Solvation and Hydration Characteristics of Ibuprofen and Acetylsalicylic Acid

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ABSTRACT

Ibuprofen and acetylsalicylic acid were studied by thermoanalytical methods: sublimation calorimetry, solution calorimetry, and with respect to solubility. Upon measuring the temperature dependences of the saturated vapor pressure, enthalpies of sublimation, ΔH_{sub}^0 , as well as the entropies of sublimation, ΔS_{sub}^0 , and their respective relative fractions in the total process were calculated. The Gibbs energy of solvation in aliphatic alcohols as well as the enthalpic and entropic fractions thereof were also studied and compared with the respective properties of model substances and other nonsteroidal antiinflammatory drugs (benzoic acid, diflunisal, flurbiprofen, ketoprofen, and naproxen). In all cases, enthalpy was found to be the driving force of the solvation process. Correlations were derived between Gibbs energy of solvation in octanol, ΔG_{solv}^{Oct} , and the transfer Gibbs energy from water to octanol, ΔG_{tr}^0 . Influence of mutual octanol and water solubilities on the driving force of partitioning is discussed. An enthalpy-entropy-compensation effect in octanol was observed, and consequences of deviation from the general trend are also discussed.

KEYWORDS: ibuprofen, acetylsalicylic acid, NSAID, sublimation, solvation, hydration, plasma half-life

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INTRODUCTION

Understanding the mechanism of passive transport is one of the most important issues in the design of new drugs. Since penetration of drugs through biological barriers is in many cases a major prerequisite for the biological effect, numerous attempts have been made to describe this process adequately. To cover the variability in biophysical characteristics of different membrane types, a set of 4 solvent systems has been used, sometimes called the “critical quartet”¹: octanol-water (amphiphilic, aprotic solvent); propylenglycoldipelargonat-water (hydrogen bond acceptor); chloroform-water (hydrogen bond donor); and cyclohexane-water (purely hydrophobic).

Diffusion is the main mechanism of passive transport. However, diffusion coefficients of drug molecules vary widely not only for various transport routes but also within the same route for different drug molecules; for example, the lateral diffusion coefficient D_{lat} of diclofenac (molecular weight [MW] 318.0 Da) is $9.65 \cdot 10^{-9} \text{ cm}^2 \cdot \text{sec}^{-1}$, whereas for ephedrine (MW 165.2 Da) it is $1.05 \cdot 10^{-6} \text{ cm}^2 \cdot \text{sec}^{-1}$.² This very large difference (a factor of approximately 100) is evidence of the sensitivity of diffusion mechanism to the molecular size and, consequently, to the size of the diffusion-activated volume. However, if the diffusion coefficients of the compounds are compared with approximately the same MW but with widely different molecular structure and topology, an even larger variability (a factor of approximately 325) is found: anisol ($1.84 \cdot 10^{-6} \text{ cm}^2 \cdot \text{sec}^{-1}$); benzaldehyde ($4.81 \cdot 10^{-6} \text{ cm}^2 \cdot \text{sec}^{-1}$); benzyl alcohol ($5.92 \cdot 10^{-8} \text{ cm}^2 \cdot \text{sec}^{-1}$); o-phenylenediamine ($3.78 \cdot 10^{-7} \text{ cm}^2 \cdot \text{sec}^{-1}$). This demonstrates once more that differently sized aggregates (subunits) take part in the elementary steps of diffusion, and that these subunits determine the diffusion mechanism (activation volume, activation thermodynamic parameters of the diffusion, and so on).

It is the present authors' opinion that for a better understanding of the passive transport, it is necessary to (1) analyze the solvation and hydration characteristics of drug molecules; (2) analyze the size and energetic pa-

rameters of the respective solvation shells (which are most probably part of the subunits in the elementary diffusion); (3) study the effect of size, symmetry, topology, and ionic state of the drug molecule on the properties of the solvation shell; and (4) study the resolution (rebuilding) process of the solvation shells during the transport through biological barriers.

