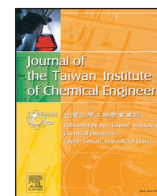




Contents lists available at ScienceDirect

Journal of the Taiwan Institute of Chemical Engineers

journal homepage: www.elsevier.com/locate/jtice

Solution thermodynamics and preferential solvation of sulfamethazine in ethylene glycol + water mixtures

Abdelkarim Aydi^{a,b}, Claudia Patricia Ortiz^c, Diego Ivan Caviedes-Rubio^d, Cherifa Ayadi^{e,f}, Souhaira Hbaieb^g, Daniel Ricardo Delgado^{d,*}

^a LETIAM, Lip (Sys)2, IUT d'Orsay, Plateau de Moulon, Université Paris-Sud, 91400 Orsay, France

^b Laboratory of Materials Molecules and Applications, Preparatory Institute for Scientific and Technical Studies, University of Carthage, Tunisia

^c Programa de Administración en Seguridad y Salud en el Trabajo, Grupo de Investigación en Seguridad y Salud en el Trabajo, Corporación Universitaria Minuto de Dios-UNIMINUTO, Neiva, Huila, Colombia

^d Grupo de Investigaciones GRIAUC, Facultad de Ingeniería, Programa de Ingeniería, Ingeniería Civil, Universidad Cooperativa de Colombia, Calle 11 No. 1-51, Neiva-Huila, Colombia

^e Laboratory of Materials, Treatment and Analysis (LMTA), National Institute of Research and Physicochemical Analysis (INRAP), BiotechPole Sidi-Thabet, Ariana 2020, Tunisia

^f Faculté des Sciences de Tunis, Université Tunis El Manar, Campus Universitaire El Manar, Tunis 2092, Tunisia

^g Faculté des Sciences de Tunis, Université Tunis El Manar, LR/18/ES/08 "Caractérisations, Applications et Modélisation de Matériaux", 2092, Tunisia

ARTICLE INFO

Article History:

Received 24 November 2020

Revised 25 December 2020

Accepted 28 December 2020

Available online xxx

Keywords:

Sulfamethazine

Solubility

Preferential solvation

vant Hoff

Solution thermodynamics

ABSTRACT

The solubility of sulfamethazine (SMT) in ethylene glycol (EG) + water (W) cosolvent mixtures was determined at nine temperatures (278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K) by means of the stirring method. From the solubility data, the thermodynamic functions of solution, transfer and mixing were calculated using the Gibbs and vant Hoff equations. On the other hand, the preferential solvation parameters of SMT were determined by means of the method of the inverse integrals of Kirkwood-Buff (IKBI). In general terms, the solubility of SMT is favored by the increase in temperature and the decrease in the polarity of the cosolvent system, thus the maximum solubility is reached in pure EG at 318.15 K and the minimum in pure water at 278.15 K. Gibbs energy is positive in all cases, with a higher contribution from the energy component (enthalpy of solution). Regarding enthalpy-entropic compensation, the process is driven in all cases by the enthalpy of solution. Finally, SMT is preferentially solvated by water in mixtures with higher polarity and by EG in less polar mixtures.

© 2020 Published by Elsevier B.V. on behalf of Taiwan Institute of Chemical Engineers.

1. Introduction

Sulfamethazine (Fig. 1) (4-amino-N-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide; $C_{12}H_{14}N_4O_2S$; CAS: 57-68-1), is a long-acting bacteriostatic agent, used both in human and animal therapy [1,2] due to its wide spectrum against Gram positive and Gram negative bacteria [3]. Its massive use, especially in veterinary products, has made SMT an emerging, highly dangerous contaminant [4], which has led to develop studies that point to the development of more efficient industrial processes and the generation of information for the treatment of these pollutants.

In this sense, one of the most relevant studies that provides essential data for the optimization of processes in the pharmaceutical industry are solubility studies, since these intervene in formulation, pre-formulation, crystallization, dosage, stability processes, among others [5]; in addition, these data are essential for the development

of mathematical models, which are the best tool for optimizing processes, tending to reduce the use of resources, therefore, leading on reducing the potential environmental impact generated by the pharmaceutical industry. Moreover, the solubility data are implemented in the development of models that allow the calculation of data such as bioavailability, lethal dose 50%, and partition coefficient, which have great biological and environmental importance [5,6].

In this order of ideas, thermodynamic analysis from solubility data is another important line of research, which leads to rationalize industrial processes, thus, the calculation of thermodynamic functions, through Gibbs and vant Hoff equations, allow us to understand the molecular interactions that occur between the solute and the solvent. Deepening the understanding of molecular interactions, the analysis of solvation preferences through the inverse integrals of Kirkwood-Buff (IKBI) allows understanding the molecular interactions from a perspective of the close environment of the solute molecule, understanding how it interacts preferentially with one or more solvents [7–9].

* Corresponding author.

E-mail address: danielr.delgado@campusucc.edu.co (D.R. Delgado).

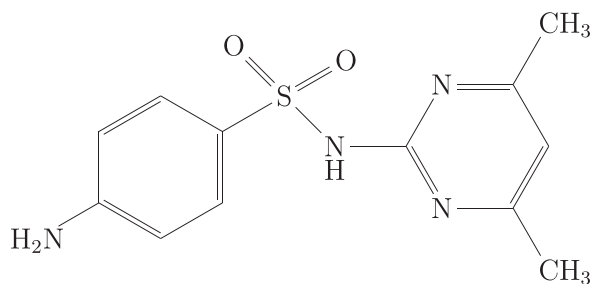


Fig. 1. Molecular structure of the sulfamethazine.

In this context, the objective of this research is to present the solubility data of SMT in ethylene glycol + water co-solvent mixtures at 9 temperatures, performing a thermodynamic analysis and solvation preferences, thus strengthening the theoretical bases regarding the physicochemical properties of the solution's process of this drug.

2. Materials and methods

2.1. Reagents

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

2.2. Preparation of solvent mixtures

The procedure is similar to that used in other investigations of the research group [3]. So all {EG (1) + water (2)} solvent mixtures were prepared by mass in quantities of 20.00 g, using an analytical balance with sensitivity $\pm 0.1 \text{ mg}$ (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

The procedure is similar to the one developed in previous work by the research group [10]. The Higuchi and Connors [11] flask shaking method was implemented. Thus, adding an amount of SMT to 20 ml of solvent or co-solvent mixture, until obtaining a solid phase of the drug in equilibrium with the saturated solution after having subjected the system to ultrasound for at least 30 min. The equilibrium time at each study temperature was 36 h. The determination of solubility was carried out by UV/vis spectrophotometry, taking a sample of each drug, filtering this sample through membranes with a pore size of $0.45 \mu\text{m}$ (Millipore Corp. Swinnex-13, USA) and making the respective dilutions with NaOH at 0.1 to avoid drug precipitation.

2.4. Calorimetric study

The temperature and melting enthalpy of five SMT samples were determined using differential scanning calorimetric (DSC) (DSC 204

F1 Phoenix, Germany) (original sample, solid phase in equilibrium with saturated water, solid phase in equilibrium with saturated EG, and solid phase in equilibrium with saturated mixture of $w_1 = 0.50$).

The samples were weighed using 5–10 mg of the drug in an aluminum crucible and placed inside the calorimeter with 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 $10 \text{ K}\cdot\text{min}^{-1}$. The equipment was calibrated using 99.99% pure Indium.

3. Results

3.1. Solubility of SMT in EG + W cosolvent mixtures

In Table 2, the solubility of SMT in co-solvent EG+W mixtures is presented at nine temperatures (278.15, 283.15, 288.15, 293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K). The solubility data for SMT in water were taken from Blanco et al. [3].

The solubility of SMT (Fig. 2) rise with increasing temperature, indicating an endothermic process, and also increases as the concentration of EG in the mixture increases. Thus, the lowest solubility is obtained in pure water at 278.15 K and the highest at 318.15 K in pure EG.

Delgado et al., have reported the solubility of SMT in different cosolvent systems, among which are methanol + water [12], ethanol + water [13], n-propanol + water [14], acetonitrile + water [3], propylene glycol + water [15]. On co-solvent mixtures where the solubility parameter of the SMT ($27.42 \text{ MPa}^{1/2}$) is greater than the one of the organic solvent (Ethanol: $26.1 \text{ MPa}^{1/2}$, n-propanol: $24.9 \text{ MPa}^{1/2}$, Acetonitrile: $24.8 \text{ MPa}^{1/2}$ [16]) the maximum solubility of the drug is reached in a cosolvent mixture with a solubility parameter similar to that of the drug; and in mixtures where the solubility parameter of the SMT is lower than that of the organic solvent (Methanol: $29.7 \text{ MPa}^{1/2}$ and propylene glycol: $30.7 \text{ MPa}^{1/2}$ [16]), the maximum solubility is reached in the organic solvent, as reported on this research. In the EG + W mixture, the maximum solubility is reached in the pure EG whose solubility parameter is $34.9 \text{ MPa}^{1/2}$ [16].

Fig. 3 shows the DSC thermograms of the original SMT sample and of the solid phases in equilibrium with the solutions saturated in pure water, $w_1 = 0.50$, and pure EG. According to previous reports [3], Maury et al., Sorrenti et al., and Zhang et al. reported polymorphic transitions and/or solvate formations [17–19]. However, in the present study, the thermograms show a similar endothermic peak in all DSC analyses, which indicates that in EG + W cosolvent mixtures, as in MeCN + W cosolvent mixtures [3] these transitions or solvates do not appear.

