Chapter VII : Correlation of CT transition energies of the cloxacillin sodium complexes with DFT calculated LUMO energies of the acceptors

7.1 Introduction

The density functional theory (DFT)[1,2] has been found to be useful for quantum chemical calculation of molecular structures[3,4] and reaction paths[5,6] involving molecules or ions of moderate size within affordable computation time. Attempts are currently[7,8] being made to calculate the CT transition energies of molecular complexes by considering the donor-acceptor adduct as a supermolecule, but always it has been found that the CT transition energy is under-estimated.[7,8] It is known that prediction of CT excitation energy by the time-dependent density functional theory (TDDFT) is difficult.[9-11] This is because in standard TDDFT, the exchange correlation functionals correspond to potentials which do not exhibit the correct 1/r asymptotic behavior[12] (where r is the electron-nucleus distance) but fall off rapidly.[13] Application of the straight-forward TDDFT method always underestimates the CT transition energy, sometimes by an extent[13] of 60% of the exact $h\nu_{CT}$. However, using Mulliken's theory[14,15] and by calculating ionization potentials of donors and electron affinities of acceptors one can explain the observed trends in CT transition energies of a series of complexes. Several such works were reported in the past where the vertical ionization potentials (I_D^V) of a series of structurally similar π-electron donors were calculated by perturbation

theory[16,17] and graph theory[18,19] within the Hückel molecular orbital formalism, and CT transition energies ($h\nu_{CT}$) of their complexes with a given acceptor were shown to be linearly correlated to I_D^V. The vertical ionization potential of a compound means the minimum energy required to remove the most loosely bound electron from an isolated gaseous molecule in its lowest energy state without changing the molecular geometry, and according to Koopmans theorem[20] it is equal to the negative of the energy of the highest occupied molecular orbital (HOMO). No such theorem exists for the relation between the energy of the lowest unoccupied molecular orbital (LUMO) of a molecule and its vertical electron affinity (E_A^V), which means the minimum energy released when an electron is added to the LUMO of the molecule to form an isolated gaseous uni-negative ion keeping the geometry the same as that of the neutral molecule. However, E_A^V must be related to $-E_{LUMO}$, and for a series of CT complexes with a fixed donor and a number of acceptors in a particular medium, one expects a correlation between the observed $h\nu_{CT}$ of the complexes and $-E_{LUMO}$ of the acceptors. The objective of the work described in this chapter is to investigate whether such a correlation exists between the observed transition energies of the cloxacillin sodium complexes studied in chapter III and the LUMO energies of the acceptors, namely, p-chloranil, o-chloranil, menadione, 2,3-dichloro 1,4-naphthoquinone and 2,3-dichloro 5,6-dicyano 1,4-benzoquinone (DDQ); if such a correlation exists the CT nature of the transitions is completely established.

7.2 Computational details

Computations were performed on a Pentium computer with the Gaussian 03 Revision-D.01 suit of programmes.[21] DFT calculations were done by using the combination of the Becke's three-*para*meter hybrid[22]exchange potential with the correlation functional of Lee,Yang and Parr[23] (B3LYP). The basis set 6-31++G(d,p) was used for optimization of ground state geometries of the acceptor molecules.

7.3 Results and Discussion

In order to get reliable values of the LUMO energies of the acceptors, their molecular structures were optimized at the DFT/B3LYP/6-31++G(d,p) level of theory. The optimized structures are given in Figures 7.1 – 7.5. The LUMO energies corresponding to the optimized geometries of the acceptor molecules are given in Table 7.1 along with the experimentally observed transition energies ($h\nu_{CT}$) of their complexes with cloxacillin sodium as reported in chapter III. The plot of hν against the theoretically calculated values of $-E_{LUMO}$ of the acceptors are shown in Figure 7.6. (The required LUMO energy eigenvalues in Hartree unit obtained from the Gaussian output files have been converted into eV by multiplying by a factor of 27.21141087 eV/Hartree). The correlation is linear with a negative slope as required by Mulliken's theory:[14,15]

$$h\nu_{CT} = -0.3430E_{LUMO} + 4.0378 \; ; \; |\text{correlation coeff.}| = 0.825$$

7.4 Conclusion

The linear correlation between the DFT calculated LUMO energies of the quinone type acceptors and electronic transition energies of their complexes

with cloxacillin sodium is in accordance with Mulliken's theory and thus the CT nature of the transitions is theoretically established.

