VITAE, REVISTA DE LA FACULTAD DE QUÍMICA FARMACÉUTICA
ISSN 0121-4004 Volumen 15 número 1, año 2008.
Universidad de Antioquia, Medellín, Colombia. págs. 132-140

THERMODYNAMIC ASPECTS OF SOLVATION AND DILUTION FOR ACETANILIDE AND PHENACETIN IN SOME AQUEOUS AND ORGANIC SOLVENTS MUTUALLY SATURATED

ASPECTOS TERMODINÁMICOS DE LA SOLVATACIÓN Y LA DILUCIÓN DE ACETANILIDA Y FENACETINA EN ALGUNOS SOLVENTES ORGÁNICOS Y ACUOSOS MUTUAMENTE SATURADOS

Yolima BAENA A.[1], Edgar F. VARGAS E.[2], Fleming MARTÍNEZ R.[1*]

Recibido: Febrero 6 de 2008 Aceptado: Abril 22 de 2008

ABSTRACT

Acetanilide (ACN) and phenacetin (PNC) are compounds structurally related with acetaminophen widely used as model drugs in pharmaceutical chemistry. Based on published thermodynamic quantities for dissolution, partitioning and sublimation of ACN and PNC, at 25.0 °C, thermodynamic quantities for drugs solvation in cyclohexane-saturated water ($W_{(CH)}$) and water-saturated cyclohexane ($CH_{(W)}$), chloroform-saturated water ($W_{(CLF)}$) and water-saturated chloroform ($CLF_{(W)}$), and isopropyl myristate-saturated water ($W_{(IPM)}$) and water-saturated isopropyl myristate ($IPM_{(W)}$), as well as the drugs dilution in the organic solvents were calculated. The Gibbs energies of solvation were favourable in all cases. Respective enthalpies and entropies were negative indicating an enthalpy-driving for the solvation process in all cases. Otherwise, the Gibbs energies of dilution were favourable for ACN and PNC in $IPM_{(W)}$ but unfavourable in the other organic solvents, whereas the respective enthalpies and entropies were negative for both drugs in all the organic solvents, except for PNC in $CH_{(W)}$ indicating enthalpy-driving for the dilution process in the former cases and entropy-driving for the later. From obtained values for the transfer processes, an interpretation based on solute-solute and solute-solvent interactions was developed.

Keyword: Acetanilide, phenacetin, solvation, dilution, partition coefficient, organic solvents, solution thermodynamics

RESUMEN

La acetanilida (ACN) y la fenacetina (FNC) son dos compuestos estructuralmente relacionados con el acetaminofeno que son ampliamente utilizados en química farmacéutica como fármacos modelo. Con base en valores termodinámicos publicados para los procesos de disolución, reparto y sublimación de la ACN y la FNC, presentados a 25,0 °C, se calculan las funciones termodinámicas de solvatación de los dos fármacos en agua saturada de ciclohexano ($W_{(CH)}$), ciclohexano saturado de agua ($CH_{(W)}$), agua saturada de cloroformo ($W_{(CLF)}$), cloroformo saturado de agua ($CLF_{(W)}$), agua saturada de miristato de isopropilo ($W_{(MIP)}$) y miristato de isopropilo saturado de agua ($MIP_{(W)}$), así como las respectivas funciones

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

2 Departamento de Química, Universidad de los Andes, Bogotá D.C., Colombia.

* Autor a quien se debe dirigir la correspondencia: fmartinezr@unal.edu.co

termodinámicas de los fármacos en los solventes orgánicos. Las energías libres de Gibbs de solvatación son favorables en todos los casos. Las respectivas entalpías y entropías son negativas indicando una conducción entálpica para el proceso de solvatación en todos los casos. De otro lado, las energías libres de dilución son favorables para ACN y PNC en $MIP_{(W)}$ pero desfavorables en los otros solventes orgánicos, mientras que las respectivas entalpías y entropías son negativas para los dos fármacos en todos los solventes orgánicos, excepto para PNC en $CH_{(W)}$, lo que indica que el proceso de dilución es conducido entálpicamente en los primeros casos y entrópicamente en el último. A partir de los valores termodinámicos obtenidos para los procesos de transferencia se desarrolla una interpretación en términos de interacciones soluto-soluto y soluto-solvente.

Palabras clave: Acetanilida, fenacetina, solvatación, dilución, coeficiente de reparto, solventes orgánicos, termodinámica de soluciones.