Thus the temperature and enthalpy of fusion of the original sample, the solid phase in equilibrium with water, the solid phase in equilibrium with $w_{0.5}$ and the solid phase in equilibrium with the EG are $198.3 \pm 0.5 \text{ }^\circ\text{C}$; $33.9 \pm 0.5 \text{ kJ}\cdot\text{mol}^{-1}$, $198.5 \pm 0.5 \text{ }^\circ\text{C}$ - $34.1 \pm 0.5 \text{ kJ}\cdot\text{mol}^{-1}$, $198.3 \pm 0.5 \text{ }^\circ\text{C}$; $34.0 \pm 0.5 \text{ kJ}\cdot\text{mol}^{-1}$, $197.9 \pm 0.5 \text{ }^\circ\text{C}$; $33.8 \pm 0.5 \text{ kJ}\cdot\text{mol}^{-1}$, respectively. The data of the original sample, coincide with those reported by Blanco et al. ($198.4 \pm 0.5 \text{ }^\circ\text{C}$; $34.1 \pm 0.5 \text{ kJ}\cdot\text{mol}^{-1}$) [3].

On the other hand, the values presented in this work are similar to those reported by other researchers. So, Delgado et al. $196.1 \pm 0.2 \text{ }^\circ\text{C}$;

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
Sulfametazine (SMT)	57-68-1	C ₁₂ H ₁₄ N ₄ O ₂ S	278.33	Sigma-Aldrich, USA	>0.990	HPLC
Ethylene glycol	107-21-1	HOCH ₂ CH ₂ OH	62.07	Sigma-Aldrich, USA	0.998	GC
Water	7732-18-5	H ₂ O	18.02	Obtained by distillation	>0.999	–

^a Chemical Abstracts Service Registry Number.

^b HPLC is high-liquid-performance chromatography; GC is gas chromatography.

Table 2Experimental solubility of SMT (3) in EG (1) + W (2) cosolvent mixtures expressed in mole fraction ($10^4 \times x_3$) at different temperatures. Experimental pressure p : 0.1 MPa^a.

x_1	Temperature /K								
	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15	318.15
0.00	0.1138±0.0029	0.1317±0.0018	0.1744±0.0032	0.222±0.001 ^d	0.281±0.001 ^d	0.367±0.003 ^d	0.433±0.001 ^d	0.555±0.004 ^d	0.6612±0.009
0.05	0.1275±0.0023	0.148±0.004	0.1766±0.0020	0.242±0.005	0.307±0.005	0.377±0.010	0.460±0.005	0.562±0.002	0.655±0.020
0.10	0.154±0.005	0.199±0.002	0.249±0.005	0.315±0.005	0.383±0.001	0.441±0.005	0.539±0.013	0.629±0.017	0.748±0.002
0.15	0.2037±0.0016	0.260±0.006	0.321±0.008	0.389±0.010	0.413±0.006	0.545±0.019	0.631±0.020	0.750±0.031	0.972±0.026
0.20	0.2437±0.0006	0.294±0.005	0.357±0.006	0.434±0.008	0.480±0.006	0.628±0.012	0.748±0.009	0.890±0.030	1.00±0.06
0.25	0.2839±0.0031	0.355±0.009	0.416±0.004	0.519±0.010	0.579±0.002	0.729±0.019	0.867±0.022	0.972±0.011	1.23±0.04
0.30	0.362±0.009	0.423±0.011	0.498±0.023	0.637±0.013	0.687±0.011	0.883±0.016	1.06±0.04	1.25±0.05	1.43±0.03
0.35	0.436±0.011	0.538±0.009	0.626±0.013	0.789±0.014	0.871±0.023	1.104±0.020	1.34±0.05	1.499±0.016	1.63±0.03
0.40	0.558±0.019	0.627±0.008	0.738±0.027	0.921±0.020	1.12±0.06	1.35±0.06	1.50±0.07	1.833±0.024	2.00±0.06
0.45	0.670±0.017	0.873±0.014	1.034±0.023	1.251±0.033	1.280±0.033	1.71±0.04	1.96±0.06	2.30±0.04	2.56±0.04
0.50	0.851±0.017	1.026±0.027	1.212±0.020	1.461±0.025	1.62±0.06	2.09±0.07	2.29±0.04	2.84±0.08	3.048±0.009
0.55	1.08±0.04	1.281±0.024	1.584±0.037	1.842±0.033	1.96±0.05	2.60±0.09	2.81±0.10	3.46±0.04	4.05±0.07
0.60	1.284±0.033	1.62±0.08	1.87±0.06	2.09±0.03	2.31±0.07	3.01±0.04	3.47±0.06	4.13±0.11	4.78±0.14
0.65	1.69±0.08	1.96±0.09	2.62±0.07	2.74±0.05	3.01±0.07	4.02±0.17	4.62±0.08	5.48±0.12	5.93±0.27
0.70	2.24±0.09	2.53±0.06	3.04±0.12	3.33±0.11	3.86±0.13	4.89±0.05	5.58±0.11	6.61±0.16	7.46±0.05
0.75	3.23±0.06	3.39±0.05	3.78±0.13	4.49±0.08	5.55±0.08	6.26±0.08	7.30±0.10	8.70±0.20	9.36±0.019
0.80	4.12±0.05	5.11±0.13	5.53±0.12	6.50±0.08	7.40±0.10	8.43±0.15	9.30±0.16	10.14±0.24	11.37±0.09
0.85	5.25±0.11	6.08±0.10	7.08±0.06	7.67±0.20	9.06±0.29	9.98±0.05	11.26±0.31	12.56±0.14	13.5 ± 0.4
0.90	6.849±0.033	8.09±0.10	9.31±0.11	10.05±0.16	11.141±0.014	12.77±0.26	13.75±0.14	15.57±0.26	16.91±0.12
0.95	13.085±0.013	14.29±0.20	15.6 ± 0.3	17.36±0.18	20.0 ± 0.6	21.9 ± 0.6	24.6 ± 0.6	27.4 ± 0.4	29.9 ± 0.9
1.00	18.50±0.31	20.6 ± 0.4	22.08±0.21	24.3 ± 0.4	27.8 ± 0.7	31.6 ± 0.7	35.5 ± 0.3	39.1 ± 0.4	40.53±0.06

^a The experimental pressure was about 0.096 MPa, a standard uncertainties $u(P)=0.001$.^b w_1 is the mass fraction of EG (1) in the EG (1) + W (2) mixtures free of SMT (3).^c T is the absolute temperature, Standard uncertainties u is $u(T)=0.05$ K.^d Values from reference [3].

34.1 ± 0.5 kJ.mol⁻¹ [12]; Hamada et al. 200 ± 0.3 °C; 33.96 kJ.mol⁻¹ [20], Sunwoo and Eisen 198.45 °C; 31.12 kJ.mol⁻¹ [21], Bustamante et al. 198.5 °C; 31.12 kJ.mol⁻¹ [22], Martínez and Gómez 195.85 °C; 39.22 kJ.mol⁻¹ [23], Khattab 195.45 °C; 44.81 kJ.mol⁻¹ [24], Maury et al. 197 – 198 °C [17] and Lu and Rohani, 199.05 °C [25].

3.2. Activity coefficients

The activity coefficients (Table 3) are a measure of the deviation from the ideality of the process [26], which is calculated using Eq. (1). From the activity coefficients, it is possible to infer about the solute-solvent molecular interactions using Eq. (2).

$$\gamma_3 = x_3^{\text{id}} x_3^{-1} \quad (1)$$

$$\ln \gamma_3 = (e_{11} + e_{33} - 2e_{13}) \left(V_3 \phi_1^2 / RT \right) \quad (2)$$

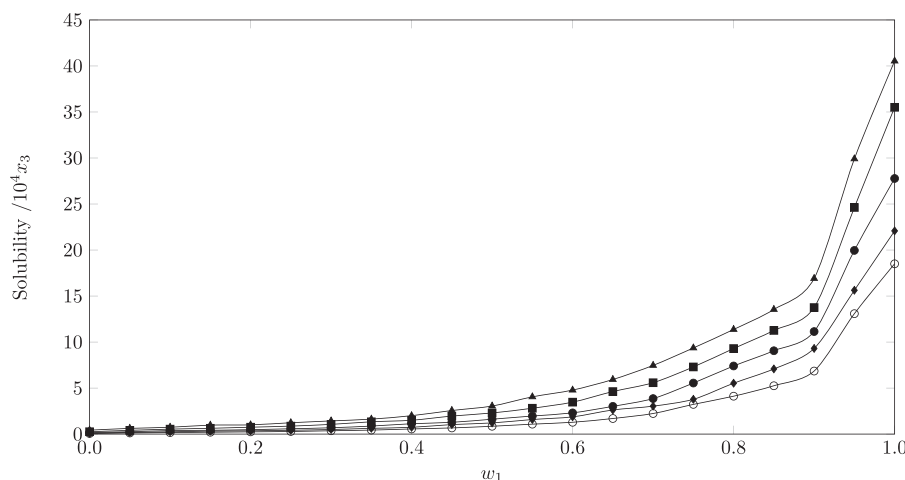


Fig. 2. Solubility of sulfamerazine (3) expressed in mole fraction ($10^4 \times x_3$) in EG (1) + W (2) cosolvent mixtures as a function of mass fraction of EG at different temperatures. ○: 278.15; ◆: 288.15 K; •: 298.15 K; □: 308.15 K and ▲: 318.15 K.

