

Preferential solvation of sulfadiazine, sulfamerazine and sulfamethazine in ethanol + water solvent mixtures according to the IKBI method



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ABSTRACT

The preferential solvation parameters of sulfadiazine, sulfamerazine and sulfamethazine in ethanol + water binary mixtures were derived from their thermodynamic properties by means of the inverse Kirkwood–Buff integrals (IKBI) method. From solvent effect studies, it is found that these sulfonamides are sensitive to solvation effects, so the preferential solvation parameter by ethanol $\delta\chi_{E,S}$, is negative in water-rich and ethanol-rich mixtures but positive in compositions from 0.24 to 0.54–0.58 in mole fraction of ethanol according to the sulfonamide. It is conjecturable that in water-rich mixtures the hydrophobic hydration around aromatic rings and/or methyl groups plays a relevant role in the solvation. The more solvation by ethanol in mixtures of similar co-solvent compositions could be due mainly to polarity effects. Finally, the preference of these drugs for water in ethanol-rich mixtures could be explained in terms of the bigger acidic behavior of water interacting with hydrogen-acceptor groups in the sulfonamides.

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1. Introduction

Solubility determination of drugs in all possible co-solvent mixtures is very important for pharmaceutical and chemical scientists involved in several development stages such as drug purification and design of liquid medicines [1]. Although co-solvency has been employed in pharmacy for centuries it has been recently that the mechanisms involved in the processes to increase or decrease drugs solubility started to be approached from a physicochemical point of view [2].

Sulfonamides are drugs extensively used for the treatment of several infections caused by gram-positive and gram-negative microorganisms, some fungi, and certain protozoa. Although the advent of the antibiotics has diminished the clinical use of sulfonamides, these drugs still occupy an important place in the therapeutic resources of physicians and veterinarians [3,4].

Several thermodynamic works have been published about the enthalpic and entropic contributions to the Gibbs energy of solution of some sulfonamides in binary mixtures conformed by ethanol or propylene glycol and water [5–9]. Nevertheless, the drug preferential solvation, i.e. the co-solvent specific composition around the drug molecules has not been studied for sulfonamides. Therefore, the main goal of this paper is to evaluate the preferential solvation of some structurally related sulfonamides in ethanol + water co-solvent mixtures, based on well-established thermodynamic definitions. Sulfonamides under study were sulfadiazine (SD, Fig. 1, CAS RN: [68-35-9], 4-

amino-*N*-2-pyrimidinyl-benzenesulfonamide), sulfamerazine (SMR, Fig. 1, CAS RN: [127-79-7], 4-amino-*N*-(4-methylpyrimidin-2-yl) benzenesulfonamide), and sulfamethazine (SMT, Fig. 1, CAS RN [57-68-1], 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide). Thus, this work is similar to the ones presented previously in the literature for some analgesic drugs in co-solvent mixtures [10–13].

The use of inverse Kirkwood–Buff integral (IKBI) is a powerful tool for evaluating the preferential solvation of non-electrolytes in solvent mixtures, describing the local compositions around a solute with respect to the different components present in the solvent mixture [14–16].

In the present case, this treatment depends on the values of the standard molar Gibbs energies of transfer of the sulfonamides from neat water to the ethanol + water solvent mixtures and the excess molar Gibbs energy of mixing for the co-solvent binary mixtures. As has been indicated previously, this treatment is very important in pharmaceutical sciences to understand the molecular interactions of solute–solvent because most of the solubility studies developed have been directed towards correlating or modeling the solubilities and possibly predicting them from the solubilities in the neat solvents, but not to analyzing the local environment around the drug molecules describing the local fraction of the solvent components in the surrounding of solute (S) [17]. As was indicated earlier, in this paper the IKBI approach is applied to evaluate the preferential solvation of the structurally related sulfonamides sulfadiazine, sulfamerazine and sulfamethazine in the binary mixtures conformed by ethanol (E or EtOH) and water (W). The results are expressed in terms of the preferential solvation parameter $\delta\chi_{E,S}$ of the solute by the co-solvent ethanol.

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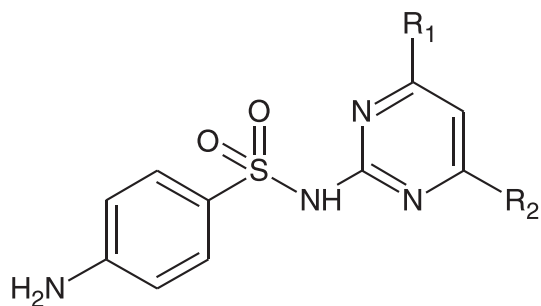


Fig. 1. Molecular structure of the sulfonamides analyzed. Sulfadiazine: R_1 and $R_2 = H$. Sulfamerazine: $R_1 = H$, $R_2 = CH_3$. Sulfamethazine: R_1 and $R_2 = CH_3$.

