Calorimetric Enthalpies of Solution for Lidocaine−HCl and Procaine−HCl in Water at 298.15 K

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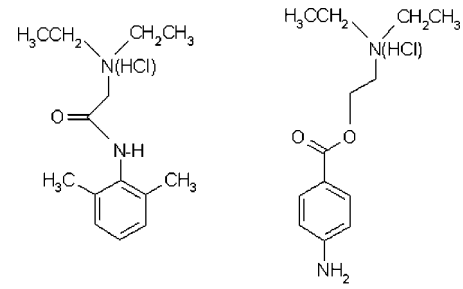
The solution enthalpy (ΔH^0_{soln}) of lidocaine−HCl (LC−HCl) and procaine−HCl (PC−HCl) in water was determined by isoperibolic solution calorimetry at 298.15 K. It was found that ΔH^0_{soln} for LC−HCl diminishes as the drug concentration increases, whereas the behavior was the opposite for PC−HCl. On the other hand, the calorimetric values obtained as a function of the drug concentration were significantly different with respect to those calculated by using the van't Hoff method, based on solubility determinations at several temperatures. It was demonstrated that the van't Hoff method is not fully reliable for the determination of ΔH^0_{soln} values in the specific case of highly soluble organic hydrochloride salts. The observed phenomena could be explained by the presence of strong solute−solute interactions at high salt concentrations, in addition to the respective solute−solvent and solvent−solvent interactions.

Introduction

Local anesthetics are amphiphilic molecules that have hydrophobic and hydrophilic domains that are separated by an intermediate alkyl chain. The hydrophilic group can be a tertiary or secondary amine, and the hydrophobic domain is an aromatic residue. They are classified in ester types and amide types; it depends on the group that binds to the aromatic residue. The nature of this bond determines several pharmacological properties for these drugs.[1]

Knowledge about the physicochemical properties of drugs in aqueous media is very important in the preformulation and formulation of novel pharmaceutical liquid dosage forms. In particular, the dissolution thermodynamic properties exhibited by the different components in solution are also important because they allow estimation of their physical stability.[2] For these reasons, Torres et al.[3] studied the apparent molar volumes of lidocaine−HCl (LC−HCl, Figure 1) and procaine−HCl (PC−HCl, Figure 1) in water as a function of the drugs concentration and temperature. It was found that this physicochemical property decreased for LC−HCl as the drug concentration increased, whereas for PC−HCl the obtained behavior was the opposite. On the basis of this fact, these authors concluded that LC−HCl acts as a water-structure maker, whereas PC−HCl acts as water-structure breaker.[3]

Related to any other drug solution properties, it is well-known that the solution enthalpy (ΔH^0_{soln}) could be determined by either one of two ways, i.e., directly by calorimetry or indirectly by studying the respective equilibrium constants (solubility in this case) as a function of temperature. The later strategy is known as the van't Hoff method and is widely used in chemistry. In the method, the slope obtained in a plot of ln K vs $1/T$, multiplied by $-R$ (8.314 J·mol^{-1}·K^{-1}), is used to determine ΔH^0_{soln} for nonelectrolyte solutes.[4] Although both methods could be used to determine the enthalpic change associated to several physicochemical processes, for several years the equivalence between both methods has been a subject of controversy in the case of some noncovalent reactions involving secondary valences, such as protein autoassociation to form supramolecular structures,[5] the binding of cytidine 2′-monophosphate to ribonuclease A,[6] and the complexation of the ion Ba^{2+} with the cyclic ether 18-crown-6.[7] Otherwise, any other studies confirm the concordance between both methods, in particular for the last two reactions.[8]



LD-HCl **PC-HCl**

Figure 1. Molecular structures of lidocaine−HCl (LD−HCl) and procaine−HCl (PC−HCl).

