

THERMODYNAMICS OF THE MIXING PROCESS OF SEVERAL SODIUM SULFONAMIDES IN ETHANOL + WATER COSOLVENT MIXTURES

ESTUDIO TERMODINÁMICO DEL PROCESO DE MEZCLA DE ALGUNAS SULFONAMIDAS SÓDICAS EN MEZCLAS COSOLVENTES ETANOL + AGUA

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ABSTRACT

Sodium sulfonamides have been extensively used for the treatment of certain infections caused by several types of microorganisms. Although sulfonamides are still widely used in therapeutics, the physicochemical information about their aqueous solutions has not been completed. In this context, the thermodynamic functions of mixing three structurally related sodium sulfonamides were evaluated: Gibbs energy, enthalpy, and entropy. The quantities of mixing were calculated based on the fusion calorimetric values obtained from differential scanning calorimetry measurements and equilibrium solubility values reported in the literature for all the drugs with ethanol + water mixtures. By means of an enthalpy-entropy compensation analysis, non-linear ΔH_{mix}^0 vs. ΔG_{mix}^0 plots with negative slopes from neat ethanol to a 0.60 ethanol mass fraction, and positive slopes from the latter composition to neat water were obtained. From these results, it was concluded that the dissolution process of these drugs in ethanol-rich mixtures was entropy-driven; whereas, in water-rich mixtures the process was enthalpy-driven. Nevertheless, the molecular and ionic events involved in the dissolution of these drugs in this cosolvent system remain unclear.

Keywords: Sodium sulfonamides, mixing process, cosolvency, ethanol, solution thermodynamics.

RESUMEN

Las sulfonamidas sódicas han sido ampliamente utilizadas en el tratamiento de ciertas infecciones causadas por diferentes microorganismos. Si bien las sulfonamidas siguen siendo ampliamente usadas en la terapéutica actual, la información fisicoquímica de sus soluciones acuosas aún no es completa. En este contexto, estudiamos aquí las funciones termodinámicas de mezcla de tres sulfonamidas sódicas relacionadas estructuralmente y que fueron calculadas a partir de las propiedades calorimétricas de fusión y de los valores de solubilidad en equilibrio en mezclas etanol + agua publicados en la literatura. Mediante análisis de compensación entálpica-entrópica se obtuvieron gráficos no lineales de ΔH_{mix}^0 vs. ΔG_{mix}^0 exhibiendo pendientes negativas desde el etanol puro hasta la mezcla cosolvente de 0,60 en fracción másica de etanol y pendientes positivas desde esta mezcla hasta el agua pura; de acuerdo a este resultado se tiene que el proceso de disolución de estos fármacos en mezclas ricas en etanol es conducido

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entrópicamente, mientras que en mezclas ricas en agua el proceso es conducido entálpicamente. Sin embargo, los eventos moleculares e iónicos involucrados en el proceso de disolución de este fármaco en este sistema cosolventes aún no son claros.

Palabras clave: sulfonamidas sódicas, proceso de mezcla, cosolvencia, etanol, termodinámica de soluciones.

INTRODUCTION

Sodium sulfonamides (Sulfadiazine: Na-SD, Sulfamerazine: Na-SMR, and Sulfamethazine: Na-SMT, which molecular structures are presented in figure 1) are drugs extensively used for the treatment of certain infections caused by several types of microorganisms (1). Although these drugs are widely used nowadays in therapeutics, the physicochemical information about their aqueous solutions is not complete at present, even though several physicochemical studies have been done. Thus, the solution thermodynamics in aqueous media for these drugs (as dissociate and non-dissociate compounds) has been presented in the literature (2, 3). Moreover, the transfer physicochemical aspects of these drugs (as non-dissociate compound) from aqueous media up to octanol and some phospholipidic vesicles have also been reported (4). In addition, the apparent molar volumes in water and ethanol have also been studied as a function of drug concentration at 298.15 K (2, 5). Finally, the solubility in ethanol + water cosolvent mixtures has been studied as a function of cosolvent composition and temperature, and the results have been correlated by means of the Jouyban-Acree solubility model (6). Similarly, the thermodynamic quantities of the Na-SD solution were reported in the literature (7).

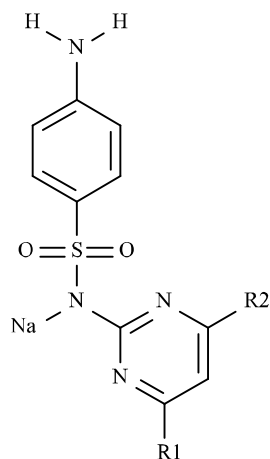


Figure 1. Molecular structure of sodium sulfonamides. Na-SD: R1 = H, R2 = H; Na-SMR: R1 = CH₃, R2 = H; Na-SMT: R1 = CH₃, R2 = CH₃.

As it has been already described, the solubility behavior of drugs in cosolvent mixtures is very important because cosolvent blends are frequently used in purification methods, preformulation studies, and pharmaceutical dosage forms designs, among other applications (8). For these reasons, it is important to systematically determine and collect data about the equilibrium solubility of pharmaceutical compounds. It is also particularly important because it is not possible yet to predict the solubility of drugs in water, organic solvents and/or mixed solvent systems with an acceptable margin of error in the prediction (9). Moreover, temperature-solubility dependence allows us to carry out the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms, involved toward the solution processes (10).

In this context, the main objective of this research is to evaluate the effect of the cosolvent composition on the thermodynamics of mixing of Na-SD, Na-SMR and Na-SMT in some ethanol (EtOH) + water cosolvent mixtures. This study is based on both the calorimetric properties of fusion obtained by differential scanning calorimetry (DSC), and the van't Hoff treatment of equilibrium solubility values reported in the literature (6, 7).

