for cyclohexane the summation yields 3.00, from which 1/√2x2 must be subtracted to yield χ = 2.50. Aromatic molecules treated in the same way. Thus benzene has χ = 2.50.

This simple way of calculation of connectivity index completely ignores the degree of unsaturation of the bonds. A refinement was therefore made by Kier et. al.(6) considering the valency of atoms. They assume that a π-bond increases the connectivity by one unit, e.g., H_2C = has connectivity 2, RHC - has connectivity 3, R_2C = connectivity 4, -C≡ connectivity 3 and O = connectivity 2. This refinement, however, is not essential for hydrocarbons.

1.3 Correlations between Molecular Orbital (MO) Parameters and Connectivity Index:

Kier et. al. (4-9) have recently shown a significant correlation between connectivity index and many physicochemical properties and biological activities of compounds. Since several physicochemical properties and biological activities of compounds have been found (10-11) to be the function of [illegible], a correlation between χ and different MO parameters is also expected. Hence studies to this effect were made and MO parameters which were found significantly co related with χ are described below. In all cases values of χ used were those calculated by

simple method i.e. ignoring the valence.

(i) ___ of ___:

The energy of HOMO of alkanes as well as of aromatic hydrocarbons was found to be significantly correlated with χ. With the use of data given in Table 4.1 for alkanes, the regression analysis revealed the two significant correlations as ... 4.1 and 4.2.

$$\text{...} = -0.021\chi^2 + 0.550\chi + 0.506 \qquad (4.1)$$

$$n = 15,\ r = 0.881,\ s = 0.270,\ F^2_{12} = 20.89$$

$$\text{...} = 0.495\chi + 0.530 \qquad (4.2)$$

$$n = 15,\ r = 0.875,\ s = 0.265,\ F^1_{13} = 42.51$$

... stands for the energy of HOMO and n is the number of data points. In both the equations, the statistical parameters, r (correlation coefficient), s(standard deviation) ... ratio between the variances of calculated and ... (a) represent equally high degree of correlation ... χ. In both the equations F values are significant at ... present level ($F^2_{12}(0.01) = 6.93$, $F^1_{13}(0.01) = 9.07$).

In case of cyclic hydrocarbons (Table 4.2) only the parabolic correlation as given by Eqn. 4. 3 was found to be most significant.

$$\text{...} = 0.019\chi^2 - 0.\text{...}\chi + 1.608 \qquad (4.3)$$

$$n = 11,\ r = 0.787,\ s = 0.133,\ F^2_8 = 6.51$$

Table 4.1

Molecular connectivity index and energy of HOMO of some alkanes.

Compound	$^{1}\chi$	$\pi(\ )$		
		obsd[a]	calcd, Eq.1	calcd, Eq.2
Methane	0.000	0.000	0.506	0.530
Ethane	1.000	1.000	1.035	1.025
Propane	1.414	1.414	1.242	1.230
Butane	1.914	1.618	1.482	1.478
Pentane	2.414	1.732	1.713	1.725
Hexane	2.914	1.802	1.932	1.973
Heptane	3.414	1.848	2.142	2.221
Cyclopentane	2.000	1.618	1.523	1.520
Cyclohexane	2.500	2.000	1.751	1.768
Isobutane	1.732	1.732	1.396	1.387
Isopentane	2.270	1.848	1.647	1.654
2-Methylhexane	3.270	1.902	2.083	2.149
3-Methylhexane	3.309	1.932	2.305	2.169
2,3-Dimethylbutane	2.643	2.000	1.939	1.839
Methylcyclohexane	2.725	2.101	1.850	1.879

a HMO data taken from 'Molecular Orbital Theory for Organic Chemists' by A. Streitwieser, Jr., John Wiley andSons, Inc., New York, London (1961). p. 198.

Table 4.2

connectivity index and energy of HOMO of some
romatic hydrocarbons.