INTRODUCTION

Phenacetin (PNC) was used as analgesic and antipyretic drug long time ago but it was removed from the market because it can induce nephropathy and cancer. Otherwise, acetanilide (ACN) is mainly used as an intermediate in the synthesis of some drugs and dyes (1). Both compounds have a good molecular similarity between them as it can be seen in Table 1.

On the other hand, as useful information in medicinal chemistry, the thermodynamics of transfer of drug compounds can be studied by measuring the partition coefficient and/or solubility as a function of temperature. Such data can be used for the prediction of absorption, membrane permeability, and *in vivo* drug distribution (2).

Semi-polar solvents have been found to yield better correlations with partitioning of solutes obtained in model membranes compared to non-polar solvents such as cyclohexane (CH), which interacts only by non-specific 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 (3). Isopropyl myristate (IPM) has also been used acting as a hydrogen acceptor as well, and it has been used especially for determining drug hydrophobic constants since it simulates most closely the corneum stratum/water partition. IPM is best related to skin/transdermal absorption because its polar/non-polar balance simulates the complex nature (polar/non-polar matrix) of the skin (4-6). Moreover, chloroform (CLF) has also been used in these kinds of studies since it acts mainly as a hydrogen donor for establishing hydrogen bonds with Lewis basic solutes (7). Thus, the effect of hydrogen bonding on partitioning would be studied completely.

As a contribution to systematization of physicochemical information about drugs' transfer properties, the main goal of this study was to analyze the solvation and dilution behavior of ACN and PNC in the cyclohexane/water (CH/W), chloroform/water (CLF/W) and isopropyl myristate/water (IPM/W) systems by employing a thermodynamic approach based on solubility (7), partitioning (8) and sublimation processes (1). From the obtained values of the corresponding thermodynamic quantities of drugs' transfer, an interpretation based on solute-solvent and solvent-solvent interactions was developed.

Theoretical

The partition coefficient expressed in molality ($K^{m}_{o/w}$), for any solute between organic and aqueous phases is calculated by means of:

$$K^{m}_{o/w} = W_w \frac{C_1 - C_2}{C_2 W_o} \qquad (1)$$

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 solute (usually in $\mu g\ mL^{-1}$) before and after the transfer of solute from the aqueous phase to the organic medium, respectively (2). If the drug concentrations in both phases are lower than 10^{-4} mol Kg^{-1}, the rational partition coefficients ($K^{X}_{o/w}$, expressed in mole fraction) are calculated from $K^{m}_{o/w}$ values as:

$$K^{X}_{o/w} = K^{m}_{o/w}(M_o / M_w) \qquad (2)$$

where, M_o and M_w are the molar masses of the organic and aqueous phases, respectively (9).

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

$$\Delta G^{0X}_{w\to o} = -RT \ln K^{X}_{o/w} \quad (3)$$

Otherwise, the enthalpy change for the transfer may be obtained indirectly by means of the analysis of the temperature-dependence for partitioning by using the van't Hoff method. This procedure permits to obtain the standard enthalpy change ($\Delta H^{0X}_{w\to o}$) from:

$$\left(\frac{\partial \ln K^{X}_{o/w}}{\partial(1/T)}\right)_{P} = -\frac{\Delta H^{0X}_{w\to o}}{R} \quad (4)$$

Therefore, $\Delta H^{0X}_{w\to o}$ is determined from the slope of a weighted 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:

$$\Delta S^{0X}_{w\to o} = \frac{\Delta H^{0X}_{w\to o} - \Delta G^{0X}_{w\to o}}{T} \quad (5)$$

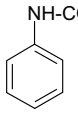
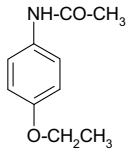
The thermodynamic functions $\Delta H^{0X}_{w\to o}$ and $\Delta S^{0X}_{w\to o}$ represent the standard changes in enthalpy and entropy, respectively, when one mole of drug is transferred from the aqueous medium to the organic system at infinite dilution expressed in the mole fraction scale (2).

On the other hand, for the dissolution process of drugs some equations similar to 3, 4 and 5 have been used for calculating the respective thermodynamic functions. In this case, X_2 is used instead of $K^{X}_{o/w}$ (7).

RESULTS AND DISCUSSION

All the experimental values of solubility, partitioning and sublimation for the evaluated drugs have been taken from the literature (1, 7, 8). The molecular structure and some physicochemical properties of the drugs are summarized in Table 1 (1, 10). The solubility in water and the ROH/W partitioning was determined at pH 7.4 (resembling the blood physiological value). At this pH value both compounds are present mainly in their molecular form without dissociation and therefore they have their lowest aqueous solubility and highest partitioning.

