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Spectrophotometric, FTIR and theoretical studies of the charge-transfer complexes between Lamotrigine and the acceptors (chloranilic acid, *o*-chloranil and dichlorodicyanobenzoquinone) in acetonitrile and their thermodynamic properties†

K. Sharma[a] and S. C. Lahiri[b]*

[a]Vivekananda Mahavidyalaya, Haripal, Hooghly, West Bengal, India

E-mail : ksharma71@yahoo.co.in

[b]Central Forensic Science Laboratory, 30, Gorachand Road, Kolkata-700 014, India

E-mail : sujitclahiri@yahoo.com *Fax* : 91-33-22849442

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Abstract : Lamotrigine, a well-known and extensively used antiseizure drug was found to form beautifully colored charge-transfer complexes with *o*-chloranil, chloranilic acid and dichlorodicyanobenzoquinone in acetonitrile. The absorption maxima of the complexes were 543 nm and 576 nm; 521 nm; 408 nm, 459 nm and 587 nm respectively (where Lamotrigine had no absorption but the acceptors had absorptions in these regions). The compositions of the complexes were determined to be 1 : 1 from the Job's method of continuous variations. FTIR spectra of the complexes and the corresponding acceptors were compared. The complexes showed considerable shifts in absorption peaks, change in intensities of the peaks and formation of new band probably due to H-bonding. The thermodynamic association constants of the complexes and other thermodynamic properties were determined spectrophotometrically taking D and A in stoichiometric ratios. The complex formations were found to be spontaneous and associated with negative changes of ΔG°, ΔH° and ΔS° values. The energies $h\nu_{CT}$ of the charge-transfer complexes and vertical ionization potential $I_D{}^V$ of Lamotrigine were compared with the theoretical values of $h\nu_{CT}$ obtained from HOMO and LUMO of the donors and acceptors calculated using Density Function Theory utilizing different basis sets. The agreement between the results can be regarded to be reasonable. Oscillator strengths and dipole strengths of the complexes were determined theoretically and experimentally and the limitations of the calculations were outlined. A physico-chemical approach has been put forward to explain the causes for the onset of seizures and suggest a probable molecular mechanism underlying the effects of Lamotrigine to counter seizures based on the physico-chemical properties of drugs.

Keywords : Charge-transfer complexes, DFT calculations, FTIR, Lamotrigine, vertical ionization potential.

Introduction

Drug target binding forces and the specific reversible binding of drug to a receptor or protein i.e. drug-receptor interactions are some fundamental aspects which determine the mechanism of drug action and can serve as useful model for drug design. The pharmacological response of a drug is regarded to be the ultimate consequence of a number of physico-chemical interactions between the drug and the functionally important molecules in living organisms known as 'receptors'[1]. Though a large number of physico-chemical interactions are involved but some of the interactions appear to play a vital role in understanding drug-receptor interactions. Drugs, in general (except in case of chemotherapeutic agents, antihelminthic agents etc.) do not form covalent or strong ionic bonds but some weak interactions like charge-transfer (CT), H-bonding, hydrophobic and van der Waal's interactions are responsible for drug-receptor interactions. These are important to understand drug action on the molecular level. The importance of charge-transfer and H-bonding interactions in different biological processes were emphasized by Mulliken[2], Syzent-Gyorgi and Korolkovas[3]. These considerations led Lahiri and co-workers[4] to undertake studies on charge-transfer and H-bonding interactions between

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drugs and various acceptor molecules. The enhanced antibacterial activities of amino-acridines with purine bases[5] and TCNQ complexes of floxacin groups of drugs[6], CT complexes of proline with thiamine in neuro conduction processes[7] are examples of the utility of CT complexes. Other important areas of applications of the CT complexes are :

(i) rechargeable batteries, photovoltaic and non-linear optical devices and solar cells, dendrimers and semiconductors[8],

(ii) kinetics of chemical reaction and photocatalysis[9].

But the major applications for which the charge-transfer complexes are known are the separation, identification and quantification of hydrocarbons, alkaloids, explosives and drugs[10]. Lamotrigine is an useful anticonvulsant drug used initially in the treatment of epilepsy[11] (consisting of different types of seizures including severe seizures like Lennex-Gastaut syndrome) and bipolar disorder (bipolar type I) or mood stabilizer (like lithium). The drug has several side effects too but the drug is currently much in use for the treatment of about all types of seizures. In view of its increasing uses, the determination of sensitive methods for the estimation of Lamotrigine in pharmaceutical dosage forms and urine samples etc. is of great importance. Recently, Alizadeh *et al.*[12] and Rajendraprasad *et al.*[13] suggested a method of spectrophotometric estimation of Lamotrigine in pharmaceutical dosage forms and in urine based on the formation of charge-transfer complexes between LTG with donors like bromocresol green (BCG), bromocresol purple (BCP) and chlorophenol red (CPR). The increasing use of Lamotrigine and the works of Alizadeh *et al.*[12] led us to study the charge-transfer complexes between the donor Lamotrigine (LTG) and the acceptors of *o*-chloranil (*o*-ClN), chloranilic acid (Cl-A), dichlorodicyanobenzoquinone (DDQ). Fortunately, all the acceptors gave beautifully colored complexes with Lamotrigine. The composition, the accurate association constants and thermodynamics of the complexes were determined spectrophotometrically. The correlation of the experimental CT energies obtained for the complexes with the theoretical energy values using DFT calculations utilizing different basis sets was made. It was also possible to prepare solid CT complexes between Lamotrigine with the acceptors by the simple addition of donor and acceptors in acetonitrile. The precipitated complexes were isolated, washed with acetonitrile, dried and FTIR spectra of the complexes were studied. Lastly, a physico-chemical approach has been put forward to explain the causes for the onset of seizures and suggest a probable molecular mechanism underlying the effects of Lamotrigine to counter seizures based on the physico-chemical properties of drugs. The results of our investigations are reported in this communication.

Materials and methods :

Lamotrigine (99.8% purity), obtained from Dr. (Ms.) N. Saha, Central Drug Laboratory, Kolkata was used without further purification. *o*-Chloranil (Fluka) 98%, chloranilic acid (Aldrich, Sigma R & D grade) 98% and DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) (Aldrich, Sigma R & D grade) 98% were used as such. Acetonitrile (ACN), dimethyl sulfoxide (DMSO) and other solvents were of HPLC grade from E. Merck. *o*-Chloranil in DMSO gave yellow color initially which turned violet with time. DDQ was found to interact with DMSO. Lamotrigine was found to be insoluble in water, alcohols etc. but it was found to be fairly soluble in DMSO and acetonitrile. But no interaction was observed for the acceptors in acetonitrile which made acetonitrile to be the desired solvent for the study of charge-transfer interactions between Lamotrigine with acceptors like *o*-chloranil, chloranilic acid and DDQ. When Lamotrigine (0.2552 g) in ACN (100 ml) was mixed with *o*-chloranil (0.2462 g) in ACN (100 ml), a dark colour was obtained. Lamotrigine (0.0256 g) in ACN (100 ml) when mixed with chloranilic acid (0.0209 g) in ACN (100 ml), a beautiful purple colour was observed. A red colouration was observed when Lamotrigine (0.0259 g) in ACN (100 ml) was mixed with DDQ (0.0231 g) in ACN (100 ml). The colored complexes of Lamotrigine with *o*-ClN, Cl-A and DDQ had absorption maxima at 543 nm and 576 nm; 521 nm; 408 nm, 459 nm and 587 nm respectively. But the peaks at 576 nm, 521 nm and 587 nm were selected for the absorption measurements to study the association constants and other thermodynamic parameters of LTG + *o*-ClN, LTG + Cl-A and LTG + DDQ complexes in acetonitrile solutions. At these wavelengths, the complexes absorbed strongly, LTG did not absorb but the acceptors had weak absorptions. The composition of the complexes were determined to be 1 : 1 from absorption measurements of solutions containing equimolar solutions of Lamotrigine and the desired acceptors successively in the ratios 2 : 8, 3 : 7, 4 : 6, 5 : 5, 6 : 4, 7 : 3 and 8 : 2 against the same concentrations of the respective acceptors in acetonitrile as blank solutions. The measurements of op-

tical densities of the experimental solutions were carried out at the wavelengths of maximum absorptions of the complexes at five different temperatures namely, 288 K, 293 K, 298 K, 303 K and 308 K respectively.

Shimadzu Double Beam UV-Visible spectrophotometer (Model UV 2550) fitted with Peltier controlled thermo-regulated cell compartment was used for spectrophotometric measurements. The analysis of the spectrophotometric data was made with UV-probe software. The absorbance data of CT complexes of Lamotrigine and different acceptors are given in Tables 1-3.

