Thermodynamic and Structural Aspects of Some Fenamate Molecular Crystals

ARTICLE *in* CRYSTAL GROWTH & DESIGN · JUNE 2009

Impact Factor: 4.89 · DOI: 10.1021/cg900002q

4 AUTHORS:

Artem Surov
Institute of Solution Chemistry of RAS
28 PUBLICATIONS **130** CITATIONS
SEE PROFILE

Irina V. Terekhova
Russian Academy of Sciences
61 PUBLICATIONS **362** CITATIONS
SEE PROFILE

Annette Bauer-Brandl
University of Southern Denmark
92 PUBLICATIONS **1,345** CITATIONS
SEE PROFILE

German L Perlovich
Institute of Solution Chemistry of RAS
141 PUBLICATIONS **1,437** CITATIONS
SEE PROFILE

CRYSTAL GROWTH & DESIGN
2009
VOL. 9, NO. 7
3265–3272

Thermodynamic and Structural Aspects of Some Fenamate Molecular Crystals

Artem O. Surov,[†] Irina V. Terekhova,[†] Annette Bauer-Brandl,[‡,§] and German L. Perlovich*[,†]

Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Ivanovo, Academicheskaya str., 1, Russia, Institute of Pharmacy, University of Tromsø, Breivika, N-9037 Tromsø, Norway, and Department of Physics and Chemistry, University of Southern Denmark, DK 5230 Odense C, Denmark

Received January 2, 2009; Revised Manuscript Received May 23, 2009

ABSTRACT: Crystal lattice characteristics from the literature for different polymorphic forms of some nonsteroidal anti-inflammatory drugs (diclofenac, niflumic, flufenamic, tolfenamic, mefenamic acid) and structural relative compounds (*N*-phenylanthranilic acid and diphenylamine) were summarized and compared. Molecular conformational states in the crystal lattices and hydrogen bond networks were described and analyzed. Temperature dependencies of vapor pressure of the molecular crystals were measured and sublimation thermodynamic parameters calculated. Thermodynamic characteristics of fusion and vaporization processes were derived. Relationships between the sublimation thermodynamic functions and the torsion angles between the benzene motives of the compounds and the polymorphic forms were revealed. Dependence between the sublimation enthalpies and the melting points was observed. Correlation of the fusion entropies with the free volume per molecule in the crystal lattices was found. The absolute values of the crystal lattices energies of the polymorphic forms I and II of mefenamic acid and forms I and III of flufenamic acid were evaluated on basis of the sublimation and solution calorimetric experiments.

Introduction

At present, the most common opinion of the predominant mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) is to inhibit cyclooxygenasis which catalyzes the biosynthesis of prostaglandins. Structure−activity−relationships have revealed that most—but not all—of the nonspecific NSAIDs contain a free carboxylic group and a lipophilic moiety which interact with the receptors to inhibit the natural substrates of the cyclooxygenase to be converted into prostaglandins and the respective endoperoxides.[1,2]

NSAIDs are in general poorly soluble in both water and aqueous buffers at physiological pH. This fact restricts their effective use particularly for the preferred oral route. One possible means to solve the problem is to modify the structure of the molecules in order to decrease crystal lattice energy, while the pharmacological effect needs to be maintained. For this purpose, in addition to predictive structure−activity-relationship models for improved molecular structure, methods to estimate crystal lattice energies are needed. It is well-known that crystal lattice energy can be evaluated by sublimation enthalpy, and there are various experimental methods available for this. However, these methods are less commonly used for drug molecular crystals than fusion methods. Therefore, the main objective of the present work was to study thermodynamic aspects of fusion and sublimation processes of molecular crystals, and to study correlations between these characteristics and the structural parameters of the drug molecules.

Fenamates as being effective and commonly used NSAIDs were chosen as a subject of investigation, and drug compounds of similar structure selected as depicted in Figure 1: niflumic acid (Nif), flufenamic acid (Flu), tolfenamic acid (Tolf), mefenamic acid (Mef), *N*-phenylanthranilic acid (N-PA). Moreover structurally relative substances such as diclofenac acid (*Dic*) and diphenylamine (*DA*) (marked by italic type) were considered in order to compare impact of carboxylic group and methylene bridge between the phenyl ring and the carboxylic group on the studied structural and thermodynamic characteristics.

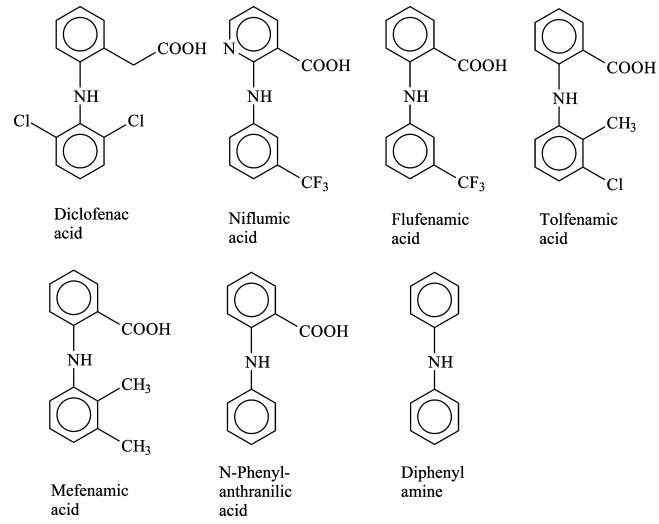

Figure 1. Molecular structure of the studied compounds.

Experimental data for fusion processes of the chosen compounds are available.[3–6] However, thermodynamic aspects of sublimation have not been investigated so far. One of the reasons may be connected with experimental difficulties due to chemical degradation rather than sublimation of the substances at higher temperatures. It should be noted that particularly sublimation thermodynamic functions are important experimental characteristics from a fundamental point of view, because they are in many cases used as the reference values for theoretical calculations of crystal lattice energies.[7]

Experimental Section

Materials and Solvents. Flufenamic acid (2-[[3-(trifluoromethyl)-phenyl]amino]benzoic acid, Flu, $C_{14}H_{10}F_3NO_2$, MW 281.23, Lot

* To whom correspondence should be addressed. Tel: +7-4932-533784. Fax: +7-4932- 336237. E-mail glp@isc-ras.ru.
[†] Russian Academy of Sciences.
[‡] University of Tromsø.
[§] University of Southern Denmark.

10.1021/cg900002q CCC: $40.75
Published on Web 06/10/2009

122K1018, CAS 530-78-9), niflumic acid (2-[3-(trifluoromethyl)anilino]nicotinic acid, Nif, $C_{13}H_9F_3N_2O_2$, MW 282.2, Lot 12K1486, CAS 4394-00-7), mefenamic acid (2-[(2,3-dimethylphenyl)amino]benzoic acid, Mef, $C_{15}H_{15}NO_2$, MW 241.29, Lot 052K1611, CAS 61-68-7), tolfenamic acid (2-[(3-chloro-2-methylphenyl)amino]benzoic acid, Tolf, $C_{14}H_{12}ClNO_2$, MW 261.7, Lot 110H0469, CAS 13710-19-5) were from Sigma Chemical Co., St. Louis, MO. Diclofenac acid (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, *Dic*, $C_{14}H_{11}Cl_2NO_2$, MW 296.15, Lot DFA/303002, CAS 15307−86−5) were from Alchemie USA, INC (Plantsville). *N*-Phenylanthranilic acid ($C_{13}H_{11}NO_2$, N-PA, MW 213.24, Lot 78150, CAS 91-40-7), diphenylamine ($C_{12}H_{11}N$, *DA*, MW 169.23, Lot 1164708, CAS 122-39-4) were from Fluka (Milwaukee, WI). The purity of the compounds was better than 99.8%. Methanol HPLC grade was from Merck (Darmstadt, Germany), Lot K27636907.

