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Thermodynamics of Partitioning of Propranolol in Some Organic Solvent/Buffer Systems

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Propranolol (PPN) partitioning thermodynamics was studied at five temperatures in several solvent/buffer systems, namely, cyclohexane (CH/W), octanol (ROH/W), isopropyl myristate (IPM/W), and chloroform (CLF/W). In all cases, the mole fraction partition coefficients ($K_{o/w}^X$) were greater than unity; therefore, the standard Gibbs energies of transfer are negative, indicating a high affinity of PPN for all organic media evaluated. $K_{o/w}^X$ values were approximately 57 times higher in the ROH/W system with respect to CH/W, thus indicating a high degree of hydrogen bonding contribution to partitioning, whereas in the case of the IPM/W and CLF/W systems, the $K_{o/w}^X$ values were similar to those observed in ROH/W. In all cases, standard enthalpies and entropies of transfer of PPN from water to organic solvents were positive. These results indicate some degree of participation of the hydrophobic hydration in the PPN partitioning processes.

Introduction

Propranolol (PPN) is a nonselective β -adrenergic blocker that is widely used in the treatment of hypertension, angina pectoris, and cardiac dysrhythmias.¹ Although PPN is currently widely used in therapeutics, physicochemical information about the transfer processes of this drug, like other therapeutic compounds, is not complete at present. As useful information in pharmaceutical and medicinal chemistry, the thermodynamics of transfer of drug compounds can be studied by measuring the mole fraction partition coefficient as a function of temperature by means of the van't Hoff method. Such data can be used for the prediction of absorption, membrane permeability, and in vivo drug distribution.²

According to Leo et al.,³ semipolar solvents have been found to yield better correlations with the partitioning of solutes obtained in model membranes compared with nonpolar solvents such as cyclohexane (CH), which interact only by nonspecific forces (London interactions). In particular, octanol (ROH) has been found to be a useful solvent as the reference for extrathermodynamic studies in a variety of systems.⁴ Isopropyl myristate (IPM), which acts as a hydrogen acceptor, especially has been used for determining drug hydrophobic constants because it simulates the corneum stratum/water partition most closely.⁵ Chloroform (CLF) is useful in establishing hydrogen bonds with Lewis basic solutes because it mainly acts as a hydrogen donor. Therefore, the effect of hydrogen bonding on partitioning would be studied in more detail.⁶

As a contribution to the generation and systematization of physicochemical information about drugs' transfer properties, the main goal of this study was to compare the partitioning of PPN in different organic medium/buffer systems, namely, cyclohexane (CH/W), octanol (ROH/W), isopropyl myristate (IPM/W), and chloroform (CLF/W), by employing a thermodynamic approach based on the mole fraction partitioning

variation with respect to temperature. With that purpose, an interpretation in terms of solute–solvent interactions based on the corresponding thermodynamic functions of transfer was developed.

Theoretical Section

The apparent partition coefficient expressed in molality ($K_{o/w}^{m\text{-app}}$) for any solute between organic and aqueous phases (at any pH value, which would imply drug dissociation) is calculated by means of

$$K_{o/w}^{m\text{-app}} = W_w \frac{C_1 - C_2}{C_2 W_o} \quad (1)$$

where W_w and W_o are the masses (usually in g) of aqueous and organic phases, respectively, and C_1 and C_2 are the solute aqueous concentrations (usually in $\mu\text{g} \cdot \text{cm}^{-3}$) before and after the transfer from the aqueous phase to the organic medium, respectively.⁷ For obtaining the real molal partition coefficients ($K_{o/w}^m$), the following equation is commonly used for basic drugs such as PPN⁶

$$K_{o/w}^m = K_{o/w}^{m\text{-app}}(1 + 10^{\text{p}K_a - \text{pH}}) \quad (2)$$

In turn, the mole fraction partition coefficients ($K_{o/w}^X$) are calculated from $K_{o/w}^m$ values as

$$K_{o/w}^X = K_{o/w}^m (M_o/M_w) \quad (3)$$

where M_o and M_w are the molar masses of the organic and aqueous phases, respectively.⁶ The definition of $K_{o/w}^m$ and $K_{o/w}^X$ implies that no drug association or dissociation takes place in any of the respective phases; that is, the partitioning obeys the Nernst limit law.

