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Thermodynamic analysis and preferential solvation of sulfamethazine in acetonitrile + water cosolvent mixtures

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ABSTRACT

This paper presents the solubility of sulfamethazine (SMT) in the acetonitrile (MeCN) + water (W) cosolvent system at nine temperatures. From the solubility experimental data, the thermodynamic functions of solution, mixing, and transfers are calculated and analyzed using the Perlovich graphical method. On the other hand, an enthalpy–entropy compensation analysis is performed and the preferential solvation parameters are calculated using the Kirkwood-Buff (IKBI) inverse integral method. The result of the performed calculations indicates that the SMT solution process is endothermic with entropic favor, where the addition of MeCN has a positive cosolvent effect between pure water and the mixture with $w_1 = 0.90$. As for the preferential solvation, the SMT molecule is preferentially surrounded by water in water- and MeCN-rich mixtures, and in intermediate mixtures, the SMT molecule tends to be surrounded by MeCN.

1. Introduction

Sulfamethazine (SMT; 4-amino-N-(4,6-dimethylpyridine-2-yl) benzenesulfonamide; CAS number 57-68-1, T_f: 469.2 K [1]) (Fig. 1) [2] is a broad-spectrum antimicrobial agent used to treat bacterial infections causing bronchitis, prostatitis, and urinary tract infections, besides being widely used in veterinary medicine for the treatment of pathologies such as intestinal infections (produced especially by coccidia), pneumonia, and soft tissue infections [3]. This widespread use of pharmaceutical products containing SMT has led to environmental institutions such as the NORMAN network considering this drug as an emerging high-risk contaminant, classifying it as an eco-toxic agent, which affects beneficial microorganisms such as bacteria and protozoa [4] and upper aquatic plants [5], due to their antichloroplastic properties [5,6], and aquatic animals [7,8].

In addition, the pharmaceutical industry is a potential source of contamination, since most processes, such as synthesis, purification of raw materials, chemical analysis for quality assessment, and preformulation and formulation studies, tend to produce large masses of waste containing these chemical agents [9,10].

In this sense, the development of strategies that lead to the design of more environmental-friendly methodologies, focused on environmental management systems supported by ISO 14001, and leading to promoting the development of cleaner production practices have been consolidated as an important tool for the prevention and correction of contaminating processes [11]. Thus, the generation of experimental data and the development of mathematical models that allow predicting properties such as

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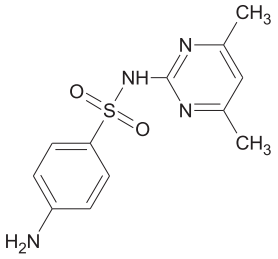

Fig. 1. Molecular structure of sulfamethazine.

solubility contribute greatly to reducing experimental tests, which in turn decreases the mass of pollutants (e.g., drugs, solvents, disposable material, and energy) produced in processes of the pharmaceutical industry [12].

In this context, mathematical models tending to predict the solubility of drugs in different solvents and/or cosolvents at different temperatures have become an important tool for the pharmaceutical industry [13], not only for drugs but also for other large organic molecules, such as polycyclic aromatic hydrocarbons, which, like drugs, are also a source of contamination by the oil industry [14,15]. Thus, based on thermodynamic properties, models such as the "nearly ideal binary solvent" approach by Acree et al. allow to successfully determine solubility in some types of cosolvent mixtures [16,17]. Another model, which is an improvement of the previous one, is that proposed by Jouyban et al., which involves polar and non-polar solvents [18,19]. Other models based on area surfaces, contribution of UNIFAC groups, Hildebrand solubility parameters, and Kirkwood-Buff integrals have been proposed and refined to improve their predictability [20–23].

Therefore, the main objective of this study is to present the solubility of SMT at nine temperatures (278.15–318.15 K) in acetonitrile + water cosolvent mixtures, thermodynamic fusions calculated from Gibbs and van't Hoof equations, and the parameters of preferential solvation using the Kirkwood-Buff inverse integral model, which are significant data for the industry [24].