Methods. (a) Differential Scanning Calorimetry (DSC). DSC was carried out using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin-Elmer Analytical Instruments, Norwalk, CT) 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 ± 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 semimicrobalance).

(b) Sublimation Experiments. These experiments were carried out by the transpiration method as previously described.[8] 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 vapor of the substance under investigation. The vapor is condensed at some point downstream, and the mass of the sublimate and its purity are determined. The vapor pressure over 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 ΔH^0_{sub} = 90.5 ± 0.3 kJ·mol^{-1}. This is in good agreement with the value recommended by IUPAC of ΔH^0_{sub} = 89.7 ± 0.5 kJ·mol^{-1}.[9] The saturated vapor pressures were measured at least 5 times at each temperature, with the statistical error being within 3−5%. The experimentally determined vapor pressure data are described in (ln(P);1/T) coordinates by the equation

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

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

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

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

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

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

Sublimation measurements were carried out at elevated temperatures for experimental reasons. In order to improve the extrapolation to room conditions, heat capacity (C_{pc}^{298} value) of the crystals was estimated using the additive scheme proposed by Chickos et al.[10] Heat capacity was introduced as a correction for the recalculation of the ΔH^T_{sub} value at 298 K (ΔH^{298}_{sub} value), according to the equation[10]

$$\Delta H^{298}_{sub} = \Delta H^T_{sub} + \Delta H_{cor} = \Delta H^T_{sub} + (0.75 + 0.15C_{pc}^{298})(T - 298.15) \quad (4)$$

(c) Solution Calorimetry. Enthalpies of solution were measured by means of isothermal calorimeter. A detailed description of the calorimeter was presented in our previous work.[11,12] The temperature stability was better than 2 × 10^{-3} K. The accuracy of weight measurements corresponded to ±10^{-6} g. The calorimeter was calibrated using KCl (analytical grade >99.5%, from Merck) in water in a wide concentration interval with a number of measurements of more than 10. The obtained standard value of solution enthalpy was 17225 ± 50 J·mol^{-1}. This is in good agreement with the value 17217 ± 33 J·mol^{-1} recommended by the IUPAC.[9]

(d) Calculation Procedure. van der Waals's molecular volumes (V^{vdw}) were calculated using program GEPOL[13] and Kitaigorodskyi's atomic radii.[7] The free volume per molecule (V^{free}) in the crystal lattice was obtained by the equation

$$V^{free} = (V_{cell} - ZV^{vdw})/Z \quad (5)$$

where V_{cell} is a unit cell volume and Z is number molecules in the unit cell.

In order to estimate molecular packing density in the crystal lattices, the following parameter was introduced:

$$\beta = V^{free}/V^{vdw} \quad (6)$$

Results

Structural Aspects. The respective crystal structures of the outlined compounds have already been described in literature in detail: First, it should be noted that for diclofenac, three polymorphic modifications have been characterized by X-ray diffraction experiments: $P2_1/c$ (form I),[14] $C2/c$ (form II),[14] *Pcan* (form III).[15] Form II ($C2/c$) was used for the present experiments (prepared by slow vaporization of a saturated methanol solution), as this modification is thermodynamically most stable within the studied temperature interval. The structure of the polymorphic phase used was confirmed by X-ray diffraction data.[16] Flufenamic acid crystallizes, among others, in two monoclinic crystal lattices with space groups $C2/c$ (form III)[17] and $P2_1/c$ (form I),[18] respectively. Flufenamic acid was received from Sigma and corresponds to the polymorphic form I. Tolfenamic acid crystallizes in five polymorphic forms: crystal lattices with space groups $P2_1/c$ (white, form I),[6] $P2_1/n$ (yellow, form II),[6] $P2_1/c$ (form III),[31] $P1$ (form IV),[31] $P1$ (form V).[31] For the experiments form I was applied, prepared by slow vaporization of the toluene solution.[20] In literature for niflumic acid only one polymorphic form ($P2_1/n$) was found,[21] as well as for *N*-phenylanthranilic acid ($P\bar{1}$)[22] and for diphenylamine ($P\bar{1}$).[23] The low temperature modification (form I) of mefenamic acid ($P\bar{1}$)[24] has a temperature of enantiotropic phase transition to the high temperature form (form II) at 165−175 °C.[25] Therefore, the experimental temperature interval for the mefenamic acid was kept below and within the region of thermodynamic stability of form I. The crystal structures of all materials used were confirmed by powder X-ray diffraction prior to experiments. The obtained diffractograms were in good agreement with those theoretically calculated based on single crystal X-ray data described in the literature. The structural parameters of the crystal lattices studied, the graph set notations of their hydrogen bond networks,[26] and their van der Waals molecular volumes are summarized in Table 1.

The hydrogen bond geometries of the studied compounds are presented in Table 2 (where atom numbering corresponds to Scheme 1). The considered substances create two types of hydrogen bonds: intermolecular, with networks described by graph set notation $R^2_2(8)$; and intramolecular, S(n). The geometry of the intramolecular hydrogen bonds of diclofenac acid differs from analogous bonds for the other compounds, because seven atoms take part in the intramolecular ring in contrast to the other substances, where it is six atoms. The geometry of the intermolecular hydrogen bonds does not essentially differ from each other; they form a dimer organization in all the crystal lattices. Slight deviations of the angle ∠D−H···A for flufenamic, tolfenamic and mefenamic acids from the ideal value (as for N-PA) are connected

Table 1. Crystal Lattice Parameters of the Substances under Investigation[a]

	Dic (form II)	Nif	Flu (form I)	Tolf (form I)	Mef (form I)	N-PA	*DA*
ref	14	21	18	6	24	22	23
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	triclinic	triclinic
space group	*C*2/*c*	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a, Å	20.226(4)	5.111(2)	12.523(4)	4.826(2)	14.556	8.099	9.853
b, Å	6.971(3)	15.330(2)	7.868(6)	32.128(11)	6.811	9.826	9.882
c, Å	20.061(4)	15.479(2)	12.874(3)	8.041(4)	7.657	14.059	37.944
α, deg	90.00	90.00	90.00	90.00	119.57	85.96	83.85
β, deg	109.64(2)	95.5(3)	95.2(2)	104.88(3)	103.93	88.62	88.53
γ, deg	90.00	90.00	90.00	90.00	91.30	73.39	89.86
V_{cell}, Å^3	2664(1)	1207.22	1263.27(2)	1205(2)	631.77	1069.64	3672.0
D_x, g·cm^{-3}	1.477	1.55	1.47	1.443	1.268	1.324	1.224
Z	8	4	4	4	2	4	16
graph set notation	$R_2^2(8)$; S(7)	$R_2^2(8)$; S(6)	$R_2^2(8)$; S(6)	$R_2^2(8)$; S(6)	$R_2^2(8)$; S(6)	$R_2^2(8)$; S(6)	
V^{vdw}, Å^3	231.03	212.7	217.47	212.6	218.92	193.58	170.60
V_{mol},[b] Å^3	333.00	301.81	315.82	301.25	315.89	267.41	229.50
V^{free},[c] Å^3	101.97	89.11	98.35	88.65	96.97	73.83	58.90
V^{free}/V^{vdw}, %	44.13	41.89	45.22	41.7	44.29	38.14	34.53

[a] In brackets are displayed the standard deviations. [b] $V_{mol} = V_{cell}/Z$. [c] $V^{free} = (V_{cell} - ZV^{vdw})/Z$.