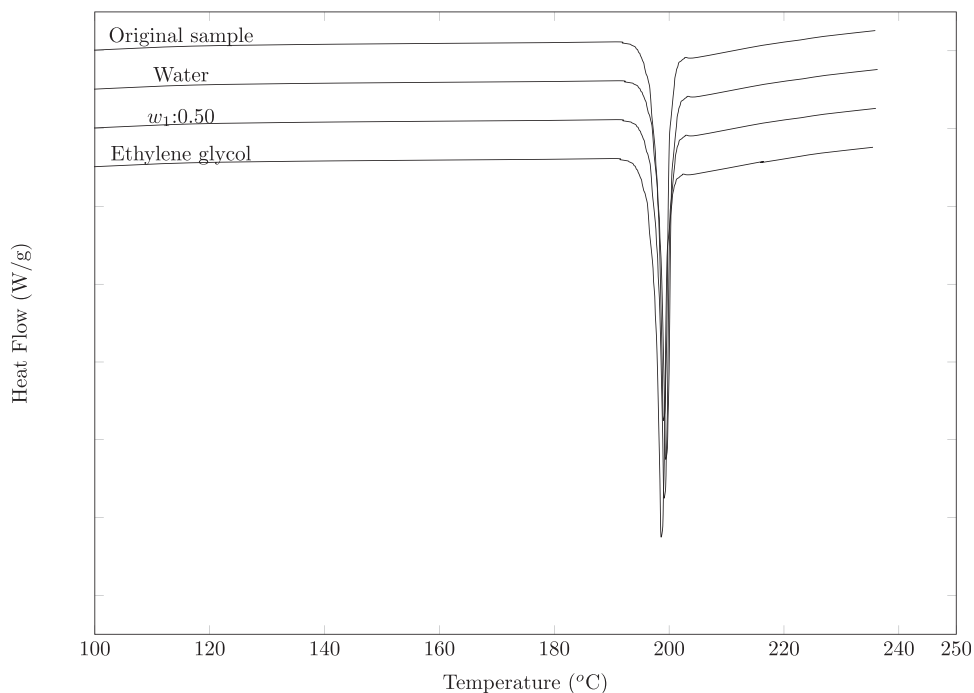


Fig. 3. DSC thermograms of sulfamethazine (Original sample, Pure water, $w_1 = 0.50$, and pure EG).

3.3. Thermodynamic functions of solution

From the experimental solubility data (Table 2), the solution thermodynamic functions are calculated, using the equations proposed by Gibbs and vant Hoff, modified by Krug [29,30]:

$$\Delta_{\text{soln}}H^{\circ} = -R \frac{\partial \ln x_3}{\partial (T^{-1} - T_{\text{hm}}^{-1})} \quad (3)$$

$$\Delta_{\text{soln}}G^{\circ} = -RT_{\text{hm}} \times \text{intercept} \quad (4)$$

$$\Delta_{\text{soln}}S^{\circ} = (\Delta_{\text{soln}}H^{\circ} - \Delta_{\text{soln}}G^{\circ})T_{\text{hm}}^{-1} \quad (5)$$

$$\zeta_H = \left| \Delta_{\text{soln}}H^{\circ} \left[\left| \Delta_{\text{soln}}H^{\circ} \right| + \left| T\Delta_{\text{soln}}S^{\circ} \right| \right]^{-1} \right. \quad (6)$$

$$\zeta_{TS} = \left| T\Delta_{\text{soln}}S^{\circ} \left[\left| \Delta_{\text{soln}}H^{\circ} \right| + \left| T\Delta_{\text{soln}}S^{\circ} \right| \right]^{-1} \right. \quad (7)$$

Table 3

Coefficient activity of SMT (3) in EG (1) + W (2) cosolvent mixtures at different temperatures and pressure $p = 0.096 \text{ MPa}^a$.

w_1^b	Temperature/K ^c									
	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15	318.15	
0.00	242.3	249.3	223.3	207.6	193.5	174.3	173.3	158.2	166.1	
0.05	216.3	221.6	220.6	190.1	176.9	169.6	163.2	156.2	156.5	
0.10	178.8	165.0	156.7	146.4	142.0	144.9	139.3	139.5	137.0	
0.15	135.4	126.4	121.4	118.4	131.5	117.3	119.0	117.1	105.4	
0.20	113.2	111.8	109.0	106.2	113.2	101.8	100.4	98.7	100.1	
0.25	97.2	92.4	93.6	88.9	93.9	87.7	86.5	90.4	83.1	
0.30	76.1	77.6	78.1	72.3	79.1	72.4	71.1	70.1	71.6	
0.35	63.3	61.1	62.3	58.4	62.4	57.9	56.1	58.6	63.1	
0.40	49.4	52.4	52.8	50.0	48.3	47.5	49.9	47.9	51.3	
0.45	41.2	37.6	37.7	36.8	42.5	37.3	38.3	38.1	40.0	
0.50	32.4	32.0	32.1	31.5	33.6	30.7	32.7	31.0	33.6	
0.55	25.5	25.6	24.6	25.0	27.7	24.6	26.7	25.4	25.3	
0.60	21.5	20.3	20.8	22.0	23.6	21.3	21.6	21.3	21.4	
0.65	16.3	16.7	14.9	16.8	18.0	15.9	16.2	16.0	17.3	
0.70	12.3	13.0	12.8	13.8	14.1	13.1	13.4	13.3	13.7	
0.75	8.5	9.7	10.3	10.3	9.8	10.2	10.3	10.1	11.0	
0.80	6.7	6.4	7.0	7.1	7.3	7.6	8.1	8.7	9.0	
0.85	5.3	5.4	5.5	6.0	6.0	6.4	6.7	7.0	7.6	
0.90	4.0	4.1	4.2	4.6	4.9	5.0	5.5	5.6	6.1	
0.95	2.1	2.3	2.5	2.7	2.7	2.9	3.0	3.2	3.4	
1.00	1.5	1.6	1.8	1.9	2.0	2.0	2.1	2.2	2.5	

^a The experimental pressure was about 0.096 MPa, a standard uncertainties $u(P) = 0.001$.

^b w_1 is the mass fraction of EG (1) in the EG (1) + W (2) mixtures free of SMT (3).

^c T is the absolute temperature, Standard uncertainties u is $u(T) = 0.05 \text{ K}$.

Table 4

Thermodynamic functions of solution of SMT (3) in EG (1) + W (2) cosolvent mixtures at 297.6 K and pressure $p = 0.096 \text{ MPa}^a$.

w_1	$\Delta_{\text{soln}}G^\circ/\text{kJ mol}^{-1}$	$\Delta_{\text{soln}}H^\circ/\text{kJ mol}^{-1}$	$\Delta_{\text{soln}}S^\circ/\text{J mol}^{-1}\text{K}^{-1}$	$T\Delta_{\text{soln}}S^\circ/\text{kJ mol}^{-1}$	ζ_H	ζ_{TS}
0.00	26.0 ± 0.2	32.9 ± 0.4	23.3 ± 0.4	6.91 ± 0.11	0.826	0.174
0.05	25.8 ± 0.5	31.7 ± 0.5	19.6 ± 0.5	5.84 ± 0.14	0.844	0.156
0.10	25.3 ± 0.4	28.7 ± 0.4	11.25 ± 0.24	3.35 ± 0.07	0.895	0.105
0.15	24.8 ± 0.6	27.3 ± 0.6	8.31 ± 0.27	2.47 ± 0.08	0.917	0.083
0.20	24.5 ± 0.5	26.6 ± 0.4	7.11 ± 0.19	2.12 ± 0.06	0.920	0.080
0.25	24.1 ± 0.4	26.3 ± 0.4	7.35 ± 0.17	2.19 ± 0.05	0.923	0.077
0.30	23.6 ± 0.7	25.9 ± 0.5	7.93 ± 0.26	2.36 ± 0.08	0.917	0.083
0.35	23.1 ± 0.5	25.1 ± 0.4	6.69 ± 0.19	1.99 ± 0.06	0.926	0.074
0.40	22.6 ± 0.7	24.9 ± 0.5	7.57 ± 0.29	2.25 ± 0.09	0.917	0.083
0.45	22.0 ± 0.5	24.2 ± 0.5	7.62 ± 0.24	2.27 ± 0.07	0.915	0.085
0.50	21.5 ± 0.5	24.0 ± 0.4	8.45 ± 0.23	2.52 ± 0.07	0.905	0.095
0.55	20.9 ± 0.5	23.9 ± 0.5	10.02 ± 0.32	2.98 ± 0.10	0.889	0.111
0.60	20.5 ± 0.6	23.7 ± 0.6	10.6 ± 0.4	3.16 ± 0.11	0.882	0.118
0.65	19.9 ± 0.6	23.6 ± 0.7	12.5 ± 0.5	3.73 ± 0.16	0.863	0.137
0.70	19.3 ± 0.5	22.8 ± 0.5	11.7 ± 0.4	3.47 ± 0.12	0.868	0.132
0.75	18.6 ± 0.3	21.4 ± 0.6	9.32 ± 0.30	2.77 ± 0.09	0.885	0.115
0.80	17.91 ± 0.31	18.25 ± 0.32	1.136 ± 0.028	0.338 ± 0.008	0.982	0.018
0.85	17.4 ± 0.3	17.59 ± 0.27	0.548 ± 0.014	0.163 ± 0.004	0.991	0.009
0.90	16.82 ± 0.19	16.22 ± 0.24	-2.03 ± 0.04	-0.605 ± 0.011	0.964	0.036
0.95	15.41 ± 0.29	15.68 ± 0.29	0.893 ± 0.024	0.266 ± 0.007	0.983	0.017
1.00	14.56 ± 0.21	15.4 ± 0.3	2.87 ± 0.08	0.855 ± 0.022	0.947	0.053

^a The experimental pressure was about 0.096 MPa, a standard uncertainties $u(P) = 0.001$.

