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Thermodynamic study of the transfer of acetanilide and phenacetin from water to different organic solvents

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The molar ($K^C_{o/w}$) and rational ($K^X_{o/w}$) partition coefficients in the octanol/buffer, *i*-propyl myristate/buffer, chloroform/buffer, and cyclohexane/buffer systems were determined for acetanilide and phenacetin at 25.0, 30.0, 35.0, and 40.0 °C. In all cases except for cyclohexane, the $K^C_{o/w}$ and $K^X_{o/w}$ values were greater than unity. This demonstrates that these two drugs have predominantly lipophilic behavior. Gibbs and van't Hoff thermodynamic analyses have revealed that the transfer of these drugs from water to organic solvents is spontaneous and that it is mainly driven enthalpically for *i*-propyl myristate and chloroform, and entropy-driven for octanol and cyclohexane.

Keywords: acetanilide, phenacetin, partition coefficient, thermodynamics

Acetanilide and phenacetin were used as common analgetics for a long time. Despite the fact that nowadays they have no therapeutic utility, these drugs are still useful as model compounds in thermodynamics of pharmaceutical solutions. This interest is mainly due to their simple molecular structures that permit the analysis of interactions between the drugs and the model organic solvents used in QSAR studies (Quantitative Structure-Activity Relationships).

Thermodynamics of the transfer of drug compounds can be studied by measuring the partition coefficient as a function of temperature. Such data can be used for predicting absorption, membrane permeability, and *in vivo* drug distribution (1). Semipolar solvents have been found to yield better correlations with the partitioning of solutes obtained in model membranes compared to non-polar solvents such as cyclohexane (CH), which interact only by non-specific forces (London interactions). In particular, octanol (ROH) has been found to be a useful reference solvent for extrathermodynamic studies (such as enthalpy-entropy compensation of partitioning in a variety of systems (2, 3), although *i*-propyl myristate (IPM) has also been used. It has been specially used in order to determine hydrophobic constants because it most closely simulates stratum corneum-water partition (4, 5). IPM is best related to skin/transdermal absorption because its polar and non-polar nature mimics the complex nature (polar/non-polar matrix) of the

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skin (6). On the other hand, chloroform (CHL) has also been used in this kind of studies because it acts mainly as a hydrogen donor to form hydrogen bonds with the solutes (unpublished data).

The molal partition coefficient ($K^m_{o/w}$) for any solute between organic and aqueous phases is calculated by means of:

$$K^m_{o/w} = W_w \frac{c_1 - c_2}{c_2 W_o} \tag{1}$$

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 aqueous concentrations of the solute (usually in μg mL^{-1}) before and after the solute transfer from the aqueous phase to the organic medium, respectively (1, 7).

If the solutions are very diluted, the molar partition coefficient ($K^C_{o/w}$) is calculated as $K^m_{o/w}(\rho_o/\rho_w)$, where ρ_o and ρ_w are the densities of the organic and aqueous phases, respectively. On the other hand, the rational partition coefficient ($K^X_{o/w}$, in mole fraction) is calculated as $K^C_{o/w}(V_o/V_w)$, where V_o and V_w are the molar volumes of the organic and aqueous phases, respectively (unpublished data).

The standard change of Gibbs free energy for the transfer of a solute from the aqueous phase to an organic medium is calculated as follows:

$$\Delta G^{0X}_{w\to o} = -RT \ln K^X_{o/w} \tag{2}$$

Otherwise, the enthalpy change for the transfer may be obtained directly by thermometric microcalorimetry titration or indirectly as the difference of the respective heats of solution in each of the phases, which may be obtained by solution calorimetry (8). As said previously, a method widely used in the physicochemical study of pharmaceutical compounds (such as drugs) is the analysis of the temperature-dependence of partitioning with the use of van't Hoff method. This procedure gives the standard enthalpy change:

$$\left(\frac{\partial \ln K^X_{o/w}}{\partial (1/T)}\right)_p = -\frac{\Delta H^{0X}_{w\to o}}{R} \tag{3}$$

Therefore, $\Delta H^{0X}_{w\to o}$ is determined from the slope of the pondered linear plot of $\ln K^X_{o/w}$ as a function of $1/T$. The standard entropy change of transfer is obtained by means of:

$$\Delta S^{0X}_{w\to o} = \frac{\Delta H^{0X}_{w\to o} - \Delta G^{0X}_{w\to o}}{T} \tag{4}$$

$\Delta H^{0X}_{w\to o}$ and $\Delta S^{0X}_{w\to o}$ represent the standard changes in enthalpy and entropy, respectively, when one mole of drug is transferred from the aqueous medium to the organic system at infinite dilution.