Molecule	χ	m(β)		
		obsd[a]	cald, Eq.3	cald, Eq.4
Benzene	2.500	1.000	0.984	0.821
Naphthalene	3.967	0.618	0.537	0.707
Anthracene	5.433	0.414	0.560	0.592
Phenanthrene	5.525	0.605	0.552	0.585
Tetracene	6.900	0.295	0.472	0.478
1,2-Benzanthracene	6.916	0.452	0.472	0.477
Chrysene	7.750	0.520	0.560	0.412
Triphenylene	6.950	0.684	0.471	0.474
3,4-Benzphenanthrene	7.750	0.568	0.460	0.412
Pyrene	5.933	0.445	0.521	0.553
Perylene	7.433	0.347	0.461	0.436

a HMO data taken from ref. 11, p. 85.

The linear correlation as

$$m = -0.078x + 1.016 \qquad (4.4)$$

$$n = 11,\ r = 0.669,\ s = 0.151,\ F_9^1 = 7.32$$

was little less significant. However, in both correlations F values are significant at 95 percent level ($F_8^2(0.05) = 4.46$, $F_9^1(0.05) = 5.12$).

(b) Parabolic Correlation:

The most significant correlation of x was found with delocalization energy (DE) of the conjugated systems. The data that were used in the regression analysis were those of Table 4.3. In this case, parabolic as well as linear correlations (Eqn. 4.5 and 4.6) both were found to possess very high degree of correlation

$$DE = -0.025x^2 + 1.256x - 1.242 \qquad (4.5)$$

$$n = 11,\ r = 0.972,\ s = 0.480,\ F_8^2 = 69.69$$

$$DE = 1.077x - 0.484 \qquad (4.6)$$

$$n = 11,\ r = 0.970,\ s = 0.464,\ F_9^1 = 147.89$$

In both Eqns. 4.5 and 4.6, F values are significant at 99 percent level ($F_8^2(0.01) = 8.65$, $F_9^1(0.01) = 10.56$). Another simple form of parabolic correlation as

$$DE = -0.[illegible]x^2 + 2.626 \qquad (4.7)$$

$$n = 11,\ r = 0.937,\ s = 0.680,\ F_9^1 = 64.29$$

Table 4.3

Mole connectivity index and dolocalization energy of some ated systems.

Molecule	^{x}	DE (β)			
		obsd[a]	cald, Eq.5	cald, Eq.6	cald. Eq.7
Benzene	2.500	2.000	1.999	2.208	3.183
Naphthalene	3.967	3.683	4.005	3.788	3.137
Anthracene	5.433	5.314	5.408	5.366	5.256
Phenanthrene	5.525	5.448	5.508	5.465	5.346
Tetracene	6.900	6.932	6.953	6.946	6.869
1,2-Benzanthracene	6.916	7.101	6.969	6.963	6.889
Chrysene	7.750	7.190	7.800	7.861	7.979
Triphenylene	6.950	7.275	7.004	7.000	6.931
3,4-Benzphenanthrene	7.750	7.187	7.800	7.861	7.977
Pyrene	5.933	6.506	5.947	5.904	5.763
Perylene	7.433	8.245	7.488	7.520	7.550

a HMO data taken from ref. 11, p. 11.

differed only a little in degree of correlation from Eqns. 4.5 & 4.6. In Eqn. 4.7 also F value is significant at 99 percent level.

(C) Localization Energy:

The localization energy of compounds was also found to be correlated with χ . In Table 4.4 is mentioned the radical localization energy (L_r) for some conjugated systems. With the use of these L_r values and calculated χ values for these compounds, regression analysis revealed a significant parabolic correlation as given by Eqn. 4.8, and a little less significant linear correlation as given by Eqn. 4.9.

$$L_r = 0.018\chi^2 - 0.273\chi + 3.148 \qquad (4.8)$$

$$n = 10,\ r = 0.831,\ s = 0.115,\ F_7^2 = 6.71$$

$$L_r = -0.084\chi + 2.687 \qquad (4.9)$$

$$n = 10,\ r = 0.704,\ s = 0.137,\ F_8^1 = 7.87$$

In both equations F values are significant at 95 percent level ($F_7^2(0.05) = 5.59$, $F_8^1(0.05) = 5.32$).

Thus only three of the seven MO parameters attempted were found to be correlated with the molecular connectivity index. All the three parameters are related to energy. This type of study would be important from the chemical as well as biological point of view, as all those physicochemical, chemical and biochemical properties, which are related or can be related to these three MO parameters, can be made the function of molecular connectivity index also.

Table 4.4

Molecular connectivit index and radical localization energy of some conjugated systems.

