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Thermodynamic and structural study of tolfenamic acid polymorphs

Artem O. Surov[a], Piotr Szterner[b], Wojciech Zielenkiewicz[b], German L. Perlovich[a,*]

[a] Institute of Solution Chemistry, Russian Academy of Sciences, Akademicheskaya 1, 153045 Ivanovo, Russia
[b] Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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ABSTRACT

The article deals with the study of two polymorphic modifications in the space groups $P2_1/c$ (white form) and $P2_1/n$ (yellow form) of the tolfenamic acid. It also describes how the white form vapor pressure temperature dependence was determined by using the transpiration method and how thermodynamic parameters of the sublimation process were calculated. We have estimated the difference between the crystal lattice energies of the two polymorphic forms by solution calorimetry and found that the crystal lattice energy of the yellow form is 6.7 ± 1.2 kJ mol^{-1} higher than that of the white form, whereas Gibbs free energies of the forms obtained from the vapor pressure temperature dependence are practically the same. The modifications under consideration are monotropically related. From the practical point of view, the white form is more preferable due to its lower crystal lattice energy and better performing procedure. We have also studied the solubility, solvation and transfer processes of the tolfenamic acid white form in buffers (with various values of pH and ionic strengths), *n*-hexane and *n*-octanol. The thermodynamic parameters of the investigated processes have been discussed and compared with those determined for others fenamates. In the study we estimated specific and non-specific contributions of the solvation enthalpic term of the fenamate molecules with the solvents as well. The driving forces of the transfer processes from the buffers with pH 7.4 and different ionic strengths to *n*-octanol were analyzed. It was found that the relationship between the enthalpic and entropic terms depends essentially on the ionic strength. For the considered fenamates the transfer processes of the neutral molecules and the ionic forms are enthalpy-determined, whereas for the niflumic acid this process is entropy-determined.

1. Introduction

Tolfenamic acid (Fig. 1a) is a nonsteroidal anti-inflammatory drug (NSAID), belonging to the fenamate group compounds (niflumic, mefenamic and flufenamic acids). Fenamates are widely applied in medicine and veterinary as febrifugal and anti-inflammatory drugs [1,2]. The most common opinion of the predominant mechanism of the action these drugs produce is inhibiting cyclo-oxygenases which catalyses the biosynthesis of prostaglandins in inflammation pathogenesis [3–6].

The determination of the tolfenamic acid properties was the subject of previous research [7–15]. The pharmacodynamic and pharmacokinetic characteristics were investigated by Pedersen [7], whereas aqueous solubility by Bergstro et al. [8]. Recently there have been several papers about the analysis of the tolfenamic acid impact on the conductivity of ionic channels and opportunities to use this group of substances for Alzheimer disease treatment [9–11].

It is well known that most of the fenamates have several polymorphic forms. The tolfenamic acid is also a typical drug, which exhibits polymorphism. The literature on this subject described two polymorphic modifications: form I with space group $P2_1/c$ (white form) [12] and form II, $P2_1/n$ (yellow form) [13]. However, recently three new forms have been identified [14]: form III with space groups $P2_1/c$; form IV, *P* 1bar; form V, *P* 1bar. The analysis of IR spectrums of white and yellow polymorphic forms was carried out by Gilpin and Zhou [15]; however the question about the nature of the polymorphic modifications is still under discussion. Moreover, it should be noted that the thermodynamic and thermophysical aspects of the forms have not been studied yet. Furthermore, the sublimation and solvation processes of the tolfenamic acid in the solvents, imitating biological media, have not been investigated either. The present work is devoted to the abovementioned problems.

2. Materials and methods

2.1. Compounds and solvents

The tolfenamic acid (2-[(3-chloro-2-methylphenyl)amino] benzoic acid, white form, $C_{14}H_{12}ClNO_2$, MW 261.7, lot

* Corresponding author. Tel.: +7 4932 533784; fax: +7 4932 336237.
E-mail address: glp@isc-ras.ru (G.L. Perlovich).

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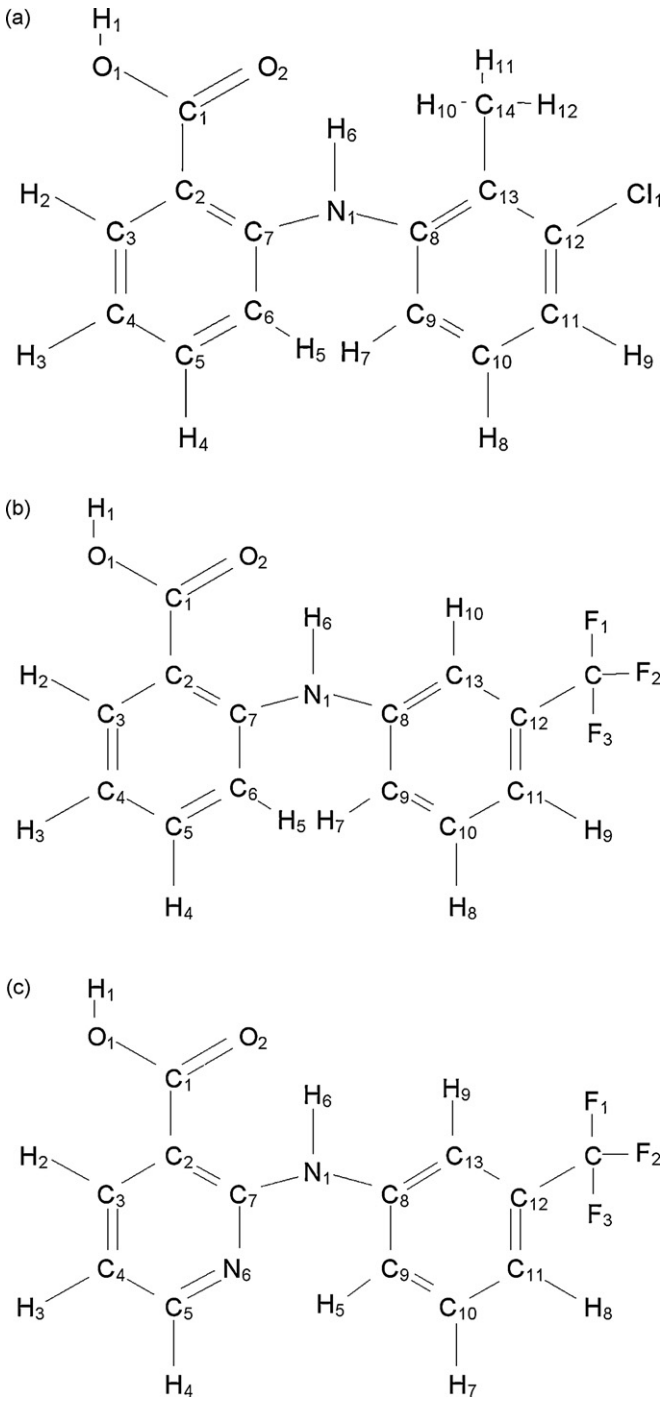


Fig. 1. Structural formula of tolfenamic acid with atomic numbering (a), flufenamic (b) and niflumic (c) acids.

110H0469, CAS 13710-19-5), flufenamic acid (2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid, $C_{14}H_{10}F_3NO_2$, FW 281.23, lot 122K1018, CAS 530-78-9) and niflumic acid (2-[3-(trifluoromethyl)anilino]nicotinic acid, $C_{13}H_9F_3N_2O_2$, FW 282.2, lot 12K1486, CAS 4394-00-7) were purchased from the Sigma Chemical Co., Ltd., St. Louis, USA. The purity of the compounds was over 99.8%.