Preparation of solid complexes of Lamotrigine with the acceptors and FTIR measurement of the complexes :

Solid CT complex (1 : 1) of Lamotrigine with acceptors *o*-ClN, Cl-A and DDQ were prepared by mixing saturated solutions of the reactants in acetonitrile almost in the ratio 1 : 1 in small porcelain crucibles. Immediate red colored crystals of LTG + DDQ (1 : 1) separated out when the saturated solutions were mixed. Crystal was isolated, washed with little acetonitrile and dried. The crystal was placed under auto image

Table 1. Absorbance data for the CT complex between Lamotrigine + *o*-chloranil in acetonitrile against *o*-chloranil in acetonitrile at five different temperatures

Sl. no.	Conc. of LTG (10^{-3} mol dm^{-3})	Conc. of *o*-ClN (10^{-3} mol dm^{-3})	Absorbance at 576 nm at				
			288 K	293 K	298 K	303 K	308 K
1.	7.97	2.00	0.24218	0.2089	0.19713	0.18323	0.17324
2.	6.97	3.00	0.31448	0.30113	0.27324	0.24024	0.21659
3.	5.98	4.00	0.39981	0.34678	0.32455	0.30486	0.29218
4.	4.98	5.01	0.44173	0.42481	0.3859	0.3618	0.32964
5.	3.28	6.01	0.33991	0.3155	0.2965	0.27506	0 25439
6.	2.99	7.01	0.21452	0.18951	0.18466	0.1769	0.16947

Table 2. Absorbance for the CT complex between Lamotrigine + chloranillic acid against chloranilic acid in acetonitrile at five different temperatures

Sl. no.	Conc. of LTG (10^{-4} mol dm^{-3})	Conc. of Cl-A (10^{-4} mol dm^{-3})	Absorbance at 521 nm at				
			288 K	293 K	298 K	303 K	308 K
1.	7.01	3.00	0.40935	0.39836	0.38954	0.37279	0.36278
2.	6.01	4.01	0.51031	0.49864	0.46861	0.44969	0.43818
3.	5.01	5.01	0.59086	0.57288	0.53606	0.51288	0.49673
4.	4.01	6.01	0.50043	0.49843	0.48927	0.47652	0.46254
5.	3.00	7.01	0.37376	0.35605	0.3396	0.33936	0.32877
6.	2.00	8.01	0.2685	0.2653	0.26036	0.23141	0.23062

Table 3. Absorbance data for the CT complex between Lamotrigine + DDQ against DDQ in acetonitrile at five different temperatures

Sl. no.	Conc. of LTG (10^{-4} mol dm^{-3})	Conc. of Cl-A (10^{-4} mol dm^{-3})	Absorbance at 587 nm at				
			288 K	293 K	298 K	303 K	308 K
1.	4.06	1.02	0.24393	0.23299	0.22073	0.21447	0.20566
2.	3.55	1.52	0.31475	0.30952	0.29239	0.28274	0.27645
3.	3.05	2.03	0.42254	0.40222	0.38522	0.37158	0.36502
4.	2.54	2.54	0.43523	0.42596	0.41342	0.39985	0.39156
5.	2.03	3.05	0.38208	0.36318	0.34262	0.3351	0.32848
6.	1.52	3.55	0.28059	0.27095	0.25305	0.24513	0.23892
7.	1.02	4.06	0.1637	0.1571	0.15099	0.14889	0.1392

microscope to get the magnified image of the crystal and FTIR spectra of the crystal at a number of points were taken to get the IR spectra of the complex. In other cases, mixtures were kept overnight. Purple colored 1 : 1 complex of LTG + Cl-A was precipitated in acetonitrile solution. The complex was filtered out, washed with little acetonitrile and dried. But in case of LTG + *o*-ClN mixture, dark red complex was observed. The solvent was evaporated to get red colored complex in the middle with other ingredients. The complex was scooped out, washed with little acetonitrile. The solvent was decanted and the complex was dried.

FTIR spectra of the complexes of LTG + *o*-ClN and LTG + Cl-A were taken using KBr pellets. However complete purification of the complexes were not possible due to paucity of Lamotrigine at our disposal. Moreover, saturated solutions of Lamotrigine and acceptors did not have the same concentrations. Naturally, the complex obtained contained a little Lamotrigine and acceptors. But IR studies could be done without difficulties.

FTIR measurements were carried out by Perkin-Elmer Spectrum GX FTIR system with auto image microscope having MCT detector working at 77 K. The scan range was 4000–700 cm^{-1} having a resolution of 4 cm^{-1}. The spectra were the averages of sixteen scans. Further scans did not improve the results.

Results

LTG was found to form 1 : 1 complexes with the acceptors from the Job's method of continuous variations (Fig. 1).

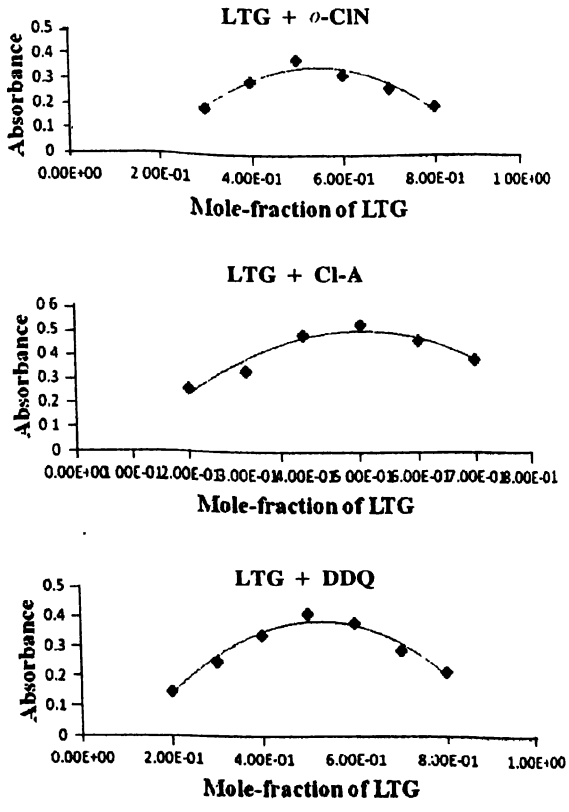


Fig. 1. Job's method of continuous variation (plot of absorbance vs mole-fraction).

The association constant K_{DA} for the reaction

$$D + A = DA \quad (1)$$

can be represented as

$$K_{DA} = \frac{[DA]_{eq}}{[D]_{eq}[A]_{eq}} \times \frac{\gamma_{DA}}{\gamma_D \times \gamma_A} \approx \frac{[DA]_{eq}}{[D]_{eq}[A]_{eq}} \quad (2)$$

$\left(\frac{\gamma_{DA}}{\gamma_D \times \gamma_A}\right.$ can be taken to be unity for the reaction involving neutral molecules at low concentrations).

Taking c_1, c_2 and x to be the initial concentrations of D, A and equilibrium concentration of DA, the [eq. (2)] can be written as

$$K_{DA} = \frac{x}{(c_1 - x)(c_2 - x)} \quad (3)$$

Under the condition of the experiment, Lamotrigine did not absorb in the region of measurement though slight absorption was observed for [A]. The measurements of the optical densities of the experimental solutions were made against the respective blank solutions [containing the same concentration of A as were present in the experimental solutions]. The [eq. (3)] can thus be changed to

$$\frac{c_1}{x} = 1 + \frac{1}{K_{DA}(c_2 - x)} \quad (4)$$

or,

$$\frac{c_1}{d} = \frac{1}{\varepsilon l} + \frac{1}{K_{DA}(c_2 - x)\,\varepsilon l} \quad (5)$$

where d and ε were the optical density and extinction coefficient of the experimental solutions and the complex respectively.

The equation is akin to Benesi-Hildebrand[14] equation but not under conditions D ≫ A. In the present experiment, D and A were almost in stoichiometric ratios. K_{DA} and ε values were obtained using the process of iteration taking $x = 0$ initially. Enthalpy changes of reaction (1) (for the different acceptors) were obtained from the slope of the plot of log K_{DA} against $1/T$ using Van't Hoff equation (Fig. 2) assuming C_P to be constant in the range of temperature (288–308 K) used. ΔG^o and ΔS^o were obtained from the relations

$$\Delta G^o = -RT \ln K \quad (6)$$

and

$$\Delta G^o = \Delta H^o - T\Delta S^o \quad (7)$$

The results are presented in Table 4.

