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Thermodynamic properties of flufenamic and niflumic acids—Specific and non-specific interactions in solution and in crystal lattices, mechanism of solvation, partitioning and distribution

German L. Perlovich [a,b], Artem O. Surov [b,c], 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*
[c] *Ivanovo State University of Chemical Sciences and Technology, 153460 Ivanovo, Russia*

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Abstract

Temperature dependency of saturated vapour pressure and the thermochemical characteristics of the fusion process were measured for flufenamic acid and niflumic acid, and thermodynamic functions of sublimation, fusion and evaporation calculated. An approach to split specific and non-specific energetic terms in crystal lattices is developed. The melting points of the considered molecules correlate with the ratio between specific and non-specific interactions in crystal lattices. Temperature dependencies of the solubility in buffers with pH 2.0 and 7.4, in *n*-octanol and in *n*-hexane were measured. The thermodynamic functions of solubility, solvation and transfer processes were deduced. Specific and non-specific solvation terms were distinguished by the transfer from "inert" *n*-hexane to the other solvents. Comparison of the ratio between specific and non-specific interactions in solid state and in the solutions was carried out. A diagram to analyse energetic terms of partitioning and distribution processes is introduced.

Keywords: Flufenamic acid; Niflumic acid; Sublimation thermodynamics; Solubility; Solvation; Transfer; Crystal lattice energy; Specific and non-specific interactions; Partitioning; Distribution

1. Introduction

One of the key issues in drug design is to let the molecules actually reach their target. Each stage of the processes involved, as there are liberation (dissolution), absorption, distribution, and passive transport, is determined by the solvation characteristics of the drug molecules. So far, these questions have been addressed mainly from the point of view of relative thermodynamic functions in the form of partitioning and distribution coefficients (log *P*, log *D*). In our previous work [1–3] we have approached this problem by analysis of the thermodynamic functions in absolute energetic scales, in order to understand the mechanisms and driving forces of the drug transport and drug delivery processes.

The subjects for the present investigation are flufenamic acid and niflumic acid (Fig. 1) as further examples of NSAIDs (non-steroidal antiinflammatory drugs). These molecules were chosen because they are structurally closely related and differ only by the aromatic motif, being a phenyl or a pyridin ring, respectively. It is interesting to analyse the effect of this structural difference on crystal lattice energies, solubility in different solvents, solvation energies in these solvents, and on the partitioning (distribution) properties. It should be noted that in the literature there are some articles devoted to studies of the crystal lattice structures of niflumic acid [4] and flufenamic acid [5]. Thermochemical characteristics of the fusion process of niflumic acid have been investigated by Pinvidic et al. [6] using DTA, DSC, and TG methods. Solubility of niflumic acid has been analysed in solvent mixtures and has been related to the polarity of these mixtures by Bustamante et al. [7]. Protonation constants of niflumic acid in various solutions and in octanol/water, as well as partitioning and distribution coefficients of different molecular forms have been studied by Takacs-Novak et al. [8].

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

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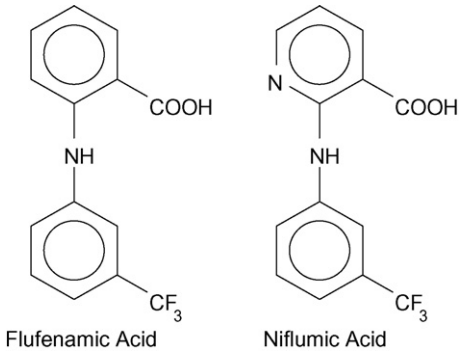


Fig. 1. Structure formula of flufenamic and niflumic acids.

In the present study we try: (a) to split specific and non-specific interaction terms in the crystals with those in pharmaceutical important media (aqueous buffers with pH 2.0 and 7.4 and *n*-octanol) in absolute energetic scale values and compare the relative fractions thereof; (b) to study the mechanism and driving forces of partitioning (distribution) processes.

2. Materials and methods

Flufenamic acid (2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid, $C_{14}H_{10}F_3NO_2$, FW 281.23, lot 122K1018) and niflumic acid (2-[3-(trifluoromethyl)anilino]nicotinic acid, $C_{13}H_9F_3N_2O_2$, FW 282.2, lot 12K1486) were from Sigma Chemical Co., St. Louis, USA.

1-Octanol (*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2, lot 11K3688) ARG from Sigma Chemical Co. (USA). *n*-Hexane (C_6H_{14}, MW 86.18, lot 07059903C) ARG from SDS (Peypin, France). 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 pH 7.4. All the chemicals were of AR grade. The pH values were controlled using a pH meter (Electroanalytical Analyser, Type OP-300, Radelkis, Budapest) calibrated with solutions of pH 1.68 and 9.22.

Sublimation experiments were carried out by the transpiration method as previously described [2]. In brief: a stream of an inert gas passes the sample at a given constant temperature and at a known slow constant flow rate in order to achieve saturation of the carrier gas with the vapour of the substance under investigation. The vapour is condensed at some point downstream, and the mass of the sublimate and its purity determined. The vapour pressure above the sample at this temperature can be calculated from the amount of sublimated material and the volume of the inert gas used.

The equipment was calibrated using benzoic acid. The standard value of sublimation enthalpy obtained was $\Delta H^\circ_{sub} = 90.5 \pm 0.3\,kJ\,mol^{-1}$. This is in good agreement with the value recommended by IUPAC of $\Delta H^\circ_{sub} = 89.7 \pm 0.5\,kJ\,mol^{-1}$ [9]. The saturated vapour pressures were measured at least five times at each temperature, with the statistical error being within 3–5%. The experimentally determined vapour pressure data are described in ($\ln P$; $1/T$) co-ordinates by Eq. (1):

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

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

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

The entropy of sublimation at a given temperature T was calculated from the following relationship:

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

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

Solubility experiments. All the experiments were carried out by the isothermal saturation method at five temperature points: $20, 25, 30, 37, 42 \pm 0.1\,^\circ C$. The solid phase was removed by both centrifugation and isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size). The experimental results stated are the average of at least five replicated experiments. The molar solubilities of the drugs studied were measured spectrophotometrically with an accuracy of 2–2.5% using a protocol described previously [1].