^b w_1 is the mass fraction of EG (1) in the EG (1) + W (2) mixtures free of SMT (3).

Where G , H and S are the Gibbs energy, the enthalpy, and the entropy respectively, T_{hm} is the harmonic mean of the study temperatures and R is the gas constant. ζ_H and ζ_{TS} are the contributions of the enthalpy and entropy to the Gibbs energy of solution.

Table 4 shows the thermodynamic functions of solution of the SMT in the EG + W cosolvent system. The Gibbs energy is positive in all cases, decreasing from water to pure EG, due to the positive cosolvent effect of EG on SMT solubility. As for the standard enthalpy of solution, it is positive in all cases indicating an endothermic process, unlike what usually occurs in organic solvent + water systems where an initial increase of enthalpy occurs, possibly due to the structuring of the water around the non-polar groups of the SMT [3,13]; in this case, the enthalpy decreases from pure water to pure EG.

The solution entropy decreases from pure water to the co-solvent mixture $w_1=0.9$ where it reaches negative values, from this mass fraction of EG to pure EG there is an increase in entropy. Finally, from Eqs. (6) and (7) it can be inferred that the greatest contributor to Gibbs energy is the energy factor (enthalpy of solution), which in most cases is greater than 82%.

A graph that allows verifying the results obtained through Eqs. (6) and (7) is the one presented by Pécovich et al. [31,32] (Fig. 4), which consists of a plot ($T\Delta_{\text{soln}}S^\circ$ vs $\Delta_{\text{soln}}H^\circ$) of 8 triangular sectors; four sectors (I, IV, V and VIII) where the absolute value of $\Delta_{\text{soln}}H^\circ$ is greater than the absolute value of $T\Delta_{\text{soln}}S^\circ$, indicating enthalpy conduction, and four other sectors (II, III, VI and VII) where the absolute value of $\Delta_{\text{soln}}H^\circ$ is less than the value absolute of $T\Delta_{\text{soln}}S^\circ$, indicating entropy conduction.

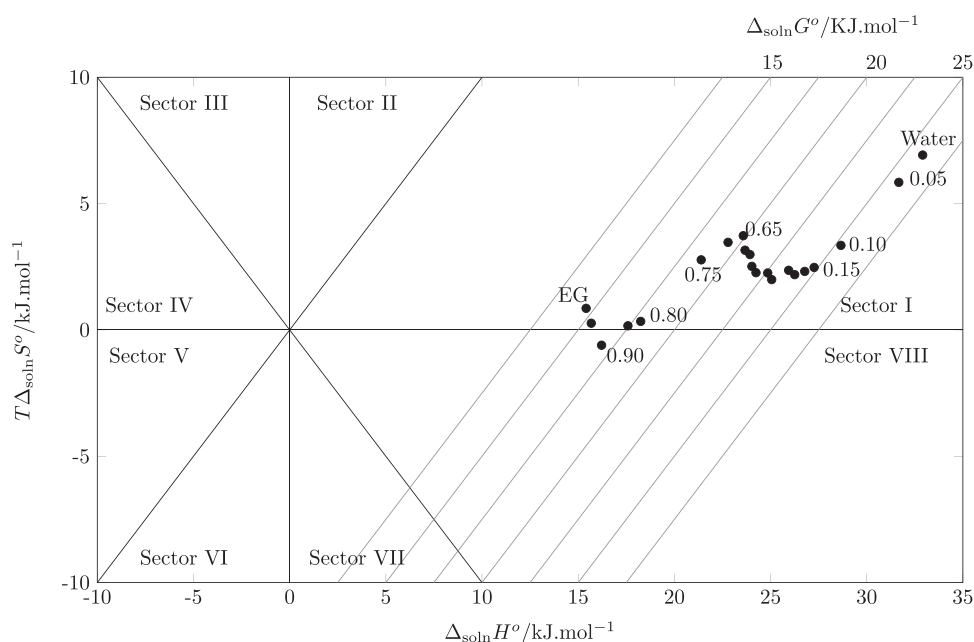


Fig. 4. Relation between enthalpy ($\Delta_{\text{soln}}H^\circ$) and entropy ($T\Delta_{\text{soln}}S^\circ$) terms of the process of SMT solution in EG (1) + water (2) cosolvent mixtures at 297.6 K. The isoenergetic curves for $\Delta_{\text{soln}}G^\circ$ are represented by dotted lines.

Table 5

Thermodynamic functions of transfer of SMT (3) in EG (1) + W (2) cosolvent mixtures at 297.6 K and pressure $p = 0.096 \text{ MPa}^a$.

More polar \rightarrow less polar	$\Delta_{tr}G^0/\text{kJ mol}^{-1}$	$\Delta_{tr}H^0/\text{kJ mol}^{-1}$	$\Delta_{tr}S^0/\text{J mol}^{-1}\text{K}^{-1}$	$T\Delta_{tr}S^0/\text{kJ mol}^{-1}$
^b $w_{0.00} \rightarrow w_{0.25}$	-1.9 ± 0.5	-6.7 ± 0.6	-15.9 ± 0.4	-4.73 ± 0.09
$w_{0.25} \rightarrow w_{0.30}$	-0.5 ± 0.8	-0.3 ± 0.6	0.58 ± 0.31	0.17 ± 0.09
$w_{0.30} \rightarrow w_{0.35}$	-0.5 ± 0.8	-0.9 ± 0.6	-1.24 ± 0.32	-0.37 ± 0.10
$w_{0.35} \rightarrow w_{0.65}$	-3.2 ± 0.8	-15 ± 0.5	5.8 ± 0.6	1.74 ± 0.17
$w_{0.65} \rightarrow w_{0.90}$	-3.0 ± 0.7	-7.4 ± 0.7	-14.6 ± 0.5	-4.33 ± 0.16
$w_{0.90} \rightarrow w_{1.0}$	-2.26 ± 0.28	-0.8 ± 0.4	4.91 ± 0.08	1.46 ± 0.03

^a The experimental pressure was about 0.096 MPa, a standard uncertainties $u(P) = 0.001$.

^b w_1 is the mass fraction of EG (1) in the EG (1) + W (2) mixtures free of SMT (3).

Thus, from pure water to $w_1=0.85$ and from $w_1=0.95$ to pure EG (Sector I: ($\Delta_{\text{soln}}H^0 > T\Delta_{\text{soln}}S^0 > 0$)) the process is driven by enthalpy as is the point $w_1=0.90$, unique negative point located in sector VIII ($\Delta_{\text{soln}}H^0 < 0$, $T\Delta_{\text{soln}}S^0 < 0$, $|\Delta_{\text{soln}}H^0| > |T\Delta_{\text{soln}}S^0|$).

This is due to the fact that the absolute value of the $\Delta_{\text{soln}}H^0$ is greater than the absolute value of $T\Delta_{\text{soln}}S^0$, so that the values of the Gibbs energy of solution depend in greater proportion of the enthalpy [32].

3.4. Thermodynamic transfer functions

From the thermodynamic transfer functions, the cosolvent effect of EG on the solubility of SMT can be identified. Starting from a hypothetical process of transfer from a higher polarity system to a lower polarity system, expressed mathematically as [33]:

$$\Delta_{tr}f^0 = \Delta_{\text{soln}f^0_{\text{less polar}}} - \Delta_{\text{soln}f^0_{\text{more polar}}} \quad (8)$$

Being f , the solution functions (Gibbs Energy, Enthalpy or Entropy).

Table 5 shows the transfer functions of the SMT, in all cases the Gibbs energy of transfer is negative, indicating the affinity of the SMT by less polar means, which implies that the EG has a positive cosolvent effect. Thus from $w_{0.00} \rightarrow w_{0.25}$ the transfer process is favored by enthalpy, but presents entropic disadvantage, $w_{0.25} \rightarrow w_{0.30}$, the transfer process is favored by enthalpy and entropy, $w_{0.30} \rightarrow w_{0.35}$, again presents enthalpy favoring and entropic disadvantage, $w_{0.35} \rightarrow w_{0.65}$ the process presents enthalpic and entropic favoring, $w_{0.65} \rightarrow$

$w_{0.90}$, the transfer process is favored by enthalpy but presents entropic disadvantage, finally $w_{0.90} \rightarrow w_{1.0}$ again the process is favored by both enthalpy and entropy.

