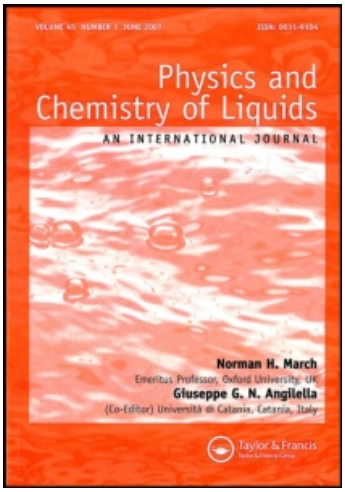

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Temperature-dependence of the solubility of some acetanilide derivatives in several organic and aqueous solvents

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TEMPERATURE-DEPENDENCE OF THE SOLUBILITY OF SOME ACETANILIDE DERIVATIVES IN SEVERAL ORGANIC AND AQUEOUS SOLVENTS

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The thermodynamic functions free energy, enthalpy, and entropy of solution, were evaluated from the solubility data of acetanilide, acetaminophen, and phenacetin, determined at several temperatures in water, octanol, isopropyl myristate, and chloroform. These three organic solvents mutually saturated with water, and finally, in cyclohexane. In the aqueous media, the solubility was determined at pH 7.4 and ionic strength 0.15 mol L^{-1}. The excess free energy and the activity coefficients of the solutes were also determined. The solubility for acetanilide and phenacetin was higher in organic media such as octanol and chloroform than is those obtained in the aqueous media and cyclohexane, while for acetaminophen the solubility was higher in octanol than those obtained in the other solvents.

Keywords: Acetanilide; Acetaminophen; Phenacetin; Solubility; Activity coefficients

INTRODUCTION

The first basic step in the physicochemical characterization of a pharmaceutical compound is the solubility study. This can be afforded by a complete thermodynamic description of the system that includes the enthalpic and the entropic contributions towards the solution process. For many pharmaceutical purposes, especially in the preformulation studies, it is necessary to measure the solubility of a drug in several solvents at various temperatures and to express the data as solubility–temperature curves [1].

These studies have been carried out for pharmaceutical solutes, such as sulfonamides in some alcohols [2–4], parabens in water and in aliphatic alcohols [5,6], some steroids in water [7], some phenols in aqueous solutions and octanol [8,9], acetaminophen, adipic acid and parabens in water [1], acetaminophen in edulcorated aqueous solutions [10], barbituric acid derivatives in aqueous media [11]. Martínez and Gómez presented

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the thermodynamics of solutions of some sulfonamides in octanol, water, and the mutually saturated solvents [12], and more recently, Ávila and Martínez presented the behavior of benzocaine in several organic and aqueous solvents [13]. Other studies with benzocaine have been development by Schwartz and Paruta [14] and by Paruta [15], who studied the solution thermodynamics of alkyl *p*-aminobenzoates in methanol, ethanol, and propanol, and in aqueous solutions, respectively.

In this article, the thermodynamic study of solubility of acetanilide, acetaminophen, and phenacetin in several model solvent systems used in the QSAR studies (Quantitative Structure–Activity Relationships) is presented. This study was made with a basic purpose to present a more complete and systematic information about the properties of transfer for these drugs.

The solubility at different temperatures was determined in buffer solution (pH 7.4 and ionic strength 0.15 mol L^{-1}: the physiological values [16,17]), in octanol, isopropyl myristate, chloroform, water-saturated octanol, water-saturated isopropyl myristate, water-saturated chloroform, octanol-saturated buffer, isopropyl myristate-saturated buffer, chloroform-saturated buffer, and cyclohexane. From this information, the respective thermodynamic analysis was performed.

Octanol has been used as a standard organic medium for the partition experiments in the development of the QSAR studies, because the octanol–water partition coefficient P is an important parameter for modeling biological membranes and predicting the fate, transport, and distribution of drugs [18]. Octanol acts as a hydrogen acceptor as well as a donor. Isopropyl myristate is best related to skin/transdermal absorption because its polar and non-polar nature mimics the complex nature (semipolar matrix) of the skin [19]. Isopropyl myristate acts as a hydrogen acceptor. Chloroform acts mainly as a hydrogen donor. Cyclohexane is a lipophilic hydrocarbon solvent, purely non-polar, therefore, it permits to evaluate hydrophobic interactions.

