available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevier.com/locate/ejps

The difference between partitioning and distribution from a thermodynamic point of view: NSAIDs as an example

German L. Perlovich[a,b], *Sergey V. Kurkov*[b], *Annette Bauer-Brandl*[a,*]

[a] *University of Tromsø, Institute of Pharmacy, Breivika, N-9037 Tromsø, Norway*
[b] *Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Ivanovo, Russia*

ARTICLE INFO

Article history:
Received 9 May 2005
Received in revised form 17 August 2005
Accepted 6 September 2005
Available online 25 October 2005

Keywords:
Solvation
Driving forces
NSAIDs
Thermodynamic functions
Partitioning/distribution
Ionic and unionic forms
Buffer
n-Octanol

ABSTRACT

Solubility and solvation of some NSAIDs were studied in their non-ionic (aqueous buffers of pH 2.0) and ionic molecular form (pH 7.4) over a wide temperature interval. Absolute scale values for the thermodynamic terms (Gibbs energy, enthalpy and entropy) were obtained. Thermodynamic parameters of the transfer of the molecules from one buffer to the other (representing protonation/deprotonation) were derived. It has been found that the thermodynamic characteristics of solvation (hydration) of (+)- and (±)-IBP in the buffers show a difference, which is larger than the experimental error. This may be explained by differences in the association states of the molecules in solution. For the other NSAIDs studied, a correlation between the Gibbs energy of transfer, ΔG_{tr} (pH 7.4 → pH 2.0) and the pK_a-value, and a compensation effect between the enthalpic and entropic terms have been revealed. Thermodynamic aspects of the transfer process from the buffers to *n*-octanol were analysed. The two types of the transfer processes (non-dissociated molecule to octanol (partitioning), and dissociated form to octanol (distribution)) have essentially different driving forces: partitioning is enthalpy driven, whereas the transfer of the ionic form is entropy driven. The following points are discussed: (a) significance of using water–octanol systems (log*P* as a measure of drug lipophilicity) to describe biological membranes (lipid systems); (b) differences in thermodynamic aspects of the partitioning/distribution processes of these systems; (c) advantages of the present transfer method approach in comparison with temperature dependencies of log*P* to analyse the driving forces of partitioning/distribution.

1. Introduction

Drug transport and delivery in the body, if restricted to passive processes, comprises, amongst others, of absorption of drug molecules, their distribution between different tissues, redistribution from deep compartments, and finally excretion. The named processes are determined by the physicochemical characteristics of the drug molecules, for example their solubility and partitioning properties in water/octanol systems, which represent well recognised and regularly used descriptors. These properties are determined by the solvation abilities of the drug molecules in different environments (compartments). The ratio of the enthalpic and entropic terms of the Gibbs energy determines not only the driving forces of the solvation, but also the mechanisms thereof. A number of works have analysed thermodynamics of solubility and partitioning (for example Rogers and Davis, 1980; Rogers and Wong, 1980; Da et al., 1992). Unfortunately, little has been published about the thermodynamic aspects of drug solvation in terms of absolute scale values. The reason for this is probably the absence

* *Corresponding author*. Tel.: +47 77646160; fax: +47 77646151.
E-mail address: annetteb@farmasi.uit.no (A. Bauer-Brandl).

0928-0987/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2005.09.003

of experimental data on crystal lattice energies of drugs in the literature. In recent studies, we analysed the solvation characteristics of some NSAIDs (non-steroidal anti-inflammatory drugs) (Perlovich and Bauer-Brandl, 2003a, 2004; Perlovich et al., 2003b,c, 2004a,b) and parabens (Perlovich et al., 2005) with respect to these data.

It has been a matter of thorough discussion whether the commonly used water–octanol system (and the partition coefficient in the form of log *P* as a measure of drug lipophilicity) is suitable as a simple model to describe biological membranes with respect to the estimation of passive transport properties (Rogers and Wong, 1980). Furthermore, it is still an open question whether the octanol–water system is at all suitable to describe partitioning/distribution processes in terms of thermodynamic aspects. However, due to the absence of reliable and quantitative experimental data for the solvation characteristics of drug molecules, it has in the past been difficult to clarify this problem. Furthermore, little is known about solvation (in absolute terms) of the dissociated forms of the drug molecules compared to the respective non-dissociated forms. However, this should be particularly important with respect to different degrees of acidity in different compartments of the body, and it will not only affect the rate of absorption of perorally administered drugs from different sections of the gastro-intestine, but also distribution and excretion. It is therefore of high relevance for a better understanding of biopharmaceutical characteristics of drug molecules.

The present work is a continuation of former work on solvation characteristics of some NSAIDs (Perlovich and Bauer-Brandl, 2003a, 2004; Perlovich et al., 2003b,c, 2004a,b, 2005), focussing on dissociated and non-dissociated molecules in aqueous buffers and in *n*-octanol. This approach enables one to find all the thermodynamic functions of the solvation process in order to calculate the driving forces of partitioning/distribution on an absolute energetic scale and, consequently, yield a deeper understanding of the nature of passive transport processes. The present approach to theoretically analyse the driving forces for partitioning/distribution processes (by the outlined transfer method) is essentially different from former approaches where temperature dependencies of partition coefficients were studied (Rogers and Davis, 1980; Rogers and Wong, 1980). It is the present authors' opinion that the main advantage of the new approach is to study "pure" effects of the transferring molecules without interference of mutual solubility of the oil (octanol)- and water phases, which change considerably with temperature (Perlovich and Bauer-Brandl, 2004; Beezer and Hunter, 1983; Kinkel et al., 1981; Da et al., 1992).