The main objective of this study was to compare the partitioning behavior of acetanilide (ACN) and phenacetin (PNC) in the organic solvent/aqueous buffer (pH 7.4) systems: octanol/buffer (ROH/W), *i*-propyl myristate/buffer (IPM/W), chloroform/buffer (CHL/W), and cyclohexane/buffer (CH/W), using the thermodynamic approach based on the variation of partitioning with temperature (van't Hoff aquation). A comparison of the partitioning behavior of both drugs would be useful in medicinal chemistry. These compounds allow evaluating the effect of the ethoxy moiety present in PNC on several processes of drugs transfer between liquid phases in comparison with ACN.

EXPERIMENTAL

Chemicals

The following chemicals were used in this investigation: acetanilide, standard reagent grade (Merck, Germany), phenacetin, analytical reagent grade (BDF, UK), octanol extra pure (Merck), *i*-propyl myristate for synthesis (Merck), cyclohexane, analytical reagent (Merck), chloroform, analytical reagent (Mallinckrodt, USA), distilled water (conductivity < 2 μS), potassium chloride, analytical reagent (Merck), sodium mono and dihydrogen phosphates, analytical reagents (Merck).

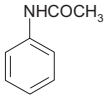
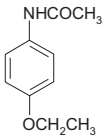
Shake flask method

Both aqueous and organic solvents were saturated before performing the experiments. Solutions of known concentration of each compound were prepared in aqueous phosphate buffer adjusted to pH 7.4 at ionic strength of 0.15 mol L^{-1} (physiological values, 9). Then, specified volumes of organic solvent were added to specified volumes of aqueous solutions of ACN and PNC in glass flasks (the volumes employed were as follows: for ROH/W: 5 mL of ROH and 20 mL of 20 μg mL^{-1} for ACN or 50 μg mL^{-1} for PNC aqueous solutions, for CH/W: 45 mL of CH and 5 mL of 10 μg mL^{-1} for ACN or 12 μg mL^{-1} for PNC, for IPM/W: 10 mL of IPM and 10 mL of 20 μg mL^{-1} for ACN or PNC, for CHL/W, 5 mL of CHL and 20 mL of 20 μg mL^{-1} for ACN or 50 μg mL^{-1} for PNC). All aliquots were weighed on a digital analytical balance (Mettler AE 160, Germany, sensitivity ± 0.1 mg). The mixtures were then stirred on a Wrist Action Burrel model 75 (USA) mechanical shaker for one hour. Samples were allowed to stand in Magni Whirl Blue (M. Electric Company, USA) water baths kept at 25.0, 30.0, 35.0, and 40.0 °C (± 0.1 °C) for at least 48 hours under sporadic stirring. After this time the aqueous phase was separated and the drug concentration was determined by measuring UV absorbance, followed by interpolation from the previously constructed calibration curve for each compound (Hewlett Packard 8452A spectrophotometer, USA). The molal partition coefficients were calculated by mass balance according to Eq. (*1*) and converted to molar and rational partition coefficients by means of the respective relationships. Densities of the liquid phases at several temperatures were determined using a digital density meter (DMA 45 Anton Paar, Austria). All the partitioning experiments were repeated at least three times and averaged.

RESULTS AND DISCUSSION

The molecular structure and some physicochemical properties of ACN and PNC are summarized in Table I. The pK_a values were corrected to ionic strength μ = 0.15 mol L^{-1} [similar to that of the gastrointestinal tract and blood (9)], by means of the Debye-Hückel equation (10). Partitioning was determined at pH 7.4 (physiological value of blood). At this pH these drugs have their highest distribution coefficient values because the molecular compound without dissociation dominates (11). The pH value was regulated with phosphate buffer having the capacity of 0.01 mol L^{-1} calculated by means of the Koppel-Spiro–Van Slyke equation (10), using pK_a values corrected to μ = 0.15 mol L^{-1}.