Table 2. Hydrogen Bond Geometry of the Compounds Studied

$R_2^2(8)$[a]	*Dic* (form II)	Nif	Flu (form I)	Tolf (form I)	Mef (form I)	N-PA	
D−H···A	O2−H2···O1^{i} [b]	O2−H2···O1^{i}	O2−H2···O1^{i}	O2−H2···O1^{i}	O2−H2···O1^{i}	O2−H2···O11	
D−H [Å]	0.87(3)	1.1(2)	0.862	0.972(5)	0.973	1.0	1.0
H···A [Å]	1.77(3)		1.793	1.686(5)	1.685	1.7	1.7
D···A [Å]	2.646(2)	2.67(1)	2.646	2.648(3)	2.655	2.670(3)	2.668(3)
∠D−H···A [deg]	178.2		170.0	170.2	174.1	180	180
S(*n*)[a]	S(7)	S(6)	S(6)	S(6)	S(6)	S(6)	
D−H···A	N1−H1···O1	N1−H1···O1	N1−H1···O1	N1−H1···O1	N1−H1···O1	N1−H1···O1	
D−H [Å]	0.75(2)	0.8(2)	0.840	0.788(3)	0.912	1.03(3)	0.94(3)
H···A [Å]	2.31(2)		1.979	2.018(3)	1.892	1.98(3)	2.00(3)
D···A [Å]	2.946(3)	2.69(1)	2.646	2.676(3)	2.636	2.659(3)	2.645(3)
∠D−H···A [deg]	143.1		135.6	140.8	137.3	121(2)	124(2)

[a] Graph set notation of the hydrogen bond networks, which include the hydrogen bond. [b] i: Symmetry code.

Scheme 1. Numbering of Atoms in Fenamic Acid

with molecular conformational strains due to steric hindrance by the substituents at the second phenyl ring.

Molecular conformational states of the fenamates can be completely described by three torsion angles: twisting the carboxylic group with regard to axis C2−C7 (∠O2−C7−C2-C1); bend of the bridge group relative to axis C1−N1 (∠C2−C1−N1−C8) and, finally, twisting the second phenyl group with regard to axis N1−C8 (∠C1−N1−C8−C9). The values of the noted angles are shown in Table 3. It is a common feature of the carboxylic groups of all the fenamates (O2C7O1) to be approximately coplanar to the first phenyl ring (Ph1). Similarly, as a result of resonance interactions and internal hydrogen bonds, the bridging amino group is also coplanar:[27] All the ∠C2−C1−N1−C8 values are approximately the same with slight deviation from 180° to the one or the other side. The maximum deviation is observed for diclofenac acid (≈14°) and can be attributed to the perpendicular arrangement of the carboxylic group with regard to Ph1 (in contrast to the rest of the substances, where this group is in parallel with Ph1). In contrast to the previous two angles, the angles ∠C1−N1−C8−C9, being connected with the out-of-plane rotation of the second ring, differ considerably between the substances and their respective polymorphic phases. For the modifications studied, a regularity can be found for the torsion angles: For example, similarity of values is observed for diclofenac (−123.2°) and mefenamic (−120°) acids; flufenamic acid (−130.1°) and N-PA (molecule A in the asymmetric unit: −136°); tolfenamic acid (−75°) and N-PA (molecule B in the asymmetric unit: −71°). The molecules of the niflumic acid have no similarity in this respect with any of the other considered molecules, and this fact can be explained by the presence of a heteroatom (N) in the first ring.

Sublimation and DSC Measurements. The temperature dependencies of the vapor pressures for the fenamates and the respective correlation equations are presented in Table 4. The thermodynamic parameters of sublimation, fusion and vaporization processes are summarized in Table 5.

Chemical stabilities of the compounds during the sublimation experiments were verified using a spectrophotometric method by comparison of the respective spectra of the initial compounds and the substances before and after experiments. It is assumed that the molecules of the compounds are monomolecularly distributed in the gas phase, because, first, the vapor pressures of the substances in general are of low values (0.001−1 Pa) (Table 4) within the considered temperature intervals. Vapor pressures do not deviate from linearity at higher temperatures. Second, thermogravimetric experiments of sublimation were carried out at low heating rates for the fenamates and related compounds (data not shown). These processes follow equations of zero order kinetics, and the respective activation energies coincide (within experimental errors) with the sublimation enthalpies.

Table 3. Some Torsion Angle Values of the Compounds Studied[a]

	Dic (form II)	Nif	Flu (form I)	Tolf (form I)	Mef (form I)	N-PA	
∠O2−C7−C2−C1		−177.2	175.8	−178.5	178.6	180	179
∠C2−C1−N1−C8	−165.6	174.4	−179.2	180	−179.3	172.1	177.5
∠C1−N1−C8−C9	−123.2	−4.5	−130.1	−75.0	−120	−136 (47)	−71 (111)[b]

[a] Numbering corresponds to Scheme 1. [b] In brackets are presented the values which appear from ambiguity of interpretation (due to absence of substituents at Ph2).

Table 4. The Temperature Dependencies of Saturation Vapor Pressure of the Compounds Studied