2. Experimental

2.1. Materials and solvents

(+)-Ibuprofen ((+)-IBP) (S-(+)-2-(4-isobutylphenyl)propionic acid, $C_{13}H_{18}O_2$, MW 206.3) was purchased from Fluka (lot no. 357891/1), Diflunisal (DIF) (5-[2,4-difluorophenyl]salicylic acid; $C_{13}H_8F_2O_3$, MW 250.2)—from ICN Biomedicals Inc., Aurora Ohio, USA (lot no. 89887), whereas the following drugs were purchased from Sigma Chemical Co., St. Louis, USA: (±)-ibuprofen ((±)-IBP) ((±)-2-(4-isobutylphenyl)propionic acid) (lot no. 26H1368); ketoprofen (KETO) (2-[3-benzoylphenyl]-propionic acid, $C_{16}H_{14}O_3$, MW 254.3) (lot no. 10K1185); flurbiprofen (FBP) ((±)-2-fluoro-α-methyl-4-biphenylacetic acid, $C_{15}H_{13}FO_2$, MW 244.3) (lot no. 38H1398); (+)-naproxen (NAP) (S-6-methoxy-α-methyl-2-naphthaleneacetic acid, $C_{14}H_{14}O_3$, MW 230.3) (lot 120K3657).

The buffer solutions were prepared by mixing solutions of hydrochloric acid and potassium chloride for pH 2.0, and appropriate sodium and potassium salts of phosphoric acid for the pH 7.4, as described elsewhere (Lazarev et al., 1976). All the chemicals were of AR grade. The pH values were controlled using a pH meter (Gomel, Belorussia) standardised with pH 1.68 and 9.22 solutions.

2.2. Solubility determination

All the experiments were carried out by the isothermal saturation method at five temperature points: 20, 25, 30, 37, and 42 ± 0.1 °C. The solid phase was removed by isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size). The experimental results are stated as the average of at least three replicated experiments. The molar solubilities of the drugs were measured spectrophotometrically with an accuracy of 2–2.5% using a protocol described previously (Perlovich and Bauer-Brandl, 2003a).

2.3. Calculation of thermodynamic functions

Standard Gibbs energies of the dissolution processes ΔG°_{sol} were calculated using the following equation:

$$\Delta G^\circ_{sol} = -RT \ln X_2 \quad (1)$$

where X_2 is the drug molar fraction in the saturated solution. The statistical error for repeated experiments was within 3%.

The standard solution enthalpies ΔH°_{sol} were calculated using the van't Hoff equation:

$$\frac{d(\ln X_2)}{dT} = \frac{\Delta H^\circ_{sol}}{RT^2} \quad (2)$$

assuming that the activity coefficients of the considered drugs in the solvents are equal to one and solution enthalpies are independent of concentration. The temperature dependencies of the solubilities of the drugs within the chosen temperature interval can be described by a linear function:

$$\ln X_2 = -A - \frac{B}{T} \quad (3)$$

This indicates that the change in heat capacity of the solutions with the temperature is negligibly small.

The standard solution entropies ΔS°_{sol} were obtained from the well-known equation:

$$\Delta G^\circ_{sol} = \Delta H^\circ_{sol} - T\Delta S^\circ_{sol} \quad (4)$$

Based on the parameters mentioned above and sublimation enthalpies earlier calculated (Perlovich and Bauer-Brandl, 2004), the thermodynamic parameters of solvation (and

hydration, respectively), ΔG°_{solv}, ΔH°_{solv}, $T\Delta S^{\circ}_{solv}$, of the drugs were calculated using the following equation:

$$\Delta Y^{\circ}_{solv} = \Delta Y^{\circ}_{sol} - \Delta Y^{\circ}_{sub} \quad (5)$$

where Y is one of the respective thermodynamic functions H or G.

2.4. Statistical analysis

Regression analysis of the data was performed by standard statistical procedures (least square method).

3. Results and discussion

The thermodynamic cycle of the relationships between the thermodynamic parameters of a drug molecule HD and its dissociate $D^- + H^+$ is shown in Scheme 1. The thermodynamic parameters of solution and solvation are presented in Tables 1 and 2.

3.1. Solvation characteristics of dissociated and non-dissociated (+)- and (±)-IBP

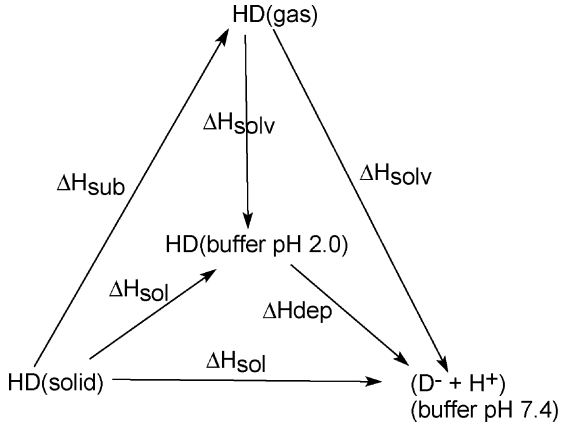
The respective solution enthalpies, ΔH°_{sol}, were calculated using the van't Hoff relationship, which was —in contrast to other works (Dwivedi et al., 1992)—found to be satisfactorily linear. Further it was found that the dissolution of ibuprofen in the buffers, both the racemate and the pure enantiomer, is endothermic (Table 2). Moreover, the values of the entropy of the dissolution process, ΔS°_{sol} (calculated from solubility and enthalpy) are negative. Probably, while a molecule transfers from the solid state into the solution, some structure is built in the solvation shell and in the surrounding solvent, overcompensating the increase in entropy caused by the dissolution due to a "hydrophobic effect" (Connors, 1997; Tomlinson, 1983; Jencks, 1969; van der Jagt et al., 1970) of solvation.

