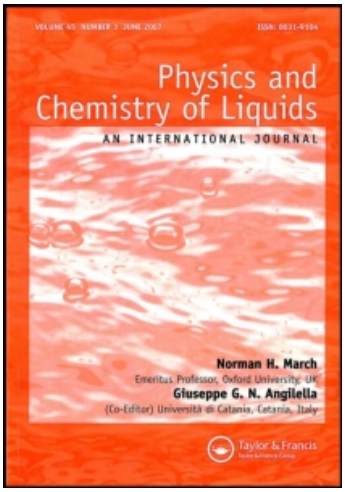

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Carolina P. Mora[a]; Fleming Martínez[a]
[a] Departamento de Farmacia, Universidad Nacional de Colombia, Bogotá D.C., Colombia

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Thermodynamic quantities relative to solution processes of Naproxen in aqueous media at pH 1.2 and 7.4

CAROLINA P. MORA and FLEMING MARTÍNEZ*

Departamento de Farmacia, Universidad Nacional de Colombia,
A.A. 14490, Bogotá D.C., Colombia

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Based on van't Hoff and Gibbs equations, the thermodynamic functions Gibbs free energy, enthalpy, and entropy of solution, mixing and solvation of naproxen (NAP) in water at pH 1.2 and 7.4, were evaluated from solubility values determined at several temperatures. The solubility at pH 7.4 and 25.0°C was almost 150 times higher with respect to pH 1.2. The enthalpies of solution were positive and greater for pH 1.2, while the entropies of solution were both negative, thereby implying a greater molecular organization at pH 7.4. The results were discussed in terms of solute–solvent interactions.

Keywords: Naproxen; Aqueous solubility; Solution thermodynamics; Deprotonation; pH

1. Introduction

Naproxen (NAP) is a nonsteroidal anti-inflammatory drug (NSAID). NAP has also analgesic and antipyretic action without producing addiction [1]. This drug is widely used in Colombia and administered mainly by peroral route as tablets, capsules, and suspensions. On the other hand, this drug is also available as a gel intended for topical use, and injectable solution intended for intramuscular administration [2].

Aqueous solubility of drugs is a very important property in the physicochemical characterization of pharmaceuticals, as well as in dosage forms design. On the other hand, the solubility temperature dependence allows to carry out the respective thermodynamic analysis, which, at the same time, permits to explain the molecular mechanisms, involved in the solution processes [3].

The main objective of this study is to evaluate the effect of pH on aqueous solubility of NAP and on its respective solution thermodynamics. The analysis is based on van't Hoff method, including the respective contributions by mixing and solvation

*Corresponding author. Email: fmartinezr@unal.edu.co

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of the drug on the solution processes. This investigation expands the concepts developed for this drug by Perlovich *et al*. in aqueous media [4, 5].

2. Experimental

2.1. *Materials*

Naproxen USP [6]; distilled water (W), conductivity $<2\,\mu S$ from Laboratory of Pharmaceutics of the Universidad Nacional de Colombia; potassium chloride from A.R. Merck; mono and disodium phosphates from A.R. Merck; hydrochloric acid from A.R. Merck; Millipore Corp. Swinnex®-13 filter units.

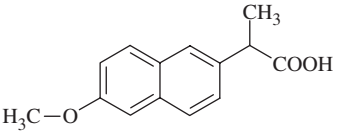
2.2. *Solubility determinations*

An excess of NAP was added to $20\,cm^3$ of each aqueous media (pH-metric controlled buffers of pH 1.2 and 7.4 adjusted at ionic strength, μ 0.15 mol L^{-1}, which are common physiological values for gastric juice and blood, respectively [7, 8]) in glass flasks. Solid–liquid mixtures were stirred in a mechanical shaker (Wrist Action, Burrel, model 75) for 1 h. Samples were then allowed to stand in water baths (Magni Whirl Blue M. Electric Company) kept at 40.0 ± 0.05°C at least for 5 days to reach the equilibrium (this equilibrium time was established by quantifying the drug concentration up to obtain a constant value). After this time the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Concentrations were determined by measuring absorbance after appropriate dilution and interpolation from previously constructed UV spectrophotometry calibration curves for NAP in each pH (UV/Vis Unicam UV2-100 v 4.00 spectrophotometer). After the procedure already described the temperature was decreased by 5.0°C and therefore, it was stabilized at 35.0°C during at least 2 days allowing the precipitation of the drug dissolved in excess and quantifying the drug concentration in equilibrium. These procedures were developed varying by 5.0°C up to reach 20.0°C. All the solubility experiments were repeated at least three times. In order 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).