EXPERIMENTAL

Materials

In this investigation, the following materials were used: acetanilide S.R. Merck (ACN); acetaminophen USP [20] QAC (ACP); phenacetin A.R. BDF (PNC); octanol extra pure Merck (ROH); isopropyl myristate A.R. Merck (IPM); chloroform A.R. Mallinckrodt (CHL); cyclohexane A.R. Merck (CH); distilled water (W) conductivity $< 2\,\mu S$, Laboratory of Pharmaceutics, National University of Colombia; alcohol USP [20], Empresa Licorera de Cundinamarca; potassium chloride A.R. Merck; sodium mono and dihydrogen phosphates A.R. Merck; Millipore Corp. Swinnex®-13 filter units.

Solubility Determinations

An excess of substance was added to 20 mL of each solvent in glass flasks. The mixtures were then stirred in a Wrist Action Burrel model 75 mechanical shaker for 1 h. The samples were allowed to stand in a Magni Whirl Blue M. Electric Company water bath kept at 25.0, 30.0, 35.0, and $40.0 \pm 0.1^{\circ}C$ for 72 h. After this time, the supernatant solutions were filtered to ensure that the solutions were particulate matter-free before sampling. The solution concentrations were determined by measuring the

UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each compound in a Hewlett Packard 8452A spectrophotometer, with diode array. All solubility experiments were repeated at least three times. The densities of the saturated solutions were determined by using a DMA 45 Anton Paar digital density meter according to a previously reported procedure to facilitate the conversion of the concentration scales between molarity and mole fraction [21].

RESULTS AND DISCUSSION

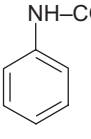
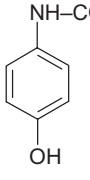
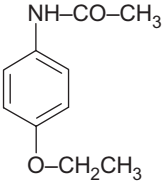
The molecular structures of the studied compounds, their abbreviations, and some of their physicochemical properties are summarized in Table I [22,23]. The maximum wavelength values are in good agreement with those of literature [22]. The solubility of compounds in water were determined at pH 7.4. This pH value was regulated by phosphate buffer having 0.01 in β capacity, using pK_a values corrected to $\mu = 0.15\,\text{mol}\,L^{-1}$ (gastrointestinal tract value [17]) by means of Debye–Hückel Eq. [24].

Ideal Solubility

The ideal solubility of a crystalline solute in a liquid solvent can be calculated by Eq. (1):

$$\ln x_2^i = -\frac{\Delta_{\text{fus}} H(T_{\text{fus}} - T)}{RT_{\text{fus}}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{\text{fus}} - T)}{T} + \ln\left(\frac{T}{T_{\text{fus}}}\right)\right] \quad (1)$$

TABLE I Some physicochemical properties of the compounds studied [22,23]

Compound	*Abbreviation*	*Molecular structure*	*Molar mass*/ $g\,mol^{-1}$	pK_a[a]	λ_{max}/nm[b]
Acetanilide	ACN		135.16	0.47	240 246
Acetaminophen	ACP		151.16	9.78	242 250
Phenacetin	PNC		179.21	2.1	242 250

[a] Corrected to $\mu = 0.15\,\text{mol}\,L^{-1}$ by means of the Debye–Hückel Eq. (24).
[b] First value in water at pH 7.4 and second in alcohol USP.

TABLE II Properties of melting and ideal solubilities of compounds studied [27,28]

Compound	t_{fus}/°C	$\Delta_{fus}H$/kJ mol^{-1}	$\Delta_{fus}S$/J mol^{-1} K^{-1}	x_2^i			
				25.0°C	*30.0*°C	*35.0*°C	*40.0*°C
ACN	114.3	20.30	52.43	0.1521	0.1741	0.1985	0.2254
ACP	169.5	27.71	62.60	0.02602	0.03127	0.03740	0.04442
PNC	134.5	30.72	75.38	0.03582	0.04393	0.05356	0.06489

where x_2^i is the ideal solubility of the solute as mole fraction, $\Delta_{\text{fus}}H$ 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, 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 [25,26].

