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Thermodynamic analysis and applications of the Abraham solvation parameter model in the study of the solubility of some sulfonamides

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Summary

Solubility of sulfadiazine (SD), sulfamerazine (SMR) and sulfamethazine (SMT) in cosolvent mixtures octanol+methanol was investigated to 278.15 K, 298.15 and 313.15 K. In all cases, the lowest solubility of each drug was obtained in pure octanol at 278.15 K. The maximum solubility depends on the polarity of the drug, thus SMR and SMT reached their maximum solubility in cosolvent mixtures methanol-rich.

The solution thermodynamic functions were calculated from the experimental solubility data, using the van't Hoff and Gibbs equations, following the approach proposed by Krug *et al*. The enthalpy of solution is positive in all cases, which is an indication of the endothermic process with a marked entropic favor. Theoretical solubility and mean lethal concentration were calculated using the Abraham model.

Key words: Sulfonamides, Solubility, van't Hoff, Abraham model, lethal median molar concentration.

Resumen

Análisis termodinámico y aplicaciones del modelo de parámetros de solvatación de Abraham en el estudio de la solubilidad de algunas sulfonamidas

Se investigó la solubilidad de sulfadiazina (SD), sulfamerazina (SMR) y sulfametazina (SMT) en mezclas codisolventes de octanol + metanol a 278,15 K, 298,15 y 313,15 K. En todos los casos, la solubilidad más baja de cada fármaco se obtuvo en octanol puro a 278,15 K. La solubilidad máxima depende de la polaridad del fármaco, por lo que SMR y SMT alcanzaron su máxima solubilidad en mezclas cosolventes ricas en metanol. Las funciones termodinámicas de solución se calcularon a partir de los datos experimentales de solubilidad, utilizando las ecuaciones de van't Hoff y Gibbs, siguiendo el enfoque propuesto por Krug *et al*. La entalpía de la solución es positiva en todos los casos, lo cual es una indicación del proceso endotérmico con un marcado favorecimiento entrópico. La solubilidad teórica y la concentración letal media se calcularon utilizando el modelo de Abraham.

Palavras-chave: Sulfonamidas, solubilidad, van't Hoff, modelo de Abraham, concentración letal media.

Introduction

Sulfonamides, first synthetic antimicrobial drugs [1], have been extensively used for human health treatment, in animal husbandry and management [2, 3]. Sulfonamides are effective against Gram-positive bacteria, and their spectrum of actions includes many Gram-negative bacteria, as well as some protozoa and fungi [4]. Sulfonamides also experience other pharmacological activities, namely antitumor [5], diuretic [6], anti-neuropathic pain [7] and anti-carbonic anhydrase [8] actions.

Owing to its extensive use, sulfonamides have become a relatively serious environmental problem, and it is one of the emerging pollutants with a greater presence in wastewater, aquifers, and bodies of water such as lakes. This could eventually put aquatic ecosystems at high risk [9]. This makes these antimicrobial agents one of the most dangerous emerging contaminants for beneficial aquatic microorganisms due to its toxicity, with the corresponding risk for human health as well [10].

Although the solubility studies are of great importance for the activities of the design and development of medicines, due to the environmental problems that have been generated by their release into the environment. A clear example is the significant

fraction of the pharmaceutically active compounds sold each year find their way into the environment as the result of human/animal urine and feces excretion (excreted unchanged drugs or as drug metabolites). Or by direct disposal of unused household drugs by flushing into sewage systems, accidental spills and releases from manufacturing production sites, and underground leakage from municipal sewage systems and infrastructures. Currently, several thousand tons of medicinal compounds find their way into aquatic environments on an annual basis. The occurrence of pharmaceutical residues and metabolites in the environment is of significant public concern. Therefore, reports from the NORMAN network, promote that solubility studies have regained importance in environmental studies and/or development of more efficient methodologies for remediation processes. In this context, another area where the solubility has incurred is cleaner production [11].

Therefore, the primary objectives of this investigation were to determine the solubility of SD, SMR and SMT (figure 1) in {octanol (1) + methanol (2)} {OcOH (1) + MeOH (2)] cosolvent mixtures at nine different temperatures from 278.5 K to 313.15 K and to evaluate its thermodynamic behavior using the van't Hoff and Gibbs equations.

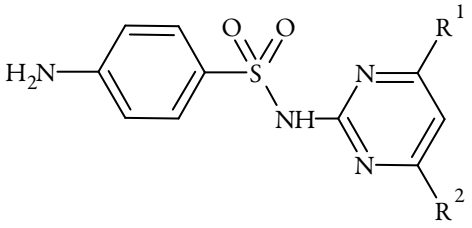

Figure 1. Molecular structure of sulfadiazine ($R^1 = H$, $R^2 = H$), sulfamethazine ($R^1 = CH_3$, $R^2 = H$) and sulfamethazine ($R^1 = CH_3$, $R^2 = CH_3$).

Experimental

Reagents

The following reagents were used in this investigation: Sulfadiazine, sulfamerazine and sulfamethazine (Sigma-Aldrich, USA, approximate purity 0.990 in mass fraction); methanol, ethanol, and octanol (Merck AR, Germany, approximate purity 0.998 in mass fraction).

Preparation of the solvent mixture

The {OcOH (1) + MeOH (2)} mixtures were prepared in quantities of 10 g, using an analytical balance with sensitivity ±0.0001 g (RADWAG AS 220.R2, Poland). The

mass fractions of OcOH varied by 0.10 from 0.10 to 0.90. Each mixture was prepared in triplicate.