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Table 7.1 Experimental transition energies (hv_{CT}) of complexes of cloxacillin sodium with a series of acceptors and LUMO energies of the acceptors calculated by DFT/B3LYP method using 6-31++G(d,p) basis set

Acceptor	**$-E_{LUMO}$ / eV**	**hv_{CT} /eV**
DDQ	5.4003	2.158
o-chloranil	4.6398	2.224
p-chloranil	4.5522	2.734
2,3-dichloro 1,4-napththo quinone	3.8602	2.789
menadione	3.4150	2.783

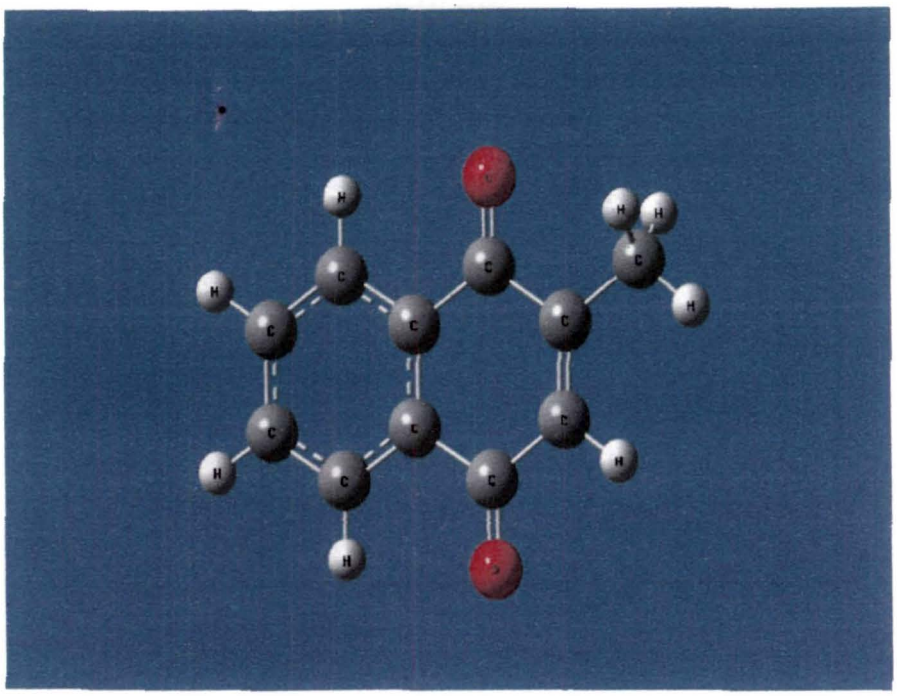

Figure 7.1 DFT/B3LYP/6-31++G(d,p) optimized structure of menadione

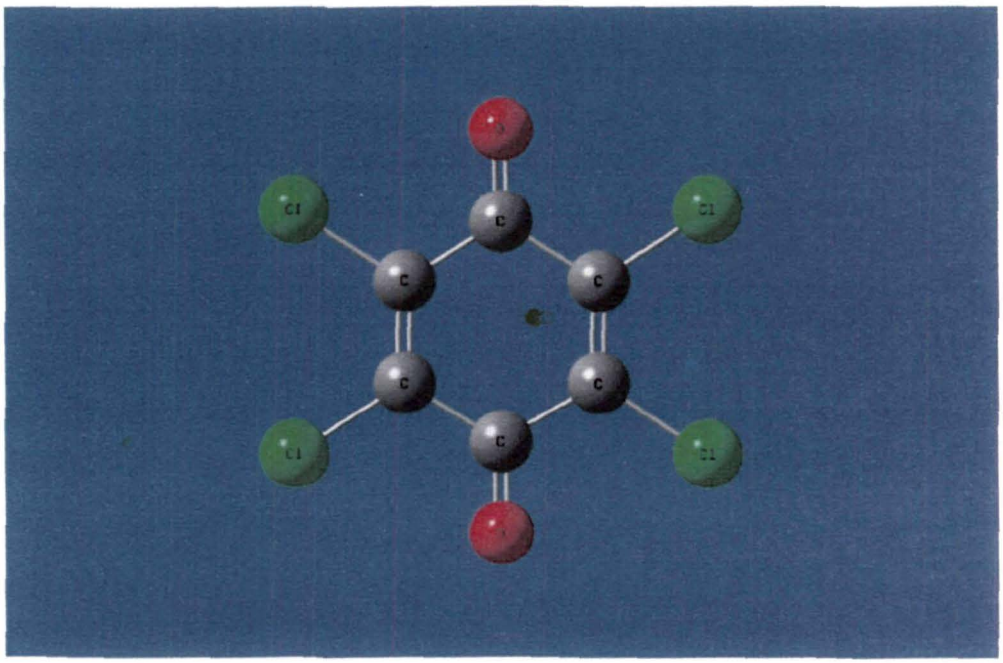

Figure 7.2 DFT/B3LYP/6-31++G(d,p) optimized structure of *p*-chloranil

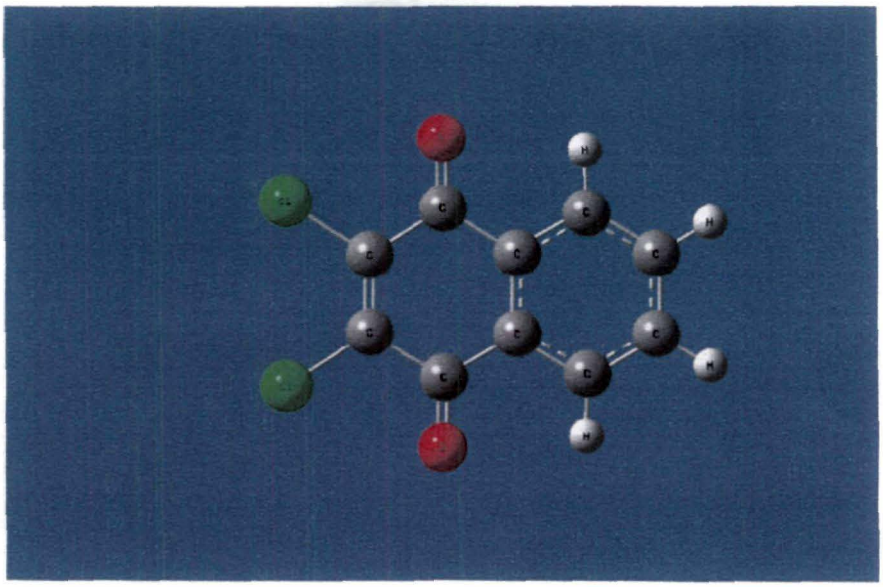

Figure 7.3 DFT/B3LYP/6-31++G(d,p) optimized structure of 2,3-dichloro 1,4-naphthoquinone

