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Charge transfer complexation of the anticholinergic drug clidinium bromide and picric acid in different polar solvents: Solvent effect on the spectroscopic and structural morphology properties of the product

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ABSTRACT

The spectroscopic and structural morphology properties of the charge transfer (CT) complex of the anticholinergic drug clidinium bromide (CB) with picric acid (PA) have been studied in three polar solvents—acetonitrile (MeCN), methanol (MeOH) and ethanol (EtOH)—at room temperature. The formed CT complex in each solvent was characterized in both solution and solid state using electronic, IR, and ^{1}H and ^{13}C NMR spectroscopies and XRD, SEM, TEM, and CHN elemental analyses. The outcome suggests that the formation of the CT complex is high in less polar solvent and that its spectroscopic and morphologic characteristics are markedly affected by the variation in solvent polarity. The CT complex exhibited a significant microstructural change from tubal-like aggregates in MeCN solvent to mixed irregularly polygonal and spherical shapes in MeOH solvent to rounder spheres in EtOH solvent.

1. Introduction

1.1. The CT interaction

The term charge transfer (CT) was first introduced by Mulliken [1,2] and has been widely discussed by Foster [3]. Mulliken [4,5] demonstrated that the CT interactions within a molecular complex formed from an electron donor, D, and an electron acceptor, A, involve resonance with an electron partially transferred from D to A. He broadly described the interactions between a number of donors and π-acceptors. The donor molecule is an electron-rich aromatic compound, an olefin or a molecular with an unshared pair of electrons. The acceptor is an electron-deficient molecule, which may be a proton, a Lewis acid, a halogen, an electron-poor aromatic ring or a transition metal ion. Organic molecules with an electron-releasing substituent act as electron donors, and organic molecules with an electron-withdrawing substituent act as an electron acceptor [6]. Molecular CT interactions are generally associated with the appearance of a new absorption band in the UV or visible part of the spectrum at a longer wavelength than any of the component spectra and are known as CT bands [3]. CT complexes have been defined in a number of ways. Saito and Matsunaga introduced the protonic CT complex [7]. According to Pauling, CT interaction is a special case of hydrogen bonding [8]. Atkins said that a proton transfer (PT) complex was evidence of dipole–dipole (or electrostatic) forces [9].

1.2. Importance of CT interaction with drugs

The chemistry of CT, PT or H-bonding interactions between either drugs or biological compounds and small organic or inorganic molecular acceptors in solid state and in solution has increasingly attracted great attention, considerable interest and growing importance in recent years and has become a popular area of research for the following reasons:

- Relevant, important topic in pharmacology, chemistry, biology and medicine.
- Significant physical and chemical properties of the formed complexes [10–19].
- Useful in understanding drug–receptor binding and the drug's mechanism of action [20–25].
- Useful in studying the thermodynamics and pharmacodynamics of drug molecules [26,27].
- Obtains quantitative estimates of drugs in pure form or in pharmaceutical preparations that are cheaper, simpler, rapid and accurate [28–32].

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- Plays important roles in many biological fields such as DNA-binding, antibacterial, antifungal and insecticidal [33–36].
- Several CT complexes of drugs exhibit antimicrobial activities against Gram-positive and Gram-negative bacteria and fungi [37–54].
- Removes and utilizes discarded drugs from environments [55].

1.3. Aim of the work

The effects of solvent on the spectroscopic and thermodynamic properties of the CT complexes caused by drugs or biological compounds and different electron acceptors have been extensively studied [56–66]. However, no studies have appeared in the literature on effects on the structural morphologies and particle sizes of the CT complexes with drugs. Therefore, there is a great motivation to study such effects. For this purpose, we select one vital drug: clidinium bromide (CB) (Scheme 1). CB is a quaternary ammonium and cholinergic muscarinic receptor antagonist with effects similar to atropine. It is an anticholinergic drug that may help symptoms of cramping and abdominal stomach pain by reducing stomach acid and slowing the intestines [67–70]. The CT complex of drug CB as an electron donor with picric acid (PA) as an electron acceptor has been prepared in there different polar solvents including MeCN, MeOH and EtOH. The obtained complexes have then been characterized stoichiometrically, spectroscopically and morphologically using a range of physicochemical and spectroscopic techniques, such as electronic, IR, and ^{1}H and ^{13}C NMR spectroscopies and XRD, SEM, TEM, and elemental analyses, to determine the extent to which the dose of the solvent naturally affects the structural morphology of the CT complex and other spectroscopic properties.

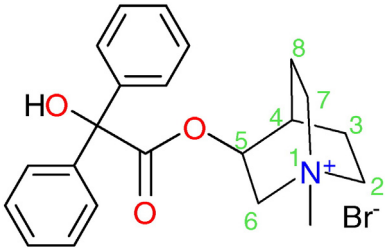
2. Experiment

2.1. Chemicals

All chemicals used were of analytical grade and were used as purchased. Clidinium bromide chemically 3-[(hydroxyl-diphenylacetyl)-oxy]-1-methyl-1-azoniabicyclo [2.2.2] octanebromide (CB; $C_{22}H_{26}NO_3Br$; 432.36) and picric acid (PA; $C_6H_3N_3O_7$; 229.10) were supplied by Sigma-Aldrich Chemical Co. (USA). HPLC-grade acetonitrile (MeCN), methanol (MeOH) and ethanol (EtOH) were purchased from Merck (Darmstadt, Germany) and used without modification.