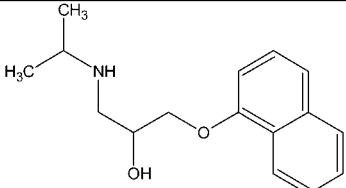
The enthalpy change for the transfer of solutes from aqueous phases to organic systems may be indirectly obtained by means of the analysis of the temperature dependence for partitioning. It is well known that the making of graphs on the basis of the logarithm of partition coefficients as a function of the reciprocal

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Table 1. Some Physical and Chemical Properties of PPN

Molecular structure ^(a)	M / g·mol ⁻¹ (a)	pK _a ^(b)	λ _{max} / nm ^(c)
	259.34	9.6	289

^a From Budavari et al.²⁰ ^b From Thomas and Rubino²¹ at I = 0 mol·dm⁻³ and corrected at I = 0.15 mol·dm⁻³ by means of the extended Debye–Hückel equation.²² ^c In aqueous buffer at pH 7.4 and I = 0.15 mol·dm⁻³.

of absolute temperature allows estimation of the enthalpic change of transfer from aqueous media to organic systems ($\Delta H_{w \rightarrow o}^{OX}$) by means of the classical van't Hoff equation.⁶ Nevertheless, in more recent treatments, the mean harmonic temperature (T_{hm}) has been introduced to the van't Hoff equation to facilitate the regression treatment. When temperature intervals from (293.15 to 313.15) K (varying in 5.00 K) are evaluated, the T_{hm} value obtained is only 303 K.^{6,7} Therefore, the modified expression can be written as follows

$$\left(\frac{\partial \ln K_{o/w}^X}{\partial (1/T - 1/303)} \right)_p = - \frac{\Delta H_{w \rightarrow o}^{OX}}{R} \quad (4)$$

The standard Gibbs energy change for the transfer process ($\Delta G_{w \rightarrow o}^{OX}$), considering the approach proposed by Krug et al.,⁷ is calculated at 303 K by means of

$$\Delta G_{w \rightarrow o}^{OX} = -R \cdot 303 \cdot \text{intercept} \quad (5)$$

in which the intercept used is that obtained from $\ln K_{o/w}^{OX}$ versus $(1/T - 1/303)$ plots (eq 4). The $\Delta G_{w \rightarrow o}^{OX}$ value obtained by using eq 5 is slightly different with respect to that calculated as $-RT \ln K_{o/w}^{OX}$ at 303.15 K because in the former case, this property depends on all of the partitioning data, whereas in the traditional form, it solely depends on the value obtained at the specified temperature.

The standard entropic change for the transfer process ($\Delta S_{w \rightarrow o}^{OX}$) is obtained from the respective $\Delta H_{w \rightarrow o}^{OX}$ and $\Delta G_{w \rightarrow o}^{OX}$ values at 303 K by using

$$\Delta S_{w \rightarrow o}^{OX} = \frac{\Delta H_{w \rightarrow o}^{OX} - \Delta G_{w \rightarrow o}^{OX}}{303} \quad (6)$$

The thermodynamic functions $\Delta H_{w \rightarrow o}^{OX}$ and $\Delta S_{w \rightarrow o}^{OX}$ represent the standard changes in enthalpy and entropy, respectively, when 1 mole of drug is transferred from the aqueous medium to the organic system at infinite dilution and expressed on the mole fraction scale.^{2,8}

Experimental Section

Chemicals. The following chemicals were used: propranolol–HCl USP,⁹ cyclohexane AR (Mallinckrodt), octanol extra pure grade (Merck), *i*-propyl myristate for synthesis (Scharlau), chloroform AR (Mallinckrodt), potassium chloride AR (Merck), sodium mono- and dihydrogen phosphates AR (Merck), and distilled water (conductivity < 2 μS·cm⁻¹).