Molecule	χ	$L_r(\beta)$		
		obsd[a]	cald, Eq.8	cald, Eq.9
Benzene	2.500	2.550	2.581	2.476
Biphenyl	4.967	2.390	2.244	2.268
Naphthalene	3.967	2.300	2.354	2.352
Phenanthrene	5.525	2.300	2.198	2.221
Chrysene	7.750	2.250	2.130	2.033
Pyrene	5.933	2.200	2.172	2.187
Stilbene	5.950	2.160	2.171	2.185
Benzanthracene	6.916	2.050	2.134	2.104
Anthracene	5.433	2.010	2.041	2.229
Naphthacene	6.900	1.950	2.135	2.105

a HMO data taken from ref. 11, p.75

4.4 Correlation between Biological Responses and Substituents Contributions to Molecular Connectivity Index in substituted Molecules:

In the present section are reported the studies on correlations between biological responses and molecular connectivity index of the compounds. Since the substituted molecules are dealt with, only substituents contribution $\bar{x}$ to the molecular connectivity has been considered in the correlation.

We have chosen four examples for our purpose. All of these have been taken from the literature (12-13).

Example 1 is the case of bromoacetamide analogs. Their fungal activities of these analogs alongwith other constants used in the regression analysis are given in Table 4.6. The following three types of correlations between activities and $\bar{x}$ (unrefined) were obtained from the regression analysis.

$$\log 1/c = -0.094\,\bar{x} + 4.280 \qquad (4.10)$$

$n = 14,\ r = 0.176,\ s = 0.861,\ F^{1}_{12} = 0.39$

$$\log 1/c = -0.023\,\bar{x}^{2} + 4.251 \qquad (4.11)$$

$n = 14,\ r = 0.350,\ s = 0.819,\ F^{1}_{12} = 1.68$

$$\log 1/c = -0.453\,\bar{x}^{2} + 1.126\,\bar{x} + 1.135 \qquad (4.12)$$

$n = 11,\ r = 0.848,\ s = 0.483,\ F^{2}_{11} = 12.89$

Table 4.5

Substituents contribution to molecular connectivity, electronic parameter and observed and calculated antifungal activities of bromoacetamide analogs.

$BrCH_2CONHR$

R	$\bar{\chi}$ [a]	σ^{*} [b]	Log 1/c		
			obsd [b]	cald, Eq.12	cald, Eq.16
Pr	1.540(1.563)	-0.12	4.40	3.50	3.46
Allyl	1.540(1.563)	0.13	4.00	3.50	4.32
i-Pr	1.394(1.417)	0.19	3.40	3.33	3.03
[illegible]	2.040(2.063)	-0.13	4.10	4.01	3.98
i-Bu	1.894(1.917)	-0.13	4.00	3.88	3.83
Sec-Bu	[illegible]	-0.21	3.10	3.91	3.60
[illegible]	[illegible]	-0.13	4.40	4.40	4.41
[illegible]	[illegible]	[illegible]	3.40	4.34	4.08
[illegible]	2.550(2.573)	-0.15	4.00	4.41	4.35
Cyclonex	3.040(3.063)	-0.13	5.00	4.65	4.70
n-Hex	3.540(3.563)	-0.13	5.00	4.79	4.85
n-Hept	4.040(4.063)	-0.13	5.00	4.79	4.87
n-Oct	5.040(4.563)	-0.13	4.70	4.42	4.50
n-Dec	7.040(7.063)	-0.13	2.00	2.17	2.12
$n\text{-}C_{14}H_{29}$					

a Within [illegible] is the refined value of $\bar{\chi}$.

b Data taken from ref. 12.