Determination of solubility

The method used for determining the solubility of the three sulfonamides (SD, SMR and SMT) was the bottle-shaking method proposed by Higuchi and Connors [12] and previously reported in several investigations by our research groups [13, 14]. This method consists of placing approximately 10 g of pure solvent or solvent mixture in an amber glass bottle and then adding excess sulfonamide until a solid phase is reached at the bottom of the bottle. Subsequently, the flasks (solvent + solute) are placed in a thermostatized recirculation bath (Medingen K-22/T100, Germany) for 72 h, stirring periodically until reaching the saturation equilibrium (constant solubility). A sample of the saturated solution is taken after 72 h using a syringe under isothermal conditions and filtered using a membrane with 0.45 μm pore size to ensure the absence of solid particles in the sample, which will be tested. The concentration of the drug in each sample was determined using UV/Vis spectrophotometry (EMC-11-UV UV/VIS spectrophotometer, Germany), making the corresponding dilutions with ethanol to avoid the precipitation of the drug during the dilution. Each solubility experiment was performed three times.

Results and discussion

Solubility of SD, SMR and SMT in {octanol (1) + methanol (2)} cosolvent mixtures

Table 1 shows the solubility of SD, SMR and SMT in {OcOH (1) + MeOH (2)} cosolvent mixtures at three temperatures (278.15, 293.15 and 313.15) K and nine cosolvent mixtures ($0.10 < w_1 < 0.90$ and varying by 0.10 in mass fraction) and the two pure solvents, MeOH and OcOH.

Figures 2, 3 and 4 show the behavior of the solubility of SD, SMR and SMT in the cosolvent mixture octanol + methanol three temperatures, in all cases, the solubility increases because of temperature increments, implying that the drugs solution process in the cosolvent mixtures {octanol (1) + methanol (2)} is favored by supplying power to the system. Further, demonstrating that the process is endothermic, where the minimum solubility values of the all sulfonamides are obtained in pure octanol at 278.15 K and the maximum solubility, which depends on the polarity of the sulfonamide. In the case of SD, it is obtained in pure methanol ($\delta_{SD} = 28.89$ MPa; $\delta_2 = 29.3$ MPa [15]) at 318.15 K; for SMR in the cosolvent mixture $w_1 = 0.1$ ($\delta_{SMR} = 28.10$ MPa [16]; $\delta_{w=0.1} = 28.14$ MPa [17]) at 318.15 K; and for SMT in the cosolvent mixture $w_1 = 0.2$ ($\delta_{SMT} = 27.42$ MPa [18]; $\delta_{w=0.1} = 27.64$ MPa [17]) at 318.15 K. In all cases, the maximum solubility of the substances studied is reached in the solvent or cosolvent mixtures whose polarity is like that of each of the sulfonamides.

Table 1. Solubility of SD, SMR and SM (3) expressed in mole fraction (x 10^5)[b] in {octanol (1) + methanol (2)} cosolvent mixtures at different temperatures (K).

w_1[a]	SD			SMR			SMT		
	278.15	**293.15**	**313.15**	**278.15**	**293.15**	**313.15**	**278.15**	**293.15**	**313.15**
0.00	32.31	13.76	7.91	123.60	68.78	46.91	375.25	147.57	81.24
0.10	26.19	12.71	6.05	135.58	78.72	47.98	384.98	166.54	82.86
0.20	21.14	9.03	4.86	134.16	81.13	46.76	391.29	186.73	81.13
0.30	15.19	7.07	3.22	123.82	63.17	40.68	381.65	172.08	77.64
0.40	12.34	5.49	2.48	97.17	48.16	30.92	375.13	145.84	73.33
0.50	9.31	3.55	1.75	61.55	31.07	17.47	299.34	121.23	56.04
0.60	7.73	3.42	1.37	35.27	17.43	8.17	247.51	105.66	45.35
0.70	5.55	1.74	0.85	29.32	11.64	6.71	176.86	62.90	31.13
0.80	4.67	1.52	0.70	24.42	10.18	4.87	117.77	44.52	19.62
0.90	3.91	1.34	0.56	17.49	6.79	3.41	63.61	24.77	10.70
1.0	3.31	1.07	0.45	14.72	6.15	2.55	44.19	23.85	8.10
Ideal	150	254	494	287	482	924	524	888	1725

[a] w_1 is the mass fraction of OcOH in the cosolvent mixture free of solute.
[b] The standard uncertainty of temperature is $u(T) = 0.05$ K; The relative standard uncertainty of solubility is $u_r(x_3) = 0.05$.

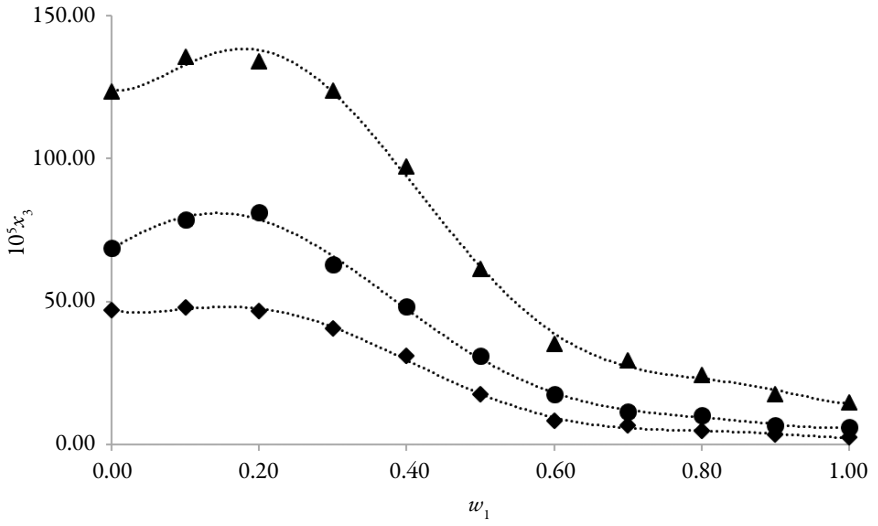

Figure 2. Solubility of SD (3) expressed in mole fraction (x 10^5) in {octanol (1) + methanol (2)} cosolvent mixtures at different temperatures (♦ = 278.15 K, ● = 293.15 K and ▲ = 313.15 K).