2.2. Solutions

Standard stock solutions of the CB donor and the PA acceptor at a concentration of 5.0×10^{-3} M were freshly prepared prior to each series of measurements by dissolving precisely weighed quantities in a 100 mL volumetric flask using MeCN, MeOH or EtOH solvent. The stock solutions of donors and acceptors were protected from light. Solutions for spectroscopic measurements were prepared by mixing appropriate volumes of the CB donor and the PA acceptor stock solutions with the solvent immediately before recording the spectra.



Scheme 1. Chemical structure of clidinium bromide (CB).

2.3. Stoichiometry determination

2.3.1. In solution state

The stoichiometries of the CT interactions in solution-state in the different solvents were obtained from the spectrophotometric titrations by the determination of the conventional molar ratio according to previously published protocols [71]. These titrations were performed for the reactions of the BA donor with the PA acceptor for their detectable bands in each solvent. Briefly, 0.25, 0.50, 0.75, 1.00, 1.50, 2.0, 2.50, 3.00, 3.50 or 4.00 mL of a standard solution (5.0×10^{-4} M) of the PA acceptor in the appropriate solvent was added to 1.00 mL of the CB donor at 5.0×10^{-4} M, dissolved in the same solvent. The final volume of the mixture was 5 mL. The concentration of the donor (C_d) was maintained at 5.0×10^{-4} M, whereas the concentration of the acceptor (C_a) varied from 0.25×10^{-4} M to 4.00×10^{-4} M to produce solutions with a (donor:acceptor) molar ratio that varied from 4:1 to 1:4. The absorbance of each complex was plotted against the volume of the added acceptor.

2.3.2. In solid state

To ascertain the constituents, the purity and compositions of the synthesized complex in each solvent, elemental analyses of the carbon, hydrogen and nitrogen contents were analyzed with a Perkin-Elmer 2400 series CHN microanalyzer (USA).

2.4. Reaction chemistry

A typical procedure for the preparation is briefly described as follows. First, 2 mmol of the CB donor in MeOH solvent (20 mL) was added to 20 mL of a solution containing 2 mmol of the PA acceptor in the same solvent. The resulting mixture was stirred at room temperature for approximately 0.5 h. The solution was allowed to evaporate slowly at room temperature, resulting in the precipitation of the solid CT complex. The precipitate was isolated, filtered and further purified using the same solvent and a recrystallization process to obtain the pure product. The product was then collected and dried in vacuo for 48 h. The CT complex was prepared in MeCN and EtOH solvents via the same procedure.

2.5. Characterization

2.5.1. Free CB donor

White powder; m.p., 240–242 °C. Anal. data, calculated for $C_{22}H_{26}NO_3Br$ (432.36), Calc, %: C, 61.06; H, 6.01; N, 3.24. Found, %: C, 61.12; H, 6.05; N, 3.19. IR data (KBr, cm^{-1}): υ_{max} 3226 ν(O–H), 3067, 2972 and 2890 ν_s(C–H) + ν_{as}(C–H); CH_2 + CH_3, 1727 ν_{as}(C═O), 1633 ν_s(C═O), 1456 ν(C═C), 1383 δ_{def}(C–H), 1240 ν(C–O); ester linkage, 1189 ν_{as}(C–N), 1071 ν_a(C–N), 1009 δ(C–H); out-of-plane bending, 764 δ_{rock}(C–H). ^{1}H NMR data (DMSO-d_6, 600 MHz): δ = 1.56 (m, 1H, C_8H_a), 1.76 (m, 1H, C_3H_a), 1.81 (m, 1H, C_3H_e), 1.91 (m, 1H, C_8H_e), 1.94 (m, 1H, C_4H), 2.23 (s, 1H, OH), 2.97 (s, 3H, CH_3), 3.15 (m, 2H, $C_{2,7}H_a$), 3.17 (m, 1H, C_6H_a), 3.94 (m, 1H, C_6H_e), 3.98 (m, 2H, $C_{2,7}H_e$), 5.18 (m, 1H, C_5H), 7.29 (d, 4H, Ar–H *ortho*), 7.38 (d, 4H, Ar–H *meta*), 7.41 (d, 2H, Ar–H *para*). ^{13}C NMR data (DMSO-d_6, 600 MHz): δ = 21.7, 41.0, 49.8, 56.9, 58.4, 75.8, 80.1 (5CH_2, CH_3, CH and C-sp^3 carbons), 126.2, 127.1, 129.2, 144.7 and 173.0 (C═C and C═O).

2.5.2. Free PA acceptor

Yellow solid; m.p., 121–123 °C. Anal. data, calculated for $C_6H_3N_3O_7$ (229.1), Calc, %: C, 31.43; H, 1.31; N, 18.33. Found, %: C, 31.47; H, 1.37; N, 18.28. IR data (KBr, cm^{-1}): υ_{max} 3427 ν(O–H), 3103 and 2876 ν_s(C–H) + ν_{as}(C–H), 1633 ν_{as}(NO_2), 1531 ν(C═C), 1434 δ_{def}(C–H), 1343 ν_s(NO_2), 1272 ν(C–O), 1150 ν_{as}(C–N), 1086 ν_a(C–N), 918 δ(C–H); out-of-plane bending, 731 δ(NO_2), 704 Ω(NO_2). ^{1}H NMR data (DMSO-d_6, 600 MHz): δ = 8.59 (s, 2H, picric acid C_3, C_5 protons), 9.94