Differential scanning calorimetry (DSC) was carried out using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin-Elmer Analytical Instruments, Norwalk, CT, USA) and Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing ($20\,ml\,min^{-1}$) dry nitrogen gas of high purity 99.990% using standard closed aluminum sample pans. The DSC was calibrated with indium from Perkin-Elmer (P/N 0319-0033). The value of the determined enthalpy of fusion corresponded to $28.48\,J\,g^{-1}$ (reference value $28.45\,J\,g^{-1}$). The melting point was $429.7 \pm 0.1\,K$ ($n = 10$). All the DSC-experiments were carried out at a heating rate of $10\,K\,min^{-1}$. The accuracy of weight measurements was ±0.005 mg (Sartorius M2P semi-microbalance).

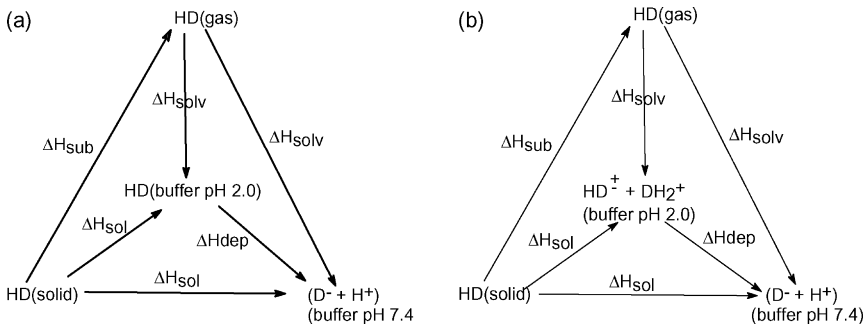
3. Results and discussion

Before starting to study the solvation process, let us first introduce some basic definitions. The solvation of 1 mol of solute molecules in the solvent can be defined as the total change of the standard thermodynamic functions (ΔG°, ΔH°, ΔS°) of the compound when transferring it from the gas phase (ideal gas; single molecules without interaction) into the solvent. The thermodynamic cycle of solvation is illustrated in Scheme 1, from which it follows that

$$\Delta Y^\circ_{solv} = \Delta Y^\circ_{sol} - \Delta Y^\circ_{sub} \tag{4}$$

where ΔY° is the standard change of any of the thermodynamic functions of the solvation (ΔY°_{solv}), dissolution (ΔY°_{sol}), or sublimation (ΔY°_{sub}) process. Therefore, the following equations may be defined

$$\Delta G^\circ_{solv} = \Delta G^\circ_{sol} - \Delta G^\circ_{sub} \tag{5}$$



Scheme 1.

$$\Delta H^{\circ}_{solv} = \Delta H^{\circ}_{sol} - \Delta H^{\circ}_{sub} \quad (6)$$

$$T\,\Delta S^{\circ}_{solv} = T\,\Delta S^{\circ}_{sol} - T\,\Delta S^{\circ}_{sub} \quad (7)$$

In order to study the solvation process, which is not directly experimentally accessible, one needs to investigate the other two processes: sublimation and dissolution.

4. Sublimation experiments

The experimental results in terms of temperature dependencies of saturation vapour pressures are summarized in Table 1. Calculated thermodynamic parameters of sublimation, fusion and evaporation processes are presented in Table 2.

Sublimation data are yielded at elevated temperatures for experimental reasons. However, in comparison to fusion methods, the temperatures are much lower, which makes extrapolation to room conditions easier. In order to further improve the extrapolation to room conditions, heat capacities ($C^{298}_{p,cr}$-value) of the crystals were estimated using the additive scheme proposed by Chickos and Acree [10]. Heat capacity was introduced as a correction for the recalculation of the sublimation enthalpy ΔH^{T}_{sub}-value at 298 K (ΔH^{298}_{sub}-value), according to Eq. (8) [10]:

$$\Delta H^{298}_{sub} = \Delta H^{T}_{sub} + \Delta H_{cor} = \Delta H^{T}_{sub} + (0.75 + 0.15C^{298}_{p,cr})(T - 298.15) \quad (8)$$

where T corresponds to the minimal temperature of the experimental interval.

The projections of molecular packing in the crystal lattices of flufenamic and niflumic acids are shown in Fig. 2a and b, respectively. It should be noted that the drug molecules are arranged in the form of dimer structures. The hydrogen bond network

Table 1
Temperature dependencies of saturation vapour pressure of flufenamic and niflumic acids

Flufenamic acid[a]		Niflumic acid[b]	
t (°C)	P (Pa)	t (°C)	P (Pa)
65.5	1.04×10^{-2}	81.5	6.41×10^{-3}
68.0	1.40×10^{-2}	85.0	1.04×10^{-2}
70.5	1.87×10^{-2}	86.5	1.25×10^{-2}
72.0	2.35×10^{-2}	91.0	2.11×10^{-2}
72.5	2.47×10^{-2}	93.0	2.55×10^{-2}
73.5	2.84×10^{-2}	95.0	3.33×10^{-2}
78.0	4.46×10^{-2}	97.5	4.24×10^{-2}
82.0	7.35×10^{-2}	100.0	5.61×10^{-2}
84.0	9.44×10^{-2}	102.5	7.28×10^{-2}
88.0	1.44×10^{-1}	104.0	8.80×10^{-2}
91.0	2.14×10^{-1}	106.0	1.08×10^{-1}
95.0	3.17×10^{-1}	108.5	1.38×10^{-1}
96.0	3.40×10^{-1}	113.5	2.25×10^{-1}
97.0	3.87×10^{-1}	117.0	3.53×10^{-1}
103.0	6.84×10^{-1}	120.0	4.54×10^{-1}
		123.0	6.57×10^{-1}