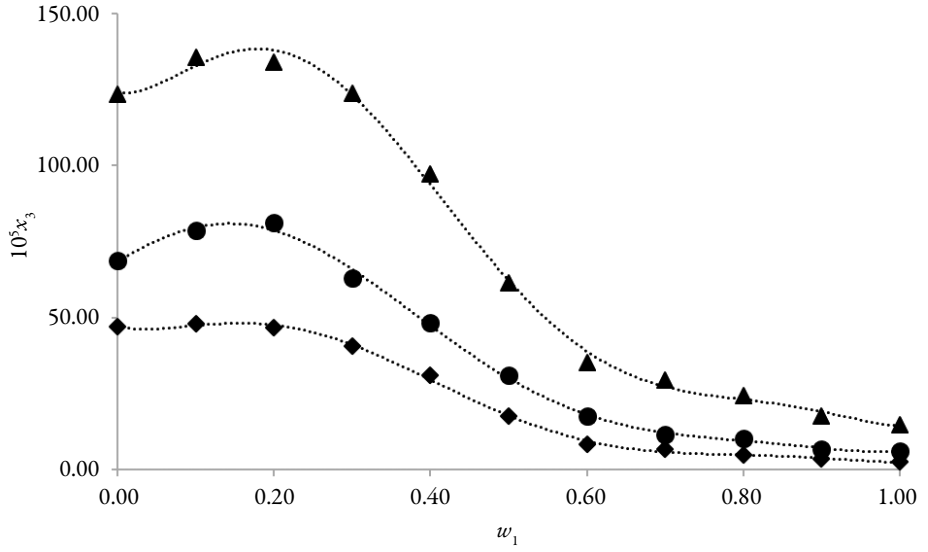

Figure 3. Solubility of SMR (3) expressed in mole fraction (x 10^5) in {octanol (1) + methanol (2)} cosolvent mixtures at different temperatures (♦ = 278.15 K, ● = 293.15 K and ▲ = 313.15 K).

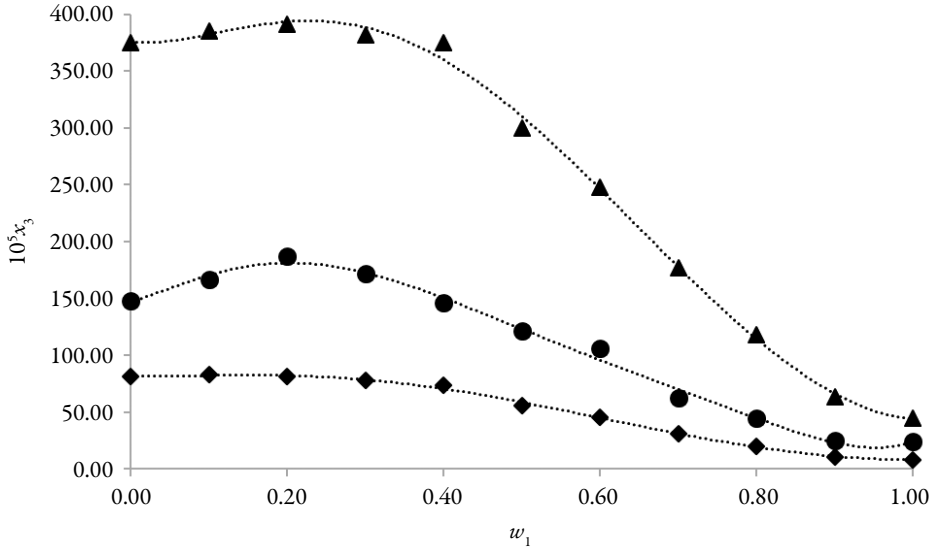

Figure 4. Solubility of SMT (3) expressed in mole fraction (x 10^5) in {octanol (1) + methanol (2)} cosolvent mixtures at different temperatures (♦ = 278.15 K, ● = 293.15 K and ▲ = 313.15 K).

Activity coefficients

The activity coefficient (table 2) is calculated through equation 1, and can be interpreted based on possible molecular interactions solute-solute, solvent-solvent and solute solvent according to equation 2 [19].

$$\gamma_3 = x_3^{Id}\left(x_3^{Exp}\right)^{-1} \quad \text{(Eq. 1)}$$

$$\ln\gamma_3 = \left(e_{11} + e_{22} - 2e_{13}\right)V_3\phi_1^2\left(RT\right)^{-1} \quad \text{(Eq. 2)}$$

Table 2. Activity coefficients (γ_3) of SD, SMR and SMT in cosolvent mixtures {octanol (1) + methanol (2)} at different temperatures (K).

w^a	SD			SMR			SMT		
	278.15	**293.15**	**313.15**	**278.15**	**293.15**	**313.15**	**278.15**	**293.15**	**313.15**
0.00	4.64	18.45	62.43	2.32	7.01	19.70	1.40	6.02	21.29
0.10	5.73	19.98	81.69	2.12	6.12	19.26	1.36	5.33	20.88
0.20	7.09	28.12	101.65	2.14	5.94	19.76	1.34	4.76	21.32
0.30	9.88	35.95	153.31	2.32	7.63	22.71	1.37	5.16	22.28
0.40	12.16	46.27	199.05	2.95	10.01	29.88	1.40	6.09	23.59
0.50	16.11	71.56	282.18	4.66	15.52	52.89	1.75	7.33	30.87
0.60	19.40	74.33	361.77	8.14	27.65	113.11	2.12	8.40	38.15
0.70	27.03	145.96	582.00	9.79	41.41	137.66	2.96	14.12	55.57
0.80	32.14	167.05	704.43	11.75	47.37	189.84	4.45	19.95	88.18
0.90	38.37	189.75	878.83	16.41	71.03	270.64	8.24	35.85	161.68
1.00	45.37	238.10	1097.18	19.49	78.36	362.72	11.86	37.24	213.51

[a] w_1 is the mass fraction of OcOH in the cosolvent mixture free of solute.

