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Research paper

Thermodynamics of solutions III: comparison of the solvation of (+)-naproxen with other NSAIDs

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Abstract

Naproxen was studied by classical thermoanalytical methods, namely sublimation calorimetry, solution calorimetry and the solubility method. Temperature dependence of a saturated vapor pressure was obtained and the sublimation enthalpy, ΔH^0_{sub}, and entropy, ΔS^0_{sub}, and their relative fraction of the total process were calculated. These parameters yielded for naproxen were compared to the respective data of other naphthalene derivatives. The crystal lattice energy of naproxen was calculated by two force fields (Gavezzotti et al. and Mayo et al.) and compared to the experimental data. Contributions of different motifs of the naproxen molecule to the total packing energy were analyzed. The Gibbs energy of solvation as well as enthalpic and entropic terms thereof in aliphatic alcohols have been studied for naproxen, and compared to model substances and other non-steroid anti-inflammatory drugs (benzoic acid, diflunisal and flurbiprofen). The major driving force of the solvation process is the enthalpy. The respective contributions of the specific and the non-specific solvation interactions in terms of absolute and relative values have been investigated.

Keywords: Naproxen; Sublimation; Solubility; Solvation; Isothermal calorimetry; Thermodynamic; Organic solvents

1. Introduction

The pharmacokinetic properties of drug molecules are strongly dependent on their interaction with biological membranes. The main qualification for the ability of a drug molecule to passively penetrate through membranes by diffusion is their lipophylic–hydrophilic balance. However, the diffusion rate depends strongly both on the concentration gradient and the energetic parameters of the drug–membrane interaction. The diffusion process consists of a number of elementary activation steps, each having a definite energy barrier. These energy barriers may be split into two general forms: (a) non-specific drug–membrane interactions (van der Waals interactions) and (b) specific interactions (hydrogen bonding, donor–acceptor interactions). The overall diffusion characteristics are a function of both the absolute strength of these interactions, and the balance between them. In other words, the solvation properties of drug molecules, i.e. an understanding of the nature of interactions and the estimation of relative and absolute energetic terms thereof, are the key to understanding not only the mechanism of passive transport, but also the mechanism of drug–receptor interactions. In the past, relative measures of the lipophylic–hydrophilic properties of drug molecules, like the logarithm of the partitioning coefficient between water and octanol, log *P*, have been used extensively. In recent publications [1,2], we have in contrast tried to define an absolute lipophylicy scale for drug molecules of the group of non-steroid anti-inflammatory drugs (NSAID). The present work is a continuation of these studies, based on the analysis of drug solvation characteristics, where the experimental data were obtained by using classical thermoanalytical methods, namely sublimation, solution calorimetry and the solubility method. In contrast to previous work, where phenyl derivatives (acetylsalicylic and benzoic acids) [1] and biphenyl derivatives (diflunisal and flurbiprofen) [2] have been considered, in the present study (+)-naproxen (NAP) was chosen as a representative of the same class of drugs (NSAID), but having a more complicated structure

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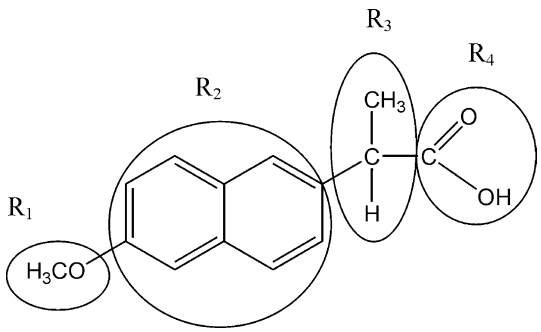


Fig. 1. Structure of the (+)-naproxen molecule; fragmentation of the molecule for calculations.

(naphthalene motif, Fig. 1). This enables one to compare solvation characteristics of a wide spectrum of compounds using quantitative parameters derived from experimental data. The objective may be to correlate these to pharmokinetic and pharmodynamic properties of drugs.

The solubility of naproxen in various organic solvents [3] and its distribution in water–octanol systems [4] have already been studied by other authors and methods. Bustamante et al. [3] estimated the different terms of the total solubility parameter of naproxen corresponding to dispersion, polar, hydrogen bonding, proton–donor and proton–acceptor interactions by means of both three- and four-parameter models. Estimation of regression coefficients of the expanded Hansen equation [5] showed that naproxen as a solute is more of a proton donor than a proton acceptor, while the non-specific term changes only little in any solvent more or less independently of the parameters of the solvents. Betageri et al. [4] obtained the temperature dependencies of partitioning coefficients log K in water–octanol and in water–lipid systems for naproxen, and based on the data the thermodynamic functions of transfer have been analyzed. The transfer enthalpies and transfer entropies from water to octanol have positive values, whereas the values of these functions for water–liposome systems are negative. According to the authors this fact is due to the ability of naproxen to create hydrogen bonds between its polar group and the lipid bilayer.

2. Experimental section

2.1. Materials and solvents

The studies of NAP ((*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid, $C_{14}H_{14}O_3$, MW 230.3) was carried out using commercially available substance from Sigma, St Louis, USA (lot 120K 3657).