Of these three equations, the parabolic Eqn. 4.12 represents the best correlation. In this equation the F value is significant even at 99 percent level ($F^2_{11}(0.01) = 7.20$). The three corresponding equations obtained with the use of refined values of $\bar{x}$ are as follows:

$$\log 1/c = -0.094\ (\bar{x}) + 4.285 \qquad (4.13)$$

$$n = 14,\ r = 0.177,\ s = 0.861,\ F^1_{12} = 0.39$$

$$\log 1/c = -0.023\ (\bar{x}^2) + 4.253 \qquad (4.14)$$

$$n = 14,\quad r = 0.549,\ s = 0.819,\ F^1_{12} = 1.668$$

$$\log 1/c = -\ 0.252(\bar{x}^2) + 1.935\ (\bar{x}) + 1.095 \qquad (4.15)$$

$$n = 14,\ r = 0.847,\ s = 0.484,\ F^2_{11} = 12.78$$

($\bar{x}$ or $\bar{x}^2$ with-in bracket will always stand for refined $\bar{x}$ or $\bar{x}^2$). The statistical parameters of these equations show almost no improvement over the previous equations.

However, if the electronic parameter, σ^* (Taft constant (12)), is included in the correlation, the three equations of either set are correspondingly improved, and thus Eqn. 4.12 which gives the best correlation changes to

$$\log 1/c = -0.272\,\bar{x}^2 + 2.096\,\bar{x} + 3.466\,\sigma^* + 1.291 \qquad (4.16)$$

$$n = 14,\ r = 0.908,\ s = 0.399,\ F^3_{10} = 14.23$$

while σ^* itself is very poorly correlated with c.

$$\log 1/c = 1.845\,\sigma^* + 4.243 \qquad (4.17)$$

$$n = 14,\ r = 0.176,\ s = 0.861,\ F^1_{12} = 0.39$$

... is the case with examples 2 and 3. Example 2 is ... stituted phenols and example 3 is that of ... -dimethyl-2-bromophenethylamines. The biolo- ... tivities and other parameters used in the regression ... for these two examples are given respectively in ... 4.6 and 4.7.

... example 2 the three different equations relating activity with unrefined $\bar{x}$ are as follows:

$$\log 1/c = 0.567\bar{x} + 2.898 \qquad (4.18)$$

$$n = 18,\ r = 0.804,\ s = 0.401,\ F_{16}^{1} = 29.29$$

$$\log \ldots - 0.159\bar{x}^2 + \ldots \qquad (4.19)$$

$$n = 18,\ \ldots = 0.707,\ s = 0.477, F_{16}^{1} = 16.05$$

$$\log 1/c = -0.308\,\bar{x}^2 + 1.512\,\bar{x} + 2.433 \qquad (4.20)$$

$$\ldots = 18,\ r = 0.865,\ s = 0.349,\ F_{1}^{2} = 20.91$$

Here ... we see that parabolic Eqn. 4.20 represents the ... correlation, though the linear equation (Eqn. 4.18), unlike that in example 1, also shows satisfactory correlation. The F value in Eqn. 4.20 is significant at 99 percent level ($F_{16}^{2}(0.01) = 6.36$). In this case also, almost no improvement in the correlation is made by the use of refined values $\bar{x}$. The corresponding three equations obtained with the ... of latter are as follows:

$$\log 1/\ldots = \ldots(\bar{x}) + 2.863 \qquad (4.21)$$

$$n = 18,\ r = 0.799,\ s = 0.405,\ F_{16}^{1} = 28.40$$

contribution to mo

rved and calculated antifungal

R	$\bar{x}$ [a]	δ	Log 1/c obsd	Log 1/c calcd, Eq. 20	Log 1/c calcd, Eq. 24
	. (.)	0.00	2.30	2.43	2.26
	. (.)	.	3.30	2.98	3.26
-Cl	. (.)	-0.14	2.70	3.00	2.81
-	. (.)	.	3.70	3.45	3.67
- - -	. (.)	-0.07	2.60	2.98	2.88
3-	. (.)	.	3.70	3.45	3.75
3- - -	. (.)	-0.	3.35	3.47	3.22
-	. (.)	-0.	4.40	3.81	3.93
-Cl	1.115(1.)	-0.14	3.36	3.43	3.35
-Cl	. (.)	0.00	4.22	3.81	4.11
-Cl	1.215(1.)	-0.25	3.35	3.89	3.79
-Cl	1.321(1.360)	0.00	4.30	4.12	4.33
-I	1.715(1.770)	-0.59	3.70	4.23	3.68
-Cl-Br	2.016(2.077)				
-Cl- -tert-Bu	2.421(2.414)	-0.36	4.30	4.29	3.98
-Cl-4-Ph-Cl					
tert-Bu	2.420(.382)	-0.53	4.00	4.29	4.13
-Cyclo	2.677(2.352)	0.00	4.40	4.23	4.27
-Cyclo -4-Cl		0.00	4.10	4.29	4.42
	2.425(1.353)	0.35	4.52	4.23	4.56
4-Ph	2.877(.243)				
3-Ph-4-Cl					

