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Studies on the Charge Transfer Interaction of Selected Antiviral Drugs with the II–Acceptors

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ABSTRACT

The formation of molecular complexes between electron donors and acceptors is an important phenomenon and has been well established. Charge transfer complexes of eight donors (antiviral drugs) with π-acceptors such as substituted quinines have been studied to understand the reactivity of drugs directly by calculating CT energies and ionization potentials of the drug molecules. CT complexes of intense colour are developed by interacting donor and acceptors in 1:1 ratio in dichloromethane. CT transition energies and ionization potential were calculated from the absorption maxima (nm) of the CT complexes. Abacavir, oseltamivir, ritonavir and tenofovir have formed strong complexes with the π-acceptors i.e. the interaction between them is high when compared with other donors.

Keywords: Antiviral drugs, π-Acceptors, CT transition energies, Ionization potential

INTRODUCTION

The formation of molecular complexes between electron donors and acceptors is an important phenomenon and has been well established [1,2]. The molecular complexes are usually colored and give rise to new absorption bands in the electronic spectra. These intense colored solutions are due to involving weak Charge Transfer (CT) interactions between one molecule, donor, and another molecule, acceptor. The extent of interaction is very weak in the case of aliphatic hydrocarbons as well as aromatic hydrocarbons and strong if the donors contain hetero atoms like nitrogen, sulphur and oxygen. The CT complex formation cannot be explained in terms of dispersion, dipole-dipole, dipole-induced dipole and such other forces. Before a CT interaction can take place, the molecules or parts of the molecules must be in sufficient proximity to each other so that the difference in the electron potential can be recognized. In many cases the conditions, which are favorable for a charge sharing or CT to take place, are the vary conditions which favor chemical changes, as a result their effects are over taken by chemical changes.

The formation of CT complexes of eight donors (antiviral drugs) with π-acceptors such as substituted quinines in the present study may help in understanding the reactivity of drugs directly. Nagakura and coworkers [3-5] studied the interaction between aniline and substituted anilines with p-chloranil and suggested that substitution reactions occur through outer and inner complexes. It is, however, possible that a chemical reaction may also proceed by an electron transfer from the donor to the acceptor and subsequent formation of the ionized species, D^+ and A^- (radical ions), as reaction intermediates in solvents of high ionizing power. The ionized species have characteristic absorption spectra in the visible region. For example, in the reaction between N,N,N′,N′-Tetramethyl-p-Phenylenediamine (TMPD) and chloranil in methanol [6], the bands at 426 and 452 nm have been assigned to the chloranil anion radical and those at 568 and 616 nm to the cation radical, $TMPD^+$. Certain biomolecules were also formed to from semiquinone ion with chloranil [5], Shah and Murthy [7] have demonstrated that radical ions form in the interaction between triethylamine and p-chloranil in various solvents by electron absorption spectroscopy.

Reports on the interaction of several non-drug and a few drug molecules with p-chloranil, o-chloranil, bromanil and a few substituted derivatives have appeared in the literature [8-12]. The CT bands of p-chloranil with some drugs have been found in the range 460-560 nm, and they varied in the order: Naproxen < Nerolin < Methyl Anthranilate < Isoxsuprine < Nylidrin [13]. The ionization potentials have been estimated by them using the relation $h\upsilon_{CT} = 0.93.I_D - 4.88$, where, I_D is the ionization potential. The estimated ionization potentials were in the range 7.52- 8.13 eV [13].

In the foregoing investigation there is scant evidence for the presence of charge transfer band in the spectra, although such an existence was suggested in explaining further spectral features. Drugs, functioning as electron donors, with their somewhat complex structure are expected to show evidence for a charge transfer transition. In this the results on the CT interaction of the drugs with several π-acceptors is presented. The charge transfer energies and ionization potentials of the drug molecules are likely to help in understanding the reactivity of drugs. The acceptors vary in electron accepting abilities depending on the nature of substituents. The substituents are all electron with drawing, making them better acceptors.