The methanol HPLC grade was supplied by the Merck (Darmstadt, Germany), lot K27636907. 1-Octanol (*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2, lot 11K3688) ARG was purchased from the Sigma Chemical Co. (USA). *n*-Hexane (C_6H_{14}, MW 86.18, lot 07059903C) ARG was supplied by the SDS (Peypin, France).

The buffer solutions were prepared by mixing solutions of hydrochloric acid and potassium chloride for pH 2.0, and appropriate sodium and potassium salts of phosphoric acid for the pH 7.4, as described in [16]. The ionic strength was adjusted by adding potassium chloride. All the chemicals were of AR grade. The pH values of buffered solutions were controlled by using Electroanalytical Analyzer, Type OP-300, Radelkis, Budapest standardized with pH 1.68, 6.86 and 9.22 solutions.

2.1.1. Preparation of white form

The tolfenamic acid white form was prepared by recrystallization from absolute ethanol. No heat events were observed on the DSC curves up to the melting point, which corresponds to $T_m = 484.18 \pm 0.2$ K and $\Delta H_{fus} = 41.0 \pm 0.5$ kJ mol^{-1}.

2.1.2. Preparation of yellow form

The tolfenamic acid yellow form was prepared by rapid cooling of boiling ethanol (96%) solution using an ice bath. No heat effects were observed on the DSC curves up to the melting point, which corresponds to $T_m = 485.78 \pm 0.2$ K and $\Delta H_{fus} = 49.0 \pm 0.5$ kJ mol^{-1}.

2.2. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out using a DSC 204 F1 "Foenix" (Netzsch, Germany). DSC runs were performed in the atmosphere of flowing (25 ml min^{-1}) dry argon gas of high purity 99.996% using standard aluminium sample pans and the heating rate of 10 K min^{-1}. The DSC was calibrated using five standard substances: mercury, biphenyl, indium, tin and bismuth. The sample mass was determined with the accuracy of 1×10^{-5} g using the balance Sartorius M2P.

The procedure of determining the heat capacity of the crystals under investigation, $C_{p,cr}(exp)$, was as follows. The measurements were performed differentially, in relation to the empty crucible in the temperature range from 289.15 to 421.15 K at the heating rate of 0.5 K min^{-1}. All the samples were prepared in the same way. The compounds were placed in a stainless steel crucible of 150 μl volume. The stainless steal cover was crimped with an aluminum seal by using a crimping press. The uncertainty of the temperature was 0.1 K. The DSC device was calibrated using benzoic acid received from the Fluka (lot 73983) as a standard substance. The experimentally determined standard molar heat capacity, $C^0_{p,cr}$, value of benzoic acid equal to 146.9 ± 1.3 J K^{-1} mol^{-1} agreed with that recommended by the IUPAC [17] (146.8 J K^{-1} mol^{-1}).

2.3. Sublimation experiments

Sublimation experiments were carried out by the transpiration method as described in [18]. 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. The amount of sublimated substance is determined by dissolving the condensed substance in a definite volume V_{sol} of the solvent (here: ethyl alcohol). The mass of the substance is quantified spectroscopically (absorbance A of the solution was measured by using Cary 50, Varian Spectrophotometer Australia). Knowing the value of the extinction coefficient ε (dm^3 mol^{-1} cm^{-1}) of the studied compound dissolved in the solvent one can express the concentration of the solution c (mol dm^{-3}) according to the Lambert–Beer law, by the following relation:

$$A = \varepsilon \cdot c \cdot l \quad (1)$$

whereas the mass of the sublimated substance is calculated from:

$$m = c \cdot V_{sol} \cdot M \quad (2)$$

where l is the absorption path length, and M is the molar mass of the studied substance. Considering that the vapor pressure of the substance is very low, the ideal gas rule can be applied:

$$P \cdot V_x = n \cdot R \cdot T \tag{3}$$

where V_x is the total volume of the inert gas at temperature T corrected by its thermal expansivity coefficient; R is a gas constant; $n = m/M$ is the number of moles of the sublimated substance. The V_x value is calculated from the equation:

$$\frac{V_x}{V_{gas}} = \frac{T}{T_r} \tag{4}$$

where T_r is the temperature of the water thermostat (25 °C), V_{gas} (dm^3) is the gas volume at temperature T_r, calculated by

$$V_{gas} = \nu \cdot \tau \tag{5}$$

where ν (dm^3/h) is the gas flow velocity; τ (h) is the time for sublimation. Taking into account Eqs. (2)–(5), we obtain:

$$P(\text{Pa}) = c \cdot \left(\frac{V_{sol}}{V_{gas}}\right) RT_r \tag{6}$$

The velocity of the carrier gas flow through the sublimation chamber should be chosen very carefully in order to establish and maintain the conditions of thermodynamic equilibrium for the substance present in the solid and in the vapor state. The sublimation device was tested before starting the experiments by determining the relation between P and ν and choosing the gas flow velocity value adequate to the appearance of a plateau on the $P = f(\nu)$ curve. The velocity of the carrier gas flow for the compounds under study was 1.8 (dm^3/h). The purity of the sublimate was determined by two methods. Firstly, we compared UV spectrums and, secondly, DSC curves of the initial and sublimated compound.

The device was calibrated by using benzoic acid. The standard value of sublimation enthalpy obtained here was $\Delta H^0_{sub} = 90.5 \pm 0.3$ J mol^{-1}. This value is in good agreement with the one recommended by IUPAC of $\Delta H^0_{sub} = 89.7 \pm 0.5$ J mol^{-1} [19]. The saturated vapor pressures were measured at each temperature 5 times with the standard deviation of 3–5%. Because the saturated vapor pressure of the investigated compounds is low, it may be assumed that the heat capacity change of the vapor with the temperature is so small that it can be neglected. The experimentally determined vapor pressure data are usually presented by co-ordinates ($\ln P$; $1/T$) in the following way:

$$\ln(P) = \frac{A + B}{T} \tag{7}$$

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

$$\Delta H^T_{sub} = RT^2 \cdot \frac{\partial(\ln P)}{\partial(T)} \tag{8}$$

whereas the sublimation entropy at a given temperature T is calculated by the following relation:

$$\Delta S^T_{sub} = \frac{\Delta H^T_{sub} - \Delta G^T_{sub}}{T} \tag{9}$$

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

The sublimation data are obtained at elevated temperatures for experimental reasons. However, in comparison to effusion methods, the temperatures are much lower, which makes extrapolation to room conditions easier. In order to further improve the extrapolation to room conditions, we measured the heat capacity ($C^0_{p,cr}$) of the crystal by DSC and used it to recalculate the sublimation enthalpy ΔH^T_{sub}-value at 298 K (ΔH^{298}_{sub}-value), according to the equation [20]:

$$\begin{aligned}\Delta H^{298}_{sub} &= \Delta H^T_{sub} + \Delta H_{cor} \\ &= \Delta H^T_{sub} + (0.75 + 0.15 \cdot C^0_{p,cr}) \cdot (T - 298.15)\end{aligned} \tag{10}$$

2.4. Solubility determination

All the experiments were carried out by the isothermal saturation method for five temperatures 20, 25, 30, 37, 42 ± 0.1 °C (air thermostat) by rotating the ampoules for stirring at 8 rpm for 24 h. After the experiment was completed, the solid phase was removed by centrifugation (Heraeus Biofuge stratus (Thermo Scientific)) with 23,300 rpm rotation speed and isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size). The experiments were repeated three times for each compound. The solubilities were calculated as the mean values of all the relevant experimental data. The molar solubilities of the drugs were measured spectrophotometrically (Cary 50, Varian, Australia) with the accuracy of 2–2.5% using a protocol described previously [21].