Regarding SD, the activity coefficients increase from pure methanol to pure octanol; however, they diminish with and decrease in temperature. For SMR and SMT, the coefficient of activity, decrease from pure methanol to w_1 = 0.1 or w_1 = 0.2 and the activity coefficient values increase from w_1 = 0.1 or w_1 = 0.2 to pure octanol.

Although in all cases the solute–solute (e_{11}) and solvent–solvent (e_{22}) molecular interactions are greater regarding the solute–solvent molecular interactions (e_{12}),

according to the results analyzed from Eq. (2), the unfavorable interactions (e_{11} and e_{22}) decrease to such an extent that the solution behaves almost as an ideal solution, where the solute–solute and solvent–solvent molecular interactions are equal to the solute–solvent molecular interactions.

Thermodynamic functions of solution

Thermodynamic functions (tables 3-5) are calculated from experimental solubility data (table 1), using the van't Hoff and Gibbs equations, following the approach proposed by Krug *et al.* [20-22]:

$$\Delta_{soln}G^{o} = -RTa \qquad \text{(Eq. 3)}$$

$$\Delta_{soln}H^{o} = -R\left\{\partial \ln x_3 \Big/ \partial\left[\left(1/T\right) - \left(1/T_{hm}\right)\right]\right\} \qquad \text{(Eq. 4)}$$

$$T_{hm}\Delta_{soln}S^{o} = \Delta_{soln}H^{o} - \Delta_{soln}G^{o} \qquad \text{(Eq. 5)}$$

$$\Delta_{soln}S^{o} = \left(\Delta_{soln}H^{o} - \Delta_{soln}G^{o}\right)\Big/T_{hm} \qquad \text{(Eq. 6)}$$

where $\Delta_{soln}H°$, $\Delta_{soln}G°$ and $\Delta_{soln}S°$ denote the enthalpy, Gibbs energy and entropy of the solution, respectively. T_{hm} denotes the harmonic average of the study temperatures, and R denotes the universal constant of the gases. The intercept (a) corresponds to the linear equation of the plot of $\ln x_3$ vs ($T^{-1} - T_{hm}^{-1}$).

The contribution of the energy factors (solution enthalpy) and organizational aspects (entropy) to the Gibbs energy of the solution can be obtained by using Eqs. 7 and 8 [23]:

$$\varsigma_H = \left|\Delta_{soln}H^{o}\right| \Big/ \left(\left|\Delta_{soln}H^{o}\right| + \left|T_{hm}\Delta_{soln}S^{o}\right|\right) \qquad \text{(Eq. 7)}$$

$$\varsigma_{TS} = 1 - \varsigma_H \qquad \text{(Eq. 8)}$$

Table 3. Apparent thermodynamic functions relative to solution process of SD in cosolvent mixtures {octanol (1) + methanol (2)} at 294.12 K.

w_1[a]	$\Delta_{soln}G°$ (J.mol^{-1}.K^{-1})	$\Delta_{soln}H°$ (J.mol^{-1}.K^{-1})	$\Delta_{soln}S°$ (J.mol^{-1}.K^{-1})	$T\Delta_{soln}S°$ (J.mol^{-1}.K^{-1})	ζ_H	ζ_{TS}
0.00	21.50	29.22	26.24	7.72	0.79	0.21
0.10	21.95	30.25	28.20	8.29	0.78	0.22
0.20	22.58	30.49	26.86	7.90	0.79	0.21
0.30	23.39	31.99	29.25	8.60	0.79	0.21
0.40	23.98	33.11	31.05	9.13	0.78	0.22
0.50	24.85	34.65	33.34	9.81	0.78	0.22
0.60	25.23	35.74	35.72	10.51	0.77	0.23
0.70	26.44	39.01	42.75	12.57	0.76	0.24
0.80	26.85	39.33	42.44	12.48	0.76	0.24
0.90	27.28	40.16	43.79	12.88	0.76	0.24
1.00	27.78	41.31	46.02	13.54	0.75	0.25

[a] w_1 is the mass fraction of OcOH in the cosolvent mixture free of solute.

Table 4. Apparent thermodynamic functions relative to solution process of SMR in cosolvent mixtures {octanol (1) + methanol (2)} at 294.12 K.

w_1[a]	$\Delta_{soln}G°$ (J.mol^{-1}.K^{-1})	$\Delta_{soln}H°$ (J.mol^{-1}.K^{-1})	$\Delta_{soln}S°$ (J.mol^{-1}.K^{-1})	$T\Delta_{soln}S°$ (J.mol^{-1}.K^{-1})	ζ_H	ζ_{TS}
0.00	17.64	20.11	8.41	2.47	0.89	0.11
0.10	17.44	21.47	13.71	4.03	0.84	0.16
0.20	17.44	21.73	14.57	4.28	0.84	0.16
0.30	17.83	23.11	17.97	5.28	0.81	0.19
0.40	18.47	23.79	18.08	5.32	0.82	0.18
0.50	19.66	26.06	21.75	6.40	0.80	0.20
0.60	21.21	30.16	30.44	8.95	0.77	0.23
0.70	21.85	30.65	29.94	8.81	0.78	0.22
0.80	22.37	33.38	37.43	11.01	0.75	0.25
0.90	23.26	33.87	36.09	10.61	0.76	0.24
1.00	23.72	36.21	42.47	12.49	0.74	0.26

[a] w_1 is the mass fraction of OcOH in the cosolvent mixture free of solute.