Discussion

Structures of Lamotrigine, *o*-chloranil, chloranilic acid and dichlorodicyanobenzoquinone given in Fig. 3 show that the aza aromatics are capable of both $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. Hydrogen bonding capabilities and hydrophobic interactions of LTG with two -NH_2 groups

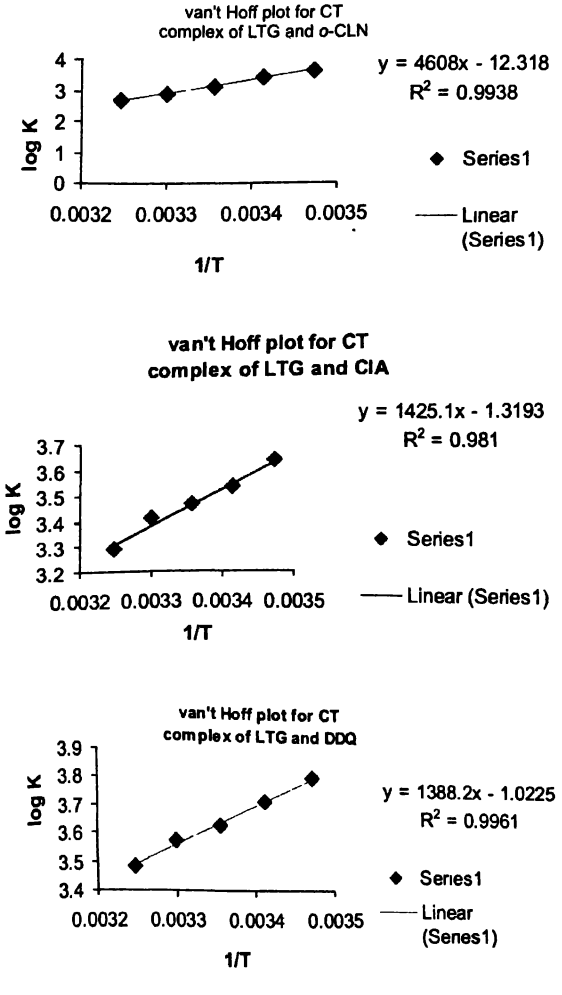


Fig. 2. Van't Hoff plots for different CT complexes of Lamotrigine with different acceptors like *o*-chloranil (*o*-ClN), chloranilic acid (Cl-A) and dichlorodicyanobenzoquinone (DDQ).

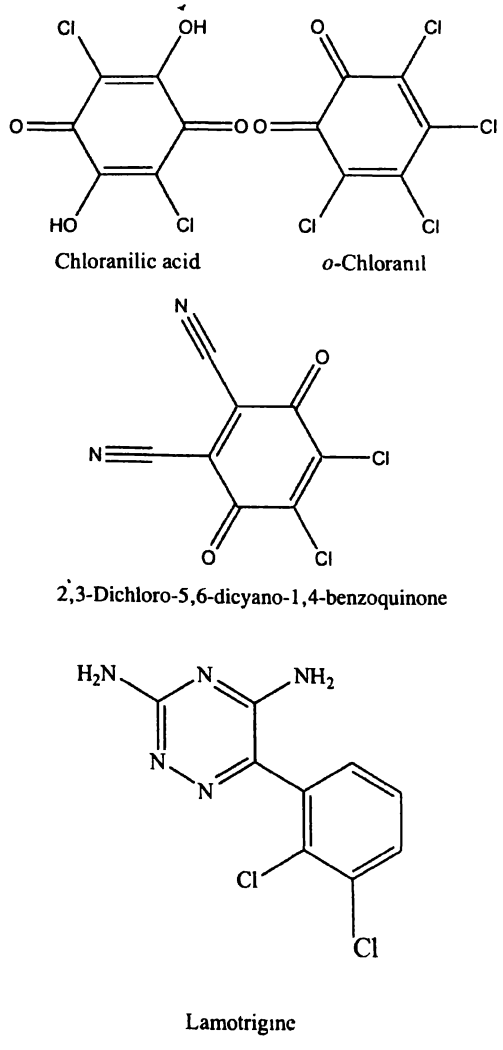


Fig. 3. Structures of chloranilic acid, *o*-chloranil, DDQ and Lamotrigine.

Table 4. Association constants (K_{AD}), extinction coefficients (ε), Gibbs energy changes ($\Delta G°$), enthalpies ($\Delta H°$) and entropies ($\Delta S°$) of formation of the CT complexes of Lamotrigine with different acceptors

Acceptor	Temp. (K)	K_{AD} × (10^3 mol dm^{-3})	ε (dm^3 mol^{-1} cm^{-1})	$\Delta G°$ (kJ mol^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (JK^{-1} mol^{-1})
o-ClN	288	4.57 ± 0.05		-20.18		
	293	2.86 ± 0.02		-19.39		
	298	1.38 ± 0.03	87.23	-17.91 ± 0.12	-88.23 ± 0.01	-235.84 ± 0 12
	303	0.72 ± 0.03		-16.57		
	308	0.46 ± 0.04		-15.69		
Cl-A	288	4.27 ± 0.04		-20.18		
	293	3.39 ± 0.05		-19.39		
	298	2.94 ± 0.03	2101.89	-19.79 ± 0.08	-27.29 ±0.01	-25.26 ± 0.08
	303	2.57 ± 0.04		-19.78		
	308	1.94 ± 0.04		-19.40		
DDQ	288	6.31 ± 0.03		-20.95		
	293	5.16 ± 0.05		-20.83		
	298	4.26 ± 0.04	3300.22	-20.70 ± 0.10	-26.58 ± 0.01	-21.95 ± 0.10
	303	3.73 ± 0.03		-20.71		
	308	3.02 ± 0.03		-20.52		

make the compounds insoluble in hydroxylic solvents. DMSO interacted with some of the acceptors like DDQ, *o*-chloranil etc. to give colored solutions whose intensities changed with time. Acetonitrile was found to be an ideal solvent for the study of CT complexes. The absorption maxima of the acceptors and Lamotrigine in acetonitrile are given in Table 5.

Table 5. Absorption maxima of LTG, *o*-ClN, Cl-A and DDQ in acetonitrile

Name of the compound	Absorption peaks (nm)	Type of transition
Lamotrizine	258.5	$\pi \rightarrow \pi^*$
	305.0	$n \rightarrow \pi^*$
o-Chloranil	439.0	$n \rightarrow \pi^*$
Chloranilic acid	438.0	$n \rightarrow \pi^*$
DDQ	373.0	-
	547.5	$\pi \rightarrow \pi^*$
	589.0	$n \rightarrow \pi^*$

Charge-transfer complexes and determination of vertical ionization potential ($I_D{}^V$) of Lamotrigine from the experimental results :

The beautifully colored complexes between Lamotrigine and the acceptors were charge-transfer complexes and were established from the plots of $h\nu_{CT}$ (transition energy) of the complexes against $E_A{}^V$ (vertical electron affinity of the acceptors) in accordance to the relation

$$h\nu_{CT} = I_D{}^V - E_A{}^V - W \qquad (8)$$

(McConnell-Ham-Platt equation)[15]

Here $I_D{}^V$ and W are vertical ionization potential of the donor and the dissociation energy of the charge-transfer complex in the excited state. $E_A{}^V$ s, the vertical electron affinity of the acceptors were obtained from DFT calculations[16].

Experimental energy $h\nu_{CT}$ values of the complexes were compared with the theoretical $h\nu_{CT}$ (HOMO-LUMO) values from DFT calculations using different basis sets. The results given in Table 6 agree well considering the limitations of the calculations. The energy values calculated using different basis sets vary considerably. It is apparant from the table that calculations based on B3LYP and TD-LSDA level of theories do not give desired results and can be discarded.

However, true ionization energy values (I_D and E_A) are the energies involved in the transition of electron from the outermost orbital (HOMO) to infinity or from

Table 6. Comparison of the theoretical energy values [$(h\nu_{CT})_{theo}$] of the CT complexes utilizing DFT calculations with their corresponding experimental energy values [$(h\nu_{CT})_{exp}$]

Name of the compound	Level of theory	Basis set	$[(h\nu_{CT})_{theo}]$ (eV)	Abs. peak (nm)	$[(h\nu_{CT})_{exp}]$ (eV)
LTG + *o*-ClN	B3LYP	6-31G(d)	0.468	576	2.15
	TD-LSDA	6-31G(d)	-0.813		
	TD-B3LYP	3-21G(d)	0.650		
	TD-B3LYP	6-31G(d)	0.942		
	TD-B3LYP	6-311G(d,p)	0.946		
	TD-B3PW91	6-31G(d)	0.881		
LTG + Cl-A	B3LYP	6-31G(d)	0.510	521	2.381
	TD-LSDA	6-31G(d)	-0.511		
	TD-B3LYP	3-21G(d)	1.119		
	TD-B3LYP	6-31G(d)	1.204		
	TD-B3LYP	6-311G(d,p)	1.200		
	TD-B3PW91	6-31G(d)	1.156		
LTG + DDQ	B3LYP	6-31G(d)	-0.531	587	2.11
	TD-LSDA	6-31G(d)	-0.1.499		
	TD-B3LYP	3-21G(d)	0.030		
	TD-B3LYP	6-31G(d)	0.237		
	TD-B3LYP	6-311G(d,p)	0.239		
	TD-B3PW91	6-31G(d)	0.177		

infinity to HOMO or LUMO. These are adiabatic ionization potential (I_D^{Ad}) and adiabatic electron affinity (E_A^{Ad}). The true values of ionization energies I_D^{Ad} and E_A^{Ad} can be obtained from photoionization experiments supported by mass-spectrophotometric identification of product ions[17]. In absence of these values, attempts were made to determine true ionization potentials (I_D^{Ad}) and electron affinities theoretically using DFT (with limitations) from the energy differences of (i) Lamotrigine and its cation and (ii) acceptors and their anions. I_D^{Ad} and E_A^{Ad} values are included in Table 7 for comparison. In case of charge-transfer complexes, I_D^V and E_A^V as used by Mulliken is a better approximation than the use of I_D^{Ad} and E_A^{Ad} utilized by Ichida *et al.*[18] in calculating $h\nu_{CT}$ of CT complexes. In the formation of CT complexes, complete transfer of charges is not a reality and only partial charge transfers are involved.