The origin and grades of the alcohols were as follows: methanol (MeOH, CH_3OH, MW 32.04) HPLC grade from Merk (Germany), lot K27636907; ethanol (EtOH, CH_3CH_2OH, MW 46.2) extra pure grade (99.6% v/v, maximum water content 0.4%); 1-propanol (*n*-propanol, $CH_3(CH_2)_2OH$, MW 60.10) HPLC grade from Aldrich (Germany), lot U00874; 1-butanol (BuOH, $CH_3(CH_2)_3OH$, MW 74.12) analytical reagent grade (ARG) from Merk (Germany), lot K22047090; 1-pentanol (*n*-pentanol, $CH_3(CH_2)_4OH$, MW 88.15) ARG from Aldrich (Germany), lot 35757-101; 1-hexanol (*n*-hexanol, $CH_3(CH_2)_5OH$, MW 102.18) ARG from Aldrich (Germany), lot 31562-011; 1-heptanol (*n*-heptanol, $CH_3(CH_2)_6OH$, MW 116.2) ARG from Sigma (USA), lot 60K3706; 1-octanol (*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2) ARG from Sigma (USA), lot 11K3688.

The organic solvents were as follows: *n*-hexane (C_6H_{14}, MW 86.18) ARG from SDS (Peypin, France), lot 07059903C; Benzene (C_6H_6, MW 78.12) ARG from Merk (Germany), lot K26454983.

2.2. Solubility determination

Solubilities of NAP were obtained at 25 ± 0.1 °C. The solubility in benzene was determined by the weighing method with a reproducibility of about 3%. All the other experiments were carried out by a spectrophotometrical method with an accuracy of about 2.5% using the protocol described previously [6].

2.3. Solution calorimetry

Enthalpies of solution at a concentration m (ΔH^m_{sol}) were measured using an isothermal precision solution calorimeter (development and engineering of Institute of Solution Chemistry of Russian Academy of Sciences) described in detail in Ref. [7]. The sum of variability of the heat effect of each respective experiment does not exceed 1%. The measuring temperature was 25 ± 0.0001 °C, volume of the vessel 100 ml, stirrer speed 500 rev./min and the mass of each sample approximately 18 mg. The accuracy of weight measurements (Sartorius M2P) corresponded to ±1 μg. The calorimeter was calibrated using KCl (analytical grade >99.5%, from Merck) in water in a wide concentration interval with more than 10 measurements. The standard value of solution enthalpy obtained was $\Delta H^0_{sol} = 17,225 \pm 50$ J mol^{-1}. This is in good agreement with the value recommended by IUPAC of $\Delta H^0_{sol} = 17,217 \pm 33$ J mol^{-1} [8].

2.4. Sublimation experiments

Sublimation experiments were carried out by the transpiration method, as previously described [9]. The equipment was calibrated using benzoic acid (standard substance obtained from Polish Committee of Quality and Standards) with an enthalpy of combustion of $\Delta H_c = -3228.07$ kJ mol^{-1} and a heat of melting corresponding to $\Delta H_{fus} = 18.0$ kJ mol^{-1}. The standard value of sublimation enthalpy obtained was $\Delta H^0_{sub} = 90.5 \pm 0.3$ J mol^{-1}. This is in good agreement

with the value recommended by IUPAC of $\Delta H^0_{sol} = 89.7 \pm 0.5$ J mol^{-1} [8]. The saturated vapor pressures were measured at each temperature at least five times with the statistical error being within 3–5%. The experimentally determined vapor pressure data were described in (ln P; 1/T) co-ordinates by Eq. (1)

$$\ln(P) = A + \frac{B}{T} \quad (1)$$

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

$$\Delta H^T_{sub} = -R\frac{\partial(\ln P)}{\partial(1/T)} \quad (2)$$

whereas the entropy of sublimation at a given temperature T was calculated from the following relation

$$\Delta S^T_{sub} = \frac{(\Delta H^T_{sub} - \Delta G^T_{sub})}{T} \quad (3)$$

where $\Delta G^T_{sub} = -RT \ln(P/P_0)$ and $P_0 = 1.013 \times 10^5$ Pa.

2.5. Statistical analysis

Regression analysis of the data was performed using standard statistical procedures by in-house software.

2.6. Energy calculation procedure

Molecular crystals consist of discrete molecules, which interact by intermolecular non-bonded interactions. Therefore the crystal lattice energy, E_{latt}, may be divided into three main terms: van der Waals, E^{vdw}; electrostatic (Coulombic), E^{coul}, and hydrogen bonds energy, E^{HB}

$$E_{latt} = E^{vdw} + E^{coul} + E^{HB} \quad (4)$$

Non-bonded van der Waals interactions of the crystal lattice energy have been calculated as the sum of atom–atom interactions [10]. Two types of force fields are common: Mayo et al. [11] (Lenard-Jones 12-6) (**M**) and Gavezzotti [12] (exponential-6 form) (**G**), and in the present study both are used and compared. The calculation procedure has been described earlier [13].

3. Results and discussion

3.1. Thermodynamics of naproxen sublimation

Temperature dependencies of saturation vapor pressure, thermodynamic parameters of sublimation and fusion processes of naproxen are summarized in Table 1.

It is a prerequisite of the method that during the whole experiment and within the temperature interval used, neither any chemical decomposition of the compound both in the measuring cell and in the sublimated products nor a temperature dependence of the stripping gas vapor pressure occurs. Then, the dependencies of the saturation vapor pressure of the compounds on the temperature may be described using Eqs. (1)–(3) and yielding linearity that can be extrapolated to standard conditions. The results of the linear regression as well as the calculated standard Gibbs energy, entropy as well as enthalpy of sublimation are listed in Table 1.