LC−HCl and PC−HCl are drugs which are extremely soluble in water, and only a thermodynamic study about the solution processes based on the van't Hoff method has been previously reported.[9] As was already said, the characterization of the interactions present by the saline drugs in aqueous media is very important to estimate the physical and chemical stability of

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pharmaceutical dosage forms because it allows the identification of possible incompatibilities.[10−13]

For these reasons, to evaluate the equivalence between the values obtained by the two methods, in the present communication, the ΔH^0_{soln} values for LC−HCl and PC−HCl in water were determined by using solution isoperibolic calorimetry.[14] The enthalpy values obtained were then compared with those calculated using the van't Hoff method employing the drug solubility values expressed in molality as a function of temperature.[9]

Experimental

Materials. The local anesthetics, procaine (PC−HCl) and lidocaine (LD−HCl), are in agreement with the quality requirements indicated in the American Pharmacopeia[15] and were used without further purification. KCl and THAM (trihydroxyaminomethane) were obtained from Merck and Aldrich, respectively, and used after drying for 24 h at 373 K. HCl was also obtained from Merck. All solutions were prepared by weight at room temperature using a Ohaus Analytical Plus balance with a precision of 0.01 mg. Water was doubly distilled (conductivity <2 $\mu S \cdot cm^{-1}$) and treated according to a method cited in the literature.[16]

Calorimetric Determination of Solution Enthalpies (ΔH^{cal}_{soln}). Samples Preparation. The solvent samples (water, HCl) near 50.00 g and solute samples (KCl, THAM, LC−HCl, PC−HCl) varying from 0.0400 g up to 0.2500 g were determined according to the calorimeter dimensions. The concentrations were expressed in terms of the solute mass/solvent mass quotient. Five different concentrations were studied for each drug at 298.15 K.

Calorimetric Procedure. A solution isoperibolic calorimeter designed and developed in the Department of Chemistry of the Universidad de los Andes was used in all calorimetric determinations. This calorimeter has been described in the literature.[14] As the temperature was controlled and stabilized, the procedure was the following: the specified solute quantity was weighed in the cell; the specified solvent quantity was weighed in the Dewar flask; the closed cell was placed into the release mechanism; the Dewar flask was placed to allow the solvent to cover the cell, the thermistor, and the calibration resistor; the calorimeter was placed inside the thermostatic bath and placed on the agitation system; the solute and solvent were placed separately in the thermostatic bath for 1 h to obtain constant temperature, and at this time the data intake was made to verify thermal equilibrium in the pure solvent; the release system inside the cell was activated to release the solute into the solvent; the thermal change presented as a consequence of the reaction observed was recorded; a similar heating, proportional to the voltage change observed during the dissolution process, was carried out; several other additional heating treatments were carried out by following the same methodology used in the previous stage; finally, by considering these additional calibrations, the ΔH^{cal}_{soln} value, corresponding to the solution process, was calculated.

Data Treatment. The extrapolation of the calorimetric data at infinite dilution (up to the drug concentration equal to 0 $mol \cdot kg^{-1}$, that is, the ΔH^{0-cal}_{soln} value) was developed by means of parabolic regression using the least-squares method. The mean values and their experimental uncertainties were used.

Results and Discussion

To verify the calorimeter performance, some reaction enthalpy determinations were carried out using as reference systems KCl + H_2O and THAM 1.0 N + HCl. In both cases, five heating procedures were made for each one of the determinations. Table 1 shows the experimental results, which were compared with respect to literature values.[17−19] Good agreement was found in both cases.

Table 1. Verification of the Calorimeter

	$\Delta H^{0-cal}_{reaction}$ obtained	$\Delta H^{0-cal}_{reaction}$ literature	
system	($kJ \cdot mol^{-1}$)	($kJ \cdot mol^{-1}$)	ref.
KCl + H_2O[a]	17.31 (0.03) [a]	17.58 (0.05)	Uriano[17]
		17.584 (0.017)	Wadso and Goldberg[18]
		17.32 (0.02)	Ramos et al.[10]
THAM + HCl	−29.76 (0.05)	−29.75 (0.02)	Hill et al.[19]
		−29.72 (0.02)	Ramos et al.[10]

[a] In the system KCl + H_2O, $\Delta H^0_{reaction}$ corresponds to ΔH^0_{soln}.