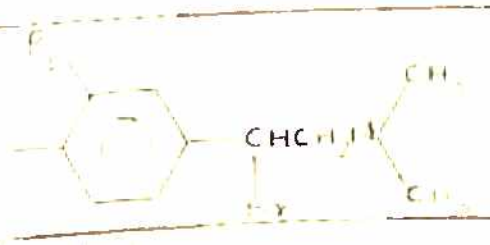
$\bar{x}$.

a Within brackets is the r dical v lue of $\bar{x}$.

b ref. 12.

Table 4.1

Substitution to molecular connectivity, electronic [illegible] calculated adrenaline antagonic activities of [illegible]-dimethyl-2-bromophenethylamines.



[illegible]	[illegible]	$\overline{\chi}^{a}$	$\delta^{+,a}$	[illegible]	[illegible]	[illegible]
				[illegible]^{b}	[illegible]	[illegible]
H	H	0.000(0.000)	0.00	7.46	7.46	7.46
H	F	0.394(0.410)	[illegible]	8.16	8.51	8.65
	Cl	[illegible]	[illegible]	8.68	8.51	8.53
	Br	[illegible]	[illegible]	8.89	8.51	8.51
H	F	[illegible]	0.14	9.25	8.51	8.52
	[illegible]	[illegible]	0.31	[illegible]	8.51	8.79
F	H	[illegible]	0.35	7.52	8.51	8.39
Cl		.394(0.[illegible]	0.40	8.16	8.51	8.36
Br		[illegible]	0.41	[illegible]	8.51	8.35
I	H	[illegible]	0.36	8.40	8.51	8.38
[illegible]		[illegible]	-0.07	[illegible]	8.51	8.65
Cl	F	0.805(0.[illegible]	0.39	[illegible]	8.98	8.91
Br	F	0.805(0.[illegible]	[illegible]	[illegible]	8.98	8.91
CH_3	F	0.805(0.[illegible]	-0.14	[illegible]	8.98	9.20
Cl	Cl	0.805(0.[illegible]	[illegible]	[illegible]	8.98	8.80
Br	Cl	0.805(0.[illegible]	0.52	8.92	8.98	8.80
CH_3	Cl	0.805(0.[illegible]	0.04	[illegible]	8.98	9.09
Cl	Br	0.805(0.[illegible]	[illegible]	9.00	8.98	8.78
Br	Br	[illegible]	[illegible]	[illegible]	8.98	8.77
CH_3	Br	[illegible]	0.08	9.22	8.98	9.07
CH_3	CH_3	[illegible]	[illegible]	9.30	8.98	9.35
Br	[illegible]	[illegible]	0.10	[illegible]	8.98	9.06

a [illegible] the [illegible] value of $\overline{\chi}$.

b [illegible] from ref. 13.

$$\log 1/c = 0.173(\bar{x}^2) + 3.253 \qquad (4.22)$$

$$n = 18,\ r = 0.615,\ s = 0.492,\ F^1_{16} = 14.19$$

$$\log 1/c = -0.340(\bar{x}^2) + 1.600(\chi) + 2.374 \qquad (4.23)$$

$$n = 18,\ r = 0.870,\ s = 0.343,\ F^2_{15} = 21.93$$

The electronic parameter (Hammett's constant (12), σ) however, when used in regression analysis, leads Eqn. 4.20 to

$$\log 1/c = -0.437\bar{x}^2 + 1.953\bar{x} + 1.267\sigma + 2.263 \qquad (4.24)$$

$$n = 18,\ r = 0.945,\ s = 0.234,\ F^3_{14} = 33.86$$

and Eqn. 4.18 to

$$\log 1/c = 0.598\bar{x} + 0.798\sigma + 2.913 \qquad (4.25)$$

$$n = 18,\ r = 0.843,\ s = 0.375,\ F^2_{15} = 17.25$$

where they show better degree of correlations. Equation 4.24, like Eqn. 4.16 in example 1, will be preferred here over all. In this example too the correlation between the electronic parameter itself and the activity is very poor.