Dic (form II)[a]		Nif[b]		Flu (form I)[c]		Mef (form I)[d]		Tolf (form I)[e]		N-PA[f]		*DA*[g]	
T, K	*P*, Pa	*T*, K	*P*, Pa	*T*, K	*P*, Pa	*T*, K	*P*, Pa	*T*, K	*P*, Pa	*T*, K	*P*, Pa	*T*, K	*P*, Pa
323.2	9.19×10^{-3}	354.7	6.41×10^{-3}	338.7	1.04×10^{-2}	356.7	2.84×10^{-2}	345.7	3.92×10^{-2}	353.2	1.09×10^{-2}	302.7	9.53×10^{-2}
326.2	1.27×10^{-2}	358.2	1.04×10^{-2}	341.2	1.40×10^{-2}	359.2	4.12×10^{-2}	349.2	5.61×10^{-2}	365.2	4.87×10^{-2}	303.7	1.19×10^{-1}
329.2	1.94×10^{-2}	359.7	1.25×10^{-2}	343.7	1.87×10^{-2}	360.7	4.88×10^{-2}	351.7	7.73×10^{-2}	368.2	7.41×10^{-2}	304.7	1.32×10^{-1}
330.2	2.09×10^{-2}	364.2	2.11×10^{-2}	345.2	2.35×10^{-2}	362.2	6.14×10^{-2}	353.2	1.00×10^{-1}	373.2	1.33×10^{-1}	305.7	1.53×10^{-1}
333.2	2.87×10^{-2}	366.2	2.55×10^{-2}	345.7	2.47×10^{-2}	367.2	9.63×10^{-2}	354.2	1.24×10^{-1}	379.2	2.17×10^{-1}	307.2	1.93×10^{-1}
335.2	4.12×10^{-2}	368.2	3.33×10^{-2}	346.7	2.84×10^{-2}	370.2	1.37×10^{-1}	357.2	1.59×10^{-1}	381.2	2.66×10^{-1}	308.2	2.20×10^{-1}
338.2	5.34×10^{-2}	370.7	4.24×10^{-2}	351.2	4.46×10^{-2}	372.2	1.77×10^{-1}	358.2	1.83×10^{-1}	387.2	4.25×10^{-1}	310.7	3.09×10^{-1}
341.2	7.73×10^{-2}	373.2	5.61×10^{-2}	355.2	7.35×10^{-2}	375.2	2.59×10^{-1}	359.2	2.10×10^{-1}	390.2	7.02×10^{-1}	311.7	3.60×10^{-1}
344.2	1.11×10^{-1}	375.7	7.28×10^{-2}	357.2	9.44×10^{-2}	378.2	3.13×10^{-1}	361.2	2.52×10^{-1}	392.2	7.33×10^{-1}	312.2	3.75×10^{-1}
345.2	1.31×10^{-1}	377.2	8.80×10^{-2}	361.2	1.44×10^{-1}	381.2	4.27×10^{-1}	363.7	3.53×10^{-1}	397.2	1.26	313.2	4.12×10^{-1}
347.2	1.79×10^{-1}	379.2	1.08×10^{-1}	364.2	2.14×10^{-1}	384.2	6.98×10^{-1}	366.2	4.72×10^{-1}	399.2	1.83	315.2	5.89×10^{-1}
350.7	2.49×10^{-1}	381.7	1.38×10^{-1}	368.2	3.17×10^{-1}	387.2	9.15×10^{-1}	367.7	4.92×10^{-1}	402.2	2.07	316.7	6.74×10^{-1}
352.2	2.89×10^{-1}	386.7	2.25×10^{-1}	369.2	3.40×10^{-1}	390.2	1.42	369.2	6.64×10^{-1}	406.2	3.08	317.7	8.10×10^{-1}
355.2	4.11×10^{-1}	390.2	3.53×10^{-1}	370.2	3.87×10^{-1}	392.2	1.46	370.2	7.05×10^{-1}	411.2	4.21	319.2	9.24×10^{-1}
		393.2	4.54×10^{-1}	376.2	6.84×10^{-1}	394.7	2.14	373.2	8.96×10^{-1}				
		396.2	6.57×10^{-1}			398.2	3.10						

[a] $\ln(P, \text{Pa}) = (37.9 \pm 0.5) - (13791 \pm 159)/T$; $\sigma = 5.09 \times 10^{-2}$; $r = 0.999$; $n = 14$; ref 16. [b] $\ln(P, \text{Pa}) = (38.3 \pm 0.3) - (15361 \pm 93)/T$; $\sigma = 3.25 \times 10^{-2}$; $r = 0.999$; $n = 16$; ref 34. [c] $\ln(\text{P, Pa}) = (37.8 \pm 0.2) - (14363 \pm 81)/T$; $\sigma = 2.87 \times 10^{-2}$; $r = 0.999$; $n = 15$; ref 34. [d] $\ln(\text{P, Pa}) = (41.2 \pm 0.3) - (15967 \pm 100)/T$; $\sigma = 3.70 \times 10^{-2}$; $r = 0.999$; $n = 16$. [e] $\ln(\text{P, Pa}) = (40.5 \pm 0.6) - (15119 \pm 214)/T$; $\sigma = 5.10 \times 10^{-2}$; $r = 0.998$; $n = 15$. [f] $\ln(\text{P, Pa}) = (37.7 \pm 0.6) - (14877 \pm 218)/T$; $\sigma = 6.22 \times 10^{-2}$; $r = 0.997$; $n = 14$. [g] $\ln(\text{P, Pa}) = (41.4 \pm 0.5) - (13231 \pm 147)/T$; $\sigma = 2.98 \times 10^{-2}$; $r = 0.999$; $n = 14$.

Table 5. Thermodynamic Characteristics of Sublimation, Fusion, and Vaporization Processes of the Compounds Studied

	Dic (form II)	Nif	Flu (form I)	Tolf (form I)	Mef (form I)	N-PA	*DA*
$\Delta G_{\text{sub}}^{298}$ [kJ·mol^{-1}]	49.3 ± 0.5	61.3 ± 0.4	54.3 ± 0.4	53.9 ± 0.4	59.2 ± 0.1	58.9 ± 0.5	35.9 ± 0.1
$\Delta H_{\text{sub}}^{T}$ [kJ·mol^{-1}]	114.7 ± 1.3	127.7 ± 0.8	119.4 ± 0.7	125.7 ± 0.8	132.7 ± 0.8	123.0 ± 1.3	110.0 ± 1.0
$C_{p_c}^{298}$ [J·mol^{-1}·K^{-1}]	302.1	292.6	296.2	283.1	291.0	235.8	191.7
$\Delta H_{\text{sub}}^{298}$ [kJ·mol^{-1}]	115.6 ± 1.3	130.2 ± 0.8	121.2 ± 0.7	128.4 ± 0.8	136.2 ± 0.8	126.0 ± 1.3	110.0 ± 1.0
$T\Delta S_{\text{sub}}^{298}$ [kJ·mol^{-1}]	66.3 ± 1.3	68.9 ± 1.2	66.9 ± 1.1	74.8 ± 1.2	76.2 ± 0.9	68.0 ± 1.8	74.0 ± 1.1
$\Delta S_{\text{sub}}^{298}$ [J·mol^{-1}·K^{-1}]	222 ± 4	231 ± 4	224 ± 4	216 ± 4	213 ± 3	193 ± 6	211 ± 4
ς_{H}, %[a]	63.6	65.4	64.4	63.2	64.0	65.1	59.7
ς_{TS}, %[a]	36.4	34.6	35.6	36.8	36.0	34.9	40.3
T_{m}, K	452.6 ± 0.2	478.5 ± 0.2	405.3 ± 0.2	484.3 ± 0.2	503.5 ± 0.2	458.2 ± 0.2	326.1 ± 0.2
$\Delta H_{\text{fus}}^{T}$ [kJ·mol^{-1}]	40.4 ± 0.5	36.5 ± 0.5	26.7 ± 0.5	38.6 ± 0.5	38.7 ± 0.5	39.7 ± 0.5	19.9 ± 0.5
$\Delta H_{\text{fus}}^{298}$ [b] [kJ·mol^{-1}]	26.6 ± 0.5	22.7 ± 0.5	19.6 ± 0.5	23.8 ± 0.5	22.9 ± 0.5	25.8 ± 0.5	18.2 ± 0.5
$\Delta S_{\text{fus}}^{T}$ [c] [J·mol^{-1}·K^{-1}]	89 ± 3	76 ± 2	66 ± 2	79.7 ± 2.5	76.9 ± 0.5	86.7 ± 2.5	61.0 ± 2.5
$\Delta H_{\text{vap}}^{T}$ [d] [kJ·mol^{-1}]	74.3 ± 1.8	91.2 ± 1.3	92.7 ± 1.2	87.2 ± 1.3	94.1 ± 1.3	83.9 ± 1.3	90.1 ± 1.5
$\Delta H_{\text{vap}}^{298}$ [kJ·mol^{-1}]	89.0 ± 1.8	107.5 ± 1.3	101.6 ± 1.2	104.9 ± 1.3	112.5 ± 1.3	101.3 ± 1.8	92.3 ± 1.5

[a] $\varsigma_{\text{H}} = (\Delta H_{\text{sub}}^{298}/(\Delta H_{\text{sub}}^{298} + T\Delta S_{\text{sub}}^{298})) \times 100\%$; $\varsigma_{\text{TS}} = (T\Delta S_{\text{sub}}^{298}/(\Delta H_{\text{sub}}^{298} + T\Delta S_{\text{sub}}^{298})) \times 100\%$. [b] $\Delta H_{\text{fus}}^{298} = \Delta H_{\text{fus}}^{T} - \Delta S_{\text{fus}}^{T}(T_{\text{m}} - 298.15)$. [c] $\Delta S_{\text{fus}}^{T} = \Delta H_{\text{fus}}^{T}/T_{\text{m}}$. [d] $\Delta H_{\text{vap}}^{298} = \Delta H_{\text{sub}}^{T} - \Delta H_{\text{fus}}^{T}$.

