PART - II
CHAPTER-VII

INTRODUCTION

Molecules are entities having independent existence and usually termed as ionic, covalent and co-ordinate covalent compounds depending on the nature of bonding between the atoms in the molecules.

In addition to chemical forces or interatomic forces, the molecules usually possess long range intermolecular or physical forces like dipole-dipole, dipole-induced dipole interactions, dispersion interactions, vanderwaal’s forces etc. These forces are weak and very difficult to determine but the combination of small forces make them sufficiently strong to form weak reversible interaction between two or more components to form complexes. A complex is defined as a specimen formed due to some molecular interactions having some measurable features and definite stoichiometry and the forces leading to the formation of complex is known as specific interaction [1].

Molecular association may be formed by the combination of donors and acceptors and stabilized by partial transfer of charges of the electrons from the donor to the acceptor known as charge-transfer (CT) or electron-donor acceptor (EDA) complexes[2].

H- bonding interactions or hydrogen bonded complex formation may be regarded to be charge-transfer complex formation[3] in which a hydrogen atom serves to hold two electronegative atoms with at least one unshared electron pair together with a complete octet. The atoms are F, O, N and to a lesser degree Cl and S.
Interaction between electron donors and electron acceptors to form complexes is well-known. Pfeiffer[5] first showed that certain aromatic hydrocarbons and their derivatives combine with a wide variety of compounds (both organic and inorganic) to form molecular complexes having certain characteristic features[6]. These are:

a) The molecular complexes are formed rapidly and in simpler molecular ratios.
b) The distances separating the donor and acceptor molecules in crystalline addition complexes are usually much greater than those corresponding to covalent or ionic bonds.
c) The stability of the molecular complexes is related to both ionization potential of the donor and the electron affinity of the acceptor.

In case of strong CT interactions between donor and acceptor, characteristic transition due to charge-transfer appears as a separate band at considerably longer wavelengths than the absorptions of the component molecules. The complexes usually have moderately high molar absorptivity (extinction coefficient) at the wavelength of the maximum absorption. A direct determination of intensity cannot normally be made because the degree of dissociation of the complex in solution is usually significant and particularly if there are overlap of the spectral intensities on the absorption of the complex[6].

However, the term 'charge-transfer' has been contested [7-9] as in many cases of CT complexes, charge transfer forces do not provide the major binding forces in the ground
state. There are evidences where there is little or no transfer of charge in the ground states of these complexes. Moreover, in many cases, it is experimentally difficult to demonstrate the presence of the characteristic CT absorption band [6]. This is particularly true when both the components and the complex absorb in the same region.

However, the divisions of molecules as electron donors or electron acceptors are only relative e.g. for self-complexes of benzene, benzene acts both as donor and acceptor.

Theory:

A successful quantum mechanical (valence bond) treatment for the formation of charge-transfer complexes and explanation of the characteristic electronic absorption in terms of an intermolecular charge transfer transition was put forward by Mulliken. In terms of Mulliken treatment the interaction of no-bond ground state $\psi_0 (DA)$ and the polar excited state $\psi_1 (D^+ A^-)$ was considered to produce a stabilized ground state having a wave function $\psi_N$ given by the expression:

$$\psi_N = a \psi_0 (DA) + b \psi_1 (D^+ A^-) \quad \ldots \ldots \ldots (1)$$

and an excited state (charge transfer state) having a wave function:

$$\psi_E = a^* \psi_1 (D^+ A^-) - b^* \psi_0 (DA) \quad \ldots \ldots \ldots (2)$$

$\psi_0$ and $\psi_1$ are wave functions of the no-bond and ionic structures corresponding to states in which D and A are held together by classical Vander waal's forces and in
which an electron has been transferred from the electron donor D to the electron acceptor A.

Since the wave function are normalized, the coefficients a and b are related by the expression,

\[ a^2 + 2abS_{01} + b^2 = 1 \]

where \( S_{01} = \int \Psi_0 \Psi_1 d\tau \).