[a] $\ln(P\ (\text{Pa})) = (37.8 \pm 0.2) - (14363 \pm 81)/T$; $\sigma = 2.87 \times 10^{-2}$; $r = 0.9998$; $F = 31{,}453$; $n = 15$.
[b] $\ln(P\ (\text{Pa})) = (38.3 \pm 0.3) - (15361 \pm 93)/T$; $\sigma = 3.25 \times 10^{-2}$; $r = 0.9999$; $F = 27{,}169$; $n = 16$.

topology of both crystal lattices can be described by one graph set assignment [11] in the following way: $R^2_2(8)$ for the dimer, and $S(6)$ for the intramolecular hydrogen bond.

As a next step of our investigation we tried to split up specific and non-specific interactions in the crystal lattices. The common method for doing so is to use calculation procedures with adaptation of various forces fields [12]. However, it should be mentioned that in these calculations it is difficult to take terms

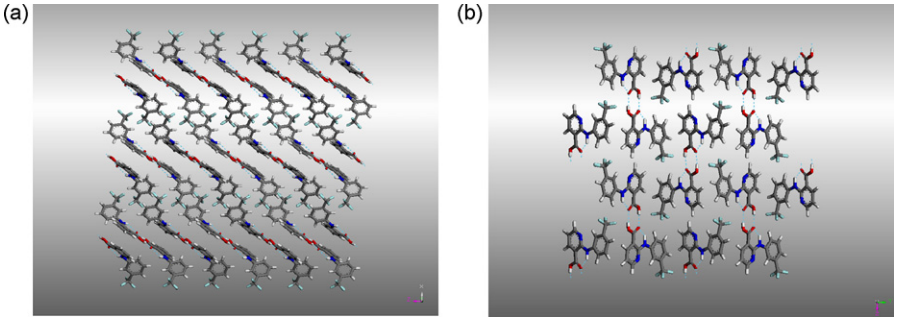


Fig. 2. Packing architectures of flufenamic (a) and niflumic (b) acids.

Table 2
Thermodynamic characteristics of sublimation, fusion, vaporization of flufenamic and niflumic acids

	ΔG^{298}_{sub} (kJ mol^{-1})	ΔH^{T}_{sub} (kJ mol^{-1})	ΔH^{298}_{sub} (kJ mol^{-1})	$C^{298}_{p,cr}$ [a] (J mol^{-1} K^{-1})	ΔS^{298}_{sub} (J mol^{-1} K^{-1})	T_m (K)	ΔH_{fus} (kJ mol^{-1})	ΔH^{298}_{fus} (kJ mol^{-1})	ΔS_{fus} (J mol^{-1} K^{-1})	ΔH^{298}_{vap} (kJ mol^{-1})
Flufenamic	54.3	119.4 ± 0.7	121.2 ± 0.7	296.2	224 ± 2	405.3 ± 0.2	26.7 ± 0.5	19.6	66 ± 2	101.6
Niflumic	61.3	127.7 ± 0.8	130.2 ± 0.8	292.6	231 ± 2	478.4 ± 0.2	36.5 ± 0.5	22.7	76 ± 2	107.5

[a] Calculated by Chickos's additive scheme [10].

describing the conformational strength of the molecules in the crystal lattice into account. Introducing correction to the functions of the pair potentials is a complicated procedure, which even needs to be done individually for each molecular substance or at least for different molecular structure motifs. Moreover, this contribution becomes significant for conformational flexible molecules, particularly those including several cyclic fragments, as is the case with the compounds under investigation. Another prerequisite in splitting the contributions of specific and non-specific interactions by a calculation procedure is the availability of solved crystal structures. In some cases it is not possible to grow single crystals of a drugs and drug-like molecular compounds which are suitable for X-ray diffraction experiments.

In order to overcome this problem, the following approach was taken: the sublimation enthalpies of molecular crystals were taken from Chickos and Acree's [10] database. The van der Waals's molecular volumes were calculated by the program GEPOL [13] and from Kitaigorodsky's atomic radii [14]. In order to build the energetic level of non-specific molecular interaction in the crystal lattices, which include contribution of the molecular conformational strength, from all the available values the following have been chosen: (a) those that are without any hydrogen bond networks, (b) groups of compounds with various topological structures (benzene, biphenyl, naphthalene, benzophenone, biphenyl ether, diphenylamine derivatives and other bicycle substances with a connecting bridge including several atoms (not more than three)); (c) the sizes of substituents do not exceed the size of *t*-Bu fragment. There were 71 molecular crystals fulfilling these conditions, and they can be described by following correlation equation (Fig. 3):

$$\Delta H^{vdw}_{sub} = (11 \pm 2) + (0.46 \pm 0.02)V^{vdw}$$
$$(r = 0.973;\ s = 4.1;\ n = 71) \quad (9)$$

This correlation is used to calculate the fraction of non-specific interaction in the crystal lattice for the studied compounds, and the difference to the experimental value of sub-