3. Results and discussion

In table 1, the molecular structure of NAP and some of their physicochemical properties are summarized. The pKa value was corrected to μ 0.15 mol L^{-1} by means of the extended Debye–Hückel equation [9], from the value presented by Betageri *et al*. [10]. The melting point, the enthalpy of fusion, and the enthalpy of sublimation were reported by Perlovich *et al*. [4]. This drug acts in solution mainly as a Lewis acid in order to establish hydrogen bonds with proton–acceptor groups in the solvent (oxygen in –OH groups). Although it also may act as Lewis base by means of its carbonyl and methoxyl groups.

Table 1. Some physicochemical properties of NAP.

Molecular structure[a]	Molar mass[a] ($g\,mol^{-1}$)	pKa[b]	Melting point[c] (K)	ΔH_{fus}[c] ($kJ\,mol^{-1}$)	ΔH_{subl}[c] ($kJ\,mol^{-1}$)
	230.26	4.1	427.6	31.5 (2.1)	128.3 (0.5)

[a]From [11].
[b]From [10] and corrected to μ 0.15 $mol\,L^{-1}$ by means of extended Debye–Huckel equation [9].
[c]From [4].

3.1. *Ideal and experimental solubility of NAP*

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

$$\ln X_2^{id} = -\frac{\Delta H_{fus}(T_{fus} - T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{fus} - T)}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right] \quad (1)$$

where X_2^{id} is the ideal solubility of the solute as mole fraction, ΔH_{fus} the molar enthalpy of fusion of the pure solute (at the melting point), T_{fus} the absolute melting point, T the absolute solution temperature, R the universal gas constant ($8.314\,J\,mol^{-1}\,K^{-1}$), and ΔC_p 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 [3]. Since ΔC_p cannot be easily determined, in this investigation it is assumed that ΔC_p may be approximated to the entropy of fusion (ΔS_{fus}).

Table 2 summarizes the experimental solubilities of NAP, expressed as molarities and mole fractions at pH 1.2 and 7.4, and the ideal solubilities calculated by means of equation (1) from the ΔH_{fus} and T_{fus} values presented in table 1. The drug activity coefficients (γ_2) calculated as X_2^{id}/X_2 (for the non-electrolyte compound) at pH 1.2 are also presented in table 2.

The solubility values expressed in mole fraction at pH 1.2 (table 2) are in good agreement with those presented by Perlovich *et al.* [5] at 20, 25, and 30°C at pH 2.0, that is, 1.00×10^{-6}, 1.22×10^{-6}, and 1.47×10^{-6}, respectively. Nevertheless, the respective values at pH 7.4 are in total disagreement with those also presented by Perlovich *et al.* [5], that are, 1.34×10^{-5}, 1.39×10^{-5}, and 1.44×10^{-5} at the same temperatures. Those differences would be attributed to buffer compositions employed; in particular the ionic strength 0.15 $mol\,L^{-1}$ and the use of KCl, which as it is well known, may affect the water structure. The solubility of NAP at 25.0°C and pH 7.4 is almost 150-fold higher with respect to that corresponding to pH 1.2, which indicates more affinity of dissociated drug for water.

Equation (2) has been traditionally used in order to calculate the solubility as a function of pH for weak acids such as NAP when the difference between pKa and pH is lower than 2.0. S_0 is the intrinsic solubility corresponding to molecular drug without dissociation [12]. If equation (2) is used to calculate the NAP solubility in molarity

Table 2. Experimental solubility of NAP in aqueous media at pH 1.2 and 7.4 expressed in molarity and mole fraction including ideal solubility and drug activity coefficients at pH 1.2 at several temperatures.

	Mol L^{-1}		Mole fraction			γ_2
	pH		pH			pH
Temperature (°C)	1.2	7.4	1.2	7.4	Ideal	1.2
20.0	$6.67\ (0.08) \times 10^{-5}$	$1.210\ (0.013) \times 10^{-2}$	$1.201\ (0.014) \times 10^{-6}$	$2.190\ (0.023) \times 10^{-4}$	3.527×10^{-2}	29,381
25.0	$8.28\ (0.05) \times 10^{-5}$	$1.273\ (0.016) \times 10^{-2}$	$1.492\ (0.010) \times 10^{-6}$	$2.307\ (0.029) \times 10^{-4}$	4.098×10^{-2}	27,469
30.0	$9.69\ (0.11) \times 10^{-5}$	$1.363\ (0.004) \times 10^{-2}$	$1.747\ (0.020) \times 10^{-6}$	$2.473\ (0.007) \times 10^{-4}$	4.748×10^{-2}	27,173
35.0	$1.169\ (0.017) \times 10^{-4}$	$1.455\ (0.028) \times 10^{-2}$	$2.11\ (0.03) \times 10^{-6}$	$2.65\ (0.05) \times 10^{-4}$	5.489×10^{-2}	25,997
40.0	$1.493\ (0.021) \times 10^{-4}$	$1.556\ (0.006) \times 10^{-2}$	$2.70\ (0.04) \times 10^{-6}$	$2.836\ (0.010) \times 10^{-4}$	6.330×10^{-2}	23,419