Solution Calorimeter Measurements. (a) Studying Polymorphic Forms I and II of Mefenamic Acid. Mefenamic acid commercial product was found to be modification I, and this fact was verified by DSC experiments: the endothermal effect corresponding to the I → II phase transition was observed at $T = 450$ K. In order to prepare homogeneous polycrystals of form II for the solution calorimetry experiments, the following procedure was used: The crystals of modification I were put into a DSC sample pan and heated in the DSC in an inert gas atmosphere with a heating rate of 10 K·min^{-1} to a temperature of 5 K above the temperature at which the heat effect of the phase transition process I → II ceased (~453 K). Then, the freshly prepared phase II was cooled down at 40 K·min^{-1} to room temperature, and under moisture protection powdered (by spatula, in order to protect it from phase transition, which is observed if mortar and pestle are used intensively) and immediately transferred to the ampule for solution calorimetry. The time consumed for a complete procedure from filling the ampule until the end of the solution calorimetry experiment was approximately 2 h. The presented preparation scheme turned out to provide full control over nucleation and growth processes of phase II from the amorphous phase.

For the calorimetric experiments, a sample mass (approximately 20 mg, accurately weighed) was used to make a concentration of approximately 1.5×10^{-3} mol·kg^{-1}. The energy difference of the crystal lattices was estimated from the difference in solution enthalpies obtained by dissolution in the same solvent (in this case MeOH). We have used this approach earlier for measuring differences of modifications of glycine.[28] Methanol as a solvent was chosen here because the drug under investigation dissolves well with a large endothermic heat effect. The results of the calorimetric experiments are presented in Table 6.

From Table 6 it follows that the crystal lattice energy of form I is higher by $\Delta H_{\text{tr}}^{298}(\text{II}\rightarrow\text{I}) = 3.6 \pm 1.0$ kJ·mol^{-1} in comparison

Table 6. The Solution Enthalpies, ΔH^{m}_{sol}, of the Different Polymorph Modifications of Mefenamic and Flufenamic Acids

	mefenamic acid				flufenamic acid			
	form I		form II		form I		form III	
N	g^a [mg]	ΔH^{m}_{sol} [kJ·mol^{-1}]	g^a [mg]	ΔH^{m}_{sol} [kJ·mol^{-1}]	g^a [mg]	ΔH^{m}_{sol} [kJ·mol^{-1}]	g^a [mg]	ΔH^{m}_{sol} [kJ·mol^{-1}]
1	21.204	25.3	20.597	21.9	21.000	19.1	11.100	20.6
2	20.079	26.6	20.642	22.0	17.050	19.0	10.020	22.7
3	20.579	25.5	20.517	20.9	17.550	18.9	11.230	22.1
4	20.500	25.2	20.763	22.5	12.050	19.3	15.530	21.1
5	20.746	25.4	20.360	22.2	21.900	18.4	15.440	21.3
6	20.708	25.9	20.664	21.8	33.520	18.9		
7			20.633	22.4				
	ΔH^{m}_{sol}	25.6 ± 0.5	ΔH^{m}_{sol}	22.0 ± 0.5	ΔH^{m}_{sol}	18.9 ± 0.3	ΔH^{m}_{sol}	21.6 ± 0.8

[a] Total weight.

to form II. This result is in good agreement with the value obtained by Urakami et al.[29] at 298 K in DMFA by solution calorimetry: 3.67 kJ·mol^{-1}. The crystal lattice energy of form II can be estimated through the sublimation enthalpy of form I and the phase transition enthalpy: $\Delta H^{298}_{sub}(II) = \Delta H^{298}_{sub}(I) - \Delta H^{298}_{tr}(II \rightarrow I) = 132.6 \pm 1.8$ kJ·mol^{-1}.

(b) Studying Polymorphic Forms I and III of Flufenamic Acid. The flufenamic acid was received from Sigma and corresponds to the polymorphic form I, as it was mentioned before. The melting point of this modification is 405.3 K and in good agreement with the literature data 407.2 K.[30] The polymorphic form III was prepared by the protocol described earlier:[19] the toluene solution was cooled from 80 to 0 °C quickly under intensive stirring. On the DSC curve is observed enantiotropic phase transition of form III to form I at 315.2 K (heating rate 10 K·min^{-1}). This value is in good agreement with the data published by Burger and Ramberger.[31] The solution calorimetry experiment was carried out in the same manner as was described for the polymorphic modifications of mefenamic acid. The results of the experiments are presented in Table 6. As it follows from Table 6, the crystal lattice energy of form III is 2.7 ± 1.1 kJ·mol^{-1} higher than form I. If one takes into account the sublimation enthalpy of form I ($\Delta H^{298}_{sub}(I) = 121.2 \pm 0.7$ kJ·mol^{-1}) and the obtained heat of the phase transition ($\Delta H^{298}_{tr}(I \rightarrow III)$), one can estimate the sublimation enthalpy of form III: $\Delta H^{298}_{sub}(III) = \Delta H^{298}_{sub}(I) + \Delta H^{298}_{tr}(I \rightarrow III) = 123.9 \pm 1.8$ kJ·mol^{-1}.

Discussion

Thermodynamic functions of the sublimation process depend on a number of parameters, among which are structure and topology of molecules studied, nature of atoms, molecular packing architecture in the crystal lattice, molecular conformational state, and topology of hydrogen bond networks. It is therefore very difficult to pick a single descriptor to describe the thermodynamic functions. On the other hand, it appears inappropriate to search for multiparameter equations due to the restricted number of compounds studied. Therefore, we tried to find regularities between the thermodynamic functions and some structural characteristics of the crystals. From X-ray diffraction experiments it follows that all the considered molecules (with diphenylamine as an exception) create dimers in the respective crystal lattices between the coplanar carboxylic groups at the first benzene rings. The second benzene ring may have restricted conformational mobility depending on the size of the substituents. In this case, the benzene motives twist to compensate strains of the steric hindrances and to minimize the molecular packing energy of the crystal lattices. Therefore it can be assumed that particularly the angle of tilt between the two benzene rings (α) will be connected to the molecular