For weak complexes, \( S_{01} \) is small and \( a^2 \gg b^2 \), \( b^2 \) represents the weight of the dative structure or fraction of electron transferred from D to A in the ground state and \( a^2 + b^2 = 1 \).

For weak interactions, the ground state energy \( (W_N) \) will be the energy of the two separated components \( (W_r) \) modified by the ‘no-bond’ energy term \( G_0 (\text{+ve or -ve}) \) and by the resonance energy \( (X_0) \) of interaction between the states \( \psi_0 (DA) \) and \( \psi_1 (D^+ A^-) \), thus

\[ W_N = W_r + G_0 - X_0 = W_0 - X_0 \]

For weak interactions \( W_N \) is approximately

\[ W_N = \int \Psi_N \hat{H} \Psi_N d\tau = W_0 - \frac{(H_{01} - S_{01} W_0)^2}{(W_1 - W_0)} \]

\( W_0 = \int \Psi_0 \hat{H} \Psi_0 d\tau \); \( W_1 = \int \Psi_1 \hat{H} \Psi_1 d\tau \) is the energy of the dative structure \( D^+ A^- \).

\[ H_{01} = \int \Psi_0 \hat{H} \Psi_1 d\tau . \]

\( H \) is the exact Hamiltonian operator for the entire set of nuclei and electrons.
The approximate relation of the co-efficients $a$ and $b$ is given by

$$b/a = (H_{01} - S_{01}W_0)/(W_1 - W_0) \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots (6)$$

For the excited states,

$$\int \Psi_{E}^* \Psi_{E} \, dx = a^2 + b^2 - 2a^*b^* S_{01} = 1 \quad \ldots \ldots \ldots \ldots (7)$$

The charge transfer bond of the complexes was considered by Mulliken to be associated with the electron transition $\psi_N \rightarrow \psi_E$ and since $a^2 \gg b^2$, the transition is essentially a transfer of an electron from $D$ to $A$.

For relatively weak interactions, the energy of the excited state ($W_E$) will be greater than $W_1$ by the resonance energy ($X_1$):

$$W_E = W_1 + X_1 \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots \ldots (8)$$

By the second order perturbation approximation,

$$W_E = W_1 + \frac{(H_{01} - S_{01}W_1)^2}{(W_2 - W_0)} \quad \ldots \ldots \ldots \ldots (9)$$

And the coefficient $a^*$ and $b^*$ are related by

$$(b^*/a^*) = - (H_{01} - S_{01}W_1)/(W_1 - W_0) \quad \ldots \ldots \ldots \ldots (10)$$

A diagram showing the relationship between the various terms are given in Fig. 1.

Contd.
Excited state of complex \( \psi_E(DA) \rightarrow W_E \) \( \xrightarrow{\uparrow X_1} \) \( D^+A^- \) \( \leftrightarrow \) DA

\( W_1 \) \( \xrightarrow{\uparrow} \) \( D^+A^- \)

\( W_a \) \( \xrightarrow{\uparrow G_0} \) \( D+A \)

\( W_0 \xrightarrow{\uparrow X_0} \) DA

Ground state of complex

\( \psi_0(DA) \rightarrow W_E \) \( \xrightarrow{\uparrow} \) \( D^+A^- \)

Fig. 1.

For interaction between the structures \( \Psi_0 \) and \( \Psi_1 \) both \( S_{01} \) and \( H_{01} \) must be non-zero. The functions \( \Psi_0 \) and \( \Psi_1 \) are of the same spin-type and same orbital species.

For an interpretation of electron donor-electron acceptor molecule pairs, the theoretical process \( \Psi_0 \rightarrow \Psi_1 \) involves the jump of one of a pair of electrons from highest occupied molecular orbital (HOMO) in \( D(\Psi_D) \) to a lowest empty molecular orbital (LEMO) in \( A(\Psi_A) \). This must occur in such a way that the excited electron still remains paired to its original electron partner. It is shown that

\[ S_{01} = \sqrt{2S_{DA}(1 + S_{DA}^2)^{1/2}} \]

(11)

where \( S_{DA} = \int \Psi_A \Psi_D d\tau \). This is the overlap integral between highest filled molecular orbital of the donor and the lowest vacant molecular orbital of the acceptor.