Table 5. Apparent thermodynamic functions relative to solution process of SMT in cosolvent mixtures {octanol (1) + methanol (2)} at 294.12 K.

w_1[a]	$\Delta_{soln}G°$ (J.mol^{-1}.K^{-1})	$\Delta_{soln}H°$ (J.mol^{-1}.K^{-1})	$\Delta_{soln}S°$ (J.mol^{-1}.K^{-1})	$T\Delta_{soln}S°$ (J.mol^{-1}.K^{-1})	ζ_H	ζ_{TS}
0.00	15.67	31.78	54.79	16.11	0.66	0.34
0.10	15.53	31.79	55.27	16.26	0.66	0.34
0.20	15.44	32.42	57.74	16.98	0.66	0.34
0.30	15.56	32.87	58.85	17.31	0.66	0.34
0.40	15.76	33.84	61.48	18.08	0.65	0.35
0.50	16.31	34.67	62.39	18.35	0.65	0.35
0.60	16.75	35.03	62.15	18.28	0.66	0.34
0.70	17.76	36.05	62.19	18.29	0.66	0.34
0.80	18.75	37.09	62.35	18.34	0.67	0.33
0.90	20.22	36.86	56.56	16.63	0.69	0.31
1.00	20.78	34.75	47.51	13.97	0.71	0.29

[a] w_1 is the mass fraction of OcOH in the cosolvent mixture free of solute.

The Gibbs energy of solution is positive in all the cases. As for the SD, the Gibbs energy increase from pure MeOH to pure OcOH, because the solubility of the SD decreases with the decrease of the polarity of the system, as a consequence of the addition of octanol.

SMR and SMT, the Gibbs energy decrease from pure MeOH to mixture with a mass fraction of 0.10-0.20 OcOH, beginning from this mixture, the Gibbs energy of the solution denotes an increase up to pure OcOH because the solubility decreases, possibly due to the effects of the polarity change of the medium, making it less favorable with respect to SMR and SMT.

On the other hand, the enthapy of soluctión is positive in all cases, therefore the process us always endothermic [24, 25], so, the entropy solution like enthalpy, is positive in all cases favoring the porcess of solution [26-28].

Although, main contributor to the (positive) standard molar Gibbs energy of solution (ζ_H > 65%) is the enthalpy, the process presents an important entropic favorice.

Thermodynamic functions of the SD, SMR and SMT mixing

The solute behavior in the dissolution process can generally be divided into two stages, the solute fusion and its subsequent mixing with the solvent, so this hypothetical process can be represented according to the following scheme [29, 30]:

$$\text{Solute}_{(\text{Solid})} \text{ at } T \rightarrow \text{Solute}_{(\text{Solid})} \text{ at } T_{\text{fus}} \rightarrow \text{Solute}_{(\text{Liquid})} \text{ at } T_{\text{fus}} \rightarrow \text{Solute}_{(\text{Liquid})} \text{ at } T \rightarrow \text{Solute}_{(\text{Solution})} \text{ at } T$$

In this way, thermodynamic solution functions can be represented by the following equation:

$$\Delta_{\text{soln}} f^{o} = \Delta_{\text{f}} f^{o} + \Delta_{\text{mix}} f^{o} \qquad \text{(Eq. 9)}$$

where f represents the thermodynamic functions (G, H or S) and the subscripts **f** and **mix** represent fusion and mixing, respectively.

Thus, the mixing functions are determined as:

$$\Delta_{\text{mix}} f^{o} = \Delta_{\text{soln}} f^{o} - \Delta_{\text{f}} f^{o} \qquad \text{(Eq. 10)}$$

where $\Delta_{\text{f}} f^{\text{o}}$ is replaced by the ideal thermodynamic functions, which are thus calculated as:

$$\Delta_{\text{mix}} G^{o} = \Delta_{\text{soln}} G^{o} - \Delta_{\text{soln}} G^{o-\text{id}} \qquad \text{(Eq. 11)}$$

$$\Delta_{\text{mix}} H^{o} = \Delta_{\text{soln}} H^{o} - \Delta_{\text{soln}} H^{o-\text{id}} \qquad \text{(Eq. 12)}$$

$$\Delta_{\text{mix}} S^{o} = \Delta_{\text{soln}} S^{o} - \Delta_{\text{soln}} S^{o-\text{id}} \qquad \text{(Eq. 13)}$$

From Perlovich's analysis (figures 5, 6 and 7) [31], the mixing process for the three sulfonamides has a positive Gibbs energy (dotted lines), indicating that the melting process is what drives the solution process. For SD the mixing enthalpy is positive in all cases, so first, it does not favor the dissolution process and is greater in octanol-rich mixtures, possibly due to a higher energy requirement for the formation of the cavity necessary to house the solute. Regarding the mixing entropy, it is negative in MeOH-rich mixtures, which disadvantages the mixing process and is positive

in OcOH-rich mixtures favoring the mixing process. The other hand, SMT, in mixtures rich in MeOH, enthalpy contributes to the mixing process and entropy does not contribute to the process, in mixtures rich in OcOH the opposite occurs. Regarding the SMT, both the mixing enthalpy and the mixing entropy are positive, indicating that the mixing entropy is the only thermodynamic function that contributes to the process.