Table 1. Some physicochemical properties of the drugs studied.

Drug	Molecular structure [a]	M / g mol^{-1} [a]	ΔH_{fus} / kJ mol^{-1} [b]	T_{fus} / K [b]
ACN		135.16	21.2 (0.5)	386.1 (0.2)
PNC		179.21	31.3	407.2

[a] From Budavari *et al.* (10); [b] From Perlovich *et al.* (1).

Thermodynamics of dissolution and solvation at saturation

Table 2 summarizes the thermodynamic functions relative to dissolution processes in cyclohexane-saturated water ($W_{(CH)}$), water-saturated cyclohexane ($CH_{(W)}$), chloroform-saturated water ($W_{(CLF)}$), water-saturated chloroform ($CLF_{(W)}$), isopropyl myristate-saturated water ($W_{(IPM)}$) and water-saturated isopropyl myristate ($IPM_{(W)}$) which were taken from the literature (7).

The solution process may be represented by the following hypothetic stages (11):

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

where, the respective partial processes toward the solution are solute sublimation and solvation, which permits calculate the partial thermodynamic contributions to solution process by means of equations 6 and 7, respectively, whereas the free energy of solvation is calculate by means of Eq. 8:

$$\Delta H^{0}_{\text{soln}} = \Delta H^{0}_{\text{subl}} + \Delta H^{0}_{\text{solv}} \quad (6)$$

$$\Delta S^{0}_{\text{soln}} = \Delta S^{0}_{\text{subl}} + \Delta S^{0}_{\text{solv}} \quad (7)$$

$$\Delta G^{0}_{\text{soln}} = \Delta G^{0}_{\text{subl}} + \Delta G^{0}_{\text{solv}} \quad (8)$$

The ΔH^0_{subl} values presented in Table 3 were taken from Perlovich et al. (1), and therefore, the function ΔH^0_{solv} was calculated from ΔH^0_{soln} values presented in Table 2.

Table 2. Thermodynamic quantities for drugs dissolution processes in the aqueous and organic media at 25.0 °C [(a)].

ACN				
Solvent	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}**
$W_{(CH)}$	17.64 (0.01)	21.3 (1.4)	12.2 (0.8)	3.6 (0.2)
$W_{(IPM)}$	17.63 (0.04)	28.5 (2.6)	36 (3)	10.7 (0.9)
$W_{(CLF)}$	17.84 (0.01)	29.7 (1.6)	39.7 (2.2)	11.8 (0.7)
$CH_{(W)}$	21.60 (0.04)	69 (5)	159 (11)	47.4 (3.3)
$IPM_{(W)}$	9.16 (0.03)	21.2 (0.5)	40.2 (0.9)	12.0 (0.3)
$CLF_{(W)}$	4.75 ((0.04)	34.0 (1.9)	98 (6)	29.2 (1.8)
PNC				
Solvent	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}**
$W_{(CH)}$	22.98 (0.02)	44 (4)	69 (6)	20.6 (1.8)
$W_{(IPM)}$	22.98 (0.03)	24.4 (2.6)	4.8 (0.5)	1.43 (0.15)
$W_{(CLF)}$	22.79 (0.06)	18.0 (1.4)	–15.9 (1.3)	–4.7 (0.4)
$CH_{(W)}$	25.44 (0.01)	81.0 (1.2)	186 (3)	55.6 (0.9)
$IPM_{(W)}$	14.12 (0.02)	30.2 (2.0)	54 (4)	16.1 (1.2)
$CLF_{(W)}$	8.22 (0.01)	27.3 (2.8)	64 (7)	19.1 (2.1)

[(a)] From Baena *et al.* (7)

Table 3. Thermodynamic quantities for drugs sublimation processes at 25.0 °C [(a)].

Drug	ΔG^0_{subl} / kJ mol^{-1}	ΔH^0_{subl} / kJ mol^{-1}	ΔS^0_{subl} / J mol^{-1} K^{-1}	$T\Delta S^0_{subl}$ / kJ mol^{-1}
ACN	40.5	99.8 (0.8)	197 (2)	58.7 (0.6)
PNC	52.3	121.8 (0.7)	226 (2)	67.4 (0.6)

[(a)] From Perlovich *et al.* (1).