Organic Solvent/Buffer Partitioning. The procedures followed were similar to those reported in the literature.^{6,10–18} For CLF/W partitioning, the aqueous and organic solvents were mutually saturated before the experiments were performed, whereas for the other partitioning systems, only the organic solvent was saturated with water. Aqueous solutions of PPN–HCl at known concentrations were prepared in

aqueous buffers adjusted to pH 7.4 at an ionic strength (I) of 0.15 mol·dm⁻³.¹⁹ Then, appropriate volumes of organic solvents were added to specific volumes of PPN–HCl aqueous solutions as follows: for CH/W, (10/10) cm³ of (100 μg·cm⁻³) PPN–HCl solution; for ROH/W, (5/20) cm³ of (200 μg·cm⁻³) PPN–HCl solution; for IPM/W, (5/20) cm³ of (100 μg·cm⁻³) PPN–HCl solution; for CLF/W, (5/20) cm³ of (200 μg·cm⁻³) PPN–HCl solution. All aliquots were weighed on a digital analytical balance (Mettler AE 160) whose sensitivity was ± 0.1 mg.

Mixtures were then stirred on a mechanical shaker (Burrell Wrist-Action model 75) for 1 h. Samples were placed in thermostatic water baths (Blue M Electric Magni Whirl, Julabo SW23, or Thermo Neslab RTE 10 Digital One) at (293.15, 298.15, 303.15, 308.15, and 313.15) K (± 0.05 K) for at least for 72 h (except at 313.15 K, where 48 h was used) with sporadic stirring to achieve the partitioning equilibrium, as previously reported.^{6,15–18} After that, the aqueous phases were removed and drug concentration was determined by means of UV absorbance referred to a previously constructed calibration curve for PPN–HCl in buffer at pH 7.4 (UV/vis BioMate 3 Thermo Electron) through a validated methodology.

The $K_{o/w}^{m-APP}$ values were calculated by the use of eq 1 and were then converted to $K_{o/w}^m$ values by means of eq 2, in which the parentheses term on the right side is equal to 159.5 because the pH is 7.4 and the pK_a of PPN corrected to an I value of 0.15 mol·dm⁻³ is 9.6 (Table 1). From $K_{o/w}^m$ values, the partition coefficients expressed in mole fraction ($K_{o/w}^X$) were calculated from eq 3 by employing the following molar masses: 99.47 g·mol⁻¹ for water-saturated ROH, 263.72 g·mol⁻¹ for water-saturated IPM, 113.89 g·mol⁻¹ for water-saturated CLF, 84.16 g·mol⁻¹ for water-saturated CH, 18.16 g·mol⁻¹ for (ROH, IPM, or CH) organic-solvent-saturated buffers, and 18.29 g·mol⁻¹ for CLF-saturated buffer.⁶

Results and Discussion

Physical and Chemical Properties of Propranolol. The molecular structure and some physicochemical properties of PPN are summarized in Table 1.²⁰ The literature pK_a value²¹ was corrected to an I value of 0.15 mol·dm⁻³ (similar to that of the gastrointestinal tract and blood)¹⁹ by means of the extended Debye–Hückel equation.²² The partitioning was determined at pH 7.4 (resembling the blood physiological value). Such pH value was regulated with phosphate buffer with a β capacity of 0.01 calculated by the Koppel–Spiro–Van Slyke equation,²² using pK_a values corrected to an I value of 0.15 mol·dm⁻³. At pH 7.4 the PPN has a lower apparent partition coefficient value because its protonated form predominates (pK_a = 9.6) and thus has more affinity for water. For this reason, it is necessary to use eq 2 to obtain the true values of partitioning that would follow the Nernst law⁴

Table 2. Mole Fraction Partition Coefficient of PPN in Different Partitioning Systems as a Function of Temperature (± 0.05 K)^a

system	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
CH/W	96(7)	284(3)	399(59)	599(111)	835(296)
ROH/W	13.7 (0.5)·10 ³	18.4 (0.2)·10 ³	22.8 (1.0)·10 ³	30.1 (0.3)·10 ³	36.8 (0.4)·10 ³
IPM/W	15.7 (0.2)·10 ³	18.1 (0.4)·10 ³	21.5 (0.3)·10 ³	24.7 (0.1)·10 ³	29.6 (0.9)·10 ³
CLF/W	12.1 (0.2)·10 ³	21.1 (0.1)·10 ³	28.6 (1.2)·10 ³	33.0 (0.8)·10 ³	32.1 (1.6)·10 ³

^a Values in parentheses are standard deviations.