The present work is an attempt to understand the solvation characteristics of ibuprofen (IBP) and acetylsalicylic acid (ASA) in alcohols and in water. It is a continuation of work formerly done in the same field for nonsteroidal antiinflammatory drugs (NSAIDs).³⁻⁶ In contrast to previous work, in which biphenyl derivatives (diflunisal [DIF] and flurbiprofen [FBP])⁴ naphthalene derivatives ([+]-naproxen)⁵ and a derivative of benzophenone (ketoprofen)⁶ were considered, in the present study, IBP and ASA were chosen as representatives of the same class of drugs (NSAIDs), but being phenyl derivatives (**Figure 1**). This method enables the comparison of solvation characteristics of a wide spectrum of compounds using quantitative thermodynamic parameters derived from experimental data. The objective may be to correlate these data to pharmacokinetic properties of drugs.

Figure 1. Structures of the acetylsalicylic acid and ibuprofen molecules.

MATERIALS AND METHODS

Materials and Solvents

IBP ([±]-2-[4-isobutylphenyl]propionic acid, C₁₃H₁₈O₂, MW 206.3 Da) was purchased from Sigma (Lot 26H1368, St Louis, MO). ASA (analytical reagent grade, aspirin, C₉H₈O₄, MW 180.16 Da) was obtained from Norsk Medisinaldepot (Oslo, Norway).

The alcohols were as follows: methanol (high-performance liquid chromatography [HPLC] grade, lot K27636907, Merck, Darmstadt, Germany); ethanol (extra pure grade, 99.6% vol/vol, maximum water content 0.4%, Arcus AB, Oslo, Norway); 1-propanol (HPLC grade, lot U00874, Aldrich, Taufkirchen, Germany); 1-butanol (analytical reagent grade [ARG], lot K22047090, Merck); 1-pentanol (ARG, lot 35757-101, Aldrich); 1-hexanol (ARG, lot 31562-011, Aldrich); 1-

heptanol (ARG, lot 60K3706, Sigma); and 1-octanol (ARG, lot 11K3688, Sigma).

The organic solvents were as follows: n-hexane (ARG, lot 07059903C, SDS, Peypin, France); benzene (ARG, lot K26454983, Merck).

Solubility Determination

Solubilities of the named compounds were obtained at 25°C ± 0.1°C. All the experiments were performed by a spectrophotometrical method with an accuracy of ~2.5% using the protocol described previously.⁷

Solution Calorimetry

Enthalpies of solution (ΔH_{sol}^m) at concentrations m were measured using an isothermal precision solution calorimeter as described in detail in.⁸ The sum of variability of the heat effects of each respective experiment does not exceed 1%. The measuring temperature was 25°C ± 10⁻⁴°C; volume of the vessel, 100 mL; stirrer speed, 500 rpm; and the mass of each sample, ~18 mg. The accuracy of weight measurements corresponded to ±0.0005 mg. The calorimeter was calibrated using KCl (analytical grade >99.5%, Merck) in water in a wide concentration interval with more than 10 measurements. The standard value of solution enthalpy obtained was $\Delta H_{sol}^0 = 17\,225 \pm 50 \text{ J}\cdot\text{mol}^{-1}$. This is in good agreement with the value recommended by the International Union of Pure and Applied Chemistry (IUPAC) of $\Delta H_{sol}^0 = 17\,217 \pm 33 \text{ J}\cdot\text{mol}^{-1}$.⁹

Sublimation Experiments

Sublimation experiments were performed by the transpiration method as was described elsewhere.¹⁰ In brief, a stream of an inert gas passes above the sample at a constant temperature and at a known slow constant flow rate in order to achieve saturation of the carrier gas with the vapor of the substance under investigation. The vapor is condensed at some point downstream, and the mass of sublimate and its purity are determined. The vapor pressure over the sample at this temperature can be calculated from the amount of sublimated sample and the volume of the inert gas used.

The equipment was calibrated using benzoic acid (standard substance obtained from Polish Committee of Quality and Standards). The standard value of sublimation enthalpy obtained here was $\Delta H_{sub}^0 = 90.5 \pm 0.3$

J·mol⁻¹. This is in good agreement with the value recommended by IUPAC of $\Delta H_{sub}^0 = 89.7 \pm 0.5 \text{ J·mol}^{-1}$.⁹ The saturated vapor pressures were measured at each temperature 5 times with the SD being within 3% and 5%. Because the saturated vapor pressure of the investigated compounds is low, it may be assumed that the heat capacity change of the vapor with temperature is so small that it can be neglected. The experimentally determined vapor pressure data may be described in (lnP; 1/T) coordinates by Equation 1:

$$\ln(P) = A + B/T \quad (1)$$

where P is saturated vapor pressure; T is absolute temperature, A and B are correlation coefficients.

