Thermodynamic Study of the Solubility of Procaine HCl in Some Ethanol + Water Cosolvent Mixtures

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By using the van't Hoff and Gibbs equations, the thermodynamic functions of Gibbs energy, enthalpy, and entropy of solution for procaine HCl in ethanol + water cosolvent mixtures were evaluated from solubility data determined at temperatures from (278.15 to 308.15) K. The drug solubility was greatest in neat water and lowest in neat ethanol at all of the temperatures studied. This behavior showed the negative cosolvent effect for this electrolyte drug in this solvent system. By means of enthalpy−entropy compensation analysis, a nonlinear $\Delta H_{soln}^{0\text{-app}}$ versus $\Delta G_{soln}^{0\text{-app}}$ plot with a positive slope from neat ethanol up to 0.10 mass fraction of water and negative from 0.10 to 0.30 mass fraction of water was obtained, whereas from this composition up to neat water a positive slope was obtained again. Accordingly to this result and to the transfer properties, it follows that the dissolution process of this drug in ethanol-rich and water-rich mixtures is enthalpy-driven, whereas between 0.10 and 0.30 mass fraction of water, the process is entropy-driven.

Introduction

Procaine HCl (PC-HCl, Figure 1) is a local anesthetic drug used in allopathic medicine,[1] as well as in neural therapy.[2] Although PC-HCl is widely used nowadays in therapeutics, the physicochemical information about their aqueous solutions is not complete at present, although several physicochemical studies have been done. In this way, the solution thermodynamics in aqueous media for this drug has been presented in the literature.[3,4] These studies have been made by using the van't Hoff method[3] and calorimetric techniques.[4] On the other hand, the physical aspects of the transfer of this drug from aqueous media up to phospholipidic vesicles have also been reported.[5] In a similar way, the surface tension in water has also been studied for this drug alone and in combination with phospholipidic monolayers.[6] Ultimately, the apparent molar volumes in water have also been studied as a function of drug concentration and temperature.[7]

On the other hand, it is well-known that injectable homogeneous liquid formulations supply relatively high doses of drug in small volumes, and thus, some physicochemical properties, such as the solubility of drugs and other formulation components, are very important, because they facilitate the design process of pharmaceutical dosage forms.[8]

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 design, among other applications.[9,10] For these reasons, it is important to determine systematically the solubility of pharmaceutical compounds. This information facilitates widely the labor of pharmacists associated with the research and development of new products in the pharmaceutical industry. Besides, temperature-solubility dependence allows us to carry out the respective thermodynamic analysis, which, on the other hand, also permits inside the molecular mechanisms involved with the solution processes.[11]

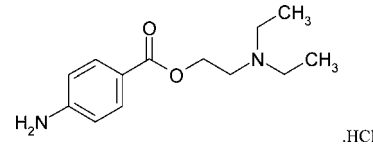

Figure 1. Molecular structure of procaine HCl. The hydrochloride form is established by the protonation of the tertiary amine group.

The main objective of this study was to evaluate the effect of the cosolvent composition on the solubility and solution thermodynamics of PC-HCl in ethanol (EtOH) (1) + water (2) cosolvent mixtures on the basis of the van't Hoff method. It is important to note that EtOH is the cosolvent more widely used in the development of liquid pharmaceutical dosage forms.[9,10]

Experimental Section

Materials. Procaine hydrochloride [4-aminobenzoic acid 2-(diethylamino)ethyl ester HCl; CAS Registry No. 51-05-8; purity: 0.9995 mass fraction] used is in agreement with the quality requirements indicated in the American Pharmacopeia, USP;[12] in a similar way, absolute ethanol A.R. (Merck) (CAS Registry No. 64-17-5; purity: 0.9990 mass fraction), distilled water (CAS Registry No. 7732-18-5; conductivity $< 2\ \mu S \cdot cm^{-1}$), molecular sieve (Merck, numbers 3 and 4), and Millipore Corp. Swinnex-13 filter units were also used.

Cosolvent Mixture Preparation. All EtOH + water cosolvent mixtures were prepared in quantities of 10.00 g by mass using an Ohaus Pioneer TM PA214 analytical balance with a sensitivity of ± 0.1 mg, in mass fractions from 0.10 to 0.90 varying by 0.10, to study nine binary mixtures and the two pure solvents.