Since ΔC_p cannot be easily determined experimentally, one of the following assumptions has to be made: (a) ΔC_p is negligible and can be considered zero or (b) ΔC_p may be approximated to the entropy of fusion, $\Delta_{\text{fus}}S$. The simplified equation is:

$$\ln x_2^i = -\frac{\Delta_{\text{fus}}H(T_{\text{fus}} - T)}{RT_{\text{fus}}T} \tag{2}$$

Table II summarizes the melting point, enthalpy and entropy of fusion of the evaluated compounds, which were reported previously in the literature [27,28], in addition to the ideal solubilities calculated by means of Eq. (2). Since the ideal solubility depends on the melting point and the enthalpy of fusion, it is important to know how these properties vary among the studied compounds. From Table II it can be seen that T_{fus} decreases in the order ACP > PNC > ACN, while ΔH_{fus} decreases in the order PNC > ACP > ACN. The enthalpy of fusion may be considered as the heat required in order to increase the intermolecular distances in crystals, allowing melting to occur. A crystal where the molecules are bound by weak forces generally has a low heat of fusion and a low melting point, whereas one bound by strong forces has a high heat of fusion and a high melting point. The forces involved are mainly hydrogen bond and van der Waals interactions, which depend on the molecular size and some geometric parameters. Unlike other pharmaceutical compounds such as barbiturates, parabens, and substituted phenols, the compounds studied here do not constitute a homologous series. Thus, the magnitudes of the physicochemical properties for each solute must be regarded only in terms of relative substituent effects.

The ideal solubility (x_2^i) is inversely proportional to the temperature of melting and the enthalpy of fusion (Eq. (2)), therefore, it is expected to follow the same sequence of x_2^i: ACN > PNC > ACP (Table II), which is coincident with the inverse order of t_f values, that is, ACN < PNC < ACP, while it is almost the inverse order of the determined enthalpies of fusion: ACN < ACP < PNC.

Experimental Solubility of Compounds

Tables III and IV summarize the experimental solubilities expressed as molarity and mole fractions respectively. In all cases the experimental variation was not greater than 2%.

TABLE III Solubility in milimolarity of the compounds studied as a function of temperature

Solute	*Solvent*	*Solubility* (mmol L^{-1})			
		25.0°C	*30.0*°C	*35.0*°C	*40.0*°C
ACN	W	44.50	52.4	57.6	67.3
	$W_{(ROH)}$	43.35	51.4	64.1	74.1
	$W_{(IPM)}$	45.0	51.2	62.0	77.4
	$W_{(CHL)}$	41.36	52.4	62.4	73.2
	CH	1.50	2.11	3.45	5.61
	ROH	601	772	874	1145
	$ROH_{(W)}$	1028	1110	1232	1340
	IPM	72.2	82.0	95.2	111.1
	$IPM_{(W)}$	79.1	91.9	105.9	119.7
	CHL	1860	2080	2450	2630
	$CHL_{(W)}$	1690	2140	2504	3170
ACP	W	101.9	124.1	168.4	223.4
	$W_{(ROH)}$	95.88	116.7	134.6	161.1
	$W_{(IPM)}$	104.5	118.7	127.8	148.3
	$W_{(CHL)}$	101.8	118.0	141.5	169.2
	CH	0.278	0.350	0.470	0.566
	ROH	135.1	150	172	201
	$ROH_{(W)}$	222	234	255.5	275
	IPM	2.723	3.169	3.71	4.53
	$IPM_{(W)}$	3.32	3.492	3.738	3.88
	CHL	3.18	3.97	5.486	8.62
	$CHL_{(W)}$	2.68	3.50	4.52	6.23
PNC	W	5.18	6.28	8.68	11.85
	$W_{(ROH)}$	5.629	6.80	7.58	8.76
	$W_{(IPM)}$	5.21	5.96	7.45	8.13
	$W_{(CHL)}$	5.64	6.15	7.159	7.904
	CH	0.3207	0.536	0.9289	1.48
	ROH	119.6	142.7	176	204.5
	$ROH_{(W)}$	161	217	262	376
	IPM	9.960	11.55	14.6	16.24
	$IPM_{(W)}$	10.55	13.53	15.58	19.3
	CHL	434	552	618	816.1
	$CHL_{(W)}$	503	539	646	714