The standard Gibbs free energies of the dissolution processes, ΔG^0_{sol}, were calculated using the following equation:

$$\Delta G^0_{sol} = -RT \ln X_2 \tag{11}$$

where X_2 is the molar fraction of the investigated substance in the saturated solution. The standard enthalpies of the solution, ΔH^0_{sol}, were calculated using the van't Hoff equation:

$$\frac{\mathrm{d}(\ln X_2)}{\mathrm{d}T} = \frac{\Delta H^0_{sol}}{RT^2} \tag{12}$$

assuming that the activity coefficients of the drugs under consideration in the solvents are equal to 1 and the solution enthalpies are independent of concentration. The temperature dependencies of the solubilities of the drugs within the chosen temperature interval can be described by the linear function:

$$\ln X_2 = \frac{A - B}{T} \tag{13}$$

This indicates that the change in heat capacity of the solutions with the temperature is negligibly small. The standard entropies of solution, ΔS^0_{sol}, were obtained from the equation:

$$\Delta G^0_{sol} = \Delta H^0_{sol} - T \cdot \Delta S^0_{sol} \tag{14}$$

2.5. Solution calorimetric experiments

The enthalpies of solution, ΔH^0_{sol}, in methanol at 298.15 K were determined experimentally using an isoperibol solution calorimeter constructed in our laboratory. The calorimeter and the working procedure were described in detail in [22,23]. The sample was weighed and introduced into a glass ampoule, which was then thermally equilibrated in the calorimetric solution. The solution process is initiated after lowering the stirrer and breaking the ampoule containing the substance studied.

Before each experiment the calorimeter was calibrated by means of the electric Joule effect. The calorimeter was additionally tested by determining the potassium chloride solution enthalpy (mass fraction 0.9999) in water [24]. For each investigated substance 6 measurements were made in the range of concentrations (from 0.246 to 0.571) × 10^{-3} mol kg^{-1}.

The phase transition enthalpy was calculated as a difference between the enthalpies of solution of the yellow (y) and white (w) forms at 298.15 K [25]:

$$\Delta H^0_{tr}(w \rightarrow y) = \Delta H^0_{sol}(y) - \Delta H^0_{sol}(w) \tag{15}$$

Table 1
Crystal lattice parameters of the white and yellow forms of tolfenamic acid[a].

	White form	Yellow form
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
a [Å]	4.826(2)	3.836(2)
b [Å]	32.128(11)	21.997(5)
c [Å]	8.041(4)	14.205(7)
α [°]	90.00	90.00
β [°]	104.88(3)	94.11(4)
γ [°]	90.00	90.00
V_{cell} [Å^3]	1205(2)	1195.5(4)
D_{exp}(293 K) [g cm^{-3}]	1.397	1.400
D_x(110 K) [g cm^{-3}]	1.443	1.450
Z	4	4
Graph set assignment	$R_2^2(8)$; S(6)	$R_2^2(8)$; S(6)
V^{vdw} [Å^3]	212.6	212.6
V_{mol}[b] [Å^3]	301.25	298.88
V^{free} [Å^3]	88.65	86.28
V^{free}/V^{vdw} [%]	41.7	40.6

[a] Ref. [12].
[b] $V_{mol} = V_{cell}/Z$.

where $\Delta H^0_{sol}(w)$ and $\Delta H^0_{sol}(y)$ are the standard solution enthalpies of white and yellow forms, respectively.

2.6. Calculation procedure

Van der Waals's molecular volumes, V^{vdw}, were calculated using the GEPOL program [26] and Kitaigorodskyi's atomic radii [27]. The free volume per molecule, V^{free}, in the crystal lattice was obtained by the equation:

$$V^{free} = \frac{(V_{cell} - Z \cdot V^{vdw})}{Z} \quad (16)$$

where V_{cell} is the unit cell volume, Z is the number of molecules in the unit cell.

All the calculations were performed by using Accelrys DFT program DMol^3. DMol^3 utilizes a basis set of numeric atomic functions that are exact solutions to the Kohn–Sham equations for the atoms [28]. In the present study, we used a polarized split valence basis set, which is termed a double numeric polarized (DNP) basis set. All structure optimizations were performed using the nonlocal BLYP (Becke exchange plus Lee–Yang–Parr correlation) functional. Geometry *optimization* of the molecules in the crystal lattice started with initial co-ordinates, obtained from X-ray diffraction experiments using the k-point set. For the numerical integration, the FINE quality mesh size of the program was adapted. The tolerances of energy, the change of the maximum force on the atom and the maximal displacement were 1×10^{-5} (Hartree), 2×10^{-3} Ha Å^{-1} and 5×10^{-3} Å, respectively.

3. Results and discussion

3.1. Crystal structure analysis of the two forms of the tolfenamic acid

The crystal lattices characteristics of the white and yellow polymorphic forms of tolfenamic acid are presented in Table 1. The molecular packing architectures of the presented polymorphs are shown in Fig. 2.

As it has been mentioned by Andersen et al. [12], the color difference of the two modifications can be connected with conformational peculiarities of the molecules in the crystal lattices. The phenyl fragments of the outlined molecules are planar and the interplanar angle for the white form is 76.6°, whereas for the yellow one is 43.5°. Therefore, it can be assumed, that a conjugated system of the yellow polymorph has a larger extension in comparison with the white form. The geometric parameters describing molecular conformational states of the polymorphs under study are summarized in Table 2. There is a significant difference between the two forms for the amino group (N_1). For the white form the difference of N1–C7 and N1–C8 bonds is bigger in comparison to the same parameter for the yellow form. The angle ∠C7–N1–C8 of the yellow polymorph exceeds the analogous angle of the white form by 4.8°. This type of polymorphism was attributed by Andersen et al. [12] to the conformational one, introduced by Bernstein et al. [29].

Table 2
The parameters describing molecular conformational states of the white and yellow forms of tolfenamic acid.

	White form	Yellow form
Distance		
N1–C7 [Å]	1.372(2)	1.377(1)
N1–C8 [Å]	1.423(2)	1.406(1)
Angle		
∠C7–N1–C8 [°]	124.3(1)	129.04(5)
∠C6–C7–N1–C8 [°]	0.5	7.9
∠C7–N1–C8–C9 [°]	107.7	42.2

Geometry of hydrogen bonds of the both modifications is presented in Table 3. The polymorphs under consideration create two types of hydrogen bonds: intermolecular (dimers) with $R_2^2(8)$ graph set assignment [30] and intramolecular with S(6) graph set assignment. The intermolecular hydrogen bonds geometry of the modifications does not differ essentially. It should be noted, that for the yellow form the angle ∠D–H···A is closer to the ideal value (176(2)°) in comparison with the white form (170(4)°). This fact testifies that the hydrogen bonds of the yellow form dimers are less strained compared to the white form dimers.

3.2. Sublimation and solution calorimetric experiments

Sublimation experiments have been carried out for the tolfenamic acid white form. The temperature dependence of saturated vapor pressure and thermodynamic characteristics of the sublimation process are summarized in Table 4.

The energy differences of the crystal lattices of the two polymorphs were estimated from the difference in the enthalpies of solution obtained by dissolution in methanol (in the same solvent MeOH). We had used the approach earlier to measure differences in the modifications of glycine [25], diflunisal [31] and diclofenac [32]. In the present study methanol was chosen as the solvent, because the drug under investigation dissolves well with a large endothermic heat effect. The results of the calorimetric experiments are presented in Table 5. As the table shows, no concentration dependence of the solution enthalpies for both forms is observed in the studied range of concentration. The crystal lattice energy (on the

Table 3
Hydrogen bonds geometry of the white and yellow forms of tolfenamic acid.