MATERIALS AND METHODS

Reagents

All the sodium sulfonamides (Na-SD: 4-Amino-*N*-2-pyrimidinylbenzenesulfonamide sodium salt, CAS: [547-32-0]; Na-SMR: 4-Amino-*N*-(4-methyl-2-pyrimidinyl)benzenesulfonamide sodium salt, CAS: [127-58-2]; and Na-SMT: 4-Amino-*N*-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide sodium salt, CAS: [1981-58-4] (11)) used were in agreement with the quality requirements indicated in the American Pharmacopeia, USP (12), as well as in the British Pharmacopoeia, BP (13).

Calorimetric study

Melting point and enthalpy of fusion of three sodium sulfonamides were determined through

DSC studies (DSC 823E Mettler Toledo). Thermal analyses were performed at a heating rate of 10 K min⁻¹ in a dynamic nitrogen atmosphere (60 mL min⁻¹). Approximately 1.5 mg of drugs were used. The equipment was calibrated using Indium as a standard (14).

RESULTS AND DISCUSSION

Before presenting the results, it is important to consider that these drugs (in similar way to procaine hydrochloride and sodium naproxen) have an electrolyte behavior (15, 16). Therefore, such drugs dissociate in aqueous solution, interacting with the cosolvent mixture by strong ion-dipole interactions, as well as by other weak non covalent interactions due to their nonpolar groups. Thus, they also could act as a Lewis acid (-NH₂ group) or as a Lewis base (-NH₂ and -SO₂- groups), in order to establish hydrogen bonds with proton-acceptor or donor functional groups in the solvents (-OH groups) (17, 18).

Ideal solubility of sodium sulfonamides

The ideal solubility of non-electrolyte crystalline solutes in a liquid solvent can be calculated by means of equation 1:

$$\ln x_2^{\text{id}} = -\frac{\Delta H_{\text{fus}}(T_{\text{fus}} - T)}{RT_{\text{fus}}T} + \left(\frac{\Delta C_p}{R}\right) \left[\frac{(T_{\text{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\text{fus}}}\right) \right] \quad \text{Equation 1.}$$

where x_2^{id} is the ideal solute solubility as mole fraction; ΔH_{fus} is the molar enthalpy of fusion of the pure solute (at the melting point); T_{fus} is the absolute melting point; T is the absolute solution temperature; R is the gas constant (8.314 J mol⁻¹ K⁻¹); and ΔC_p is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid form, both at the solution temperature (19). Since ΔC_p cannot be easily experimentally determined, it is usual to assume that it may be approximated to the entropy of fusion, which is calculated as follows: $\Delta S_{\text{fus}} = \Delta H_{\text{fus}}/T_{\text{fus}}$. The main reasons for the last assumption have been well discussed in the literature (20). Although equation 1 was developed for non electrolyte compounds, it has also been used to estimate ideal solubilities of some electrolyte drugs (21, 22).

In this context, tables 1 and 2 summarize the thermodynamic properties of fusion and the ideal solubilities of the three sodium sulfonamides, respectively. At the same temperature, x_2^{id} diminishes in the following order: Na-SMR > Na-SD > Na-SMT; whereas for the respective molecular drugs it diminishes in the following order: SMT > SMR > SD (3). In the case of sulfamethazine, the ideal solubilities are similar for the sodium salt and the molecular form (1.068 x 10⁻² and 1.051 x 10⁻² for Na-SMT, and molecular SMT at 298.15 K, respectively). Now, in the case of sulfadiazine, the ideal solubilities are also similar but slightly greater for sodium salt (4.03 x 10⁻³ and 3.03 x 10⁻³ for Na-SD and molecular SD at 298.15 K, respectively). Finally, in the case of sulfamerazine, the ideal solubilities are greater for the molecular form in comparison to sodium salt (2.458 x 10⁻³ and 5.46 x 10⁻³ for Na-SMR and SMR at 298.15 K, respectively).

Moreover, the experimental equilibrium solubility values for these drugs have been reported in the literature (6).

Table 1. Thermodynamic properties of sodium sulfonamides fusion^a.

Drug	$T_{\text{fus}} / \text{K}$	$\Delta H_{\text{fus}} / \text{kJ mol}^{-1}$	$\Delta S_{\text{fus}} / \text{J mol}^{-1} \text{K}^{-1}$
Na-SD	652.0	38.2 (0.4)	58.6 (0.6)
Na-SMR	644.4	41.8 (0.4)	64.8 (0.6)
Na-SMT	582.8	32.8 (0.3)	56.3 (0.6)

^a Values in parentheses are standard deviations.

Table 2. Ideal solubility of sodium sulfonamides at several temperatures^a.

T / K	Na-SD	Na-SMR	Na-SMT
278.15	2.469 (0.025) x 10 ⁻³	1.431 (0.014) x 10 ⁻³	6.67 (0.07) x 10 ⁻³
283.15	2.800 (0.028) x 10 ⁻³	1.644 (0.016) x 10 ⁻³	7.53 (0.08) x 10 ⁻³
288.15	3.17 (0.03) x 10 ⁻³	1.884 (0.019) x 10 ⁻³	8.47 (0.08) x 10 ⁻³
293.15	3.58 (0.04) x 10 ⁻³	2.154 (0.022) x 10 ⁻³	9.52 (0.10) x 10 ⁻³
298.15	4.03 (0.04) x 10 ⁻³	2.458 (0.025) x 10 ⁻³	1.068 (0.011) x 10 ⁻²
303.15	4.53 (0.05) x 10 ⁻³	2.798 (0.028) x 10 ⁻³	1.195 (0.012) x 10 ⁻²
308.15	5.08 (0.05) x 10 ⁻³	3.18 (0.03) x 10 ⁻³	1.335 (0.013) x 10 ⁻²

^a Values in parentheses are standard deviations.