Solubility Determinations. An excess of PC-HCl was added to 5 cm^3 of each cosolvent mixture, in stoppered dark glass

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Table 1. Experimental Solubility of Procaine HCl (3) in Ethanol (1) + Water (2) Cosolvent Mixtures Expressed in Mole Fraction (·10^2) at Several Temperatures[a]

	T/K						
μ_1[b]	278.15	283.15	288.15	293.15	298.15	303.15	308.15
0.00	6.322 (0.016)	7.072 (0.028)	7.779 (0.024)	8.54 (0.04)	9.39 (0.06)	10.20 (0.07)	11.24 (0.06)
0.10	6.25 (0.03)	6.96 (0.04)	7.71 (0.04)	8.43 (0.05)	9.23 (0.06)	10.03 (0.09)	11.03 (0.06)
0.20	6.11 (0.03)	6.87 (0.03)	7.56 (0.05)	8.28 (0.05)	9.13 (0.06)	9.86 (0.04)	10.81 (0.07)
0.30	5.922 (0.019)	6.664 (0.021)	7.38 (0.05)	8.06 (0.04)	8.86 (0.07)	9.61 (0.04)	10.46 (0.07)
0.40	5.679 (0.012)	6.368 (0.020)	7.10 (0.04)	7.81 (0.05)	8.56 (0.04)	9.39 (0.05)	10.18 (0.06)
0.50	5.353 (0.018)	5.975 (0.020)	6.624 (0.027)	7.278 (0.029)	7.95 (0.03)	8.74 (0.04)	9.59 (0.04)
0.60	4.987 (0.018)	5.442 (0.014)	6.00 (0.03)	6.64 (0.04)	7.330 (0.022)	8.10 (0.03)	8.89 (0.04)
0.70	3.933 (0.011)	4.398 (0.017)	4.770 (0.018)	5.326 (0.019)	5.923 (0.021)	6.615 (0.022)	7.31 (0.05)
0.80	2.904 (0.008)	3.148 (0.009)	3.469 (0.016)	3.816 (0.021)	4.262 (0.018)	4.726 (0.014)	5.250 (0.020)
0.90	1.673 (0.006)	1.844 (0.010)	2.044 (0.004)	2.258 (0.010)	2.486 (0.008)	2.698 (0.011)	2.985 (0.008)
1.00	0.4652 (0.0007)	0.5488 (0.0010)	0.6409 (0.0019)	0.739 (0.003)	0.831 (0.003)	0.9389 (0.0019)	1.055 (0.003)

[a] Values in parentheses are standard deviations. [b] μ_1 is the mass fraction of ethanol in the cosolvent mixture free of solute.

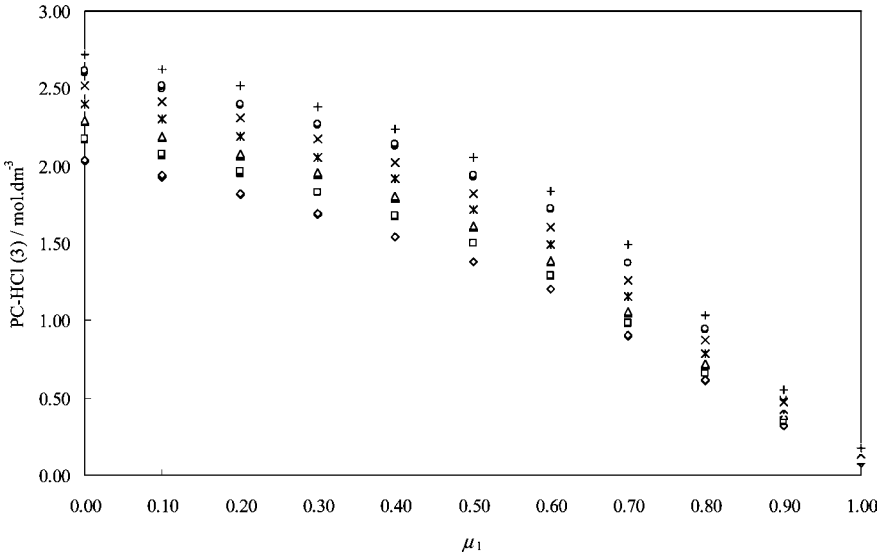

Figure 2. Experimental solubility of procaine HCl (3) in the ethanol (1) + water (2) mixtures expressed in molarity. μ_1 is the mass fraction of ethanol in the cosolvent mixture free of solute. ◇, T = 278.15 K; □, T = 283.15 K; △, T = 288.15 K; ∗, T = 293.15 K; ×, T = 298.15 K; ○, T = 303.15 K; +, T = 308.15 K.