Table 2. Dissolution Enthalpy of Drugs as a Function of Molal Concentration at 298.15 K

lidocaine−HCl		procaine−HCl	
LC−HCl	ΔH^{cal}_{soln}	PC−HCl	ΔH^{cal}_{soln}
(10^3 $mol \cdot kg^{-1}$)	($kJ \cdot mol^{-1}$)	(10^3 $mol \cdot kg^{-1}$)	($kJ \cdot mol^{-1}$)
0.00	43.5 (1.5)[a]	0.00	30.5 (0.5)[a]
2.80	35.83 (0.07)	3.00	31.91 (0.07)
5.63	31.10 (0.09)	5.88	33.35 (0.05)
8.14	25.98 (0.05)	8.82	33.82 (0.03)
10.93	23.43 (0.10)	11.73	34.94 (0.13)
13.97	22.41 (0.11)	17.76	35.44 (0.19)

[a] ΔH^0_{soln}: Obtained by extrapolation to a drug concentration of 0 $mol \cdot kg^{-1}$ in the parabolic equations.

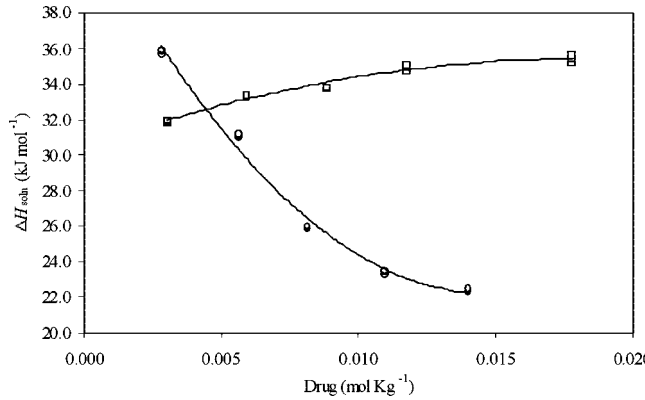

Figure 2. Calorimetric enthalpies of solution for both drugs as a function of molal concentration at 298.15 K. The parabolic equations are: ○, LC−HCl with parabolic equation: $\Delta H_{soln} = 43.5\ (1.5) - 2889\ (409)m + 98\ 252\ (23\ 915)m^2$, with r^2 adjusted, 0.992, and typical error, 0.71; and □, PC−HCl with parabolic equation: $\Delta H_{soln} = 30.5\ (0.5) + 539.46\ (109)m - 14\ 595\ (5089)m^2$, with r^2 adjusted, 0.976, and typical error, 0.27.

With respect to the calorimetric determinations made with LC−HCl and PC−HCl, it follows that the enthalpy values were positive for all the concentrations evaluated. Moreover, the enthalpy variation showed nonlinear trends as a function of the molality. For LC−HCl a positive slope was obtained, whereas for PC−HCl the behavior was opposite (Table 2, Figure 2). By extrapolating the adjusted parabolic equations to a concentration of 0 $mol \cdot kg^{-1}$, the respective dissolution molar enthalpies at infinite dilution (ΔH^{0-cal}_{soln}) were determined. The obtained values were (43.5 ± 1.5) $kJ \cdot mol^{-1}$ and (30.5 ± 0.5) $kJ \cdot mol^{-1}$ for LC−HCl and PC−HCl, respectively (Table 2).