at 25.0°C and pH 7.4, a value of $0.1654\,\mathrm{mol\,L^{-1}}$ is obtained, which is very different with respect to the experimental value ($1.273 \times 10^{-2}\,\mathrm{mol\,L^{-1}}$). This demonstrates that equation (2) is not useful for pKa–pH differences greater than 3.0.

$$S_{(\mathrm{pH})} = S_0(1 + 10^{(\mathrm{pH}-\mathrm{pKa})}) \tag{2}$$

From the γ_2 values presented in table 2 a rough estimate of solute–solvent intermolecular interactions at pH 1.2 (where the molecular compound without significant dissociation dominates) can be made by considering the following expression:

$$\ln \gamma_2 = (w_{11} + w_{22} - 2w_{12})\frac{V_2\phi_1^2}{RT} \tag{3}$$

where w_{11}, w_{22}, and w_{12} represent the water–water, NAP–NAP and water–NAP interaction energies, respectively; V_2 is the molar volume of the supercooled liquid solute, and finally, ϕ_1 is the volume fraction of the solvent. For pH 1.2 the term $(V_2\phi_1^2/RT)$ is constant at the same temperature, and then γ_2 depends almost exclusively on w_{11}, w_{22}, and w_{12} [13]. The w_{11} and w_{22} terms are unfavorable for solubility, while the w_{12} term favors the NAP solution process. The term w_{11} is high for water (Hildebrand solubility parameter, $\delta = 47.9\,\mathrm{MPa}^{1/2}$) [14]. On the other hand, the term w_{22} is relatively high for NAP according to T_{fus} and ΔH_{fus} values (table 1). For these reasons, w_{12} would be low in order to obtain high γ_2 values.

3.2. *Thermodynamic functions of solution*

The making of weighted graphs based on the logarithm of solubility as a function of reciprocal absolute temperature permits to obtain the enthalpic change of solution ($\Delta H^0_{\mathrm{soln}}$) by means of van't Hoff equation [equation (4)] if the drug solubility is relatively low as it is the NAP case in aqueous media,

$$\left(\frac{\partial \ln X_2}{\partial(1/T)}\right)_p = -\frac{\Delta H^0_{\mathrm{soln}}}{R} \tag{4}$$

In more recent treatments, some corrections have been introduced to equation (4) in order to reduce the propagation of errors, and therefore, to separate the chemical effects from those due only to statistical treatments used in Arrhenius, van't Hoff, and compensation plots. For this reason, the mean harmonic temperature (T_{hm}) is used in van't Hoff analysis. T_{hm} is calculated as $n/\sum_i^n (1/T)$, where n is the number of tested temperatures. In our case the T_{hm} value obtained was just 303 K. The corrected expression more widely used can be written as follows [15]:

$$\left(\frac{\partial \ln X_2}{\partial(1/T - 1/T_{\mathrm{hm}})}\right)_p = -\frac{\Delta H^0_{\mathrm{soln}}}{R} \tag{5}$$

Figures 1 and 2 show the modified van't Hoff plots for NAP in aqueous media at both pH values. Linear models with good determination coefficients were obtained in both systems studied. For this reason, the equation (5) is useful to estimate the $\Delta H^0_{\mathrm{soln}}$ values.