Thermodynamic quantities of sodium sulfonamide solution

Due to the fact that the drugs considered in this study are electrolyte compounds, it is important to keep in mind that in general terms, it could be stated that a strong electrolyte dissociates according to the following expression: $C_{\nu+}A_{\nu-} \rightarrow \nu_+ C^{z+} + \nu_- A^{z-}$, where ν_+ is the number of cations (C^{z+}) of valence

z_+ , and ν_- is the number of anions (A^{z-}) of valence z_- . The concept of mean ionic activity (a_{\pm}^{ν}) is used because is not possible to determine experimentally the activity of ions separately. Thus, the thermodynamic activity for an electrolyte can be defined as follows: $a_2 = a_+^{\nu_+} a_-^{\nu_-} = a_{\pm}^{\nu}$ (23-25).

The three sodium sulfonamides are electrolyte solutes of type one-one, which means that they dissociate in aqueous solutions to generate two species: a monovalent anion and a monovalent cation, respectively. If the inter-ionic interactions are not considered, the ν value for these drugs could be ideally assumed to be 2, in a first approach, thus this value could be used to calculate the apparent thermodynamic solution functions (7, 15, 16).

Therefore, according to van't Hoff's analysis, the apparent standard enthalpy change of solution (ΔH_{soln}^0) for electrolytes type one-one (such as the sodium sulfonamides studied here), is obtained using the mean harmonic temperature (T_{hm} is 292.8 K in our case) according to equation 2 (7, 15, 16), that is if the inter-ionic interactions are not considered.

$$\left(\frac{\partial \ln x_{\text{Na-Sulf}}}{\partial (1/T - 1/T_{\text{hm}})} \right)_p = - \frac{\Delta H_{\text{soln}}^0}{2 \cdot R} \quad \text{Equation 2.}$$

where, R is the universal gas constant (8.314 J mol⁻¹ K⁻¹). In all the studied cases, linear models with good determination coefficients were obtained.

The apparent standard Gibbs energy change for the solution process (ΔG_{soln}^0) of electrolytes type one-one was calculated at the mean harmonic temperature by means of equation 3, considering the approach proposed by Krug *et al.*, 1976 (26).

$$\Delta G_{\text{soln}}^0 = -2 \cdot R \cdot T_{\text{hm}} \cdot \text{intercept} \quad \text{Equation 3.}$$

in which, the intercept used was the one obtained in the analysis taking $\ln x_{\text{Na-Sulf}}$ as a function of $1/T - 1/T_{\text{hm}}$. Finally, the apparent standard entropic change for the solution process (ΔS_{soln}^0) was obtained from the respective ΔH_{soln}^0 and ΔG_{soln}^0 values by means of the following equation:

$$\Delta S_{\text{soln}}^0 = \frac{(\Delta H_{\text{soln}}^0 - \Delta G_{\text{soln}}^0)}{T_{\text{hm}}} \quad \text{Equation 4.}$$

Table 3 summarizes the apparent standard thermodynamic functions for the experimental solution process of sodium sulfonamides in all EtOH + water cosolvent mixtures. In order to calculate the thermodynamic quantities for the experimental solution processes, some uncertainty propagation methods were used (27). As it was expected, it was found that the standard Gibbs energy of the solution is positive in all cases because the mole fraction is always lower than the unit; thus its logarithmic term is negative, therefore, the standard Gibbs energy will be a positive quantity.

The apparent enthalpy of solution is positive in all cases, therefore, the process is always endothermic. Similarly, the entropy of solution is also positive for Na-SMT in all solvent systems and Na-SMR in compositions from neat water to 0.80 in a mass fraction of EtOH. Oppositely, this quantity is negative for Na-SD in all solvent systems and Na-SMR in the mixture of 0.90 in mass fraction of EtOH and neat EtOH. These results do not show enthalpy or entropy-driving overall in the solution process for the last indicated systems. For all sodium sulfonamides, ΔH_{soln}^0 values increase from neat water to 0.60 in mass fraction of EtOH, and decrease from this EtOH proportion to neat EtOH. In contrast with enthalpy, ΔS_{soln}^0 values increase from neat water to the mixtures of 0.30, 0.40 and 0.50 in mass fraction of EtOH for Na-SD, Na-SMR and Na-SMT respectively, despite the sign obtained and diminishing beyond this composition to neat EtOH. The apparent enthalpic and entropic values obtained for the dissolution process of Na-SD in neat water are in good agreement regarding those reported in the literature (11.0 ± 0.6 kJ mol⁻¹ and -13.5 ± 0.7 J mol⁻¹ K⁻¹, respectively) (2). However, the same quantities for Na-SMT are not in agreement with those reported in the same research (10.9 ± 0.6 kJ mol⁻¹ and -19.7 ± 1.0 J mol⁻¹ K⁻¹, respectively) (2). That is why, it is important to note that the studied temperature intervals and the used analytical techniques were significantly different in both investigations.

Aiming to compare the relative contributions by enthalpy (ζ_H) and by entropy (ζ_{TS}) toward the solution process, equations 5 and 6 were respectively employed (28).

Table 3. Apparent thermodynamic quantities related to the sodium sulfonamide solution process in ethanol + water cosolvent mixtures at 292.8 K^a.