	White form	Yellow form
Intermolecular hydrogen bond with $R_2^2(8)$ graph set assignment		
D–H···A	O1–H1···O_2[a]	O1–H1···O_2[a]
D–H [Å]	0.972(5)	0.934(2)
H···A [Å]	1.686(5)	1.715(3)
D···A [Å]	2.648(3)	2.648(4)
∠D–H···A [°]	170(4)	176(2)
Intramolecular hydrogen bond with S(6) graph set assignment		
D–H···A	N1–H_6···O_2	N1–H_6···O_2
D–H [Å]	0.788(3)	0.844(2)
H···A [Å]	2.018(3)	1.962(2)
D···A [Å]	2.676(3)	2.653(3)
∠D–H···A [°]	141(2)	138(1)

[a] Symmetry code.

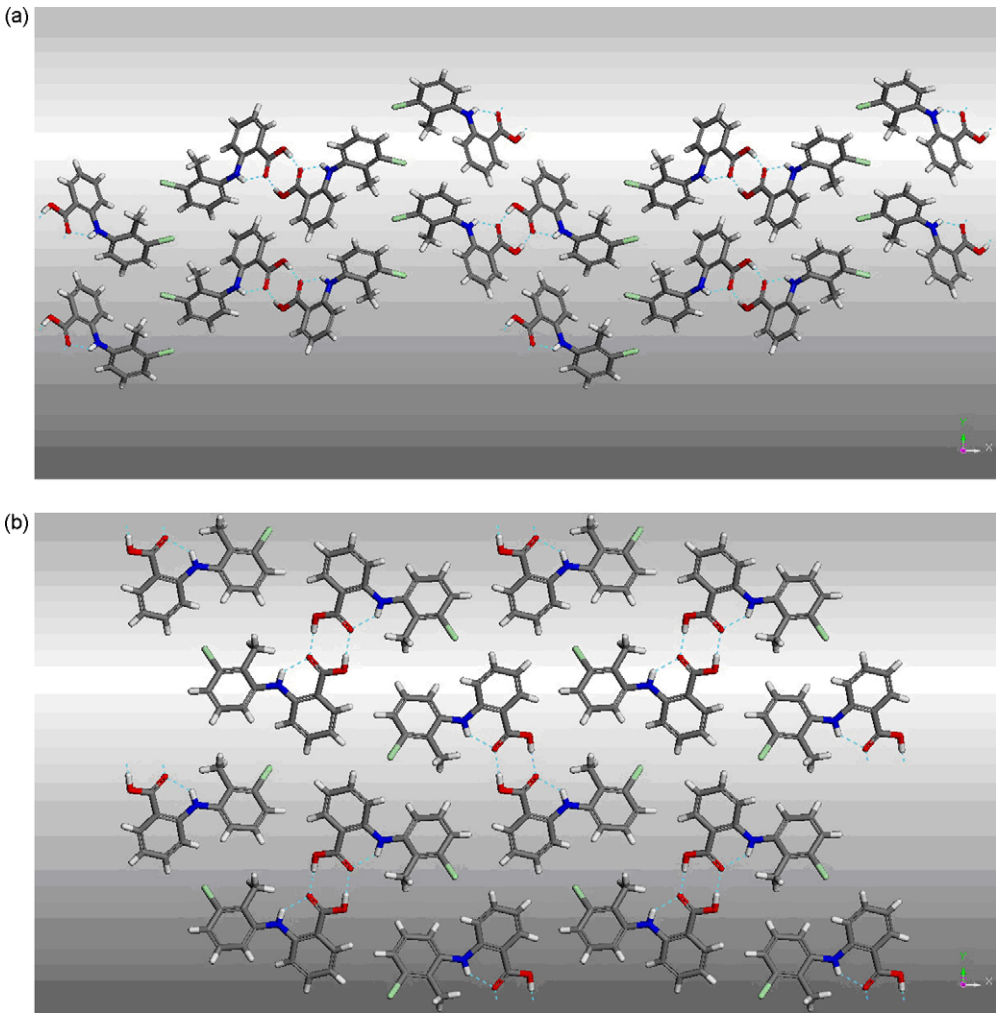


Fig. 2. Molecular packing architectures of white (a) and yellow (b) forms of tolfenamic acid in crystal lattices.

Table 4
Temperature dependency of saturation vapor pressure and sublimation thermodynamic characteristics of the white form of tolfenamic acid.

T [K]	P [Pa]	T [K]	P [Pa]
345.7	3.92×10^{-2}	361.2	2.52×10^{-1}
349.2	5.61×10^{-2}	363.7	3.53×10^{-1}
351.7	7.73×10^{-2}	366.2	4.72×10^{-1}
353.2	1.00×10^{-1}	367.7	4.92×10^{-1}
354.2	1.24×10^{-1}	369.2	6.64×10^{-1}
357.2	1.59×10^{-1}	370.2	7.05×10^{-1}
358.2	1.83×10^{-1}	373.2	8.96×10^{-1}
359.2	2.10×10^{-1}		
$\ln(P[\text{Pa}]) = (40.5 \pm 0.6) - (15{,}119 \pm 214)/T$			
$r = 0.998$; $\sigma = 5.10 \times 10^{-2}$; $n = 15$			
ΔH^{T}_{sub} [kJ mol^{-1}]	125.7 ± 0.8		
ΔH^{0}_{sub} [a] [kJ mol^{-1}]	128.4 ± 0.8		
ΔG^{0}_{sub} [kJ mol^{-1}]	53.9 ± 0.4		
$T \cdot \Delta S^{0}_{sub}$ [kJ mol^{-1}]	74.5 ± 1.2		
ΔS^{0}_{sub} [J K^{-1} mol^{-1}]	250 ± 4		
ς_H [%][b]	63.2		
ς_{TS} [%][c]	36.8		
$C^{0}_{p,cr}$ [J K^{-1} mol^{-1}]	291.9		

[a] ΔH^{298}_{sub} has been calculated by Eq. (8).
[b] $\varsigma_H(\%) = (\Delta H^{298}_{sub}/(\Delta H^{298}_{sub} + T \cdot \Delta S^{298}_{sub})) \times 100$.
[c] $\varsigma_{TS}(\%) = (T \cdot \Delta S^{298}_{sub}/(\Delta H^{298}_{sub} + T \cdot \Delta S^{298}_{sub})) \times 100$

Table 5
Solution enthalpies of the white and yellow forms tolfenamic acid in methanol at 298.15 K.

White form		Yellow form	
m [mmol kg^{-1}]	ΔH^m_{sol} [kJ mol^{-1}]	m [mmol kg^{-1}]	ΔH^m_{sol} [kJ mol^{-1}]
0.280	27.6	0.246	33.3
0.447	27.2	0.277	34.9
0.455	27.0	0.291	33.6
0.490	27.3	0.361	33.1
0.530	27.3	0.368	33.5
0.571	26.3	0.370	34.2
ΔH^0_{sol} [a]	27.1 ± 0.5	ΔH^0_{sol} [a]	33.8 ± 0.7

[a] The standard enthalpy of solution at infinite dilution.

absolute scale) of the yellow form 6.7 ± 1.2 kJ mol^{-1} is higher than that of the white form. Therefore, using the sublimation enthalpy of the white form, we have estimated the sublimation enthalpy of the yellow form which is equal to $\Delta H^0_{sub} = 135.1$ kJ mol^{-1}. This conclusion agrees with the experimental and calculated values of the molecule density in the crystal lattices (Table 1): D_x(yellow) = 1.450 > D_x(white) = 1.443 g cm^{-3}.