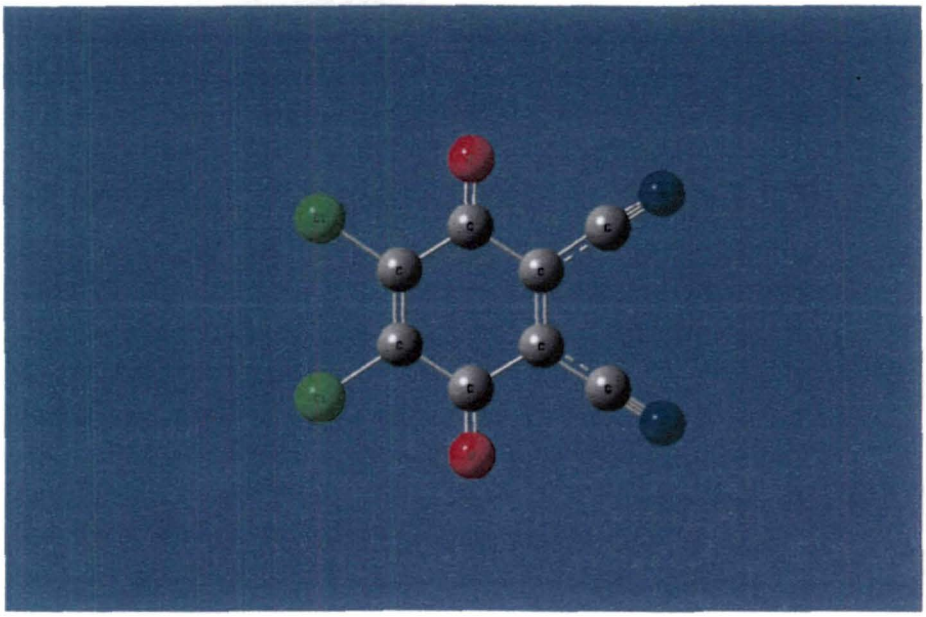

Figure 7.4 DFT/B3LYP/6-31++G(d,p) optimized structure of DDQ

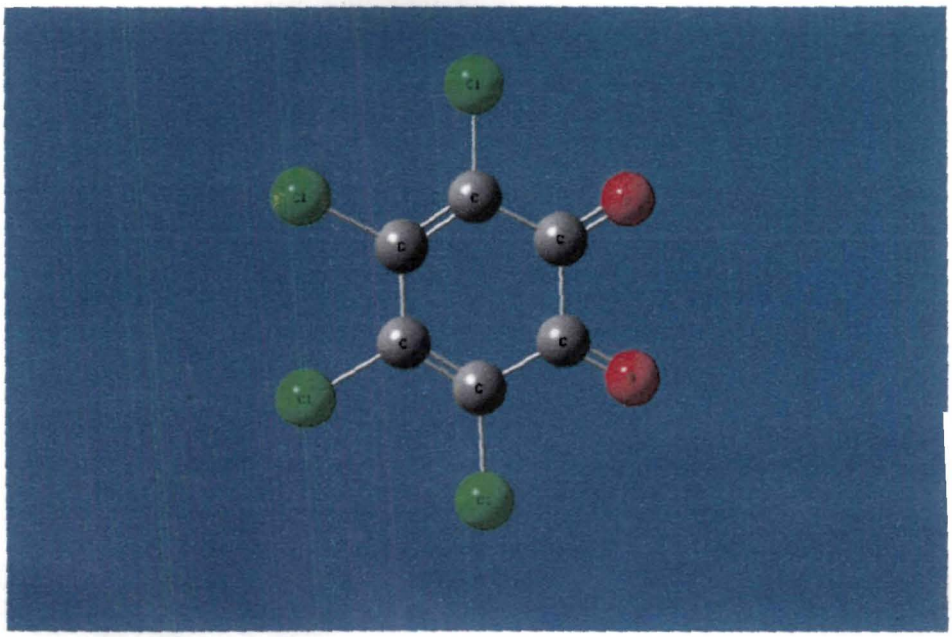

Figure 7.5 DFT/B3LYP/6-31++G(d,p) optimized structure of *o*-chloranil

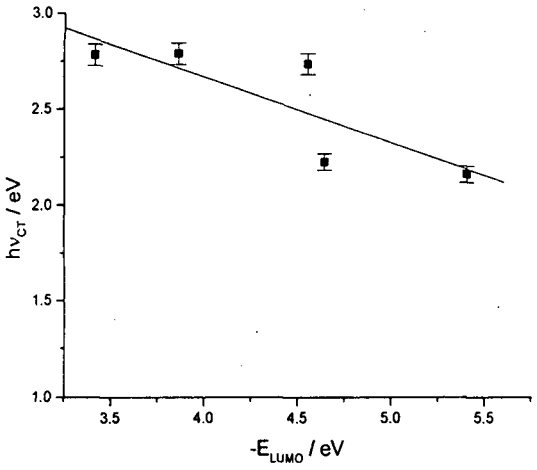

Figure 7.6. Plot of transition energies of the cloxacillin sodium complexes against negative of the LUMO energies of acceptors

Chapter VIII : Summary

CT and inclusion complexes of some pharmaceutical compounds (i.e., drugs and vitamins) have been studied in a bio-friendly medium (namely, aqueous ethanol). The important results obtained in the present work may summarized as follows.

Results of Chapter III

(Complexes of cloxacillin sodium with a series of quinones)

(a) The antibacterial drug, cloxacillin sodium (i.e., sodium (6*R*)-6-[3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamido] penicillanate) forms 1 : 1 stoichiometry with a series of electron acceptors comprising DDQ, o-chloranil, p-chloranil, 2,3-dichloro 1,4-napthoquinone and menadione (vitamin K_3) in 50% (v/v) aqueous ethanol medium.