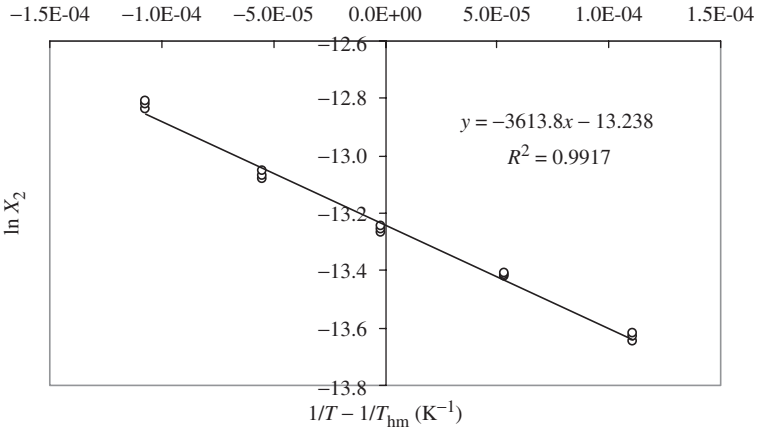


Figure 1. Temperature dependence for solubility of NAP at pH 1.2 expressed in mole fraction.

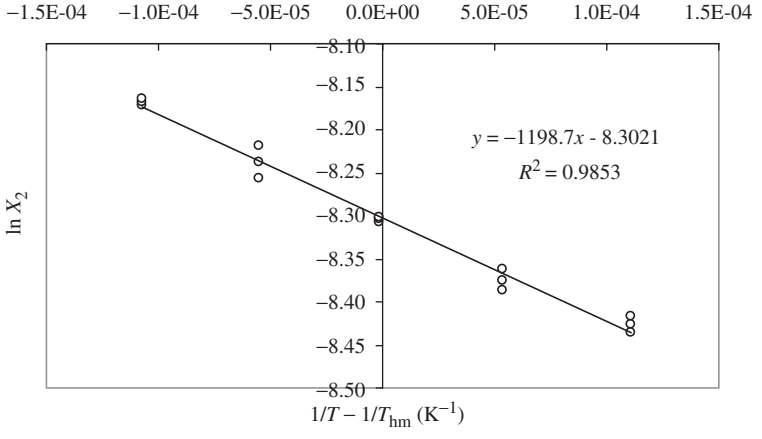


Figure 2. Temperature dependence for solubility of NAP at pH 7.4 expressed in mole fraction.

The standard Gibbs energy change for the solution process (ΔG^0_{soln}) has been traditionally calculated in literature as: $-RT\ln X_2$ [3]. Nevertheless considering the approach proposed by Krug *et al.* [16] this property is more appropriately calculated by means of:

$$\Delta G^0_{soln} = -RT_{hm} \times \text{intercept} \tag{6}$$

in which, the intercept used is the one obtained from $\ln X_2$ *versus* $(1/T - 1/T_{hm})$ plots [equation (5)].

The standard entropic change for solution process (ΔS^0_{soln}) is obtained from the respective ΔH^0_{soln} and ΔG^0_{soln} values by using:

$$\Delta S^0_{soln} = \frac{(\Delta H^0_{soln} - \Delta G^0_{soln})}{T_{hm}} \tag{7}$$

Table 3. Thermodynamic functions relative to solution process of NAP in both pH including ideal process at 303 K.

pH	ΔG^0_{soln}/ (kJ mol^{-1})	ΔH^0_{soln}/ (kJ mol^{-1})	ΔS^0_{soln}/ (J mol^{-1} K^{-1})	$T\Delta S^0_{soln}$/ (kJ mol^{-1})	ζ_H%[a]	ζ_{TS}%[a]
1.2	33.35 (0.02)	30.0 (0.8)	−10.9 (0.3)	−3.30 (0.08)	90.1	9.9
7.4	20.91 (0.01)	10.0 (0.3)	−36.1 (1.2)	−11.0 (0.4)	47.7	52.3
Ideal	7.68	22.31	48.3	14.63	60.4	39.6

[a]ζ_H% and ζ_{TS}% are the relative contributions by enthalpy and entropy toward Gibbs energy of solution. These values were calculated by means of equations (8) and (9), respectively.

Table 3 summarizes the corrected standard thermodynamic functions for experimental solution process of NAP in both aqueous media including those functions for the ideal process. In order to calculate the thermodynamic magnitudes of experimental solution some methods for estimating propagation of errors were used [17]. It is found that the standard Gibbs energy of solution is positive in both cases; i.e., 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 concentration of NAP, that is, the solid pure solute. The ΔG^0_{soln} at pH 1.2 is similar in magnitude with that presented by Perlovich *et al.* [5] at pH 2.0 (33.8 kJ mol^{-1}). Nevertheless, the value at pH 7.4 is different with respect to the same reference (27.7 kJ mol^{-1}), which is expected according to the great differences in the solubility values found at this pH.