The results of DFT calculations of total energy per molecule in the crystal lattices of the polymorphic modifications under consideration conform quantitative data to the experimental results: E^{tot}(white)/Z = −1205.852 Ha, E^{tot}(yellow)/Z = −1205.967 Ha. Therefore, the yellow form is more stable (from the point of view of the total energy criterion) than the white one.

In order to estimate the difference between the studied polymorphs of tolfenamic acid we obtained kinetic dependencies of solubility in the buffer solution with pH 7.4 and IS = 0.15 at 25 °C. For these experiments the bottom phases of the white and yellow forms were placed in separate test-tubes and small portions of the solutions were extracted from the tubes at the definite time. After that the solubility values were determined. The results of these experiments are presented in Fig. 3 which shows that the thermodynamic equilibrium between the bottom phase and the solution was reached after 10 h. Moreover, the solubility values coincide within the experimental errors. This observation is in good agreement with the results published in [14]. After the experiments the bottom phases were analyzed by DSC: the enthalpies and melting points coincide with the analogous values of the freshly prepared forms within the experimental errors. The difference of entropies of the white and yellow forms at 25 °C can be estimated on the basis

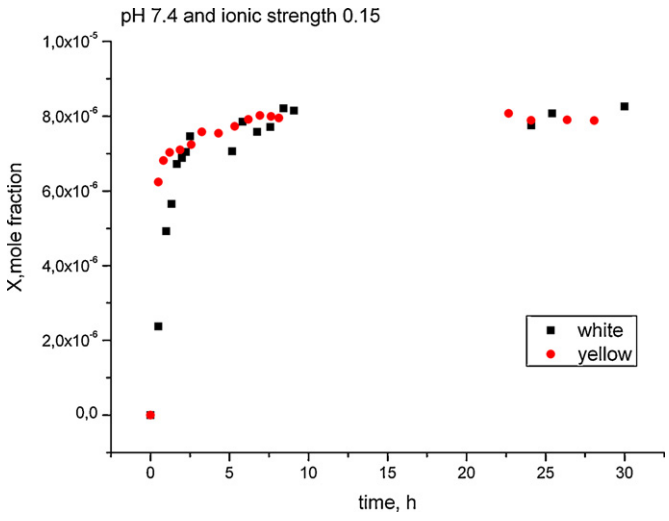


Fig. 3. Kinetic dependences of concentration of tolfenamic acid white and yellow forms in buffer with pH 7.4 and IS = 0.15 at 25 °C.

of kinetic and solution calorimetry experiments:

$$\Delta G^o_{tr}(w \to y) = \Delta H^o_{tr}(w \to y) - T \cdot \Delta S^o_{tr}(w \to y) \quad (17)$$

$$\Delta S^o_{tr}(w \to y) = \frac{\Delta H^o_{tr}(w \to y)}{T} \quad (18)$$

$\Delta S^o_{tr}(w \to y) = 22 \pm 5$ J mol^{-1} K^{-1}. So, the molecules of the crystal lattice of the yellow form are more disordered in comparison with those of the white one. The advantage of the crystal lattice energy of the yellow form over the white one is due to its increasing the entropic factor only. The data obtained agree with the value received from the melting point DSC experiments: 16.2 ± 0.3 J mol^{-1} K^{-1}. From the enthalpies $\Delta S^T_{tr}(w \to y)$ and fusion temperatures of the polymorphs we can also estimate the phase transition temperature:

$$T_{tr}(w \to y) = \frac{(\Delta H^y_{fus} - \Delta H^w_{fus})}{(\Delta H^y_{fus}/T^y_m - \Delta H^w_{fus}/T^w_m)} = 493.8 \text{ K} \quad (19)$$

It is not difficult to see, that the calculated temperature is higher than the melting temperatures of both modifications T^w_m = 484.18 < T^y_m = 485.78 < $T_{tr}(w \to y)$ = 493.8 K. In other words, the transition temperature is a hypothetic temperature of the phase transition and this fact corresponds to monotropic relationship between the white and yellow phases.

3.3. Solubility and solvation characteristics of the tolfenamic acid white form of in comparison with the flufenamic and niflumic acids

The next step was to study the dissolution and solvation processes of the tolfenamic acid white form in solutions modeling a biological medium: *n*-hexane, *n*-octanol and buffers with various values of pH and ionic strength were studied. The hydrochloric buffer with pH 2.0 and the phosphate buffer with pH 7.4 coincide with the biological pH of gastrointestinal tract and circulatory system, respectively. Moreover, *n*-octanol is a model of biological membranes, whereas *n*-hexane is usually used to characterize membranes with non-specific interactions such as a blood–brain barrier. Moreover, *n*-hexane can be applied as a reference solvent for splitting specific and non-specific interaction terms between the solvent and the solute molecules. In order to compare the solubility and solvation characteristics of tolfenamic acid with similar structural compounds, we obtained the abovementioned parameters for flufenamic and niflumic acids (Fig. 1b and c) (these data had been partly published by us earlier [33]). The temperature dependencies of solubility of the white modification of the tolfenamic acid, the flufenamic and niflumic acids in the investigated solvents are presented in Table 6. The thermodynamic functions of the dissolution and solvation processes are summarized in Table 7. To compare the thermodynamic characteristics of the studied processes in the buffers we chose two values of ionic strengths: one of them corresponds to the biological level (0.15), and the other one is several times higher (0.56). The abovementioned thermodynamic values for the buffers with pH 2.0 and different levels of ionic strengths were within the experimental errors; therefore, Table 6 shows data for the ionic strength 0.15 only.

As is shown in Table 7, the solubility processes for all systems are endothermic. Therefore, the tolfenamic acid solvation enthalpy does not compensate the crystal lattice energy. The entropic term of the solubility of Gibbs energy for the flufenamic and niflumic acids in the buffer with pH 2.0 has a negative value due to the hydrophobic effects. The dissolution entropy of tolfenamic acid in the buffer with pH 7.4 (IS = 0.56) is approximately zero, and this fact confirms that ordering molecules in the crystal lattice is approximately the same as in the buffer solution. The analogies value for

Table 6
Temperature dependencies of solubility (X_2 mol frac) of the white form of tolfenamic acid, flufenamic and niflumic acids in buffers with pHs 2.0 and 7.4, *n*-hexane and *n*-octanol.