The values reported here are different from analogous literature values (Garzón and Martínez, 2004; Dwivedi et al., 1992), where similar solubility methods were used. In the named papers, all the values for solubility are lower compared to the present ones. Nevertheless, the Gibbs energy was found in the same order of magnitude (34.27 kJ mol^{-1} in Garzón and Martínez, 2004). This indicates that Gibbs energies are less sensitive and less useful in thorough solvation discussions. However, the enthalpy of dissolution in the named work (Garzón and Martínez, 2004) is approximately double the present value, and consequently, entropy is found to be positive instead of negative (present work). This is a contradiction of the mechanism of dissolution. Reasons for this discrepancy may be in the first place that in the former study (Garzón and Martínez, 2004), although being carried out at the same pH as the present study, was done in a different buffer, where ion strength was adapted to physiological values (i.e. 0.15 mol L^{-1}). Probably potassium chloride was used, as was done in yet another study (Dwivedi et al., 1992). Potassium chloride is well known to increase the cluster structure of the water and salts out ibuprofen-molecules.

Analysing the solvation process in more detail (Table 2), it is found that in both buffers the solvation is exergonic, and Gibbs energy of solvation, ΔG°_{solv}, comprises of negative values for both its enthalpic and its entropic terms, ΔH°_{solv} and ΔS°_{solv}. In the current case, the main driving force of solvation is enthalpy, which is regarded a "classical" hydrophobic interaction as the mechanism of solvation (Connors, 1997; Tomlinson, 1983; Jencks, 1969; van der Jagt et al., 1970). The significance of the entropy for the solvation process, which is decreasing and working in the opposite direction by probably creating solvent cages around the solute molecules, is not much smaller than enthalpy (Tables 1 and 2) at room temperature.

When further comparing the racemate with the pure enantiomer, all the (absolute) values of the thermodynamic solvation functions for (+)-IBP are slightly smaller (taking into account the experimental errors) compared to (±)-IBP, for both the dissociated and non-dissociated form. This means that the solvation of racemic IBP molecules is slightly stronger compared to the pure enantiomer. This behaviour is probably connected with a difference in the molecular association states for the racemate and the pure enantiomer in the solutions. The molecules may be exposed to interaction of neighboring molecules/solvation shells present in the buffers, like dimers (or multimers). These would probably be of different symmetry in the case of the racemate compared to the pure enantiomer (similarly to the symmetry of the dimers in the crystals). Different symmetry determines small variations of the structure of the solvation shells and their thermodynamic characteristics: the more symmetrical (±)-IBP dimer has a stronger ability of solvation. However, the solubility is considerably higher (by approximately a factor of 2) for the pure enantiomer than for the racemate, which means that the distance to neighboring molecules is smaller. It is difficult to decide whether this effect accounts for the difference in solvation energy, considering the generally very low solubility.

Comparison of the enthalpy values in the respective solutions of different pH, as presented in Scheme 1 and Table 2, enables one to calculate the enthalpy of deprotonation of the molecules. Deprotonation is exothermic, the absolute value of enthalpy of protonation/deprotonation is 10 kJ mol^{-1}, coinciding within experimental error both for (+)- and (±)-IBP.



Scheme 1

Table 1 – Temperature dependencies of solubility of some NSAIDs, X_2 [mol frac], in aqueous buffers at pH 2.0 and 7.4

t (°C)	(+)-IBP, X_2 ($\times 10^6$)	(±)-IBP, X_2 ($\times 10^6$)	DIF, X_2 ($\times 10^7$)	FBP, X_2 ($\times 10^7$)	KETO, X_2 ($\times 10^6$)	NAP, X_2 ($\times 10^6$)
pH 2.0						
20	5.45	2.33	3.76	3.64	4.87	1.00
25	6.19	2.82	4.45	4.97	6.11	1.22
30	7.46	3.50	5.24	6.57	7.79	1.47
37	9.30	4.60	6.11	9.53	10.5	1.88
42	10.60	5.30	7.04	12.6	12.9	2.25
A[a]	2.3 ± 0.2	1.0 ± 0.3	6.0 ± 0.4	−2.9 ± 0.2	−1.8 ± 0.2	2.33 ± 0.02
B[a]	2874 ± 76	3518 ± 101	2582 ± 118	5195 ± 65	4123 ± 48	3367 ± 6
R[b]	0.9990	0.9988	0.9969	0.9998	0.9998	0.9999
σ[c]	1.45×10^{-2}	1.24×10^{-2}	2.27×10^{-2}	1.24×10^{-2}	9.26×10^{-3}	1.09×10^{-3}
t (°C)	(+)-IBP, X_2 ($\times 10^5$)	(±)-IBP, X_2 ($\times 10^6$)	DIF, X_2 ($\times 10^6$)	FBP, X_2 ($\times 10^6$)	KETO, X_2 ($\times 10^5$)	NAP, X_2 ($\times 10^5$)
pH 7.4						
20	0.806	5.42	7.19	9.17	1.67	1.34
25	0.891	6.08	7.72	9.44	1.86	1.39
30	0.972	7.06	8.11	9.87	2.11	1.44
37	1.123	8.46	8.56	10.57	2.39	1.52
42	1.185	9.32	9.20	11.03	2.66	1.55
A[a]	6.0 ± 0.2	4.1 ± 0.2	8.6 ± 0.2	8.8 ± 0.2	4.4 ± 0.1	9.08 ± 0.04
B[a]	1670 ± 55	2345 ± 48	952 ± 62	811 ± 54	1929 ± 32	628 ± 13
R[b]	0.9984	0.9994	0.9938	0.9934	0.9996	0.9994
σ[c]	1.06×10^{-2}	9.22×10^{-3}	1.19×10^{-2}	1.04×10^{-2}	6.22×10^{-3}	2.41×10^{-3}

[a] Parameters of the correlation equation: $\ln X_2 = -A - (B/T)$.
[b] R: pair correlation coefficient.
[c] σ: Standard deviation.