For the usually small values of \( S_{DA} \), \( S_{01} \) will vary linearly with \( S_{DA} \). \( H_{01} \) will also vary linearly with \( S_{DA} \) for small values of \( S_{DA} \). The electron donor and electron acceptor
moieties will tend to orientate themselves relative to one another in such a way as to make $S_{01}$ or $S_{DA}$, a maximum. This principle has been used to predict the geometry of certain complexes.

The theoretical and other details have been described elegantly in the classical papers of Mulliken[2,10-12], Murrel[13,14] and well documented books of Foster[6], Briegleb[15], Mulliken and Pearson[16], Foster[17] and Rose[5].

**Determination of the position of the equilibrium**

Most of the studies are carried in the liquid state and the components are usually very small to consider the solutions to be dilute.

In most cases, the compositions of the complexes formed between D and A have been assumed to be unity. The consistency of the results obtained using the derived equation based on 1:1 complex formation suggests the validity of the assumption. However, composition of a complex can be determined using the usual methods like Job's method of continuous variation, slope-ratio method, mole-ratio method etc [18].

Experimental determinations of the existence of the CT spectra and their equilibrium constants have been extensively determined using UV and Visible spectrophotometry. Other methods of importance are infrared spectrophotometry, nuclear magnetic resonance, dielectric constant measurements, direct calorimetry (gives both enthalpy and Gibbs energy changes) etc. These methods have been described elegantly in different books [5,6,17].
However, meaningful values of the stability constants ($K$) for the reaction $D + A \xrightarrow{\text{DA}}$ and molar absorptivities ($\varepsilon$) are required not only for the studying the thermodynamic properties of the compounds but also for verification of the present quantum mechanical theories on charge-transfer complexes.

The equations most widely used for the determination of $K$ and $\varepsilon$ by optical method are Benesi-Hildebrand equation [19], Scott equation [20] etc where the complex only absorbs and $[D]_0 >> [A]_0$ or Ketelaar equation[21] (where $[D]_0 >> [A]_0$ but both A and DA absorb). Other rearranged forms are also used[22,23].

It is apparent that these equations neglect certain term or terms appearing in the full expression for the stability constants of the complex. Such equations also use the approximation that the equilibrium concentrations of the complexes are negligible compared to $[D]_0$ under such conditions. Sahai and Badoni [24] have shown that the error in $K$ resulting from the above approximation may range from 3% to as high as 70% depending on the value of $K$- the error increases with increase in $K$. The error can be eliminated using the expression of $K$ in its full form. Rose and Drago [25] considered the approximations usually made to be untenable under all conditions. It is expected that the components as well as the complex may absorb in the same region and the solutions of the equation necessarily consisted the treatment of different sets of experimental data taking $\varepsilon$ values at random. An iterative method was developed by De Maine and Seawright [26] which requires an intuitive guess of a value of $K$ to start with for the convergence of iteration. Seal et al [27] suggested a rigorous method of calculation based on the principle of least squares and the use of Lagrange’s method of undetermined multipliers for constrained variation.
The equation is applicable to 1:1 complex without loss of generality.

**Determination of the association constants of the complexes and the equations used in this dissertation**

The equilibrium constant for the reaction \( D + A \rightleftharpoons DA \) can be written as,

\[
K_{AD} = \frac{[DA]}{[D][A]} = \frac{[DA]}{([D]_0 - [DA])([A]_0 - [DA])} \quad \text{......... (12)}
\]

[assuming activity coefficient to be unity in dilute solutions of non-electrolytes]. The composition of the complexes has been tacitly assumed to 1:1.