Generally speaking, for SD (figure 4), it is concluded that from pure MeOH to $w_1 = 0.50$ (sector VIII: $\Delta_{mix}H^o < 0$, $T\Delta_{mix}S^o < 0$, and $|T\Delta_{tr}S^o| < |\Delta_{ta}H^o|$), the mixing process is driven by enthalpy; between $w_1 = 0.60$ and $w_1 =$ pure OcOH (sector I: $\Delta_{mix}H^o > T\Delta_{mix}S^o$), the mixing process is driven again by enthalpy. For SMR (figure 5), from pure MeOH to $w_1 = 0.4$ (sector VI: $\Delta_{mix}H^o < 0$, $T\Delta_{mix}S^o < 0$, and $|T\Delta_{tr}S^o| > |\Delta_{ta}H^o|$) the mixing process is driven by entropy; from $w_1 = 0.4$ to $w_1 = 0.5$ (sector VII: $\Delta_{mix}H^o > 0$, $T\Delta_{mix}S^o < 0$, and $|T\Delta_{tr}S^o| > |\Delta_{ta}H^o|$) the mixing process is driven by entropy; from $w_1 = 0.6$ to $w_1 = 0.7$ (sector III: $\Delta_{mix}H^o < 0$, $T\Delta_{mix}S^o < 0$, and $|T\Delta_{tr}S^o| < |\Delta_{ta}H^o|$), the mixing process is driven by enthalpy and from $w_1 = 0.8$ to pure OcOH (sector VIII: $\Delta_{mix}H^o < 0$, $T\Delta_{mix}S^o < 0$, and $|T\Delta_{tr}S^o| < |\Delta_{ta}H^o|$), the mixing process is driven by enthalpy. For SMT (figure 6), from pure MeOH to pure OcOH (sector VIII: $\Delta_{mix}H^o < 0$, $T\Delta_{mix}S^o < 0$, and $|T\Delta_{tr}S^o| < |\Delta_{ta}H^o|$), the mixing process is driven by enthalpy [32].

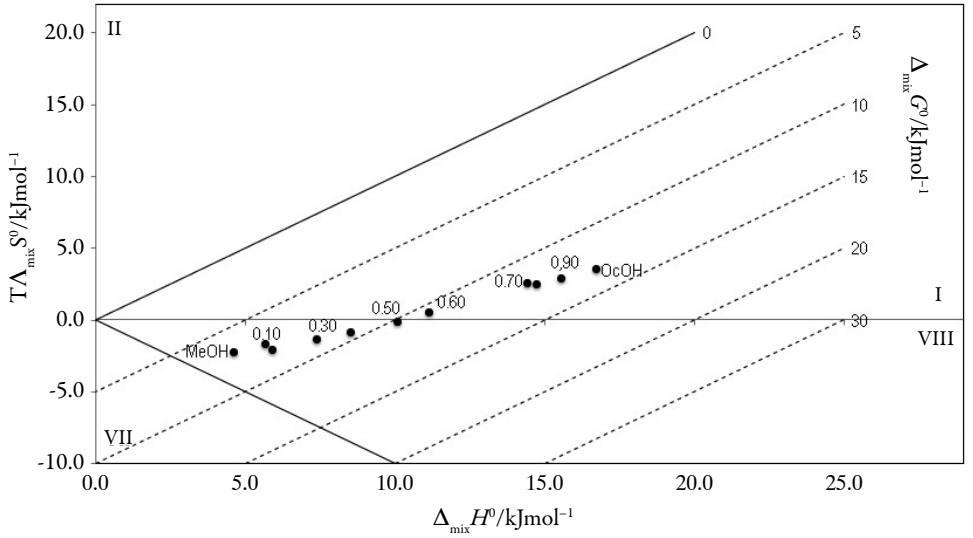

Figure 5. Relationship between the enthalpy ($\Delta_{mix}H^o$) and entropy ($T\Delta_{mix}S^o$) terms of the mixing process of SD at 294.12 K. The isoenergetic curves of $\Delta_{mix}G^o$ are represented by dotted lines.

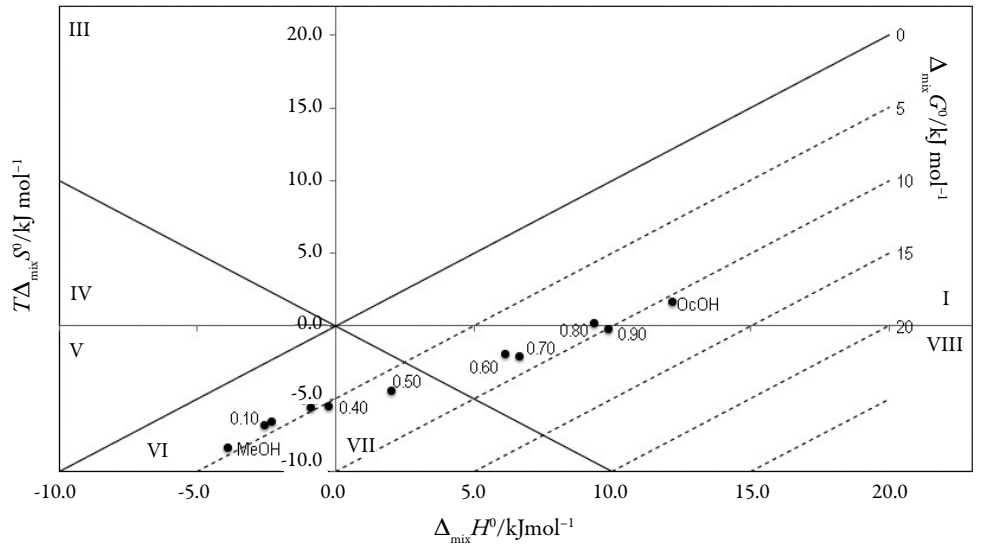

Figure 6. Relationship between the enthalpy ($\Delta_{mix}H^o$) and entropy ($T\Delta_{mix}S^o$) terms of the mixing process of SMR at 294.12 K. The isoenergetic curves of $\Delta_{mix}G^o$ are represented by dotted lines.