The value of the enthalpy of sublimation is calculated by the Clausius-Clapeyron equation:

$$\Delta H_{sub}^T = RT^2 \cdot \partial(\ln P) / \partial(T) \quad (2)$$

where R is universal gas constant.

Whereas, the entropy of sublimation at a given temperature T was calculated from the following relation:

$$\Delta S_{sub}^T = (\Delta H_{sub}^T - \Delta G_{sub}^T) / T \quad (3)$$

with $\Delta G_{sub}^T = -RT \cdot \ln(P/P_0)$, where P_0 is the standard pressure of $1.013 \cdot 10^5 \text{ Pa}$.

It should be noted that the calculations and comparisons of the thermodynamic functions were performed upon extrapolation of the vapor-pressure/temperature function to room temperature, because the values of the vapor pressure at 25°C are very small.

RESULTS AND DISCUSSION

Thermodynamics of Acetylsalicylic Acid Sublimation

The temperature dependences of the saturation vapor pressure as well as the thermodynamic sublimation functions for ASA are presented in **Figure 2**.

For IBU the respective sublimation data are listed elsewhere.¹¹

The Gibbs energy of the sublimation process at room temperature of ASA can be separated into the relative fractions of both the enthalpic and the entropic terms by the following parameters:

$$\zeta_H = [\Delta H_{sub}^{298} / (\Delta H_{sub}^{298} + T \Delta S_{sub}^{298})] 100\% \quad (4)$$

$$\zeta_{TS} = [T \Delta S_{sub}^{298} / (\Delta H_{sub}^{298} + T \Delta S_{sub}^{298})] 100\% \quad (5)$$

Results of these calculations are shown in **Table 1**; the sublimation process consists of 62.4% enthalpy and 37.6% entropy. If the same calculations are performed for a structurally related molecule, namely benzoic acid (BA), using literature values,¹⁰ the parameters found are $\zeta_H = 61.7\%$ and $\zeta_{TS} = 38.3\%$, respectively, which are approximately equal to those of ASA.

Figure 2. Temperature dependence of saturation vapor pressure of acetylsalicylic acid.

Using the thermodynamic cycle, the thermodynamic functions of evaporation of ASA may be estimated as follows (see **Table 2**):

$$\Delta H_{vap} = \Delta H_{sub} - \Delta H_{fus} \quad (6)$$

$$\Delta S_{vap} = \Delta S_{sub} - \Delta S_{fus} \quad (7)$$

As has been shown by Li et al for ephedrine and its derivatives,¹² there are correlations between the enthalpy of fusion and the van der Waals' term of the crystal lattice energy.

In order to find out whether the proposed relationship also applies to other substances, the thermodynamic functions of the sublimation of ASA in comparison to the other NSAIDs investigated earlier^{3-5,11} were studied as follows: If it is supposed that during the melting process of a crystalline substance only the number of degrees of freedom for a molecule is changed, but not the nature

Table 1. Thermodynamic Functions of the IBP and ASA Solubility and Solvation Processes in Aliphatic Alcohols at 25°C*