Partition Coefficients of Propranolol. The temperature dependence of the mole fraction partition coefficients of PPN in all tested partitioning systems is summarized in Table 2. In all cases, the $K_{o/w}^X$ values are greater than unity and increase as temperature rises. Betageri and Rogers studied PPN partitioning in ROH/W and reported their values on the molarity scale.¹¹ By converting the result reported at 303.15 K to the mole fraction scale, a value of $15.6 \cdot 10^3$ is obtained, which is slightly different with respect to that shown in Table 2. For the other tested systems, no partitioning values have been reported for PPN; therefore, other comparisons are not possible. At 303.15 K the drug partitioning decreases in the following order: CLF/W > ROH/W > IPM/W > CH/W. Similar sequences were observed with other drugs that have lipophilic semipolar properties that are similar to those of PPN.^{6,16,17}

According to Table 2, a higher preference of PPN for hydrogen-bonding organic solvents, namely, CLF, ROH, and IPM, can be observed with respect to the hydrocarbon solvent, namely, CH. This behavior is similar to that obtained for other drugs.^{6,16,17} As has been previously described in the literature, ROH has a microheterogeneous structure on water saturation.^{4,23} This structure is conformed by two hydrogen-bonded water molecules, and in turn, each of them is hydrogen bonded to three octanol molecules. The result is a tendency to form small regions like inverted micelles. For this reason, ROH could interact with PPN by hydrogen bonding through the hydroxyl, ether–oxygen, and secondary amine groups present in this drug as well as by weak interactions, such as London dispersion forces, which conduce to structural immobilization of drug molecules near the alkyl moieties of ROH.

Seiler and Other Analogue Parameters. As previously described,⁶ Seiler²⁴ proposed an equation that is analogous to eq 7 to compare partition coefficients of drugs in the ROH/W and CH/W systems. Equation 7 provides information related to the contribution of hydrogen bonding to partitioning of solutes. In a more complete treatment, other considerations such as molecular geometry and steric effects of solutes and solvents should be considered for such an aim. However, in a first approach, eq 7 is a good attempt to identify the main solute–solvent interactions that affect the solute transfer.

$$\begin{aligned} \Delta \log K_{ROH/CH}^X &= \log K_{ROH/W}^X - \log K_{CH/W}^X \\ &= \log(K_{ROH/W}^X / K_{CH/W}^X) \end{aligned} \quad (7)$$

The above equation shows the hydrogen bonding nature of the interactions between the drug and ROH with respect to CH. A value of $\Delta \log K_{ROH/CH}^X$ that is greater than 0 indicates some contribution of hydrogen bonding to the drug partitioning. Table 3 presents the values of Seiler and other analogous parameters for PPN at 303.15 K calculated from the different rational partition coefficients shown in Table 2 (which are also presented in Table 3 but as decimal logarithms).

It is well known that CH is an aprotic solvent that is unable to form hydrogen bonds as a donor or an acceptor, and therefore acts only through nonspecific interactions (London forces). However the hydroxyl group of ROH can be an acceptor or a

Table 3. Seiler and Other Analogue Parameters of PPN at (303.15 ± 0.05) K

parameter	system 1	system 2	$\log K_{o/w}^X$ (syst. 1)	$\log K_{o/w}^X$ (syst. 2)	$\Delta \log K_{o1/o2}^X$ ^a
$\Delta \log K_{ROH/CH}^X$	ROH/W	CH/W	4.358	2.601	1.757
$\Delta \log K_{IPM/CH}^X$	IPM/W	CH/W	4.332	2.601	1.731
$\Delta \log K_{CLF/CH}^X$	CLF/W	CH/W	4.456	2.601	1.855
$\Delta \log K_{ROH/IPM}^X$	ROH/W	IPM/W	4.358	4.332	0.026
$\Delta \log K_{ROH/CLF}^X$	ROH/W	CLF/W	4.358	4.456	−0.098