Table 1
Temperature dependence of vapor pressure, thermodynamic parameters of sublimation and fusion processes of (+)-naproxen

No.	t (°C)	P (Pa)
1	68.0	4.17×10^{-3}
2	71.5	6.66×10^{-3}
3	75.0	9.63×10^{-3}
4	77.5	1.38×10^{-2}
5	81.0	2.20×10^{-2}
6	86.0	3.73×10^{-2}
7	90.0	6.20×10^{-2}
8	94.0	9.56×10^{-2}
9	97.5	1.53×10^{-1}
10	99.0	1.83×10^{-1}
11	105.5	3.61×10^{-1}
12	110.5	6.19×10^{-1}
13	118.0	1.35
14	121.0	1.72
15	124.0	2.39

ΔH^0_{sub} (kJ mol^{-1})	128.3 ± 0.5
$T\,\Delta S^0_{sub}$ (kJ mol^{-1})	69.8
ΔS^0_{sub} (J mol^{-1} K^{-1})	234 ± 1
ΔG^0_{sub} (kJ mol^{-1})[a]	58.5
ς_H (%)[b]	64.8
ς_{TS} (%)[b]	35.2
T^f (°C)[c]	154.4
ΔH_{fus} (kJ mol^{-1})[c]	31.5 ± 2.1
ΔS_{fus} (J mol^{-1} K^{-1})[d]	74
ΔH_{vap} (kJ mol^{-1})	96.8
ΔS_{vap} (J mol^{-1} K^{-1})	160

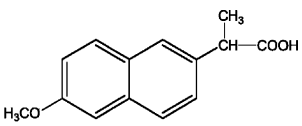
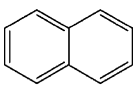
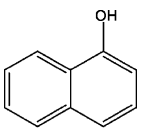
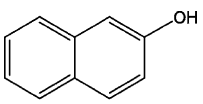
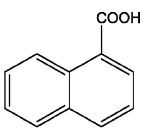
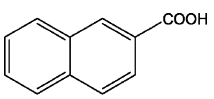
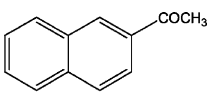
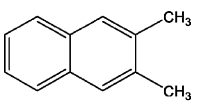
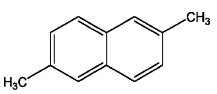
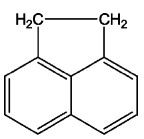
$\ln(P) = (39.7 \pm 0.2) - (15{,}431 \pm 65)/T$; $r = 0.99987$; $\sigma = 3.22 \times 10^{-2}$; $F = 58{,}613$; $n = 15$

[a] $\Delta G^0_{sub} = -RT \ln(P^{25}/P_0)$.
[b] $\varsigma_H = (\Delta H^0_{sub}/(\Delta H^0_{sub} + T\,\Delta S^0_{sub}))100\%$; $\varsigma_{TS} = (T\,\Delta S^0_{sub}/(\Delta H^0_{sub} + T \times \Delta S^0_{sub}))100\%$.
[c] Ref. [14].
[d] $\Delta S_{fus} = \Delta H_{fus}/T^f$.

In order to derive a systematic relation between the thermodynamic parameters of sublimation and the compound structure, a correlation analysis for some other naphthalene derivatives has been carried out taking into account values from the literature. Thermodynamic parameters of the sublimation process as well as the structures of the substances are shown in Table 2. The dependence between the Gibbs energy of sublimation, ΔG^0_{sub}, and the enthalpy of sublimation, ΔH^0_{sub}, is presented in Fig. 2.

As follows from Table 2, the enthalpic term of the Gibbs energy of sublimation for all the investigated compounds is more than 1.6 times bigger than the entropic one. As follows from Fig. 2, compensation effect between the thermodynamic

Table 2
Thermodynamic parameters of sublimation of some naphthalene derivatives

No.	Compound	ΔH^0_{sub} (kJ mol^{-1})	ΔG^0_{sub} (kJ mol^{-1})	$T\,\Delta S^0_{sub}$ (kJ mol^{-1})	ς_H[a] (%)	ς_{TS}[a] (%)	Ref.
1	 Naproxen	128.3 ± 0.5	58.5	69.8	64.8	35.2	tw
2	 Naphthalene	72.9 ± 0.3	22.4	50.5	59.1	40.9	[15]
3	 1-Naphthol	91.2 ± 0.4	35.3	55.9	62.0	38.0	[16]
4	 2-Naphthol	94.1 ± 0.4	38.3	55.8	62.8	37.2	[16]
5	 1-Naphtholic acid	110.4 ± 0.4	50.0	60.4	64.6	35.4	[17]
6	 2-Naphtholic acid	113.3 ± 0.8	52.5	60.8	65.2	34.8	[17]
7	 2-Acetyl-naphthalene	87.9 ± 0.4	34.9	53.0	62.4	37.6	[18]
8	 1,2-dimethyl-naphthalene	79.9 ± 0.3	30.6	49.3	61.8	38.2	[18]
9	 2,6-dimethyl-naphthalene	84.0 ± 0.4	31.0	53.0	61.3	38.7	[18]
10	 Acenaphthene	82.1 ± 0.4	31.5	61.9	61.9	38.1	[18]

$\Delta G^0_{sub} = (-23 \pm 3) + (0.65 \pm 0.03)\Delta H^0_{sub}$; $R = 0.992$; $\sigma = 1.51$; $F^{2.5\%}_{tab} = 4.36$; $F = 506.7$; $n = 10$

[a] $\varsigma_H = (\Delta H^0_{sub}/(\Delta H^0_{sub} + T\,\Delta S^0_{sub}))100\%$; $\varsigma_{TS} = (T\,\Delta S^0_{sub}/(\Delta H^0_{sub} + T\,\Delta S^0_{sub}))100\%$.

