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Spectroscopic studies on the interaction of cimetidine drug with biologically significant σ- and π-acceptors

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ABSTRACT

Spectroscopic studies revealed that the interaction of cimetidine drug with electron acceptors iodine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted through the initial formation of ionic intermediate to charge transfer (CT) complex. The CT-complexes of the interactions have been characterized using UV–vis, ^{1}H NMR, FT-IR and GC–MS techniques. The formation of triiodide ion, I_3^-, is further confirmed by the observation of the characteristic bands in the far IR spectrum for non-linear I_3^- ion with C_s symmetry at 156 and 131 cm^{-1} assigned to ν_{as}(I–I) and ν_s(I–I) of the I–I bond and at 73 cm^{-1} due to bending $\delta(I_3^-)$. The rate of formation of the CT-complexes has been measured and discussed as a function of relative permittivity of solvent and temperature. The influence of relative permittivity of the medium on the rate indicated that the intermediate is more polar than the reactants and this observation was further supported by spectral studies. Based on the spectroscopic results plausible mechanisms for the interaction of the drug with the chosen acceptors were proposed and discussed and the point of attachment of the multifunctional cimetidine drug with these acceptors during the formation of CT-complex has been established.

1. Introduction

The survey of the literature revealed that an enormous amount of work has been reported on the CT-complexes of organic compounds with variety of acceptors [1–10]; as they are significant in many fields. Some of such reports include the interactions involving 2-aminopyrimidines and σ- and π-acceptors [11], thiourea and benzoquinones [12], azacrowns and antipyrine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and iodine [13,14], N,N′-diphenylthiourea and chloranil [15], imidazole and DDQ [16], *n*-butylamines and 2,3-dichloro-1,4-naphthoquinone [17], N,N′-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane and iodine [18], 3,6,9,14-tetrathiabicyclo[9.2.1]tetradeca-11,13-diene and iodine [19] and styrene and DDQ [20]. However, studies on the spectral and kinetic aspects of such reactions, involving drug molecules are relatively fewer in number. We are interested in the spectrokinetic studies on the CT interactions of drugs with biologically significant electron acceptors [21–24]. In continuation of our earlier works on the spectrokinetic studies on the interaction of drug molecules with DDQ and iodine, here in this article we report the spectral characterization of the interaction of cimetidine (CTD) drug with a π-acceptor, DDQ, and a σ-acceptor, iodine.

Cimetidine, which is the most celebrated drug of its class, is used to treat ulcers; gastroesophageal reflux disease, a condition in which backward flow of acid from the stomach causes heartburn and injury of the food pipe; and conditions where the stomach produces too much acid, such as Zollinger–Ellison syndrome. Over-the-counter cimetidine is used to prevent and treat symptoms of heartburn associated with acid indigestion and sour stomach.

Iodine is well known for its electron accepting properties and is being used as a model acceptor to investigate the electron donating properties of organic molecules [25]. In human biology, iodine is required for the biosynthesis of the thyroid hormones, triiodothyonine and thyroin, which regulate metabolic rate [26–29]. Quinones are one of the well-known biologically important electron acceptors [30–33]. The studies of quinones for their CT interaction stem from their possible role in biological reactions. Quinones are known to be important in many biological fields [3]. Thus, the mechanism of interaction of iodine and quinones with drugs, in general, is a research topic of significant interest and hence the present study. The primary objective, therefore, of the present article is to study the spectral and kinetics aspects of the interaction between the electron acceptors DDQ and iodine with cimetidine drug with an aim to investigate the functional group (in a mul-

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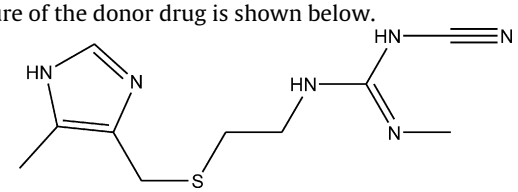
tifunctional molecule) which involve in CT interaction with these acceptors.

2. Experimental

2.1. Material and methodology

The electron acceptors DDQ (minimum assay 98%) and iodine (minimum assay 99.9%) was obtained from Aldrich, India. Commercially available spectroscopy grade solvents (Merck, India) were used without further purification. The selection of the solvents is based on the solubility of the components and so as to have a wide range of relative permittivity of the medium. The electron donor drug cimetidine was obtained as gift sample from locally available pharmaceutical company and was used as received. The purity of the drug was checked by its m.p. 139 °C and its FT-IR spectrum. The structure of the donor drug is shown below.



Solutions for the spectroscopic measurements were prepared by dissolving accurately weighed amounts of donor (D) and acceptor (A) in the appropriate volume of solvent immediately before running the spectra. The electronic absorption spectra were recorded on a JASCO (V 630, Japan) double beam spectrophotometer using 1 cm matched quartz cells. The temperature of the cell holder was controlled with a water flow (±0.2 °C). FT-IR spectra were recorded in a JASCO (FT-IR 460 Plus, Japan) spectrometer. The far FT-IR data were collected at Indian Institute Technology, Madras utilizing a Thermo Scientific Nicolet 6700 (USA) FT-IR spectrometer using the solid-substrate beamsplitter, Ever-Glo IR source and polyethylene-windowed. Samples were positioned in the sample compartment and nitrogen purge was used to eliminate interference from atmospheric water. ^{1}H NMR spectra were recorded at Madurai Kamaraj University, Madurai. The GC–MS spectra were obtained from Central Salt and Marine Research Institute, Bhavanagar, India. The conductance of the solutions was measured on an Elico, India Conductivity Bridge. For conductance measurements equimolar stock solutions of D and A were thermostated to a constant temperature and were mixed in the conductivity cell by varying the mole fraction of A. The solutions were stirred after each addition and a constant time interval was permitted to record the conductance.