MATERIALS AND METHODS

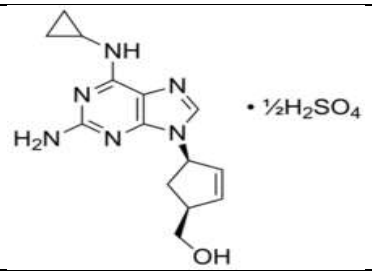
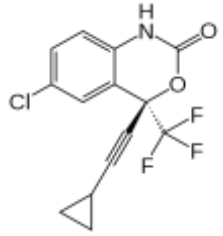
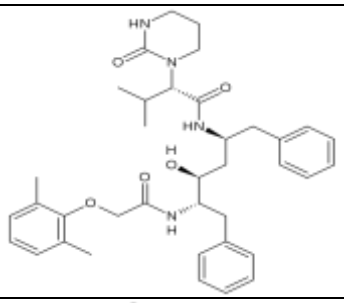
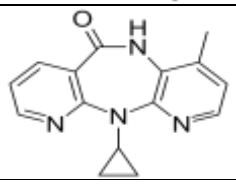
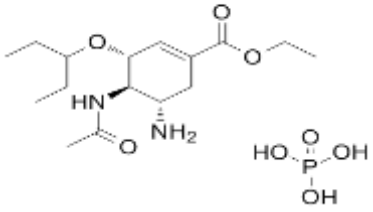
Preparation of drug solutions

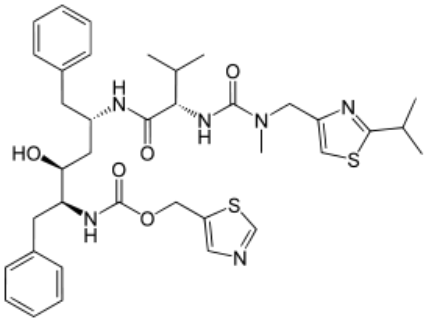
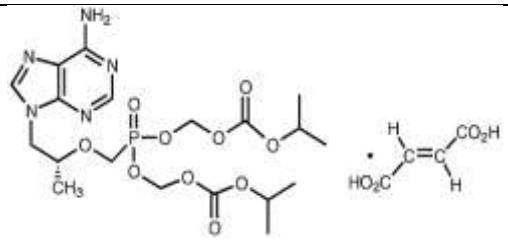
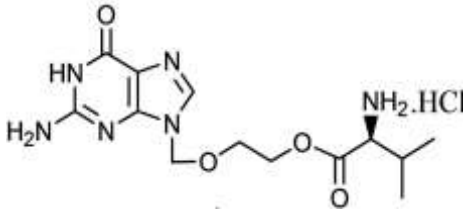
All the selected antiviral drugs were obtained in high pure form of 99.5% and above. Some of the drugs obtained were in pure base form and some in salt form and they are listed accordingly in the Table 1. All the drug molecules are referred to as donors. The drug molecules were obtained from Laurus Labs, Visakhapatnam. The pure compounds obtained were used directly without further purification. The list of acceptors selected for the study and the approximate time of formation of CT complex are presented in Table 2. All these compounds were from Sigma Aldrich, USA and Merck, Germany. The donors and acceptors were stored in separate vacuum desiccators. Dichloromethane (DCM) of HPLC grade was from Merck, Germany. Out of the eight antiviral drugs selected four drugs are in salt form, they are abacavir sulfate, oseltamivir phosphate, tenofovir disoproxil fumarate and valaciclovir hydrochloride.

Approximately 50% of all drug molecules used in medicinal therapy are in salt form as they enhance the solubility [14]. A known concentration of solution was prepared by dissolving known weight of drug in a known volume of solvent. The drugs in the salt form were extracted as its base form by the following procedure.

A known weight of drug in salt was dissolved in 100 ml distilled water to which 20 ml of 0.1 M sodium hydroxide solution was added. The solution was transferred to a separating funnel to which 20 ml of DCM was added. This extraction procedure was repeated four times with fresh 20 ml of DCM. The extracted DCM portions were transferred into a beaker. Water content was removed by filtering in anhydrous sodium sulphate. The DCM portion collected was made up to 100 ml volumetric flask. The concentration of the drug in base form was calculated using the weight of the drugs in salt form dissolved and cross checked using the reported molar extinction coefficient at UV-peak maximum.