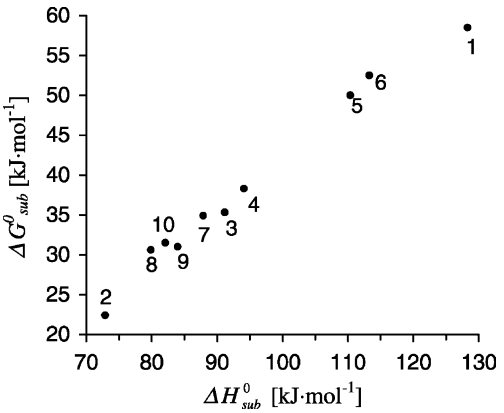


Fig. 2. Sublimation Gibbs energy, ΔG^0_{sub}, vs. sublimation enthalpy, ΔH^0_{sub}, for compounds with a naphthalene motif (numbering corresponds to Table 2).

functions ΔG^0_{sub}, and ΔH^0_{sub} is observed for the compounds regarded (corresponding correlation, see Table 2).

The nature and position of the substituents on the naphthalene ring plays an essential role for the crystal lattice energy. Introducing any of the substituents (–CH_3 (**8**, **9**); –$COCH_3$ (**6**); –OH (**3**, **4**); –COOH (**5**, **6**); –$CH(CH_3)$-COOH (**1**)) to the naphthalene motif results in an increase of the crystal lattice energy in comparison to the unsubstituted naphthalene. Moreover, for all the substituents, which can form a hydrogen bond network within the crystal lattice (–OH; –COOH, –$CH(CH_3)$COOH), this increase in crystal energy is bigger compared to non-H-bond-forming ones: (**8**, **9**) < (**3**, **4**, **5**, **6**, **1**); **7** < **6**.

The position of the respective substituents also influences the crystal lattice energy. A bigger van der Waals's molecular surface corresponds to bigger crystal lattice energy: **3** < **4**; **5** < **6**; **8** < **9**. The crystal lattice energy of naproxen itself is the maximum value of all the considered compounds. This finding may be explained by the following factors: (a) interference of all the parameters mentioned above; or (b) presence of a special topology of the hydrogen bond network consisting of helicoids lengthwise (parallel) to a screw axis of second order [19]. Based on the data, it may be proposed that moving the methoxy group from position 6- to position 5- in the naproxen molecule would essentially decrease the crystal lattice energy and, as a consequence, increases the solubility of the compound. This relative/analogue to naproxen has been described previously, but unfortunately no data on solubility are available [20].

In order to find a more appropriate theoretical approach for describing the naproxen crystal lattice energy, a calculation thereof using the two different force fields was carried out: Mayo et al. [11] (DREIDING), **M**, and Gavezzotti [12], **G**. The co-ordinates of the atoms in the unit cell obtained from the X-ray experiment [19] were used to calculate the packing energy of the crystal. The results of calculations in terms of van der Waals (E^{vdw}), electrostatic (Coulombic, E^{coul}), and hydrogen bonds energy (E^{HB}) and the lattice energy (E_{latt}) are presented in Table 3. As follows from Table 3, both the van der Waals and the hydrogen bond energy obtained by the **G**-force field exceed the analogous values for the Mayo force field **M**. However, the relative contributions of the respective terms are approximately equal for both force fields: $E^{vdw} \sim 77\%$, $E^{coul} \sim 8\%$ and $E^{HB} \sim 15\%$ of the total lattice energy E_{latt} (Table 3). In all cases the van der Waals forces are by far the strongest, followed by hydrogen bonds, and the electrostatic forces are least effective.

Table 3
The calculation results of the various energetic terms of (+)-naproxen crystal lattice obtained by the two types of the force fields

Terms	(+)-NAP (kJ mol^{-1}; % in parentheses)		
	G	**M**	**Δ(G − M)**
E^{vdw}	−111.9 (77.1)	−98.1 (76.8)	−13.8
E^{coul}_s	−10.1 (7.0)	−10.1 (7.9)	0
E^{HB}	−23.1 (15.9)	−19.4 (15.3)	−3.7
E_{latt}	−145.1 (100)	−127.6 (100)	−17.5
$\Delta H_{sub} - \lvert E_{latt}\rvert$[a]	−16.8	0.7	

M, Mayo et al. [11] and **G**, Gavezzotti et al. [12].
[a] $\Delta H_{sub} = 128.3 \pm 0.5$ kJ mol^{-1}.

By comparing the experimentally measured values of the crystal lattice energy of naproxen to the theoretically calculated values, it can be supposed that the **M**-force field describes the experimental value more adequately than the **G**-force field. Therefore, in the following the analysis of energetic terms presented below was carried out by the **M**-force field only.