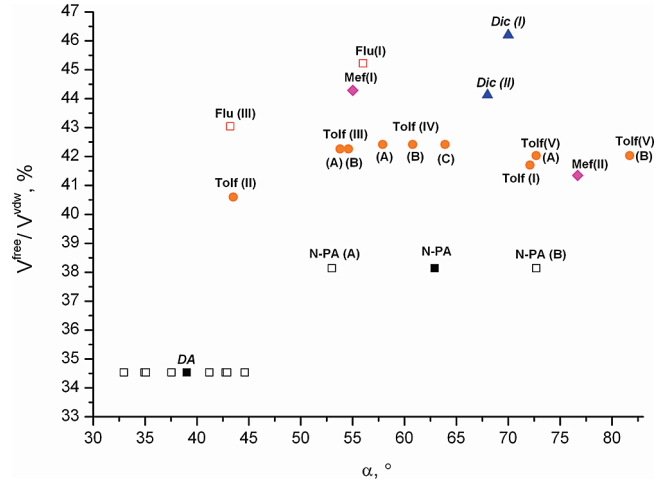

Figure 2. Dependence of $\beta = V^{free}/V^{vdw}$ on the angle between the two benzene rings (α) of the studied compounds and their polymorphic forms (the letters A, B, C correspond to various molecules in asymmetric unit of the crystal lattices).

packing density and thermodynamic sublimation functions. Dependence of the molecular packing volume $\beta = V^{free}/V^{vdw}$ on the discussed angle is presented in Figure 2 (with an exception for niflumic acids). The data for the different polymorphic modifications of the studied compounds with solved crystal lattice structures are presented in Figure 2 as well. Diphenylamine has eight molecules in the asymmetric unit, and this moment is depicted by eight empty squares, which correspond to the various angles between the phenyl rings. The average value is marked by a filled square. An analogous situation is observed for N-PA: there are two molecules in the asymmetric unit (A and B, marked by empty squares), whereas the filled square corresponds to the average value. The five polymorphic forms are shown in Figure 2 for tolfenamic acid.[32] Thermodynamic investigations have been carried out for form I. It should be mentioned that forms III and V have two molecules in asymmetric unit, whereas form III has three. The two forms (I and II) are presented for mefenamic acid, where the sublimation experiments have been done for polymorph I. In one's turn, forms I and II are shown for flufenamic acid in Figure 2, where the sublimation experiments have been performed for the polymorph I. Finally, for diclofenac acid the two forms (I with space group $P2_1/c$ and II with space group $C2/c$) are presented in the figure. The sublimation experiments have been carried out for form II.

It is not difficult to see that the considered substances can be conditionally divided into three groups in accordance with similarity of molecular conformations in the crystal lattices (classification is based on the α-value). Conformations of

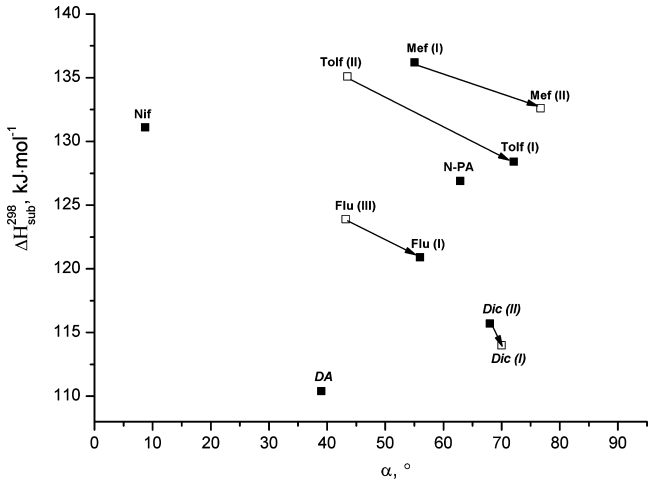

Figure 3. Dependence ΔH^{298}_{sub} on the angle between the two benzene rings (α) of the studied compounds and their polymorphic forms.

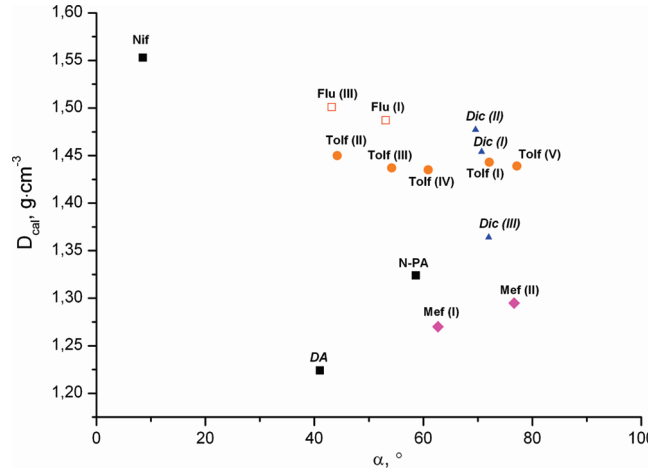

Figure 4. Dependence of the calculated density values (D_{cal}) on the angle between the two benzene rings (α).

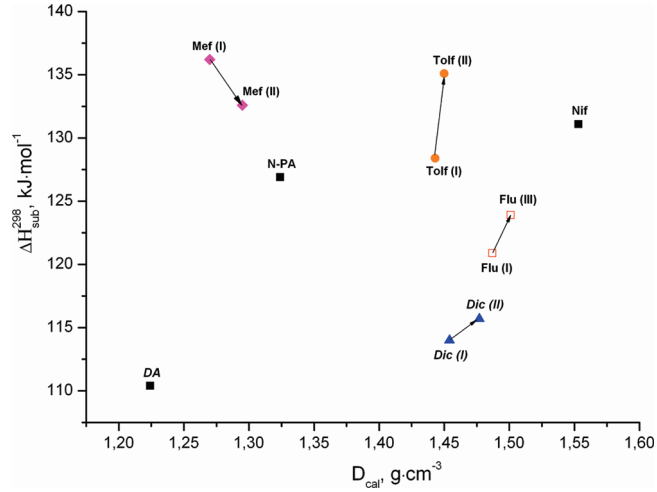

Figure 5. Dependence of ΔH^{298}_{sub} on the calculated density values (D_{cal}).

diphenylamine molecules with α values within 34−45° can be marked as an ancestor of the first group. In this group can be included form II of tolfenamic acid and form III of flufenamic acid. The molecules with conformations similar to the conformation state of molecule A of *N*-phenylanthranilic acid create the second group (with α values within 53−56°): Flu (I), Mef (I), Tolf (III) molecules A and B. Finally, the molecules with α values lying within 68−77° belong to the third group with molecular conformations similar to the molecule B of *N*-phenylanthranilic acid: *Dic (I)*, *Dic (II)*, Tolf (I), Tolf (V, molecule A), Mef (II). The polymorphic form IV and molecule B of form V of tolfenamic acid are exceptions of the outlined classification.

As the structural parameters of the crystal lattices are sensitive to alteration of the angle of tilt of the two benzene rings of the molecules (α), we tried to analyze the relationship of the thermodynamic sublimation functions and this angle. The dependence of ΔH^{298}_{sub} on α is shown in Figure 3. The same figure shows sublimation enthalpies of the alternative polymorphic forms, which have been obtained by sublimation measurements (marked by filled squares) and by solution calorimetry experiments (marked by empty squares): for *Dic (I)* and *Dic (II)*;[16] for Mef (I) and Mef (II), this work; for Flu (I) and Flu (III), this work; Tolf (I) and Tolf(II).[33] It is not difficult to see that for the same compound a higher value of the crystal lattice energy corresponds to the polymorphic form with a lower value of the α parameter.