Thus, in all cases, enthalpy promotes the transfer of SMT from the more polar solvent or cosolvent mixture to the lower polarity medium. As the entropy presents an intermittent favoring, however, it is clear the influence of the enthalpy allows the transfer process to occur.

3.5. Thermodynamic mixing functions

Hypothetical stages of the SMT dissolution process is: [14].

$\text{Solute}_{(\text{solid})} \text{ at } T \rightarrow \text{Solute}_{(\text{solid})} \text{ at } T_{\text{fus}} \rightarrow \text{Solute}_{(\text{liquid})} \text{ at } T_{\text{fus}} \rightarrow \text{Solute}_{(\text{liquid})} \text{ at } T \rightarrow \text{Solute}_{(\text{solution})} \text{ at } T$

Thus, the solution process can be expressed mathematically as:

$$\Delta_{\text{soln}}f^0 = \Delta_{tr}f^0 + \Delta_{\text{mix}}f^0 \quad (9)$$

Where f , represents the thermodynamic functions G , H or S , and the subscripts f and mix indicate fusion and mixing, respectively.

Table 6 shows the thermodynamic mixing functions, in all cases the mixing Gibbs energy is positive, so the solution process is driven by the fusion functions. Bearing in mind that for the mixing process to occur, the solvent molecules must be reorganized to form a cavity that houses the solute, a process that is endothermic, since energy must be supplied to counteract the cohesive forces of the solvent molecules, thus The decrease in the values of both the Gibbs energy and the enthalpy, indicate that the addition of EG promotes the

Table 6

Thermodynamic functions of mixing SMT (3) in EG (1) + W (2) cosolvent mixtures at 297.6 K and pressure $p = 0.096 \text{ MPa}^a$.

w_1^b	$\Delta_{\text{mix}}G^0/\text{kJ mol}^{-1}$	$\Delta_{\text{mix}}H^0/\text{kJ mol}^{-1}$	$\Delta_{\text{mix}}S^0/\text{J mol}^{-1}\text{K}^{-1}$	$T\Delta_{\text{mix}}S^0/\text{kJ mol}^{-1}$
0.00	13.06 ± 0.06	8.8 ± 0.5	-14.4 ± 0.5	-4.30 ± 0.14
0.05	12.9 ± 0.5	7.5 ± 0.6	-18.1 ± 0.6	-5.38 ± 0.17
0.10	12.4 ± 0.5	4.5 ± 0.4	-26.5 ± 0.4	-7.87 ± 0.12
0.15	11.9 ± 0.6	3.1 ± 0.6	-29.4 ± 0.4	-8.75 ± 0.12
0.20	11.5 ± 0.5	2.4 ± 0.5	-30.6 ± 0.4	-9.11 ± 0.11
0.25	11.1 ± 0.4	2.1 ± 0.4	-30.4 ± 0.4	-9.03 ± 0.11
0.30	10.7 ± 0.7	1.8 ± 0.5	-29.8 ± 0.4	-8.86 ± 0.12
0.35	10.1 ± 0.5	0.9 ± 0.5	-31.0 ± 0.4	-9.23 ± 0.11
0.40	9.7 ± 0.7	0.7 ± 0.5	-30.1 ± 0.4	-8.97 ± 0.13
0.45	9.1 ± 0.5	0.1 ± 0.6	-30.1 ± 0.4	-8.96 ± 0.12
0.50	8.6 ± 0.5	-0.1 ± 0.4	-29.3 ± 0.4	-8.71 ± 0.12
0.55	8.0 ± 0.5	-0.2 ± 0.5	-27.7 ± 0.4	-8.24 ± 0.13
0.60	7.6 ± 0.6	-0.5 ± 0.6	-27.1 ± 0.5	-8.07 ± 0.15
0.65	6.9 ± 0.6	-0.6 ± 0.7	-25.2 ± 0.6	-7.49 ± 0.18
0.70	6.4 ± 0.5	-1.4 ± 0.5	-26.1 ± 0.5	-7.75 ± 0.15
0.75	5.7 ± 0.4	-2.8 ± 0.6	-28.4 ± 0.4	-8.45 ± 0.13
0.80	4.99 ± 0.31	-5.9 ± 0.4	-36.57 ± 0.31	-10.88 ± 0.09
0.85	4.5 ± 0.3	-6.56 ± 0.32	-37.16 ± 0.31	-11.06 ± 0.09
0.90	3.90 ± 0.20	-7.93 ± 0.29	-39.74 ± 0.31	-11.83 ± 0.09
0.95	2.49 ± 0.30	-8.5 ± 0.3	-36.81 ± 0.31	-10.96 ± 0.09
1.00	1.63 ± 0.21	-8.7 ± 0.4	-34.84 ± 0.32	-10.37 ± 0.10

^a The experimental pressure was about 0.096 MPa, a standard uncertainties $u(P) = 0.001$.

^b w_1 is the mass fraction of EG (1) in the EG (1) + W (2) mixtures free of SMT (3).

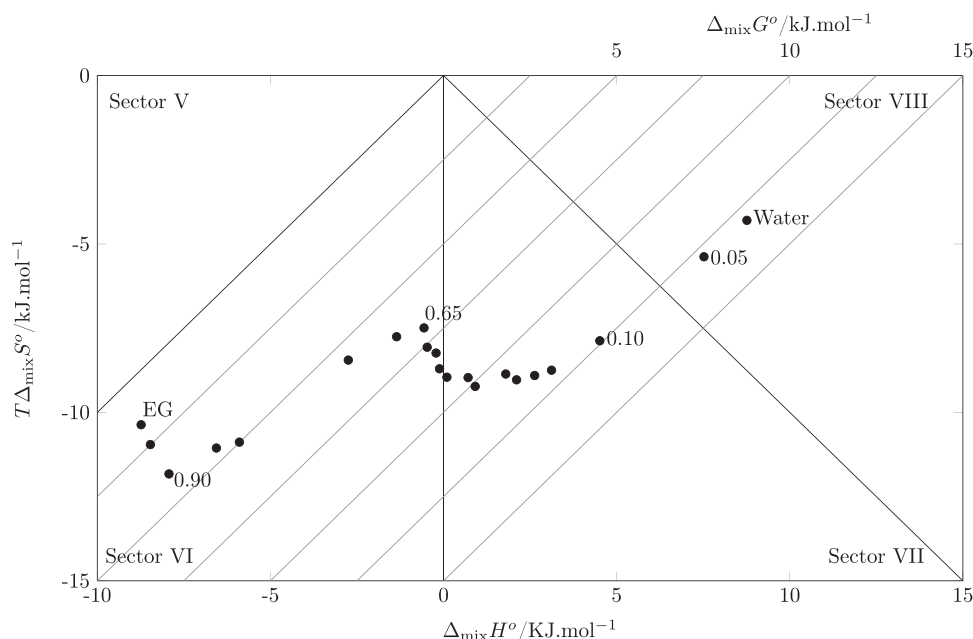


Fig. 5. Relationship between the enthalpy ($\Delta_{\text{mix}}H^\circ$) and entropy ($T\Delta_{\text{mix}}S^\circ$) terms of the mixing process of SMT at 297.6 K. The isoenergetic curves of $\Delta_{\text{mix}}G^\circ$ are represented by dotted lines.

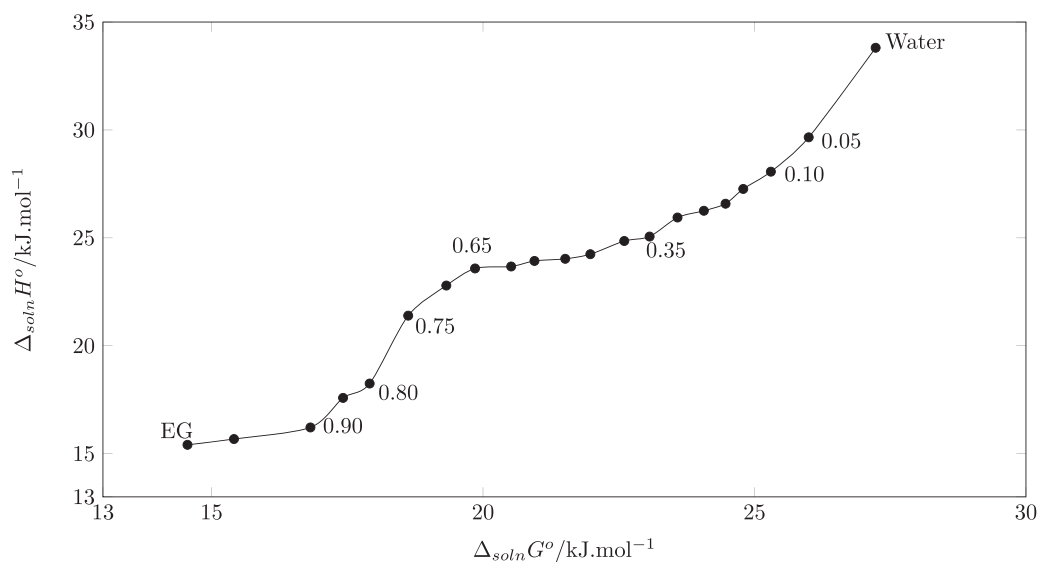


Fig. 6. Enthalpy-entropy compensation plot for the solubility of SMT (3) in EG (1) + W (2) mixtures at $T_{\text{bm}} = 297.6$ K.

formation of the cavity, which is consistent with the increase in the solubility of SMT as the concentration of EG increases, this it also implies that the solvent-solvent molecular interactions (e_{11}) decrease with the addition of EG, just as the solute-solvent interactions (e_{13}) increase.