For the determination of I_D^V or E_A^V, the theoretical eqs. (9 and 10) suggested by Mulliken[2] was used. The equations are :

$$h\nu_{CT} = I_D^V - C_1 + \frac{C_2}{I_D^V - C_1} \qquad (9)$$

where $C_1 = E_A^V + G_1 + G_0$

The equation is rearranged to

$$h\nu_{CT} = -E_A^V + C_3 + \frac{C_2}{C_3 - E_A^V} \qquad (10)$$

where

$$C_3 = I_D^V - G_1 - G_0 \qquad (11)$$

G_0 is the binding energy of no-bond function in the ground state and the binding is due to physical forces like dipole-dipole, dipole-induced dipole interactions, London dispersion forces and hydrogen bonding interactions etc. In view of the difficulties of calculations of these small physical forces, G_0 is usually assumed to be zero. G_1 is the energy of the "dative" structure of the complex corresponding to the complete transfer of one electron from donor to the acceptor. G_1 is mainly electrostatic energy of attraction between D^+ and A^- and is equal to $e^2/4\pi\varepsilon_0 r = 4.13$ eV, taking the typical D–A distance 3.5 Å as used by various workers in this field[19] and 3.4 Å used by Mulliken[2] for benzene-iodine complex. The term C_2 is related to the resonance energy of interaction between the no-bond and the dative interaction between the "no-bond" and the dative forms in the ground and excited states and is assumed to be constant for a given donor.

The [eqs. (9 and 10)] can be rearranged to

Table 7. Comparison of electron affinity values of different acceptors and ionization potential values of LTG using differences in energy values of the acceptor and the corresponding anions [E_A^{Ad}] and that of the LTG and its cation [I_D^{Ad}]; and using Mulliken's theorem [E_A^V and I_D^V]; and Koopman's theorem [E_A^V (Koop) and I_D^V (Koop)] considering both the complete transfer of electron (G_1 = 4.13) and the partial transfer of electrons (G_1') which are different for different acceptors

Level of theory and basis set/ acceptors	Electron affinity of acceptors (eV)			Ionization potential of Lamotrigine (eV)								
				Theoretical			Calculated from the experimental data					
	E_A^{Ad}	E_A^V	E_A^V (Koop)	I_D^{Ad}	I_D^V	I_D^V (Koop)	I_D^{Ad} (considering G_1 = 4.13)	I_D^V	I_D^V (Koop)	I_D^{Ad} (considering partial charge-transfer G_1')	I_D^V	I_D^V (Koop)
TD-LSDA/6-31G(d)												
o-ClN	4.62	0.29	7.02							6.05	**1.40**	8.55
Cl-A	4.16	0.66	6.72	*10.61*	**2.24**	6.21	*10.13*	5.48	12.63	6.13	**1.48**	8.63
DDQ	5.28	0.54	7.71							6.09	**1.48**	8.59
TD-B3LYP/3-21G(d)												
o-ClN	3.81	2.00	5.52							6.06	**4.32**	7.98
Cl-A	3.10	2.54	5.05	*8.16*	**4.15**	6.16	*9.09*	7.34	11.01	6.67	**4.98**	8.61
DDQ	4.30	2.42	6.13							6.14	**4.40**	8.06
B3LYP/6-31G(d)												
o-ClN	3.81	1.86	5.61							6.51	**4.00**	8.25
Cl-A	3.78	2.32	5.57	*10.07*	**4.80**	6.08	*9.67*	7.16	11.41	6.75	**4.24**	8.49
DDQ	4.95	2.27	6.61							6.45	**3.94**	8.19
TD-B3LYP/6-31G(d)												
o-ClN	4.08	1.77	5.94							6.57	**3.89**	8.33
Cl-A	3.89	2.32	5.68	*8.71*	**4.39**	6.88	*9.81*	7.13	11.57	6.92	**4.24**	8.68
DDQ	4.98	2.24	6.64							6.61	**3.93**	8.37
TD-B3LYP/6-311G(d,p)												
o-ClN	4.35	1.76	5.98							6.59	**3.86**	8.32
Cl-A	3.94	2.31	5.72	*8.71*	**4.37**	6.92	*9.90*	7.13	11.62	6.98	**4.22**	8.71
DDQ	5.01	2.24	6.69							6.67	**3.93**	8.42
TD-B3PW91/6-31G(d)												
o-ClN	4.35	1.78	5.98							6.61	**3.86**	8.33
Cl-A	3.92	2.32	5.71	*8.71*	**4.35**	6.86	*9.89*	7.13	11.61	6.98	**4.22**	8.70
DDQ	5.03	2.24	6.69							6.61	**3.91**	8.39

$$2I_D^V - h\nu_{CT} = \frac{1}{C_1} I_D^V (I_D^V - h\nu_{CT}) + \left(C_1 + \frac{C_2}{C_1}\right) \quad (12)$$

and

$$2E_A^V + h\nu_{CT} = \frac{1}{C_3} E_A^V (E_A^V + h\nu_{CT}) + \left(C_3 + \frac{C_2}{C_3}\right) \quad (13)$$

respectively.

A plot of $(2E_A^V + h\nu_{CT})$ against E_A^V $(E_A^V + h\nu_{CT})$ (presented in the Figs. 4, 5 and 6) gave $\frac{1}{C_3}$ (slope) and $\left(C_3 + \frac{C_2}{C_3}\right)$ (intercept). From the C_3 value, I_D^V value calculated using the [eq. (11)] given in Table 7 is compared with the values obtained theoretically. The values are obviously different using different basis sets but the agreement appears to be reasonably good assuming the limitations involved in the calculation.

Mulliken considered G_1 to be small due to large dis-

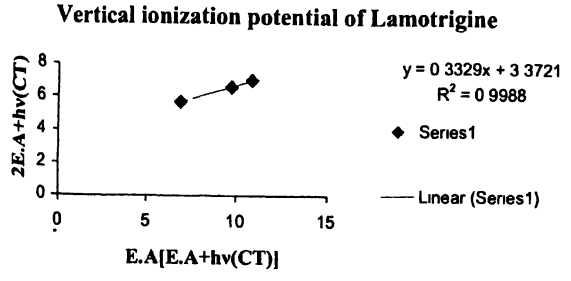


Fig. 4. Plot of $(2E_A^V + h\nu_{CT})$ against E_A^V $(E_A^V + h\nu_{CT})$ [using DFT by TD-B3LYP level of theory with 6-31G(d) basis set].

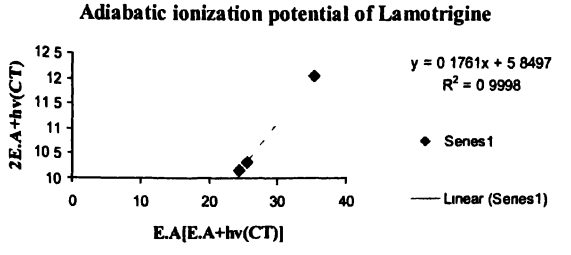


Fig. 5. Plot of $(2E_A^{Ad} + h\nu_{CT})$ against E_A^{Ad} $(E_A^{Ad} + h\nu_{CT})$ [using DFT by TD-B3LYP level of theory with 6-31G(d) basis set].

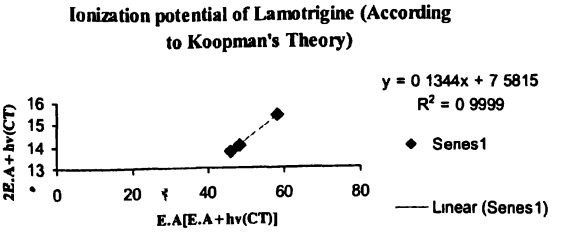


Fig. 6. Plot of $(2E_A^V + h\nu_{CT})$ against E_A^V $(E_A^V + h\nu_{CT})$ [according to Koopman's theory, using DFT by TD-B3LYP level of theory with 6-31G(d) basis set].

tance of separation of charges. G_1 was calculated considering the complete transfer of electron from donor (D) to acceptor (A), an absurdity in itself, rather partial transfer of charges (δe^+ and δe^-) should be considered.

The expression for G_1 (written as G_1') should be

$$G_1' = \frac{(\delta e^+)(\delta e^-)}{4\pi\varepsilon_0 r} \qquad (14)$$

Here, δe^+ = fraction of the total charge of LTG =

$$\frac{\text{Energy change (HOMO–LUMO)}}{\text{Total energy change due to LTG} \rightarrow \text{LTG}^+}$$

and δe^- = fraction of the total charge of the acceptors =

$$\frac{\text{Energy change (LUMO–HOMO)}}{\text{Total energy change due to A} \rightarrow \text{A}^-}$$

HOMO and LUMO energies of LTG and acceptors may be utilized following Koopman[20] to calculate the partial charges. The value of partial charges calculated for LTG, *o*-ClN, Cl-A, DDQ are presented in Table 8.