An analogous regularity is observed for the calculated density values of the studied polymorphic forms presented in Figure 4. The polymorphic modifications with a lower angle of tilt between the two benzene rings (α) have a higher density value: *Dic (II)* (1.477) > *Dic (I)* (1.454) > *Dic (III)* (1.364); Flu (III) (1.501) > Flu (I) (1.487); Tolf (II) (1.45) > Tolf (III) (1.437) ≈ Tolf (IV) (1.435) ≈ Tolf (I) (1.43) ≈ Tolf (V) (1.439). An exception is for mefenamic acid, Mef (I) (1.27) < Mef (II) (1.295), and this fact can be connected with essential change of the crystal lattice architecture at the phase transition. For the polymorphic form I close contacts correspond to distances between the methyl groups of the adjacent molecules, whereas for form II these contacts conform to the distances between the methyl groups and the phenyl fragments of the nearest molecules.

We tried to compare crystal lattice energies of the studied polymorphic forms with their calculated density values. Experimental data of the sublimation enthalpies versus the calculated densities are presented in Figure 5. As it follows from Figure 5, the polymorphic modification of the same substance with a higher density value has a higher crystal lattice energy: for tolfenamic acid, ΔH^{298}_{sub}(I) = 128.4 kJ·mol^{-1} (D_{cal}(I) = 1.43 g·cm^{-3}) < ΔH^{298}_{sub}(II) = 135.1 (D_{cal}(II) = 1.45); for flufenamic acid, ΔH^{298}_{sub}(I) = 120.9 (D_{cal}(I) = 1.487) < ΔH^{298}_{sub}(III) = 123.9 (D_{cal}(III) = 1.501); and for diclofenac acid, ΔH^{298}_{sub}(I) = 114 (D_{cal}(I) = 1.454) < ΔH^{298}_{sub}(II) = 115.7 (D_{cal}(I) = 1.477). It should be noted that, as in the previous case, an exception is observed for mefenamic acid (ΔH^{298}_{sub}(I) = 136.2 > ΔH^{298}_{sub}(II) = 132.6 whereas D_{cal}(I) = 1.27 < D_{cal}(II) = 1.295) and can be explained by essential differences of molecular packing architectures of the forms.

As a next step, the impact of various substituents (introduced to the molecule *N*-phenylanthranilic acid) on sublimation enthalpies and melting points was analyzed. The presence of a carboxylic group in the molecules determines the formation of inter- and intramolecular hydrogen bonds, and this fact produces increasing ΔH^{298}_{sub} and T_m values. For example, both the sublimation enthalpy and the melting point of *N*-phenylanthranilic acid are higher by, respectively, 16.0 kJ·mol^{-1} and 132.1 K, compared to the analogous values for diphenylamine. Introducing a $-CF_3$ group to the N-PA molecule (flufenamic acid) leads

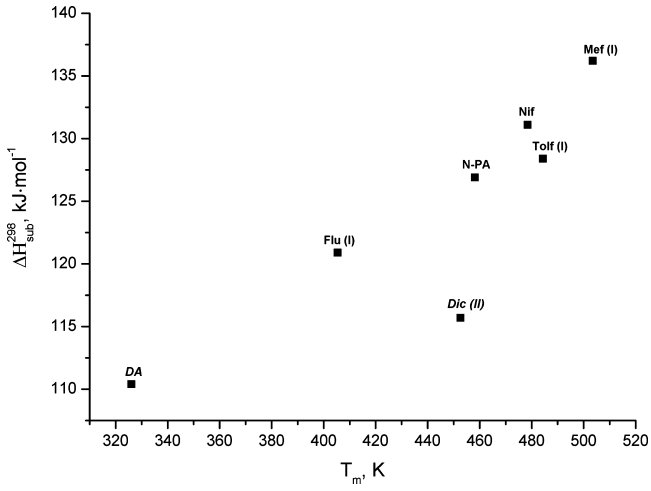

Figure 6. Dependence of the sublimation enthalpies on the melting points of the compounds studied.

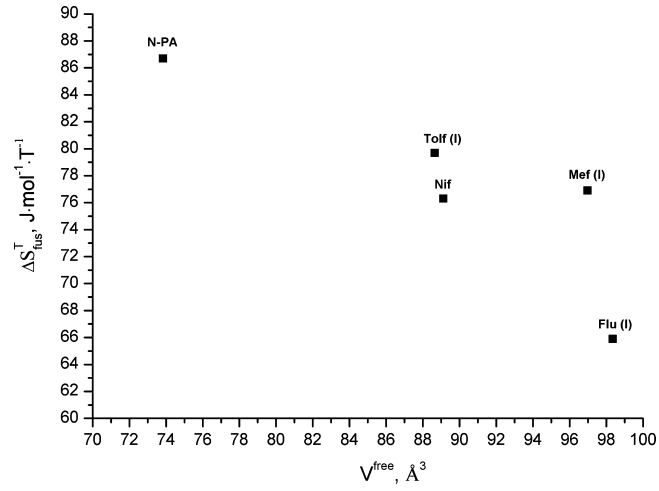

Figure 7. Dependence of the fusion entropy, ΔS^T_{fus}, on the molecular free volume in the crystal lattice, V_{free}, for the *N*-phenylanthranilic acid derivatives.

to a decrease of melting point (by 52.9 K), and sublimation enthalpy by 4.8 kJ·mol^{-1}.

As has been mentioned above, replacing the carbon atom of the flufenamic acid molecule by a nitrogen atom (i.e., niflumic acid) leads to essential changes in molecular structure, packing density, and crystal lattice energies. Dhanaraj and Vijayan,[27] studying crystal lattices of the flufenamic and niflumic acids, concluded that introducing the nitrogen heteroatom leads to disappearance of the mutual repulsion of H-atoms at the nearest benzene rings of the flufenamic acid molecule. This fact may be an explanation for the big difference in molecular tilt, expressed by α-values of flufenamic (56°) and niflumic (8.5°) acid. The sublimation enthalpy of niflumic acid is higher by 9.0 kJ·mol^{-1} compared to flufenamic acid, whereas their melting points differ by 73.2 K.

Introducing two methyl groups into the N-PA molecule (i.e., mefenamic acid) increases the crystal lattice energy by 10.2 kJ·mol^{-1} and the melting point by 45.3 K. Probably, electron donor substituents (like methyl groups) increase the total molecular electron density and, as a consequence, lead to increased sublimation enthalpy and melting point. The opposite effect is observed for electron acceptor substituents (such as $-CF_3$), as it has for example been discussed above for flufenamic acid.

Dependence of sublimation enthalpies on melting points for the studied compounds is presented in Figure 6. A clear correlation is observed between the outlined characteristics; therefore the ΔH^{298}_{sub} value for this class of substances can be estimated if the melting point is known. The anomalous behavior of diclofenac can be explained by structural differences of the compound compared to the rest of the fenamates. The carboxylic group of the diclofenac is connected with the benzene ring by an additional $-CH_2-$ group, and this fact influences the molecular conformational state (see the section Structural Aspects) as well as the geometry of the intramolecular hydrogen bond and, as a consequence, the sublimation enthalpy value.

Dependence of the fusion entropy, ΔS^T_{fus}, on the molecular free volume in the crystal lattice, V^{free}, for the *N*-phenylanthranilic acid derivatives is shown in Figure 7. The fusion entropy decreases, while the molecular free volume increases. If one takes into account that the entropy of fusion is the difference between the entropy in the melt and in the crystal, increase of molecular free volume leads to increase of molecular degrees of freedom and, as a consequence, decrease of the absolute ΔS^T_{fus} value. Diclofenac and diphenylamine have not been included in this correlation due to their different molecular structures compared to the other fenamates.