Table I. Physicochemical properties of acetanilide and phenacetin

Compound	Molecular structure	M_r	pK_a[a]	λ_{max}[b]
Acetanilide (ACN)		135.16	0.47	240
Phenacetin (PNC)		179.21	2.1	242

[a] Corrected to μ = 0.15 mol L^{-1} by means of the Debye-Hückel equation (10).
[b] Value in water at pH 7.4 and μ = 0.15 mol L^{-1}.

Table II summarizes the temperature-dependence of the molar and rational partition coefficients for the drugs studied in all partitioning systems. The $K^C_{o/w}$ and $K^X_{o/w}$ values diminish with rising temperature for ACN and PNC in IPM/W and CHL/W, but increase for both drugs in ROH/W and CH/W. The greatest partitioning was recorded for PNC in ROH/W at 40.0 °C and the lowest for ACN in CH/W at 25.0 °C. From the partitioning data ($K^C_{o/w}$ and $K^X_{o/w}$ values for both drugs are greater than 1 for ROH/W, IPM/W and CHL/W systems), it follows that both solutes show a semipolar and lipophilic, although not properly hydrophobic, behavior ($K_{CH/W}$ is << 1).

The temperature-dependence of rational partitioning is presented as van't Hoff plots in Figs. 1a and 1b for ACN and PNC, respectively. In all cases, straight lines with determination coefficients greater than 0.95 were obtained. Therefore, the van't Hoff method is useful for the respective thermodynamic analysis (8).

Table III summarizes the rational thermodynamic functions related to the transfer of both drugs from aqueous media to organic systems (octanol, cyclohexane, *i*-propyl myristate, and chloroform). In all cases except for CH/W, $\Delta G^{0X}_{w\rightarrow o}$ at 25.0 °C is negative; then, the transfer of these drugs from aqueous media to almost organic systems is spontaneous (considering the standard and reference states, that is, ideal drug solutions having

Table II. Molar (K^C) and rational (K^X) partition coefficients of ACN and PNC as a function of temperature

Compound	Partition coefficient[a]	Temperature (°C)[b]			
		25.0	30.0	35.0	40.0
ACN	$K^C_{ROH/W}$	13.60 (0.07)	16.20 (0.02)	17.50 (0.13)	21.5 (0.4)
	$K^X_{ROH/W}$	89.9 (0.5)	106.90 (0.14)	115.6 (0.9)	141.8 (2.8)
	$K^C_{CH/W}$	0.0262 (0.0002)	0.0292 (0.0007)	0.0384 (0.0009)	0.0487 (0.0014)
	$K^X_{CH/W}$	0.1571 (0.0013)	0.176 (0.004)	0.232 (0.005)	0.296 (0.009)
	$K^C_{IPM/W}$	1.83 (0.06)	1.570 (0.010)	1.15 (0.04)	1.010 (0.002)
	$K^X_{IPM/W}$	31.3 (1.1)	26.93 (0.18)	19.8 (0.6)	17.37 (0.03)
	$K^C_{CHL/W}$	7.74 (0.11)	7.05 (0.04)	6.40 (0.11)	6.14 (0.01)
	$K^X_{CHL/W}$	28.8 (0.4)	26.17 (0.14)	23.7 (0.4)	22.75 (0.05)
PNC	$K^C_{ROH/W}$	30.3 (0.4)	30.6 (0.9)	30.7 (0.7)	31.2 (0.4)
	$K^X_{ROH/W}$	199.9 (2.8)	202 (6)	203 (5)	206.2 (2.4)
	$K^C_{CH/W}$	0.0355 (0.0002)	0.0514 (0.0017)	0.066 (0.004)	0.090 (0.003)
	$K^X_{CH/W}$	0.2125 (0.0014)	0.310 (0.010)	0.402 (0.026)	0.545 (0.015)
	$K^C_{IPM/W}$	2.240 (0.014)	2.07 (0.05)	1.82 (0.05)	1.550 (0.002)
	$K^X_{IPM/W}$	38.23 (0.24)	35.5 (0.8)	31.3 (0.8)	26.64 (0.04)
	$K^C_{CHL/W}$	32.0 (0.9)	30.60 (0.18)	29.8 (0.6)	28.3 (0.5)
	$K^X_{CHL/W}$	119 (4)	113.7 (0.7)	110.4 (2.3)	104.7 (1.7)

K^C expressed in molarity, mean (SD), $n = 3$; K^X expressed in mole fraction, mean (SD), $n = 3$.