Table 8. Fraction of charges δe^+ and δe^- of the molecules LTG, *o*-ClN, Cl-A and DDQ obtained from DFT (using different level of theories and basis sets)

Level of theory	Basis set	% of charge-transfer			
		LTG	*o*-ClN	Cl-A	DDQ
B3LYP	6-31G(d)	47.67	48.82	61.38	45 86
TD-LSDA	6-31G(d)	21.11	6.28	15.86	10.23
TD-B3LYP	3-21G(d)	50.86	52.49	81.93	56.28
TD-B3LYP	6-31G(d)	50.41	43.38	59.64	44.98
TD-B3LYP	6-311G(d,p)	50.17	40.46	58.63	44 71
TD-B3PW91	6-31G(d)	49.94	40.92	59.18	44 53

Thus, G_1' values, presented in Table 9 should be different for different complexes and were utilized to calculate E_A^V and I_D^V using the relations are also presented in Table 7. From the different I_D^V values using different methods it is observed that the experimental vertical ionization potential of Lamotrigine is closer to the theoretical vertical ionization potential considering partial charge transfer than that of the total charge transfer and therefore the vertical ionization potential of Lamotrigine also differs in different charge-transfer complexes according to the nature of the acceptors.

Calculation of the degree of charge-transfer (α) :

In Mulliken's model, the ground ψ_N (DA) and excited ψ_E (DA) state wave functions are described by a linear combination of dative ψ_N (DA) and ionic ψ_E (D^+–A^-) states.

$$\begin{aligned}\psi_N(\text{DA}) &= a\,\psi_0(\text{DA}) + b\,\psi_E(\text{D}^+ - \text{A}^-) \\ &= (1-\alpha)^{1/2}\psi_0(\text{DA}) \\ &\quad + \alpha^{1/2}\psi_E(\text{D}^+ - \text{A}^-) \end{aligned} \qquad (15)$$

and

$$\begin{aligned}\psi_E(\text{DA}) &= a^*\psi_1(\text{D}^+\text{–A}^-) - b^*\psi_0(\text{DA}) \\ &= (1-\alpha)^{1/2}\psi_E(\text{D}^+ - \text{A}^-) \\ &\quad - \alpha^{1/2}\psi_0(\text{DA}) \end{aligned} \qquad (16)$$

where α is the degree of charge-transfer. α can be ob-

tained from the relation

$$\alpha = C_2/[2(I_D{}^V - E_A{}^V + C_1)^2 + C_2] \quad (17)$$

The α values for different CT complexes of Lamotrigine are presented in Table 9.

the half-width or the width of the band at half the maximum extinction.

The transition dipole defined as $-e \int \psi_E \Sigma r_i \psi_N d\sigma$ is related to ε_{max} and ν_{max} by the relation

Table 9. Comparison chart for the degrees of charge-transfer (α), W (W_1 and W_2) and the G_1 values considering the partial-transfer of charges in the CT complex formation (G_1')

Name of the compound	Level of theory	Basis set	$\alpha \times 10^3$	W (KJ mol^{-1})		
				W_1	W_2	
LTG + *o*-ClN	TD-LSDA	6-31G(d)	21.88	-395.86	-110.08	0 052
	TD-B3LYP	3-21G(d)	19.66	-414.96	-270.24	1 095
	B3LYP	6-31G(d)	20.91	-491.76	-329.48	0.97
	TD-B3LYP	6-31G(d)	25.04	-460.40	-343.86	0.89
	TD-B3LYP	6-311G(d,p)	26.33	-456.44	-343.27	0.83
	TD-B3PW91	6-31G(d)	25.82	-456.54	-334.11	0.85
LTG + Cl-A	TD-LSDA	6-31G(d)	18.57	-382.35	-103.43	0.13
	TD-B3LYP	3-21G(d)	13.01	-384.96	-263.29	1 727
	B3LYP	6-31G(d)	17.46	-469.57	-289.05	1 209
	TD-B3LYP	6-31G(d)	19.18	-429.82	-314.55	1 239
	TD-B3LYP	6-311G(d,p)	19.48	-428.37	-308.16	1 218
	TD-B3PW91	6-31G(d)	19.44	-426.25	-308.16	1 218
LTG + DDQ	TD-LSDA	6-31G(d)	20.30	-367.49	-19.20	0 087
	TD-B3LYP	3-21G(d)	18.50	-370.48	-169.81	1 180
	B3LYP	6-31G(d)	21 89	-447 86	-193.06	0 912
	TD-B3LYP	6-31G(d)	24.26	-410.91	-230.11	0 929
	TD-B3LYP	6-311G(d,p)	24.28	-406.47	-225.96	0 929
	TD-B3PW91	6-31G(d)	24.61	-407.24	-220.75	0 909

Determination of oscillator strengths (f) and the transition dipole moments (μ_T) of the complexes[21] :

The oscillator and dipole moment strengths of the complexes were determined from the relations

$$f = 4.32 \times 10^{-9} . \int \varepsilon dv \quad (18)$$

where $\int \varepsilon dv$ is the area under the curve of the extinction coefficient of the absorption band in question vs the frequency. This can be approximately taken to be equal to

$$f = 4.32 \times 10^{-9}\, \varepsilon_{max} . \Delta\nu_{1/2} \quad (19)$$

ε_{max} = the maximum extinction of the band and $\Delta\nu_{1/2}$ is

$$\mu_T = 0.0958 \left[\frac{\varepsilon_{max} . \Delta\nu_{1/2}}{\nu_{max}} \right]^{1/2} \quad (20)$$

The values f and μ_T for the complexes are presented in Table 10.

ε_{max}, determined from the intercept of the plot of $1/(c_2 - x)$ vs c_1/d was used to calculate f and μ_T. However f values determined from eqs. (18 and 19) were different. The areas of the absorption curves of the complexes were very much dependent on ε-values of the complexes (obviously ε-values were not ε_{max} values). The true values of

Table 10. Absorption maxima (λ_{max}), ν_{max}, $\Delta\nu_{half}$, oscillator strength f (f_1 [from eq. (15)] and f_2 [from eq. (16)]), transition dipole moments (μ_{ET}) and degrees of overlap (b^2/a^2) values of CT complexes between LTG and different acceptors

CT complex	λ_{max} (nm)	ν_{max} (cm^{-1})	$\Delta\nu_{half}$ (cm^{-1})	f		μ_{ET}	b^2/a^2
				f_1	f_2		
LTG + *o*-ClN	576	17361.11	2800.53	0.00025	0.001	0.359	0.43
LTG + Cl-A	521	19193.86	4864.98	0.00037	0.044	2.212	0.12
LTG + DDQ	587	17035.78	1769.97	0.00026	0.025	1.774	0.13

the oscillator strengths can hardly be determined from $\int \varepsilon dv$ as the areas of the curves change with change in the concentrations of the complexes. In case of CT complexes, total complex formation is not a reality even if D ≫ A, uncertainty exists in observed ε_{max} values using Benesi-Hildebrand equation and the half band-width $\nu_{1/2}$ cannot be obtainable for the concentration where $\varepsilon = \varepsilon_{max}$. Only in rare cases like TNT with aliphatic amines[22], metal to ligand charge transfer complexes like ferroin and related complexes[23], ε_{max} can be directly determined. Moreover, due to overlapping of CT bonds by other bands, the CT bands in many cases are poorly resolved. Thus, the values of f and μ_T should be treated with caution.

Association constants of the complexes and the related thermodynamic properties :

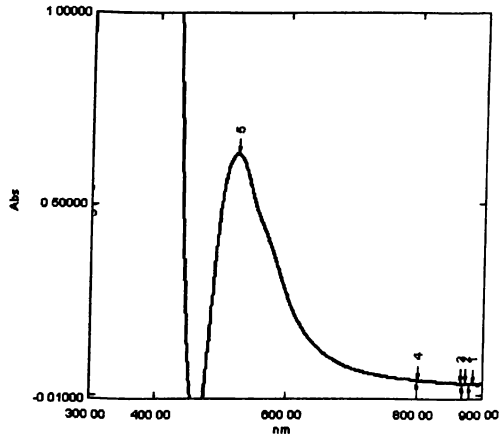
The complexes formed between LTG and the acceptors were found to be fairly stable as would be apparent from K_{DA} and ε (extinction coefficient) of the complexes reported in Table 4. The UV-Visible spectra of LTG with the acceptors are shown in Fig. 7.

However, the K_{DA} may be solvent dependent as solute-solute interaction is a universal phenomenon in all solvation processes. Naturally, complex formation between A or D with solvents to form [AS] or [DS] may be possible. Complex formation between chloranil with solvents like benzene, chloroform etc. in heptane was reported[24]. The variations of K_{DA} with solvents were also studied by Lahiri and co-workers[25]. Assuming complex formation between A or D with solvents (S), the true values of the association constants K_{DA} should be written as

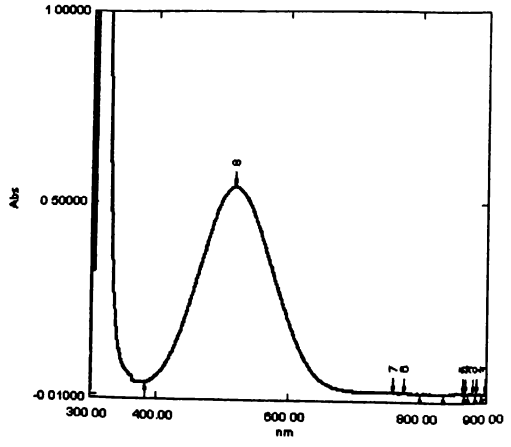
$$K_{DA}\text{ (corrected)} = K_{DA}\text{ (observed)}[1 + K^{S}_{AS}(S)][1 + K^{S}_{DS}(S)] \quad (21)[26]$$

The effect of the complex formation between the acceptors with solvent, if any, was eliminated. The blank solutions contained the same concentrations of the acceptors as they were present in the experimental solutions and LTG did not absorb in this region. Moreover, no detectable complex formation was observed between LTG and the acceptors with acetonitrile.