μ_{EtOH}^b	$\Delta G_{\text{soln}}^0 / \text{kJ mol}^{-1}$	$\Delta H_{\text{soln}}^0 / \text{kJ mol}^{-1}$	$\Delta G_{\text{soln}}^0 / \text{J mol}^{-1} \text{K}^{-1}$	$T\Delta S_{\text{soln}}^0 / \text{kJ mol}^{-1}$	ζ_H^c	ζ_{TS}^c
Na-SD ^d						
0.00	15.00 (0.02)	11.02 (0.02)	-13.59 (0.03)	-3.98 (0.01)	0.735	0.265
0.10	16.00 (0.02)	13.03 (0.03)	-10.15 (0.03)	-2.97 (0.01)	0.814	0.186
0.20	17.17 (0.04)	16.64 (0.05)	-1.80 (0.01)	-0.53 (0.00)	0.969	0.031
0.30	18.73 (0.04)	18.43 (0.05)	-1.04 (0.00)	-0.31 (0.00)	0.984	0.016
0.40	20.23 (0.07)	19.91 (0.08)	-1.11 (0.01)	-0.32 (0.00)	0.984	0.016
0.50	22.28 (0.03)	20.56 (0.07)	-5.87 (0.02)	-1.72 (0.01)	0.923	0.077
0.60	24.55 (0.06)	20.57 (0.06)	-13.60 (0.05)	-3.98 (0.02)	0.838	0.162
0.70	27.12 (0.03)	19.13 (0.04)	-27.30 (0.06)	-7.99 (0.02)	0.705	0.295
0.80	31.36 (0.10)	14.75 (0.06)	-56.73 (0.29)	-16.61 (0.09)	0.470	0.530
0.90	36.99 (0.19)	12.65 (0.10)	-83.1 (0.8)	-24.34 (0.22)	0.342	0.658
1.00	45.71 (0.05)	9.95 (0.02)	-122.1 (0.3)	-35.76 (0.10)	0.218	0.782
Ideal	14.01 (0.14)	17.15 (0.13)	10.36 (0.13)	3.14 (0.04)	0.845	0.155
Na-SMR						
0.00	20.03 (0.10)	32.17 (0.13)	41.45 (0.27)	12.14 (0.08)	0.726	0.274
0.10	20.70 (0.08)	35.27 (0.07)	49.75 (0.22)	14.57 (0.07)	0.708	0.292
0.20	21.62 (0.08)	40.02 (0.22)	62.8 (0.4)	18.39 (0.12)	0.685	0.315
0.30	22.57 (0.05)	43.86 (0.06)	72.71 (0.18)	21.29 (0.05)	0.673	0.327
0.40	23.47 (0.10)	45.51 (0.07)	75.3 (0.3)	22.04 (0.10)	0.674	0.326
0.50	24.65 (0.10)	46.11 (0.09)	73.3 (0.3)	21.46 (0.10)	0.682	0.318
0.60	26.52 (0.17)	46.65 (0.17)	68.7 (0.5)	20.12 (0.15)	0.699	0.301
0.70	28.99 (0.19)	44.61 (0.13)	53.3 (0.4)	15.62 (0.11)	0.741	0.259
0.80	32.65 (0.23)	40.61 (0.26)	27.20 (0.26)	7.96 (0.08)	0.836	0.164
0.90	37.90 (0.24)	32.09 (0.13)	-19.84 (0.15)	-5.81 (0.04)	0.847	0.153
1.00	42.95 (0.17)	23.52 (0.14)	-66.3 (0.5)	-19.43 (0.14)	0.548	0.452
Ideal	15.27 (0.15)	18.97 (0.14)	12.21 (0.15)	3.70 (0.05)	0.837	0.163
Na-SMT						
0.00	17.57 (0.12)	28.93 (0.15)	38.8 (0.3)	11.36 (0.10)	0.718	0.282
0.10	17.89 (0.13)	36.31 (0.14)	62.9 (0.5)	18.43 (0.15)	0.663	0.337
0.20	18.20 (0.08)	42.73 (0.07)	83.8 (0.4)	24.53 (0.12)	0.635	0.365
0.30	18.58 (0.07)	51.38 (0.10)	112.0 (0.5)	32.80 (0.15)	0.610	0.390
0.40	19.15 (0.09)	56.10 (0.09)	126.2 (0.6)	36.95 (0.19)	0.603	0.397
0.50	19.87 (0.12)	59.03 (0.12)	133.7 (0.8)	39.16 (0.25)	0.601	0.399
0.60	21.08 (0.12)	59.96 (0.17)	132.8 (0.8)	38.88 (0.24)	0.607	0.393
0.70	22.85 (0.12)	54.14 (0.11)	106.9 (0.6)	31.29 (0.18)	0.634	0.366
0.80	25.85 (0.12)	42.22 (0.11)	55.9 (0.3)	16.37 (0.09)	0.721	0.279
0.90	29.86 (0.07)	38.21 (0.09)	28.51 (0.10)	8.35 (0.03)	0.821	0.179
1.00	31.90 (0.10)	34.0 (0.3)	7.09 (0.07)	2.08 (0.02)	0.942	0.058
Ideal	11.57 (0.12)	16.48 (0.13)	16.18 (0.21)	4.91 (0.06)	0.771	0.229

^a Values in parentheses are standard deviations. ^b μ_{EtOH} is the mass fraction of ethanol in the solute-free cosolvent mixture. ^c ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward Gibbs energy of solution. ^d Taken from Delgado and Martinez, 2010 (7).

$$\zeta_H = \frac{|\Delta H_{\text{soln}}^0|}{|\Delta H_{\text{soln}}^0| + |T\Delta S_{\text{soln}}^0|}$$

Equation 5.