The enthalpy of solution is positive for both cases, therefore the process is always endothermic. On the other hand, the entropy of solution is negative in both cases, indicating nonenthalpy or entropy driving on overall solution processes. In similar way to solubility and ΔG^0_{soln}, at pH 1.2, the ΔH^0_{soln} value presented in table 3 is similar in magnitude with that presented by Perlovich *et al.* [5] at pH 2.0 (28.0 kJ mol^{-1}), whereas the respective value at pH 7.4 is different again (5.2 kJ mol^{-1}). Due to the differences obtained in ΔG^0_{soln} and ΔH^0_{soln} between Perlovich *et al.* and the present report, high differences in ΔS^0_{soln} values were also presented at both pH (−19.5 J mol^{-1} K^{-1} and −75.5 J mol^{-1} K^{-1}, for pH 2.0 and 7.4, respectively). All these differences, especially at pH 7.4 would be attributed to variations in the buffer compositions, which as was indicated previously, may affect the water structure and therefore affecting its solubilizing behavior.

With the aim to compare the relative contributions by enthalpy (ζ_H%) and by entropy (ζ_{TS}%) toward the solution process, equations (8) and (9) were employed respectively.

$$\zeta_H\% = 100\frac{|\Delta H^0_{soln}|}{|\Delta H^0_{soln}| + |T\Delta S^0_{soln}|} \tag{8}$$

$$\zeta_{TS}\% = 100\frac{|T\Delta S^0_{soln}|}{|\Delta H^0_{soln}| + |T\Delta S^0_{soln}|} \tag{9}$$

From table 3 it follows that the main contributor to standard free energy of solution process of NAP at pH 1.2 is the enthalpy while at pH 7.4 is the entropy.

Table 4. Thermodynamic functions relative to mixing process of NAP in both pH at 303 K.

pH	ΔG^0_{mix}/ (kJ mol^{-1})	ΔH^0_{mix}/ (kJ mol^{-1})	ΔS^0_{mix}/ (J mol^{-1} K^{-1})	$T\Delta S^0_{mix}$/ (kJ mol^{-1})	ζ_H%[a]	ζ_{TS}%[a]
1.2	25.67	7.7	−59.2	−17.94	30.1	69.9
7.4	13.23	−12.3	−84.4	−25.6	32.6	67.4

[a]ζ_H% and ζ_{TS}% are the relative contributions by enthalpy and entropy toward Gibbs energy of mixing. These values were calculated by means of equations analogous to (8) and (9), respectively.

3.3. *Thermodynamic functions of mixing*

The solution process may be represented by the following hypothetic stages [3]:

$$\text{Solute}_{(\text{Solid})} \rightarrow \text{Solute}_{(\text{Liquid})} \rightarrow \text{Solute}_{(\text{Solution})}$$

where, fusion and mixing are the respective partial processes toward the solution process at 303 K. This approximation permits to calculate the partial thermodynamic contributions to solution process by means of equations (10) and (11).

$$\Delta H^0_{soln} = \Delta H^{303}_{fus} + \Delta H^0_{mix} \quad (10)$$

$$\Delta S^0_{soln} = \Delta S^{303}_{fus} + \Delta S^0_{mix} \quad (11)$$

where ΔH^{303}_{fus} and ΔS^{303}_{fus} represent the thermodynamic functions of fusion process at harmonic temperature (303 K). ΔH^{303}_{fus} was calculated as $\Delta H^{MP}_{fus} - \Delta C_p(T_{fus} - T)$, by using ΔS^{MP}_{fus} instead of ΔC_p obtaining a value of 22.32 kJ mol^{-1}. This value is coincident with the enthalpic change for ideal solution (table 3). In contrast, the entropy of fusion at 303 K (73.7 J mol^{-1} K^{-1}) is not coincident with the entropy of ideal solution at this temperature (48.3 J mol^{-1} K^{-1}). Nevertheless, for practical purposes, the ΔS^{0id}_{soln} value was used instead of ΔS^{303}_{fus}. In table 4 the thermodynamic functions of mixing of NAP are summarized.

By analyzing the partial contributions by ideal solution (related to solute fusion process) and mixing processes to the enthalpy and entropy of solution, it is found that ΔH^{303}_{fus} and ΔS^{303}_{fus} are positive (table 3). On the other hand, the contribution of the thermodynamic functions relative to mixing process toward the solution process is variable, that is, ΔH^0_{mix} is positive at pH 1.2 and negative at pH 7.4, while the entropy of mixing (ΔS^0_{mix}) is negative in both pH values. Therefore, the entropies of solution and mixing are in general unfavorable (negative values). According to tables 3 and 4 the solution process of NAP in buffer pH 7.4 is driven by enthalpy of mixing (negative value), while at pH 1.2 there is not specific thermodynamic function driving the solution process because enthalpies and entropies (solution and mixing) are positive and negative, respectively.