Conclusion

Crystal lattice parameters obtained from the literature were summarized and compared for some nonsteroidal anti-inflammatory drugs (i.e., diclofenac, niflumic, flufenamic, tolfenamic, mefenamic acids) and structurally related compounds (*N*-phenylanthranilic acid and diphenylamine). For the various polymorphic modifications of the same compound a higher value of the crystal lattice energy corresponds to the form with a lower value of torsion angle between the benzene rings (α) of the molecules in the crystal lattice. The polymorphic forms with a lower α value have a higher density value. The polymorphic modification of the same substance with a higher density has higher crystal lattice energy. On the basis of the experimental data it can be assumed that electron donor substituents at the second phenyl ring of *N*-phenylanthranilic promote to increased sublimation enthalpy, whereas electron acceptor substituents lead to the opposite effect. A correlation between the sublimation enthalpies and the melting points of the studied substances was observed; therefore the ΔH^{298}_{sub} value for this class of substances can be estimated if the melting point is known. The relationship between the entropy of fusion, ΔS^T_{fus}, and the molecular free volume in the crystal lattice, V^{free}, was derived. The fusion entropy decreases, while the molecular free volume rises. The absolute values of the crystal lattice energies of the polymorphic forms I and II of mefenamic acid and forms I and III of flufenamic acid were evaluated on basis of the sublimation and solution calorimetric experiments: for mefenamic acid, ΔH^{298}_{sub}(form I) = 136.2 ± 0.8 and ΔH^{298}_{sub}(form II) = 132.6 ± 1.8 kJ·mol^{-1}; for flufenamic acid, ΔH^{298}_{sub}(form I) = 121.2 ± 0.7 and ΔH^{298}_{sub}(form III) = 123.9 ± 1.8 kJ·mol^{-1}.

Acknowledgment. This study was supported by the Russian Foundation of Basic Research N 06-03-96304 and N 09-03-00057.

References

(1) Bekemeier, H.; Böhm, R.; Hagen, V.; Hannig, E.; Henkel, H.-J.; Hirschelmann, R.; Wenzel, U. *Agents Actions Suppl.* **1982**, *10*, 17–34.

(2) Pouplana, R.; Lozano, J. J.; Perez, C.; Ruiz, J. *J. Comput.-Aided Mol. Des.* **2002**, *16*, 683–709.
(3) Giordano, F.; Rossi, A.; Pasquali, I.; Bettini, R.; Frigo, E.; Gazzaniga, A.; Sangalli, M. E.; Mileo, V.; Catinella, S. *J. Therm. Anal. Calorim.* **2003**, *73*, 509–518.
(4) Adam, A.; Schrimpl, L.; Schmidt, P. C. *Drug Dev. Ind. Pharm.* **2000**, *26* (5), 477–487.
(5) Pinvidic, J. J.; Gonthier-Vassal, A.; Szwarc, H.; Ceolin, R.; Toffoli, P.; Teulon, J. M.; Guechot, C. *Thermochim. Acta* **1989**, *15*, 37–45.
(6) Andersen, K. V.; Larsen, S.; Alhede, B.; Gelting, N. *J. Chem. Soc., Perkin Trans. 2* **1989**, *58*, 1443–1447.
(7) Kitaigorodski, A. I. *Molecular crystals*; Nauka: Moscow, 1971.
(8) Zielenkiewicz, W.; Perlovich, G.; Wszelaka-Rylik, M. *J. Therm. Anal. Calorim.* **1999**, *57*, 225–234.
(9) Cox, J. D.; Pilcher, G. *Thermochemistry of organic and organometallic compounds*; London: Academic Press, 1970; p 643.
(10) Chickos, J. S.; Acree, W. E., Jr *J. Phys. Chem. Ref. Data* **2002**, *31* (2), 537–698.
(11) Terekhova, I. V.; Kulikov, O. V.; Titova, E. S. *Thermochim. Acta* **2004**, *412*, 121–124.
(12) Terekhova, I. V.; Volkova, T. V.; Perlovich, G. L. *Mendeleev Commun.* **2007**, *17* (4), 244–246.
(13) Pascual-Ahuir, J. L.; Silla, E. *J. Comput. Chem.* **1990**, *11*, 1047–1060.
(14) Castellari, C.; Ottani, S. *Acta Crystallogr.* **1997**, *C53*, 794–797.
(15) Jaiboon, N.; Yos-in, K.; Ruangchaithaweesuk, S.; Chaichit, N.; Thutivoranath, R.; Siritaedmukul, K.; Hannongbua, S. *Anal. Sci.* **2001**, *17*, 1465–1466.
(16) Perlovich, G. L.; Surov, A. O.; Hansen, L.Kr.; Bauer-Brandl, A. *J. Pharm. Sci.* **2007**, *96* (5), 1031–1042.
(17) McConnell, J. F. *Cryst. Struct. Commun.* **1973**, *3*, 459–461.
(18) Murthy, H. M.; Bhat, T. N.; Vijayan, M. *Acta Crystallogr.* **1982**, *B38*, 315–317.
(19) Hu, Y.; Liang, J. K.; Myerson, A. S. *Ind. Eng. Chem. Res.* **2005**, *44*, 1233–1240.
(20) Kim, Y. B.; Chung, U. T.; Park, I. Y. *Arch. Pharm. Res.* **1996**, *19* (2), 160–162.
(21) Murthy, H. M.; Vijayan, M. *Acta Crystallogr.* **1979**, *B35*, 262–263.
(22) Sbit, M.; Dupont, L.; Dideberg, O.; Liegeois, J.-F.; Delarge, J. *Acta Crystallogr.* **1987**, *C43*, 926–928.
(23) Rodriguez, M. A.; Bunge, S. D. *Acta Crystallogr.* **2003**, *59E*, 1123–1125.
(24) McConnell, J. F.; Company, F. Z. *Cryst. Struct. Commun.* **1976**, *5*, 861–864.
(25) Romero, S.; Escalera, B.; Bustamante, P. *Int. J. Pharm.* **1999**, *178*, 193–202.
(26) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.
(27) Dhanaraj, V.; Vijayan, M. *Acta Crystallogr.* **1988**, *B44*, 406–412.
(28) Perlovich, G. L.; Hansen, L. K.; Brandl-Bauer, A. *J. Therm. Anal. Calorim.* **2001**, *66* (3), 699–715.
(29) Urakami, K.; Shono, Y.; Higashi, A.; Umemoto, K.; Godo, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1241–1245.
(30) Krs, J. *Microscope* **1977**, *25*, 31–45.
(31) Burger, A.; Ramberger, R. *Mikrochim. Acta* **1979**, *II*, 273–316.
(32) López-Mejías, V.; Kampf, J. W.; Matzger, A. J. *J. Am. Chem. Soc.* **2009**, *131* (13), 4554–4555.
(33) Surov, A. O.; Szterner, P.; Zielenkiewicz, W.; Perlovich, G. L. *J. Pharm. Biomed. Anal.*, in press.
(34) Perlovich, G. L.; Surov, A. O.; Bauer-Brandl, A. *J. Pharm. Biomed. Anal.* **2007**, *45* (4), 679–687.

CG900002Q