t [°C]	pH 2.0 (IS = 0.15)[a] $X_2 \times 10^8$	pH 7.4 (IS = 0.15)[a] $X_2 \times 10^6$	pH 7.4 (IS = 0.56)[a] $X_2 \times 10^6$	*n*-Hexane $X_2 \times 10^5$	*n*-Octanol $X_2 \times 10^2$
Tolfenamic acid					
20.0	–	6.50	6.44	1.82	2.92
25.0	–	8.75	8.20	2.74	3.32
30.0	3.05	11.94	9.36	3.86	3.60
34.0	3.79	–	–	–	–
37.0	4.34	15.29	12.68	6.28	4.19
40.0	5.21	–		–	–
42.0	6.19	19.64	14.97	9.00	4.64
A[b]	0.8 ± 0.9	3.6 ± 0.7	0.0 ± 0.5	11.7 ± 0.3	3.0 ± 0.2
B[b]	5500 ± 231	4500 ± 133	3500 ± 140	6600 ± 82	1900 ± 54
R[c]	0.994	0.996	0.997	0.999	0.999
σ[d]	3.2×10^{-2}	4.5×10^{-2}	2.7×10^{-2}	1.5×10^{-2}	1.0×10^{-2}
t [°C]	pH 2.0 (IS = 0.15)[a] $X_2 \times 10^9$	pH 7.4 (IS = 0.15)[a] $X_2 \times 10^4$	pH 7.4 (IS = 0.56)[a] $X_2 \times 10^4$	*n*-Hexane $X_2 \times 10^4$	*n*-Octanol $X_2 \times 10^2$
Flufenamic acid					
20.0	–	0.91	0.87	4.92	7.62
25.0	–	1.18	1.08	6.74	9.33
30.0	4.63	1.46	1.35	9.10	10.31
33.0	5.50	–	–	–	–
35.0	6.26	–	–	–	–
37.0	6.97	1.92	1.78	13.85	12.73
40.0	8.22	–	–	–	–
42.0	9.22	2.40	2.17	18.24	14.91
A[b]	−1.1 ± 0.2	4.4 ± 0.3	3.8 ± 0.1	11.2 ± 0.1	6.7 ± 0.4
B[b]	5480 ± 50	4000 ± 94	3860 ± 38	5500 ± 21	2700 ± 120
R[c]	0.999	0.999	0.999	0.999	0.997
σ[d]	5.2×10^{-3}	1.8×10^{-2}	7.6×10^{-3}	3.9×10^{-3}	2.4×10^{-2}
t [°C]	pH 2.0 (IS = 0.15)[a] $X_2 \times 10^6$	pH 7.4 (IS = 0.15)[a] $X_2 \times 10^4$	pH 7.4 (IS = 0.56)[a] $X_2 \times 10^4$	*n*-Hexane $X_2 \times 10^5$	*n*-Octanol $X_2 \times 10^2$
Niflumic acid					
20.0	3.28	1.80	1.63	1.40	2.59
25.0	3.67	2.22	2.09	1.65	2.94
30.0	4.17	2.54	2.69	2.03	3.36
37.0	4.78	3.33	3.92	2.47	4.09
42.0	5.23	3.97	5.00	2.91	4.68
A[b]	−5.9 ± 0.2	2.6 ± 0.3	7.5 ± 0.2	−0.6 ± 0.3	4.8 ± 0.2
B[b]	1970 ± 50	3300 ± 100	4700 ± 74	3100 ± 89	2500 ± 53
R[c]	0.999	0.998	0.999	0.998	0.999
σ[d]	9.6×10^{-3}	1.9×10^{-2}	1.4×10^{-2}	1.72×10^{-2}	1.02×10^{-2}

[a] Ionic strength.
[b] Parameters of the correlation equation: $\ln X_2 = A - B/T$.
[c] R: Pair correlation coefficient.
[d] σ: Standard deviation.

the buffer with the lower level of ionic strength (0.15) has a positive sign. The analysis of the solvation enthalpic term of the Gibbs energy shows that the interactions of the tolfenamic and flufenamic acid molecules with the solvents studied can be arranged in the following way: *n*-octanol > buffer (pH 7.4, IS = 0.56) > buffer (pH 7.4, IS = 0.15) > buffer (pH 2.0, IS = 0.15) > *n*-hexane. For the niflumic acid a slightly different regularity is observed: buffer (pH 2.0, IS = 0.15) > *n*-octanol > *n*-hexane > buffer (pH 7.4, IS = 0.15) > buffer (pH 7.4, IS = 0.56). Probably, this behavior of the niflumic acid can be explained by the fact that the molecules are situated in the buffer (pH 2.0, IS = 0.15) both in zwitter ionic ($XH^{\pm}$) and ionic forms XH_2^+ [34].

To compare the enthalpic and entropic terms of solvation, parameters ς_H and ς_{TS} were used to describe the relative fraction of solvation enthalpy and entropy, as had been suggested earlier [21]:

$$\varsigma_{Hsolv}(\%) = \frac{\left|\Delta H^0_{solv}\right|}{\left(\left|\Delta H^0_{solv}\right| + \left|T \cdot \Delta S^0_{solv}\right|\right)} \times 100 \quad (20)$$

$$\varsigma_{TSsolv}(\%) = \frac{\left|T \cdot \Delta S^0_{solv}\right|}{\left|\Delta H^0_{solv} + T \cdot \Delta S^0_{solv}\right|} \times 100 \quad (21)$$

The enthalpic terms of the Gibbs energy are higher than the entropic ones for every solvent under consideration. It should be noted that ς_H and ς_{TS} parameters of the buffers with pH 7.4 for the ionic strengths 0.15 and 0.56 do not differ essentially one from another. For every compound under study the values ς_{Hsolv} in the buffer with pH 7.4 exceed the analogous values for the buffer with pH 2.0. This fact proves essential entropic contributions to the solvation processes of the neutral molecules in comparison with the ionic forms.

The thermodynamic parameters of the transfer processes of tolfenamic acid from one solvent to another are presented in Table 8.

In order to distinguish specific and non-specific solvation 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

Table 7
Thermodynamic functions of solubility and solvation processes of the white form of tolfenamic, flufenamic and niflumic acids in the solvents studied.

Solvent	X_2^{25} (mol frac)	ΔG^0_{sol} [kJ mol^{-1}]	ΔH^0_{sol} [kJ mol^{-1}]	$T \cdot \Delta S^0_{sol}$ [kJ mol^{-1}]	ΔS^0_{sol} [JK^{-1} mol^{-1}]	$-\Delta G^0_{solv}$ [kJ mol^{-1}]	$-\Delta H^0_{solv}$ [kJ mol^{-1}]	$-T \cdot \Delta S^0_{solv}$ [kJ mol^{-1}]	$-\Delta S^0_{solv}$ [JK^{-1} mol^{-1}]	ζ_{Hsolv} [a] [%]	ζ_{TSsolv} [b] [%]
Tolfenamic acid											
pH 2.0 (IS = 0.15) [c]	2.21×10^{-8}	43.7	46.0 ± 1.6	2.1	7.0 ± 0.4	10.2	82.6	72.4	209.0	53.3	46.7
pH 7.4 (IS = 0.15) [c]	8.75×10^{-6}	28.9	38.0 ± 1.2	9.0	30 ± 2	25.0	90.5	65.5	186.0	58.0	42.0
pH 7.4 (IS = 0.56) [c]	8.20×10^{-6}	29.0	29.0 ± 1.2	0.0	0 ± 1	24.9	99.4	74.5	216.0	57.2	42.8
n-Hexane	2.74×10^{-5}	26.0	55.2 ± 0.7	29.2	98 ± 3	27.9	73.2	45.3	118.0	61.8	38.2
n-Octanol	3.32×10^{-2}	8.4	15.9 ± 0.4	7.5	25 ± 1	45.5	112.8	67.3	191.0	62.6	37.4
Flufenamic acid											
pH 2.0 (IS = 0.15) [c]	3.42×10^{-9}	48.3	45.6 ± 0.4	−2.7	−9.1 ± 0.3	6.0	75.6	69.6	234.0	52.1	47.9
pH 7.4 (IS = 0.15) [c]	1.18×10^{-4}	22.4	33.3 ± 0.8	10.9	37 ± 2	31.9	87.9	56.0	188.0	61.1	38.9
pH 7.4 (IS = 0.56) [c]	1.08×10^{-4}	22.7	32.1 ± 0.3	9.5	32 ± 1	31.7	89.1	57.4	193.0	60.8	39.2
n-Hexane	6.74×10^{-4}	18.1	45.9 ± 0.3	27.8	93 ± 2	36.2	75.3	39.1	131.0	65.8	34.2
n-Octanol	9.33×10^{-2}	5.9	23.0 ± 1.0	16.8	57 ± 3	48.4	98.2	49.8	167.0	66.3	33.7
Niflumic acid											
pH 2.0 (IS = 0.15) [c]	3.67×10^{-6}	31.0	16.4 ± 0.4	−14.6	−49 ± 2	30.3	113.8	83.5	280.0	57.7	42.3
pH 7.4 (IS = 0.15) [c]	2.22×10^{-4}	20.9	27.3 ± 0.9	6.5	22 ± 1	40.5	102.9	62.4	209.0	62.2	37.8
pH 7.4 (IS = 0.56) [c]	2.09×10^{-4}	21.0	39.5 ± 0.6	18.5	62 ± 2	40.3	90.7	50.4	169.0	64.3	35.7
n-Hexane	1.65×10^{-5}	27.3	25.6 ± 0.7	−1.7	−5.5 ± 0.3	34.0	104.6	70.6	236.0	59.7	40.3
n-Octanol	2.94×10^{-2}	8.7	20.7 ± 0.5	12.0	40 ± 2	52.6	109.5	56.9	191.0	65.8	34.2