2. Experimental

2.1. Reagents

In this study, SMT (Sigma-Aldrich, USA; compound 3; with purities of at least 0.990 in mass fraction), acetonitrile (Merck A.R., Germany; the solvent component 1, purity of at least 0.998 in mass fraction), and distilled water with conductivity $<2\ \mu S\ cm^{-1}$ (solvent component 2) were used. Table 1 summarizes the sources and purities of the compounds studied.

2.2. Preparation of solvent mixtures

All {MeCN (1) + water (2)} solvent mixtures were prepared by mass in quantities of 20.000 g, using an analytical balance with sensitivity ± 0.1 mg (RADWAG AS 220.R2, Poland). The mass fractions of (1), w_1, of the nine mixtures prepared varied by 0.05 from 0.05 to 0.95.

2.3. Solubility determination

In the present study, the flask agitation method proposed by Higuchi and Connors [25] was used, which is reliable and widely used in the determination of solubility.

In this way, an amount of SMT sufficient for obtaining a saturated solution in equilibrium with undissolved solid phase of SMT, was added to 20 g of the cosolvent mixture, contained in amber glass flasks of 30 ml capacity with polypropylene caps. Subsequently, each sample was subjected to ultrasound for 30 min before being placed in the thermostat at the study temperature; then, they were periodically stirred for the time required to reach equilibrium (~36 h).

After reaching equilibrium, the concentration of the saturated solution was determined; to avoid solid particles in the sample analyzed, the solid phase (undissolved drug) separates of the saturated solution, using the filtration method. The samples were filtered through membranes with a pore diameter of 0.45 μm (Millipore Corp. Swinnex-13, USA) to ensure the absence of solid particles, considering that the syringes and filters were thermostated at the study temperature. To reduce the possible errors in the determination of solubility through the sorption of the solute in the filter, a quantity of the saturated solution was passed through the filter to saturate the possible adsorption sites.

In this way, a given mass of the solution was taken from each sample, making the respective gravimetric dilutions with a 0.1 N sodium hydroxide solution. Then, the absorbances in the spectrophotometer were determined, ensuring that the absorbance of the dilution was in the linearity zone of the calibration curve obtained for the SMT.

The use of the 0.1 N NaOH solution to make the dilutions is due to the addition of the NaOH solution to the saturated solution of SMT; thus, the salt of the drug is formed, ensuring greater solubility in aqueous systems and preventing SMT from precipitating.

2.4. Calorimetric study

The temperature and melting enthalpy of five SMT samples were determined using differential scanning calorimetry (DSC) (DSC 204 F1 Phoenix, Germany) (original sample, solid phase in equilibrium with saturated water, solid phase in equilibrium with saturated MeCN, and solid phases in equilibrium with saturated mixtures of $w_1 = 0.35$ and 0.70).

The samples were weighed using 3–10 mg of the drug in an aluminum crucible and placed inside the calorimeter with a nitrogen current (10 mL/min). The samples were subjected to a temperature program in which they were heated from an initial temperature of 303.15 K to a temperature 480.15 K above the melting point of the analyzed drug, a heating rate of 10 K min^{-1}. The equipment was calibrated using 99.99% pure Indium.

Table 1
Source and purities of the compounds used in this research.

Chemical name	CAS[a]	Formula	Molar mass/g mol^{-1}	Source	Purity in mass fraction	Analytic technique[b]
Sulfamethazine (SMT)	57-68-1	$C_{12}H_{14}N_4O_2S$	278.33	Sigma-Aldrich, USA	0.990	HPLC
Acetonitrile	75-05-8	C_2H_3N	41.05	Merck, Germany	0.998	GC
Water	7732-18-5	H_2O	18.02	Obtained by distillation	>0.999	–

[a] Chemical Abstracts Service Registry Number.
[b] HPLC is high-liquid-performance chromatography; GC is gas chromatography.