Table 2 – Thermodynamic characteristics of solubility and solvation processes of some NSAIDs in aqueous buffers at pH 2.0 and 7.4 at 25 °C

	(+)-IBP	(±)-IBP	DIF	FBP	KETO	NAP
pH 2.0						
ΔG°_{sol} (kJ mol^{-1})[a]	29.7	31.7 (34.85)[b]	36.3	36.0 (35.7)[b]	29.8 (28.5)[b]	33.8 (33.72)[b]
ΔH°_{sol} (kJ mol^{-1})	23.9 ± 0.6	29.3 ± 0.8 (9.6)[b]	21.5 ± 1.0	43.2 ± 0.5 (12.5)[b]	34.3 ± 0.4 (26.4)[b]	28.0 ± 0.1 (21.3)[b]
$T\Delta S^\circ_{sol}$ (kJ mol^{-1})	−5.8	−2.4	−14.8	7.2	4.5	−5.8
ΔS°_{sol} (J K^{-1} mol^{-1})	−19.5 ± 2.1	−8.0 ± 2.7	−49.6 ± 3.4	24.1 ± 1.7	15.1 ± 1.3	−19.5 ± 0.4
$-\Delta G^\circ_{solv}$ (kJ mol^{-1})[c]	11.9	12.5	21.3	17.3	27.2	24.7
$-\Delta H^\circ_{solv}$ (kJ mol^{-1})	83.5 ± 1.1	86.5 ± 1.2	97.8 ± 1.6	65.2 ± 1.0	75.8 ± 0.9	100.3 ± 0.6
$-T\Delta S^\circ_{solv}$ (kJ mol^{-1})	71.6	74.0	76.5	47.9	48.6	75.6
$-\Delta S^\circ_{solv}$ (J K^{-1} mol^{-1})	240.1 ± 3.7	248.2 ± 4.0	256.6 ± 5.4	160.7 ± 3.4	163.0 ± 3.0	253.6 ± 2.0
$\zeta_{H\,solv}$ (%)[d]	53.8	53.9	56.1	57.6	60.9	57.0
$\zeta_{TS\,solv}$ (%)[e]	46.2	46.1	43.9	42.4	39.1	43.0
pH 7.4						
ΔG°_{sol} (kJ mol^{-1})[a]	28.8	29.8	29.2	28.7	27.0	27.7
ΔH°_{sol} (kJ mol^{-1})	13.9 ± 0.5	19.5 ± 0.4	7.9 ± 0.5	6.7 ± 0.5	16.0 ± 0.3	5.2 ± 0.1
$T\Delta S^\circ_{sol}$ (kJ mol^{-1})	−14.9	−10.3	−21.3	−22.0	−11.0	−22.5
ΔS°_{sol} (J K^{-1} mol^{-1})	−50.0 ± 1.0	−34.5 ± 1.5	−71.4 ± 1.7	−73.8 ± 1.7	−36.9 ± 1.0	−75.5 ± 0.4
$-\Delta G^\circ_{solv}$ (kJ mol^{-1})[c]	12.8	14.4	28.4	24.6	30.0	30.8
$-\Delta H^\circ_{solv}$ (kJ mol^{-1})	93.5 ± 1.0	96.3 ± 1.0	111.4 ± 1.1	101.7 ± 1.0	94.1 ± 0.8	123.1 ± 0.6
$-T\Delta S^\circ_{solv}$ (kJ mol^{-1})	80.7	81.9	83.0	77.1	64.1	92.3
$-\Delta S^\circ_{solv}$ (J K^{-1} mol^{-1})	270.7 ± 3.3	274.7 ± 3.3	278.4 ± 3.7	258.6 ± 3.4	215.0 ± 2.7	309.6 ± 2.0
$\zeta_{H\,solv}$ (%)[d]	53.7	54.0	57.3	56.9	59.5	57.1
$\zeta_{TS\,solv}$ (%)[e]	46.3	46.0	42.7	43.1	40.5	42.9

[a] Accuracy is 2%.
[b] Fini et al. (1986).
[c] Perlovich and Bauer-Brandl (2004).
[d] ς_H (%) = $(|\Delta H^\circ_{solv}|/(|\Delta H^\circ_{solv}| + |T\,\Delta S^\circ_{solv}|)) \times 100$.
[e] ς_{TS} (%) = $(|T\,\Delta S^\circ_{solv}|/(|\Delta H^\circ_{solv}| + |T\,\Delta S^\circ_{solv}|)) \times 100$.

It should be noted that the ionic state of the molecules in general is more important for the solvation thermodynamics compared to the non-ionic molecules (Table 2). This difference is higher than the differences between the racemate and the pure enantiomer at the same pH. The total solvation abilities of the (+)- and (±)-IBP for the different states of protonation overlap: $|\Delta Y^{\circ}_{solv}((+)\text{-IBP})| < |\Delta Y^{\circ}_{solv}((\pm)\text{-IBP})| < |\Delta Y^{\circ}_{solv}((+)\text{-IBP}^{-})| < |\Delta Y^{\circ}_{solv}((\pm)\text{-IBP}^{-})|$. Particularly for the entropy, the protonated/deprotonated state of the molecule is of significance. Therefore, it may be speculated that also the interaction of the solvated IBP-molecules with membranes and receptors is widely dependent on the properties of the surrounding medium in terms of pH, possibly also on ion strength and composition.