Table 1: Details of the selected antiviral drug molecules (donors)

S. No.	Name of the Compound	Structure of the compound	Molecular formula	M.W. (g/mol.)	M.P (°C)	CAS number
1	Abacavir sulfate		$C_{14}H_{18}N_6O \cdot 0.5\ H_2SO_4$	335.37	165	188062-50-2
2	Efavirenz		$C_{14}H_9ClF_3NO_2$	315.67	139-141	154598-52-4
3	Lopinavir		$C_{37}H_{48}N_4O_5$	628.80	124-127	192725-17-0
4	Nevirapine		$C_{15}H_{14}N_4O$	266.30	247-249	129618-40-2
5	Oseltamivir phosphate		$C_{16}H_{28}N_2O_4 \cdot H_3PO_4$	410.40	196-198	204255-11-8

S. No.	Name of the Compound	Structure of the compound	Molecular formula	M.W. (g/mol.)	M.P (°C)	CAS number
6	Ritonavir		$C_{37}H_{48}N_6O_5S_2$	720.94	120-125	155213-67-5
7	Tenofovir Disoproxil Fumarate		$C_{23}H_{34}N_5O_{14}P$	635.51	276-280	147127-20-6
8	Valacyclovir hydrochloride		$C_{13}H_{20}N_6O_4 \cdot HCl$	360.80	170-172	124832-27-5

M.W.=Molecular Weight; CAS No.=Chemical abstract service number; M.P.=Melting point

Instruments used for the study

UV-Visible spectrophotometer

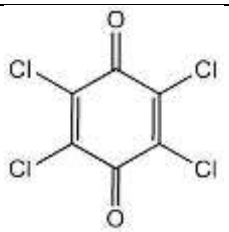
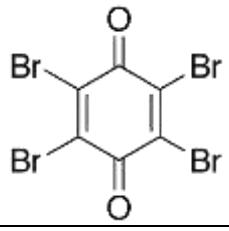
All the UV and visible spectra were recorded using Thermo Electronics Unicam UV-500 recording double beam spectrophotometer with a grating of 0.2 nm band width and equipped with temperature controlled cells (water peltier system) with an accuracy $\pm$ 1°C. Quartz quvettes of 1.0 cm equipped with air tight teflon caps were used for recording the spectra.

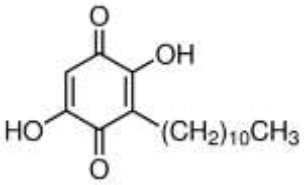
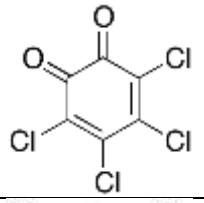
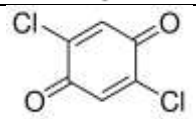
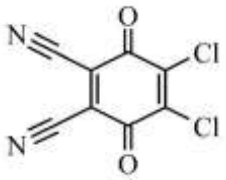
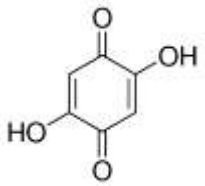
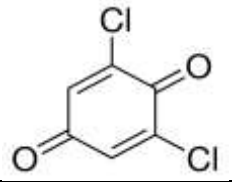
Study of interaction of drugs with π-acceptors

CT bands of complexes formed between drugs and π-acceptors

Stock solutions of the donors in Dichloromethane (DCM) were prepared afresh, just before the experiment and were diluted as per the requirement. Similarly stock solutions of acceptors were prepared in DCM. To an aliquot of dilute donor solution, saturated solutions of acceptors were added in 1:1 ratio in 5 ml volumetric flask and were made up to the mark with DCM. Upon mixing the solutions, an intense colour is developed, the spectra of the final coloured solutions were recorded and the absorption maxima of the complex were recorded.