^a $\Delta \log K_{o1/o2}^X = \log K_{o/w}^X$ (syst. 1) $- \log K_{o/w}^X$ (syst. 2).

donor of protons; moreover, as was already expressed, its alkyl moieties allow the structural immobilization of solutes because of the tetrahedral microstructure adopted in saturation by this solvent in contrast with the CH behavior.^{4,23} Therefore, $\Delta \log K_{ROH/CH}^X$ includes contributions of hydrogen bonding and of structural immobilization to the partitioning. (In this analysis, it is assumed that the nonspecific interactions are similar for all organic solvents and the drug.)

$\Delta \log K_{IPM/CH}^X$ allows us to estimate the contribution of the organic solvent as a hydrogen bonding acceptor in IPM/W rational partitioning. A comparison of the Seiler parameter ($\Delta \log K_{ROH/CH}^X$) with $\Delta \log K_{IPM/CH}^X$ shows that ROH, besides contributing to the drug partitioning as an hydrogen acceptor, may also contribute as a hydrogen donor; therefore, the $\Delta \log K_{IPM/CH}^X$ value is slightly lower than the Seiler parameter (Table 3).

We calculated a third parameter, namely, $\Delta \log K_{ROH/IPM}^X$, by comparing the ROH/W and IPM/W partition coefficients to establish the contribution of the organic solvent as a hydrogen donor to the partitioning. This third parameter is relatively low, which apparently indicates that this effect is negligible; nevertheless, this outcome indicates that any other structural solvent effects should be considered in addition to hydrogen bonding. As was previously stated, CLF mainly acts as a hydrogen donor; therefore, two other parameters were calculated to analyze the contribution of this kind of interaction to the partitioning of PPN. $\Delta \log K_{CLF/CH}^X$ accounts for the possible contribution of CLF as a hydrogen donor, whereas $\Delta \log K_{ROH/CLF}^X$ (obtained from ROH/W and CLF/W partitioning values) permits one to evaluate the behavior of ROH as a hydrogen acceptor. The acidic hydrogen atoms in this drug are those present in the hydroxyl and amine groups, whereas, the basic groups (hydrogen acceptor) in PPN are the amine and ether groups present in the alkyl tail and in the naphthyl ring, respectively, although the hydroxyl moiety could also be a proton acceptor.

Generally, the results show slightly greater values for $\Delta \log K_{o1/o2}^X$ when PPN acts as a hydrogen acceptor and the solvent acts as donor ($\Delta \log K_{CLF/CH}^X$ and $\Delta \log K_{ROH/IPM}^X$) with respect to those obtained when this drug acts as a hydrogen donor and the solvent acts as an acceptor ($\Delta \log K_{IPM/CH}^X$ and $\Delta \log K_{ROH/CLF}^X$). Therefore, it could be said that PPN mainly acts as a Lewis base. At this point, it is convenient to take into account the fact that the previous analyses were performed by considering only the effect of hydrogen bonding without considering other kinds of intermolecular interactions or geometric parameters, such as differences in molecular sizes.