The widely used spectrophotometric method is not adopted in the present investigation. An iterative method which imposes no restriction regarding the concentrations of A and D have been adopted [28-31].

Let \( C_1 \) and \( C_2 \) be the initial concentrations of the acceptor and donor respectively. Let \( x \) be the complex formed at equilibrium. Thus, we have

\[
d_1 = \varepsilon_1 C_1 l \quad \text{.................. (13)}
\]

\[
d_2 = \varepsilon_2 C_2 l \quad \text{.................. (14)}
\]

\[
d = \varepsilon_1 (C_1 - x) l + \varepsilon_2 (C_2 - x) l + \varepsilon x l \quad \text{......... (15)}
\]

where \( d_1, d_2 \) and \( d \) represent the absorptivity or optical density of solutions of D, A and the mixture containing complex and unreacted molecules.

Similarly, \( \varepsilon_1, \varepsilon_2 \) and \( \varepsilon \) represent the molar absorptivities or extinction coefficients of A, D and DA respectively.

Thus,
\[ d - d_1 - d_2 = \varepsilon_1 (C_1 - x)l + \varepsilon_2 (C_2 - x)l + \varepsilon x l - \varepsilon_1 C_1 - \varepsilon_2 C_2l \]
\[ = (\varepsilon - \varepsilon_1 - \varepsilon_2) x l \] ............(16)

or, \( x = \frac{(d - d_1 - d_2)}{(\varepsilon - \varepsilon_1 - \varepsilon_2)l} \) ............(17)

Now, \( K_{AD} = \frac{x}{(C_1 - x)(C_2 - x)} \) ............(18)

or, \( (C_1 - x) = \frac{(d - d_1 - d_2)}{K(C_2 - x)(\varepsilon - \varepsilon_1 - \varepsilon_2)l} \) ............(19)

or, \( \frac{(C_1 - x)}{x} = \frac{1}{K_{AD}(C_2 - x)} \) ............(20)

Putting the value of \( x \) and rearranging, we get

\[ \frac{C_1}{(d - d_1 - d_2)} = \frac{1}{(\varepsilon - \varepsilon_1 - \varepsilon_2)l} + \frac{1}{K(C_2 - x)(\varepsilon - \varepsilon_1 - \varepsilon_2)l} \] ............(21)

\( x \) has been notionally assumed to be zero initially. From the plot of \( C_1/(d - d_1 - d_2) \) against \( 1/C_2 \), the initial value of \( 1/(\varepsilon - \varepsilon_1 - \varepsilon_2)l \) has been obtained from the intercept from which the value of \( x \) has to be calculated. The value of \( x \) thus obtained has been used to calculate refined values of \( K \) and \( 1/(\varepsilon - \varepsilon_1 - \varepsilon_2)l \). The iteration has been repeated till constancy in \( K \) and \( (\varepsilon - \varepsilon_1 - \varepsilon_2)l \) values (l=1 cm) have been obtained.

If \( D \) or \( A \) does not absorb, the equation reduces to

\[ \frac{C_1}{d - d_1} = \frac{1}{(\varepsilon - \varepsilon_1)l} + \frac{1}{K(C_2 - x)(\varepsilon - \varepsilon_1)l} \] ............(22)

and the same procedure should be utilized to calculate \( K \) and \( \varepsilon \) of the complex[28-31].
Special Cases:

(a) When both the acceptor (A) and the complex (DA) absorb and when D is in large excess, we have,

\[
\frac{C_1}{d-d_1} = \frac{1}{(\varepsilon-\varepsilon_1)l} + \frac{1}{KC_2(\varepsilon-\varepsilon_1)l} \quad \text{(23)}
\]

\[
\frac{C_1}{\varepsilon^aC_1 l - \varepsilon_1 C_1 l} = \frac{1}{(\varepsilon-\varepsilon_1)l} + \frac{1}{KC_2(\varepsilon-\varepsilon_1)l} \quad \text{(24)}
\]

\[
\frac{1}{(\varepsilon^a - \varepsilon_1)} = \frac{1}{(\varepsilon-\varepsilon_1)} + \frac{1}{KC_2(\varepsilon-\varepsilon_1)} \quad \text{(25)}
\]

( where \(\varepsilon^a\) = arbitrary extinction coefficient and \(d = \varepsilon^a C_1 l\) )

This is Ketelaar equation [21].