(b) The trends in the CT absorption bands of the complexes of cloxacillin sodium yields the value 7.89 eV for the vertical ionization potential (I_D^v) of cloxacillin sodium.

(c) The enthalpies and entropies of formation of two complexes of cloxacillin sodium with o-chloranil and DDQ, determined by estimating the formation constants spectrophotometrically at five different temperatures, are respectively as follows: $\Delta H_f^0 = -9.84 \pm 1.47$ (kJ mol^{-1}) and $\Delta S_f^0 = 5.39 \pm 4.85$ J K^{-1} mol^{-1} for the *o*-chloranil complex and $\Delta H_f^0 = -21.06 \pm 1.14$ (kJ mol^{-1})

and $\Delta S_f^0 = -30.96 \pm 3.75$ J K^{-1} mol^{-1} for the DDQ complex. Such values are characteristic of usual weak molecular complexes.

(d) Usually quinones reduce ethanol. But the reduction of *o*-chloranil by aqueous ethanol is completely inhibited by cloxacillin sodium, a phenomenon that makes the present study of formation equilibrium possible.

Results of Chapter IV

(Complex formed between cloxacillin sodium and riboflavin)

(a) In ethanol-water mixtures cloxacillin sodium forms CT complex with riboflavin; the stoichiometry of the complex is 2 : 1 (cloxacillin sodium : riboflavin).

(b) The formation constant (*K*) of the cloxacillin sodium-riboflavin complex decreases linearly with the reciprocal of dielectric constant of the medium (i.e., with increase in water content of the aqueous ethanol medium). A plausible explanation for this may be obtained in terms of hydrolysis of the drug. Cloxacillin sodium (which may be abbreviated as D^-Na^+) at first dissociates into ions; then the anion (D^-) undergoes hydrolysis to form the corresponding free acid (DH), which forms molecular complex with riboflavin (A):

$D^-Na^+ \rightleftharpoons D^- + Na^+$; dissociation constant = K_d

$D^- + H_2O \rightleftharpoons DH + OH^-$; hydrolysis constant = K_h

$2DH + A \rightleftharpoons$ complex (DH...A...DH); equilibrium constant = K'

Overall reaction:

$$2D^-Na^+ + 2H_2O + A \rightleftharpoons \text{complex (DH...A...DH)} + 2Na^+ + 2OH^-$$

Apparent formation constant (K) of the complex = $K_d^2 K_h^2 K'$

With increase in dielectric constant at a particular temperature the values of K' and K_h do not change appreciably but K_d increases remarkably. This explains the observed increase in the apparent K with increase in dielectric constant of the medium.

Results of Chapter V

(Complex formed between Vitamin B_6 and *p*-chloranil)

(a) Vitamin B_6 (pyridoxine hydrochloride) forms a charge transfer complex of 1:1 stoichiometry with *p*-chloranil in aqueous ethanol medium. The enthalpy and entropy of complexation are, in magnitude, like those of typical weak molecular complexes.

(b) The formation constant decreases regularly with increase in dielectric constant (water content) of the medium. This can be explained by assuming that pyridoxine hydrochloride ionizes and then hydrolyses and the free pyridoxine base acts as the donor in forming the CT complex.

(c) From the trends in CT absorption bands of complexes of vitamin B_6 with a series of electron acceptors the vertical ionization potential of vitamin B_6 has been estimated to be 8.12 eV.

Results of Chapter VI

(Complex formed between riboflavin and β-CD)

(a) In aqueous solution no charge transfer absorption band is shown by mixtures of riboflavin and β-cyclodextrin (β-CD). However, the absorption intensity of riboflavin in the visible range shows systematic change with gradual addition of β-CD.

(b) Fluorimetric titration indicates that molecular complexes of both 1:1 and 1:2 (riboflavin: β-CD) stoichiometry are formed in aqueous medium.

(c) Formation constant obtained from absorption spectrometric experiment indicates that the complex should be of inclusion type, riboflavin being included in β- CD.

Results of Chapter VII

The linear correlation between the DFT calculated LUMO energies of the quinone type acceptors and electronic transition energies of their complexes with cloxacillin sodium is in accordance with Mulliken's theory. The CT nature of the transitions is thus established.