Table 2: Details of the selected π-acceptors

S. No.	Name of the π-acceptors	Structure of the π-acceptors	$\lambda_{max.}$ (nm) of acceptors in dichloromethane (DCM)	Color of CT complex	Time of formation of CT
1	p-Chloranil		267,374	Dark yellow	5 to 10 min
2	Bromanil		247, 299,388	Yellow	15 to 20 min

S. No.	Name of the π-acceptors	Structure of the π-acceptors	$\lambda_{max.}$ (nm) of acceptors in dichloromethane (DCM)	Color of CT complex	Time of formation of CT
3	2,5-Dihydroxy-3-undecyl-2,5-cyclohexadiene-1,4-dione (Embelin)		252,267,291,427	brownish	1 to 3 min
4	o-Chloranil		261,453	Intense Orange	10 to15 min
5	2,5-Dichloro-p-benzoquinone (2, 5- DCPBQ)		246,256,274,343	Light green	15 to 20 min
6	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)		241,274,286,342	Brown	1 to 2 min
7	2,5-Dihydroxy-p-benzoquinone (2, 5- DHPBQ)		260,273	Light brown	1 to 3 min
8	2,6-Dichloro-p-benzoquinone (2, 6- DCPBQ)		265,319,343	Green	20 to 25 min

RESULTS AND DISCUSSION

When a solution of a typical antiviral drug, abacavir is mixed with 2, 5-DHPBQ in DCM in 1:1 ratio a light brown colour was developed within two minutes and a new transition appeared in the visible region at 490 nm. None of the donor or acceptor absorption bands were affected to a measurable extent. The absorbance of the new transition in the visible region was stable over a period of minutes. By comparison with the spectra with other molecules (non-drugs), the new band in the visible region was assigned to charge transfer from drug to acceptor. In all the selected antiviral drugs CT band positions were measured in the DCM solvent. A typical spectrum, showing the CT band for abacavir- 2,5-DHPBQ and oseltimivir-p-chloranil in DCM are presented in Figures 1 and 2 respectively. The CT absorption maxima (nm) and charge transfer energies ($h\upsilon_{CT}$) of antiviral drugs with π-acceptors are shown in Tables 3 and 4 respectively.

The CT absorption maxima (nm) of the drugs were in the range of 415-538 nm. The maximum CT was seen for oseltimivir-bromanil and the least for nevirapine-DDQ. The use of CT spectra for the evaluation of ionization potentials is well known. In general, the relationship between the ionization potential and the frequency of maximum absorption of the CT complex is given by:

$$h\upsilon = I_D - E_A - e^2/r - \Delta \qquad (1)$$

Where, I_D is the ionization potential of the electron donor, E_A is the electron affinity of the electron acceptor, e^2/r is the coulombic interaction between the two and Δ represents all the other intermolecular forces [15]. Foster [4] obtained an empirical relationship between ionization potential of condensed ring aromatic hydrocarbons and the frequencies of maximum absorption of their CT complexes with chloranil in carbon tetrachloride. The linear relationship is:

$$h\upsilon_{CT} = 0.89\,.\,I_D - 5.13 \qquad (2)$$

Where $h\upsilon_{CT}$ is charge transfer band energy in eV and I_D is ionization potential of the donor in eV. The approximate linearity may arise because of the relative magnitude of various terms in equation (1). This relation is different from equation (3.1) which is valid only for σ -acceptors. The ionization potentials were estimated by using equation (2), which is valid for π-acceptors and the data is shown in Table 5. Using this relationship, the estimated I_D values are in the range 8.45-8.88 eV.