In Table 4 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, the equations 9 and 10 were employed.

$$\%\zeta_H = 100\frac{\left|\Delta H^{0X}_{solv}\right|}{\left|\Delta H^{0X}_{solv}\right| + \left|T\Delta S^{0X}_{solv}\right|} \quad (9)$$

$$\%\zeta_{TS} = 100\frac{\left|T\Delta S^{0X}_{solv}\right|}{\left|\Delta H^{0X}_{solv}\right| + \left|T\Delta S^{0X}_{solv}\right|} \quad (10)$$

From the values of $\%\zeta_H$ and $\%\zeta_{TS}$ presented in Table 4 it follows that the main contributing force to standard free energy of the solvation process of these drugs in all the solvents is the enthalpy, especially for PNC in $CH_{(W)}$ ($\%\zeta_H$ is 77.6 %).

Because not only the main driving force of solvation process of drug compounds is important, but also the balance between specific and non-specific solute-solvent interactions as well, therefore parameters which describe the relative ratio of specific and non-specific 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. (12):

$$\%\varepsilon_H = 100\left|\frac{\Delta H^0_{spec}}{\Delta H^0_{non-spec}}\right| \quad (11)$$

$$\%\varepsilon_S = 100\left|\frac{\Delta S^0_{spec}}{\Delta S^0_{non-spec}}\right| \quad (12)$$

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

Table 4. Thermodynamic quantities for drugs solvation processes in the aqueous and organic media at 25.0 °C obtained by considering the solubility behavior.

ACN								
Solvent	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**	**%ζ_{TS}**	**%ε_H**	**%ε_S**
$W_{(CH)}$	–22.9	–78.5 (1.6)	–185 (2)	–55.1 (0.6)	58.8	41.2	154.9	92.3
$W_{(IPM)}$	–22.9	–71.3 (2.7)	–161 (4)	–48.0 (1.2)	59.8	40.2	131.5	77.4
$W_{(CLF)}$	–22.7	–70.1 (1.8)	–157 (3)	–46.9 (0.9)	59.9	40.1	127.6	75.0
$CH_{(W)}$	–18.9	–31 (5)	–38 (11)	–11.3 (3.2)	73.1	26.9	0.0	0.0
$IPM_{(W)}$	–31.3	–78.6 (0.9)	–157 (2)	–46.7 (0.6)	62.7	37.3	155.2	74.7
$CLF_{(W)}$	–35.8	–65.8 (2.1)	–99 (6)	–29.5 (1.8)	69.0	31.0	113.6	38.4
PNC								
Solvent	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**	**%ζ_{TS}**	**%ε_H**	**%ε_S**
$W_{(CH)}$	–29.3	–78 (4)	–157 (6)	–46.8 (1.8)	62.4	37.6	90.7	63.0
$W_{(IPM)}$	–29.3	–97.4 (2.7)	–221.2 (2)	–66.0 (0.6)	59.6	40.4	138.7	97.4
$W_{(CLF)}$	–29.5	–103.8 (1.6)	–242 (2)	–72.1 (0.6)	59.0	41.0	154.4	108.5
$CH_{(W)}$	–26.9	–40.8 (1.4)	–40 (4)	–11.8 (1.2)	77.6	22.4	0.0	0.0
$IPM_{(W)}$	–38.2	–91.6 (2.1)	–172 (5)	–51.3 (1.5)	64.1	35.9	124.5	71.0
$CLF_{(W)}$	–44.1	–94.5 (2.9)	–162 (7)	–48.3 (2.1)	66.2	33.8	131.6	65.7

Cyclohexane was chosen as an "inert" solvent, which interacts with drug molecules solely by nonspecific interactions (dispersion forces), while the water and the other organic solvents interact with these drugs by specific interactions such as hydrogen bonding. Solution thermodynamics data for the drugs in CH are presented in Table 2.

The $\%\varepsilon_H$ and $\%\varepsilon_S$ values for the drugs' solvation are also presented in Table 4. These values indicate that during dissolution of these drugs in all the saturated solvents studied, the specific solute-solvent interactions (hydrogen bonding, mainly) effectively affect the entropic term of Gibbs free energy with respect to non-specific interactions, especially for PNC in $W_{(CLF)}$ ($\%\varepsilon_S$ 108.5 %), although it is also significant for all the other systems ($\%\varepsilon_S$ greater than 63.0 % in almost all cases), except for ACN in $CLF_{(W)}$ ($\%\varepsilon_S$ 38.4 %). With regard to the enthalpic term the specific solute-solvent interactions predominate for both drugs in all the solvents ($\%\varepsilon_H > 113.6$ % in almost all cases), except for PNC in $W_{(CH)}$ although it is also important ($\%\varepsilon_H$ 90.7 %).