The van der Waals term of the crystal lattice energy is studied in more detail in order to compare the contribution of several structural fragments of the complex naproxen molecule. For this purpose the molecule has been divided into four fragments, as is shown in Fig. 1. The results of the calculations using the **M**-force field, both as absolute and relative values, are presented in Table 4. As follows from Table 4, the impact which is by far the biggest is attributed to the naphthalene–naphthalene interaction (43.2%) and the next biggest to the interaction between the naphthalene- and the methoxy-fragment (10.2%). The contributions of the other fragments are approximately equal and small. It is interesting to note that the energy term for the van der Waals interaction between two carboxylic groups is positive. This fact probably is a consequence of the creation of hydrogen bonding by the fragment.

The enthalpy of evaporation may be estimated using the value of the enthalpy of fusion taken from the literature [14] and the measured enthalpy of sublimation by Eq. (5)

$$\Delta H^0_{sub} = \Delta H_{fus} + \Delta H_{vap} \quad (5)$$

The respective value for the enthalpy of evaporation of naproxen is $\Delta H_{vap} = 96.8$ kJ mol^{-1} (Table 1). This value

Table 4
The calculation results of the Van der Waals terms of the packing energy from the various fragments of (+)-naproxen molecule (using Mayo et al. [11] force field)

Terms (kJ mol^{-1})	R_1	R_2	R_3	R_4	Terms[a]	R_1	R_2	R_3	R_4
R_1	−1.2				R_1	1.3			
R_2	−9.8	−41.6			R_2	10.2	43.2		
R_3	−3.2	−4.4	−3.1		R_3	3.4	4.6	3.2	
R_4	−4.0	−4.5	−3.5	8.3	R_4	4.1	4.7	3.7	−8.7

[a] $(E^{R_i-R_j}/E^{vdw})100\%$ (%).

resembles approx. 3/4 of the enthalpy of sublimation, whereas the enthalpy of fusion, ΔH_{fus}, accounts for the residual 1/4 of the enthalpy of sublimation.

3.2. Thermodynamics of naproxen solvation in aliphatic alcohols

The thermodynamic parameters of dissolution and solubility (ΔG^0_{sol}, ΔH^0_{sol}, $T\,\Delta S^0_{sol}$) and of the solvation processes (ΔG^0_{solv}, ΔH^0_{solv}, $T\,\Delta S^0_{solv}$) of naproxen in aliphatic alcohols, benzene and hexane are presented in Tables 5 and 6, respectively, where $\Delta H^0_{solv} = \Delta H^0_{sol} - \Delta S^0_{sub}$ and $\Delta S^0_{solv} = \Delta S^0_{sol} - \Delta S^0_{sub}$. The concentration of naproxen in the respective alcohols is near the ideal solubility only in *n*-heptanol, in all other cases it is less than the ideal value.

ΔG^0_{solv} is plotted versus the alcohol chain length (n) in Fig. 3 together with analogous values for benzoic acid, BA as a model, and the NSAIDs diflunisal, DIF, and flurbiprofen, FBP, taken from earlier studies [1,2]. As can be seen from Fig. 3, the noted drugs may be arranged in the order of increasing absolute values of the Gibbs energy of solvation: BA < FBP < NAP < DIF. Apparently there are two distinct groups: BA on the one hand, and FBP, NAP and DIF on the other. All the drugs are solvated approx. 1.7 times stronger in the alcohols compared to BA. This fact may be due to the second phenyl fragment in the structure of all the molecules in the group of the drug substances. It is interesting to note that for the compounds belonging to the second group, naproxen is solvated stronger than FBP, but less than DIF. Probably, the particularly strong solvation ability of the diflunisal molecule is due to the existence of two hydroxy-groups which can form hydrogen bonds (whereas naproxen and FBP have only one).

The enthalpy of solvation ΔH^0_{solv} versus the alcohol chain length (n) for naproxen is plotted in Fig. 4 (again analogous values for BA, DIF and FBP are plotted for better comparison from Refs. [1,2]). The function for naproxen is not monotonous and has a maximum at $n = 5$. The analyzed compounds may be arranged according to increasing ΔH^0_{solv} absolute values in the higher alcohols as follows: BA < FBP < NAP < DIF, which is the same rank order as mentioned above for ΔG^0_{solv}, It should be noted that at $n < 4$, the NAP and DIF exchange places in the rank order. In contrast to ΔG^0_{solv}, where all three drug substances yield roughly similar values, the solvation enthalpy ΔH^0_{solv} of FBP is considerably smaller (absolute value) compared to NAP and DIF.

This difference in the behavior of flurbiprofen needs to be related to the entropy of solvation. The dependence of the entropy term of the Gibbs energy of solvation $T\,\Delta S^0_{solv}$ versus the alcohol chain length (n) for the studied substances is shown in Fig. 5 (naproxen values from the present study, BA, DIF and FBP from Refs. [1,2]). For the entropy of solvation ΔS^0_{solv} (absolute values) the following rank order is found:

Table 5
Thermodynamic functions of the naproxen solubility process in aliphatic alcohols at 25 °C