The net variation in ΔH^0_{mix} values results from the contribution of several kinds of interactions. The enthalpy of cavity formation is endothermic because energy must be supplied to overcome the cohesive forces of the solvent. This process decreases solubility. On the other hand, the enthalpy of solute–solvent interaction is exothermic and it is originated mainly from the van der Waals, Lewis acid–base, and/or ion–dipole interactions. The structuring of water molecules around the nonpolar groups of non-electrolyte solutes (hydrophobic hydration) contributes to decrease the net heat of mixing to small or even negative values in aqueous solutions [18].

Table 5. Thermodynamic functions relative to solvation process of NAP in both pH at 303 K.

pH	ΔG^0_{solv}/ (kJ mol^{-1})	ΔH^0_{solv}/ (kJ mol^{-1})	ΔS^0_{solv}/ (J mol^{-1} K^{-1})	$T\Delta S^0_{solv}$/ (kJ mol^{-1})	ζ_H%[a]	ζ_{TS}%[a]	ε_H%[b]	ε_S%[b]
1.2	−23.95	−98.3	−245.2	−74.3	56.9	43.1	38.8	109.8
7.4	−36.41	−118.3	−270.4	−81.9	59.1	40.9	67.2	132.4

[a]ζ_H% and ζ_{TS}% are the relative contributions by enthalpy and entropy toward Gibbs energy of solvation. These values were calculated by means of equations analogous to (8) and (9), respectively.
[b]ε_H% and ε_S% are the relative ratio of specific and nonspecific solute–solvent interactions expressed in terms of enthalpy and entropy. These values were calculated by means of equations (15) and (16).

Nevertheless, apparently this fact is not observed in the case of NAP in water at pH 1.2 (positive value: table 4).

On the other hand, the water-structuring process also contributes to decrease the entropy of mixing, which is observed for NAP at both pH values (table 4). The differences obtained in the thermodynamic magnitudes between pH 1.2 and 7.4 are due to the predominant form for the drug at each pH, that is, molecular form at pH 1.2 and dissociate form at pH 7.4, which lead to different kind of solute–solvent interactions. At pH 1.2, NAP interacts with water mainly by hydrogen bonding and hydrophobic hydration around hydrocarbon moieties, while at pH 7.4, the dissociate drug interacts with water by ion–dipole interaction, which implies immobilization of water molecules around the ionic carboxylic group. These events imply entropy diminishing at both pH values.

3.4. *Thermodynamic functions of solvation*

In addition to the hypothetic fusion-mixing stages previously exposed, the solution process may also be represented by the following hypothetic stages [3]:

$$\text{Solute}_{(\text{Solid})} \rightarrow \text{Solute}_{(\text{Vapor})} \rightarrow \text{Solute}_{(\text{Solution})}$$

where the respective partial processes toward the solution process, are in this case, sublimation and solvation. This treatment permits calculating the partial thermodynamic contributions to solution process by means of equations (12) and (13), respectively, while the Gibbs energy of solvation was calculated by means of equation (14):

$$\Delta H^0_{soln} = \Delta H^0_{subl} + \Delta H^0_{solv} \tag{12}$$

$$\Delta S^0_{soln} = \Delta S^0_{subl} + \Delta S^0_{solv} \tag{13}$$

$$\Delta G^0_{soln} = \Delta G^0_{subl} + \Delta G^0_{solv} \tag{14}$$

where $\Delta H^0_{subl} = 128.3\,\text{kJ mol}^{-1}$ was taken from Perlovich *et al.* [4] and therefore, the function ΔH^0_{solv} was calculated from ΔH^0_{soln} values presented in table 3. The respective entropy of sublimation (ΔS^0_{subl}) was calculated as $(\Delta H^0_{subl} - \Delta G^0_{subl})/T$ at 303 K, where $\Delta G^0_{subl} = -RT\log(p/p_0)$ with $p = 1.33 \times 10^{-5}$ Pa at 303 K (calculated from some values presented by Perlovich *et al.* [4]) and $p_0 = 101{,}325$ Pa; then $\Delta G^0_{subl} = 57.32\,\text{kJ mol}^{-1}$,

and therefore $\Delta S^0_{\text{subl}} = 234.3\,\text{J mol}^{-1}\,\text{K}^{-1}$ at the same temperature. In table 5 the thermodynamic functions of solvation are presented, while on the other hand, with the aim to compare the relative contributions by enthalpy ($\zeta_H\%$) and entropy ($\zeta_{TS}\%$) toward the solvation process, two equations analogous to equations (8) and (9) were employed.