flasks. Solid−liquid mixtures were stirred in a mechanical shaker (Burrel, Wrist Action Shaker, model 75) at room temperature at least for 4 h. The flasks were kept at each temperature (± 0.05 K) in recirculating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company) with sporadic stirring at least for 5 days to reach the equilibrium. After this time the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined by measuring absorbance after appropriate dilution with water and interpolation from a previously constructed UV spectrophotometric calibration curve (UV/vis BioMate 3 Thermo Electron Company spectrophotometer). All of the solubility experiments were run at least in triplicate. To make the equivalence between molarity and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) connected to the same recirculating thermostatic baths.

Results and Discussion

Before showing the solubility results, it is important to consider that this drug exhibits electrolyte behavior, and thus, it dissociates in aqueous solution interacting with the solvent by ions−dipole interactions, as well as by other noncovalent interactions; in this way, it also could act as a Lewis acid (−NH_2 group) or Lewis base (−NH_2 group and −COO− groups) to establish hydrogen bonds with proton-acceptor or donor functional groups in the solvents (−OH groups).[13,14]

Experimental Solubility. Table 1 summarizes the experimental solubility of PC-HCl, expressed in mole fraction at all of the temperatures studied. In all cases the percent coefficients of variation were smaller than 1.0 %.

It could be observed that the solubility expressed in mole fraction, in almost all cases, was greatest in neat water and lowest in neat EtOH at all temperatures studied. This behavior shows the negative cosolvent effect present for this electrolyte drug in this solvent system. This behavior is in agreement with that expected according to the literature,[9,10] since the PC-HCl solubility is greatest in neat water as could be expected because of its large dielectric constant value (78.5 at 298.15 K).[13] Our solubility values in water are in good agreement with those reported in the literature at temperatures from (298.15 to 308.15) K.[3] Unfortunately, in the literature there are no reported quantitative solubility values for this drug in neat EtOH or EtOH (1) + water (2) mixtures, and therefore, no other direct comparison is possible. Nevertheless, a solubility value of 1 g in 30 cm^3 of alcohol has been reported without specifying the temperature,[15] finding a good agreement with our drug solubility value in neat ethanol at 293.15 K (3.40 g in 100 cm^3 of solution).

On the other hand, it is important to keep in mind that the number of grams of solute in 100 cm^3 of solution is the

concentration scale most widely used by pharmacists to formulate liquid dosage forms.[16] For this reason, Figure 2 shows the drug solubility which is expressed in molarity ($mol \cdot dm^{-3}$), a volumetric concentration scale, which is easily converted to grams of solute in 100 cm^3 of solution.

Because PC-HCl is an electrolyte drug, it is important to note that, in general terms, it could be stated that a strong electrolyte dissociates according to the expression $C_{\upsilon+}A_{\upsilon-} \rightarrow \upsilon_+C^{z+} + \upsilon_-A^{z-}$, where υ_+ is the number of cations (C^{z+}) of valence $z+$ and υ_- is the number of anions (A^{z-}) of valence $z-$. Because is not possible to determine experimentally the activity of ions separately, the concept of mean ionic activity ($a^{\upsilon}{}_{\pm}$) is used. Thus, the thermodynamic activity for an electrolyte can be defined as $a_2 = a_+^{\upsilon+}a_-^{\upsilon-} = a_{\pm}^{\upsilon}$.[17−19]

On the same way, in terms of individual ionic activity coefficients (γ_+ and γ_-), the mean activity coefficient ($\gamma_\pm$) could be defined as $\gamma_\pm^{\upsilon} = \gamma_+^{\upsilon+}\gamma_-^{\upsilon-}$, which is equal to $\gamma_\pm = (\gamma_+^{\upsilon+}\gamma_-^{\upsilon-})^{1/\upsilon}$. Thus, if the drug concentration is expressed in mole fraction, the solute thermodynamic activity in the solution could be calculated as $a_\pm^x = \gamma_\pm^x x_\pm$, where $\gamma_\pm^x$ is the rational activity coefficient, and it is a deviation criterion with respect to the ideal solution.