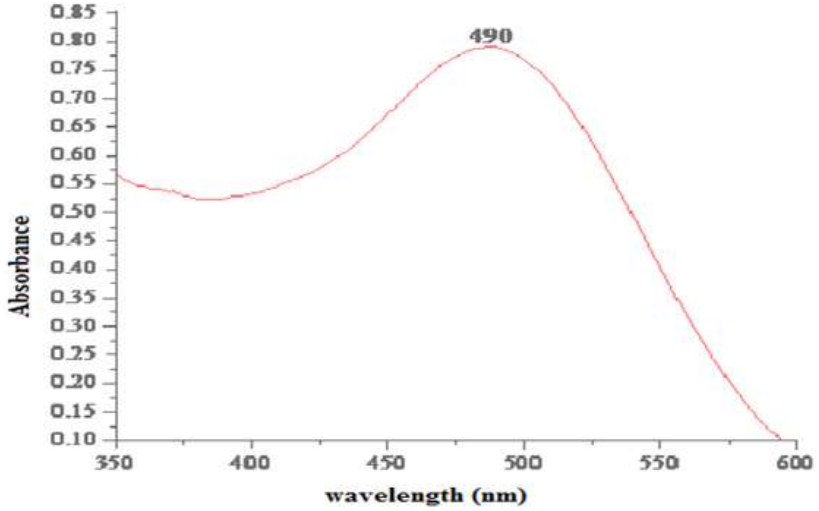


Figure 1: CT band position for abacavir -2,5-DHPBQ complex in CH_2Cl_2

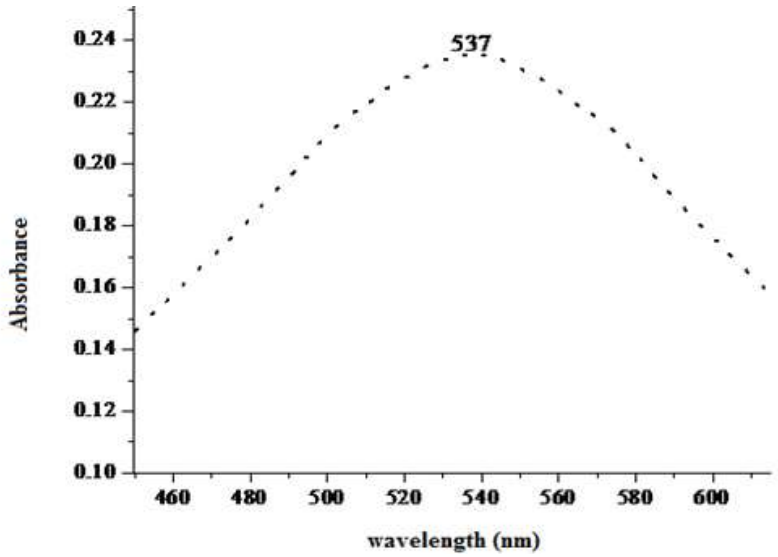


Figure 2: CT band position for oseltimivir p-Chloranil complex in CH_2Cl_2

Table 3: The absorption CT maxima (nm) of the antiviral drugs with various π acceptors

S. No.	Donors(Drugs) Acceptors	Abacavir	Efavirenz	Lopinavir	Nevirapine	Oseltamivir	Ritonavir	Tenofovir	Valaciclovir
1	p-Chloranil	530	475	472	483	537	522	520	518
2	Bromonil	532	485	485	489	538	503	537	503
3	Embilin	508	440	448	475	525	505	490	460
4	o-Chloranil	515	474	515	515	518	513	514	513
5	2,5-DC-1,4-BQ	518	438	435	458	525	508	510	463
6	DDQ	466	417	416	415	496	450	480	418
7	2,5-DH-1,4-BQ	490	438	430	470	495	479	488	477
8	2,6-DC PBQ	525	426	422	430	530	520	522	510

Note: All these values are ±4 nm accuracy. This is due to the broadness of the bands

Table 4: The CT transition energies (eV) of the antiviral drug- π-acceptor complexes

S. No.	Donors (Drugs) Acceptors	Abacavir	Efavirenz	Lopinavir	Nevirapine	Oseltamivir	Ritonavir	Tenofovir	Valaciclovir
1	p-Chloranil	2.3465	2.6182	2.6349	2.5749	2.3160	2.3825	2.3917	2.4009
2	Bromonil	2.3377	2.5643	2.5643	2.5433	2.3116	2.4725	2.3160	2.4725
3	Embilin	2.4482	2.8265	2.8590	2.6182	2.3689	2.4627	2.5381	2.7036
4	o-Chloranil	2.4149	2.6238	2.4149	2.4149	2.4009	2.4243	2.4196	2.4243
5	2,5-DC-1,4-BQ	2.4009	2.8394	2.8590	2.7154	2.3689	2.4482	2.4386	2.6861
6	DDQ	2.6688	2.9824	2.9896	2.9968	2.5074	2.7637	2.5910	2.9753
7	2,5-DH-1,4-BQ	2.5381	2.8394	2.8922	2.6461	2.5125	2.5964	2.5485	2.6073
8	2,6-DC PBQ	2.3689	2.9194	2.9471	2.8922	2.3465	2.3917	2.3825	2.4386
Average		**2.4405**	**2.7767**	**2.7701**	**2.6752**	**2.3916**	**2.4927**	**2.4532**	**2.5886**