From the values of $\zeta_H\%$ and $\zeta_{TS}\%$ presented in table 5 it follows that the main contributing force to standard Gibbs energy of the solvation process of NAP in both buffers is the enthalpy ($\zeta_H\%$ are greater than 57%).

It is because that not only the main driving force of solvation process of drug compounds is important, but also the balance between specific and nonspecific solute–solvent interactions as well, therefore, parameters which describe the relative ratio of specific and nonspecific solute–solvent interaction in terms of enthalpies ($\varepsilon_H\%$) and in terms of entropies ($\varepsilon_S\%$), were used according to the following definitions introduced by Perlovich *et al.* [19]:

$$\varepsilon_H\% = 100\left|\frac{\Delta H^0_{\text{spec}}}{\Delta H^0_{\text{non-spec}}}\right| \tag{15}$$

$$\varepsilon_S\% = 100\left|\frac{\Delta S^0_{\text{spec}}}{\Delta S^0_{\text{non-spec}}}\right| \tag{16}$$

where, $\Delta H^0_{\text{spec}} = \Delta H^0_{\text{soln(W)}} - \Delta H^0_{\text{soln(CH)}} = \Delta H^0_{\text{soln(CH}\rightarrow\text{W)}}$, $\Delta H^0_{\text{non-spec}} = \Delta H^0_{\text{soln(CH)}} - \Delta H^0_{\text{subl}} = \Delta H^0_{\text{solv(CH)}}$, $\Delta S^0_{\text{spec}} = \Delta S^0_{\text{soln(W)}} - \Delta S^0_{\text{soln(CH)}} = \Delta S^0_{\text{soln(CH}\rightarrow\text{W)}}$, and finally, $\Delta S^0_{\text{non-spec}} = \Delta S^0_{\text{soln(CH)}}$.

Cyclohexane (CH) was chosen as an 'inert' solvent, which interacts with drug molecules solely by nonspecific interactions (dispersion forces), while the aqueous media interacts with NAP by specific interactions such as hydrogen bonding or ion–dipole. Benzene and hexane have also been used as inert solvents in the study of NAP although important differences have been found between these two solvents, indicating some effect of π electrons and planar geometry of benzene on nonspecific interactions of that drug [4]. Solution thermodynamic magnitudes of NAP in cyclohexane at 303 K were $\Delta G^0_{\text{soln(CH)}} = 23.7 \pm 0.1\,\text{kJ mol}^{-1}$, $\Delta H^0_{\text{soln(CH)}} = 57.5 \pm 1.2\,\text{kJ mol}^{-1}$, and $\Delta S^0_{\text{soln(CH)}} = 111.5 \pm 2.3\,\text{mol}^{-1}\,\text{K}^{-1}$ [20].

The $\varepsilon_H\%$ and $\varepsilon_S\%$ values for NAP solvation are also presented in table 5. These values indicate that during dissolution of NAP in both aqueous media studied, the specific solute–solvent interactions (hydrogen bonding, mainly) affect the entropic term of free energy with respect to nonspecific interactions. With regard to the enthalpic term the nonspecific solute–solvent interactions dominate, especially at pH 1.2.

3.5. *Transfer of NAP from pH 1.2 to pH 7.4*

Figure 3 shows the relationships between the thermodynamic parameters for NAP as solid, vapor and dissolved (at pH 1.2) molecular compound, and its dissolved dissociate form (at pH 7.4). The thermodynamic functions of transfer of NAP from pH 1.2 to pH 7.4 calculated as $\Delta\Psi^0_{1.2\rightarrow7.4} = \Delta\Psi^0_{\text{mix(pH7.4)}} - \Delta\Psi^0_{\text{mix(pH1.2)}}$ (where, Ψ is G, H or S) from data of table 4 are the following: $-12.44\,\text{kJ mol}^{-1}$

