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Studies on the weak interactions and CT complex formations between chloranilic acid, 2,3-dichloro-5,6-dicyano-p-benzoquinone, tetracyanoethylene and papaverine in acetonitrile and their thermodynamic properties, theoretically, spectrophotometrically aided by FTIR

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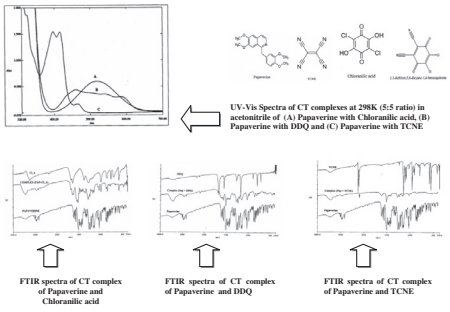
HIGHLIGHTS

- Exploration of the role of charge-transfer complexes in drug–receptor interaction.
- Thermodynamics of charge-transfer complexes of papaverine and acceptors in solution.
- Correlation of the theoretical (using DFT) and experimental charge-transfer energies.
- Measurements of FTIR spectra of the complexes.

GRAPHICAL ABSTRACT



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ABSTRACT

Spectrophotometric, FTIR and theoretical studies of the charge-transfer complexes between mild narcotic drug papaverine and the acceptors chloranilic acid (Cl-A), 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and tetracyanoethylene (TCNE) in acetonitrile, their association constants, thermodynamic (ΔG^0, ΔH^0 and ΔS^0) and other related properties had been described. Papaverine was found to form colored charge-transfer complexes with Cl-A, DDQ and TCNE in acetonitrile. The absorption maxima of the complexes were 518.5, 584.0 and 464.0 nm for Cl-A complex, DDQ complex, and TCNE complex respectively. The compositions of the papaverine complexes were determined to be 1:1 from Job's method of continuous variation. Solid complexes formed between papaverine and the acceptors were isolated. Comparison of the FTIR spectra of the solid complexes between papaverine and the acceptors and their constituents showed considerable shift in absorption peaks, changes in intensities of the peaks and formation of the new bands on complexation. However, no attempt has been made to purify the complexes and study the detailed spectra both theoretically and experimentally.

The energies $h\nu_{CT}$ of the charge-transfer complexes were compared with the theoretical values of $h\nu_{CT}$ of the complexes obtained from HOMO and LUMO of the donor and the acceptors. The reasons for the

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differences in hv_{CT} values were explained. Density function theory was used for calculation. hv_{CT} (experimental) values of the transition energies of the complexes in acetonitrile differed from hv_{CT} (theoretical) values. I_D^V value of papaverine was calculated.

Charge-transfer complexes were assumed to be partial electrovalent compounds with organic dative ions D^+ and A^- (in the excited state) and attempts had been made to correlate the energy changes for the formation of the complexes with the energy changes for the formation of electrovalent compounds between M^+ and X^- ions.

Introduction

Diseases and drugs are intimately associated. Generally, drugs are substances with medicinal properties for curing diseases. However, the action of drugs are usually specific i.e., a particular drug is used for particular purpose. Drugs may be curative but toxic, associated with side effects. Therefore, there is always a drive to produce new drug for better efficiency and for avoidance of toxicity or other side effects.

Drugs are usually organic molecules having varied drug activities which may be due to different physico-chemical properties like solubility, partition coefficients (between water/octanol, (octanol really is a poor substitution for lipids), ionization constants, surface active properties and (the most important) stereo specific properties. The properties are important and relevant to assess drug activities but these are probably secondary to understand drug action. Drugs are used in minute doses usually. 2 mg of drug (molecular weight 200–300 g/mol mostly) given to a patient having a body weight of 60–70 kg will contain about 6×10^{18} molecules. The human organism contains approximately 3×10^{13} cells or 3×10^{23} molecules as erythrocyte cell contains approximately 1×10^{10} molecules. The ratio of number of molecules in human cell to the number of molecules of drug is of the order of 10^5:1. The calculation is too simple as drugs are usually administered orally. In traveling from gum to receptor site through gastrointestinal tract, the drug has to cross water/lipid membranes and undergo multiple metabolic transformations in its journey through pharmaceutical, pharmacokinetic and pharmacodynamic phases. Naturally a very minute amount of drug i.e. much less than 10^5:1 reach the site of action known as receptor (proteins, DNA, enzyme etc), the active site of the etiological agent of the disease. The receptors are also organic molecules and they are embedded in water molecules which control the orientation, folding or unfolding and the conformations of proteins, DNA, enzymes due to different orientations of water molecules [1–6]. Water, the most important biological fluid constitutes approximately 70% of the body weight (variations due to age may be there), but the role of water in the drug receptor interactions and drug actions has yet to be explored and understood. Very little attempt has been made in this direction.