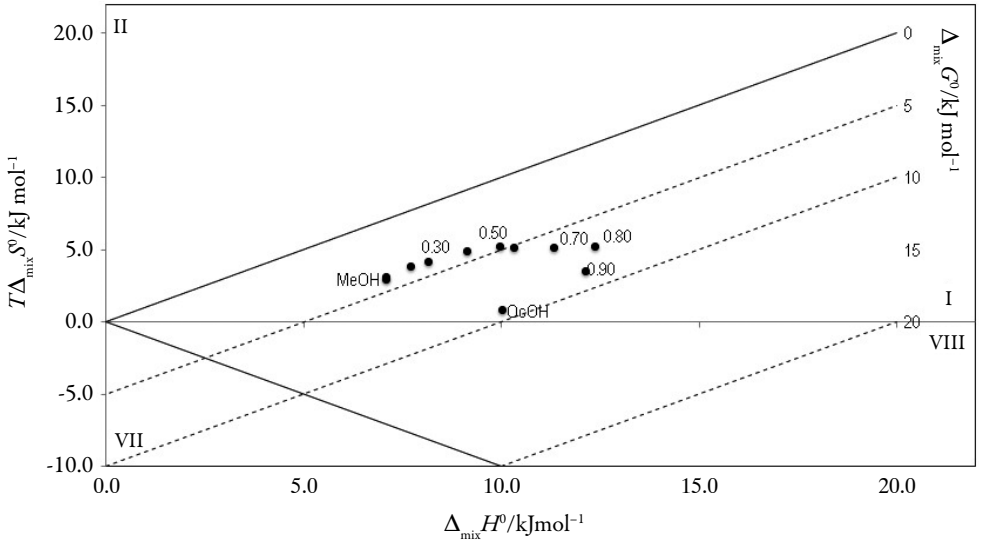

Figure 7. Relationship between the enthalpy ($\Delta_{mix}H^o$) and entropy ($T\Delta_{mix}S^o$) terms of the mixing process of SMT at 294.12 K. The isoenergetic curves of $\Delta_{mix}G^o$ are represented by dotted lines.

Enthalpy-Entropy compensation

Changes in the free energy landscape upon tethering can be attributed to changes in entropy or enthalpy [33-35]. Very often, the changes in entropy and enthalpy are coupled. In many cases, a perturbation produced by a change in the solvent composition, leads to a change in the enthalpy of solution processes is correlated with a similar change in entropy in what is commonly referred to as "entropy–enthalpy compensation" [36]. Entropy–enthalpy compensation is reported for many chemical processes and is often accounted for as a general thermodynamic principle. In this case, analysis has been used to identify the mechanism of the co-solvent action [37-39].

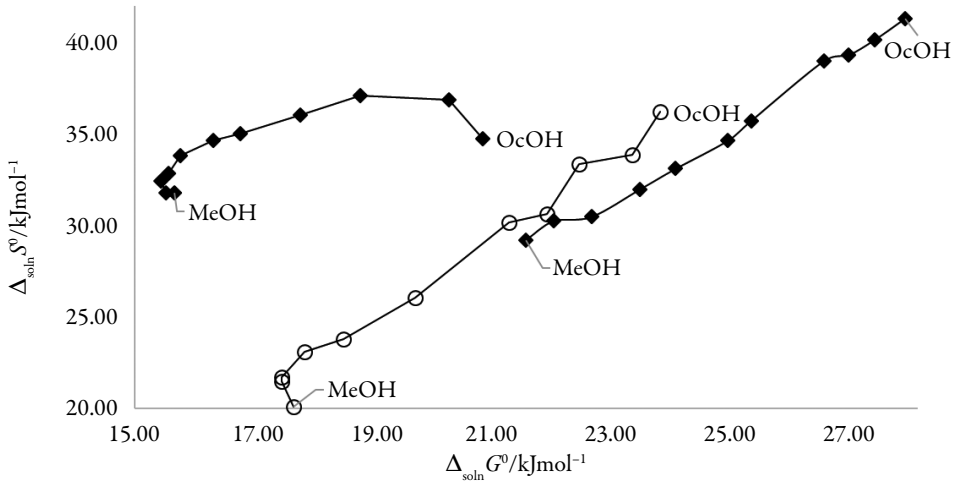

Figure 8. Enthalpy–entropy compensation graph $\Delta_{soln}H^o$ vs $\Delta_{soln}G^o$ for the solution process of SD, SMR and SMT (3) in {octanol (1) + methanol (2)} cosolvent mixtures at 294.12 K.

Figure 8 shows that sulfonamides (SD, SMR and SMT) in {OcOH (1) + MeOH(2)} cosolvent mixtures at 294.12 K presents a non-linear $\Delta_{soln}H^o$ vs. $\Delta_{soln}G^o$ curve. SD, it presents a positive slope throughout the curve, indicating an enthalpic conduction; SMR, presents an enthalpy-driven (positive slope) [40] in mixtures OcOH-rich and intermediate and an entropy-driven (negative slope) [40] in mixtures MeOH-rich; finally the SMT, presents an entropy-driven (negative slope) in mixtures OcOH-rich and in mixtures MeOH-rich, and an enthalpy-driven in intermediate mixtures (positive slope).