For the conversion of the concentration scales, the experimental densities of solutions and the octanol–water liquid–liquid equilibriums data presented by Dallos and Liszi [29] were used. The water content in water-saturated IPM was determined by the Karl-Fischer method, being this value 0.0270 expressed in mole fraction. On the other hand, the water content in water-saturated chloroform is 0.01834 while, the content of chloroform in chloroform-saturated water is 0.0289 in mole fraction, respectively, which were determined by means of a refractive metric method.

The mole fraction solubility values for ACP in water are in good agreement with those presented by Bustamante *et al.* [27,28]. The fact that the $x_{W(ROH)}$ and $x_{W(IPM)}$ values differ only slightly from x_W can be attributed to the very low solubility of octanol and IPM in water, that is, these organic solvents act more as solutes than cosolvents. On the other hand, $x_{ROH(W)}$ value differ enough from x_{ROH}, that is, the drugs are more soluble in the water-saturated octanol. The main reason for the above observation is the high solubility of water in octanol (0.726 in mole fraction [29]); elsewhere, the role of water in the rise of solubility is not clear. The solubilities determined for the three compounds, studied in water, octanol, and the mutually saturated solvents, indicate

TABLE IV Solubility in mole fraction of the compounds studied as a function of temperature

Solute	*Solvent*	$10^4 \times$ *mole fraction*			
		25.0°C	*30.0°C*	*35.0°C*	*40.0°C*
ACN	W	8.067	9.54	10.52	12.33
	$W_{(ROH)}$	7.446	9.28	11.6	13.43
	$W_{(IPM)}$	8.10	9.23	11.21	14.03
	$W_{(CHL)}$	7.44	9.44	11.28	13.26
	CH	1.627	2.287	3.74	6.09
	ROH	928	1187	1338	1746
	$ROH_{(W)}$	1248	1361	1514	1660
	IPM	226.4	257	298	347
	$IPM_{(W)}$	242	280	322	364
	CHL	1600	1821	2179	2365
	$CHL_{(W)}$	1419	1820	2158	2786
ACP	W	18.58	22.74	31.1	41.70
	$W_{(ROH)}$	17.37	21.21	24.55	29.5
	$W_{(IPM)}$	18.98	21.60	23.30	27.11
	$W_{(CHL)}$	18.45	21.4	25.8	31.0
	CH	0.301	0.380	0.510	0.618
	ROH	212.6	236	271	315
	$ROH_{(W)}$	267	282	307.6	331
	IPM	8.66	10.05	11.8	14.34
	$IPM_{(W)}$	10.34	10.86	11.64	12.08
	CHL	2.635	3.318	4.608	7.30
	$CHL_{(W)}$	2.099	2.75	3.545	4.88
PNC	W	0.931	1.130	1.56	2.134
	$W_{(ROH)}$	1.007	1.22	1.359	1.573
	$W_{(IPM)}$	0.932	1.068	1.336	1.461
	$W_{(CHL)}$	1.008	1.101	1.282	1.418
	CH	0.3457	0.585	1.017	1.638
	ROH	190	227.0	281.0	328.0
	$ROH_{(W)}$	194	264	321	468
	IPM	31.64	36.7	46.45	51.60
	$IPM_{(W)}$	32.70	41.9	48.2	59.6
	CHL	367	470	528	703.9
	$CHL_{(W)}$	347.8	438	528	586