3.2. *Solvation characteristics of dissociated and non-dissociated forms of the other NSAIDs*

As follows from Table 1 and as is shown in Table 2, dissolution in aqueous buffers both at pH 2.0 and 7.4 is endothermic for all drugs studied. This is evidence for solvation enthalpies not overweighing the respective crystal lattice energies (as was discussed above for IBP). The entropies of dissolution, as a rule (with the exception of FBP and KETO at pH 2), are negative. Therefore, the degree of order in the solvation shells and in the solvent structure increases (i.e. a hydrophobic effect). In all cases, the enthalpic term of the Gibbs energy of solvation exceeds the entropic term. The ratio of the enthalpic and entropic terms ($\zeta_{H\,solv}$) is between 53.8% (for (+)-IBP at pH 2.0) and 60.9% (for KETO at the same pH).

It is interesting to note that the enthalpy of transition from pH 7.4 to 2.0, ΔH_{tr} (pH 7.4 → pH 2.0), which characterises the protonation process, is endothermic in all cases. The values vary from a minimum for (±)-IBP (9.8 kJ mol^{-1}) to the maximum for FBP (36.5 kJ mol^{-1}) by a factor of more than three. All these values exceed by far the enthalpy of proton ionisation in dilute aqueous solutions, which have been reported for some aromatic acids (Christensen et al., 1967). Probably, in the present case, solvation effects play an essential role in the transfer of the molecules from one buffer to the other. It can be assumed that the fluorine atoms (as an electron acceptor) in the molecules of diflunisal and flurbiprofen induce an essential redistribution of the electron density from the COO^{-} group to the phenyl ring (by conjugation effects). As a consequence thereof, solvation effects are increased by both specific and non-specific interaction (electrostatic interactions and hydrogen bond energy terms). Probably, the outlined effect of the F-atoms is the reason for the extraordinary large increase in solubility with pH that is found for DIF and FBP (Table 1) compared to the other compounds studied.

It is not difficult to see a regularity between transfer energy ΔG_{tr} (pH 7.4 → pH 2.0)-values and pK_a (Fig. 1): the weaker the acid, the lower the value of the driving force for the transfer process (and the easier it is to protonate the corresponding base). It should also be noted that a compensation effect is observed between the thermodynamic functions of transfer, which can be described by the following equation:

$$T\Delta S_{tr} = (-8.2 \pm 0.2) + (0.8 \pm 0.1)\Delta H_{tr}, \quad \sigma = 2.29, \quad r = 0.970,$$
$$F = 64.4, \quad F^{2.5\%}_{tab} = 9.365, \quad n = 6 \qquad (6)$$

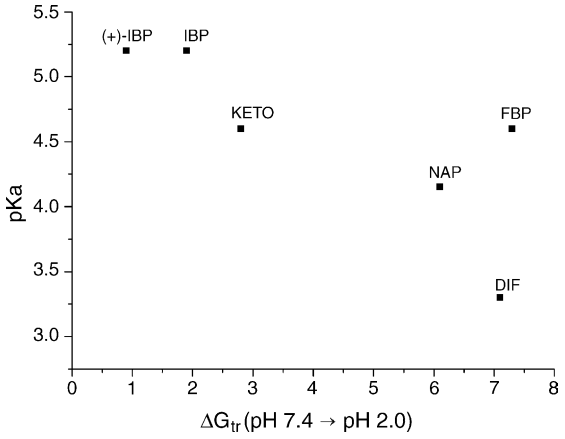


Fig. 1 – Dependence of pK_a-values on the Gibbs energy of solvation for the transfer from buffer at pH 7.4 to buffer at pH 2.0; ΔG_{tr} (pH 7.4 → pH 2.0) = $\Delta G_{solv}{}^{\circ pH\,2.0} - \Delta G_{sol}{}^{\circ pH\,7.4}$.

In other words, the entropic term of the Gibbs energy is 0.8 times less compared to the enthalpic term.

It should also be kept in mind that determination of pK_a-values of poorly soluble drugs is a delicate experiment, and the values may differ considerably according to the method used. In the case of IBP for example, using apparent pK_a-values in different solvent/water mixtures and extrapolating to 0% solvent content, the pK_a-value varies between 5.2 and 4.3 (Avdeef et al., 1999). The pK_a-values reported for other NSAIDs vary by similar ranges (Ràfols et al., 1997). In the present study, this has not been taken into consideration, neither for correlation analysis nor in Fig. 1, because it would not affect the key messages anyway.

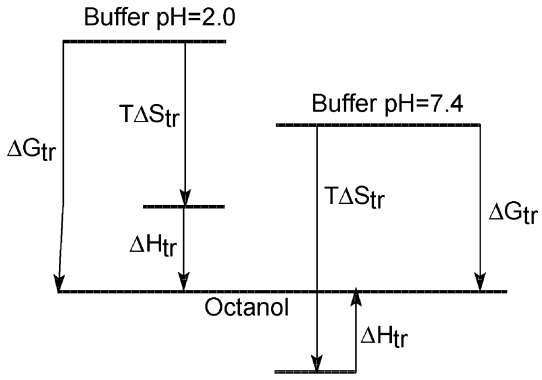
3.3. *Solvation characteristics of transfer process of dissociated and non-dissociated molecules from buffer to n-octanol*

Taking into account those thermodynamic data of solvation for the discussed NSAIDs in octanol, which have been measured earlier (Perlovich and Bauer-Brandl, 2004), it is possible to calculate the transfer energies of the dissociated and non-dissociated molecules from the respective buffer solution to the octanol phase. The thermodynamic connections between the parameters are illustrated in Scheme 2. Knowledge about hydration and solvation characteristics of the drug molecules exclusively enables one to use an absolute energetic scale, and no need to account for galvanic potentials in the interface. The discussed thermodynamic parameters together with related literature data are presented in Table 3.