Estimation of solubility and lethal median molar concentration of SD, SMR and SMT towards aquatic organisms from Abraham model solute descriptors

The solubility of each of the sulfonamides (SD, SMR and SMT) can be calculated from Abraham model (equation 14), the solute descriptors can be from were

calculated using the page of the Helmholtz Environmental Research Center-UFZ, or from solubility data of each sulfonamide in pure solvents [41].

$$\log C_{3,\text{org}} - \log C_{3,\text{water}} = c_p + e_p E_p + s_p S_p + a_p A_p + b_p B_p + v_p V_p \qquad \text{(Eq. 14)}$$

The numerical values of the solvent coefficients (c_p, e_p, s_p, a_p, b_p, v_p) are tabulated in table 6 [39].

Table 6. Coefficients of equation (14) for various partitioning and solubility ratio processes at 298.15 K [42].

Solvent	c_p	e_p	s_p	a_p	b_p	v_p
Methanol	0.276	0.334	-0.714	0.243	-3.2	3.549
Octanol	0.088	0.562	-1.054	0.034	-3.46	3.814

Descriptors *E*, *S*, *A*, *B* and *V* of the SD, SMR and SMT are presented in table 7 [42].

Table 7. Descriptors *E*, *S*, *A*, *B* and *V* of the SD, SMR and SMT for Abraham model.

Drug	*A*	*E*	*S*	*A*	*B*	*V*
SD	2.08	2.55	0.65	1.37	1.7225	10.504
SMR	2.1	2.65	0.65	1.42	1.8634	11.027
SMT	2.13	2.53	0.59	1.53	2.0043	11.504

The experimental solubility and the calculated solubility from equation 14 are presented in table 8.

Table 8. Calculated solubility of sulfonamides in {octanol (1) + methanol (2)} mixtures by using Abraham model at 298.15 K.

Drug	Solvent	Experimental solubility / mol/L	Calculated solubility/ mol/L	%Dev[a]
SD	Methanol	4.70×10^{-3} [15]	2.93×10^{-3}	38
SMR	Methanol	2.13×10^{-2} [16]	1.94×10^{-2}	9
SMT	Methanol	4.90×10^{-2} [23]	5.42×10^{-2}	11
SD	Octanol	8.80×10^{-5} [36]	7.09×10^{-5}	19
SMR	Octanol	1.92×10^{-4} [36]	1.46×10^{-4}	24
SMT	Octanol	1.60×10^{-3} [36]	1.52×10^{-3}	5

[a] Calculated as $\%\text{Dev} = 100 \times \left(C_3^{\text{Exp}} - C_3^{Cal}\right) / C_3^{\text{Exp}}$ [37].

The model results show a good approximation to the experimental data. Although deviation percentages of 38% are presented, which could be considered high, any theoretical approach to solubility data is of great importance.

The main advantage that the Abraham model is that can be used to predict other solute properties such as the toxicity of organic compounds towards different aquatic organisms. Yue *et al.* [35], has compiled Abraham model equation coefficients for predicting the median lethal molar concentration of organic compounds towards five species of fish (fathead minnow, guppy, bluegill, golden orfe and Medaka high-eyes) [43-44] and three species of water fleas (*Daphnia magna*, *Ceriodaphnia dubia* and *Daphnia pulex*) [45].

In table 9 show tabulated the predicted median lethal molar concentration of SD, SMR and SMT calculated using equation 15 towards various species of fish and water fleas based the solute descriptors. the results reflect that species like Golden Orfe and Medaka high-eyes, they are extremely sensitive to sulfonamides, which shows the great danger to which some aquatic organisms are exposed, due to the dumping of these substances into the aquatic environment.

$$-\log LC_{50} = c_p + e_p E_p + s_p S_p + a_p A_p + b_p B_p + v_p V_p \qquad \text{(Eq. 15)}$$

Table 9. Predicted median lethal molar concentration of SD, SMR and SMT, as LC_{50}, towards various species of fish and water fleas.

Aquatic organism	Endpoint	Drug		
		SD	SMR	SMT
Fathead minnow	96 hours	2.55×10^{-3}	1.32×10^{-3}	1.07×10^{-3}
Guppy	96 hours	3.22×10^{-4}	1.62×10^{-4}	1.14×10^{-4}
Bluegill	96 hours	1.19×10^{-3}	6.42×10^{-4}	6.52×10^{-4}
Golden Orfe	96 hours	2.02×10^{-6}	8.15×10^{-7}	6.19×10^{-7}
Medaka high-eyes	96 hours	2.45×10^{-7}	9.95×10^{-8}	6.88×10^{-8}
Daphnia magna	48 hours	7.41×10^{-4}	3.47×10^{-4}	2.73×10^{-4}
Ceriodaphnia dubia	48 hours	1.27×10^{-3}	7.52×10^{-4}	6.38×10^{-4}
Daphnia pulex	48 hours	1.57×10^{-4}	6.79×10^{-5}	5.93×10^{-5}

Conclusions

The solubility of the three sulfonamides is thermodependent, increasing with increasing temperature, indicating an endothermic process, and the peak of maximum solubility is reached where the cosolvent mixture has a polarity like that of the sulfonamide. Regarding the thermodynamics of solution, both enthalpy and entropy are positive, indicating an entropic conduction of the solution process. The Abraham model, allows the calculation of the solubility of sulfonamides in an acceptable way, the calculation of the LC_{50}, indicates that some aquatic species are extremely sensitive to these drugs and evidences the environmental problem that is being generated by the dumping of drugs to water bodies.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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