In general, from pure water up to $w_1=0.45$, both the enthalpy and the entropy of the mixture disfavor the solution process, from $w_1=0.45$ to the pure EG, the enthalpy of the mixture favors the solution process, however, entropic disadvantage continues.

According to the Perlovich graph (Fig. 5), in the mixing process, from water to $w_1=0.05$ the greatest contributor is the standard mixing enthalpy, because the absolute value of the enthalpy of mixture is greater than the absolute value of the entropy term (Sector VIII: $\Delta_{\text{mix}}H^\circ < 0$, $T\Delta_{\text{mix}}S^\circ < 0$, $|\Delta_{\text{mix}}H^\circ| > |T\Delta_{\text{mix}}S^\circ|$), from $w_1=0.10$ to $w_1=0.45$ (Sector VII: $\Delta_{\text{mix}}H^\circ < T\Delta_{\text{mix}}S^\circ$, $|\Delta_{\text{mix}}H^\circ| < |T\Delta_{\text{mix}}S^\circ|$) the mixing process is driven by entropy and finally from $w_1=0.50$ to the pure EG (Sector VI: $\Delta_{\text{mix}}H^\circ < 0$, $T\Delta_{\text{mix}}S^\circ < 0$, $|\Delta_{\text{mix}}H^\circ| < |T\Delta_{\text{mix}}S^\circ|$) again the

process is driven by entropy, In both sectors VI and VII, the absolute value of $T\Delta_{\text{mix}}S^\circ$ is greater than the absolute value of $\Delta_{\text{mix}}H^\circ$ [34].

3.6. Enthalpy-entropic compensation

The enthalpy-entropic compensation analysis allows identifying the mechanisms involved in the cosolvent action. Furthermore, this analysis allows us to recognize the thermodynamic consequences of the formation of solute-solvent bonds, where the hydrogen bond is the most important interaction [35–37].

This analysis is performed by plotting $\Delta_{\text{soln}}H^\circ$ vs $\Delta_{\text{soln}}G^\circ$, where negative slopes indicate processes driven by entropy and positive slopes indicate processes driven by enthalpy [38,39].

Fig. 6 presents the enthalpy-entropic compensation of the SMT solution process in EG + W co-solvent mixtures. A non-linear behavior with a positive slope can be observed in all cases, indicating an enthalpy conduction of the solution process.

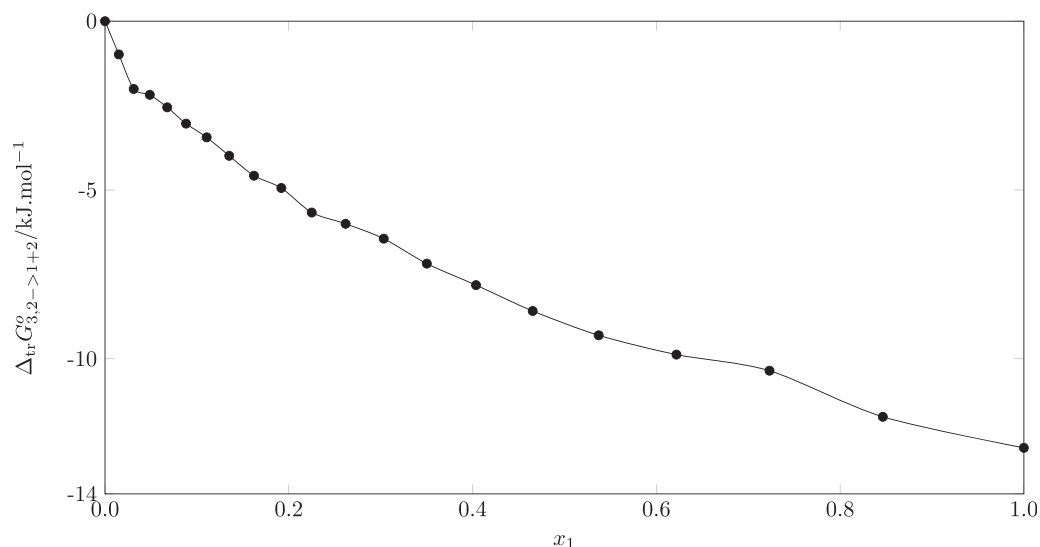


Fig. 7. Gibbs energy of SMT transfer from pure water to coving mixtures at 298.15 K.

3.7. Preferential solvation

Preferential solvation analysis allows identifying the local composition of the solvation sphere surrounding the solute molecule. Ben-Naim, presents an approach called Inverse Integrals of Kirkwood-Buff integral (IKBI), which assesses solvation as a function of the preferential solvation parameter $\delta x_{1,3}$ [40,41]

The mathematical development of the IKBI approach is presented as:

$$\delta x_{1,3} = [x_1(1-x_1)(G_{1,3} - G_{2,3})][x_1G_{1,3} + (1-x_1)G_{2,3} + V_{cor}]^{-1} \quad (10)$$

$$G_{1,3} = RT\kappa_T - V_3 + (1-x_1)V_2DQ^{-1} \quad (11)$$

$$G_{2,3} = RT\kappa_T - V_3 + x_1V_1DQ^{-1} \quad (12)$$

$$V_{cor} = 2522.5 \left[r_3 - 0.1363^3 \sqrt{(x_{1,3}^4 V_1) + (x_{2,3}^4 V_2)} - 0.085 \right]^3 \quad (13)$$

$$V_1 = V + x_2 dV/dx_1 \quad (14)$$

$$V_2 = V + x_1 dV/dx_2 \quad (15)$$

$$Q = d\Delta_r G_{3,2 \rightarrow 1+2}^0 / dx_1 \quad (16)$$

$$D = RTx_1(1-x_1) \left(d^2 G_{1,2}^E / dx_2^2 \right) \quad (17)$$

Where $G_{1,3}$ y $G_{2,3}$ are the Kirkwood-Buff integrals (in $\text{cm}^3 \cdot \text{mol}^{-1}$) calculated from the thermodynamic data using Eqs. (11) and (12), V_{cor} is the volume of correlation around the SMT (in this case) where preferential solvation occurs. In Eqs. (11) and (12) ($\kappa_{T-W} = 0.457 \text{ GPa}^{-1}$, $\kappa_{T-W} = 0.392 \text{ GPa}^{-1}$ [42]), V_3 is the partial molar volume of the solute ($179.0 \text{ cm}^3 \cdot \text{mol}^{-1}$), and V_1 y V_2 are those of the solutes (in $\text{cm}^3 \cdot \text{mol}^{-1}$), calculated using Eqs. (14) and (15) from the density of the solute-free cosolvent mixtures reported by Egorov et al. [43], D and Q (in $\text{kJ} \cdot \text{mol}^{-1}$ as well as RT) are parameters calculated from $G_{3,2 \rightarrow 2}^0$

Table 8

Some properties associated to preferential solvation of SMT (3) in EG (1) + W (2)) mixtures at 298.15 K.

x_1^a	$D/\text{kJ} \cdot \text{mol}^{-1}$	$Q/\text{kJ} \cdot \text{mol}^{-1}$	$V_1/\text{cm}^3 \cdot \text{mol}^{-1}$	$V_2/\text{cm}^3 \cdot \text{mol}^{-1}$	$G_{1,3}/\text{cm}^3 \cdot \text{mol}^{-1}$	$G_{2,3}/\text{cm}^3 \cdot \text{mol}^{-1}$	$V_{cor}/\text{cm}^3 \cdot \text{mol}^{-1}$	100 $\delta x_{1,3}$
0.00	-23.20	2.479	53.97	18.08	-347.0	-177.9	890.4	0.000
0.05	-21.26	2.559	54.26	18.07	-320.5	-200.4	949.8	-0.751
0.10	-19.45	2.605	54.53	18.05	-299.2	-218.6	1012.3	-0.889
0.15	-17.77	2.627	54.76	18.02	-281.5	-233.5	1075.6	-0.698
0.20	-16.21	2.633	54.97	17.97	-266.4	-245.6	1138.0	-0.354
0.25	-14.77	2.631	55.15	17.92	-253.4	-255.3	1199.2	0.036
0.30	-13.46	2.627	55.31	17.86	-241.9	-262.9	1258.7	0.409
0.35	-12.27	2.626	55.44	17.80	-232.0	-268.6	1316.5	0.729
0.40	-11.20	2.631	55.56	17.73	-223.2	-272.6	1372.6	0.979
0.45	-10.26	2.643	55.65	17.66	-215.6	-275.2	1426.9	1.155
0.50	-9.44	2.663	55.73	17.59	-209.1	-276.7	1479.9	1.260
0.55	-8.75	2.692	55.79	17.52	-203.6	-277.7	1531.5	1.304
0.60	-8.18	2.725	55.84	17.46	-198.9	-278.5	1582.1	1.299
0.65	-7.73	2.760	55.87	17.40	-195.0	-279.7	1631.5	1.256
0.70	-7.41	2.793	55.90	17.35	-191.8	-281.8	1680.4	1.184
0.75	-7.21	2.816	55.91	17.31	-189.1	-285.4	1728.4	1.089
0.80	-7.13	2.822	55.92	17.28	-186.7	-291.1	1775.9	0.972
0.85	-7.18	2.803	55.92	17.26	-184.6	-299.8	1822.6	0.826
0.90	-7.36	2.747	55.93	17.26	-182.6	-312.8	1869.1	0.637
0.95	-7.65	2.643	55.92	17.27	-180.5	-331.8	1914.5	0.379
1.00	-8.07	2.479	55.92	17.30	-178.0	-360.1	1959.2	0.000

^a x_1 is the mole fraction of ethylene glycol (1) in the EG (1) + W (2)) mixtures free of SMT (3).