Solvents	X_2	γ^a	ΔG^0_{sol} (kJ mol^{-1})	ΔH^0_{sol} (kJ mol^{-1})	$T\,\Delta S^0_{sol}$ (kJ mol^{-1})	ΔS^0_{sol} (J K^{-1} mol^{-1})	$\Delta H^{Ben\,b}_{tr}$ (kJ mol^{-1})	$\Delta H^{Hex\,b}_{tr}$ (J mol^{-1} K^{-1})
Benzene	0.00372	5.62	13.9	26.3 ± 0.2	12.4	41.6	0	
n-Hexane	0.000957	21.8	17.2	48.1 ± 0.5	30.9	103.6		0
MeOH	0.00857	2.44	11.8	24.2 ± 0.2	12.4	41.6	−2.1	−23.9
EtOH	0.0107	1.95	11.2	25.3 ± 0.2	14.1	47.3	−1.0	−22.8
n-Propanol	0.0122	1.71	10.9	24.9 ± 0.2	14.0	47.0	−1.4	−23.2
n-BuOH	0.0139	1.50	10.6	25.8 ± 0.2	15.2	51.0	−0.5	−22.3
n-Pentanol	0.0147	1.42	10.5	26.9 ± 0.2	16.4	55.0	0.6	−21.2
n-Hexanol	0.0166	1.26	10.2	26.1 ± 0.2	15.9	53.3	−0.2	−22.0
n-Heptanol	0.0201	1.04	9.7	24.6 ± 0.2	14.9	50.0	−1.7	−23.5
n-Octanol	0.0146	1.43	10.5	21.2 ± 0.2	10.7	35.9	−5.1	−26.9

[a] $\gamma = X_2^{id}/X_2$, $\ln X_2^{id} = (\Delta H_{fus}/R)(1/T^f - 1/T)$; $X_2^{id} = 0.0209$ (see Table 1 and Ref. [14]).
[b] $\Delta H^{Ben}_{tr} = \Delta H^0_{sol}$(solvent) − ΔH^0_{sol}(benzene); $\Delta H^{Hex}_{tr} = \Delta H^0_{sol}$(solvent) − ΔH^0_{sol}(hexane).

Table 6
Thermodynamic functions of the naproxen solvation process in aliphatic alcohols at 25 °C

Solvents	$-\Delta G^0_{solv}$ [a] (kJ mol^{-1})	$-\Delta H^0_{solv}$ (kJ mol^{-1})	$-T\,\Delta S^0_{solv}$ (kJ mol^{-1})	ς_H [b] (%)	ς_{TS} [c] (%)	ε_H(Ben)[d] (%)	ε_H(Hex) (%)
Benzene	44.6	102.0	57.4	64.0	36.0	0	–
n-Hexane	41.3	80.2	38.9	67.3	32.7	–	0
MeOH	46.7	104.1	57.4	64.5	35.5	2.0	29.8
EtOH	47.3	103.0	55.7	64.9	35.1	1.0	28.4
n-Propanol	47.6	103.4	55.8	64.9	35.1	1.4	28.9
n-BuOH	47.9	102.5	54.6	65.2	34.8	0.5	27.8
n-Pentanol	48.0	101.4	53.4	65.5	34.5	−0.6	26.4
n-Hexanol	48.3	102.2	53.9	65.5	34.5	0.2	27.4
n-Heptanol	48.8	103.7	54.9	65.4	34.6	1.7	29.3
n-Octanol	48.0	107.1	59.1	64.4	35.6	5.0	33.5

[a] $\Delta G^0_{solv} = \Delta G^0_{sol} - \Delta G^0_{sub}$.
[b] $\varsigma_H = (|\Delta H^0_{solv}|/(|\Delta H^0_{solv}| + |T\,\Delta S^0_{solv}|))100\%$.
[c] $\varsigma_{TS} = (|T\,\Delta S^0_{solv}|/(|\Delta H^0_{solv}| + |T\,\Delta S^0_{solv}|))100\%$.
[d] $\varepsilon_H = |\Delta H_{spec}/\Delta H_{nonspec}|100\%$, where $\Delta H_{spec} = \Delta H_{tr}$ and $\Delta H_{non\text{-}spec} = \Delta H^0_{solv}$ (Ben or Hex).

FBP < BA < NAP < DIF. It is concluded that the solvation shells of NAP and DIF in the alcohols are more ordered compared to FBP and BA. Moreover, it is surprising that FBP (the enthalpy of solvation of which (absolute value) is even bigger than that of BA) has solvation shells that are of anomalously low order compared to the other substances.

As also follows from Table 6, the enthalpy term of Gibbs energy of solvation for naproxen in the considered solvents exceeds the entropy term. In order to quantitatively estimate the fraction of the respective terms of the total Gibbs energy of solvation the following parameters were introduced

$$\varsigma_H = \frac{|\Delta H^0_{solv}|}{(|\Delta H^0_{solv}| + |T\,\Delta S^0_{solv}|)}100\% \quad (6)$$

$$\varsigma_S = \frac{|T\,\Delta S^0_{solv}|}{(|\Delta H^0_{solv}| + |T\,\Delta S^0_{solv}|)}100\% \quad (7)$$

Dependence $\varsigma_H = f(n)$ for naproxen and the other NSAIDs is shown in Fig. 6. The main driving force of the solvation process for all the considered compounds is the enthalpy. The investigated substances, in the order of decreasing ς_H, can be arranged: FBP > DIF ≈ NAP > BA.

It can be said more generally that for all substances the solvation is enthalpy-driven with a fraction of 60–70%.