[a] $\zeta_{Hsolv}(\%) = (|\Delta H^0_{solv}| / (|\Delta H^0_{solv}| + |T \cdot \Delta S^0_{solv}|)) \times 100$.
[b] $\zeta_{TSsolv}(\%) = (|T \cdot \Delta S^0_{solv}| / (|\Delta H^0_{solv}| + |T \cdot \Delta S^0_{solv}|)) \times 100$.
[c] Ionic strength.

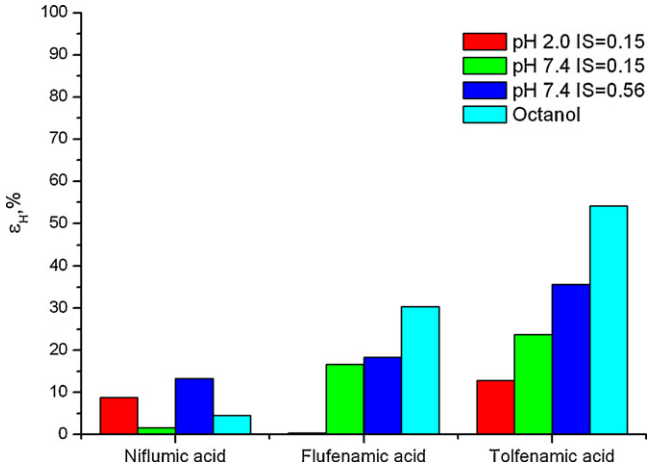


Fig. 4. Specific interactions (ε_H) of niflumic, flufenamic and tolfenamic acids with solvents under study.

specific interaction in comparison to the non-specific one, the ε_H parameter had been introduced before in [21]:

$$\varepsilon_H(\%) = \frac{|\Delta H_{spec}|}{|\Delta H_{non\text{-}spec}|} \times 100 \quad (22)$$

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

The parameter ε_H for some fenamates is presented in Fig. 4. Fig. 4 shows, that the non-specific interactions play an essential role in the enthalpic term of the Gibbs energy. It should be mentioned, that for the tolfenamic and flufenamic acids the same regularity of ε_H parameters in the studied solvents is observed: buffer (pH 2.0, IS = 0.15) < buffer (pH 7.4, IS = 0.15) < buffer (pH 7.4, IS = 0.56) < *n*-octanol. Whereas, for the niflumic acid this regularity does not appear and that can be connected with the presence of zwitter ionic form ($XH^{\pm}$) of the molecule in the solutions.

3.4. Analysis of transfer processes from the buffers to n-octanol

The transfer process buffer → *n*-octanol characterizes the distribution of drug molecules between hydrophilic and lipophilic phases. The analysis of the processes is very important for medicine, chemistry and pharmaceutics. The main criterion of drug distribution is partitioning coefficients log *P* (molecular form) and log *D* (ionic form). However, the knowledge of enthalpic and entropic transfer terms makes it possible to understand the process deeper. The experimental data of the thermodynamic functions of the outlined process for the studied compounds are presented in Fig. 5.

The diagram is divided into four triangular sectors, where each of them corresponds to a different relationship between the enthalpic and entropic terms of the Gibbs energy. The regions where ($T\,\Delta S^0_{tr} > \Delta H^0_{tr} > 0$) ≡ triangular sector **I**, and ($\Delta H^0_{tr} < 0$; $T\ \Delta S^0_{tr} > 0$; $|T \cdot \Delta S^0_{tr}| > |\Delta H^0_{tr}|$) ≡ triangular sector **II** correspond to entropy-determined processes. The regions of the diagram where ($\Delta H^0_{tr} < 0$; $T\,\Delta S^0_{tr} > 0$; $|\Delta H^0_{tr}| > |T \cdot \Delta S^0_{tr}|$) ≡ triangular sector **III**, and ($\Delta H^0_{tr} < 0$; $T\ \Delta S^0_{tr} < 0$; $|\Delta H^0_{tr}| > |T \cdot \Delta S^0_{tr}|$) ≡ triangular sector **IV** correspond to enthalpy-determined processes. A schematic depiction of these relationships is given in Scheme 1. Isoenergetic curves/lines of the ΔG^0_{tr} function are marked as dotted lines in Fig. 5.

As is seen in the diagram, the main force of the transfer process (the Gibbs energy) is maximal for the neutral molecules and

Table 8
Transfer thermodynamic functions of the white form of tolfenamic acid.

	ΔG^0_{tr} [kJ mol^{-1}]	ΔH^0_{tr} [kJ mol^{-1}]	$T \cdot \Delta S^0_{tr}$ [kJ mol^{-1}]	ς_{Htr}[a] [%]	ς_{TStr}[b] [%]	ε_H[c] [%]
Tolfenamic acid						
n-Hexane → pH 2.0 (IS = 0.15)[d]	17.7	−9.4	−27.1	25.8	74.2	12.8
n-Hexane → pH 7.4 (IS = 0.15)[d]	2.9	−17.3	−20.2	46.2	53.8	23.7
n-Hexane → pH 7.4 (IS = 0.56)[d]	3.0	−26.2	−29.2	47.3	52.7	35.6
n-Hexane → *n*-octanol	−17.6	−39.6	−22.0	64.3	35.7	54.1
pH 2.0 (IS = 0.15) → *n*-octanol	−35.3	−30.2	5.1	85.7	14.3	–
pH 7.4 (IS = 0.15) → *n*-octanol	−20.5	−22.3	−1.8	92.4	7.6	–
pH 7.4 (IS = 0.56) → *n*-octanol	−20.6	−13.4	7.2	65.0	35.0	–
Flufenamic acid						
n-Hexane → pH 2.0 (IS = 0.15)[d]	30.2	−0.3	−30.5	1.0	99.0	0.4
n-Hexane → pH 7.4 (IS = 0.15)[d]	4.3	−12.6	−16.9	42.7	57.3	16.7
n-Hexane → pH 7.4 (IS = 0.56)[d]	4.5	−13.8	−18.3	43.0	57.0	18.3
n-Hexane → *n*-octanol	−12.2	−22.9	−10.7	68.2	31.8	30.4
pH 2.0 (IS = 0.15) → *n*-octanol	−42.4	−22.6	19.8	53.3	46.7	–
pH 7.4 (IS = 0.15) → *n*-Octanol	−16.5	−10.3	6.2	62.4	37.6	–
pH 7.4 (IS = 0.56) → *n*-octanol	−16.7	−9.1	7.6	54.5	45.5	–
Niflumic acid						
n-Hexane → pH 2.0 (IS = 0.15)[d]	3.7	−9.2	−12.9	41.6	58.4	8.8
n-Hexane → pH 7.4 (IS = 0.15)[d]	−6.5	1.7	8.2	17.2	82.8	1.6
n-Hexane → pH 7.4 (IS = 0.56)[d]	−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 2.0 (IS = 0.15) → *n*-octanol	−22.3	4.3	26.6	13.9	86.1	–
pH 7.4 (IS = 0.15) → *n*-octanol	−12.1	−6.6	5.5	54.5	45.5	–
pH 7.4 (IS = 0.56) → *n*-octanol	−12.3	−18.8	−6.5	74.3	25.7	–

[a] $\varsigma_{Htr}(\%) = (\Delta H^0_{tr}/(\left|\Delta H^0_{tr}\right| + \left|T \cdot \Delta S^0_{tr}\right|)) \times 100$.