2.2. Kinetic procedure

In both CTD-I_2 and CTD–DDQ cases, the kinetics of the interaction was followed at three different temperatures in various solvents under pseudo-first-order conditions, keeping [D] ≫ [A]. The increase in absorbance of the new peaks around 400 nm in the case of DDQ and around 360 nm in the case of iodine (depending on the solvent) was followed as a function of time. The pseudo-first-order rate constants (k_1) were calculated from the gradients of $\log(A_\infty - A_t)$ against time plots, where A_∞ and A_t represent the absorbance at infinity and time t respectively. The second order rate constants were calculated by dividing k_1 by [D].

3. Results and discussion

3.1. Stoichiometry of the reaction

The stoichiometry of the CT-complex, in both the cases, was determined by applying Job's continuous variation method [34].

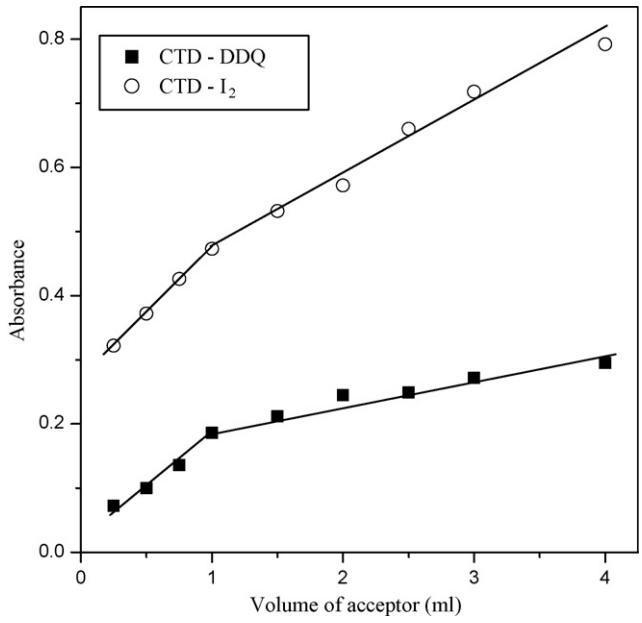


Fig. 1. Photometric titration plots for CTD with DDQ and Iodine. CTD–DDQ system in *iso*-butanol, CTD-iodine system in ethyl acetate at 298 K.

The symmetrical curves with maximum at 0.5 mole fraction indicated the formation of a 1:1 (D:A) CT-complex (figure not shown). The photometric titration measurements were also performed for the determination of the stoichiometry in these interactions. The concentration of the donor in the reaction mixtures was kept fixed while the concentrations of iodine and DDQ were varied over a wide range. The results of the photometric curves (Fig. 1) also indicated that the stoichiometry of the interaction, in both the cases, is 1:1 (D:A) [35].

3.2. Characterization of the complex

In both CTD-I_2 and CTD–DDQ cases, the CT-complex was obtained by allowing the reactants to react for 24 h under equal molar conditions in a given solvent as reported [39] and subjected to MPLC separation. The FT-IR spectra of the products were recorded and the peak assignments for important peaks are given in Table 1. The results indicated that the shifts in positions of some of the peaks could be attributed to the expected symmetry and electronic structure modification in both donor and acceptor units in the formed CT-complex relative to the free molecules. Some of the significant shifts are: the peak due to ν(N–H) vibrations of the free cimetidine occurs at 3225 cm^{-1} and in DDQ and iodine complexes they are appear at 3158 and 3152 cm^{-1}, respectively indicating the involvement of one of the N–H groups in the CT interaction with the acceptor. The ν(C–CH_3) and δ(C–CH_3) vibrations of the free cimetidine occur at 2943 and 2933 cm^{-1} and for the DDQ and iodine complexes they are appear at 2925 and 2925 cm^{-1} and 2857 and 2862 cm^{-1} respectively. The ν(C=O), ν(C≡N) and ν(C–Cl) stretching vibrations in the DDQ species appeared at 1679, 2226 and 799 cm^{-1} respectively. In the CT-complexes these stretching vibrations occurred at 1598, 2169 and 764 cm^{-1}, respectively. Such a bathochromic shift could be indicative of a higher charge density on the carbonyl and cyano groups of the DDQ molecule [21].

The ^{1}H NMR spectra of the donor and CTD–DDQ complex were recorded in DMSO-d^6 and are shown in Fig. 2. Using the proton NMR technique, we can identify the nature of interaction between the donor and acceptor in the resulted complex. The characteristic pyrazole N–H peak lies at 11.78 ppm in the free donor. In the complex, it appeared at 14.17 ppm. In the donor the pyrazole C–H lies at