Using Table 3 and Scheme 2, the relationship between the outlined functions can be described as follows:

$$\text{Buffer pH 2.0} \rightarrow \text{octanol}: \quad \Delta H_{tr} < 0,$$
$$\Delta S_{tr} > 0, \qquad |\Delta H_{tr}| < |T\Delta S_{tr}|$$

$$\text{Buffer pH 7.4} \rightarrow \text{octanol}: \quad \Delta H_{tr} > 0,$$
$$\Delta S_{tr} > 0, \qquad |\Delta H_{tr}| \ll |T\Delta S_{tr}|$$



Scheme 2

Thus, the two types of the transfer processes (non-dissociated molecule to octanol phase, and dissociated molecule to octanol) are basically different regarding their respective driving force. Here, partitioning is a typically enthalpy driven process, whereas the second case, i.e. distribution of the charged form of the molecules, in contrast, is entropy driven (Rogers and Wong, 1980; Connors, 1997; Tomlinson, 1983; van der Jagt et al., 1970).

It has extensively been discussed in the literature in how far water–octanol systems can be used to predict transport properties through biological membranes. One of the strongest arguments against this approach was the difference of the nature of the driving forces of the processes: the system octanol–water was classified as enthalpy driven, whereas the lipid phase–water system should be entropy driven (Rogers and Wong, 1980). Unfortunately, the works devoted to studies of the partitioning/distribution processes, analysed only the change in Gibbs energy ($\log P$, $\log D$). This approach does not provide the opportunity to understand the mechanism of the process. However, from the present results it follows, that these basic differences claimed between the thermodynamics of the transfer in octanol–water and lipid–water systems, do not exist. The nature of the driving forces of the processes as well as the ratio between enthalpic and entropic terms is determined by an eventual charge of the drug molecule, and the energetic state of this molecule within the respective phase. In a buffer at pH 7.4, the charged drug molecule shows stronger interactions with the solvation shell (by additional electrostatic interactions) compared to the uncharged molecule at pH 2. As a consequence of this, more energy is needed for the resolvation of a charged molecule in comparison to an uncharged molecule during partitioning/distribution. Moreover, the enthalpy needed for the resolvation of a charged molecule is not completely compensated by the solvation enthalpy in the octanol phase. This fact may be a strong argument for the assumption that drug molecules may transfer (during partitioning/distribution processes) with partly retained solvation shells. The volume and structure of the "accompanying"

Table 3 – Thermodynamic characteristics of the transfer process from *n*-octanol to buffer (pH 2.0/pH 7.4) of some NSAIDs at 25 °C

	(±)-IBP	DIF	FBP	KETO	NAP
n-Octanol					
$-\Delta G^{\circ}_{solv}$ (kJ mol^{-1})	40.2[a]	49.3	47.1	50.4	48.0
$-\Delta H^{\circ}_{solv}$ (kJ mol^{-1})	90.9[b]	108.6	86.5	82.5	107.1
$-T\Delta S^{\circ}_{solv}$ (kJ mol^{-1})	50.7[c]	59.3	39.4	32.1	59.1
$\Delta Y_{tr} = \Delta Y^{Octanol}_{solv} - \Delta Y^{pH\ 2.0}_{solv}$					
ΔG_{tr} (kJ mol^{-1})	−27.7 (24.35)[d] (−25.7)[e]	−28.0	−29.8 (−28.0)[d] (−23.8)[e]	−23.2 (−21.96)[d] (−17.8)[e]	−23.3 (−23.8)[d] (−20.0)[e]
ΔH_{tr} (kJ mol^{-1})	−4.4 (6.7)[d] (−6.1)[e]	−10.8	−21.3 (−4.6)[d] (−15.6)[e]	−6.7 (−1.7)[d] (−5.2)[e]	−6.8 (0.0)[d] (−13.3)[e]
$T\Delta S_{tr}$ (kJ mol^{-1})	23.3	17.2	8.5	16.5	16.5
ζ_H (%)[f]	15.9	38.6	71.5	28.9	29.2
ζ_{TS} (%)[g]	84.1	61.4	28.5	71.1	70.8
$\Delta Y_{tr} = \Delta Y^{octanol}_{solv} - \Delta Y^{pH7.4}_{solv}$					
ΔG_{tr} (kJ mol^{-1})	−25.8	−20.9	−22.5	−20.4	−17.2
ΔH_{tr} (kJ mol^{-1})	5.4	2.8	15.2	11.6	16.0
$T\Delta S_{tr}$ (kJ mol^{-1})	31.2	23.7	37.7	32.0	33.2
ζ_H (%)[f]	14.8	10.6	28.7	26.6	32.5
ζ_{TS} (%)[g]	85.2	89.4	71.3	73.4	67.5
$\log(P_{2.0})$[h]	3.50	4.44	4.16	3.12	3.34
$\log(D_{7.4})$[h]	1.07	0.76	0.85	−0.25	0.33
pK_a[h]	5.2	3.3	4.6	4.6	4.15

[a] 42.6 kJ mol^{-1}, Garzón and Martínez (2004).
[b] 84.2 kJ mol^{-1}, Garzón and Martínez (2004).
[c] 41.4 kJ mol^{-1}, Garzón and Martínez (2004).
[d] Fini et al. (1986).
[e] Burgot and Burgot (1995).
[f] ζ_H (%) = $(|\Delta H_{tr}|/(|\Delta H_{tr}|+|T\Delta S_{tr}|)) \times 100$.
[g] ζ_{TS} (%) = $(|T\Delta S_{tr}|/(|\Delta H_{tr}|+|T\Delta S_{tr}|)) \times 100$.
[h] Barbato et al. (1997).

