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Spectroscopic and DFT study of solvent effects on the electronic absorption spectra of sulfamethoxazole in neat and binary solvent mixtures

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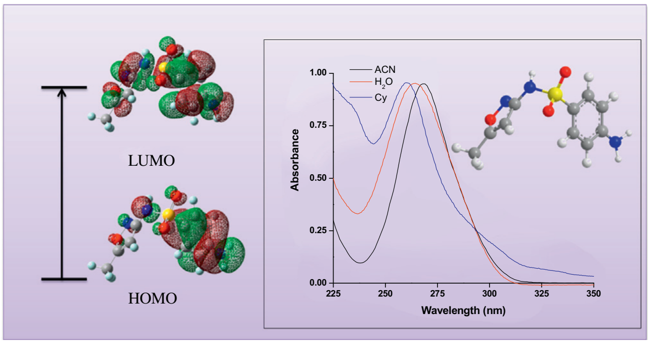
HIGHLIGHTS

- The solvatochromism of sulfamethoxazole (SMX) was studied by UV–vis spectroscopy.
- The spectral shifts of SMX were analyzed in neat and binary solvent mixtures.
- The multiparametric equation of Kamlet and Taft explain the observed solvent effect.
- The TD-DFT simulated UV-Vis spectra were in good agreement with the experimental ones.
- Preferential solvation is observed in all analyzed binary mixtures.

GRAPHICAL ABSTRACT



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ABSTRACT

The solvatochromic behavior of sulfamethoxazole (SMX) was investigated using UV–vis spectroscopy and DFT methods in neat and binary solvent mixtures. The spectral shifts of this solute were correlated with the Kamlet and Taft parameters (α, β and π^*). Multiple lineal regression analysis indicates that both specific hydrogen-bond interaction and non specific dipolar interaction play an important role in the position of the absorption maxima in neat solvents. The simulated absorption spectra using TD–DFT methods were in good agreement with the experimental ones. Binary mixtures consist of cyclohexane (Cy)-ethanol (EtOH), acetonitrile (ACN)-dimethylsulfoxide (DMSO), ACN–dimethylformamide (DMF), and aqueous mixtures containing as co-solvents DMSO, ACN, EtOH and MeOH. Index of preferential solvation was calculated as a function of solvent composition and non-ideal characteristics are observed in all binary mixtures. In ACN–DMSO and ACN–DMF mixtures, the results show that the solvents with higher polarity and hydrogen bond donor ability interact preferentially with the solute. In binary mixtures containing water, the SMX molecules are solvated by the organic co-solvent (DMSO or EtOH) over the whole composition range. Synergistic effect is observed in the case of ACN–H_2O and MeOH–H_2O, indicating that at certain concentrations solvents interact to form association complexes, which should be more polar than the individual solvents of the mixture.

Introduction

The sulfonamides are a family of compounds with a variety of pharmaceutical and biological properties [1–4]. Among sulfonamides, sulfamethoxazole, 4-amino-*N*-(5-methyl-2*H*-oxazol-3-yl) benzenesulfonamide, is an effective antibacterial compound frequently used as primary agent in the prophylaxis and therapy for several infectious diseases [5–7], especially in urinary tract infections. It is a competitive antagonist of *p*-aminobenzoic acid (PABA), acting as inhibitor of the folic acid synthesis since PABA is an integral component of the structure of folic acid [8]. Moreover,

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sulfamethoxazole (SMX) also presents interesting physicochemical properties, such as polymorphism [9], fluorescence quenching [10] and the ability to form metallic complexes of pharmaceutical interest [11].

It is well known that solvent plays an important role in physical and chemical processes. The presence of specific and non-specific interaction between the solvent and the solute molecules are responsible for the change in several properties like the molecular geometry, the electronic structure and dipolar moment of the solute. These interactions affect the electronic absorption spectrum of the solute and this phenomenon is referred to as solvatochromism [12]. Currently, there is a great number of single and multiparameter empirical solvent scales developed to describe and quantify the solute–solvent interactions at a molecular level [13]. Among all the existing solvent polarity scales, in this work we use the empirical solvatochromic scale of Kamlet and Taft [14,15]. The effect of solvent dipolarity/polarizability and hydrogen bonding on the spectral shifts can be interpreted by means of a linear solvation energy relationship (LSER). This treatment uses a multiparameter equation of the form:

$$\bar{\nu} = \bar{\nu}_0 + s\pi^* + a\alpha + b\beta \qquad (1)$$

where $\bar{\nu}$ is the solute maximum absorption wavenumber, $\bar{\nu}_0$ is the value of this property for the same solute in an hypothetical solvent for which $\pi^* = \alpha = \beta = 0$, π^* is an index of the solvent dipolarity/polarizability, α is a measure of the solvent hydrogen-bond donor (HBD) capacity, β is a measure of the solvent hydrogen-bond acceptor (HBA) capacity and s, a and b are susceptibility constants.

