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Spectroscopic studies on the formation of molecular complexes of sulfamethoxazole with novel 2,3,5-trichloro-6-alkoxy-1,4-benzoquinones

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HIGHLIGHTS

- New 2,3,5-trichloro-6-alkoxy-1,4-benzoquinones were employed as acceptors in CT interaction.
- The mechanism/structure of the products were characterized using various spectral techniques.
- Electronic effects of the substituents determine electron accepting property of quinones.

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ABSTRACT

UV–Vis, ^{1}H NMR, FT-IR, LC–MS and fluorescence spectral techniques were employed to investigate the mechanism of interaction of sulfamethoxazole with alkoxy substituted 2,3,5-trichloro-1,4-benzoquinones and to characterize the reaction products. The interactions of these quinones with sulfamethoxazole (SULF) were found to proceed through the formation of donor–acceptor complex, containing radical anion and its conversion to the product. Fluorescence quenching studies indicated that the interaction between the donor and the acceptors are spontaneous. Correlation of association constants of the CT complexes with Taft's polar and steric constants indicated that polar factor plays a significant role in governing the reactivity. The results indicated that the electronic effects of the substituents play significant role in governing the reactivity of the quinones when compared to steric factor.

1. Introduction

In recent years considerable attention has been given to study the charge transfer (CT) or electron donor acceptor (EDA) complexes formed between organic donor compounds and σ or π acceptors [1–5]. This growing importance is due its interesting optical and electronic properties [6]. CT phenomenon has enormous applications in the field of organic light emitting diodes [7], organic photovoltaics [8], sensors [9], organic field effect transistor [10], nonlinear optics [11], magnetic materials [11], organic solar cells [12], xerogel nanoparticles [13] and in the quantitative estimation of drugs [14]. Drug–receptor mechanism can also be explained by CT phenomenon in addition to weak interactions such as hydrogen bonding and hydrophobic interactions together with van der Waal's forces like dipole–dipole, dipole induced dipole and dispersion interactions. Understanding the drug–receptor mechanism is a complex issue, but collection of data of the interactions like CT, hydrogen bonding even in organic solvents can shed some light on drug–receptor mechanism [15,16]. As a primary step to determine whether CT phenomenon at any level involved, the ability of the donor drugs and related compounds to form charge transfer complexes with acceptors should be studied.

Quinones are important class of organic molecules which notably plays an essential role in oxido-reduction reactions such as respiration and photosynthesis [17]. Quinones are capable of accepting one or two electrons to form the corresponding radical anion ($Q^{\cdot-}$) and hydroquinone dianion (Q^{2-}). The biological activity of the quinones is reportedly due to the redox chemistry of the quinone system [18]. It is well known that a modification in the direct substitution pattern on the quinone ring impact its capability to accept electrons and thus its capacity to mediate biological reactions [19–21]. The key electron acceptors in the photosynthetic processes are menoquinones, plastoquinones and ubiquinones are exist in the form of substituted 1,4-benzoquinone module [22,23]. Also, these naturally occurring quinones possess variable number of alkoxy substituents in their units. Although good amount of work, on the study of charge transfer (CT) complexes of number of quinones with variety of donors, has been carried out [24–27], reports related to quinones with systematic variation of substituents is rare in literature.

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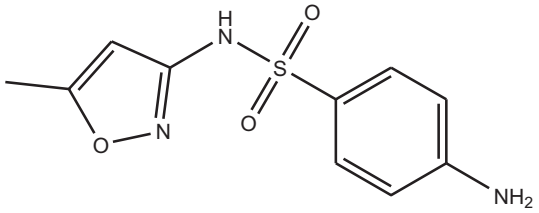
Thus, the mechanism of interaction of quinone with drugs, in general, is a research topic of significant interest and hence the present study. The objective, therefore, of the present article is to study the spectral, thermodynamic and kinetic aspects of the interaction of 1,4-benzoquinones with variable alkyl chain of alkoxy groups with sulfamethoxazole (SULF) drug with an aim to investigate the mechanism of the interaction and to characterize the structure of the products formed in these interactions. In general, drugs are poly-functional organic molecules and the present study aims at to investigate the actual site of attack during the formation of charge transfer complexes. Such a study would undeniably shed some light on to the mechanism of the drug action in real pharmacokinetic study. Sulfamethoxazole is chemically known as 4-amino-*N*-(5-methylisoxazol-3-yl)-benzene sulfonamide which is used as an antibacterial agent and to treat urinary tract infections [27,28]. It can also used in the treatment of sinusitis, toxoplasmosis and pneumocystis pneumonia which affects primarily patients with HIV. Though these chosen 1,4-benzoquinones are known to organic chemists as intermediates, it is the first systematic attempt to utilize them as acceptors with the drug. Such a structural variation of the quinones would certainly helps to tune the redox chemistry of them and hence its biological activity. Attempts have also been made to investigate the effect of substituents on the CT interaction using the techniques of correlation analysis by employing Taft's substituent constants.