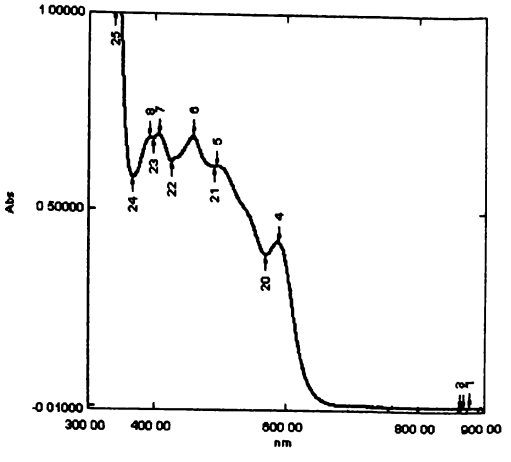
The possibility of termolecular or isomeric complex formations can not be ruled out under conditions where D ≫ A (B-H equation). K_{DA} calculated using D ≫ A and D and A in stoichiometric ratios differ considerably[27]. Comparison of the results from the determination of as-



Spectrum 1



Spectrum 2



Spectrum 3

Fig. 7. The UV-Visible spectra of LTG with *o*-ClN (Spectrum 1), LTG with Cl-A (Spectrum 2) and LTG with DDQ (Spectrum 3) respectively at 298 K.

sociation constants K_{DA} of complexes under various conditions and using different methods led Foster[28] to conclude that more weight should be given to K_{DA} values obtained from optical data when [D] = [A]. K_{DA} values obtained from NMR shift data though had been adjuged to be the best but K_{DA} values using NMR data are few. But whatever may be the method, K_{DA} values can in no way be regarded to be thermodynamic when D ≫ A. D ≫ A means forcing A to combine with D to have measurable concentration of the complex x. Thus, with increase in the concentration of D, x and $x/(c_2 - x)$ increase but c_1 also increases. Thus, the association constant $K_{DA} = x/c_1(c_2 - x)$ will almost be close to $1/c_1$ with slight variations[29]. The observation is corroborated from the values of K_{DA} in the literature[28]. Thus K_{DA} values determined by us can be regarded to be accurate thermodynamic data as D and A were in stoichiometric ratios.

Thermodynamics of Lamotrigine complexes :

Accurate thermodynamic data are few for CT complexes and most of the data determined spectrophotometrically are based on Benesi-Hildebrand equation using D ≫ A. Obviously the values are inaccurate. K_{DA} values of LTG with *o*-ClN, Cl-A, DDQ were fairly high indicating the stability of complexes. These were substantiated by fairly high exothermic enthalpy changes (ΔH^o) and negative entropy changes (ΔS^o) indicating good overlap between the donor and the acceptors in the excited state and probably also to some extent in the ground state. Degree of overlap (α) and $b^2/a^2 = -\frac{\Delta H^o}{h\nu_{CT}}$ calculated also corroborated the findings presented in Table 9 and Table 10 respectively.

The negative entropy values indicated an ordered system where more mobilization of solvent molecules around the complexes compared to those in D and A were supposed to take place.

The facts indicated that complexes were fairly stable $\pi \rightarrow \pi^*$ complexes having fairly good contribution of the ground state structure. A relationship between the stability of the complex and the intensity of the CT band is expected according to Mulliken's theory; the more stable the complex the more intense the band. This is found to be true with Lamotrigine complexes. But the conclusion cannot be correlated with the calculated oscillator strengths though the experimental values differ for the reasons cited before.

An attempt has been made to interpret the thermodynamics in a different way. CT complexes can be regarded to be akin to electrovalent compounds with differences. Here, partial transfer of charges occur mainly in the excited state with energy changes given by the relationship

$$h\nu_{CT} = I_D{}^V + E_A{}^V + W \qquad (22)$$

(with proper signs)

similar to the energy changes associated with the formation of electrovalent compounds with corresponding values.

$$\Delta H^o{}_{lattice} = I_P{}^o + E_A{}^o + \Delta H_f{}^o \qquad (23)$$

(algebraic addition with proper sign of $I_P{}^o$, $E_A{}^o$ etc.).

$h\nu_{CT}$ is akin to $\Delta H^o{}_{lattice}$, W is akin to $\Delta H_f{}^o$. $\Delta H_f{}^o$ is heat of formation, a combination of energy values arising from a number of unknown forces for stabilization of the molecule and could not be properly analyzed. Similarly W represents unknown forces of stabilization of the complex which includes electrostatic interactions besides the weak physical and van der Waal's forces like ion-dipole, dipole-dipole, dipole-induced dipole, hydrogen bonding etc. The [eq. (23)] does not include the contributions (though very small) due to no bond structure. However, in the complex formation, there must be energy changes for stabilization due to resonance hybridization of two wave functions. W values obtained from experimental $h\nu_{CT}$ values (W_1) differed from those using theoretical $h\nu_{CT}$ values (W_2) (Table 9).

The differences in ΔH^o of the complexes must be due to differences in energies due to electrostatic forces associated with other physical forces and entropy changes due to spatial or configurational changes of the reactants to form complexes. However, nothing positive could be said regarding these effects and these are not reflected in ΔG^o – values of the complexes due to compensation effects.

Interpretaion of IR spectra :

The formation and isolation of beautifully colored complexes of Lamotrigine with the acceptors (*o*-ClN, Cl-A and DDQ) gave enough indication of CT complex formation. The magnified pictures of Lamotrigine,

Lamotrigine + chloranilic acid and Lamotrigine + DDQ using auto-image microscope are presented in Figs. 8, 9 and 10 respectively.

FTIR measurements of the CT complexes were made

Fig. 8. Magnified picture of white amorphous Lamotrigine.

Fig. 9. Magnified picture of violet colored LTG and chloranilic acid CT complex crystal.

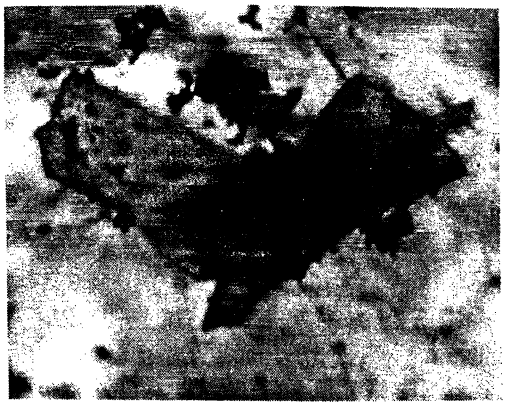


Fig. 10. Magnified picture of brown colored LTG and DDQ CT complex crystal.

to study IR characteristics of the CT complexes. The complex formations are usually accompanied by

(i) formation of new absorption peaks,

(ii) frequency shifts of IR bands of Lamotrigine and the acceptors,

(iii) change in the intensity of the absorption bands.

All the characteristic features mentioned above were observed, as would be apparent from the IR spectra (Figs. 11, 12 and 13) of Lamotrigine, the acceptors and their complexes. In general, the intensity of most of the bands are modified but emphasis was made regarding the formation of new bands due to complex formations and shifts or disappearance of the absorption bands of Lamotrigine and the acceptors. These are presented in tabular forms (Table 11).

In case of LTG + *o*-ClN CT complex new peak appears at 3208.75 cm^{-1} indicating the presence of >N-H····O=C< bond[30] and the disappeared peaks indicate that the stretching mode of >C=O and corresponding C-C and C-Cl of *o*-chloranil as well as the stretching of $-NH_2$ group of triazine ring of Lamotrigine are hindered. For LTG + Cl-A CT complex new peak appears at 3143.22 cm^{-1} indicating the presence of >N-H····O=C< bond and the disappeared peaks indicate that the stretching of $-NH_2$ group of triazine ring of Lamotrigine is hindered. In case of LTG + DDQ CT complex new peak appears at 3156.95 cm^{-1} indicating the presence of >N-H.....O=C< bond and the disappeared peaks indicate that the stretching mode of >C=O and corresponding C-C and C-Cl of DDQ as well as the stretching of $-NH_2$ group of triazine ring of Lamotrigine are hindered.

It is to be noted that IR spectra of the complexes are regarded to be the superimposition of spectra of the components LTG and acceptors. However, the spectra of the complex can be obtained by computer subtraction of the spectra of the components from the respective complexes. These are presented in Figs. 14, 15 and 16 respectively. The spectra show new peaks, shift in peaks and disappearance of peaks of LTG and the acceptors in consonance with the observations previously reported.