On the other hand, as was already said, the variation of drug solubility as a function of temperature, by means of the van't Hoff method, allows calculation of the apparent standard enthalpic change for the solution process (ΔH^{0m-vH}_{soln}). In the case

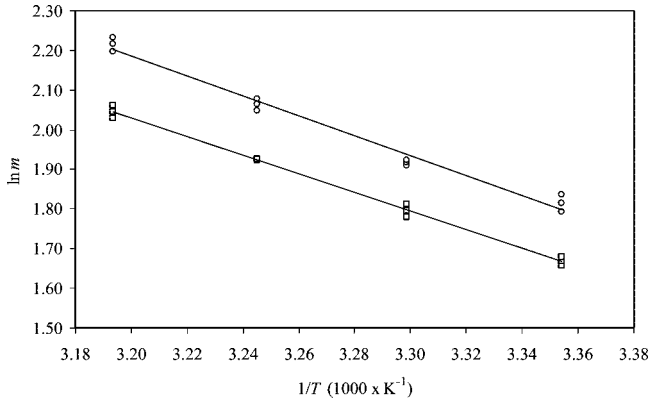

Figure 3. van't Hoff plots for the drugs solubility expressed in molality. ○, LC−HCl with linear equation: ln m = 10.22 (0.36) − 2511 (109)/T, with r^2 adjusted, 0.980, and typical error, 0.023. □, PC−HCl with linear equation: ln m = 9.57 (0.19) − 2355 (57)/T, with r^2 adjusted, 0.994, and typical error, 0.012.

of the drugs studied here (which are considered as uni-univalent electrolytes),[20] by assuming complete dissociation and without considering the possible interionic interactions, the van't Hoff equation has the form

$$\left(\frac{\partial \ln m}{\partial T^{-1}}\right)_P = -\frac{\Delta H_{\text{soln}}^{0m-\text{vH}}}{2R} \tag{1}$$

where the solubility values are expressed in the molality scale. The aqueous solubility of both drugs at several temperatures was studied by Labastidas and Martínez obtaining very large values for this property (6.14 mol·kg^{-1} and 5.30 mol·kg^{-1} at 298.15 K for LC−HCl and PC−HCl, respectively).[9] Figure 3 shows the respective van't Hoff plot, obtained from the values presented in the literature.[9] The $\Delta H_{\text{soln}}^{0m-\text{vH}}$ values were calculated as: $-2Rb$ (where b is the observed slope), obtaining (41.7 ± 1.8) kJ·mol^{-1} and (39.2 ± 0.9) kJ·mol^{-1} for LC−HCl and PC−HCl, respectively.

The calorimetric values obtained (Table 2) fully confirm the information presented in the literature about the endothermic nature of the dissolution process of these drugs in water.[9] Otherwise, by comparing the $\Delta H_{\text{soln}}^{0}$ values obtained by the van't Hoff method in the molality scale with respect to those obtained at infinite dilution by means of the calorimetric method, no significant difference was observed for LC−HCl, whereas for PC−HCl, a little, but significant, difference was found. This result apparently indicates that the former method is valid (within the experimental uncertainty) to determine the solution enthalpy of highly soluble electrolyte drugs. Nevertheless, it is necessary to keep in mind that using solution calorimetry and the van't Hoff method (solubility values), in addition to solute−solvent interactions, it is also necessary to consider the respective solute−solute interactions. The later interactions have great importance in our case because of the high solubility presented by both drugs, which are 0.0996 and 0.0872 in mole fraction at 298.15 K for LC−HCl and PC−HCl, respectively.[9] These values are greater than those considered as high dilution ($X_2 < 0.0001$).[21,22] On the other hand, the calorimetric determinations in the present work were made in the moderately dilute concentration range, thus minimizing the solute−solute interactions. Moreover, the extrapolation up to infinite dilution was made, and therefore, the solute−solvent and solvent−solvent interactions predominate. For these reasons, some caution should be taken in the analysis of these thermodynamic quantities