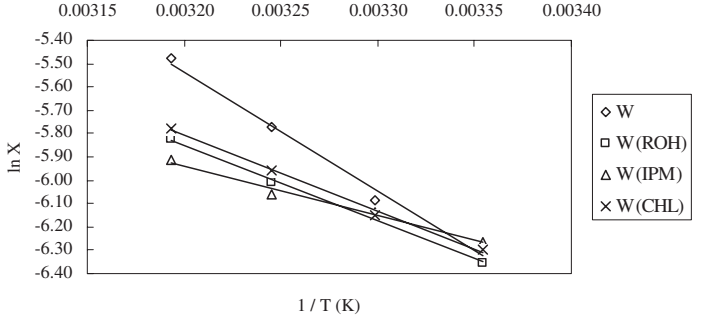


FIGURE 1 Temperature-dependence of solubility for ACP in aqueous media (solubility x_2, mole fraction).

that a mutual saturation of water and octanol plays a special role in the solubility of this compound. This behavior is similar to that found by Kristl and Vesnaver on guanine derivatives [30], Martínez and Gómez on some sulfonamides [12], and Ávila and Martínez on benzocaine [13].

Figures 1–3 show the temperature–solubility dependence (van't Hoff plots) for ACP (drug extensively used nowadays in therapeutics): (a) in aqueous media

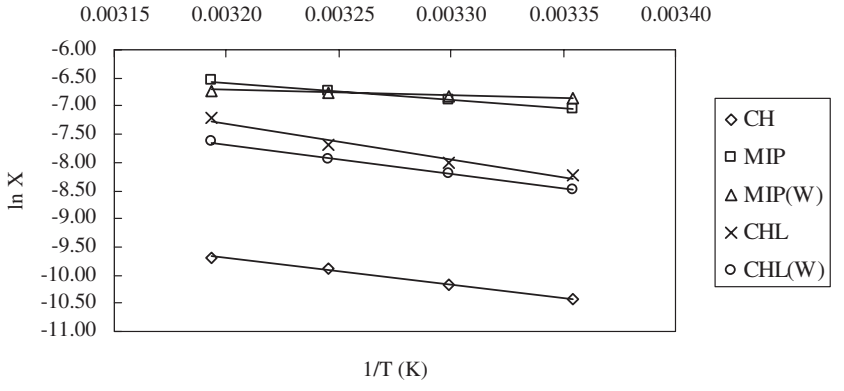


FIGURE 2 Temperature-dependence of solubility for ACP in several organic solvents (solubility x_2, mole fraction).

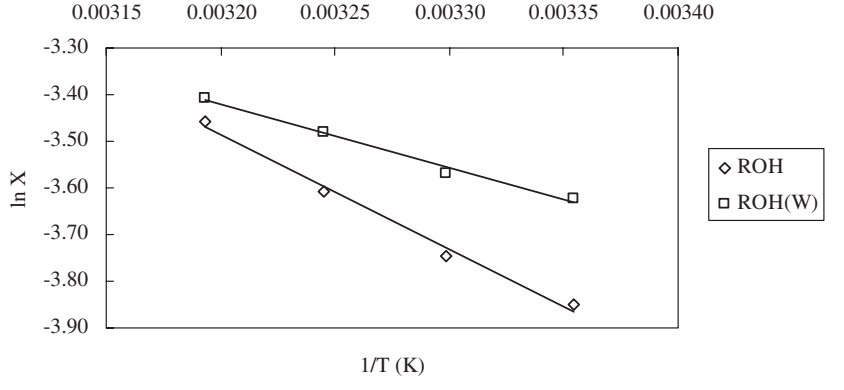


FIGURE 3 Temperature-dependence solubility for ACP in octanol and water saturated-octanol (solubility x_2, mole fraction).

(Fig. 1): (b) in the other organic without octanolic media (Fig. 2), and finally, (c) in octanol and water-saturated octanol (Fig. 3), in mole fraction, respectively. Straight lines with determination coefficients r^2, greater than 0.95 were obtained in all solubility analyses for all the compounds studied by the method of van't Hoff, and then the enthalpies of solution were calculated from the respective slopes of the graphs.