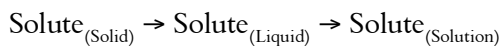
$$\zeta_{TS} = \frac{|T\Delta S_{\text{soln}}^0|}{|\Delta H_{\text{soln}}^0| + |T\Delta S_{\text{soln}}^0|}$$

Equation 6.

From the ζ_H and ζ_{TS} values shown in table 3, it was concluded that the main contributor of the standard Gibbs energy of the solution process of SD-Na is enthalpy, except for Na-SD in the following cosolvent composition interval: $0.80 \leq \mu_{\text{EtOH}} \leq 1.00$. This result evidences the relevance of the energetic factor on the dissolution processes of these drugs.

Thermodynamic quantities of the sodium sulfonamide mixture

The solution process can be represented by the following hypothetical stages (10):



where, the respective partial processes regarding the solution are solute fusion and mixing at the same temperature (292.8 K), which allows calculating the partial thermodynamic contributions to the overall solution process by means of equations 7 and 8, respectively.

$$\Delta H_{\text{soln}}^0 = \Delta H_{\text{fus}}^{292.8} + \Delta H_{\text{mix}}^0 \quad \text{Equation 7.}$$

$$\Delta S_{\text{soln}}^0 = \Delta S_{\text{fus}}^{292.8} + \Delta S_{\text{mix}}^0 \quad \text{Equation 8.}$$

where, $\Delta H_{\text{fus}}^{292.8}$ and $\Delta S_{\text{fus}}^{292.8}$ represent the thermodynamic functions of the fusion process at the harmonic temperature (292.8 K). $\Delta H_{\text{fus}}^{292.8}$ was calculated by means of the following equation: $\Delta H_{\text{fus}}^T = \Delta H_{\text{fus}}^{\text{MP}} - \Delta C_p(T_{\text{fus}} - T)$, using $\Delta S_{\text{fus}}^{\text{MP}}$ instead of ΔC_p , for obtaining the values of 17.16, 18.98 and 16.49 kJ mol⁻¹ for Na-SD, Na-SMR, and Na-SMT, respectively. These values coincide with the enthalpic changes for the ideal solution processes, as it is shown in table 3. In contrast, the entropies of fusion at 292.8 K (58.6, 64.8, and 56.3 J mol⁻¹ K⁻¹ for Na-SD, Na-SMR, and Na-SMT, respectively) do not coincide with the entropic changes of the ideal solution processes at this temperature, as it is also shown in table 3. For this reason and for practical purposes, $\Delta S_{\text{soln}}^{\text{oid}}$ values were used instead of $\Delta S_{\text{fus}}^{292.8}$, as it was previously done with several non electrolyte drugs in EtOH + water cosolvent mixtures (10, 29 - 31). Table 4 summarizes the thermodynamic quantities of the sodium sulfonamide mixing processes. The Gibbs energy of mixing was positive in all the systems studied. It is interesting to note that the Gibbs energies of transfer from water to EtOH (calculated as the difference between Gibbs energies of mixing in EtOH and water) diminish in the following order: Na-SD (30.7 kJ mol⁻¹) > Na-SMR (22.9 kJ mol⁻¹) > Na-SMT (14.3 kJ mol⁻¹).

When the partial contributions of the ideal solution (related to the solute fusion process) and mixing processes to the enthalpy and entropy of solution were analyzed, it was found that $\Delta H_{\text{soln}}^{\text{oid}}$ and $\Delta S_{\text{soln}}^{\text{oid}}$ are positive (as it is shown in table 4), while the contribution of the thermodynamic quantities related to the mixing process toward the solution processes is variable. Thus, ΔH_{mix}^0 is positive for all sodium sulfonamides except for Na-SD in the following cosolvent composition interval: $0.30 \leq \mu_{\text{EtOH}} \leq 0.70$. However, the entropy of mixing (ΔS_{mix}^0) is negative for Na-SD in all mixtures, whereas for Na-SMR and Na-SMT, this quantity is positive from neat water to 0.80 or 0.90 in mass fraction of EtOH, respectively. If the contribution of the mixing processes to the dissolution processes is considered, it can be concluded that, i) the mixing process is driven by enthalpy ($\Delta H_{\text{mix}}^0 < 0$ and $\Delta S_{\text{mix}}^0 < 0$) for Na-SD in the intervals $0.00 \leq \mu_{\text{EtOH}} \leq 0.20$ and $0.80 \leq \mu_{\text{EtOH}} \leq 1.00$, ii) the mixing process is driven by entropy ($\Delta H_{\text{mix}}^0 > 0$ and $\Delta S_{\text{mix}}^0 > 0$) for Na-SMR in the interval $0.00 \leq \mu_{\text{EtOH}} \leq 0.80$; and iii) the mixing process is also driven by entropy ($\Delta H_{\text{mix}}^0 > 0$ and $\Delta S_{\text{mix}}^0 > 0$) for Na-SMT in the interval $0.00 \leq \mu_{\text{EtOH}} \leq 0.90$. It was found that all other cases were not enthalpy or entropy-driven ($\Delta H_{\text{mix}}^0 > 0$ and $\Delta S_{\text{mix}}^0 < 0$).