[a] $K_{ROH/W}$: octanol/buffer (pH 7.4, μ = 0.15 mol L^{-1}) partitioning, $K_{CH/W}$: cyclohexane/buffer (pH 7.4, μ = 0.15 mol L^{-1}) partitioning, $K_{IPM/W}$: *i*-propyl myristate/buffer (pH 7.4, μ = 0.15 mol L^{-1}) partitioning, $K_{CHL/W}$: chloroform/buffer (pH 7.4, μ = 0.15 mol L^{-1}) partitioning.

[b] ± 0.1 °C

unity in mole fraction in each phase). On the other hand, the same results may be explained as a higher solute affinity for organic media. Magnitudes of these properties are also proportional to the degree of lipophilicity of the drugs (2, 3). The enthalpies of transfer ($\Delta H^{0X}_{w\to o}$) of the drugs are negative for IPM/W and CHL/W, indicating enthalpy-driving for transfer in these systems, and positive for ROH/W and CH/W. Negative enthalpies indicate the presence of significant hydrogen bonding (considered as the most important interaction of transfer) between molecules of the drugs and IPM and CHL. CHL can establish hydrogen bonding as a donor of hydrogen, while IPM acts as an acceptor (that is, the latter solvent is an ester Lewis base). The entropies of transfer ($\Delta S^{0X}_{w\to o}$) are negative for ACN in IPM/W and in CHL/W and for PNC in IPM/W, and positive in other cases. These results indicate that the transfer of these drugs is mainly entropy driven in ROH/W and CH/W for ACN, and also in ROH/W and CH/W for PNC, while for the latter drug the transfer is enthalpy-entropy driven in the CHL/W system.

Eqs. (*5*) and (*6*) were used to evaluate the respective contributions in absolute values for enthalpy (ζ_H) and entropy (ζ_{TS}) toward the standard free energy of transfer and

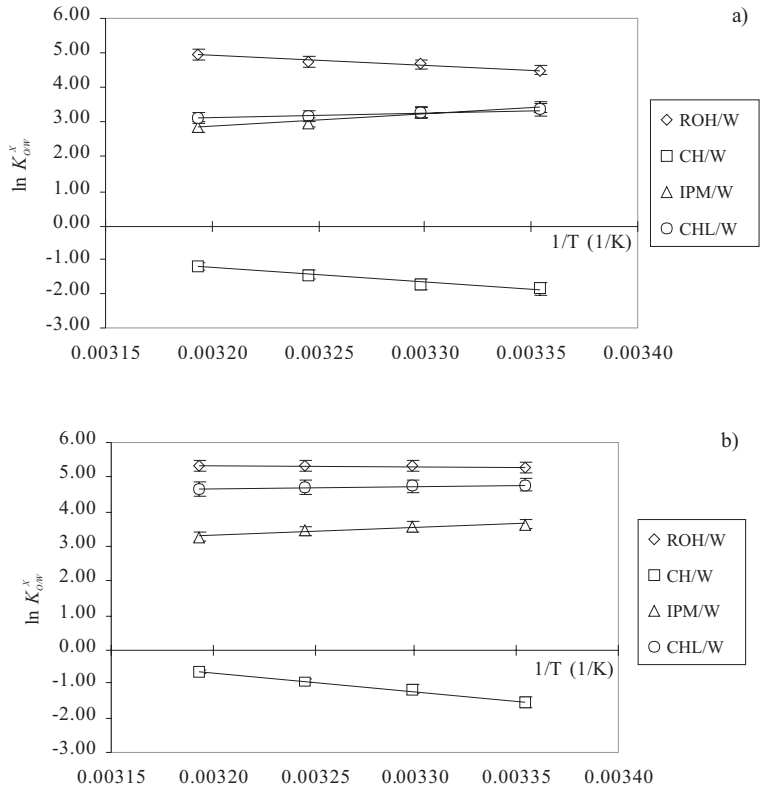


Fig. 1. Partitioning-temperature dependence for: a) ACN and b) PNC expressed in mole fractions (mean ± SD, n = 3).