PC-HCl is an electrolyte solute of type one−one, that is, it dissociates in aqueous solutions to generate two species, a monovalent cation and a monovalent anion, respectively. If the interionic interactions are not considered, in a first approach the υ value could be ideally assumed as 2 for this drug.[3]

Thermodynamic Functions of Solution. According to the van't Hoff analysis, the apparent standard enthalpy change of solution ($\Delta H_{soln}^{0\text{-app}}$) is obtained from the slope of a ln x_3 versus $1/T$ plot. Nevertheless, in several thermodynamic treatments some adjustments have been introduced in the van't Hoff equation to reduce the propagation of errors and, therefore, to separate the chemical effects from those due only to statistical treatments used when enthalpy−entropy compensation analyses are carried out. In this context, the mean harmonic temperature (T_{hm}) is used in van't Hoff analysis. T_{hm} is calculated as $n/\sum_{i=1}^{n}(1/T)$, where n is the number of temperatures considered (i.e., seven for our present values, from (278.15 to 308.15) K). In the present case the T_{hm} value obtained is 292.8 K. For electrolytes type one−one, such as PC-HCl (3), if the interionic interactions are not considered, the modified expression more widely used is the following,[20,21]

$$\left(\frac{\partial \ln x_3}{\partial(1/T - 1/T_{hm})}\right)_P = -\frac{\Delta H_{soln}^{0\text{-app}}}{2R} \quad (1)$$

where R is the universal gas constant (8.314 $J \cdot mol^{-1} \cdot K^{-1}$). As an example, Figure 3 shows the modified van't Hoff plot for PC-HCl in mixtures containing 0.80 and 0.90 mass fraction EtOH and in neat EtOH. In all cases studied, linear models with good determination coefficients were obtained.

Table 2. Apparent Thermodynamic Functions Relative to the Solution Process of Procaine HCl (3) in Ethanol (1) + Water (2) Cosolvent Mixtures at 292.8 K

	$\Delta G_{soln}^{0\text{-app}}$	$\Delta H_{soln}^{0\text{-app}}$	$\Delta S_{soln}^{0\text{-app}}$	$T\Delta S_{soln}^{0\text{-app}}$		
μ_1[a]	kJ·mol^{-1}	kJ·mol^{-1}	J·mol^{-1}·K^{-1}	kJ·mol^{-1}	ζ_H[b]	ζ_{TS}[b]
0.00	12.003 (0.006)	26.93 (0.18)	51.0 (0.3)	14.93 (0.10)	0.643	0.357
0.10	12.074 (0.007)	26.61 (0.21)	49.7 (0.4)	14.54 (0.11)	0.647	0.353
0.20	12.158 (0.008)	26.72 (0.25)	49.7 (0.4)	14.57 (0.13)	0.647	0.353
0.30	12.300 (0.009)	26.72 (0.25)	49.2 (0.5)	14.42 (0.14)	0.649	0.351
0.40	12.468 (0.008)	27.67 (0.22)	51.9 (0.4)	15.20 (0.12)	0.645	0.355
0.50	12.793 (0.005)	27.45 (0.15)	50.0 (0.3)	14.65 (0.08)	0.652	0.348
0.60	13.202 (0.010)	27.77 (0.28)	49.7 (0.5)	14.57 (0.15)	0.656	0.344
0.70	14.253 (0.013)	29.4 (0.4)	51.8 (0.7)	15.18 (0.20)	0.660	0.340
0.80	15.844 (0.016)	28.4 (0.5)	42.9 (0.7)	12.57 (0.21)	0.693	0.307
0.90	18.490 (0.006)	27.42 (0.17)	30.5 (0.2)	8.93 (0.06)	0.754	0.246
1.00	24.027 (0.013)	38.7 (0.4)	50.0 (0.5)	14.63 (0.15)	0.725	0.275

[a] μ_1 is the mass fraction of ethanol in the cosolvent mixture free of solute. [b] ζ_H and ζ_{TS} are the relative contributions by enthalpy and entropy toward the Gibbs energy of solution. These values were calculated by means of eqs 4 and 5, respectively.