The net variation in ΔH_{mix}^0 values results from the contribution of several types of interaction. The enthalpy of the cavity formation (required for solute accommodation) is endothermic because the energy must be supplied against the cohesive forces of the solvent. This process decreases solubility. On the other hand, the enthalpy of solute-solvent interaction is exothermic and results mainly from ion-dipole, van der Waals and Lewis acid-base interactions. In the case of non-electrolyte drugs, the structuring of water molecules around the nonpolar groups of solutes (hydrophobic hydration) contributes to reduce the net heat of the mixing process to minor or even negative values in aqueous solutions, as it is the case of pure water (as it is shown in table 4 for Na-SD). Nevertheless, these drugs are electrolyte and, therefore, they interact with the solvent through ion-dipole interactions, which could lead to hydrophilic hydration around the anionic group.

Table 4. Apparent thermodynamic quantities related to the sodium sulfonamide mixing process in ethanol + water cosolvent mixtures at 292.8 K^a.

μ_{EtOH}^b	$\Delta G_{\text{mix}}^0 / \text{kJ mol}^{-1}$	$\Delta H_{\text{mix}}^0 / \text{kJ mol}^{-1}$	$\Delta S_{\text{mix}}^0 / \text{J mol}^{-1} \text{K}^{-1}$	$T\Delta S_{\text{mix}}^0 / \text{kJ mol}^{-1}$	ζ_H^c	ζ_{TS}^c
Na-SD						
0.00	0.99 (0.14)	-6.13 (0.14)	-23.95 (0.13)	-7.12 (0.04)	0.463	0.537
0.10	2.00 (0.14)	-4.11 (0.14)	-20.51 (0.13)	-6.11 (0.04)	0.402	0.598
0.20	3.16 (0.15)	-0.50 (0.14)	-12.16 (0.13)	-3.67 (0.04)	0.121	0.879
0.30	4.73 (0.15)	1.28 (0.14)	-11.40 (0.13)	-3.44 (0.04)	0.271	0.729
0.40	6.23 (0.16)	2.77 (0.16)	-11.46 (0.13)	-3.46 (0.04)	0.444	0.556
0.50	8.27 (0.14)	3.41 (0.15)	-16.22 (0.13)	-4.86 (0.04)	0.413	0.587
0.60	10.54 (0.15)	3.42 (0.15)	-23.96 (0.14)	-7.12 (0.04)	0.324	0.676
0.70	13.12 (0.14)	1.98 (0.14)	-37.66 (0.15)	-11.13 (0.04)	0.151	0.849
0.80	17.35 (0.17)	-2.40 (0.15)	-67.1 (0.3)	-19.75 (0.09)	0.108	0.892
0.90	22.99 (0.23)	-4.49 (0.17)	-93.5 (0.8)	-27.48 (0.22)	0.141	0.859
1.00	31.71 (0.15)	-7.19 (0.14)	-132.5 (0.4)	-38.90 (0.11)	0.156	0.844
Na-SMR						
0.00	4.76 (0.18)	13.20 (0.19)	29.2 (0.3)	8.44 (0.09)	0.610	0.390
0.10	5.44 (0.17)	16.30 (0.16)	37.54 (0.27)	10.87 (0.08)	0.600	0.400
0.20	6.36 (0.17)	21.05 (0.26)	50.6 (0.4)	14.69 (0.13)	0.589	0.411
0.30	7.30 (0.16)	24.89 (0.15)	60.51 (0.24)	17.59 (0.07)	0.586	0.414
0.40	8.21 (0.18)	26.55 (0.15)	63.1 (0.4)	18.34 (0.11)	0.591	0.409
0.50	9.38 (0.18)	27.15 (0.16)	61.1 (0.4)	17.76 (0.11)	0.604	0.396
0.60	11.26 (0.23)	27.68 (0.22)	56.5 (0.5)	16.42 (0.15)	0.628	0.372
0.70	13.73 (0.24)	25.64 (0.19)	41.1 (0.4)	11.92 (0.12)	0.683	0.317
0.80	17.38 (0.28)	21.6 (0.3)	15.0 (0.3)	4.26 (0.09)	0.835	0.165
0.90	22.63 (0.28)	13.12 (0.19)	-32.05 (0.21)	-9.51 (0.06)	0.580	0.420
1.00	27.68 (0.23)	4.56 (0.19)	-78.5 (0.5)	-23.13 (0.14)	0.165	0.835
Na-SMT						
0.00	6.00 (0.17)	12.45 (0.20)	22.6 (0.4)	6.45 (0.12)	0.659	0.341
0.10	6.31 (0.17)	19.84 (0.20)	46.8 (0.5)	13.52 (0.16)	0.595	0.405
0.20	6.63 (0.14)	26.25 (0.15)	67.6 (0.5)	19.62 (0.13)	0.572	0.428
0.30	7.01 (0.14)	34.91 (0.16)	95.8 (0.5)	27.89 (0.16)	0.556	0.444
0.40	7.58 (0.15)	39.62 (0.16)	110.0 (0.7)	32.04 (0.20)	0.553	0.447
0.50	8.30 (0.17)	42.55 (0.18)	117.6 (0.9)	34.26 (0.25)	0.554	0.446
0.60	9.51 (0.16)	43.49 (0.22)	116.6 (0.8)	33.98 (0.25)	0.561	0.439
0.70	11.28 (0.17)	37.66 (0.17)	90.7 (0.6)	26.39 (0.19)	0.588	0.412
0.80	14.28 (0.17)	25.74 (0.17)	39.7 (0.4)	11.46 (0.11)	0.692	0.308
0.90	18.29 (0.14)	21.73 (0.16)	12.33 (0.23)	3.44 (0.07)	0.863	0.137
1.00	20.33 (0.15)	17.5 (0.4)	-9.09 (0.22)	-2.83 (0.07)	0.861	0.139

^a Values in parentheses are standard deviations. ^b μ_{EtOH} is the mass fraction of ethanol in the solute-free cosolvent mixture. ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward Gibbs energy mixing.