indeed to identify the main effect on transfer, that is, energy changes (included in ζ_H) or molecular organization changes (included in ζ_{ST}). Similar equations have been used recently to evaluate the relative contributions by enthalpy and entropy to the free energy of solvation of some non-steroidal anti-inflammatory drugs (NSAIDs) in the process of solution in several solvents (12, 13). The respective contributions of all the partitioning systems evaluated are presented in Table III.

$$\zeta_H\,(\%) = 100\,\frac{\left|\Delta H_{w\to o}^{0X}\right|}{\left|\Delta H_{w\to o}^{0X}\right| + \left|T\Delta S_{w\to o}^{0X}\right|} \tag{5}$$

$$\zeta_{TS}\,(\%) = \frac{\left|T\Delta S_{w\to o}^{0X}\right|}{\left|\Delta H_{w\to o}^{0X}\right| + \left|T\Delta S_{w\to o}^{0X}\right|} \tag{6}$$

Table III. Gibbs free energy, enthalpy, entropy, and enthalpy and entropy contributions to Gibbs free energy of ACN and PNC transfer from aqueous media to several organic solvents at 25.0 ± 0.1 °C

Compound	Partitioning system	$\Delta G^{0X}_{w\to o}$ (kJ mol^{-1})[a]	$\Delta H^{0X}_{w\to o}$ (kJ mol^{-1})[a]	$\Delta S^{0X}_{w\to o}$ (J K^{-1}mol^{-1})[a]	ζ_H (%)	ζ_{TS} (%)
ACN	ROH/W	–11.210 (0.013)	22.4 (2.6)	113 (13)	39.9	60.1
	CH/W	4.590 (0.020)	34 (4)	98 (12)	53.8	46.2
	IPM/W	–8.53 (0.09)	–32 (4)	–79 (9)	57.6	42.4
	CHL/W	–8.33 (0.04)	–12.5 (1.3)	–14.0 (1.5)	75.0	25.0
PNC	ROH/W	–13.10 (0.04)	1.53 (0.19)	49 (6)	9.5	90.5
	CH/W	3.840 (0.017)	47.8 (2.2)	147 (7)	52.2	47.8
	IPM/W	–9.030 (0.015)	–18.7 (2.3)	–32 (4)	66.2	33.8
	CHL/W	–11.80 (0.07)	–6.5 (0.5)	18.0 (1.4)	54.8	45.2

[a] Mean (± SD), n = 3.

From the data for ζ_H (%) and ζ_{TS} (%) from Table III, it follows that transfer of ACN and PNC from water to IPM and CHL is driven mainly by energetic change but for ROH/W the process is mainly driven by organizational change. In the case of CH/W, almost equivalent contributions of enthalpy and entropy toward the transfer processes for both drugs are assumed.

The results obtained for the CH/W system are apparently in contradiction with those presented in Table III. It should be kept in mind that the thermodynamic functions in Eqs. (*5*) and (*6*) are used as absolute values without considering the endothermic or exothermic nature of the process. In the relevant literature (1, 3, 7), the analysis made considering the sign of the respective thermodynamic function has been traditionally regarded as more relevant (Table III). The dominant effect of entropy on free energy of transfer from water to ROH could be due to the disorder increase in the micro-heterogeneous structure of water-saturated octanol by the solute accommodation (14), especially in the case of PNC.