Similar to earlier investigated compounds [1,2], for naproxen a linear correlation between enthalpic and entropic terms of the Gibbs energy of solution is observed in the alcohols (so-called compensation effect [21,22]), Fig. 7. Detailed results of the correlation analysis are given in Table 7. As follows from the values, the studied compounds can be divided into two classes. Firstly, there are those substances for which the enthalpic term of the solution (solvation) process is less sensitive to a change of the properties of the solvent, i.e. alcohol chain length, in comparison to the entropic term ($A_1 < 1$) : to this group belong NAP, DIF and ASA. To the second group, which shows stronger dependence of the enthalpy of solution on the alcohol chain length ($A_1 > 1$), belong FBP and BA.

However, partitioning coefficients log *P* of drug substances in water–octanol systems are generally used to

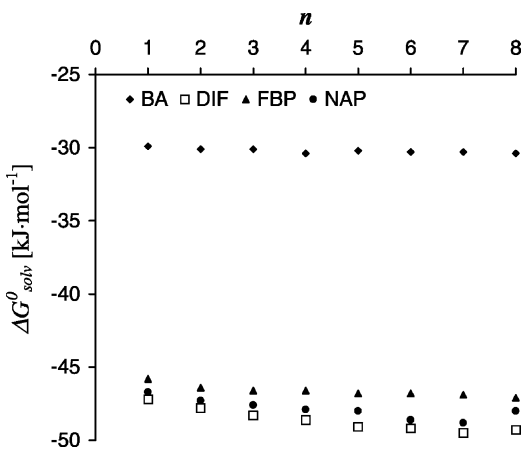


Fig. 3. Dependence of solvation Gibbs energy, ΔG^0_{solv}, on the alcohol chain length (*n*).

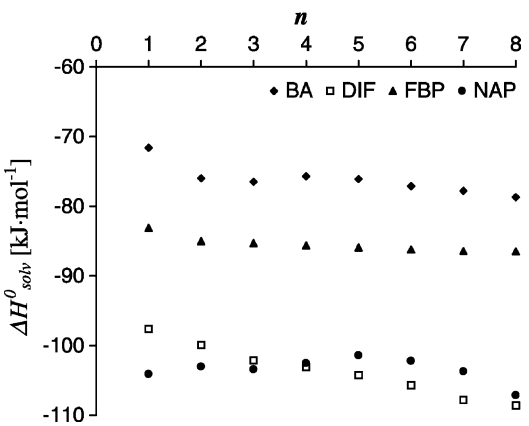


Fig. 4. Dependence of solvation enthalpy, ΔH^0_{solv}, on the alcohol chain length (*n*).

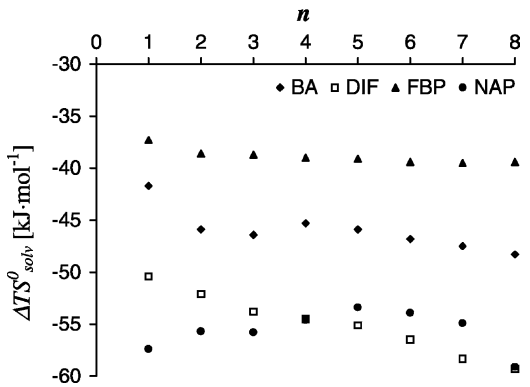


Fig. 5. Dependence of entropy term of solvation Gibbs energy, $T\,\Delta S^0_{solv}$, on the alcohol chain length (n).

describe the dissolution in different media. The partition coefficients of the respective unionized form of the drugs (at pH 2.0) are listed in Table 8, and give the following increasing rank order: $\log P_{2.0}(\text{BA}) < \log P_{2.0}(\text{NAP}) < \log P_{2.0}(\text{FBP}) < \log P_{2.0}(\text{DIF})$. From the data it follows that the high value of $\log P_{2.0}$(FBP) and a lower ΔH^0_{solv}-value in octanol (both in comparison to NAP and DIF, see Fig. 4) may be connected with an essential influence of the hydrophobic effect on the $P_{2.0}$-value. Based on the water solubility data of these compounds and Gibbs energies of sublimation, the Gibbs energies of hydration ΔG^0_{hydr} can be estimated (Table 8). As follows from the data, naproxen is hydrated stronger than FBP but less than DIF. This information is useful for the estimation of the passive transport properties, particularly through the paracellular route (i.e. between cells), which is supposed to be modeled as a water-filled pathway [23].

In previous studies [1,2] we introduced a method on how to estimate the balance between specific and non-specific interactions in the solvation process. As mentioned above, this balance can be assumed to be a key characteristic of passive transport properties of drug substances. Since for the passive transport of a molecule through a membrane

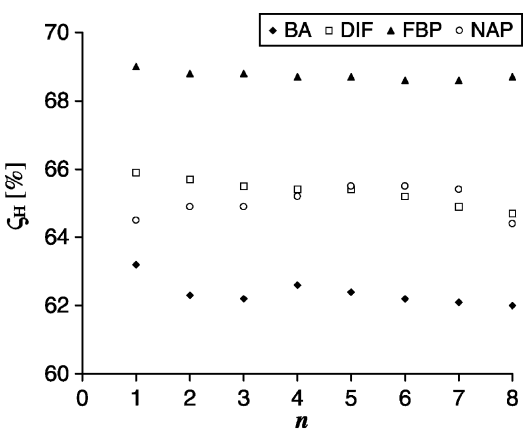


Fig. 6. ς_H, the relative fraction of the solvation enthalpy, ΔH^0_{solv}, in the solvation Gibbs energy, ΔG^0_{solv} (see text) vs. the alcohol chain length (n).