The concentration of LTG in saturated solutions was always less than that of saturated solution of any acceptor in acetonitrile and the residual solutions after complex

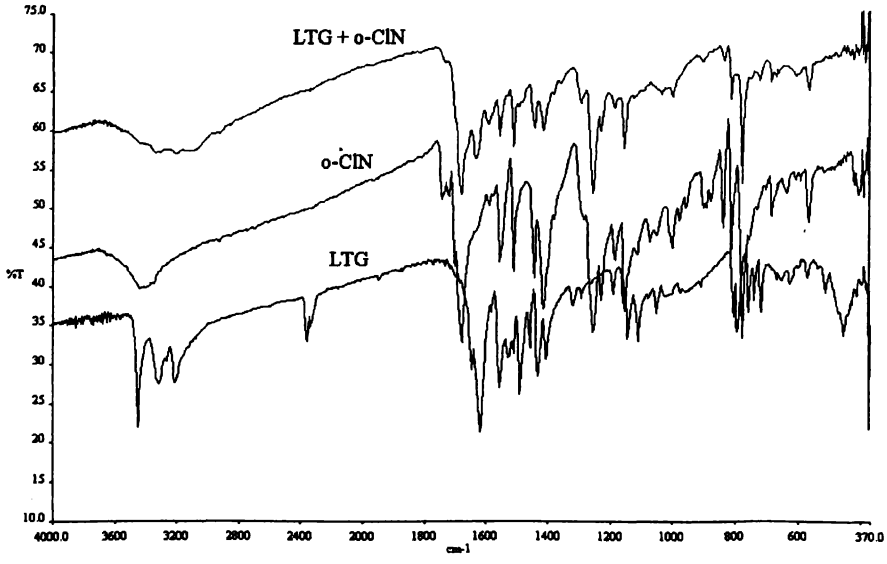


Fig. 11. FTIR spectra of Lamotrigine, *o*-chloranil and CT complex.

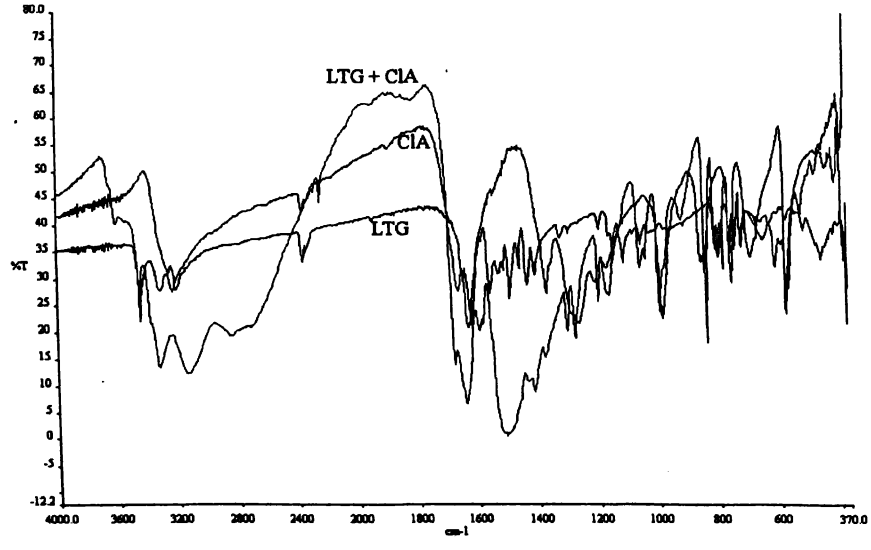


Fig. 12. FTIR spectra of Lamotrigine, chloranilic acid and CT complex.

formation contained less LTG compared to those of the acceptors. The observation is found to be true from the correlation coefficient and factor (Table 12) calculated using the expression

$$\text{Correlation} = \frac{\Sigma w_i A_i B_i}{\sqrt{\Sigma w_i A_i A_i \times \Sigma w_i B_i B_i}} \qquad (24)$$

where A_i and B_i are the absorbance values in spectra A and B at frequency i and w_i is a weighting that depends on the filters selected and

Factor = Least squares fit factor of B on A (25)[31] It is obvious that lesser the value of correlation co-efficient, CT complex formation is more pronounced.

The effects of Lamotrigine to counter seizures based on the physico-chemical properties of drugs :

Our experiments in non-biological organic solvent ACN

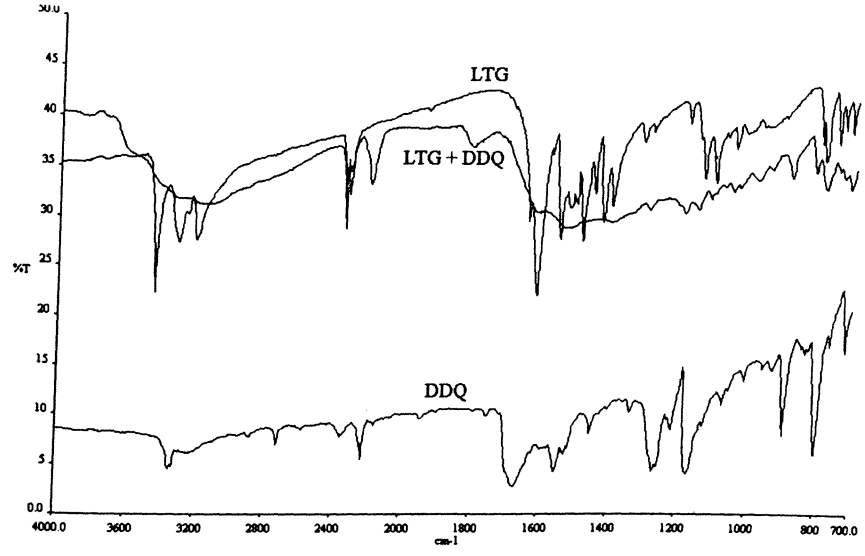


Fig. 13. FTIR spectra of Lamotrigine, DDQ and CT complex.

Table 11. The change of IR peaks of LTG, *o*-ClN, Cl-A, DDQ and the corresponding CT complexes

CT complex	Peaks of LTG absent (cm^{-1})	Peaks of acceptors absent (cm^{-1})	Shifting of peaks (cm^{-1})	New peaks in the complex (cm^{-1})
LTG + *o*-ClN	456.24, 512.85, 625.24, 1108.59, 1318.0, 1406.92, 1432.01, 1459.49, 1487.8, 1647.28, 2342.31, 2361.13, 3212.61, 3315.98, 3451.43 and 3575.07	592.98, 636.75, 877.71, 900.68, 956.03, 975.59, 1072.01, 1702.12, 1722.74, 1744.74 and 3437.98	-	1634.21 and 3208.75
LTG+ Cl-A	451.71, 1108.59, 1557.78, 2342.31, 2361.13, 3212.61, 3575.07, 3603.39, 3630.46 and 3736.92	689.13, 1206.79, 1541.39, 2342.87, 2362.08 and 3237.2	1262.35 (Cl-A) → 1274.96 (CT)	440.41, 916.34, 1122.2, 1274.0, 1300.0, 1592.5, 1678.1, 1812.08, 2246.49, 2848.27, 3143.22 and 3605.93
LTG + DDQ	1318.0, 1432.0, 1529.15, 1946.23, 3212.61, 3263.45, 3315.98 and 3451.45	765.35, 802.43, 931.57, 957.31, 1009.7, 1071.9 1169.57, 1217.29, 1455.36, 1668.75, 1752.88, 1767.68, 2724.0 and 3343.0	2233.74 (DDQ) → 2216.81 (CT)	820.37, 1122.07, 1298.09, 1813.32 and 3156.95

can hardly be used to interpret drug action but it is possible to advance our observations for the probable physicochemical reasons for anti-seizure activities of LTG and other drugs.

Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and all kinds of seizures[32]. The suggested mechanisms of drug actions are :

(i) Inhibition of voltage sensitive sodium channels to limit the firing of neurons.

(ii) Enhancement of γ-aminobutyric acid (GABA) mediated synaptic inhition.

(iii) Inhibition to activation of a voltage activated Ca^{2+}-channel (in rare cases).

The explanations are not equivocal or substantiated properly.

These are, however, not the causes of seizures but

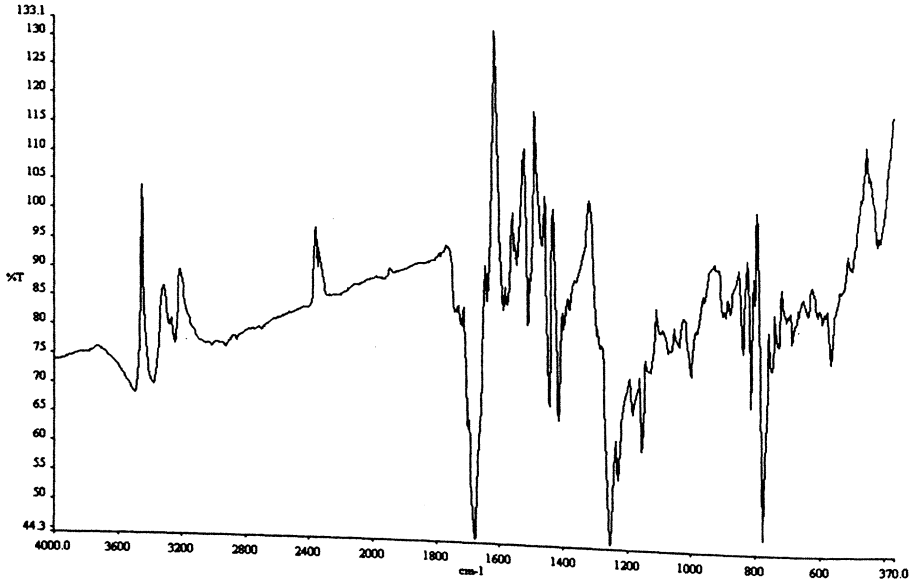


Fig. 14. IR spectra of CT complex of LTG + *o*-ClN – IR spectra of LTG – IR spectra of *o*-ClN.