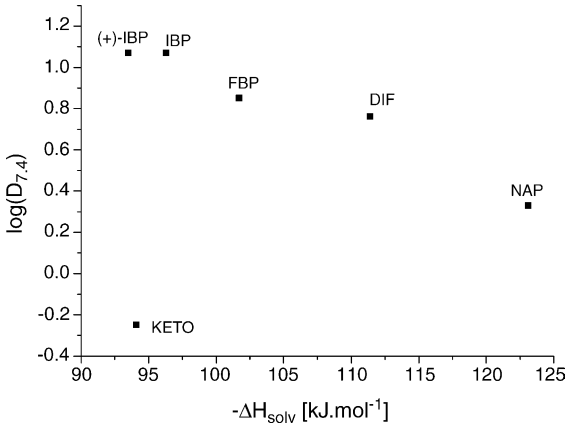


Fig. 2 – Dependence of distribution coefficient buffer/octanol in the form of log($D_{7.4}$) on solvation enthalpy in buffer pH 7.4.

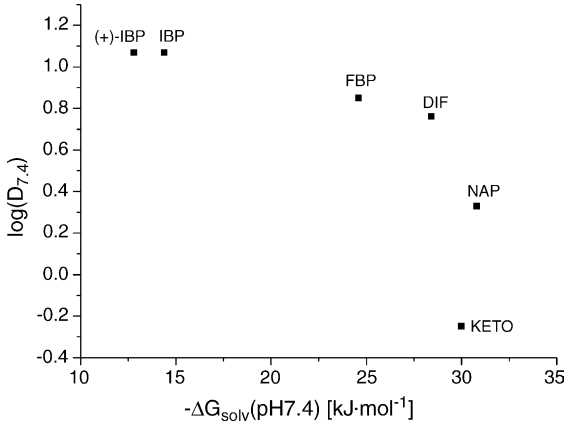


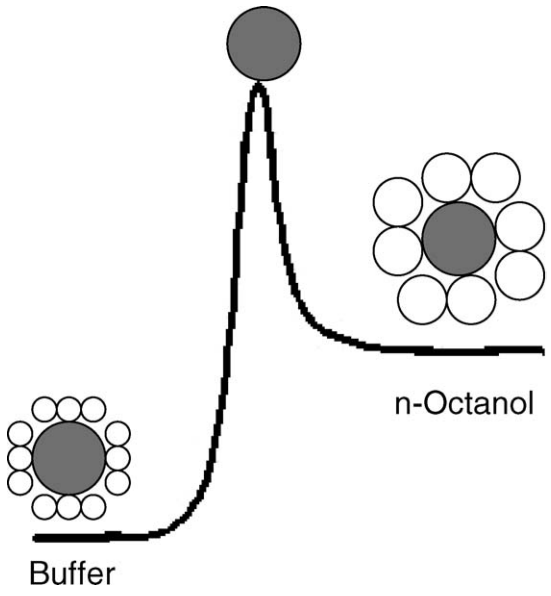
Fig. 3 – Dependence of log($D_{7.4}$) on Gibbs energy of solvation in buffer pH 7.4.

shell is determined by the ratio of all the thermodynamic parameters.

It is interesting to compare the solvation characteristics of the drugs derived in the present study with their experimentally determined partitioning properties taken from the literature (Table 3). The dependence of log $D_{7.4}$ plotted versus ΔH_{solv} (pH 7.4) is shown in Fig. 2.

As the absolute values of ΔH_{solv} increase, the respective log $D_{7.4}$-values decrease (with an exception for KETO). Probably, this regularity is connected with considerable energy absorption which accompanies the resolvation of the molecules during the transfer from the buffer to the octanol phase. Because a compensation effect between the solvation functions is observed for the buffer pH 7.4, the characteristic of the correlation dependencies between log $D_{7.4}$-values and entropic term is analogous. It should be noted that the value for KETO does not deviate from the correlation between log $D_{7.4}$ and ΔG_{solv}, in contrast to its value for ΔH_{solv} which does so (Fig. 3). This fact confirms that the enthalpic and entropic terms are more sensitive to the nature of the occurring processes than Gibbs energies (Da et al., 1992).

As another consequence of this fact, the widely studied (and in many cases relatively poor) correlations between



Scheme 3

Gibbs energy of drug–cyclodextrin complexation and log P are of limited value as a measure of hydrophobicity, because the comparison of Gibbs energies of two different processes (complexation and partitioning/distribution) does not consider their respective driving forces (Connors, 1997). It is obvious that a good correlation can only be expected observed in cases where the values and signs of the enthalpic and entropic terms of both processes are identical.

Finally, let us consider the distribution/partitioning process from the point of view of solvation. In order to transfer a molecule from one phase (buffer) to another (octanol) it needs to overcome a potential barrier, which is "hypothetical" and equal to the solvation enthalpy in the buffer (Scheme 3). The height of this barrier determines the kinetic parameters of the partitioning/distribution process. Obviously, the outlined process does not desolvate the molecule completely: the resolvation process is a complicated process where the old solvation shell is destroyed simultaneously as the new one is created. As a consequence of this competition, the height of the activation barrier decreases considerably. The value of the activation barrier may be estimated from kinetic parameters of the partitioning/distribution process, which may in the future be helpful for further characterisation of biopharmaceutical properties of drug molecules.

Acknowledgments

Personal grants to German Perlovich and Sergey Kurkov from the Russian Science Support Foundation are appreciated.