Table 3. Apparent Thermodynamic Functions of Transfer of Procaine HCl (3) from Less Polar Solvents to More Polar Solvents in Ethanol (1) + Water (2) Cosolvent Mixtures at 292.8 K

μ_2[a]		$\Delta G_{A\rightarrow B}^{0\text{-app}}$	$\Delta H_{A\rightarrow B}^{0\text{-app}}$	$\Delta S_{A\rightarrow B}^{0\text{-app}}$	$T\Delta S_{A\rightarrow B}^{0\text{-app}}$
A	B	kJ·mol^{-1}	kJ·mol^{-1}	J·mol^{-1}·K^{-1}	kJ·mol^{-1}
0.00	0.10	−5.537 (0.014)	−11.2 (0.4)	−19.5 (0.5)	−5.70 (0.16)
0.10	0.30	−4.237 (0.014)	2.0 (0.4)	21.4 (0.7)	6.25 (0.20)
0.30	1.00	−2.251 (0.014)	−2.5 (0.49)	−0.9 (0.8)	−0.26 (0.22)

[a] μ_2 is the mass fraction of water in the cosolvent mixture free of solute; A and B are the less polar and more polar media, respectively.

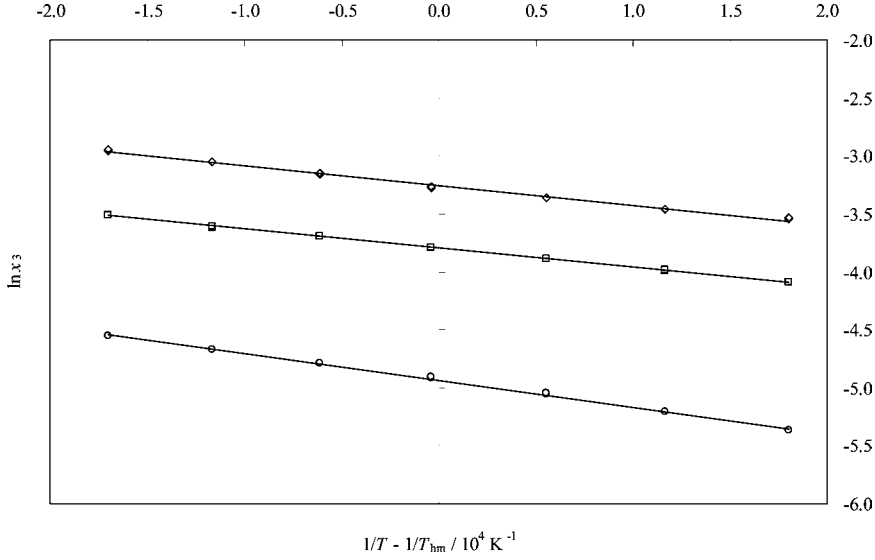

Figure 3. Modified van't Hoff plot for experimental solubility of procaine HCl (3) in some ethanol (1) + water (2) mixtures expressed in mole fraction. ◇, 0.80 mass fraction of ethanol; □, 0.90 mass fraction of ethanol; ○, neat ethanol. The lines interconnecting points are the respective linear regression models.