Thermodynamics of transfer according to partitioning

Table 5 summarizes the thermodynamic functions relative to transfer processes of the drugs from aqueous medium up to octanol phase taken from Baena et al. (8). The Gibbs free energy of transfer are favorable for both drugs from aqueous media up to $IPM_{(W)}$ and $CLF_{(W)}$, whereas it is unfavorable for both drugs from $W_{(CH)}$ up to $CH_{(W)}$.

Table 5. Thermodynamic quantities for drugs transfer processes from water to organic media at 25.0 °C obtained from partitioning [(a)].

ACN				
System	$\Delta G^0_{w\to o}$ / **kJ mol^{-1}**	$\Delta H^0_{w\to o}$ / **kJ mol^{-1}**	$\Delta S^0_{w\to o}$ / **J mol^{-1} K^{-1}**	$T\Delta S^0_{w\to o}$ / **kJ mol^{-1}**
CH/W	4.60 (0.02)	34 (4)	98 (12)	29.2 (3.6)
IPM/W	–8.53 (0.09)	–32 (4)	–79 (9)	–23.6 (2.7)
CLF/W	–8.33 (0.04)	–12.5 (1.3)	–14.0 (1.5)	–4.2 (0.4)
PNC				
System	$\Delta G^0_{w\to o}$ / **kJ mol^{-1}**	$\Delta H^0_{w\to o}$ / **kJ mol^{-1}**	$\Delta S^0_{w\to o}$ / **J mol^{-1} K^{-1}**	$T\Delta S^0_{w\to o}$ / **kJ mol^{-1}**
CH/W	3.84 (0.02)	47.8 (2.2)	147 (7)	43.8 (2.1)
IPM/W	–9.03 (0.02)	–18.7 (2.3)	–32 (4)	–9.5 (1.2)
CLF/W	–11.80 (0.07)	–6.5 (0.5)	18.0 (1.4)	5.4 (0.4)

[(a)] From Baena *et al.* (8).

Both the enthalpic and entropic changes of transfer imply respectively, all the energetic requirements and the molecular randomness (increase or decrease in the molecular disorder), involved in the net transfer of the drugs 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.

Since initially the drugs are present only in water, then, it is necessary to create a cavity in the organic medium in order to accommodate the solute after the transfer process. This is an endothermic event, since 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 due to solute-organic solvent interactions. This event would imply an entropy increase in this medium due to the associated mixing process.

In turn, after a certain number of solute molecules have migrated 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 have been now 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 keep in mind 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 due to the separation of some water molecules which originally were associated among them by hydrogen bonding (13).

From Table 5 it can be observed that for both drugs, the transfer processes from water up to $IPM_{(W)}$ and $CLF_{(W)}$ were exothermic and negentropic (except for PNC in CLF/W, in which case is exothermic and entropic positive), whereas it was endothermic and entropic positive for both drugs from water up to $CH_{(W)}$. In principle, it could be said that the obtained values in enthalpy and entropy for both drugs in the CH/W system are due mainly to disruption of water-icebergs present around the hydrocarbon groups of these drugs (methyl, ethyl, and/or phenyl groups), and on the other hand, the creation of a cavity in the organic solvent to accommodate the solute. Both events, as was already said, imply an energy intake and a disorder increase at the molecular level. Nevertheless, it is necessary to keep in mind that any other experimental information is required, such as spectral analyses, in order to fully explain the thermodynamic values obtained in terms of intermolecular interactions

For those solvents in which $\Delta H^0_{w\to o}$ and $\Delta S^0_{w\to o}$ were negative, these values could be explained in terms of a possible organization in the water-saturated solvent due to the replacement of some solvent molecules by drug molecules. The previous event could release energy and compensate the molecular disorder produced by the drug-organic solvent mixing process, in addition to the energy intake required in the aqueous media to separate the water molecules present around the non polar groups of these drugs. Unfortunately, no information about the structural properties for these water-saturated organic solvents is available at the moment (as it is available in the literature for water-saturated octanol (3, 14)), and therefore, it is not possible to explain these interesting results at the molecular level.