Solvents	X ₂	$\gamma^\dagger$	ΔG_{sol}^0 kJ·mol ⁻¹	ΔH_{sol}^0 kJ·mol ⁻¹	T· ΔS_{sol}^0 kJ·mol ⁻¹	ΔS_{sol}^0 J·K ⁻¹ ·mol ⁻¹	$-\Delta G_{sol}^0$ kJ·mol ⁻¹	$-\Delta H_{sol}^0$ kJ·mol ⁻¹	$-T \cdot \Delta S_{sol}^0$ kJ·mol ⁻¹	$\zeta_H^{\parallel}$ %	$\zeta_{ITS}^{\parallel}$ %
IBP											
MeOH	0.0601	4.46	7.0	25.5 ± 0.2	18.5	62.0	37.2	90.3	18.5	63.0	37.0
EtOH	0.0833	3.22	6.2	26.2 ± 0.2	20.0	67.2	38.0	89.6	20.0	63.5	36.5
n-Propanol	0.142	1.89	4.8	25.2 ± 0.2	20.4	68.3	39.4	90.6	20.4	63.9	36.1
n-BuOH	0.162	1.65	4.5	25.7 ± 0.2	21.2	71.1	39.7	90.1	21.2	64.0	36.0
n-Pentanol	0.148	1.81	4.7	25.0 ± 0.2	20.3	68.0	39.5	90.8	20.3	63.9	36.1
n-Hexanol	0.221	1.21	3.7	25.5 ± 0.2	21.8	73.0	40.5	90.3	21.8	64.5	35.5
n-Heptanol	0.226	1.19	3.7	25.0 ± 0.2	21.3	71.5	40.5	90.8	21.3	64.4	35.6
n-Octanol	0.198	1.35	4.0	24.9 ± 0.2	20.9	70.1	40.2	90.9	20.9	64.2	35.8
ASA											
MeOH	0.0719	0.433	6.5	25.0 ± 0.2	18.5	62.0	37.1	84.7	47.6	64.0	36.0
EtOH	0.0855	0.364	6.1	25.9 ± 0.3	19.8	66.4	37.5	83.8	46.3	64.4	35.6
n-Propanol	0.0418	0.744	7.9	26.5 ± 0.2	18.6	62.5	35.7	83.2	47.5	63.7	36.3
n-BuOH	0.0453	0.687	7.7	27.0 ± 0.2	19.3	64.8	35.9	82.7	46.8	63.9	36.1
n-Pentanol	0.0395	0.787	8.0	27.2 ± 0.2	19.2	64.3	35.6	82.5	46.9	63.8	36.2
n-Hexanol	0.0393	0.791	8.0	26.2 ± 0.2	18.2	61.0	35.6	83.5	47.9	63.5	36.5
n-Heptanol	0.0386	0.806	8.1	25.8 ± 0.3	17.7	59.5	35.5	84.0	48.5	63.4	36.6
n-Octanol	0.0341	0.912	8.4	25.5 ± 0.2	17.1	57.4	35.5	84.2	49.0	63.2	36.8

*IBP indicates ibuprofen; and ASA, acetylsalicylic acid.

$\dagger \gamma = X_2^{id} / X_2$; $\ln X_2^{id} = (\Delta H_{fus} / R) \cdot (1/T^f - 1/T)$; X_2^{id} (IBP) = 0.268⁹; X_2^{id} (ASA) = 0.204 (Perlovich and Brandl-Bauer.³)

$\ddagger \Delta G_{sol}^0 = \Delta G_{sol}^0 - \Delta G_{sub}^0$; ΔG_{sub}^0 (IBP) = 44.2 kJ · mol⁻¹ (Perlovich et al¹⁶)

$\S \Delta H_{sol}^0 = \Delta H_{sol}^0 - \Delta H_{sub}^0$; ΔH_{sub}^0 (IBP) = 115.8 ± 0.6 kJ · mol⁻¹ (Perlovich et al¹⁶)

$\parallel \zeta_H = [(\Delta H_{sol}^0) / (\Delta H_{sol}^0 + |T \cdot \Delta S_{sol}^0|)] \cdot 100\%$

$\P \zeta_{ITS} = [T \cdot \Delta S_{sol}^0 / (\Delta H_{sol}^0 + |T \cdot \Delta S_{sol}^0|)] \cdot 100\%$

Table 2. Thermodynamic Functions of Acetylsalicylic Acid

ΔG_{sub}^{298} [kJ·mol ⁻¹]	43.6	T^f [°C]	141.0 ± 0.5 [†]
ΔH_{sub}^{298} [kJ·mol ⁻¹]	109.7 ± 0.5	ΔH_{fus} [kJ·mol ⁻¹]	30.2 ± 0.2 [†]
$T \cdot \Delta S_{sub}^{298}$ [kJ·mol ⁻¹]	66.1	ΔS_{fus} [J·mol ⁻¹ · K ⁻¹] ^c	72.9
ΔS_{sub}^{298} [J·mol ⁻¹ · K ⁻¹]	222 ± 2	ΔH_{vap} [kJ·mol ⁻¹]	79.5
ζ_H [%]*	62.4	ΔS_{vap} [J·mol ⁻¹ · K ⁻¹]	149
ζ_{TS} [%]*	37.6		

* $\zeta_H = [\Delta H_{sub}^{298} / (\Delta H_{sub}^{298} + T \cdot \Delta S_{sub}^{298})] \cdot 100\%$; $\zeta_{TS} = [T \cdot \Delta S_{sub}^{298} / (\Delta H_{sub}^{298} + T \cdot \Delta S_{sub}^{298})] \cdot 100\%$.