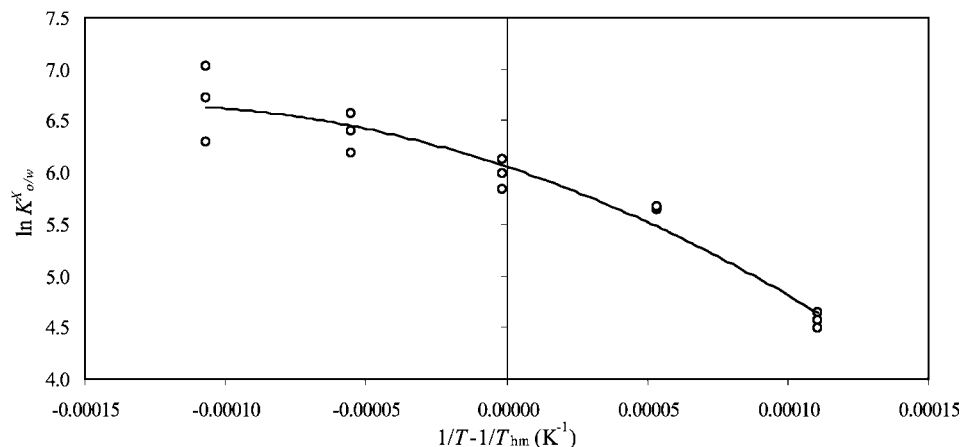


Figure 1. Modified van't Hoff plot for the PPN partitioning in the CH/W system.

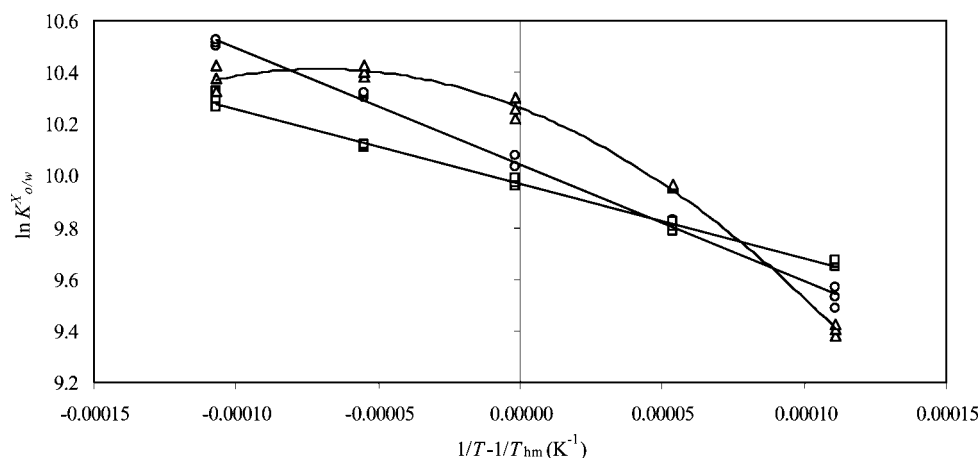


Figure 2. Modified van't Hoff plot for the PPN partitioning in the other organic solvent/buffer systems. O, ROH/W; □, IPM/W; Δ, CLF/W.

Table 4. Standard Gibbs Energy ($\Delta G_{w \rightarrow o}^{OX}$), Enthalpy ($\Delta H_{w \rightarrow o}^{OX}$), and Entropy ($\Delta S_{w \rightarrow o}^{OX}$) of PPN Transfer from Water to Different Organic Systems and Relative Contributions of Enthalpy (% ζ_H) and Entropy (% ζ_{TS}) toward Transfer Processes At 303 K^a

system	$\Delta G_{w \rightarrow o}^{OX}$ kJ·mol ⁻¹	$\Delta H_{w \rightarrow o}^{OX}$ kJ·mol ⁻¹	$\Delta S_{w \rightarrow o}^{OX}$ J·mol ⁻¹ ·K ⁻¹	$T\Delta S_{w \rightarrow o}^{OX}$ kJ·mol ⁻¹	% ζ_H	% ζ_{TS}
CH/W	-15.25 (0.22)	75 (6)	298 (24)	90 (7)	45.4	54.6
ROH/W	-25.30 (0.02)	37.6 (0.8)	207 (5)	62.9 (1.4)	37.4	62.6
IPM/W	-25.12 (0.01)	24.0 (0.6)	162 (4)	49.1 (1.2)	32.8	67.2
CLF/W	-25.85 (0.03)	35.8 (0.8)	203 (5)	61.6 (1.5)	36.7	63.3

^a Values in parentheses are standard deviations.

Thermodynamics of Partitioning for Propranolol. Figures 1 and 2 show the modified van't Hoff plots for partitioning of PPN in the CH/W system and in the ROH/W, IMP/W, and CLF/W systems, respectively. For ROH/W and IMP/W systems, linear models with regression determination coefficients (r^2) of 0.993 and 0.992 were obtained, whereas, for CH/W and CLF/W systems, parabolic regression models with r^2 values of 0.934 and 0.995 were obtained, respectively.