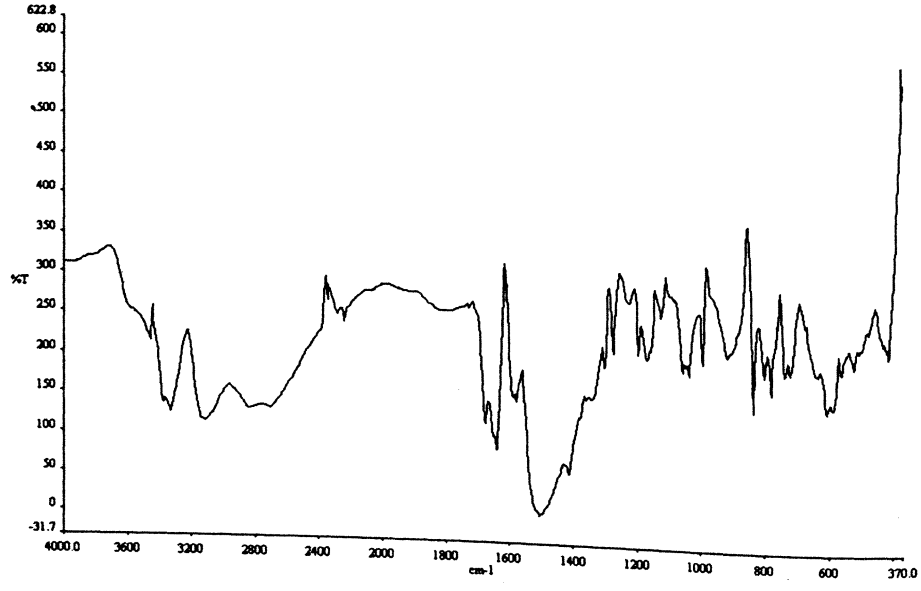


Fig. 15. IR spectra of CT complex of LTG + Cl-A – IR spectra of LTG – IR spectra of Cl-A.

suggested mechanisms of drug action. Initiation of seizures must be due to physico-chemical interaction or stimulation due to light or heat in the body system which causes change in potential gradient between the inner and outer membranes or possible changes in the protein or enzyme structures to stimulate firing due to local discharge of gray matter. The anti-seizure drugs must have to possess physico-chemical properties to counter the attack.

Water is the dominant component in living systems and it plays a very important role in the complex bio-interactions taking place for every physiological actions. Without water practically no biological reaction is possible[32]. The unbalanced nature of water, its co-planarity and orientation dependent properties help the biomolecules

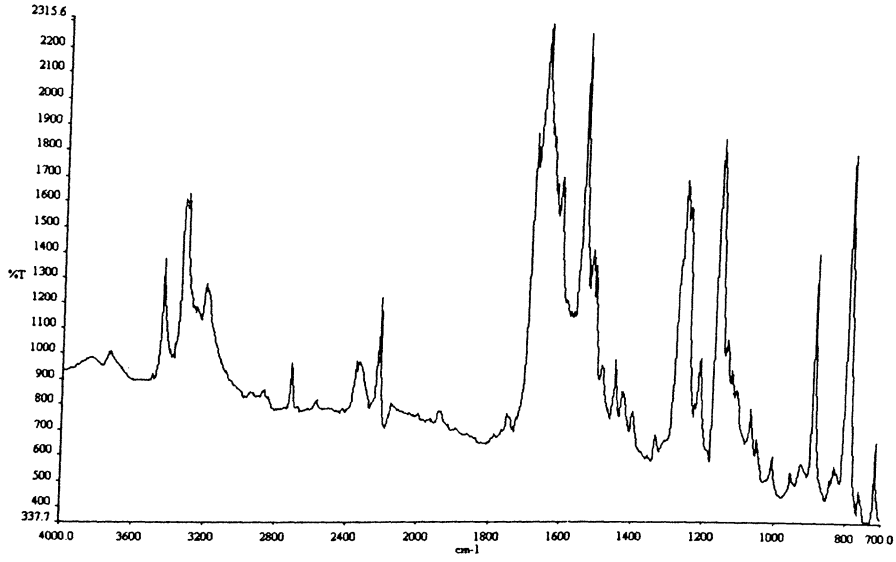


Fig. 16. IR spectra of CT complex of LTG + DDQ – IR spectra of LTG – IR spectra of DDQ.

Table 12. Comparison of IR spectra with correlation-coefficient and factor values

Name of the complex	Ref. compound	Correlation coefficient	Factor
LTG + *o*-ClN	*o*-ClN	0.8181	0.3569
	LTG	0.0185	0.0074
LTG + Cl-A	Cl-A	0.2485	0.6998
	LTG	0.1489	0.4276
LTG + DDQ	DDQ	0.1800	0.0547
	LTG	0.2105	0.0683

(proteins, enzymes, receptors etc.) to fold, assume shapes and assemble. It is responsible for the self-association or self assembly of the bio-molecules which give them extreme specificity and complexity for bio-interactions[32]. These properties are lost in organic solvents. Water also controls the hydration of ions and ion-channels. Water is thus rightly called "the matrix of life"[33].

According to Jackson[34] seizures are caused by "occasional, sudden, excessive, rapid and local discharge of Gray matter" and has been ascribed to "defective synaptic function" (reduction of inhibitory synaptic activity or enhancement of excitory synaptic activity).

Seizures are assumed to arise from the cerebral cortex and not from other central nervous system (thalamus, brainstem or cerebellum) though reciprocal firing from the thalamus and cerebral cortex have been suggested for absence seizures[11]. The possible reasons for seizures may be :

(i) Solar energies are trapped and stored in chemical bonds[35] in presence of water by living organisms to be used as a source of energy in the cortex and different organs. Photoionization or heat energy may trigger physiological impulses in the cortex to cause different neurological processes like seizures. Due to the orienting capabilities of water, amphiphilic substances tend to aggregate in aqueous solutions to form membrane like lipid bilayers and many biological energy transductions take place at the interface of membranes of such substances[36,37].

Membranes are amphiphilic lipid bilayers where half of the molecules are submerged in the lipid phase while the other half stick out of aqueous surroundings[35]. The arrangement is responsible for the proper orientations of the proteins, enzymes and other bio-molecules in the body-system. The interior of the membrane sacks differs in ionic composition from the exterior. A Na^+/K^+ gradient is maintained which can be upset by permeability changes in the membrane. This may be due to action of light or heat to cause change in the optimum water concentrations or ionic concentrations (Na^+/K^+) in the membrane sacks in the region of the cortex/thalamus leading to a change in electronic impulses or configurational changes in protein or enzyme structure with concomitant changes in water structures causing synaptic dysfunction and seizure.

The pharmacological responses of a drug are the ultimate consequences of some physico-chemical interactions of a drug with biological molecules. It has been observed that the anti-seizure drugs are non-specific in nature i.e. drugs with different structures (Lamotrigine, Carbamazepine, Phenytoin, Valproate, Gabapentine, Tiagabine, Topiramate, Zonisamide, Primidone, Phenobarbitals etc.) but with some common or similar physico-chemical properties. The compounds in question may act as competitive antagonists in drug receptor interactions. Lamotrigine with a number of N- and -NH_2 groups with multiple lone pair of electrons can effectively take part in electron transport processes. Lamotrigine is co-planar and capable of forming CT and H-bonding complexes (H-bonding complexes with acceptors can be inferred from FTIR spectra though H-bonding in solutions is not reported here) with biological moieties like proteins, enzymes etc. Lamotrigine can cross blood-brain barrier easily and can undergo hydrophobic interactions with water and tend to aggregate in bio-fluids. These properties may be responsible for the changes in the concentration of water in the active region i.e. cortex (brain tissue water fraction = 0.798[38]) or may control the Na^+/K^+ ionic gradient and mediate the voltage sensitive Na^+ channel or voltage activated Ca^{2+} channel. Lamotrigine may form complexes with GABA, glutamate, aspartic acid etc. Physico-chemical characteristics definitely suggest Lamotrigine to be an effective anti-seizure drug. It can effectively prevent inhibition of voltage active Na^+ channel or inhibit the Ca^{2+} channels etc. Extensive works are needed to study the role of water and other weak interactions in biological systems and other aspects.

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