Thermodynamics of solvation according to partitioning

According to Katz and Diamond (15), the values of thermodynamic functions of partitioning, $\Delta G^{0X}_{w\to 0}$, $\Delta H^{0X}_{w\to 0}$ and $\Delta S^{0X}_{w\to 0}$, depend both upon interactions between drug and water and upon interactions between drug and organic medium. In order to obtain quantities that can be discussed solely in terms of drug-organic medium interactions, the contributions of drug-water must be removed. This can be accomplished by referring to hypothetic processes presented in Fig. 1:

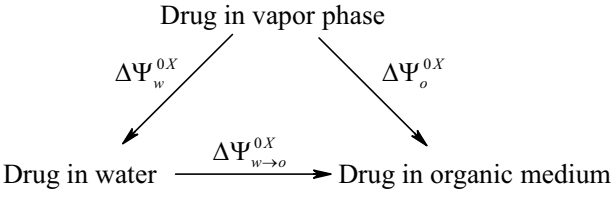


Figure 1. Transfer processes of drugs between water, organic medium, and vapor phase.

in which, Ψ^{0X}, stands for any thermodynamic function whose change can be measured when one mole of drug is transferred between water,

organic medium and the vapor phase. The term $\Delta\Psi_w^{0X}$ represents the standard Gibbs free energy, enthalpy, or entropy of solvation of drug in water, while the term $\Delta\Psi_o^{0X}$ represents correspondingly the standard Gibbs free energy, enthalpy, or entropy of solvation of drug in organic medium. From this, the following equations can be stated:

$$\Delta\Psi_{w\to o}^{0X} = \Psi_o^{0X} - \Psi_w^{0X} \quad (13)$$

$$\Delta\Psi_o^{0X} = \Psi_o^{0X} - \Psi_v^{0X} \quad (14)$$

$$\Delta\Psi_w^{0X} = \Psi_w^{0X} - \Psi_v^{0X} \quad (15)$$

where, Ψ_v^{0X} is the respective thermodynamic value of the function in the vapor phase. The $\Delta\Psi_{w\to o}^{0X}$ values for the drugs obtained from partitioning experiments are presented in Table 5. On the other hand, the $\Delta\Psi_w^{0X}$ values of solvation for these drugs in the organic solvents-saturated water are presented in Table 4. From these values, the $\Delta\Psi_o^{0X}$ values were calculated by means of Eq. 16:

$$\Delta\Psi_o^{0X} = \Delta\Psi_{w\to o}^{0X} + \Delta\Psi_w^{0X} \quad (16)$$

Table 6 shows the standard thermodynamic functions of solvation of the drugs in all the organic solvents obtained by considering the partitioning processes. In all cases, the $\Delta G_{\text{solv}}^{0X}$, $\Delta H_{\text{solv}}^{0X}$, and $\Delta S_{\text{solv}}^{0X}$ values were negative. These results as well as those presented in Table 4 indicate the preference of these drugs by the organic media respect to its vapor phase independently of their concentrations (at saturation in solubility and highly diluted in partitioning), and also indicate that the solvation processes are enthalpy driven. Because the $\Delta S_{\text{solv}}^{0X}$ values were negative, this implies a diminishing in the molecular randomness by the passing of drug molecules from vapor state to these liquid media. According to $\%\zeta_H$ and $\%\zeta_{TS}$ values presented in Table 4, the enthalpy is the main property contributing to solvation process in all media, including the aqueous phase.

Table 6. Thermodynamic quantities for drugs solvation processes in the organic solvents at 25.0 °C obtained by considering the partitioning behavior.

ACN				
Solvent	ΔG_{solv}^0 / **kJ mol^{-1}**	ΔH_{solv}^0 / **kJ mol^{-1}**	ΔS_{solv}^0 / **J mol^{-1} K^{-1}**	$T\Delta S_{\text{solv}}^0$ / **kJ mol^{-1}**
$CH_{(W)}$	–18.3	–45 (4)	–87 (12)	–25.9 (3.6)
$IPM_{(W)}$	–31.4	–103 (4)	–240 (9)	–71.6 (2.7)
$CLF_{(W)}$	–31.0	–82.6 (1.5)	–171 (3)	–51.1 (0.9)
PNC				
Solvent	ΔG_{solv}^0 / **kJ mol^{-1}**	ΔH_{solv}^0 / **kJ mol^{-1}**	ΔS_{solv}^0 / **J mol^{-1} K^{-1}**	$T\Delta S_{\text{solv}}^0$ / **kJ mol^{-1}**
$CH_{(W)}$	–25.5	–30.0 (2.3)	–10 (7)	–3.0 (2.1)
$IPM_{(W)}$	–38.4	–116.1 (2.4)	–253 (4)	–75.5 (1.2)
$CLF_{(W)}$	–41.3	–97.3 (0.9)	–224 (4)	–66.8 (1.2)