From the estimated slopes in the modified van't Hoff plots, the respective standard enthalpic changes for transfer were calculated by means of eq 4 using methods of errors propagation.²⁵ Then, the transfer enthalpies ($\Delta H_{w \rightarrow o}^{OX}$) were calculated as the product of slopes multiplied by $-R$ (that is, $-8.314 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) and are summarized in Table 4 in addition to standard Gibbs energy for transfer ($\Delta G_{w \rightarrow o}^{OX}$) of PPN from water to different organic systems (expressed in mole fraction at 303 K). The $\Delta G_{w \rightarrow o}^{OX}$ values were calculated by means of eq 5 on the basis of all of the partitioning data presented in Table 2. In

all cases, $\Delta G_{w \rightarrow o}^{OX}$ was negative, indicating the preference of this drug for organic media. If the partitioning value reported by Betageri and Rogers¹¹ at 303.15 K in the ROH/W is expressed as mole fraction, then the $\Delta G_{w \rightarrow o}^{OX}$ value obtained is $-24.3 \text{ kJ}\cdot\text{mol}^{-1}$, which is similar to that presented in Table 2. In the same way, the van't Hoff enthalpy value reported by Betageri and Rogers¹¹ ($33.2 \text{ kJ}\cdot\text{mol}^{-1}$) is in good agreement with that obtained in the present research. In contrast, the calorimetric enthalpy reported by Burgot et al.²⁶ ($4.9 \text{ kJ}\cdot\text{mol}^{-1}$) is in total disagreement with those obtained by means of the van't Hoff method.¹¹ Although these discrepancies could be expected because the calorimetry is a direct measure of the heat evolved in the process, whereas the van't Hoff is an indirect method to estimate this property. Nevertheless, the explanation of this discrepancy is unclear.

From $\Delta G_{w \rightarrow o}^{OX}$ and $\Delta H_{w \rightarrow o}^{OX}$ values, the respective standard entropic changes of transfer ($\Delta S_{w \rightarrow o}^{OX}$) in mole fraction were calculated from eq 6. These values are also presented in Table 4. The enthalpies and entropies of transfer of PPN were positive in all cases, and they were relatively high compared with those obtained for other drugs.^{6,16,17}

For the ROH/W system, from the Betageri and Rogers¹¹ values expressed as a mole fraction, a $\Delta S_{w \rightarrow o}^{OX}$ value of $190 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ was obtained, which is also in good agreement with that obtained in the present report. Otherwise, in a way similar to enthalpy of transfer, for the ROH/W system, these entropy values are not concordant with that reported by Burgot et al.²⁶ ($96 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ if the mole fraction is used). This is

a consequence of the disagreement found in the respective enthalpy values.

The enthalpic and entropic changes account, respectively, for all of the energetic requirements and the molecular randomness (increase or decrease in the molecular disorder) involved in the net transfer of the drug from water to different organic media. In general terms, it should be considered independently of the behavior presented in each phase before and after the partitioning process.

Because the PPN is initially present in only water, it is necessary to create a cavity in the organic medium to accommodate the solute after the transfer process. This is an endothermic event because an energy supply is necessary to separate the organic solvent molecules (to overcome the cohesive forces). When the solute molecules are accommodated into the organic phase, an amount of energy is released because of solute–organic-solvent interactions. This event would imply an entropy increase in this medium due to the drug–organic-solvent mixing process.

In turn, after a certain number of solute molecules have diffused from the aqueous phase to the organic medium to reach the partitioning equilibrium, the original cavities occupied by the drug molecules in the aqueous phase become occupied by water molecules. This event produces an energy release due to water–water interactions. However, depending on the solute's molecular structure, it is also necessary to consider the possible disruption of water structure, that is, the water molecules organized as icebergs around the alkyl or aromatic groups of the drug (namely, hydrophobic effect or hydrophobic hydration). This event in particular implies an intake of energy in addition to a local entropy increase by separation of some water molecules that were originally associated by hydrogen bonding.²⁷

From Table 4, it can be observed that for all cases the PPN transfer processes from water to organic media were endothermic. Therefore, it could be said that the obtained values of enthalpy and entropy for the CH/W system are mainly due to the disruption of water icebergs present around the hydrocarbon groups of this drug (one naphthyl, two methylene, and two methyl groups) and to the creation of a cavity in the cyclohexane to accommodate the solute. Both events, as was already said, imply an energy intake and a disorder increase at the molecular level.