2. Theoretical

The KBIs (Kirkwood–Buff integrals, $G_{i,S}$) are given by the following expression:

$$G_{i,S} = \int_0^{r_{cor}} (g_{i,S} - 1) 4\pi r^2 dr \quad (1)$$

Here $g_{i,S}$ is the pair correlation function for the molecules of the solvent i in the ethanol + water mixtures around the sulfonamide, r is the distance between the centers of the molecules of sulfonamide and ethanol or water, and r_{cor} is the correlation distance for which $g_{i,S}$ ($r > r_{cor}$) ≈ 1 . Thus, for all distances $r > r_{cor}$ up to infinite, the value of the integral is essentially zero. Therefore, the results are expressed in terms of the preferential solvation parameter $\delta x_{i,S}$ for the sulfonamide in solution by the component solvents ethanol and water [17,18]. For ethanol (E) this parameter is defined as

$$\delta x_{E,S} = x_{E,S}^L - x_E = -\delta x_{W,S} \quad (2)$$

where x_E is the mole fraction of ethanol in the bulk solvent mixture and $x_{E,S}^L$ is the local mole fraction of ethanol in the environment near to the drug. If $\delta x_{E,S} > 0$ then the sulfonamide is preferentially solvated by ethanol; on the contrary, if it is < 0 the drug is preferentially solvated by water, within the correlation volume, $V_{cor} = (4\pi/3)r_{cor}^3$, and the bulk mole fraction of ethanol, x_E . Values of $\delta x_{E,S}$ are obtainable from those of $G_{E,S}$, and these in turn, from thermodynamic data of the co-solvent mixtures with the solute dissolved on it, as shown below [16].

Algebraic manipulation of the basic expressions presented by Newman [19] leads to expressions for the Kirkwood–Buff integrals (in $\text{cm}^3 \text{mol}^{-1}$) for the individual solvent components in terms of some thermodynamic quantities as shown in Eqs. (3) and (4). These equations show whether S (sulfonamide) is surrounded preferentially

by molecules of the ethanol (if $G_{E,S} > G_{W,S}$) or by molecules of the water (if $G_{E,S} < G_{W,S}$). Thus, the relative magnitudes of Kirkwood–Buff integrals $G_{E,S}$ and $G_{W,S}$, which are measurements of the affinities of ethanol and water for the sulfonamides, determines the preferential solvation of these solutes in the binary solvent mixtures of ethanol and water [10,12,17]:

$$G_{E,S} = RT\kappa_T - V_S + x_W V_W D/Q \quad (3)$$

$$G_{W,S} = RT\kappa_T - V_S + x_E V_E D/Q \quad (4)$$

where κ_T is the isothermal compressibility of the ethanol + water solvent mixtures (in GPa^{-1}), V_E and V_W are the partial molar volumes of the solvents in the mixtures (in $\text{cm}^3 \text{mol}^{-1}$), similarly, V_S is the partial molar volume of solute in these mixtures (in $\text{cm}^3 \text{mol}^{-1}$). The function D is the derivative of the standard molar Gibbs energies of transfer of the sulfonamide (from neat water to ethanol + water mixtures) with respect to the solvent composition (in kJ mol^{-1} , as also is RT) and the function Q involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents ($G_{E,W}^{Exc}$) with respect to the water proportion in the mixtures (also in kJ mol^{-1}) [10]:

$$D = \left(\frac{\partial \Delta_{tr} G_{(S,W \rightarrow E+W)}^0}{\partial x_E} \right)_{T,P} \quad (5)$$

$$Q = RT - x_E x_W \left(\frac{\partial^2 G_{E,W}^{Exc}}{\partial x_W^2} \right)_{T,P} \quad (6)$$

Because the dependence of κ_T on composition is not known for a lot of the systems investigated and because of the small contribution of $RT\kappa_T$ to the IKBI the dependence of κ_T on composition could be approximated by considering additive behavior from individual isothermal compressibilities of components according to the following equation [19,20]:

$$\kappa_{T,mix} = \sum_{i=1}^n x_i \kappa_{T,i}^0 \quad (7)$$

where x_i is the mole fraction of component i in the mixture and $\kappa_{T,i}^0$ is the isothermal compressibility of the pure component i .

Ben-Naim [14] showed that the preferential solvation parameter can be calculated from the Kirkwood–Buff integrals as follows:

$$\delta x_{E,S} = \frac{x_E x_W (G_{E,S} - G_{W,S})}{x_E G_{E,S} + x_W G_{W,S} + V_{cor}} \quad (8)$$

Table 1

Gibbs energy of transfer (kJ mol^{-1}) of the sulfonamides from neat water to ethanol + water co-solvent mixtures at several temperatures.

x_{EtOH}^a	Sulfadiazine			Sulfamerazine			Sulfamethazine		
	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K	293.15 K	303.15 K	313.15 K
0.0000	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.0417	-1.09	-1.28	-1.25	-0.74	-1.01	-1.19	-1.51	-1.38	-1.68
0.0891	-2.76	-2.86	-3.13	-2.29	-2.57	-3.00	-3.03	-2.98	-3.60
0.1436	-4.46	-4.77	-4.96	-4.21	-4.50	-4.89	-4.76	-5.01	-5.54
0.2068	-5.99	-6.03	-6.07	-5.73	-6.11	-6.37	-6.19	-6.50	-7.03
0.2812	-7.13	-7.09	-7.04	-7.05	-7.21	-7.60	-7.49	-7.70	-8.25
0.3698	-7.75	-7.76	-7.64	-7.84	-8.02	-8.30	-8.50	-8.67	-9.18
0.4772	-8.22	-8.23	-8.08	-8.36	-8.43	-8.80	-9.15	-9.30	-9.69
0.6101	-8.26	-8.28	-8.17	-8.53	-8.65	-8.84	-9.49	-9.61	-9.88
0.7788	-7.74	-7.79	-7.54	-8.16	-8.29	-8.45	-9.28	-9.21	-9.52
1.0000	-6.83	-6.75	-6.49	-7.36	-7.50	-7.82	-8.57	-8.54	-8.79

^a x_{EtOH} is the mole fraction of ethanol in the ethanol + water co-solvent mixtures free of sulfonamide.

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