[†]Perlovich and Brandl-Bauer¹⁵; ^c $\Delta S_{fus} = \Delta H_{fus} / T^f$.

of the molecular interactions (ie, the ratio between the respective energetic terms of the crystal lattice energy), then a correlation between the enthalpies of sublimation and evaporation should be expected. The proposed relationship between ΔH_{sub}^0 and ΔH_{vap}^0 is depicted in

Figure 3, where ΔH_{vap}^0 is plotted vs ΔH_{sub}^0 . As follows from **Figure 3**, it is DIF that clearly deviates from the otherwise marked trend line by an anomalously low ΔH_{vap}^0 value. This behavior may be explained by the fact that each DIF molecule in contrast to the others has 3 hydrogen bonding centers (-OH and -COOH). In the crystal lattice, all of them take part in the intermolecular bonding, and in the molten state part of them continue, whereas others form an intramolecular hydrogen bond.

Figure 3. Dependence of evaporation enthalpy, ΔH_{vap}^0 , vs sublimation enthalpy, ΔH_{sub}^0 .

Dependence of the ratio $\Delta H_{fus} / \Delta H_{sub}^0$ on the temperature of fusion T^f is presented in **Figure 4**. It is not difficult to see that there is a correlation between these variables. Taking into consideration that $\Delta S_{fus} = \Delta H_{fus} / T^f$, the entropy of fusion increases proportionally with the crystal lattice energy, with ΔH_{sub}^0 being a measure thereof. This regularity is also in accordance with the finding of Li et al¹² as mentioned above.

Figure 4. Dependence of $\Delta H_{fus} / \Delta H_{sub}^0$ vs melting temperature, T^f .

Thermodynamics of Solvation of IBP and ASA in Aliphatic Alcohols

The thermodynamic parameters of solubility (ΔG_{sol}^0 , ΔH_{sol}^0 , $T \Delta S_{sol}^0$) and of the solvation processes (ΔG_{solv}^0 , ΔH_{solv}^0 , $T \Delta S_{solv}^0$) of IBP and ASA in aliphatic alcohols

Table 3. The Values of Partitioning, Solubility, and Gibbs Energy of Hydration*

	Log $D_{7.4}$	Solubility in Water [†]	Solubility in Octanol [‡]	ΔG_{hydr}^0 §	ΔG_{solv}^{Oct} § Octanol	$\Delta G_{hydr}^0 - \Delta G_{solv}^{Oct}$
ASA	-1.2	$1.78 \cdot 10^{-2}$	$3.41 \cdot 10^{-2}$	-24.2	-35.2	11.0
IBP	1.07	$1.74 \cdot 10^{-4}$ [#]	$1.98 \cdot 10^{-1}$	-12.8	-40.2	27.4
Ketoprofen	-0.25	$5.58 \cdot 10^{-3}$ ^{**}	$6.91 \cdot 10^{-2}$ ^{††}	-34.2	-50.4	16.2
Benzoic Acid	-	$2.82 \cdot 10^{-2}$ [#]	$1.987 \cdot 10^{-1}$ ^{‡‡}	-15.6	-30.4 ^{‡‡}	14.8
Naproxen	0.33	$6.31 \cdot 10^{-5}$ [#]	$1.46 \cdot 10^{-2}$ ^{§§}	-24.6	-48.0 ^{§§}	23.4
Flurbiprofen	0.85	$1.82 \cdot 10^{-4}$	$8.17 \cdot 10^{-2}$ ^{¶¶}	-22.0	-47.1 ^{¶¶}	25.1
Diflunisal	0.76	$6.39 \cdot 10^{-4}$ ^{##}	$3.52 \cdot 10^{-2}$ ^{¶¶}	-29.4	-49.3 ^{¶¶}	19.9

*ASA indicates acetylsalicylic acid; IBP, ibuprofen. Data are taken in part from the literature.

[†][mol·L⁻¹]

[‡][mol fraction]

§[kJ·mol⁻¹] concentration has been recalculated in mol fraction.