Table 5: The ionization potentials (eV) of the antiviral drugs estimated with different π-acceptors

S. No.	Donors (Drugs) Acceptors	Abacavir	Efavirenz	Lopinavir	Nevirapine	Oseltamivir	Ritonavir	Tenofovir	Valaciclovir
1	p-Chloranil	8.40	8.71	8.72	8.66	8.37	8.44	8.45	8.46
2	Bromonil	8.39	8.65	8.65	8.62	8.36	8.54	8.37	8.54
3	Embilin	8.51	8.94	8.98	8.71	8.43	8.53	8.62	8.80
4	o-Chloranil	8.48	8.71	8.48	8.48	8.46	8.49	8.48	8.49
5	2,5-DC-1,4-BQ	8.46	8.95	8.98	8.82	8.43	8.51	8.50	8.78
6	DDQ	8.76	9.12	9.12	9.13	8.58	8.87	8.68	9.11
7	2,5-DH-1,4-BQ	8.62	8.95	9.01	8.74	8.59	8.68	8.63	8.69
8	2,6-DC PBQ	8.43	9.04	9.08	9.01	8.40	8.45	8.44	8.50
Average		**8.51**	**8.88**	**8.88**	**8.77**	**8.45**	**8.56**	**8.52**	**8.67**

From Table 3, it can be seen that the CT energies of the complexes of π-acceptors with drugs are measured in the DCM solvent. The average CT transition energies between the drug and π-acceptors are in the following order: Oseltamivir < abacavir < tenofovir < ritonavir < valacyclovir < nevirapine < efavirenz < lopinavir. The CT energies of efavirenz are less when compared to lopinavir among all π-acceptors except o-chloranil.

The CT transition energies of the CT complexes suggests that oseltamivir, abacavir, tenofovir, ritonavir form strong complexes with π-acceptors i.e. the interaction between them is high. Efavirenz and lopinavir forms the weak complexes with π-acceptors among the antivirals i.e., the interaction between them is less. Oseltamivir and tenofovir strongly interact with bromonil acceptor among the selected antiviral drugs with CT values 2.3116 and 2.3160 eV respectively.

The estimated I_D values are moderately large in magnitude. Veeraiah and coworkers [13] have been calculated by using different relationship and reported the range 7.52-8.13 eV for the drugs. It may be seen that the ionization potentials are in general, large for drugs. This is possibly due to the overall size of molecules and uncertainty in the site of ionization. Unfortunately, there is no experimental data on the ionization potentials of drug molecules for comparison.

The estimated I_D values for drugs are almost of the same magnitude with all the selected acceptors from equation 2. The values are in the range 8.45-8.88 eV is observed using all selected π-acceptors. A low ionization potential for the donor 'D' and high electron affinity for the electron acceptor 'A' should favour the formation of a stable molecular or CT complex as suggested by Weiss [1]. The low Ip values are in this order: Oseltamivir < abacavir < tenofovir < ritonavir < valacyclovir < nevirapine < efavirenz ≤ lopinavir. This clearly shows that the strong complexes are formed with π-acceptors for oseltamivir, abacavir, tenofovir, ritonavir and the rest follows. The moderately high values of ionization potentials suggest that they do not ionize easily when administered into the system. The drug, as a whole interacts with target.

CONCLUSION

In an attempt to understand the reactivity of the selected drugs, studies of CT complexes between the selected antiviral drugs and π-acceptors have been reported. From the CT bands of the complexes, the N-ionization potentials of the drugs have been estimated. Abacavir, oseltamivir, ritonavir and tenofovir have formed CT complexes by giving intense color at less time than the other drugs taken for study. Interestingly, the ionization potential values estimated for selected drugs are almost same with all the selected acceptors. There is no literature report on the ionization potential values of these drugs using other experimental methods.

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