As it was already stated, the energy of the cavity formation process should be lower as the proportion of EtOH increases because the polarity of the medium decreases, which is a fact that favors solute-solvent interactions, except for ion-dipole. This fact is shown in table 4, where ΔH_{mix}^0 decreases as the proportion of cosolvent increases in EtOH-rich mixtures. According to Romero *et al.*, 1996 (32), for non-electrolytes in the initial portion of the solubility curve, the hydrogen bonding of the drug will increase according to the EtOH concentration. For large cosolvent proportions (from 0.60 in mass fraction of EtOH to neat EtOH), this interaction

may be saturated, becoming a constant contribution. However, nonspecific and cavity effects are not saturated, and vary according to the EtOH concentration. Nevertheless, these considerations do not explain the behavior observed in water-rich mixtures, where the ion-dipole interactions predominate for all sodium sulfonamides.

Enthalpy-Entropy Compensation of sodium sulfonamide mixing process

According to the literature, weight graphs of $\Delta H_{\text{soln}}^{0\text{-app}}$ as a function of $\Delta G_{\text{soln}}^{0\text{-app}}$ at the mean harmonic temperature allows us to observe similar

mechanisms for the solution process according to the tendencies that can be seen in the results (33, 34).

In this context, figure 2 comprehensively shows that sodium sulfonamides, in the EtOH + water cosolvent system, present non-linear $\Delta H_{\text{soln}}^{0-\text{app}}$ vs. $\Delta G_{\text{soln}}^{0-\text{app}}$ compensation with negative slopes if the composition interval $0.60 \leq \mu_{\text{EtOH}} \leq 1.00$ is considered for all sodium sulfonamides; whereas from this EtOH proportion to neat water, positive slopes are obtained. According to this graph, it can be concluded that the driving function for the drug mixing processes is the entropy in the former case, while in the latter the driving function is the enthalpy. Nevertheless, the molecular and ionic events, which are involved in the dissolution of these drugs in this cosolvent, system are unclear.

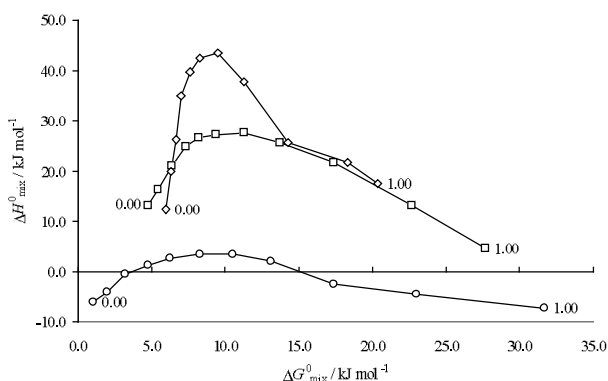


Figure 2. ΔH_{mix}^0 vs. ΔG_{mix}^0 enthalpy-entropy compensation plot for solubility of sodium sulfonamides in ethanol + water cosolvent mixtures at 292.8 K. (\diamond): Na-SMT, (\square): Na-SMR; (\circ): Na-SD.

CONCLUSIONS

From all the previously discussed topics, it can be concluded that the mixing processes of these sodium sulfonamides in EtOH + water mixtures is variable according to the cosolvent composition. Also, non linear enthalpy-entropy compensation was found for the drugs evaluated in this cosolvent system. In this context, the solution processes in compositions from pure EtOH to the mixture having 0.60 in mass fraction of ethanol were found to be enthalpy-driven; whereas, the systems from this ethanol proportion to neat water were found to be enthalpy-driven. Finally, it can be stated that the thermodynamic quantities presented in this report broaden the physicochemical information about electrolyte drugs in aqueous and alcoholic solutions.

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REFERENCES

- Gennaro AR, editor. Remington: The Science and Practice of Pharmacy. 21 ed. Philadelphia, United States: Lippincott Williams & Wilkins; 2005. Gelone S, O'Donnell JA. Anti-Infectives; p. 1630-1633.
- Labastidas I, Martínez F. Aspectos termodinámicos de la solubilidad acuosa de algunas sales orgánicas de interés farmacéutico. Acta Farm Bonaerense. 2006 Mar; 25 (1): 55-63.
- Martínez F, Gómez A. Thermodynamic study of the solubility of some sulfonamides in octanol, water, and the mutually saturated solvents. J Solution Chem. 2001 Oct; 30 (10): 909-923.
- Martínez F, Gómez A. Thermodynamics of partitioning of some sulfonamides in 1-octanol/buffer and liposome systems. J Phys Org Chem. 2002 Dec; 15 (12): 874-880.
- Martínez F, Gómez A, Ávila CM. Volúmenes molales parciales de transferencia de algunas sulfonamidas desde el agua hasta la mezcla agua-etanol ($X = 0.5$). Acta Farm Bonaerense. 2002 Jun; 21 (2): 107-118.
- Delgado DR, Martínez F, Fakhree MAA, Jouyban A. Study of the solubility of some sodium sulfonamides in ethanol + water cosolvent mixtures and correlation with the Jouyban-Acree cosolvent model. Biomed Int. 2011 Jun; 2 (1): 5-11.
- Delgado DR, Martínez F. Thermodynamic study of the solubility of sodium sulfadiazine in some ethanol + water cosolvent mixtures. Vitae. 2010 May-Aug; 17 (2): 191-198.
- Swarbrick J, Boylan JC (editors). Encyclopedia of Pharmaceutical Technology, Vol. 3. New York, United States: Marcel Dekker; 1988. Rubino JT. Cosolvents and Cosolvency; p. 375-398.
- Jouyban A. Solubility: still a challenging subject in pharmaceutical sciences. Vitae. 2010 Sep-Dec; 17 (3): 241-242.
- Pacheco DP, Martínez F. Thermodynamic analysis of the solubility of naproxen in ethanol + water cosolvent mixtures. Phys Chem Liq. 2007 Oct; 45 (5): 581-595.
- Budavari S, O'Neil MJ, Smith A, Heckelman PE, Obenchain Jr. JR, Gallipeau JAR, et al. The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals. 13 ed. Whitehouse Station, NJ, United States: Merck & Co., Inc.; 2001. p. 1586-1589.
- US Pharmacopeia 23 ed. United States Pharmacopeial Convention, Rockville, MD, United States; 1994. p. 1456.
- British Pharmacopoeia 1988. Vol. I. Her Majesty's Stationery Office, London, England; 1988. p. 545.
- Brittain HG (editor). Physical Characterization of Pharmaceutical Solids. New York, USA: Marcel Dekker, Inc.; 1995. McCauley SA, Brittain HG. Thermal methods of analysis; p. 223-251.
- Delgado DR, Vargas EF, Martínez F. Thermodynamic study of the solubility of procaine-HCl in some ethanol + water cosolvent mixtures. J Chem Eng Data. 2010 Aug 12; 55 (8): 2900-2904.
- Delgado DR, Ruidiaz MA, Gómez SM, Gantiva M, Martínez F. Thermodynamic study of the solubility of sodium naproxen