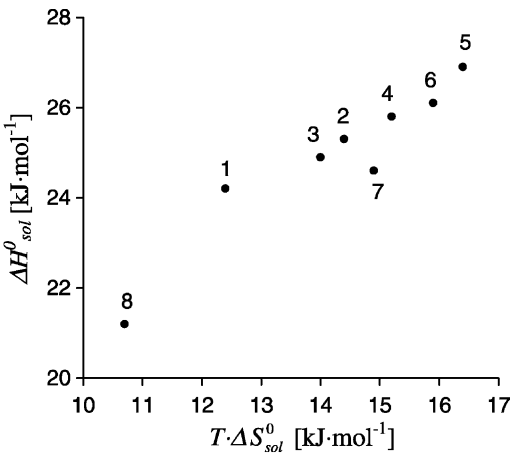


Fig. 7. Relationship between the entropic term of the solubility process, ΔH^0_{sol}, and the enthalpic term, $T\,\Delta S^0_{sol}$, for naproxen (numbering corresponds to the alcohol chain length, n).

the activation energy of the diffusion step depends on the number and strength of hydrogen bonds being created, we introduced the parameters ε_H and ε_S which as a way of estimation of the outlined properties.

In a first step, the virtual transition of a molecule from a solution in an 'inert' solvent (only non-specific interactions) into the alcoholic solution is considered and the respective energy difference calculated according to Eq. (8)

$$\Delta H^{Ben}_{tr} = \Delta H^0_{sol}(\text{alcohol}) - \Delta H^0_{sol}(\text{inert solvent}) \quad (8)$$

The next step is to normalize the transition enthalpy in order to compare different substances using Eq. (9)

$$\varepsilon_H = |\Delta H_{spec}/\Delta H_{non\text{-}spec}|100\% \quad (9)$$

where $\Delta H_{spec} = \Delta H_{tr}$ and $\Delta H_{non\text{-}spec} = \Delta H^0_{solv}$ (inert solvent).

For ASA, BA, DIF and FBP, in previous studies [1,2] benzene was chosen as the inert solvent (which does not enter into any specific interaction with the drug molecules). In the present study another inert solvent—*n*-hexane is used in addition to benzene for the same type of calculations. The reason for this is first of all that it is interesting to check how the nature of the inert solvent would affect the estimated values of ε_H. Secondly, it is reasonable to choose the inert solvent as to have a similar structure motif to the investigated drug molecule (e.g. the common phenyl). The calculated transfer enthalpies of naproxen, being transferred from a benzene or a hexane solution, respectively, into the various alcoholic solutions are presented in Table 5, and the corresponding normalized ε_H-values in Table 6. As follows from Tables 5 and 6, the choice of the inert solvent markedly influences the estimation of the ε_H value. It is the authors' opinion that charge transfer interactions considerably contribute to the non-specific benzene–naproxen interaction. This example can be assessed as a typical case for compounds

Table 7
The results of regression analysis for equation $\Delta H^0_{sol} = A_0 + A_1(T\,\Delta S^0_{sol})$ in aliphatic alcohols

Compounds	A_0	A_1	σ	R	F	$F^{2.5\%}_{tab}$	n
Naproxen	13 ± 2	0.86 ± 0.13	0.626	0.941	46.8	5.696	8
Flurbiprofen[a]	−1.4 ± 0.8	1.50 ± 0.05	0.0882	0.998	898	9.365	6
Diflunisal[a]	10.2 ± 0.7	0.91 ± 0.09	1.02	0.968	90.6	5.696	8
Benzoic acid[b]	3.0 ± 0.1	1.12 ± 0.03	0.146	0.998	1456	5.696	8
Acetylsalicylic acid[b]	12 ± 1	0.76 ± 0.06	0.123	0.986	140	9.365	6

[a] Ref. [1].
[b] Ref. [2].

Table 8
The values of partitioning, solubility and Gibbs energy of hydration (partly from the literature)

	log $P_{2.0}$	Solubility in water (mol l^{-1})	Solubility in octanol[a]	ΔG^0_{hydr} (kJ mol^{-1})[b]	ΔG^0_{solv} [b] octanol (kJ mol^{-1})
Benzoic acid	1.87[c]	2.82×10^{-2}[c]	1.987×10^{-1}[d]	−15.6	−30.4[d]
Naproxen	3.54[e]	6.31×10^{-5}[c]	1.46×10^{-2}	−24.6	−48.0
Flurbiprofen	4.16[e]	1.82×10^{-4}[f]	8.17×10^{-2}[g]	−22.0	−47.1[g]
Diflunisal	4.44[e]	6.39×10^{-4}[h]	3.52×10^{-2}[g]	−29.4	−49.3[g]

[a] Mol fraction.
[b] Concentration have been recalculated in mol fraction.
[c] Ref. [24].
[d] Ref. [1].
[e] Ref. [25].
[f] Ref. [26].
[g] Ref. [2].
[h] Ref. [27].

with phenyl and naphthalene motifs. Probably, these non-specific charge transfer effects are approximately as strong as the specific interactions between naproxen and the respective alcohol, and therefore the total transfer effect equals zero. If, in contrast, hexane is used in analogous calculations, the noted effects are not observed. Therefore it may be more correct to determine the contributions of specific interaction, which forms approximately 30% (it depends from the alcohol) of (from) the non-specific one.

The present work attempts to elucidate drug transport and delivery phenomena from the point of view of the solvation of molecules in different media.

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