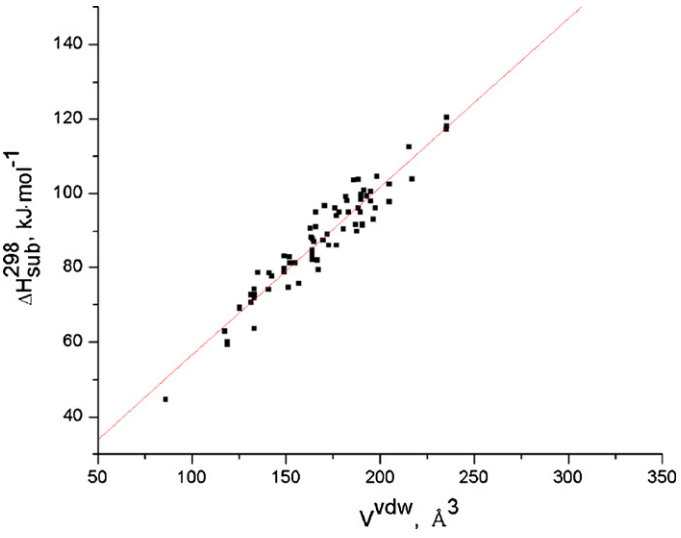


Fig. 3. Relationship between sublimation enthalpies, ΔH^{298}_{sub}, and van der Waals volumes, V^{vdw}, of some molecular crystals (see text).

Table 3
Calculated values of non-specific, $\Delta H_{sub}^{non\text{-}spec}$, and specific, ΔH_{sub}^{spec}, sublimation enthalpy terms of flufenamic and niflumic acids

	ΔH_{sub}^{T} (kJ mol^{-1})	$\Delta H_{sub}^{non\text{-}spec}$ [a] (kJ mol^{-1})	ΔH_{sub}^{spec} (kJ mol^{-1})	ε_{sub} [b] (%)
Flufenamic	121.2 ± 0.7	106.3	14.9	14
Niflumic	130.2 ± 0.8	106.7	23.5	22

[a] Calculated by the correlation equation (9) $\Delta H_{sub}^{non\text{-}spec} = \Delta H_{sub}^{vdw}$.
[b] $\varepsilon_{sub} = (\Delta H_{sub}^{spec} / \Delta H_{sub}^{non\text{-}spec}) \times 100\%$.

limation enthalpy is attributed to the specific interaction, thereby splitting specific and non-specific terms within the crystal lattices without detailed structure information and crystal structure calculations, the values of which are presented in Table 3.

It is quite obvious that the two compounds under investigation, as having approximately the same van der Waals volumes, they also have approximately the same non-specific interaction, leading to a fraction of the specific interaction for niflumic acid of 22%, whereas for the flufenamic acid the respective value is 14%. Probably this difference is due to the additional possibility for H-bonding in the niflumic acid compared to the flufenamic acid.

In the literature [15] it has been extensive discussed the relationship between the melting points of substances (which are relatively easily experimentally available) and the crystal lattice energetic terms. Based on previously obtained experimental data on the thermodynamic parameters of the sublimation of crystals, as being a measure for the crystal lattice energy, we address this question once more [1,2,16,17], and introduce the above outlined approach for distinguishing specific and non-specific terms as well. Melting points of a number of drugs and drug-like compounds are plotted versus the ratio between specific and non-specific terms of the crystal lattices in Fig. 4.

The compounds plotted in Fig. 4 can conditionally be divided into two groups: (a) phenyl derivatives and (b) compound comprising several cyclic fragments. For each group linear correlation between the noted parameters is observed. This would mean that the more specific interaction in the crystal lattice, the higher the melting point. Moreover, for the group of the phenyl derivatives, the slope of the correlation line is lower compared to the other group: at the same value for the discussed ratio between specific and non-specific interaction the melting point is higher for the group of compounds with a more complex structure (several cyclic motives). In other words: the ratio between specific and non-specific interaction is more sensitive to a change of T_m. Probably this fact also explains the better correlation of the phenyl derivatives in comparison to the other group.

5. Thermodynamics of solubility, solvation and transfer processes

To estimate specific and non-specific solvation terms in absolute energetic scale and to compare these to analogous terms in the respective crystal lattices, temperature dependencies of solubility in pharmaceutical relevant solvents were measured (where aqueous buffers of pH 2.0 and 7.4 were chosen as well as *n*-octanol as a widely used solvent for the evaluation of lipophyl-

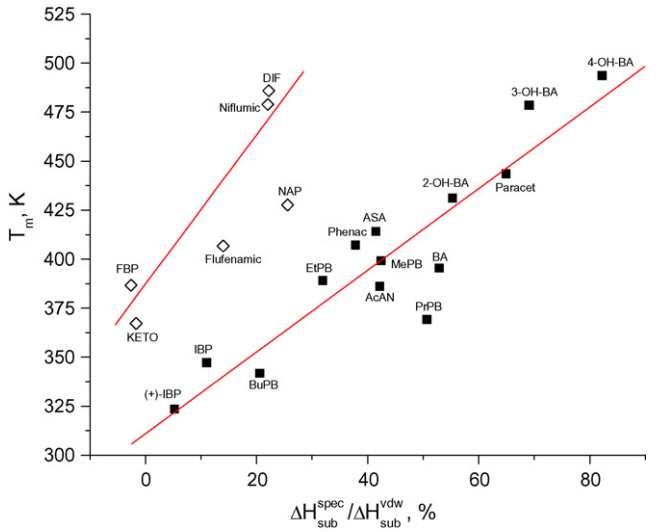


Fig. 4. Dependence the melting points, T_m, vs. the ratio between specific and non-specific terms, $\Delta H_{sub}^{spec}/\Delta H_{sub}^{vdw}$, of the crystal lattices ((+)-IBP: (+)-ibuprofen; IBP: (±)-ibuprofen; MePB: methyl-paraben; EtPB: ethyl-paraben; PrPB: propyl-paraben; BuPB: butyl-paraben; ASA: acetylsalicylic acid; AcAN: acetanilide; Paracet: paracetamol; Phenacet: phenacetin; 2-OH-BA: 2-hydroxy-benzoic acid; 3-OH-BA: 3-hydroxy-benzoic acid; 4-OH-BA: 4-hydroxy-benzoic acid; KETO: ketoprofen; NAP: (+)-naproxen; FBP: flurbiprofen; DIF: diflunisal; Niflumic: niflumic acid; Flufenamic: flufenamic acid).