Thermodynamic Functions of Solution

The Gibbs energy, the enthalpy, and the entropy of solution were calculated by means of Eqs. (3)–(5):

$$\Delta_{\mathrm{sol}}G = -RT\ln x_2 \tag{3}$$

$$\left[\frac{\partial(-\ln x_2)}{\partial(1/T)}\right]_p = \frac{\Delta_{\mathrm{sol}}H}{R} \tag{4}$$

$$\Delta_{\mathrm{sol}}G = \Delta_{\mathrm{sol}}H - T\Delta_{\mathrm{sol}}S \tag{5}$$

TABLE V Thermodynamic functions for solution of compounds studied at 25.0°C

Solute	*Solvent*	*Enthalpy* (kJ mol^{-1})		*Entropy* (J mol^{-1} K^{-1})		*Free energy* (kJ mol^{-1})		
		$\Delta_{sol}H$	$\Delta_{mix}H$	$\Delta_{sol}S$	$\Delta_{mix}S$	$\Delta_{sol}G$	$\Delta_{SOL}G^{i}$	$\Delta_{sol}G^{E}$
ACN	W	21.3	0.97	12.2	−40.2	17.64	4.67	12.97
	$W_{(ROH)}$	30.9	10.6	43.9	−8.48	17.84	4.67	13.17
	$W_{(IPM)}$	28.5	8.22	36	−15.9	17.63	4.67	12.96
	$W_{(CHL)}$	29.7	9.38	39.7	−12.7	17.84	4.67	13.17
	CH	69	48.7	159	106.6	21.60	4.67	16.93
	ROH	31	10.9	85	32.6	5.89	4.67	1.22
	$ROH_{(W)}$	14.80	−5.50	32.4	−20.1	5.15	4.67	0.480
	IPM	22.2	1.88	42.9	−9.49	9.38	4.67	4.71
	$IPM_{(W)}$	21.2	0.90	40.2	−12.2	9.16	4.67	4.55
	CHL	20.9	0.59	55	2.44	4.53	4.67	−0.140
	$CHL_{(W)}$	34	13.7	98	45.4	4.75	4.67	0.170
ACP	W	42.4	14.7	90	27.5	15.57	9.04	6.53
	$W_{(ROH)}$	26.9	−0.77	37.6	−25.0	15.74	9.04	6.70
	$W_{(IPM)}$	17.8	−9.86	7.8	−54.8	15.52	9.04	6.48
	$W_{(CHL)}$	26.7	−1.04	37.2	−25.4	15.59	9.04	6.55
	CH	38.1	10.4	41.2	−21.4	25.78	9.04	16.74
	ROH	20.4	−7.23	36.7	−25.9	9.54	9.04	0.500
	$ROH_{(W)}$	11.4	−16.3	8.0	−54.6	8.97	9.04	−0.070
	IPM	25.9	−1.82	28.2	−34.4	17.46	9.04	8.42
	$IPM_{(W)}$	8.3	−19.4	−29.0	−91.8	16.97	9.04	7.98
	CHL	52	24.7	107	44.7	20.41	9.04	11.37
	$CHL_{(W)}$	43.2	15.5	74	11.9	20.87	9.04	11.93
PNC	W	44	12.9	69	−6.28	22.98	8.23	17.75
	$W_{(ROH)}$	22.5	−8.23	−1.00	−76.4	22.79	8.23	14.56
	$W_{(IPM)}$	24.4	−6.30	4.8	−70.5	22.98	8.23	14.75
	$W_{(CHL)}$	18.0	−12.7	−15.9	−91.2	22.79	8.23	14.56
	CH	81.0	50.3	186.4	111	25.44	8.23	17.21
	ROH	28.8	−1.87	63.8	−11.5	9.82	8.23	1.59
	$ROH_{(W)}$	44	13.1	114	38.9	9.76	8.23	1.53
	IPM	26.4	−4.28	41	−34.5	14.25	8.23	6.02
	$IPM_{(W)}$	30.2	−0.55	54	−21.7	14.12	8.23	5.94
	CHL	32	1.35	80	4.77	8.18	8.23	−0.05
	$CHL_{(W)}$	27.3	−3.46	64	−11.8	8.22	8.23	−0.09

Table V summarizes the thermodynamic functions of solution process. These values were calculated from the solubilities presented in Table IV by means of Gibbs and van't Hoff equations using weighed values. As is mentioned earlier, the straight lines with determination coefficients (r) greater than 0.95 were obtained in all solubility analyses by the van't Hoff method, therefore the enthalpies of solution may be calculated from the slopes following Eq. (4).