In the case of the ROH/W system, the enthalpy of transfer is also positive but is lower than that in CH/W system, whereas the entropy of transfer has a high value but is not comparable to the corresponding value for the CH/W system. These values could be explained in terms of a possible disorganization in the water-saturated octanol due to the replacement of an octanol molecule by a voluminous drug molecule. This replacement would be present in some centers conformed by two water molecules and six octanol molecules inside the microheterogeneous structure of this water-saturated organic solvent.^{4,23} The previous event increases the molecular disorder produced by the drug–organic-solvent mixing process but not in the same way as in the CH/W system.

In contrast with data obtained with other drugs in the CLF/W system,^{6,16,17} the enthalpy and entropy of transfer are similar in magnitude to those obtained with the ROH/W system; nevertheless, the meaning of these results is unclear because of the great differences between both organic solvents. Otherwise, the respective thermodynamic values found for the IPM/W system are the lowest among all values obtained. In this solvent (Lewis base), the drug mainly acts as an acid compound, but

the molecular meaning of these thermodynamic quantities is also unclear. Unfortunately, no information about the structural properties of these two water-saturated organic solvents is available at the moment; therefore, it is not possible to explain these interesting results at the molecular level.

Equations 8 and 9 were used to evaluate the respective contributions of enthalpy and entropy, in absolute values, toward the standard Gibbs energy of transfer and indeed to identify the dominant effect on transfer, that is, either energy changes or molecular organization changes. These equations have been introduced by Perlovich et al.,²⁸ who studied naproxen solubility in several solvents, and they have been previously used to evaluate the partitioning behavior of some analgesic drugs^{6,17} as well as some acetanilide derivatives.²⁹ The respective contributions of all of the partitioning systems evaluated are also presented in Table 4.

$$\% \zeta_H = 100 \frac{|\Delta H_{w \rightarrow o}^{OX}|}{|\Delta H_{w \rightarrow o}^{OX}| + |T\Delta S_{w \rightarrow o}^{OX}|} \quad (8)$$

$$\% \zeta_{TS} = 100 \frac{|T\Delta S_{w \rightarrow o}^{OX}|}{|\Delta H_{w \rightarrow o}^{OX}| + |T\Delta S_{w \rightarrow o}^{OX}|} \quad (9)$$

On the basis of data for $\% \zeta_H$ and $\% \zeta_{TS}$ from Table 4, it follows that transfer of PPN from water to the organic systems is mainly driven by organizational changes. This result confirms the event previously observed for the signs of entropies of transfer, which are positive in all cases. Therefore, the partitioning is only entropy-driven for all partitioning systems evaluated. The IPM/W system has the highest entropy contribution toward drug transfer, followed by CLF/W and ROH/W systems and finally by the CH/W system. This behavior is opposite to those obtained with other drugs.^{5,17,29} As previously stated, the dominant effect of entropy on Gibbs energy of transfer of PPN from water to ROH could be due to the increase in disorder presented in the microheterogeneous structure of water-saturated octanol by the solute accommodation.^{4,23}

Conclusions

From the previous analyses, it could be concluded that PPN has mainly semipolar lipophilic behavior, although this drug is certainly not a hydrophobic compound because its $K_{o/w}^X$ values in the CH/W system are the lowest among those of all systems tested. Besides, the hydrogen bonding in the organic systems plays a crucial role in the partitioning of this drug. The drug transfer processes are entropy-driven in all tested systems (positive values), whereas in the same way, the main contributor toward transfer is also the entropy (values greater than 55 %). In this context, it could be concluded that the hydrophobic effect plays a crucial role in the partitioning of PPN, as was described for other drugs.

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