[b] $\varsigma_{TStr}(\%) = (T \cdot \Delta S^0_{tr}/\left|\Delta H^0_{tr}\right| + \left|T \cdot \Delta S^0_{tr}\right|)) \times 100$.

[c] $\varepsilon_H\,(\%) = (\Delta H_{spec}/\Delta H_{non\text{-}spec}) \times 100$, where $\Delta H_{spec} = \Delta H^0_{tr}(n\text{-hexane} \rightarrow \text{solvent})/\Delta H^0_{solv}\,(n\text{-hexane})$.

[d] Ionic strength.

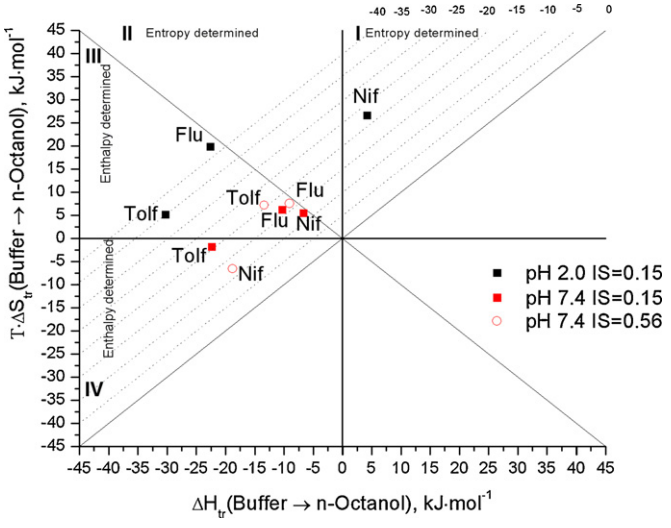
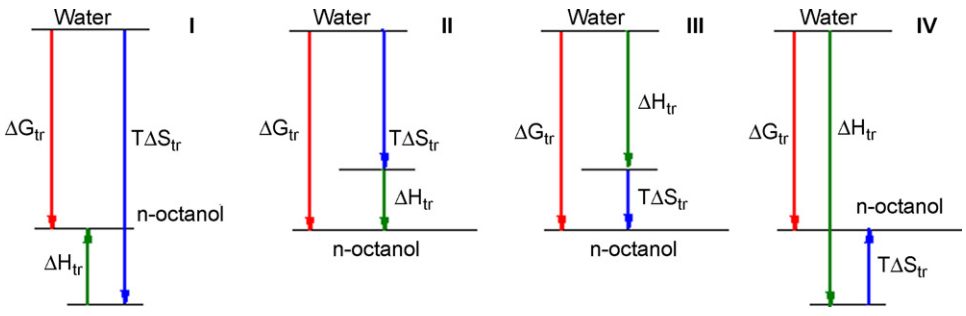


Fig. 5. Relationship between enthalpic and entropic terms of transfer functions from buffers pH 2.0 (IS = 0.15) and pH 7.4 (IS = 0.15, IS = 0.56) to *n*-octanol.

differs essentially from the ionic molecular forms: for the tolfenamic acid this difference is 15 kJ mol^{-1}, for the flufenamic acid, 25 kJ mol^{-1}. The data for the niflumic acid are exceptional due to the existence of ionic molecular forms both in the buffers with pHs 2.0 and 7.4.

As the charged molecular is transferred from the buffer to the octanolic phase, the enthalpy change has a negative sign with a lower absolute value in comparison with the neutral molecular form. The charged molecules in the buffer with pH 7.4 interact stronger with their solvation shells in comparison with the neutral molecules in the buffer with pH 2.0. Therefore, the ionic molecular forms require bigger energy inputs for the resolvation process than the neutral molecules do. It should be noted, that for the niflumic acid an essential energy loss is observed during the transfer process (a positive sign). This behavior can be connected with the existence of the zwitter ionic molecular forms in the buffer with pH 2.0.

The next part of our investigation was the analysis of the impact of ionic strength on the transfer of thermodynamic functions. It should be mentioned, that for every compound under consideration the experimental points corresponding to the transfer thermodynamic parameters both buffer (pH 7.4, IS = 0.15) → *n*-octanol and



Scheme 1.

buffer (pH 7.4, IS = 0.56) → *n*-octanol lay on the isoenergetic (Gibbs free energy) lines. This fact confirms that the driving force of the transfer process does not change at different values of the buffer ionic strength. However, the relationship between the enthalpic and entropic terms depends essentially on the ionic strength. For example, for tolfenamic and flufenamic acids, the increase of the buffer ionic strength leads to, on the one hand, a decrease in the enthalpic term of the transfer of the Gibbs free energy (on an absolute scale) and, on the other hand, an increase in the entropic term. Moreover, the sign of the entropic term changes as the ionic strength value increases from 0.15 to 0.56 for the tolfenamic acid. For the niflumic acid the opposite situation is observed. It should be noted, that for the considered fenamates the transfer processes of the neutral molecules (except the niflumic acid) and the ionic forms are enthalpy-determined. Whereas for the niflumic acid, this process is entropy-determined.

4. Conclusion

We have studied two tolfenamic acid polymorphic modifications in the space groups $P2_1/c$ (white form) and $P2_1/n$ (yellow form), measured the temperature dependence of the white form vapor pressure by the transpiration method and calculated the thermodynamic parameters of the sublimation process. We have also estimated the difference between the crystal lattice energies of the two modifications by solution calorimetry. The crystal lattice energy of the yellow form was found to be $6.7 \pm 1.2\ kJ\ mol^{-1}$ higher than that of the white form, moreover, the advantage of the energy was proved to be connected with the increase of the yellow polymorph entropy. The phase transition temperature was calculated on the basis of the fusion enthalpies and melting points of both polymorphs obtained by DSC experiments. The received value was higher than both melting points of the polymorphic forms studied. This observation confirms that the polymorphic forms are monotropically related. In this work we have studied the solubility, solvation and transfer processes of the tolfenamic acid white form in buffers with various values of pHs and ionic strengths, *n*-hexane and *n*-octanol. We have also analyzed the thermodynamic characteristics of the investigated processes and compared them with others fenamates. Specific and non-specific contributions of the solvation enthalpic term of the studied molecules with the solvents were estimated as well. It was found that the driving forces of the transfer processes from the buffers with pH 7.4 and different ionic strengths to *n*-octanol do not change at different values of the buffer ionic strength. However, the relationship between the enthalpic and entropic terms depends essentially on the ionic strength. For the considered fenamates the transfer processes of the neutral molecules (except of niflumic acid) and the ionic forms are enthalpy-determined. Whereas for the niflumic acid, this process is entropy-determined.

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