$$\log 1/c = 0.354\sigma + 3.713 \qquad (4.26)$$

$$n = 18,\ r = 0.114,\ s = 0.671,\ F^1_{16} = 0.21$$

In example 3, the three different equations relating activity and unrefined $\bar{x}$ are

$$\log 1/c = 1.415\ \bar{x} + 7.874 \qquad (4.27)$$

$$n = 22,\ r = 0.604,\ s = 0.463,\ F^1_{20} = 11.54$$

$$\log 1/c = 1.91\ \bar{x}^2 + 8.227 \qquad (4.28)$$

$$n = 22,\ r = 0.548,\ s = 0.486,\ F^1_{20} = 8.59$$

$$\log 1/c = -1.911\bar{x}^2 + 3.422\bar{x} + 7.460 \qquad (4.29)$$

$$n = 22,\ r = 0.634,\ s = 0.461,\ F^2_{19} = 6.07$$

in which same type of equation, as in example 1 and 2, i.e. Eqn. 4.29 (parabolic) is found to be the best, though in this equation the degree of correlation is not as high as in previous cases. Here the F value is significant only at 95 percent level (F^2_{19} (0.05) = 3.52). However, here too, the use of refined $\bar{x}$ makes no improvement in the degree of correlation of any equation.

$$\log 1/c = 1.391(\bar{x}) + 7.862 \qquad (4.30)$$

$$n = 22,\ r = 0.606,\ s = 0.462,\ F^1_{20} = 11.0$$

$$\log 1/c = 1.139(\bar{x}^2) + 8.220 \qquad (4.31)$$

$$n = 22,\ r = 0.549,\ s = 0.486,\ F^1_{20} = 8.65$$

$$\log 1/c = -1.755(\bar{x}^2) + 3.285(\bar{x}) + 7.460 \qquad (4.32)$$

$$n = 22,\ r = 0.634,\ s = 0.461,\ F^2_{19} = 6.07$$

But again addition of electronic parameter, σ^+ (Brown and Okamoto constant (12)), is found to improve the correlations ; thus Eqn. 4.29 is modified to

$$\log 1/c = -2.045\bar{x}^2 + 3.705\bar{x} - 0.618\sigma^+ + 7.460 \qquad (4.33)$$

$$n = 22,\ r = 0.698,\ s = 0.439,\ F^3_{18} = 5.71$$

to account for the best correlation between activity and $\bar{x}$ and σ^+. The poor correlation between activity and σ^+ is exhibited by Eqn. 4.34.

$$\log 1/c = -\ .\ \sigma^{+} + 9.754 \qquad (\ .34)$$

$$n = 22,\ r = 0.152,\ s = 0.575,\ F^{1}_{20} = 0.48$$

owever, in example 4, where we have treated the derivatives of benzyl alcohol whose antifungal activity and other parameters are given in Table 4.8, refined values of $\bar{x}$ lead to better correlations than unrefined ones. The refined ones give

$$\log 1/c = 1.234\ (\bar{x}) + 1.555 \qquad (4.35)$$

$$n = 18,\ r = 0.702,\ s = 0.525,\ F^{1}_{16} = 15.60$$

$$\log 1/c = 0.776(\bar{x}^2) + 1.920 \qquad (4.36)$$

$$n = 18,\ r = 0.681,\ s = 0.540,\ F^{1}_{16} = 13.88$$

$$\log 1/c = -0.101(\bar{x}^2) + 1.386(\bar{x}) + 1.513 \qquad (4.37)$$

$$n = 18,\ r = 0.702,\ s = 0.543,\ F^{2}_{15} = 6.82$$

and unrefined ones correspondingly give

$$\log 1/c = 0.971\,\bar{x} + 1.719 \qquad (4.38)$$

$$n = 18,\ r = 0.566,\ s = 0.608,\ F^{1}_{16} = 7.55$$

$$\log 1/c = 0.586\,\bar{x}^2 + 2.022 \qquad (4.39)$$

$$n = 18,\ r = 0.526,\ s = 0.627,\ F^{1}_{16} = 6.14$$

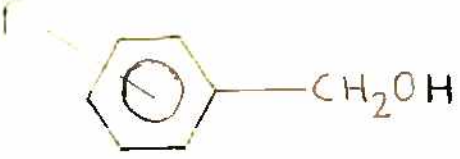
$$\log 1/c = -\ 0.641\,\bar{x}^2 + 1.937\,\bar{x} + 1.461 \qquad (4.40)$$