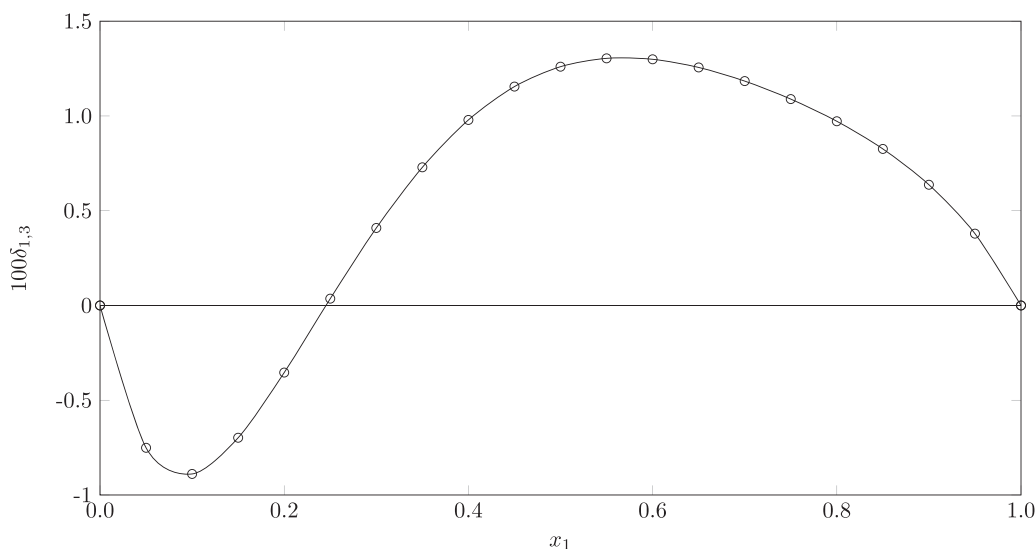


Fig. 8. $\delta_{1,3}$ values of SMT (3) in EG (1) + W (2) mixtures at 298.15 K.

which is the Gibbs energy of solute transfer (SMT) (Eq. (18)) (Fig. 7) and $G_{1,2}^E$ is the excess Gibbs energy of the solute-free cosolvent mixture (Eq. (19) [41]).

$$\Delta_r G_{3,2 \rightarrow 1+2}^E = -8.255x_1^3 + 19.944 - 23.195x_1 - 0.0502 \quad (18)$$

$$G_{1,2}^E = x_1x_2 \left[-558 + 164(1 - 2x_1) - 189(1 - 2x_1)^2 \right] \quad (19)$$

Table 8 shows some relevant data corresponding to the calculations necessary to determine the preferential solvation parameter of SMT in EG + W cosolvent mixtures. Fig. 8 shows the trend of $\delta_{1,3}$.

In this way, SMT is solvated preferentially by water from $x_1=0.00$ hasta $x_1=0.20$, this behavior usually occurs in aqueous cosolvent mixtures, and is possibly due to the structuring of water around the non-polar groups of SMT (hydration hydrophobic), however, since $\delta_{1,3} < 0.01$ solvation by water is negligible [41]. From $x_1=0.20$ to $x_1=1.00$, the values of $\delta_{1,3}$ are positive and in intermediate mixtures $\delta_{1,3} > 0.01$, indicating a clear solvation of the SMT by the EG. In principle, SMT would behave like a Lewis base in mixtures rich in water due to the pair of free electrons of its groups $-\text{SO}_2^-$, NH_2 and $=\text{N}-$ in addition to the fact that water is more acidic than EG according to the acid and basicity parameters of Kamlet-Taft ($\alpha_W=1.017 \pm 0.0236$, $\alpha_{EG}=0.792 \pm 0.004$ [44], $\beta_W=0.14$ $\beta_{EG}=0.51$ [45], and as a Lewis acid in intermediate and rich mixtures in EG due to the hydrogen of its groups $-\text{NH}_2$ and $-\text{NH}-$, besides the fact that EG is more basic than water (see β parameters).

4. Conclusions

The solubility of SMT is an endothermic process, strongly influenced by the polarity of the cosolvent system that decreases as the concentration of EG increases, which favors the solubility of SMT. The Gibbs energy of solution is positive in all cases and its value depends more on the enthalpy of solution. Regarding the thermodynamic transfer functions, the Gibbs energy is negative for which it can be inferred that the SMT prefers less polar systems than water.

From the mixing functions, it can be inferred that the solution process is favored by the fusion process, and that as the EG proportion increases, the solute-solvent molecular interactions increase favoring the solubility of the SMT. Finally, regarding the preferential solvation process, SMT is solvated preferentially by water in mixtures rich in water and is solvated preferably by EG in intermediate and EG-rich mixtures.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

We would like to express our gratitude to the National Directorate of Research and National Committee for Research Development of the Universidad Cooperativa de Colombia for providing financial support for this study with code INV2929. Furthermore, we thank the Universidad Cooperativa de Colombia at Neiva for facilitating the supply of laboratories and equipment.

References

- [1] Sophian LH, Piper DL, Schneller GH. The Sulfapyrimidines: sulfadiazine, sulfamerazine, sulfamethazine. Literary Licens. 2012.
- [2] Riviere JE, Papich MG. Veterinary pharmacology and therapeutics. 10th ed. Savannah.
- [3] Blanco-Márquez JH, Caviedes Rubio DI, Ortiz CP, Cerquera NE, Martínez F, Delgado DR. Thermodynamic analysis and preferential solvation of sulfamethazine in acetonitrile + water cosolvent mixtures. Fluid Phase Equilib 2020;505:112361. [10.1016/j.fluid.2019.112361](https://doi.org/10.1016/j.fluid.2019.112361).
- [4] Aday B, Sola P, Çolak F, Kaya M. Synthesis of novel sulfonamide analogs containing sulfamerazine/sulfaguanidine and their biological activities. J Enzym Inhib Med Chem 2016;31:1005–10. [10.3109/14756366.2015.1079183](https://doi.org/10.3109/14756366.2015.1079183).
- [5] Martin AN, Bustamante P. Physical pharmacy: physical chemical principles in the pharmaceutical sciences. 4th ed. Philadelphia: Lippincott Williams & Wilking; 1993.
- [6] Yalkowsky SH. Solubility and solubilization in aqueous media. New York: American Chemical Society; 1999.
- [7] Yalkowsky SH, He Y, Jain P. Handbook of aqueous solubility data. 2nd ed. Boca Raton: CRC Press; 2016. [10.1201/ebk1439802458](https://doi.org/10.1201/ebk1439802458).
- [8] Jouyban A, Acree WE, Martínez F. Preferential solvation of apremilast in some (Transcutol® + water) mixtures. J Mol Liq 2020;316:113905. [10.1016/j.molliq.2020.113905](https://doi.org/10.1016/j.molliq.2020.113905).
- [9] Barzegar-Jalali M, Mirheydari SN, Martínez F, Jouyban A. Lamotrigine solubility in 1-propanol + water mixtures at different temperatures: experimental data and mathematical modelling. Phys Chem Liq 2020;58:432–45. [10.1080/00319104.2019.1600141](https://doi.org/10.1080/00319104.2019.1600141).
- [10] Romero-Nieto AM, Caviedes-Rubio DI, Polania-Orozco J, Cerquera NE, Delgado DR. Temperature and cosolvent composition effects in the solubility of methylparaben in acetonitrile + water mixtures. Phys Chem Liq 2019. [10.1080/00319104.2019.1636379](https://doi.org/10.1080/00319104.2019.1636379).
- [11] Higuchi T, Connors KA. Phase-solubility techniques. Adv Anal Inst 1965;4:117–212.
- [12] Delgado DR, Almanza OA, Martínez F, Peña MA, Jouyban A, Acree WE. Solution thermodynamics and preferential solvation of sulfamethazine in (methanol + water) mixtures. J Chem Thermodyn 2016;97:264–76. [10.1016/j.jct.2016.02.002](https://doi.org/10.1016/j.jct.2016.02.002).
- [13] Delgado DR, Martínez F. Solubility and solution thermodynamics of sulfamerazine and sulfamethazine in some ethanol+water mixtures. Fluid Phase Equilib 2013;360:88–96. [10.1016/j.fluid.2013.09.018](https://doi.org/10.1016/j.fluid.2013.09.018).