icy and biopharmaceutical properties). The experimental results are summarized in Table 4. In order to distinguish the outlined terms, *n*-hexane was used as a reference solvent, which interacts with the molecules only by non-specific forces. As a measure of the specific interactions, the respective transfer functions from *n*-hexane to the other solvents were used. In order to estimate the contribution of specific in comparison to the non-specific interaction, the ε_H parameter has been introduced in previous works [1]:

$$\varepsilon_H = \left(\frac{\Delta H_{spec}}{\Delta H_{non\text{-}spec}} \right) \times 100\% \quad (10)$$

where $\Delta H_{spec} = \Delta H_{tr}^{\circ}$(*n*-hexane → solvent) and $\Delta H_{non\text{-}spec} = H_{solv}^{\circ}$ (*n*-hexane).

The thermodynamic functions of dissolution and solvation processes are presented in Table 5. As follows from Table 5, all the studied dissolution processes in aqueous buffers at pH 2.0 and 7.4, in *n*-octanol, and in *n*-hexane, are endothermic. This is evidence for solvation enthalpies not overweighing the respective crystal lattice energies.

To compare enthalpic and entropic terms of solvation, parameters ς_H and ς_{TS} are used to describe the relative fraction of enthalpy and entropy of solvation, as has been introduced previously [1]:

$$\varsigma_{H_{solv}} = \left(\frac{|\Delta H_{solv}^{\circ}|}{|\Delta H_{solv}^{\circ}| + |T\,\Delta S_{solv}^{\circ}|} \right) \times 100\% \quad (11)$$

$$\varsigma_{TS_{solv}} = \left(\frac{|T\,\Delta S_{solv}^{\circ}|}{|\Delta H_{solv}^{\circ}| + |T\,\Delta S_{solv}^{\circ}|} \right) \times 100\% \quad (12)$$

The energy of interaction of niflumic acid with molecules of the respective solvents under consideration is higher compared

Table 4
Temperature dependencies of flufenamic and niflumic acids solubility in buffers with pHs 2.0 and 7.4, *n*-hexane and *n*-octanol

t (°C)	X_2			
	pH 2.0	pH 7.4	*n*-Hexane	*n*-Octanol
Flufenamic acid				
20.0	–	0.78×10^{-4}	1.45×10^{-5}	7.72×10^{-2}
25.0	–	1.01×10^{-4}	1.98×10^{-5}	9.20×10^{-2}
30.0	4.63×10^{-9}	1.32×10^{-4}	2.59×10^{-5}	10.3×10^{-2}
33.0	5.50×10^{-9}	–	–	–
37.0	6.97×10^{-9}	1.78×10^{-4}	3.99×10^{-5}	12.8×10^{-2}
40.0	8.22×10^{-9}	–	–	–
42.0	9.20×10^{-9}	2.29×10^{-4}	5.12×10^{-5}	14.9×10^{-2}
A[a]	1.2 ± 0.2	-5.9 ± 0.3	11.2 ± 0.1	6.7 ± 0.3
B[a]	5457 ± 49	4500 ± 84	5504 ± 22	2720 ± 82
R[b]	0.9998	0.9995	0.9999	0.9986
σ[c]	5.18×10^{-3}	1.6×10^{-2}	4.2×10^{-3}	1.58×10^{-2}
t (°C)	X_2			
	pH 2.0	pH 7.4	*n*-Hexane	*n*-Octanol
Niflumic acid				
20.0	3.25×10^{-6}	1.63×10^{-4}	1.40×10^{-5}	2.59×10^{-2}
25.0	3.67×10^{-6}	2.09×10^{-4}	1.65×10^{-5}	2.94×10^{-2}
30.0	4.17×10^{-6}	2.69×10^{-4}	2.03×10^{-5}	3.36×10^{-2}
37.0	4.77×10^{-6}	3.92×10^{-4}	2.47×10^{-5}	4.09×10^{-2}
42.0	5.29×10^{-6}	5.00×10^{-4}	2.91×10^{-5}	4.68×10^{-2}
A[a]	5.7 ± 0.2	-7.5 ± 0.2	-0.6 ± 0.3	4.8 ± 0.2
B[a]	2035 ± 46	4751 ± 67	3081 ± 89	2493 ± 53
R[b]	0.9992	0.9997	0.99873	0.9993
σ[c]	8.9×10^{-3}	1.29×10^{-2}	1.72×10^{-2}	1.02×10^{-2}

[a] Parameters of the correlation equation: $\ln X_2 = -A - B/T$.
[b] Pair correlation coefficient.
[c] S.D.

to the corresponding values for flufenamic acid. The solvation process of the drugs in the solvents is in all cases enthalpy determinate. However, the hydration of flufenamic acid in buffer of pH 2.0 has an essentially higher contribution (in comparison with the other solvents) of the entropy part ($\varsigma_{TS_{solv}} = 48\%$), a fact being evidence for a typical hydrophobic effect. The hydrophobic effect is observed for niflumic acid in buffer pH 2.0 as well, but it is not so pronounced as it is for flufenamic acid. The hydrophobic effect is graded partly for the buffer with pH