- in some ethanol + water mixtures. *Quím Nova*. 2010; 33 (9): 1923-1927.
17. Martin A, Bustamante P, Chun AHC. *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*. 4th ed. Philadelphia, United States: Lea & Febiger; 1993. p. 221-237.
 18. Florence AT, Atwood D. *Physicochemical Principles of Pharmacy*. 3rd ed. London, England: MacMillan Press Ltd.; 1998. p. 64-67.
 19. Hildebrand JH, Prausnitz JM, Scott RL. *Regular and Related Solutions*. New York, United States: Van Nostrand Reinhold; 1970. 240 p.
 20. Neau SH, Flynn GL. Solid and liquid heat capacities of n-alkyl para-aminobenzoates near the melting point. *Pharm. Res*. 1990 Nov; 7 (11): 1157-1162.
 21. Bustamante P, Peña MA, Barra J. The modified extended Hansen method to determine partial solubility parameters of drugs containing a single hydrogen bonding group and their sodium derivatives: benzoic acid/Na and ibuprofen/Na. *Int J Pharm*. 2000 Jan 20; 194 (1): 117-124.
 22. Guerrieri P, Rumondor ACF, Li T, Taylor LS. Analysis of relationships between solid-state properties, counterion and developability of pharmaceutical salts. *AAPS PharmSciTech*. 2010 Sept; 11 (3): 1212-1222.
 23. Klotz IM, Rosenberg RM. *Chemical Thermodynamics: Basic Theory and Methods*. 6th ed. New York, United States: John Wiley & Sons, Inc.; 2000. p. 438-448.
 24. Bevan J, Boerio-Goates J. *Chemical Thermodynamics: Principles and Applications*. New York, United States: Academic Press; 2000. p. 295-301.
 25. Connors KA. *Thermodynamics of Pharmaceutical Systems: An Introduction for Students of Pharmacy*. Hoboken NJ, United States: Wiley-Interscience; 2002. p. 96-105.
 26. Krug RR, Hunter WG, Grieger RA. Enthalpy-entropy compensation. 2. Separation of the chemical from the statistical effects. *J Phys Chem*. 1976 Oct; 80 (21): 2341-2351.
 27. Bevington PR. *Data Reduction and Error Analysis for the Physical Sciences*. New York, United States: McGraw-Hill Book Co.; 1969. p. 56-91.
 28. Perlovich GL, Kurkov SV, Kinchin AN, Bauer-Brandl A. Thermodynamics of solutions III: Comparison of the solvation of (+)-naproxen with other NSAIDs. *Eur J Pharm Biopharm*. 2004 Mar; 57 (2): 411-420.
 29. Jiménez JA, Martínez F. Thermodynamic magnitudes of mixing and solvation of acetaminophen in ethanol + water cosolvent mixtures. *Rev Acad Colomb Cienc*. 2006 Mar; 30 (114): 87-99.
 30. Manrique J, Martínez F. Solubility of ibuprofen in some ethanol + water cosolvent mixtures at several temperatures. *Lat Am J Pharm*. 2007 Jun; 26 (3): 344-354.
 31. Gantiva M, Yurquina A, Martínez F. Solution thermodynamics of ketoprofen in ethanol + water cosolvent mixtures. *J Chem Eng Data*. 2010 Jan 14; 55 (1): 113-118.
 32. Romero S, Reillo A, Escalera B, Bustamante P. The behavior of paracetamol in mixtures of amphiprotic and amphiprotic-aprotic solvents: Relationship of solubility curves to specific and nonspecific interactions. *Chem. Pharm. Bull*. 1996 May; 44 (5): 1061-1064.
 33. Bustamante P, Romero S, Peña A, Escalera B, Reillo A. Nonlinear enthalpy-entropy compensation for the solubility of drugs in solvent mixtures: paracetamol, acetanilide and nalidixic acid in dioxane-water. *J Pharm Sci*. 1998 Dec; 87 (12): 1590-1596.
 34. Tomlinson E. Enthalpy-entropy compensation analysis of pharmaceutical, biochemical and biological systems. *Int J Pharm*. 1983 Jan; 13 (2): 115-144.