- [14] Delgado DR, Martínez F. Solubility and solution thermodynamics of some sulfonamides in 1-propanol + water mixtures. *J Solut Chem* 2014;43:836–52. [10.1007/s10953-014-0169-0](https://doi.org/10.1007/s10953-014-0169-0).
- [15] Del Mar Muñoz M, Delgado DR, Peña MÁ, Jouyban A, Martínez F. Solubility and preferential solvation of sulfadiazine, sulfamerazine and sulfamethazine in propylene glycol + water mixtures at 298.15K. *J Mol Liq* 2015;204:132–6. [10.1016/j.molliq.2015.01.047](https://doi.org/10.1016/j.molliq.2015.01.047).
- [16] Barton A. *CRC handbook of solubility parameters and other cohesion parameters*. 2nd Boca Raton (FL): CRC Press LLC; 1991.
- [17] Maury L, Rambaud J, Pauvert B, Lasserre Y, Bergé G, Audran M. Physicochemical and structural study of sulfamethazine. *J Pharm Sci* 1985;74:422–6. [10.1002/JPS.2600740411](https://doi.org/10.1002/JPS.2600740411).
- [18] Sorrenti M, Bettinetti GP, Negri A. Thermoanalytical characterization of pseudopolymorphs of sulphadimidine and sulphadimidine–trimethoprim molecular complexes. *Thermochim Acta* 1998;321:67–72. [10.1016/S0040-6031\(98\)00441-9](https://doi.org/10.1016/S0040-6031(98)00441-9).
- [19] Zhang X, Zhou L, Wang C, Li Y, Wu Y, Zhang M, et al. Insight into the role of hydrogen bonding in the molecular self-assembly process of sulfamethazine solvates. *Cryst Growth Des* 2017;17:6151–7. [10.1021/acs.cgd.7b00717](https://doi.org/10.1021/acs.cgd.7b00717).
- [20] Hamada Y, Ono M, Ohara M, Yonemochi E. The effect of structurally related impurities on crystallinity reduction of sulfamethazine by grinding. *Int J Pharm* 2016;515:416–21. [10.1016/j.ijpharm.2016.09.069](https://doi.org/10.1016/j.ijpharm.2016.09.069).
- [21] Sunwoo C, Eisen H. Solubility parameter of selected sulfonamides. *J Pharm Sci* 1971;60:238–44. [10.1002/jps.2600600217](https://doi.org/10.1002/jps.2600600217).
- [22] Bustamante P, Ochoa R, Reillo A, Escalera JB. Chameleonic effect of sulfanilamide and sulfamethazine in solvent mixtures. Solubility curves with two maxima. *Chem Pharm Bull* 1994;42:1129–33. [10.1248/cpb.42.1129](https://doi.org/10.1248/cpb.42.1129).
- [23] Martínez F, Gómez A. Thermodynamic study of the solubility of some sulfonamides in octanol, water, and the mutually saturated solvents. *J Solution Chem* 2001;30:909–23. [10.1023/A:1012723731104](https://doi.org/10.1023/A:1012723731104).
- [24] Khattab FI. Thermal analysis of pharmaceutical compounds. V. The use of differential scanning calorimetry in the analysis of certain pharmaceuticals. *Thermochim Acta* 1983;61:253–68. [10.1016/0040-6031\(83\)80280-9](https://doi.org/10.1016/0040-6031(83)80280-9).
- [25] Lu J, Rohani S. Synthesis and preliminary characterization of sulfamethazine-theophylline co-crystal. *J Pharm Sci* 2010;99:4042–7. [10.1002/jps.22142](https://doi.org/10.1002/jps.22142).
- [26] Prausnitz JM. *Termodinamica molecular de los equilibrios de fases*. 3rd ed. Madrid: Prentice Hall; 2000.
- [27] Kristl A. Thermodynamic investigation of the effect of the mutual miscibility of some higher alkanols and water on the partitioning and solubility of some guanine derivatives. *J Chem Soc Faraday Trans* 1996;92:1721–4. [10.1039/ft9969201721](https://doi.org/10.1039/ft9969201721).
- [28] Raschke TM, Levitt M. Nonpolar solutes enhance water structure within hydration shells while reducing interactions between them. *Proc Natl Acad Sci USA* 2005;102:6777–82. [10.1073/pnas.0500225102](https://doi.org/10.1073/pnas.0500225102).
- [29] Krug RR, Hunter WG, Grieger RA. Enthalpy-entropy compensation. 1. Some fundamental statistical problems associated with the analysis of van't Hoff and Arrhenius data. *J Phys Chem* 1976;80:2335–41. [10.1021/j100562a006](https://doi.org/10.1021/j100562a006).
- [30] Krug RR, Hunter WG, Grieger RA. Enthalpy-entropy compensation. 2. Separation of the chemical from the statistical effect. *J Phys Chem* 1976;80:2341–51. [10.1021/j100562a007](https://doi.org/10.1021/j100562a007).
- [31] Perlovich GL, Strakhova NN, Kazachenko VP, Volkova TV, Tkachev VV, Schaper KJ, et al. Sulfonamides as a subject to study molecular interactions in crystals and solutions: sublimation, solubility, solvation, distribution and crystal structure. *Int J Pharm* 2008;349:300–13. [10.1016/j.ijpharm.2007.07.034](https://doi.org/10.1016/j.ijpharm.2007.07.034).
- [32] Perlovich GL, Tkachev VV, Strakhova NN, Kazachenko VP, Volkova TV, Surov OV, et al. Thermodynamic and structural aspects of sulfonamide crystals and solutions. *J Pharm Sci* 2009;98:4738–55. [10.1002/jps.21784](https://doi.org/10.1002/jps.21784).
- [33] Blanco-Márquez JH, Quigua-Medina YA, García-Murillo JD, Castro-Camacho JK, Ortiz CP, Cerquera NE, et al. Thermodynamic analysis and applications of the Abraham solvation parameter model in the study of the solubility of some sulfonamides. *Rev Colomb Cienc Quím Farm* 2020;49:234–55. [10.15446/rcciquifa.v49n1.87038](https://doi.org/10.15446/rcciquifa.v49n1.87038).
- [34] 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;57:411–20. [10.1016/j.ejpb.2003.10.021](https://doi.org/10.1016/j.ejpb.2003.10.021).
- [35] Bustamante P, Romero S, Peña A, Escalera B, Reillo A. Enthalpy–entropy compensation for the solubility of drugs in solvent mixtures: paracetamol, acetanilide, and nalidixic acid in dioxane–water. *J Pharm Sci* 1998;87:1590–6. [10.1021/J5980149X](https://doi.org/10.1021/J5980149X).
- [36] Peña MA, Escalera B, Reillo A, Sánchez AB, Bustamante P. Thermodynamics of cosolvent action: phenacetin, salicylic acid and probenecid. *J Pharm Sci* 2009;98:1129–35. [10.1002/jps.21497](https://doi.org/10.1002/jps.21497).
- [37] Bustamante P, Escalera B. Enthalpy and entropy contributions to the solubility of sulphamethoxypyridazine in solvent mixtures showing two solubility maxima. *J Pharm Pharmacol* 1995;47:550–5. [10.1111/j.2042-7158.1995.tb06712.x](https://doi.org/10.1111/j.2042-7158.1995.tb06712.x).
- [38] Rezaei H, Jouyban A, Martínez F, Barzegar-Jalali M, Hemmati S, Rahimpour E. Solubility and thermodynamic profile of mesalazine in carbitol + ethanol mixtures at different temperatures. *J Mol Liq* 2020;114763. [10.1016/j.molliq.2020.114763](https://doi.org/10.1016/j.molliq.2020.114763).
- [39] Tinjacá DA, Martínez F, Almanza OA, Jouyban A, Acree WE. Solubility of meloxicam in aqueous binary mixtures of formamide, N-methylformamide and N,N-dimethylformamide: determination, correlation, thermodynamics and preferential solvation. *J Chem Thermodyn* 2020;154:106332. [10.1016/j.jct.2020.106332](https://doi.org/10.1016/j.jct.2020.106332).
- [40] Marcus Y. On the preferential solvation of drugs and PAHs in binary solvent mixtures. *J Mol Liq* 2008;140:61–7. [10.1016/j.molliq.2008.01.005](https://doi.org/10.1016/j.molliq.2008.01.005).
- [41] Marcus Y. *Solvent mixtures: properties and selective solvation*. New York: Marcel Dekker, Inc; 2002.
- [42] Marcus Y. *The properties of solvents*. New York: John Wiley & Sons Ltd; 1999.
- [43] Egorov GI, Makarov DM, Kolker AM. Volumetric properties of the water-ethylene glycol mixtures in the temperature range 278–333.15K at atmospheric pressure. *Russ J Gen Chem* 2010;80:1577–85. [10.1134/S1070363210080074](https://doi.org/10.1134/S1070363210080074).
- [44] Taft RW, Kamlet MJ. The solvatochromic comparison method. 2. The α -scale of solvent hydrogen-bond donor (HBD) acidities. *J Am Chem Soc* 1976;98:2886–94. [10.1021/ja00426a036](https://doi.org/10.1021/ja00426a036).
- [45] Kamlet MJ, Taft RW. The solvatochromic comparison method. I. The β -Scale Of Solvent Hydrogen-Bond Acceptor (HBA) Basicities. *J Am Chem Soc* 1976;98:377–83. [10.1021/ja00418a009](https://doi.org/10.1021/ja00418a009).