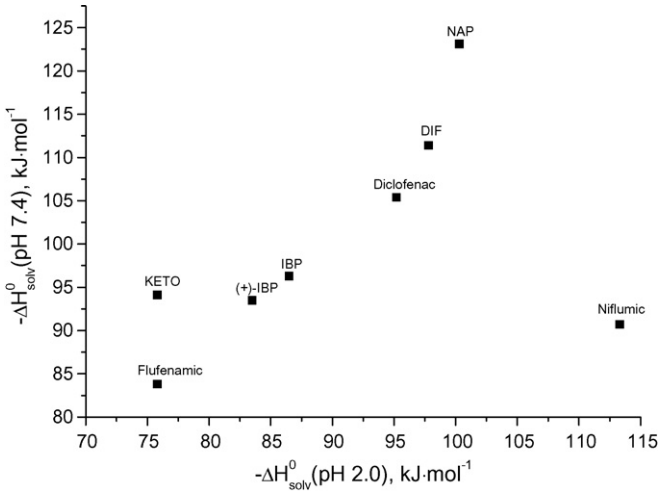


Fig. 5. Relationship between solvation (hydration) enthalpies of the drugs studied in the buffers with pH 2.0 and 7.4 (see notation for Fig. 4).

7.4 due to the salt replenishes of the buffer and ionic form of the drug molecules. The experimental data of solvation (hydration) enthalpy in the buffers of the presently investigated compounds, together with other NSAIDs that have been studied before [3], are shown in Fig. 5. It is not difficult to see that the enthalpy of solvation in the buffer pH 7.4 is larger than in acidic medium buffer pH 2.0, with the only exception being niflumic acid. Probably, this behaviour is connected with the fact that the molecules of the niflumic acid in the buffer with pH 2.0 are, in contrast to all the others, still in an ionic form, even as a mixture of the two ionic forms: H_2D^+ and $DH^{\pm}$ (zwitterionic form) [8].

The transfer processes from one solvent to the other are described by the differences of the respective thermodynamic terms in the different solvents, and the results are listed in Table 6. The transfer processes of the studied molecules from *n*-hexane to the other solvents (specific solvation) are essentially different from each other. For example, the transfer process (*n*-hexane → buffer pH 2.0) for both drugs is entropy determinate, however, the $\varsigma_{H_{tr}}$-value for flufenamic acid is about 2%, whereas for the value for niflumic acid is as high as 41%. The reason for the latter finding may be again that niflumic acid is dissociated in the aqueous medium at pH 2. The thermodynamic functions

Table 5
Thermodynamic functions of solubility and solvation processes of flufenamic and niflumic acids in solvents studied

Solvent	X_2^{25} (molar fraction)	ΔG°_{sol} (kJ mol^{-1})	ΔH°_{sol} (kJ mol^{-1})	$T\,\Delta S^\circ_{sol}$ (kJ mol^{-1})	ΔS°_{sol} (J K^{-1} mol^{-1})	$-\Delta G^\circ_{solv}$ (kJ mol^{-1})	$-\Delta H^\circ_{solv}$ (kJ mol^{-1})	$-T\,\Delta S^\circ_{solv}$ (kJ mol^{-1})	$-\Delta S^\circ_{solv}$ (J K^{-1} mol^{-1})	$\varsigma_{H_{solv}}$ (%)	$\varsigma_{TS_{solv}}$ (%)
Flufenamic acid											
pH 2.0	3.00×10^{-9}	48.4	45.4 ± 0.4	−3.0	−10 ± 1	5.9	75.8	69.9	234	52.0	48.0
pH 7.4	1.01×10^{-4}	22.8	37.4 ± 0.7	14.6	49 ± 2	31.5	83.8	52.3	175	61.6	38.4
n-Hexane	1.98×10^{-5}	26.8	45.8 ± 0.2	19.0	64 ± 1	27.5	75.4	47.9	161	61.2	38.8
n-Octanol	9.20×10^{-2}	5.9	22.6 ± 0.7	16.7	56 ± 2	48.4	98.6	50.2	168	66.3	33.7
Niflumic acid											
pH 2.0	3.67×10^{-6}	31.0	16.9 ± 0.4	−14.1	−47 ± 1	30.3	113.3	83	278	57.7	42.3
pH 7.4	2.09×10^{-4}	21.0	39.5 ± 0.5	18.5	62 ± 2	40.3	90.7	50.4	169	64.3	35.7
n-Hexane	1.65×10^{-5}	27.3	25.6 ± 0.7	−1.7	−6 ± 2	34.0	104.6	70.6	237	59.7	40.3
n-Octanol	2.94×10^{-2}	8.7	20.7 ± 0.4	12.0	40.3 ± 1.5	52.6	109.5	56.9	191	65.8	34.2

$\varsigma_{H_{solv}} = (|\Delta H^\circ_{solv}|/(|\Delta H^\circ_{solv}| + |T\,\Delta S^\circ_{solv}|)) \times 100\%$, $\varsigma_{TS_{solv}} = (|T\,\Delta S^\circ_{solv}|/(|\Delta H^\circ_{solv}| + |T\,\Delta S^\circ_{solv}|)) \times 100\%$.

Table 6
Thermodynamic parameters of transfer processes of flufenamic and niflumic acids

	ΔG°_{tr} (kJ/mol)	ΔH°_{tr} (kJ/mol)	$T\,\Delta S^{\circ}_{tr}$ (kJ/mol)	$\varsigma_{H_{tr}}$ [a] (%)	$\varsigma_{TS_{tr}}$ [b] (%)	ε_H [c] (%)
Flufenamic acid						
n-Hexane → pH 2.0	21.6	−0.4	−22.0	−1.8	−98.2	0.5
n-Hexane → pH 7.4	−4.0	−8.4	−4.4	−65.6	−34.4	11.1
n-Hexane → *n*-octanol	−20.9	−23.2	−2.3	−91.0	−9.0	30.8
pH 7.4 → pH 2.0	25.6	8.0	−17.6	31.2	−68.8	–
pH 2.0 → *n*-octanol	−42.5	−14.8	27.7	−34.8	65.2	–
pH 7.4 → *n*-octanol	−16.9	−22.8	−5.9	−79.4	−20.6	–
Niflumic acid						
n-Hexane → pH 2.0	3.7	−8.7	−12.4	−41.2	−58.8	8.3
n-Hexane → pH 7.4	−6.3	13.9	20.2	40.8	59.2	−13.3
n-Hexane → *n*-octanol	−18.6	−4.9	13.7	−26.3	73.7	4.7
pH 7.4 → pH 2.0	10.0	−22.6	−32.6	−40.9	−59.1	–
pH 2.0 → *n*-octanol	−21.6	3.8	25.4	13.0	87.0	–
pH 7.4 → *n*-octanol	−12.3	−18.8	−6.5	−74.3	−25.7	–