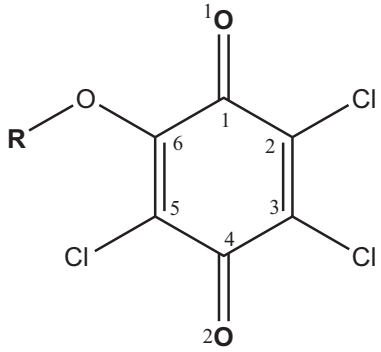
2. Experimental

2.1. Material and methodology

The electron acceptors viz. alkoxy substituted 1,4-benzoquinones were synthesized and purified by the reported method [29]. The electron donor sulfamethoxazole was obtained as gift sample from a locally available pharmaceutical company and was used as received. The purity of the drug was checked by its melting point (observed 169 °C; literature 169 °C), ^{1}H NMR and FT-IR spectra. Commercially available spectroscopic grade solvents (Merck, India) were used without further purification. The structures of the drug and the acceptors are shown below.



Chemical structure of Sulfamethoxazole



Where R= Methyl (MQ); Ethyl (EQ); Isopropyl (IPQ) and n-butyl (BQ)

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) UV–Vis double beam spectrophotometer using 1 cm matched quartz cells by using corresponding pure solvent as reference. The temperature of the cell holder was controlled with a water flow (0.2 °C). The steady state fluorescence spectra were obtained on a JASCO (FP 6200, Japan) spectrofluorimeter. The emission slit width (5 nm) and the scan rate (250 nm) was kept constant for all of the experiments. FT-IR spectra were recorded in a JASCO (FT-IR 460 Plus, Japan) spectrometer by using KBr pellet. ^{1}H NMR spectra were recorded at Madurai Kamaraj University, Madurai in a Brucker NMR spectrometer (300 MHz, Switzerland) using TMS as internal standard and DMSO-d_6 as solvent at room temperature. The LCMS spectra were obtained from University of Hyderabad in a Shimadzu (LCMS 2010) spectrophotometer with ionization potential at 70 eV (LCMS 2010, Japan). Elemental analyses for CHN was performed at Sophisticated Analytical Instrument Facility, Cochin University of Science and Technology, Kochi (Elementar Vario EL III, Germany).

2.2. Synthesis and characterization of substituted quinones

1,4-Benzoquinones possessing varying number of chloro and alkoxy substituents were synthesized and purified as reported elsewhere [29]. An excess amount of corresponding sodium alkoxide was added into a stirred solution of chloranil in the respective solvent at RT under N_2 atm. The reaction mixture was stirred for 12 h at 70 °C or 90 °C and cooled to room temperature. Then the reaction mixture was added into 200 ml of water and stirred for 1 h at RT. The crude material formed was filtered through a filter paper and residue was purified using column chromatography (Silica gel 60–120 by using 5–10% ethyl acetate pet ether mixture). The percentage yields of various quinones obtained by this method are shown in Scheme 1.

2.2.1. 2,3,5-Trichloro-6-methoxycyclohexa-2,5-diene-1,4-dione (MQ)

^{1}H NMR (DMSO-d_6, 300 MHz; Fig. 1Sa), δ (ppm) 4.19 (s, 3H), FT-IR (KBr, cm^{-1}): 1680 (C=O), 1668 (C=O), 1567 (C=C), UV–Vis in ethanol (λ_{max}): 419 nm (n–π^*), log ε 2.50, *Anal.* Calcd. for $C_7H_3Cl_3O_3$: C, 34.82; H, 1.25; found: C, 36.17; H, 1.74; m.p. 172 °C.

2.2.2. 2,3,5-Trichloro-6-ethoxycyclohexa-2,5-diene-1,4-dione (EQ)

^{1}H NMR (DMSO-d_6, 300 MHz, Fig. 1Sb), δ (ppm) 1.39 (t, J = 7.20 Hz, 3H), 4.45–4.53 (m, 2H);FT-IR (KBr, cm^{-1}): 1676, 1608 (C=O); UV–Vis in ethanol (λ_{max}): 419 nm, log ε 2.62, *Anal.* Calcd. for $C_8H_5Cl_3O_3$: C, 37.61; H, 1.97; found: C, 36.87; H, 1.84; m.p. 112 °C.

2.2.3. 2,3,5-Trichloro-6-isopropoxycyclohexa-2,5-diene-1,4-dione (IPQ)

^{1}H NMR (DMSO-d_6, 300 MHz, Fig. 1Sc), δ (ppm) 1.34 (d, J = 6.00 Hz, 6H), 4.98–5.10 (m, 1H); FT-IR (KBr, cm^{-1}): 1670, 1648 (C=O), UV–Vis in ethanol (λ_{max}): 419 nm, log ε 2.62, *Anal.* Calcd. for $C_9H_7Cl_3O_3$: C, 40.11; H, 2.62; found: C, 40.81; H, 2.56; m.p. 74 °C.

2.2.4. 2,3,5-Trichloro-6-butoxycyclohexa-2,5-diene-1,4-dione (BQ)

^{1}H NMR (DMSO-d_6, 300 MHz, Fig. 1Sd), δ (ppm) 0.9 (t, J = 6.00 Hz, 3H), 1.35–1.48 (m, 2H), 1.63–1.74 (m, 2H), 4.45 (t, J = 6.30 Hz, 2H); FT-IR (KBr, cm^{-1}): 1672, 1649 (C=O), UV–Vis in ethanol (λ_{max}): 419 nm, log ε 2.62, *Anal.* Calcd. for $C_{10}H_9Cl_3O_3$: C, 42.36; H, 3.20; found: C, 42.14; H, 3.18; m.p. 88 °C.