(b) When only the complex absorbs and \(D \gg A\), then we have \(C_{2-x} \approx C_2\).

\[
K = \frac{x}{(C_1-x)C_2} \quad \text{(26)}
\]

or, \(\frac{C_1-x}{x} = \frac{1}{KC_2} \quad \text{............(27)}\)

or, \(\frac{C_1}{x} = 1 + \frac{1}{KC_2} \quad \text{............(28)}\)

or, \(\frac{C_1 \varepsilon l}{d} = 1 + \frac{1}{KC_2} \quad \text{............(29)}\)

or, \(\frac{C_1}{d} = \frac{1}{\varepsilon l} + \frac{1}{KC_2 \varepsilon l} \quad \text{............(30)}\)

This is Benesi-Hildebrand equation [19].
Mulliken[2] in his classic paper suggested that charge-transfer complexes may play an important role in biological systems.

Szent- Gyorgi [32] postulated the significance of this type of bonding in biological systems and suggested that the powerful electron-attracting properties of 2,4-dinitrophenol and thyroxine account for their ability to uncouple oxidative phosphorylation processes.

CT complex of polycyclic aromatic hydrocarbons [33,34] has been supposed to be the primary event in their carcinogenic action.

Antibacterial action of aminoacridines has been believed to be linked to their ability to intercalate in the DNA-polymer chain and form CT complex with the purine bases[35].

CT complex of proflavine-DNA, chloroquine-DNA and actinomycin D–DNA had been reported [36,37].

Eckert [38] has shown that proline and other local anaesthetics form π-electron CT complexes with thiamine which appears on the basis of a considerable body of evidence to have a specific role in nerve conduction processes [39].

Importance of charge-transfer interactions of drugs have been stressed by Foster[6].

Production of a color when two biochemical or other reagents are mixed, can not be regarded to be the sole evidence for charge-transfer complexes. More positive evidence, such as the systematic variation of the energy of the absorption band for complexes of a series of related donors with a given acceptor or with the ionization potentials of the
donors is desirable before the attribution of a particular coloration to charge-transfer complex formation is made. The tendency to postulate CT complexes without adequate evidence has been a subject of discussion [40,41].

However, some biochemical substances like oxidation-reduction co-enzymes, pyridinium nucleotides, the isalloxazine moiety of flavine nucleic acids and nucleic acid bases, indoles, amino acids, proteins, carotenes, quinones and porphyrins have been observed to be good donors or acceptors to form CT complexes. Beukers and Szent-Gyorgi [42] reported the presence of CT bands for adenine and thymine with chloranil complexes in DMSO which has been refuted by Slifkin [43].

Karreman [44] put forwarded a hypothesis concerning the relation between drug activity and charge-transfer. Chlorpromazine forms charge transfer complex with flavinemononucleotide and serotonin [32]. It also forms a complex with rhodamine B and xanthene dyes.

Therefore the importance of charge-transfer and H-bonding in drug interaction is obvious.

**Scope and object of the work [5,6]**

The applications and uses of molecular or charge-transfer or electron donor-acceptor complexes are vast and wide and embrace medicine to chemistry. The applications and uses have been described elegantly by Rose [5], Foster [6]. Some of these are:

(a) Catalytic activities of molecular complex and absorption phenomena.
Catalytic activities of BF$_3$ : It has a marked ability to form complexes which play an useful role in acid catalysis in reactions involving polymerization, alkylation, condensation, isomerization, degradation and numerous other chemical synthesis. The presence of many other of the complexes is confirmed by the appearance of new infrared absorption bands and the shift of the UV bands of the reactants.