Seiler (15) in 1974 proposed Eq. (*7*), which compares the partition coefficients of a drug in the ROH/W and CH/W systems, for the basic purpose to obtain information related to the contribution of hydrogen bonding to the partitioning of solutes. In a more complete treatment, other considerations, such as molecular geometry and steric effects of the solute and solvents, should be considered. However, in a first approach, Eq. (*7*) is a good attempt to identify the principal solute-solvent interaction affecting the transfer:

$$\Delta \log K_{ROH/W} = \log K^{X}_{ROH/W} - \log K^{X}_{CH/W} \qquad (7)$$

The above equation shows the hydrogen bonding nature of the interactions between the drug and octanol with respect to cyclohexane. If $\Delta\log K_{ROH/W} > 0$, this indicates some contribution of hydrogen bonding to the partitioning. Table IV presents the values of the Seiler parameter and other analogous parameters for ACN and PNC at 25.0 °C, calculated from different rational partition coefficients showed in Table II. Partitioning

systems 1 and 2 were chosen based on their respective hydrogen bonding capabilities: ROH: H-donor and H-acceptor, IPM: H-acceptor, CHL: H-donor, CH: aprotic (neither H--donor or H-acceptor). Then, the difference obtained between systems 1 and 2 will be the resultant hydrogen bonding capability. For example, for $\Delta\log K_{IPM/W}$ parameter, the resultant H-bonding effect is that of an H-acceptor because IPM is H-acceptor, while CH is aprotic without capability of establishing H-bonds.

CH is an aprotic solvent not able to form hydrogen bonds either as donor or acceptor and therefore acts only by non-specific interactions (London forces). However, ROH using the hydroxyl group can be a hydrogen acceptor and/or donor, and moreover, its alkyl chain permits structural immobilization of solutes due to the tetrahedral microstructure adopted in saturation by this solvent in contrast to the CH behavior (1, 14). $\Delta\log K_{ROH/W}$ includes the contributions by hydrogen bonding and by structural immobilization to the partitioning (in this analysis, the non-specific interactions are considered similar for all organic solvents and drugs).

$\Delta\log K_{IPM/W}$ allows to estimate the contribution of the solvent as a hydrogen bonding acceptor in IPM/W rational partitioning. Comparison of the Seiler parameter ($\Delta\log K_{ROH/W}$) with $\Delta\log K_{IPM/W}$ shows that the octanol, besides contributing to the drug partitioning as hydrogen acceptor, may also contribute as hydrogen donor; therefore $\Delta\log K_{IPM/W}$ values are lower than the Seiler parameters. The third parameter, $\Delta\log K'_{ROH/W}$, was calculated and it compares the ROH/W and IPM/W partition coefficients in order to establish the contribution of the organic solvent as hydrogen donor to the partitioning. As already said, CHL acts mainly as hydrogen donor and therefore other two pa-

Table IV. Parameter of Seiler and other analogous parameters for ACN and PNC at 25.0 ± 0.1 °C

Compound	Parameter[a]	System 1	System 2	$\log K^X{}_1$	$\log K^X{}_2$	$\Delta\log K$[b]	Solvent H-bonding character[c]	Solute H-bonding character[c]
ACN	$\Delta\log K_{ROH/W}$	ROH/W	CH/W	1.954	–0.804	2.758	A, D	D, A
	$\Delta\log K_{IPM/W}$	IPM/W	CH/W	1.495	–0.804	2.299	A	D
	$\Delta\log K_{CHL/W}$	CHL/W	CH/W	1.459	–0.804	2.263	D	A
	$\Delta\log K'_{ROH/W}$	ROH/W	IPM/W	1.954	1.495	0.458	D	A
	$\Delta\log K''_{ROH/W}$	ROH/W	CHL/W	1.954	1.459	0.494	A	D
PNC	$\Delta\log K_{ROH/W}$	ROH/W	CH/W	2.301	–0.673	2.973	A, D	D, AA
	$\Delta\log K_{IPM/W}$	IPM/W	CH/W	1.582	–0.673	2.255	A	D
	$\Delta\log K_{CHL/W}$	CHL/W	CH/W	2.076	–0.673	2.748	D	AA
	$\Delta\log K'_{ROH/W}$	ROH/W	IPM/W	2.301	1.582	0.718	D	AA
	$\Delta\log K''_{ROH/W}$	ROH/W	CHL/W	2.301	2.076	0.225	A	D

[a] Expressed in mole fraction.
[b] $\Delta\log K = \log K1 - \log K2$.
[c] A – acceptor of hydrogen, D – donor of hydrogen.