^{||}Barbato et al¹³

[†]Bergström et al²¹

[#]Yang et al¹⁷

^{**}Kommury et al.²⁰

^{††}Perlovich et al⁶

^{‡‡}Perlovich and Bauer-Brandl³

^{§§}Perlovich et al⁵

^{||}Yalkowsky et al¹⁸

^{¶¶}Perlovich et al⁴

^{##}Cotton and Hux¹⁹

are presented in **Table 1**, where $\Delta H_{solv}^0 = \Delta H_{sol}^0 - \Delta H_{sub}^0$; and $\Delta S_{solv}^0 = \Delta S_{sol}^0 - \Delta S_{sub}^0$. The concentration of ibuprofen in octanol is ~1.35 times less than the ideal solubility, whereas for ASA, the respective factor is 0.912 and this value corresponds approximately to the ideal solubility.

Dependence of the standard Gibbs energy of solvation, ΔG_{solv}^0 , of the investigated drugs vs the chain length (n) of the alcoholic solvents is shown in **Figure 5** together with analogous values for BA, DIF, FBP, naproxen (NAP), and ketoprofen (KETO), obtained in earlier studies.³⁻⁶ As follows from **Figure 5**, the noted drugs may be arranged in the order of increasing absolute values as follows:

BA < ASA < IBP < FBP < NAP < DIF < KETO

Using literature data on the solubility in water, Gibbs enthalpies of hydration ΔG_{hydr}^0 were estimated as well (**Table 3**).

The equilibrium partitioning for drugs in a water-octanol system differs from the calculated value found using the Gibbs energies in pure water and pure octanol phase. It is interesting in this context to analyze the correlation

Figure 5. Dependence of solvation Gibbs energy, ΔG_{solv}^0 , vs the alcohol chain length (n).

between the driving force and the absolute value of the Gibbs energy of solvation. The dependence of the Gibbs energy of transition $\Delta G_{tr}^0 = \Delta G_{solv}^{Oct} - \Delta G_{hydr}^0$ on the Gibbs energy of solvation in octanol ΔG_{solv}^{Oct} is presented in **Figure 6**. As follows from **Figure 6**, the considered drugs may be divided into two groups: (1) KETO, DIF, NAP, FBP, and IBP; and (2) BA and ASA.

The existence of the 2 different groups (1) and (2) may possibly be explained by the essentially different structures of the solvation shells of the drugs belonging to the 2 groups. Within each group, an increase in the absolute value of Gibbs energy of solvation (or hydration) of the drug leads to a decrease in the driving force for the transition. It is probable that while the energy of solvation of the drug increases, the activation barrier of a phase transition from the water to the octanol phase also rises because of bigger energetic expenses needed for the resolution process (ie, destroying and rebuilding the respective solvation shell). As a result, within a group of compounds with similar properties, the drug with the lower Gibbs energy of solvation (in water or in octanol) should be the more suitable candidate with respect to better membrane passage properties.

Figure 6. Dependence of $\Delta G_{tr}^0 = \Delta G_{hydr}^0 - \Delta G_{solv}^{Oct}$ vs solvation energy in octanol, ΔG_{solv}^{Oct} .

As a next step, an attempt was made to analyze the effect of mutual octanol and water solubilities on the partitioning driving force. For this purpose, driving forces for the partitioning under 2 different conditions were calculated as follows: (1) $\Delta G_{tr}^0(D) = -RT \ln D_{7.4}$, where $D_{7.4}$ is the partition coefficient obtained in a water-octanol system with the pH value of the water phase being 7.4¹³; ie, the drug molecules are in their ionized form, $pK_a(\text{IBP}) = 4.41$ and $pK_a(\text{ASA}) = 3.49$; and (2) calculation of $\Delta G_{tr}^0 = \Delta G_{solv}^{Oct} - \Delta G_{hydr}^0$, the latter values being obtained by the transfer of a solute molecule from water (at the same conditions as above) into the octanol phases. Dependence of $\Delta G_{tr}^0(D) = -RT \ln D_{7.4}$ ¹² vs $\Delta G_{tr}^0 = \Delta G_{solv}^{Oct} - \Delta G_{hydr}^0$ is presented in **Figure 7**. From **Figure 7**, it was

concluded that there is a correlation between these variables that can be described by the following equation:

$$\Delta G_{tr}^0(D) = (14 \pm 3) + (0.74 \pm 0.15) \cdot \Delta G_{tr}^0 \quad (8)$$

$r = 0.930$; $\sigma = 2.0$; $F_{tab}^{2.5\%} = 9.365$; $F = 25.64$; $n = 6$

where σ is the standard deviation, $F_{tab}^{2.5\%}$ is the Fisher distribution tabulated value with confidence interval 2.5 %, F is the calculated Fisher distribution value.