Dilution thermodynamics based on dissolution and partitioning

Another interesting process is the drug dilution in the organic solvents. The respective thermodynamic functions ($\Delta\Psi_{\text{dilution}}^0$) are calculated according to:

$$\Delta\Psi_{\text{dilution}}^0 = \Delta\Psi_{\text{solv(Part)}}^0 - \Delta\Psi_{\text{solv(Solub)}}^0 \quad (17)$$

where, $\Delta\Psi_{\text{solv(Part)}}^0$ and $\Delta\Psi_{\text{solv(Solub)}}^0$ are the thermodynamic quantity of solvation in the organic solvents obtained from partitioning and dissolution processes (Tables 5 and 4), respectively. Table 7 shows the equilibrium solubilities and the drugs concentrations obtained in the organic media after the partitioning equilibria. The later values were calculated based on experimental details described in the literature (8).

Table 7. Drugs concentrations expressed in mole fraction in the organic media after dissolution (solubility) or partitioning, and drugs dilution factors.

Solvent	ACN			PNC		
	Solubility [a]	Partition	Dil. fact. [b]	Solubility [a]	Partition	Dil. fact. [b]
$CH_{(W)}$	1.63×10^{-4}	1.71×10^{-7}	203	3.46×10^{-5}	1.96×10^{-7}	177
$IPM_{(W)}$	0.0242	2.97×10^{-5}	653	0.0194	2.39×10^{-5}	810
$CLF_{(W)}$	0.1419	3.02×10^{-5}	1153	0.0348	7.68×10^{-5}	453

[a] From Baena *et al.* (7)
[b] Calculated as the quotient Solubility/Concentration after partitioning.

Based on the equilibrium solubility and the final concentrations in the organic solvents obtained after partitioning the hypothetic drugs dilutions varies from 177 for PNC in $CH_{(W)}$ up to 1153 for ACN in $CLF_{(W)}$. These dilution factors are also presented in Table 7.

Table 8 shows the respective thermodynamic quantities for the drugs' dilution processes in all organic media.

Table 8. Thermodynamic quantities for drugs dilution processes in the organic solvents at 25.0 °C obtained by considering the solubility and partitioning behavior.

ACN				
Solvent	ΔG^0_{dilut} / kJ mol^{-1}	ΔH^0_{dilut} / kJ mol^{-1}	ΔS^0_{dilut} / J mol^{-1} K^{-1}	$T\Delta S^0_{dilut}$ / kJ mol^{-1}
$CH_{(W)}$	0.63 (0.04)	–14 (6)	–49 (16)	–14.5 (4.8)
$IPM_{(W)}$	–0.06 (0.09)	–25 (4)	–83 (9)	–24.8 (2.7)
$CLF_{(W)}$	4.76 (0.08)	–16.8 (2.3)	–72 (6)	–21.6 (1.8)
PNC				
Solvent	ΔG^0_{dilut} / kJ mol^{-1}	ΔH^0_{dilut} / kJ mol^{-1}	ΔS^0_{dilut} / J mol^{-1} K^{-1}	$T\Delta S^0_{dilut}$ / kJ mol^{-1}
$CH_{(W)}$	1.38 (0.02)	10.8 (2.5)	30 (8)	8.8 (2.4)
$IPM_{(W)}$	–0.17 (0.03)	–25 (3)	–81 (6)	–24.2 (1.8)
$CLF_{(W)}$	2.77 (0.07)	–15.8 (2.8)	–62 (7)	–18.5 (2.1)

The dilution process essentially implies the diminishing in solute-solute interactions with the respective predominance of solute-solvent interactions as well as the solvent-solvent interactions. According to Table 8 the Gibbs energies of dilution were favourable for both drugs in $IPM_{(W)}$ ($\Delta G^0_{dilut} < 0$) but unfavourable for the other organic solvents ($\Delta G^0_{dilut} > 0$); whereas the respective enthalpies and entropies were negative for both drugs in almost all solvents indicating enthalpy-driving for the dilution processes, except for PNC in $CH_{(W)}$ which is entropy-driving. As was already said, because no information about the structural properties for these water-saturated organic solvents is available at the moment, then it is not possible to explain these results at molecular level. Otherwise, because energy must be supplied in order to overcome the solute-solute interactions during the dilution process, then, the drugs' partial enthalpy and entropy increases as well; whereas, the increase in the solvent-solvent interactions caused by the drug dilution process implies either a decrease in the solvent partial enthalpy and entropy.