rameters were calculated in order to analyze the contribution of this kind of interaction to the partitioning of drugs. $\Delta\log K_{CHL/W}$ allows to observe the possible contribution of the organic solvent as hydrogen donor, while $\Delta\log K''_{ROH/W}$ (obtained from ROH/W and CHL/W) allows to evaluate the behavior of the organic solvent as hydrogen acceptor. The results generally show higher $\Delta\log K$ values for PNC than ACN when the drugs act as hydrogen acceptors ($\Delta\log K_{CHL/W}$ and $\Delta\log K'_{ROH/W}$). The respective values are very similar when the drugs act as hydrogen donors using the $\Delta\log K_{IPM/W}$ parameter. This value is slightly higher for ACN, whereas the difference between the drugs is most marked for the $\Delta\log K''_{ROH/W}$ parameter. These results indicate a more acidic character for ACN than for PNC. This acid-base behavior is explained by the effect of the ethoxy group (present in PNC in contrast to ACN). Therefore, the hydrogen acid present in these drugs is the one present in the amide group of both drugs (more acidic for ACN than for PNC). On the other hand, the basic group (hydrogen acceptor) in ACN is the carbonyl moiety in the amide group. For PNC, in addition to carbonyl moiety in the amide group, there is an oxygen atom in the ethoxy group that also acts as hydrogen acceptor. At this point, it is convenient to remember that the previous analysis considered only the effect of hydrogen bonding without considering other kinds of interactions or geometric parameters (such as differences in molecular size).

CONCLUSIONS

From the free energy values for ACN and PNC partitioning, it can be concluded that the transfer of these drugs from aqueous media to organic solvents is spontaneous except for CH. The process of transfer is mainly enthalpy-driven for IPM and CHL while it is entropy-driven for ROH and CH (based on the sign of the thermodynamic functions). This could be explained basically as the difference in hydrogen bonding between the drug and the aqueous and organic solvent. In addition, the respective organizational aspects at molecular level in each phase, which are covered by the entropy contributions, should be taken into account.

The partitioning values obtained confirm the semipolar but mainly lipophilic nature of these drugs. This was previously observed by studying their solubilities in several solvents used in QSAR studies (16, 17), in dioxane-water mixtures (18, 19) and in some useful pharmaceutical cosolvent mixtures, such as ethanol-water, propylene glycol-water and polyethylene glycol-water (unpublished data). It was found that the highest solubility for ACN and PNC was obtained in mixtures rather than pure solvents (18, 19, unpublished data). Finally, similar behavior was obtained in the study of partial molar volumes at infinite dilution for these drugs in ethanol-water binary mixtures (unpublished data), because lower values of this volumetric property were found in mixtures (indicating more solvation) than in water or absolute ethanol. From Seiler and other analogous parameters, it follows that hydrogen bonding plays an important role in the transfer of both drugs.