$$n = 18,\ r = 0.579,\ s = 0.621,\ F^{2}_{15} = 3.54$$

Now in this case two equations, Eqn. 4.35 (linear) and Eqn. 4.37 (parabolic), are both of them are almost equally improved by the addition of the electronic parameter, E_s (Yamamoto

Table 4.5

Substituent contribution to molecular connectivity, electronic parameters, observed and calculated anti fungal activities of substituted benzyl alcohols.



R	$\bar{\chi}^a$	π	log 1/c		
			obsd[b]	cald, Eq.37	cald, Eq.42
H	0.000(0.000)	0.00	1.51	1.51	1.60
4-Cl	0.394(0.410)	0.10	2.07	2.06	2.13
$2,4\text{-Cl}_2$	0.805(0.827)	0.20	3.07	2.59	2.62
$3,4\text{-Cl}_2$	0.805(0.827)	0.18	3.07	2.59	2.69
$2,4,5\text{-Cl}_3$	1.215(1.244)	0.23	3.32	3.08	3.10
$3,4,5\text{-Cl}_3$	1.215(1.244)	0.26	3.63	3.08	3.17
2-Br	0.411(0.417)	0.12	2.15	2.07	2.08
4-Br	0.394(0.410)	0.12	2.27	2.06	2.06
4-I	0.394(0.410)	0.12	2.75	2.06	2.06
4-Me	0.394(0.410)	0.03	2.79	2.06	2.37
$2,4\text{-Me}_2$	0.805(0.827)	0.06	2.14	2.59	3.09
4-Cl-3,5-Me_2	1.215(1.244)	0.16	3.05	3.08	3.51
4-I-3,5-Me_2	1.215(1.244)	0.28	3.42	3.08	3.10
2-NO_2	1.321(1.311)	0.41	2.49	3.16	2.78
4-NO_2	1.304(1.020)	0.41	2.00	2.82	2.67
4-CN	0.932(0.450)	0.24	1.67	2.12	1.74
2-OH	0.411(0.417)	0.17	1.39	2.07	1.91
4-OH	0.394(0.410)	0.17	1.39	2.06	1.90

[a] Within bracket is the refined value of $\bar{\chi}$.

[b] Data taken from ref. 12.

...t (1 ...).

... $1/c = 1.921(\bar{\chi}) + 3.369\ E_R + 1.671$ (4.41)

... $n = 1$..., $r = 0.793$, $s = 0.465$, ... $= 11.93$

... $-0.191(\bar{\chi}^2)$ ... $\bar{\chi}$ $-3.334\ E_R + 1.596$ (4.42)

... $n = 18$, $r = 0.794$, $s = 0.429$, ... $= 6.86$

... poor correlation between ...tivity and E_R is obvious

... ...

... (4.43)

... $- 1.599\ E_R + 2.162$

... 18, $r = 0.254$, $s = 0.714$, $F_{16} = 1.108$

Thus we find that in case of substituted molecules the biological activi... molecules are well correlated parabolically with substitue...s contribution to molecular connectivity ... however, linear correlation is also found equally sig...t. The use of refined $\bar{\chi}$ seldom makes ... in the correlations, but ... sion ... in the parameters are invariably found to impr... the degree ... correlations, ... poor ... with the activity. The reason ... ng that the electronic param...ters account for the effect ... varyin... electronegativities of different atoms in ... substituted groups, while neither of $\bar{\chi}$'s, refined or unre...d, takes properly ... to account the electronegativity of the atoms. Hence the a...tion of electronic parameters appears to be essential ... the study of correlations between activity and molecu... connectivity index in case of substituted molecules. ... conclusion can be further evaluated

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The thesis thus contains 4 chapters in all. The contents of each chapter are summarized below.