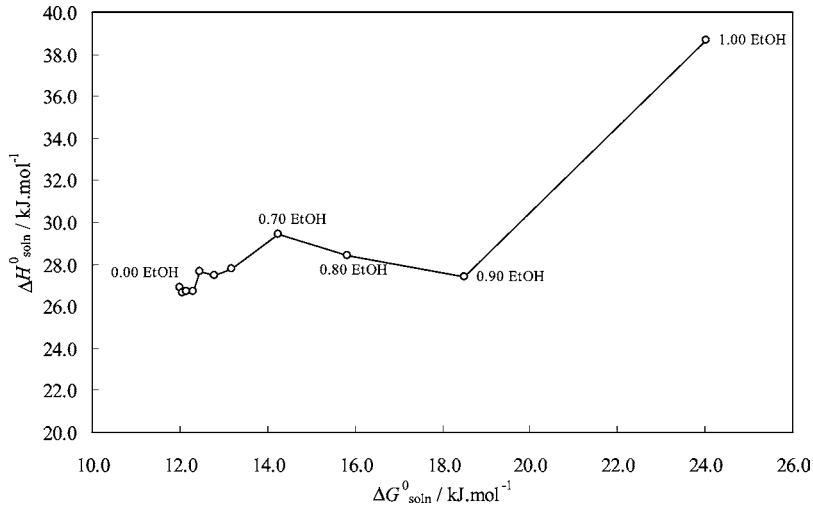

Figure 4. ΔH^0_{soln} vs ΔG^0_{soln} enthalpy−entropy compensation plot for the solubility of procaine HCl (3) in ethanol (1) + water (2) cosolvent mixtures at 292.8 K. The slopes of the lines interconnecting points define the thermodynamic functions driving the PC-HCl transfer processes.

The apparent standard Gibbs energy change for the solution process ($\Delta G^{0\text{-app}}_{soln}$) of electrolytes type one−one, considering the approach proposed by Krug et al.,[20,21] is calculated by means of,

$$\Delta G^{0\text{-app}}_{soln} = -2RT_{hm} \cdot \text{intercept} \quad (2)$$

in which the intercept used is the one obtained in the analysis by treatment of ln x_3 as a function of $1/T - 1/T_{hm}$. Finally, the apparent standard entropic change for solution process ($\Delta S^{0\text{-app}}_{soln}$) is obtained from the respective $\Delta H^{0\text{-app}}_{soln}$ and $\Delta G^{0\text{-app}}_{soln}$ values by using:

$$\Delta S^{0\text{-app}}_{soln} = \frac{(\Delta H^{0\text{-app}}_{soln} - \Delta G^{0\text{-app}}_{soln})}{T_{hm}} \quad (3)$$

Table 2 summarizes the apparent standard thermodynamic functions for the experimental solution process of PC-HCl (3) in all EtOH (1) + water (2) cosolvent mixtures. To calculate the thermodynamic quantities for the experimental solution processes, some propagation of the uncertainties' methods were used.[22] It is found that the standard Gibbs energy of solution is positive in all cases, that is, the solution process apparently is not spontaneous, which may be explained in terms of the concentration scale used (mole fraction), where the reference state is the ideal solution having the unit as the concentration of PC-HCl, that is, the solid neat solute. Besides, taking into account that the mole fraction is always lower than the unit and, thus, its logarithmic term is negative, therefore, according to eq 2, 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. In the same way, the entropy of solution is also positive, indicating the entropy-driving on the overall solution process for all of the mixtures and neat solvents. The $\Delta H^{0\text{-app}}_{soln}$ values are almost constant from neat water up to 0.60 mass fraction of EtOH and increase from this EtOH proportion up to 0.70 mass fraction of EtOH, followed by a decrease up to the mixture with 0.90 mass fraction of EtOH. Ultimately, the largest enthalpy value is found in neat EtOH. In a similar way to enthalpy, $\Delta S^{0\text{-app}}_{soln}$ values are almost constant from neat water to 0.70 mass fraction of EtOH and diminish beyond this composition, finding in neat EtOH a similar value with respect to those obtained in water-rich mixtures. The enthalpic and entropic values obtained for dissolution process of PC-HCl in water are lower with respect to those reported in the literature (34.9 kJ·mol^{-1} and 76.3 J·mol^{-1}·K^{-1}, respectively).[3]

With the aim to compare the relative contributions by enthalpy (ζ_H) and by entropy (ζ_{TS}) toward the solution process, eqs 4 and 5 were employed, respectively.[23]

$$\zeta_H = \frac{|\Delta H^0_{soln}|}{|\Delta H^0_{soln}| + |T\Delta S^0_{soln}|} \quad (4)$$

$$\zeta_{TS} = \frac{|T\Delta S^0_{soln}|}{|\Delta H^0_{soln}| + |T\Delta S^0_{soln}|} \quad (5)$$

From Table 2 it follows that in all mixtures the main contributor to standard Gibbs energy of solution process of PC-HCl is the enthalpy, in particular for EtOH-rich mixtures. The ζ_H values are greater than 0.64, indicating the relevance of the energetic factor on the dissolution processes of this drug in all of the solvent systems studied.