The phenomena of catalysis and adsorption on surfaces are interrelated. According to Mulliken[2], the adsorption of certain molecules on metallic surfaces is accompanied by a transfer of an electron from a donor atom to an acceptor atom with the resulting formation of a CT complex (strongly ionic to weak covalent) leading to catalytic activities.

CT also lead to the prediction of surface potentials and their sign [5].

Adsorption of molecular complexes and their components has extensive uses in dyeing, production of solid crystalline molecular complexes, lubrication [5].

(b) Semiconductivity [5] : CT complexes form semiconductor substances e.g., bovine plasma albumin- chloranil complex [45], benzoquinone + amino acids [46], tetracyanoethylene + phenothiazines [47], TCNQ + thiophen molecules [48].

(c) Formation of derivatives for the purpose of identification and separation e.g., aromatic hydrocarbons as picrates.

(d) Molecular weight determinations.
(e) Charge-transfer complex formation in chromatographic separation e.g., TNF (2,4,7-trinitrofluorenone) and aromatic hydrocarbons like phenanthrene, anthracene, and chrysene.

(f) Other important areas of applications of the CT complexes are:

i) rechargeable batteries [49], photovoltaic cells [50],

ii) non-linear optical devices [51-54],

iii) solar cells [55-56]

iv) dendrimers [57-59]

v) photocatalysis [60] etc.

Drug Action:

Physico-chemical interactions of drugs in a body system are responsible for drug action. Drugs may be structurally specific (where stereo-specific configuration is necessary) and non-specific (where certain physico-chemical properties are responsible for drug action). These aspects have been examined in details in the authoritative books of Burger [61], Korolkovas [62], Gisvold [63], Wermuth [64], Nowardy and Weaver [65]. It is to be noted that a drug has to traverse a long journey from the point of administration to the site of action i.e. receptor site (a biological macromolecule, enzymes etc.) to trigger biological action. But a drug molecule has to traverse many phases (pharmaceutical, pharmacokinetic and pharmacodynamics) and is subjected to multiple assaults on its structural and chemical integrity. However, all these details are beyond the scope of the present dissertation. The properties like solubility in water, partition co-efficient of drug between water/octanol,
ionization, acidity, surface activity, H-bonding and hydrophobic interactions are important. But the list is enormous for a dissertation to cover. Rather, we are interested to study the role of weak interactions like charge-transfer, H-bonding and other van der waals interactions between available drugs and known acceptors to get some idea regarding the drug-receptor interactions. However, there are important limitations. Drugs and acceptors are usually organic molecules of very low solubility in water, the most important and abundant biological solvent. Therefore, works are to be carried out in organic solvents following the known experts like Mulliken [2, 10,11], Szent-Gyorgi [32], Foster [6] etc.

Incidentally, water plays a fundamental and crucial role in determining the properties of drug molecules. It is actually the key player in determining the pharmacokinetic properties of drug. Water by virtue of its unique structure and orientating properties, directly influences the conformation of the receptor micro-molecules. Water bathes every drug and receptor molecules. Weak interactions like H-bonding, hydrophobic interaction, CT interactions play dominant roles in drug-receptor interaction. However, water is the missing link between drug and the receptor. Comprehensive studies on drug structure, drug-receptor interactions must include an equally comprehensive evaluation of the role of water.

In the present investigation, attempts have been made to study the charge-transfer interactions of lamotrigine and methyldopa (drugs lying between the borderland of scheduled and unscheduled drugs) with known acceptor
molecules like o-chloranil, chloranilic acid and 2,3-dichloro,5,6-dicyanobenzoquinone (DDQ) in acetonitrile. Charge-transfer interactions of 1,3-dinitrobenzene with aliphatic amines in DMSO were also studied. Physicochemical properties have been studied in details with proper interpretations. The works comprise the Part-II of the thesis.
References


38. T. Ekert, Naturwissenschaften, 49, 18, 1962.