REFERENCES

Avdeef, A., Box, K.J., Comer, J.E.A., Gilges, M., Hadley, M., Hibbert, C., Patterson, W., Tam, K.Y., 1999. pH-metric log P.11. pK_a determination of water-insoluble drugs in

organic solvents–water mixtures. J. Pharm. Biomed. Anal. 20, 631–641.
Barbato, F., La Rotonda, M.I., Quaglia, F., 1997. Interaction of non-steroidal anti-inflammatory drugs with phospholipids: comparison between octanol/buffer partitio coefficients and chromatographic indexes on immobilized artificial membranes. J. Pharm. Sci. 86 (2), 225–228.
Beezer, A.E., Hunter, W.H., 1983. Oscillations in some linear free energy relationships derived from partition coefficients of phenols between octanol and water. J. Med. Chem. 26, 757–759.
Burgot, G., Burgot, J.L., 1995. Thermometric titrimetry of the thermodynamic parameters of water/*n*-octanol transfer in several non-steroid anti-inflammatory drugs. Ann. Pharm. Fr. 53, 13–18.
Christensen, J.J., Izatt, R.M., Hansen, L.D., 1967. Thermodynamics of proton ionization in dilute aqueous solution. VII. ΔH° and ΔS° values for proton ionization from carboxylic acid at 25 °C. J. Am. Chem. Soc. 89 (2), 213–222.
Connors, K.A., 1997. The stability of cyclodextrin complexes in solution. Chem. Rev. 97, 1325–1357.
Da, Y.Z., Ito, K., Fujiwara, H., 1992. Energy aspects of oil/water partition leading to the novel hydrophobic parameters for the analysis of quantitative structure–activity relationships. J. Med. Chem. 35, 3382–3387.
Dwivedi, S.K., Sattari, S., Jamali, F., Mitchell, A.G., 1992. Ibuprofen racemate and enantiomers: phase diagram, solubility and thermodynamic studies. Int. J. Pharm. 87, 95–104.
Fini, A., Laus, M., Orienti, I., Zecchi, V., 1986. Dissolution and partition thermodynamic functions of some non-steroidal anti-inflammatory drugs. J. Pharm. Sci. 75 (1), 23–25.
Garzón, L.C., Martínez, F., 2004. Temperature dependence of solubility for ibuprofen in some organic and aqueous solvents. J. Sol. Chem. 33, 1379–1395.
Jencks, W.P., 1969. Catalysis in Chemistry and Enzymology. McGraw Hill, New York, p. 427.
Kinkel, J.F.M., Tomlinson, E., Smut, P., 1981. Thermodynamics and extrathermodynamics of organic solute liquid–liquid distribution between water and 2,2,4-trimethylpentane. Int. J. Pharm. 9, 121–136.
Lazarev, A.I., Kharlamov, I.P., Yakovlev, P.Y., Yakovleva, E.F., 1976. Handbook of Chem-analyst. Metallurgiya, Moscow, pp. 132–135.
Perlovich, G.L., Bauer-Brandl, A., 2003a. Thermodynamics of solutions. I. Benzoic acid and acetylsalicylic acid as models for drug substances and the prediction of solubility. Pharm. Res. 20 (3), 471–478.
Perlovich, G.L., Kurkov, S.V., Bauer-Brandl, A., 2003b. Thermodynamics of solutions. II. Flurbiprofen and diflunisal as models for studying solvation of drug substances. Eur. J. Pharm. Sci. 19 (5), 423–432.
Perlovich, G.L., Kurkov, S.V., Kinchin, A.N., Bauer-Brandl, A., 2003c. Thermodynamics of solutions. IV. Solvation of ketoprofen in comparison to other NSAIDs. J. Pharm. Sci. 92 (12), 2511–2520.
Perlovich, G.L., Kurkov, S.V., Kinchin, A.N., Bauer-Brandl, A., 2004a. Thermodynamics of solutions. III. Comparison of the solvation of (+)-Naproxen with other NSAIDs. Eur. J. Pharm. Biopharm. 57 (2), 411–420.
Perlovich, G.L., Kurkov, S.V., Kinchin, A.N., Bauer-Brandl, A., 2004b. Solvation and hydration characteristics of ibuprofen and acetylsalicylic acid. AAPS Pharm. Sci. 6 (1), Article 3, http://www.aapspharmsci.org.
Perlovich, G.L., Bauer-Brandl, A., 2004. Solvation of drugs as a key for understanding partitioning and passive transport exemplified by NSAIDs. Curr. Drug Deliv. 1 (3), 213–226.
Perlovich, G.L., Rodionov, S.V., Bauer-Brandl, A., 2005. Thermodynamics of solubility, sublimation and solvation processes of parabens. Eur. J. Pharm. Sci. 24, 25–33.
Ràfols, C., Rosés, M., Bosch, E., 1997. A comparison between different approaches to estimate the aqueous pK_a-values of several non-steroidal anti-inflammatory drugs. Anal. Chim. Acta 338, 127–134.
Rogers, J.A., Davis, S.S., 1980. Functional group contributions to the partitioning of phenols between liposomes and water. Biochem. Biophys. Acta 598, 392–404.
Rogers, J.A., Wong, A., 1980. The temperature dependence and thermodynamics of partitioning of phenols in the *n*-octanol–water system. Int. J. Pharm. 6, 339–448.
Tomlinson, E., 1983. Enthalpy–entropy compensation analysis of pharmaceutical, biochemical and biological systems. Int. J. Pharm. 13, 115–144.
van der Jagt, D.L., Killian, F.L., Bender, M.L., 1970. Cycloamyloses as enzyme models. Effects of inclusion complex formation on intramolecular participation. J. Am. Chem. Soc. 92, 1016.