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REFERENCES

1. G. V. Betageri, A. Nayernama and M. J. Habib, Thermodynamics of partitioning of nonsteroidal anti-inflammatory drugs in the *n*-octanol/buffer and liposome systems, *Int. J. Pharm. Adv*. **1** (1996) 310–319.
2. A. Leo, C. Hansch and D. Elkins, Partition coefficients and their uses, *Chem. Rev*. **71** (1971) 525–616.
3. J. Sangster, *Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry*, John Wiley, Chichester 1997.
4. N. Barker and J. Hadgraft, Facilitated percutaneous absorption: a model system, *Int. J. Pharm*. **8** (1981) 193–202.
5. A. D. Pozzo, G. Donzelli, E. Liggeri and L. Rodriguez, Percutaneous absorption of nicotinic acid derivatives in vitro, *J. Pharm. Sci*. **80** (1991) 54–57.
6. J. Jaiswal, R. Poduri and R. Panchagnula, Transdermal delivery of naloxone: ex vivo permeation studies, *Int. J. Pharm.* **179** (1999) 129–134.
7. C. M. Avila and F. Martínez, Thermodynamics of partitioning of benzocaine in some organic solvent/buffer and liposome systems, *Chem. Pharm. Bull.* **51** (2003) 237–240.
8. F. Martínez, M. Tello and A. Gómez, Organic solvents as partitioning systems in QSAR studies, *Rev. Col. Cienc. Quím. Farm*. **29** (2000) 16–25.
9. G. Cevc, *Lipid Properties as a Basis for Membrane Modeling and Rational Liposome Design*, in *Liposomes Technology* Vol. 1 (Ed. G. Gregoriadis), CRC Press, Boca Raton 1993, p. 21.
10. A. Martin, P. Bustamante and A. H. C. Chun, *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*, 4th ed., Lea & Febiger, Philadelphia 1993, pp 160–161, 174.
11. A. T. Florence and D. Attwood, *Physicochemical Principles of Pharmacy*, 3rd ed., MacMillan Press, London 1998, pp. 183–186.
12. G. L. Perlovich, S. V. Kurkov, A. N. Kinchin and A. Bauer-Brandl, Thermodynamics of solutions III: Comparison of the solvation of (+)-naproxen with other NSAIDs, *Eur. J. Pharm. Biopharm*. **57** (2004) 411–420.
13. G. L. Perlovich, S. V. Kurkov, A. N. Kinchin and A. Bauer-Brandl, Thermodynamics of solutions IV: Solvation of ketoprofen in comparison with other NSAIDs, *J. Pharm. Sci.* **92** (2003) 2502–2511.
14. S. E. DeBolt and P. A. Kollman, Investigation of structure, dynamics, and solvation in 1-octanol and its water-saturated solution: molecular dynamics and free-energy perturbation studies, *J. Am. Chem. Soc*. **117** (1995) 5316–5340.
15. P. Seiler, Interconversion of lipophilicities from hydrocarbon/water systems into the octanol/water system, *Eur. J. Med. Chem. Chim. Ther*. **9** (1974) 473–479.
16. Y. Baena, J. A. Pinzón, H. J. Barbosa and F. Martínez, Estimation of the aqueous solubility of some acetanilide derivatives from octanol-water partition coefficients and entropies of fusion, *Acta Farm. Bonarense* **23** (2004) 33–38.
17. Y. Baena, J. A. Pinzón, H. J. Barbosa and F. Martínez, Temperature-dependence of the solubility of some acetanilide derivatives in several organic and aqueous solvents, *Phys. Chem. Liquids* **42** (2004) 603–613.
18. C. Bustamante and P. Bustamante, Nonlinear enthalpy-entropy compensation for the solubility of phenacetin in dioxane-water solvent mixtures, *J. Pharm. Sci.* **85** (1996) 1109–1111.
19. P. Bustamante, S. Romero, A. Peña, B. Escalera and A. Reillo, Enthalpy-entropy compensation for the solubility of drugs in solvent mixtures: paracetamol, acetanilide, and nalidixic acid in dioxane-water, *J. Pharm. Sci.* **87** (1998) 1590–1596.

Y. Baena *et al.*: Thermodynamic study of the transfer of acetanilide and phenacetin from water to different organic solvents, *Acta Pharm.* **55** (2005) 195–205.

S A Ž E T A K

Termodinamičko ispitivanje prijelaza acetanilida i fenacetina iz vode u organska otapala

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U radu su određeni molarni ($K^{C}_{0/w}$) i razdjelni ($K^{X}_{0/w}$) particijski koeficijenti acetanilida i fenacetina u sustavima oktanol/pufer, *i*-propil-miristat/pufer, kloroform/pufer i cikloheksan/pufer na 25,0, 30,0, 35,0 i 40 °C. U svim slučajevima osim za cikloheksan, vrijednosti $K^{C}_{0/w}$ i $K^{X}_{0/w}$ bile su veće od jedan. To ukazuje da su ova dva lijeka pretežno lipofilna. Gibbsova i van't Hoffova termodinamička analiza su otkrile da je prijelaz tih lijekova iz vode u organska otapala spontan i da su uglavnom pokrenuti entalpijski za *i*-propil-miristat i kloroform te entropijski za oktanol i cikloheksan.

Ključne riječi: acetanilid, fenacetin, particijski koeficijent, termodinamika

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