It is found that the standard Gibbs energy of solution is positive in all cases, that is, the solution process is not spontaneous which is explained in terms of the standard state of reference employed, that is, ideal behavior for the solution in a solution having a concentration of unity in mole fraction. The enthalpy of solution is positive in all cases, therefore this process is always endothermic. The entropy of solution is positive for all solutes, except for ACP in $IPM_{(W)}$ and PNC in $W_{(ROH)}$ and $W_{(CHL)}$.

Thermodynamic Functions of Mixing

For a non-ideal case, the solubility process can be approximately described by the following hypothetic process:

$$\text{Solute}_{(\text{solid})} \rightarrow \text{Solute}_{(\text{liquid})} \rightarrow \text{Solute}_{(\text{solution})}$$

The above scheme has two steps: the melting of the solute and its mixing with the solvent. Therefore, the functions enthalpy ($\Delta_{mix}H$) and entropy ($\Delta_{mix}S$) of mixing can be calculated, in first place, from the enthalpy ($\Delta_{fus}H$) and the entropy ($\Delta_{fus}S$) of fusion that are determined experimentally (assuming that these properties do not change with temperature), and in second place, from the enthalpy ($\Delta_{sol}H$) and entropy ($\Delta_{sol}S$) of solution, by means of Eqs. (6) and (7), respectively, while the excess standard free energy of solution is determined from Eq. (8):

$$\Delta_{sol}H = \Delta_{fus}H + \Delta_{mix}H \tag{6}$$

$$\Delta_{sol}S = \Delta_{fus}S + \Delta_{mix}S \tag{7}$$

$$\Delta_{sol}G^E = \Delta_{sol}G - \Delta_{sol}G^i \tag{8}$$

The viewing of $\Delta_{fus}H$ and $\Delta_{fus}S$ from the data of Table V indicates that these parameters are always positive, while the contribution of the mixing process toward the solution is variable; that is, $\Delta_{mix}H$ is negative for ACN in $ROH_{(W)}$, while it is positive for all other cases of this drug. On the other hand, for ACP and PNC the behavior is variable. The entropy of mixing ($\Delta_{mix}S$) is negative for almost all compounds. It can be concluded that the process of solution is driven mainly by the entropy of solution, except for ACP in $IPM_{(W)}$ and PNC in $W_{(ROH)}$ and $W_{(CHL)}$.

The negative values of $\Delta_{mix}S$ suggest some type of structure formation in the solutions; nevertheless, it is not easy to identify the possible solute–solvent or solvent–solvent interactions that may explain the respective entropy decrease in cyclohexane, whereas in water, octanol, isopropyl myristate, or water-saturated chloroform, the main interaction is by hydrogen bonding [26].

Activity Coefficients

The activity coefficients (γ_2) calculated by means of Eq. (9) from the solubility data in Tables II and IV are presented in Table VI.

$$\gamma_2 = x_2^i/x_2 \tag{9}$$

From activity coefficients presented in Table VI the drugs may be classified into two groups based on the magnitude of this property, that is, first, ACN and PNC, where the sequence is CH > W > IPM > ROH $\approx$ CHL, and second, ACP where the sequence is CH > CHL > IPM > W > ROH. In the previous classification it is considered that activity coefficients are very similar for pure and saturated solvents. For the first group, the magnitudes of γ_2 vary from, near to 1000 in CH, 200–400 in W, near to 10 in IPM, and finally, up to 1 in ROH and CHL, while for ACP, vary from 900 in CH, near to 100 in CHL, near to 30 in IPM, near to 10 in W, and finally, up to 1 in ROH. In all almost cases the solution process is near to 'ideality' in octanol while the worst behavior is presented in cyclohexane.