Chapter one:

This chapter mentions some of the indices of electronic structure, such as charge density, free valence and energies of the highest occupied and lowest unoccupied molecular orbitals etc., which are useful in the discussion of the activity of chemicals. The properties related to them are also discussed, e.g., the +ve and -ve charge densities are mentioned to be indicative of the position of attack of nucleophilic and electrophilic reagents respectively in a molecule. Likewise the free valence is mentioned to be indicative of position of free radical attack.

The energies of HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are discussed to be of use in determining the electron-donor and-acceptor properties of the molecules respectively. Thus the properties related to all the electronic indices mentioned are discussed in this chapter.

Chapter Two:

This chapter discusses the two molecular orbital methods that have been used to calculate the electronic indices: the Hückel approximation and the Zero Differential Overlap(ZDO) approximation. How these methods are utilized

to calculate the different electronic indices is also discussed in this chapter.

Chapter 3 & 4:

Chapter 3 and 4 represent the actual work done by the author. In Chapter 3 the following things are discussed.

1. Chemical reactivity of azanaphthalenes with nucleophiles and electrophiles.

Based on the net charges on the different positions in azanaphthalenes, the relative reactivity of the different positions in these molecules towards nucleophiles and electrophiles is discussed and a fundamental reactivity pattern towards each type of substituents is interpreted.

Towards the nucleophilic substituents the general reactivity pattern of these molecules are as follows. In all azanaphthalenes, whether mono - or poly -, in which there is a nitrogen at position 1 of the ring, the most reactive centres towards nucleophilic substitution reaction would be positions 2 and 4, if they are free (no nitrogen at them), and 2 > 4. In those azanaphthalenes where position 2 is occupied by a nitrogen and position 1 is free, the most reactive centre would be position 1 and the next would be position 3, if it is free. In other azanaphthalenes the position between two nitrogen would be the most reactive and the next would be the position adjacent to one nitrogen and opposite to other.

Similarly the general reactivity patterns of these molecules towards the electrophilic substitution reaction were found to be as follows. The most reactive centre towards the electrophiles in an azanaphthalenes would be generally the position meta to the nitrogen singly present in one of the two rings. If all the nitrogens are present in one ring then it is the position 5 or 8 which will constitute the most reactive centre towards such substituents.

2. Intermolecular interaction of nitrogen heterocyclics with nucleotide bases:

The intermolecular interaction of some nitrogen heterocyclics is discussed in the light of their electronic structure. It was found that the heterocyclics interacting with nucleotide bases possess the following properties. Firstly, they have some structural similarity with the complement of the base with which they interact and secondly, the electronic charge density at their electronegative element that would participate in the hydrogen bond formation with the base is comparable to that at the same in complementary base. It was therefore inferred that, in general, a nitrogen heterocyclics having these properties will be able to interact with nucleotide bases.

3. Interaction of carboxylic acids with adenine:

The interaction of some carboxylic acids, recently observed, with adenine is interpreted theoretically to involve the charge-transfer mechanism. The interpretation

i[illegible] on the energies of their HOMO's and LUMO's.

4. Anthelmintic activity of some organophosphorus compounds:

The anthelmintic activity of organophosphorus compounds was found to be related to the charge and superdelocalizibility index at their phosphorus atom and to the bond-order of their P-O bond.

5. [illegible] relationship of antibacterial acridines.

The relationship of antibacterial activity of a series of amino and fluorinated acridines with their electronic structure is established. A statistical regression analysis reveals linear correlation between the activity and electronic charge at the ring nitrogen.

Chapter Four:

Chapter 4 introduces a new parameter known as molecular connectivity index. This molecular connectivity index, χ, has been found to be related linearly with several physical parameters and linearly or parabolically with biological activities. Presently the author has attempted in this chapter, to correlate this index with molecular orbital indices. Several molecular orbital indices, such as energy of HOMO, delocalization energy, localization energy etc., are found parabolically and linearly correlated with χ. Further attempt has also been made to correlate the substituents contribution to molecular connectivity index with biological

[illegible] substituted molecules. A parabolic correlation of the type, $\log 1/c = -\pi^2 \ldots \bar{x} \ldots c'$ between activity c and substituent contribution, $\bar{x}$. to molecular connectivity index, $^{0}\chi$, was found to be more significant. This equation is found to be further improved by addition of some appropriate electronic parameter in the regression [illegible] .