[a] $\varsigma_{H_{tr}} = (\Delta H^{\circ}_{tr}/(|\Delta H^{\circ}_{tr}| + |T\,\Delta S^{\circ}_{tr}|)) \times 100\%$.
[b] $\varsigma_{TS_{tr}} = (T\,\Delta S^{\circ}_{tr}/(|\Delta H^{\circ}_{tr}| + |T\,\Delta S^{\circ}_{tr}|)) \times 100\%$.
[c] $\varepsilon_H = (\Delta H_{spec}/\Delta H_{non\text{-}spec}) \times 100\%$, where $\Delta H_{spec} = \Delta H^{\circ}_{tr}$ (*n*-hexane → solvent)/ΔH°_{solv} (*n*-hexane).

of the transfer process of the substances (*n*-hexane → buffer pH 7.4), where both molecules are dissociated, differ considerably as well. For the flufenamic acid the noted process is enthalpy controlled, with the enthalpy term overweighing the entropy by a factor of 2, whereas for niflumic acid the process is entropy controlled with positive signs for both thermodynamic functions (ΔH°_{tr} and $T\,\Delta S^{\circ}_{tr}$).

The transfer process (*n*-hexane → *n*-octanol) of flufenamic acid is enthalpy determinate (with the enthalpy term exceeding the entropy by approximately a factor of 10), whereas for niflumic acid the same transfer process is entropy determinate (with a three-fold excess of the entropy term compared to the enthalpy, and having opposite signs).

It is interesting to analyse differences of the ratio between specific and non-specific interactions in the crystals ($\varepsilon_{sub} = \Delta H^{non\text{-}spec}_{sub}/\Delta H^{spec}_{sub}$) and in the solutions ($\varepsilon_H$). The experimental data of the ε_H-values for the buffer with pH 2.0 and for the *n*-octanol versus ε_{sub}-values are presented in Fig. 6a and b, correspondingly. For the buffer solution, ε_H values do not exceed the analogous characteristics for the crystals for any of the considered compounds with an exception for acetanilide (AcAN), which shows a higher ε_H value. When comparing the fraction of specific solvation enthalpy in octanol, however, there is a number of drugs where this value exceeds the specific interaction in the crystal lattice: $\varepsilon_H > \varepsilon_{sub}$; this behaviour is found for butylparaben (BuPB), ethylparaben (EtPB), naproxen (NAP) and flufenamic acid. The analysed ε_H and ε_{sub} parameters serves as a measure of the role of the specific interactions in solution in comparison to the solid state.

Finally, as a last step of the present investigation, the thermodynamic functions of transfer of the studied compounds from the buffers to *n*-octanol, being widely discussed as reflecting some biopharmaceutical properties of drugs, were studied (Table 6). The experimental data of the thermodynamic functions for niflumic, flufenamic acids together with some other NSAIDs [3,18] are summarized in Fig. 7, where enthalpies and entropies of transition between the respective buffers and octanol are plotted. The diagram is divided into four separate sectors, according to the values for the respective energies as follows: the regions where ($T\,\Delta S^{\circ}_{tr} > \Delta H^{\circ}_{tr} > 0$) ≡ sector I, and ($\Delta H^{\circ}_{tr} < 0; T\,\Delta S^{\circ}_{tr} > 0; |T\,\Delta S^{\circ}_{tr}| > |\Delta H^{\circ}_{tr}|$) ≡ sector II correspond to entropy determinate processes. The regions of the diagram where ($\Delta H^{\circ}_{tr} < 0; T\,\Delta S^{\circ}_{tr} > 0; |\Delta H^{\circ}_{tr}| > |T\,\Delta S^{\circ}_{tr}|$) ≡ sector III, and ($\Delta H^{\circ}_{tr} < 0; T\,\Delta S^{\circ}_{tr} <$

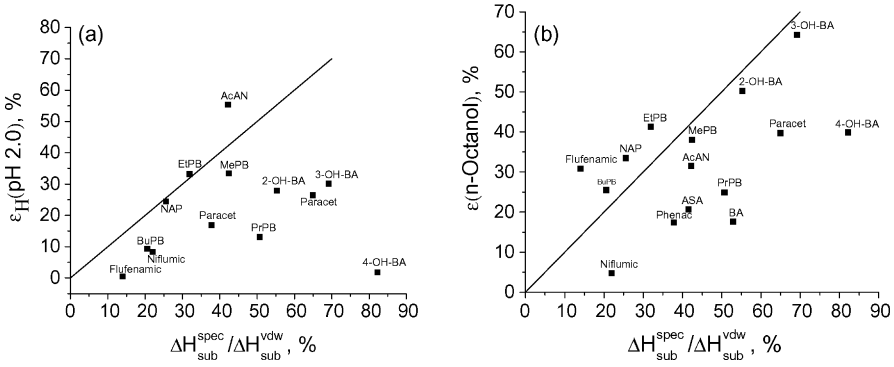
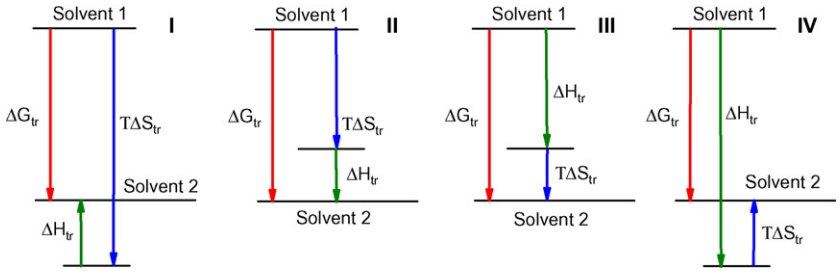