Table 3. Mass Percentage Solubility of Drugs (% m/m), Densities of Saturated Solution (ρ_{soln}) and Water (ρ_1), Apparent Molar Volume of Drugs at Saturation (ϕ_V^{sat}), and Volume Fractions of Drugs (f_2) and Water (f_1) at Saturation at Several Temperatures

lidocaine−HCl						
temp	LC−HCl	ρ_{soln}	ρ_1	ϕ_V^{sat}		
(K)	(% in mass)[a]	(g·cm^{-3})	(g·cm^{-3})[b]	(cm^3·mol^{-1})	f_2	f_1
298.15	62.42	1.0791	0.9970	238.5	0.593	0.407
303.15	64.80	1.0821	0.9957	238.7	0.618	0.382
308.15	68.05	1.0849	0.9940	239.3	0.652	0.348
313.15	71.26	1.0854	0.9922	240.6	0.687	0.313
procaine−HCl						
temp	PC−HCl	ρ_{soln}	ρ_1	ϕ_V^{sat}		
(K)	(% in mass)[a]	(g·cm^{-3})	(g·cm^{-3})[b]	(cm^3·mol^{-1})	f_2	f_1
298.15	59.11	1.1148	0.9970	224.7	0.543	0.457
303.15	62.18	1.1185	0.9957	225.8	0.576	0.424
308.15	65.16	1.1239	0.9940	226.2	0.607	0.393
313.15	67.83	1.1255	0.9922	227.6	0.637	0.363

[a] Labastidas and Martínez.[9] [b] Lide.[25]

obtained by both methods since, although they were similar in magnitude, it is also clear that the global processes considered in each case are so different, including solute−solute interactions in the van't Hoff method, which could lead to establishment of great interionic structures, such as clusters.[23,24]

In the same way, it is necessary to keep in mind that the van't Hoff method presents some limitations to calculate the $\Delta H_{\text{soln}}^{0-\text{vH}}$ values if the solutions are concentrated; in this way, great differences in $\Delta H_{\text{soln}}^{0-\text{vH}}$ values are found among them, depending on the concentration scales employed. As was demonstrated in the literature, in the case of LC−HCl, the reported $\Delta H_{\text{soln}}^{0-\text{vH}}$ values are (14.5 ± 0.5) kJ·mol^{-1} and (36.8 ± 1.5) kJ·mol^{-1}, for the molarity and mole fractions scales, respectively,[9] whereas for PC−HCl, the respective values are (15.3 ± 0.4) kJ·mol^{-1} and (34.8 ± 0.9) kJ·mol^{-1} for molarity and mole fraction, respectively.[9] These values are, of course, not comparable. The latter results, which are apparently in contradiction, could be explained in terms of the occupied volume by the solute in the saturated solution. As can be seen, the enthalpic values obtained by using the molality and mole fraction scales are similar between them,[9] whereas, if these values are compared with those obtained by using the molarity scale, no concordance is found. To illustrate this volumetric effect, Table 3 shows the respective apparent molar volumes exhibited for both drugs and the volume fractions of drugs and water, obtained at saturation, as a function of temperature. These values were calculated from data presented previously in the literature for saturated solutions.[9]

The density of the saturated solutions (ρ_{soln}) was calculated from the solubility values expressed in mole fraction (X_2) and molarity (C), by using eq 2[20]

$$\rho_{\text{soln}} = \frac{C[M_1(1 - X_2) + M_2X_2]}{1000X_2} \tag{2}$$

where M_1 and M_2 are the molar masses of water (18.02 g·mol^{-1}) and both drugs (270.80 g·mol^{-1} for LC−HCl and 272.78 g·mol^{-1} for PC−HCl).[3] Otherwise, the apparent molar volume for both drugs was calculated by means of eq 3[26]

$$\phi_V^{\text{sat}} = \frac{M_2}{\rho_{\text{soln}}} + \frac{1000(\rho_1 - \rho_{\text{soln}})}{\rho_1\rho_{\text{soln}}m} \tag{3}$$

where ρ_1 is the water density and m is the drug solubility expressed in molality. Finally, by using the percentage compositions and the apparent specific volumes (which were calculated as the quotient: ϕ_V^{sat}/M_2), the respective volume fractions, for solutes and water, were calculated in the saturated solutions. These values are also summarized in Table 3.