Thermodynamic Functions of Transfer. To verify the effect of cosolvent composition on the thermodynamic function driving the solution process, Table 3 summarizes the thermodynamic functions of transfer of PC-HCl from the less polar solvents to the more polar ones. These new functions were calculated as the differences between the thermodynamic quantities of solution in the more polar mixtures and the less polar mixtures.

If the addition of water to neat EtOH is considered (the cosolvent mixture being more polar as the water proportion increases), the following happens: from pure EtOH to 0.10 mass fraction of water ($\Delta G^{0\text{-app}}_{1\rightarrow 2} < 0$, $\Delta H^{0\text{-app}}_{1\rightarrow 2} < 0$, and $\Delta S^{0\text{-app}}_{1\rightarrow 2} < 0$) the solubility process is driven by the enthalpy, whereas from this composition to 0.30 mass fraction of water ($\Delta G^{0\text{-app}}_{1\rightarrow 2} < 0$, $\Delta H^{0\text{-app}}_{1\rightarrow 2} > 0$, and $\Delta S^{0\text{-app}}_{1\rightarrow 2} > 0$) the dissolution process is entropy-driven. Ultimately, from 0.30 mass fraction of water up to neat water ($\Delta G^{0\text{-app}}_{1\rightarrow 2} < 0$, $\Delta H^{0\text{-app}}_{1\rightarrow 2} < 0$, and $\Delta S^{0\text{-app}}_{1\rightarrow 2} < 0$), the solution process is enthalpy-driven again. The later behavior is probably due to an increase in the solvation of PC-HCl by EtOH molecules. Nevertheless, these results are not easily understood. Beyond this EtOH proportion the behavior obtained is not easily explained. At this point is important to note that drug solvation could also include cationic and anionic drug solvation by water or ethanol.

Enthalpy−Entropy Compensation of Solution. As was introduced earlier,[8] Bustamante et al.[24] have demonstrated some chemical compensation effects for the solubility of several nonelectrolyte drug compounds in aqueous cosolvent mixtures. These analyses were developed to identify the main mechanism of the cosolvent action. In this way, the making of weighted graphs of $\Delta H_{soln}^{0\text{-app}}$ as a function of $\Delta G_{soln}^{0\text{-app}}$ at the mean harmonic temperature allows us to observe similar mechanisms for the solution process according to the tendencies obtained.[25]

In this context, Figure 4 shows fully that PC-HCl (3) in the EtOH (1) + water (2) cosolvent system presents nonlinear $\Delta H_{soln}^{0\text{-app}}$ versus $\Delta G_{soln}^{0\text{-app}}$ compensation with a positive slope if an interval from pure EtOH up to 0.90 mass fraction of EtOH is considered. On the other hand, from this EtOH proportion to 0.70 mass fraction of EtOH, a negative slope is obtained. Ultimately, from this composition up to neat water, a positive slope is obtained again. Accordingly to this graph, it follows that the driving function for drug solubility is the enthalpy in the former case, whereas in the second case, the driving function is the entropy, and finally, in the later case, the driving function is the enthalpy again. Nevertheless, the molecular and ionic events involved in the dissolution of this drug in this cosolvent system are unclear.

Conclusions

From all topics discussed previously it can be concluded that the solution process of PC-HCl (3) in the EtOH (1) + water (2) mixtures is variable depending on the cosolvent composition. Nonlinear enthalpy−entropy compensation was found for this drug in this cosolvent system. In this context, enthalpy-driving was found for the solution processes in compositions from pure EtOH to the mixture having 0.10 mass fraction of water, whereas for cosolvent mixtures from this water proportion to 0.70 mass fraction of water, entropy-driving was found. Beyond this water proportion the behavior obtained is more complex, and therefore, the possible molecular events associate to solution processes are unclear. Ultimately, it can be said that the data presented in this report expand the physicochemical information about electrolyte drugs in aqueous solutions.

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