It is apparent that total numbers of cell molecules are not important for drug action, only a few molecules of the etiological agent known as receptors are capable to interact with drug to form a reversible drug-receptor complex to trigger biologic actions [1,2,6–8].

In spite of limitations, physico-chemical particularly weak interactions like charge-transfer (CT), H-bonding, hydrophobic interactions, dipole–dipole, dipole-induced dipole, dispersion interactions are key players in the formation of drug receptor complexes. Real understanding of the mechanisms of drug receptor interactions is yet to be achieved.

The importance of CT complexes in the field of science and technology is well documented. The importance of CT complexes in biological systems was studied by Mulliken et al. [9–17] Lahiri et al. [18–31] made studies on CT complexes between drugs and various acceptors to explore the role of weak interactions (CT and H-bonding) in understanding drug receptor interactions.

Physico-chemical properties and weak interactions are the potential links between drugs and their biologic properties. Though drugs are available but suitable or real receptors are very difficult to procure, i.e., studies on in situ drug receptor interactions in the laboratory are not possible.

However, acceptors are taken to study the physico-chemical properties responsible for drug acceptor interactions which are supposed to mimic drug receptor interactions. It is not known and is difficult to find exact analog for target molecules. But papaverine formed beautiful charge-transfer complexes with the acceptors Cl-A, DDQ and TCNE in acetonitrile. Quinones are known for their electron transport properties in oxidative phosphorylation in biological systems. They are also known for their profound bacteriostatic, antifungal and antitumor activities. The acceptors with suitable donors form CT complexes having semiconducting properties [14,18]. TCNE and Quinones form CT complexes to act as photosensitizers for photoconductivity of polymers like poly-N-vinylcarbazole [19]. Therefore, it is desirable to make extensive study on drug acceptor interactions to provide comprehensive data base for better comprehension about the mechanism of drug receptor interactions. But one of the most important lacuna in the study of drug acceptor interactions that the work cannot be carried out in the most abundant biological solvent water as extensive H-bonding and hydrophobic interactions will musk the CT complex formation, i.e., the studies on CT interactions should be carried out in suitable organic solvent systems and most of the reported studies were in organic solvents.

Papaverine (P) is less important opium alkaloid having isoquinoline rings. P is moderately non-specific vasodilator and antagonist of musculotropic (rather than neurotic) type of spasmolysis [32–33]. Papaverine had no absorption but acceptors had slight absorption in these regions.

The compositions, their association constants and the thermodynamic parameters like ΔG^0, ΔH^0 and ΔS^0 of the complexes were determined spectrophotometrically using temperature coefficient measurements.

Attempts were made to correlate the experimental CT energy values, hv_{CT} of the complexes with the theoretical energy values hv_{CT} calculated using DFT calculations [34].

I_D^V, the vertical ionization potentials of P was also calculated using the method suggested by Mulliken [9–11,14].

Evidence for the formation of CT complexes was also provided from the preparation of solid complexes between the drugs and the acceptors. However, no attempt was made to purify the complexes due to paucity of drugs and the laboratory is not equipped to study the solid state properties like semi conductivity or other optical properties of practical importance.

FTIR measurements of the individual components as well as of isolated solid complexes (partially pure) were done using KBr pellets. Qualitative interpretation of FTIR spectra were made but no attempt had been made to make a detailed analysis of FTIR spectra