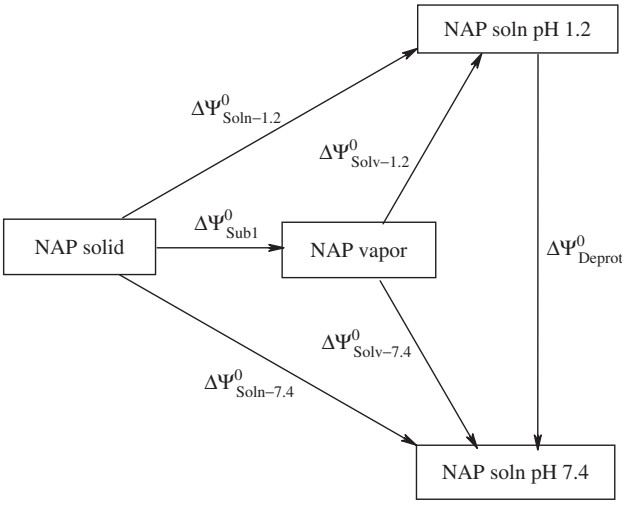


Figure 3. Transfer processes of NAP between solid phase, vapor phase, aqueous pH 1.2, and aqueous pH 7.4.

for $\Delta G^0_{1.2\rightarrow7.4}$, $-20.07\,\mathrm{kJ\,mol^{-1}}$ for $\Delta H^0_{1.2\rightarrow7.4}$, and $-25.2\,\mathrm{J\,mol^{-1}\,K^{-1}}$ for $\Delta S^0_{1.2\rightarrow7.4}$. As it was already said, these thermodynamic magnitudes imply the NAP deprotonation followed by the ion–dipole interactions generate between the dissociated drug and water molecules, which leads to the formation of solvation shells around the drug carboxylate group.

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References

[1] L.J. Roberts II, J.D. Morrow. In *Goodman & Gilman's. The Pharmacological Basis of Therapeutics*, Chap. 27, 10th Edn, J.G. Hardman, L.E. Limbird, A.G. Gilman (Eds), McGraw-Hill, New York (2001).
[2] E. Rosenstein-Ster. *Diccionario de Especialidades Farmacéuticas*, 31st Edn, Thompson P.L.M., S.A. Bogotá (2003).
[3] J.A. Jiménez, F. Martínez. *J. Braz. Chem. Soc.*, **17**, 125 (2006).
[4] G.L. Perlovich, S.V. Kurkov, A.N. Kinchin, A. Bauer-Brandl. *Eur. J. Pharm. Biopharm.*, **57**, 411 (2004).
[5] G.L. Perlovich, S.V. Kurkov, A. Bauer-Brandl. *Eur. J. Pharm. Sci.*, **27**, 150 (2006).
[6] J.T. Doluisio, D.R. Bennett, J.V. Bergen, *et al. US Pharmacopeia*, 23rd Edn, United States Pharmacopeial Convention, Rockville, MD (1994).
[7] G. Cevc. In *Liposomes Technology*, G. Gregoriadis (Ed.), pp. 1–36, CRC Press, Boca Raton, FL (1993).
[8] W.F. Ganong. *Fisiología Médica*, 17th Edn, Editorial El Manual Moderno, México (2000).
[9] A. Martin, P. Bustamante, A.H.C. Chun. *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*, 4th Edn, Lea & Febiger, Philadelphia (1993).
[10] G.V. Betageri, A. Nayernama, M.J. Habib. *Int. J. Pharm. Adv.*, **1**, 310 (1996).

[11] S. Budavari, M.J. O'Neil, A. Smith, P.E. Heckelman, J.R. Obenchain Jr, J.A.R. Gallipeau, M.A. D'Arecea. *The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals*, 13th Edn, Merck & Co., Inc., Whitehouse Station, NJ (2001).
[12] S.H. Yalkowsky. *Solubility and Solubilization in Aqueous Media*, American Chemical Society and Oxford University Press, New York (1999).
[13] A. Kristl, G. Vesnaver. *J. Chem. Soc. Faraday Trans.*, **91**, 995 (1995).
[14] A. Martin, P. Bustamante. *Anal. Real Acad. Farm.*, **55**, 175 (1989).
[15] P. Bustamante, S. Romero, A. Peña, B. Escalera, A. Reillo. *J. Pharm. Sci.*, **87**, 1590 (1998).
[16] R.R. Krug, W.G. Hunter, R.A. Grieger. *J. Phys. Chem.*, **80**, 2341 (1976).
[17] P.R. Bevington. *Data Reduction and Error Analysis for the Physical Sciences*, McGraw-Hill, New York (1969).
[18] S. Romero, A. Reillo, B. Escalera, P. Bustamante. *Chem. Pharm. Bull.*, **44**, 1061 (1996).
[19] G.L. Perlovich, S.V. Kurkov, A. Bauer-Brandl. *Eur. J. Pharm. Sci.*, **19**, 423 (2003).
[20] C.P. Mora. MSc thesis, Universidad Nacional de Colombia, Bogotá DC (2006).