In addition, the behavior of a solute in a neat solvent is very different that in mixed binary solvent mixtures. In this kind of systems, the solute may induce a change in the composition of the solvents in the cybotactic region compared to that in the bulk leading to preferential solvation. For this reason, the behavior of pharmaceutical compounds in solvent mixtures is frequently evaluated for purification, preformulation studies, and pharmaceutical dosage design [16,17]. Recently, the solvent effects on the acid–base dissociation constants (pK_a) and on the lipophilicity of SMX have been studied using the LSER methodology [18,19]. Nevertheless, the information on the solvatochromic behavior of SMX in pure solvents and in binary mixtures is very limited. In the present work, an experimental and theoretical study on the solvatochromic effects of SMX is carried out in single solvents as well as in binary mixture solvents using UV–vis spectroscopy and DFT methods in order to gain insights on the solute–solvent interactions that this compound presents.

Experimental

Reagents

SMX was purchased from Sigma–Aldrich Chemical Co. and was used without further purification. The solvent employed, cyclohexane (Cy, ⩾99.9%), *n*-heptane (*n*-Hp, ⩾99.3%), 1,4-dioxane (Dx, ⩾99.9%), acetonitrile (ACN, ⩾99.8%), *N,N*-dimethylformamide (DMF, ⩾99.9%), dimethylsulfoxide (DMSO, ⩾99.8%), 1-octanol (1-OcOH, ⩾99.0%), 1-butanol (1-BuOH, ⩾99.9%), 2-propanol (2-PrOH, ⩾99.9%), 1-propanol (1-PrOH, ⩾99.8%), ethanol (EtOH, ⩾99.9%) and methanol (MeOH, ⩾99.9%) from Merck KGaA (Germany) were all HPLC or spectroscopic grade and were used without further purification. Double-distilled water (H_2O) was purified by using a Super Q Millipore System, with conductivity lower than 1.8 μS cm^{-1}.

Procedures

The solutions of SMX were prepared with a concentration of 4.9×10^{-5} M in pure solvents. Binary mixtures (Cy–EtOH, ACN–DMF, ACN–DMSO, ACN–H_2O, DMSO–H_2O, EtOH–H_2O and MeOH–H_2O) were prepared from the corresponding solutions by mixing appropriate volumes of each pure solvent in the following ratios: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. All the solutions were prepared by weighting with an accuracy of ±0.0001 g and were stabilized at 25.0 ± 0.1 °C for 10 min. Then their spectra were recorded in a Cary 50-Varian spectrophotometer with thermostatizable cells of 1 cm optical path in the 200–400 nm interval. All spectra were corrected for solvent background by calibrating the instrument to the blank solvent and the experiments were carried out in duplicate.

Computational details

The initial molecular geometry of SMX was optimized with the GAUSSIAN 03 [20] programs package using the hybrid DFT functional B3LYP [21,22] and the 6-311G++(d,p) basis set. Initial coordinates of SMX were taken from a previous work of Vega-Hissi et al. [23]. To analyze the solvent effects on the optimized structures in gas-phase the Polarizable Continuum model with the integral equation formalism (IEF–PCM) [24] was used, and the UAHF radii were employed to build the molecular cavity. The corresponding frequencies were calculated to make sure that the structures obtained were true minima. The dielectric constants used in the PCM calculation are the default values in GAUSSIAN 03 and they are listed in Table 1. Using the minimum energy structures in solution of SMX as starting points, vertical excitation energies and the corresponding absorption wavelengths were calculated within the non-equilibrium time-dependent TD–DFT framework [25]. For this aim, two hybrid functionals have been used: B3LYP and PBE0 [26,27] in combination with the PCM method. The PBE0 does not contain any adjustable parameter fitted to specific property, and recent studied suggests that provides more reliable results relative to experimental results [28]. Different solvent–solvent dimeric complexes were optimized using the same functional and basis set employed for SMX. For these dimers, non-covalent interactions were identified using the reduced density gradient (RDG) approximation [29]. This quantity can be defined as $s = 1/(2(3\pi^2)^{1/3})|\nabla\rho|/\rho^{4/3}$, where ρ is the electron density obtained from DFT calculations. The Multiwfn program [30] was used to generate scatter plots of s vs. sign $(\lambda_2)\rho$ associated with the hydrogen bond interaction regions.

Table 1
Maximum absorption wavelength (λ) and wavenumber ($\bar{\nu}$) of sulfamethoxazole in pure solvents and relevant solvent parameters.

Solvent	λ (nm)	$\bar{\nu}$(cm^{-1})	ε	π^*	α	β
Cy	259.0	38610.0	2.024	0.00	0.00	0.00
n-Hp	258.7	38654.8	1.921	-0.08	0.00	0.00
Dx	267.9	37327.4	2.219	0.55	0.00	0.37
ACN	268.7	37216.2	36.64	0.75	0.19	0.40
DMF	271.2	36873.2	38.25	0.88	0.00	0.69
DMSO	275.5	36297.6	47.24	1.00	0.00	0.76
1-OcOH	270.2	37009.6	10.30	0.40	0.77	0.81
1-BuOH	270.2	37009.6	17.84	0.47	0.84	0.84
2-PrOH	270.1	37023.3	20.18	0.48	0.76	0.84
1-PrOH	270.3	36995.9	20.80	0.52	0.84	0.90
EtOH	269.9	37050.8	25.30	0.54	0.86	0.75
MeOH	269.7	37078.2	33.00	0.60	0.98	0.66
H_2O	266.6	37509.4	78.39	1.09	1.17	0.47