It can be seen in Table 3 that the solute volume fraction (f_2) is greater than 0.59 for LC−HCl and greater than 0.54 for PC−HCl. On the other hand, f_2 values increase as the temperature increases; in the same way, the f_2 values increase in a proportional way as the solubility increases. At this point, it is necessary to keep in mind that, to calculate rigorously the volume fractions, it would be more exact to employ the partial molar volumes at saturation ($\bar{V}_2^{sat}$) instead of the ϕ_V^{sat} values. To accomplish this requirement, it should be necessary to have the ϕ_V values as a function of the drug concentration at the different temperatures tested.[26] Unfortunately, these values are not available at present. Nevertheless, in a first approximation, the use of ϕ_V^{sat} instead of $\bar{V}_2^{sat}$ is adequate for practical purposes.

Moreover, by calculating the quotients between the van't Hoff enthalpy values obtained by using the molarity and mole fraction scales (14.5 kJ·mol^{-1}/36.8 kJ·mol^{-1} and 15.3 kJ·mol^{-1}/34.8 kJ·mol^{-1} for LC−HCl and PC−HCl, respectively), the values 0.393 and 0.439 were obtained for LC−HCl and PC−HCl, respectively, which are very close to the volume fractions of water (f_1) obtained at (298.15 and 303.15) K (Table 3). This fact is very interesting although the main reason for this result is unclear. It could be presumed a volumetric effect upon the ΔH_{soln}^{0-vH} values due to a decrease in the water proportion, present in the concentrated solutions.

On the other hand, in a more complete research, the calorimetric ΔH_{soln}^{0-cal} values could be determined at several temperatures, and on the other hand, the solubility values could be determined increasing the temperature range, i.e., from 278.15 K up to 318.15 K (range traditionally studied by thermometric titration calorimetry, according to the literature).[5−8] This treatment would be important to verify if variations in the heat capacity (ΔC_p) are present in the aqueous dissolution processes, which could demonstrate possible changes in the mechanisms involved. This event has been described for other physicochemical phenomena described in the literature.[5−8] In the same way, eq 1 must be challenged by using the thermodynamic activity values of saline drugs at saturation instead of drug concentrations. Nevertheless, for these calculations, the variation of the experimental drug activity coefficients (γ_2) with respect to the concentration is required because if it is greater than 0.15 mol·kg^{-1} the mathematical models employed for calculating the γ_2 values, such as the extended Debye−Hückel equation,[20] are not valid. Thus, other more complex expressions are required, but these expressions need some empirical values determined experimentally.[27,28]

Nowadays, the osmotic coefficients (ϕ) of several organic salts are under study in our research group by using isopiestic equipment analogous to that developed in the Laboratorio de Investigaciones Básicas of the Universidad Nacional de Colombia, which has been described in the literature.[29] If the ϕ values are available, the solute activity coefficients (γ_2) could be calculated, and therefore, the thermodynamic activity for the salts in the saturated solutions could also be calculated.

Conclusions

From the previously exposed analyses, in general terms it could be concluded that the calorimetric values of drug solution enthalpy decreased as the LC−HCl concentration increased, whereas in the case of PC−HCl, the behavior was opposite. Otherwise, although the enthalpy values obtained by means of the van't Hoff method and those obtained by isoperibolic calorimetry extrapolating at infinite dilution are similar, they should not be considered as equivalent because the respective interactions are different in each one of the experiments. In particular, these results could be explained in terms of the strong solute−solute interionic interactions present at high drug concentrations, in addition to the respective solute−solvent and solvent−solvent interactions.

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