Figure 7. Dependence of $\Delta G_{tr}^0(D) = -RT \ln D_{7.4}$ vs $\Delta G_{tr}^0 = \Delta G_{solv}^{Oct} - \Delta G_{hydr}^0$.

The $\Delta G_{tr}^0(D)$ -function is 0.74 times less sensitive than ΔG_{tr}^0 . Therefore, it may be concluded that mutual saturation of the water-octanol phases leads to a decrease in the partitioning coefficient in comparison with the pure phases (saturation of the octanol with water reduces the solubility of the drug in it). Based on this fact, it may be proposed that the partitioning of NSAIDs in living tissue will be extremely sensitive to any concentration gradients. Moreover, as also may be concluded from **Figure 7**, there is a deviation of some drugs from the main trend line. For example, DIF is more sensitive to the changes of the composition of the medium, whereas NAP is less sensitive than the average.

Dependence of the enthalpy of solvation ΔH_{solv}^0 vs the chain length (n) of the aliphatic alcohols used as solvents is shown in **Figure 8** (together with the values for BA, NAP, KETO, DIF, and FBP for comparison). The compounds may be arranged according to increasing absolute values of ΔH_{solv}^0 as follows:

BA < KETO < ASA < FBP < IBP < NAP < DIF

Figure 8. Dependence of solvation enthalpy, ΔH_{solv}^0 , vs the alcohol chain length (n).

It is not difficult to see that the studied drugs may be subdivided on the 2 main groups (from the point of view of the values of their enthalpies of solvation); one group (ie, NAP and DIF) has strong interactions with the solvents; and the other (ie, BA, KETO, ASA, FBP, and IBP), much less.

Figure 9. Dependence of entropy term of solvation Gibbs energy, $T\Delta S_{solv}^0$, vs the alcohol chain length (n).

Dependence of the entropy term of the Gibbs energy of solvation vs the alcohol chain length (n) for ASA and IBP is shown in **Figure 9** (again together with BA, DIF, FBP, KETO, and NAP for comparison). It should be mentioned that the regularity of the behavior of this function differs from ΔH_{solv}^0 and ΔG_{solv}^0 (absolute value):

KETO < FBP < BA < ASA < IBP < NAP < DIF

This term is a measure of the order of the solvent (for example octanol) molecules within the solvation shell of the respective drug molecule.

As follows from **Table 1**, the enthalpy part of the Gibbs energy of solvation for ASA and IBP exceeds the entropy in the considered solvents. In order to quantitatively estimate the ratio of these terms the following parameters were introduced:

$$\zeta_H = [|\Delta H_{solv}^0| / (|\Delta H_{solv}^0| + |T \cdot \Delta S_{solv}^0|)] 100\% \quad (9)$$

$$\zeta_S = [|T \cdot \Delta S_{solv}^0| / (|\Delta H_{solv}^0| + |T \cdot \Delta S_{solv}^0|)] 100\% \quad (10)$$

Dependence of $\zeta_H = f(n)$ for ASA, IBP, and other NSAIDs on the chain length of the alcoholic solvent is shown in **Figure 10**. The investigated substances can be arranged in the order of decreasing of ζ_H (in octanol) as follows:

KETO > FBP > DIF $\approx$ NAP > IBP > ASA > BA

For all compounds, the main driving force of solvation is the enthalpy.

Figure 10. Dependence of ζ_H (see text) vs the alcohol chain length (n).

The relationship between ΔG_{solv}^{Oct} and ΔH_{solv}^{Oct} is presented in **Figure 11**. A compensation effect¹⁴ is observed for the considered drugs (with the exception of FBP and KETO) in octanol, meaning that the higher the drug-octanol interaction energy, the higher the order of the solvent molecules within the solvation shell. How-

ever, FBP and KETO demonstrate anomalous behavior with strongly disordered solvation shells (as has been mentioned above). Therefore, it may be assumed that these molecules have unusual transport properties in terms of distribution between phases of different lipophilicity, even biopharmaceutical behavior.

Figure 11. Dependence of ΔG_{solv}^{Oct} vs ΔH_{solv}^{Oct} .

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