The thermodynamic values for the dilution processes presented in Table 8 correspond to the net result obtained by considering the partial contributions of solute-solute and solvent-solvent interactions, as well. Nevertheless, in order to clarify and understand the specific interactions presented between these drugs and all the organic solvents studied, it would be very important to dispose information about UV, IR and NMR spectral data, and DSC and dissolution calorimetric values, among others.

CONCLUSIONS

From the previously exposed analysis, in general terms it could be concluded that these drugs have mainly a lipophilic behavior but in turn they are not certainly hydrophobic drugs because the partitioning was greater for $IPM_{(W)}$ and $CLF_{(W)}$ compared with $CH_{(W)}$. Otherwise, they are greatly solvated in the organic solvents having H-bonding acceptor or donor ability. Although these drugs have great affinity for the $IPM_{(W)}$ and $CLF_{(W)}$ phases great differences in the possible mechanisms of transfer from the aqueous medium up to the organic solvent are found among them. These results are consequence of their successive substitutions on the phenyl ring passing from ACN to PNC by replace an hydrogen atom by an ethoxyl group, which in turn, changes the molar volumes and the H-bonding properties.

REFERENCES

1. Perlovich GL, Volkova TV, Bauer-Brandl A. Towards an understanding of the molecular mechanism of solvation of drug molecules: a thermodynamic approach by crystal lattice energy, sublimation, and solubility exemplified by paracetamol, acetanilide, and phenacetin. J Pharm Sci 2006; 95(10): 2158-2169.
2. Mora CP, Martínez F. Thermodynamic study of partitioning and solvation of (+)-naproxen in some organic solvent/buffer and liposome systems. J Chem Eng Data 2007; 52(5): 1933-1940.
3. Sangster J. Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry. Chichester: John Wiley & Sons; 1997.
4. Barker N, Hadgraft J. Facilitated percutaneous absorption: a model system. Int J Pharm 1981; 8: 193-202.
5. Dal Pozzo A, Donzelli G, Liggeri E, Rodriguez L. Percutaneous absorption of nicotinic acid derivatives in vitro. J Pharm Sci 1991; 80(1): 54-57.
6. Jaiswal J, Poduri R, Panchagnula R. Transdermal delivery of naloxone: ex vivo permeation studies. Int J Pharm 1999; 179: 129-134.
7. Baena Y, Pinzón JA, Barbosa H, Martínez F. Temperature dependence of the solubility of some acetanilide derivatives in several organic and aqueous solvents. Phys Chem Liquids 2004; 42(6): 603-613.
8. Baena Y, Pinzón J, Barbosa H, Martínez F. Thermodynamic study of transfer of acetanilide and phenacetin from water to organic solvents. Acta Pharm 2005; 55(2): 195-205.
9. Diamond JM, Katz Y. Interpretation of nonelectrolyte partition coefficients between dimyristoyl lecithin and water. J Membrane Biol 1974; 17(1): 121-154.
10. Budavari S, O'Neil MJ, Smith A, Heckelman PE, Obenchain Jr. JR, Gallipeau JAR, D'Arecea MA. (2001) The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals. 13 ed. Whitehouse Station (NJ): Merck & Co., Inc.; 2001.
11. Mora CP. Martínez F. Solubility of naproxen in several organic solvents at different temperatures. Fluid Phase Equilibria 2007; 255: 70-77.
12. Perlovich GL, Kurkov SV, Kinchin AN, Bauer-Brandl A. Thermodynamics of solutions III: Comparison of the solvation of (+)-naproxen with other NSAIDs. Eur J Pharm Biopharm 2004; 57(2): 411-420.
13. Tanford C. The Hydrophobic Effect: Formation of Micelles and Biological Membranes. New York: John Wiley & Sons; 1973.
14. Mora CP, Lozano HR, Martínez F. Aspectos termodinámicos de la miscibilidad parcial entre el n-octanol y el agua. Rev Bras Cienc Farm 2005; 41(1): 13-26.
15. Katz Y, Diamond JM. Thermodynamic constants for nonelectrolyte partition between dimyristoyl lecithin and water. J Membrane Biol 1974; 17(1): 101-120.