The previous results are analogous to those obtained in the study of solubility of these drugs in cosolvent–water binary systems [31], where it was found that the highest solubility is obtained in mixtures rather than pure solvents; on the other hand, a similar behavior was obtained in the study of partial molar volumes at infinite dilution for

TABLE VI Activity coefficients of compounds in various solvents at four temperatures

Solute	*Solvent*	γ_2			
		25.0°C	*30.0*°C	*35.0*°C	*40.0*°C
ACN	W	188.6	182.6	188.7	182.8
	$W_{(ROH)}$	204.3	187.6	171.2	167.8
	$W_{(IPM)}$	187.7	188.7	177.1	160.6
	$W_{(CHL)}$	204.4	184.4	175.9	170.0
	CH	934.8	761.4	530.4	369.8
	ROH	1.639	1.466	1.483	1.291
	$ROH_{(W)}$	1.219	1.279	1.311	1.361
	IPM	6.719	6.777	6.663	6.491
	$IPM_{(W)}$	6.294	6.209	6.156	6.195
	CHL	0.9488	0.9563	0.9108	0.9530
	$CHL_{(W)}$	1.072	0.9536	0.9196	0.8090
ACP	W	14.00	13.75	12.02	10.65
	$W_{(ROH)}$	14.98	14.74	15.24	15.05
	$W_{(IPM)}$	13.71	14.57	16.05	16.39
	$W_{(CHL)}$	14.10	14.57	14.48	14.30
	CH	863.8	821.9	733.1	718.2
	ROH	1.224	1.326	1.381	1.408
	$ROH_{(W)}$	0.9730	1.111	1.216	1.340
	IPM	30.05	31.11	31.8	30.98
	$IPM_{(W)}$	25.19	28.78	32.14	36.77
	CHL	98.74	94.29	81.16	60.87
	$CHL_{(W)}$	124.0	113.8	105.5	91.06
PNC	W	384.6	388.7	342.7	304.0
	$W_{(ROH)}$	355.7	360.9	394.2	412.6
	$W_{(IPM)}$	384.4	411.5	400.9	444.3
	$W_{(CHL)}$	355.3	399.1	417.7	457.7
	CH	1036	750.6	526.5	396.0
	ROH	1.89	1.935	1.906	1.978
	$ROH_{(W)}$	1.842	1.661	1.666	1.388
	IPM	11.32	11.97	11.53	12.58
	$IPM_{(W)}$	10.95	10.48	11.10	10.88
	CHL	1.030	0.9355	1.014	0.9219
	$CHL_{(W)}$	0.9913	1.003	1.015	1.107

these drugs in ethanol–water mixtures [32], because the lower value of this property is found in the mixture, rather than absolute ethanol, that is, ACN, ACP and PNC are more solvated in mixtures. Therefore, the results presented here, as well, those presented previously [31,32], confirm fully that the drugs studied have a semipolar but mainly lipophilic nature.

In the first approach the γ_2 values allow an estimate of the intermolecular interactions between the solutes and the solvent by means of Eq. (10):

$$\ln \gamma_2 = (w_{11} + w_{22} - 2w_{12}) \frac{V_2 \phi_1^2}{RT} \tag{10}$$

where w_{11}, w_{22} and w_{12} represent the solvent–solvent, solute–solute and solvent–solute interaction energies, respectively; V_2 is the molar volume of the supercooled liquid solute, and ϕ_1 is the volume fraction of the solvent. The term $(V_2\phi_1^2/RT)$ may be considered constant at the same temperature, then γ_2 depends almost exclusively on w_{11}, w_{22} and w_{12} [26,30].

It can be seen in Eq. (10) that the contribution of w_{22} is constant for each compound, since it represents the work necessary to take a molecule to the vapor state. The greater γ_2 values obtained in cyclohexane (near to 1000) compared with those obtained in ROH (near to 1), IPM and CHL (smaller than 100), which are solvents that may establish hydrogen bonds, indicate that the contribution of w_{11} in cyclohexane (aprotic solvent) is lower, hence the w_{12} values (relative to solute–solvent interactions) are also very small, while this term is significant in the other solvents, specially in those where γ_2 are smaller.

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