Fig. 6. Relationship between the ε_H-values for the buffer with pH 2.0 (a) and for the *n*-octanol (b) vs. the ratio between specific and non-specific enthalpic terms in crystal lattices.



Scheme 2.

$0; |\Delta H^{\circ}_{tr}| > |T\,\Delta S^{\circ}_{tr}|) \equiv$ sector IV correspond to enthalpy determinate processes. The diagrams describing the relationship between the transfer thermodynamic functions for each sector are resented in Scheme 2. As follows from Fig. 7, for the partitioning process (buffer pH 2.0 → *n*-octanol; filled symbols in Fig. 7), according to the classification introduced, the considered compounds appear in the following groups: sector I (niflumic and diclofenac acid); sector II (flufenamic acid, diflunisal, naproxen, ketoprofen and (±)-ibuprofen) and, finally, sector III (flurbiprofen). Here, the compensation effect is only observed for the compounds appearing in sector I. For all the compounds (with an exception for FBP), the partitioning process is entropy determinate. However, for the distribution process (buffer pH 7.4 → *n*-octanol, open symbols in Fig. 7), in contrast to the previous case, the drugs are classified only as group I (diclofenac acid, DIF, IBP, KETO, NAP, FBP), and as group IV (flufenamic and niflumic acids). Both these groups are attributed to the enthalpy–entropy-compensation effect. The distribution process for diclofenac acid, DIF, IBP, KETO, NAP, FBP is entropy determinate, whereas for flufenamic and niflumic acids it is enthalpy determinate. It should be noted that only for diclofenac acid the analysed thermodynamic function of transfer for both distribution and partitioning are situated in the same group (sector I), and therefore it may be supposed that the nature of the partitioning and distribution processes is the same, independently of whether diclofenac acid is dissociated or non-dissociated.

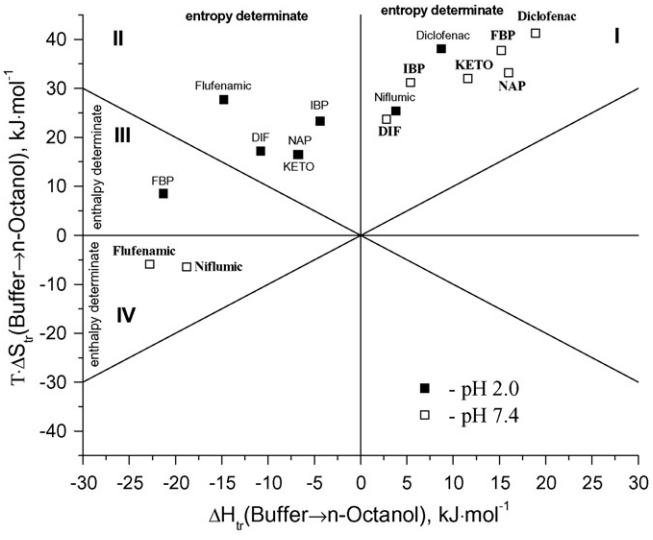


Fig. 7. Relationship between the enthalpic and entropic terms of transfer functions from the buffers (pH 2.0 and 7.4) to *n*-octanol (see notation for Fig. 4).

For all the other substances, the behavior of the transfer functions of partitioning and distribution processes differs essentially with the degree of dissociation, and it may be assumed that the mechanism of resolvation of these molecules into the medium is different as well.

6. Conclusion

The present work shows that it is possible to investigate the thermodynamic functions of drugs and drug-like molecules in the solid state and in solutions with implications for solvation and transfer processes. Enthalpies of dissolution are accessible by classical methods, whereas enthalpies of the sublimation process were yielded by the transpiration method. This approach gives us the opportunity to quantify solvation energies in different solvents on an absolute energetic scale. An approach has been applied to split specific and non-specific interactions in the crystal lattice, avoiding the necessity of explicitly resolved crystal structures. The melting points of the considered drugs and drug-like molecules correlate with the ratio between specific and non-specific interaction in crystal lattices. The respective fractions of the enthalpy and entropy terms of solvation can be deduced, which provides information on the mechanism of the solvation process. Transfer functions (calculated from the respective energetic states in the pure solvents), using hexane as a standard, distinguish between specific and non-specific interaction. Comparison analysis of specific and non-specific interactions in the solid state and in solutions becomes possible. For drugs, the water–solvent transfer energies are often studied using octanol as a model for a lipophilic compartment in the form of partition coefficients. In the current study, transfer from buffers (with pH 2.0 and 7.4) to octanol for flufenamic acid and niflumic acids was analysed together with some other drug molecules for both the enthalpic and the entropic functions. A diagram to analyse the energy relationships of partitioning and distribution processes has been introduced.

Thus, in contrast to the interpretation of Gibbs energy of transfer, being excessively used for pharmaceuticals in the form of the partition coefficient and log *P*, analysis of thermodynamic functions of the transfer process, as it is outlined in the present work, provides additional mechanistic information. This may be of importance for further evaluation of distribution and passive transport of drug molecules, thereby providing a better understanding of the biopharmaceutical properties of drugs.

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