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Vapor pressure and sublimation thermodynamics of aminobenzoic acid, nicotinic acid, and related amido-derivatives

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Abstract The inert gas transpiration technique was used for measuring the vapor pressures of the following biologically active compounds: 4-aminobenzoic acid, nicotinic acid, 4-aminobenzamide, 4-pyridinecarboxamide, *N*-(2-chloro-3-pyridinyl)-benzenesulfonamide, 4-nitro-*N*-2-thiazolyl-benzenesulfonamide, and 4-amino-*N*-(5-methyl-3-isoxazolyl)-benzenesulfon-amide in the appropriate temperature ranges. Differential scanning calorimetric analysis was applied to obtain the temperature and molar enthalpy of melting of the compounds studied. Standard molar enthalpies, entropies, and Gibbs energies of sublimation were derived at $T = 298.15$ K from the temperature dependences of the vapor pressure of the compounds. The obtained results allowed the estimation of the relationship between the sublimation thermodynamic parameters and the thermophysical properties of the substances. Correlation equations were used for calculating the saturated vapor pressures on the basis of the melting temperatures, sublimation enthalpies, and physicochemical HYBOT descriptors.

Keywords Biologically active compounds · Sublimation · Vaporization · Thermodynamics

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Introduction

Investigation of the sublimation of biologically active compounds is of great interest for the prediction of pharmaceutically important properties of drugs on their basis. The sublimation thermodynamic parameters characterize the compound crystal lattice energy and determine the solubility and solvation characteristics in different solvents. Physicochemical properties of the drug compounds both in crystal state and in solution expand our view on the interaction with the biological media of a living organism and, consequently, facilitate drug target delivery.

The class of compounds including aminobenzoic acid, nicotinic acid, and related amido-derivatives can be often considered either as a basis or as additional components of the pharmaceutical formulations and have been successfully used in pharmacology for a long time [1]. 4-aminobenzoic acid shows antiviral, local anesthetic, and antioxidative action and is widely used in ophthalmology accelerating eye cornea regeneration [2]. Gracin and Rasmuson [3] consider it as a model compound because the 4-aminobenzoic acid molecular structure contains functional groups inherent to many drug substances. Nicotinic acid is a vitamin participating in many oxidative reactions in living cells, the deficiency of which leads to Pellagra. It has been used for over 50 years to increase levels of high-density lipoprotein in the blood and has been found to decrease the risk of cardiovascular events modestly in a number of controlled human trials [4, 5]. 4-aminobenzamide and isonicotinamide are structurally similar to the above-mentioned biologically active compounds. Sulfonamides molecular structures are close to 4-aminobenzoic acid. These biologically active substances are captured by a microbe cell instead of 4-aminobenzoic acid and thereby disturbed the metabolic processes in it. A sulfanilamide

moiety and its structural similarity to 4-aminobenzoic acid permit sulfonamides to block folic acid synthesis in bacteria, which accounts for the antibacterial action of these drugs [6]. Moreover, sulfonamide derivatives found an application for antibiotic, anticancer, anti-convulsant, anti-obesity, and anti-viral agents [7, 8].

There have been numerous studies on the standard thermodynamic sublimation parameters (enthalpy, Gibbs energy) of some compounds studied in the present work [9–15], but the experimental results were obtained using different methods, often at a fixed single temperature, which makes data comparison difficult. The temperature dependences of the saturated vapor pressure allow us to calculate the thermodynamic sublimation functions and to estimate the crystal lattice energy of the substances that has a considerable effect on the solubility—a key parameter of drug compounds.

In spite of the fact that aminobenzoic acid, nicotinic acid, and related amido-derivatives have been used for a long time, they have recently attracted a lot of attention due to their ability to be involved in the design of new drug formulations. Thus, donor and acceptor groups quite easily form hydrogen bonds in their molecule structure, which is necessary for cocrystal formation [16–19]. And the knowledge of the thermochemical parameters of the individual compounds—potential cocrystal formers—can essentially improve the pharmaceutical cocrystal screening and predict the physicochemical properties both in the crystal state and in solution.

Our research group has been studying the physicochemical properties of drug and drug-like compounds at the preformulation stages [20–24]. This study represents the experimental data on the saturated vapor pressure at different temperatures, the sublimation thermodynamic parameters, and melting thermophysical characteristics for biologically active substances and parent compounds. The aim of this work is to measure experimentally the saturated vapor pressure of 4-aminobenzoic acid, 3-pyridinecarboxylic acid (nicotinic acid), 4-aminobenzamide, 4-pyridinecarboxamide, *N*-(2-chloro-3-pyridinyl)-benzenesulfonamide, 4-nitro-*N*-2-thiazolyl-benzenesulfonamide, and 4-amino-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide as a function of temperature; to discover the correlations between the experimental and calculated sublimation parameters; and to determine their relationship with the molecular structure.

Experimental

Materials

The origin, CAS numbers, and purity of all samples are presented in Table 1.

Compounds I–IV were obtained from commercial sources. The substances were purified by sublimation under reduced pressure; the final purity was determined by gas chromatography. The chemical synthesis of compounds V–VII has been described by us earlier [24–26]. The compounds were carefully purified by recrystallizing from a water–ethanol solution. The precipitates were filtered and dried at room temperature under vacuum until the masses of the compounds remained constant. The outlined procedure was repeated several times, and the product was checked by H1 NMR after each recrystallization step until the proton NMR signal correspondence to the purity of the compound was over 99 %.

Differential scanning calorimetry

Temperatures and enthalpies of melting of the compounds under investigation have been determined using a PerkinElmer Pyris 1 DSC differential scanning calorimeter (PerkinElmer Analytical Instruments, Norwalk, Connecticut, USA) with Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing 20 cm^3 min^{-1} dry helium gas of high purity 0.99996 (mass fraction) using sealed standard aluminum sample pans and a heating rate of 2 K min^{-1}. The accuracy of mass measurements was 0.005 mg. The DSC was calibrated with an indium sample from PerkinElmer (P/N 0319-0033). The value determined for the enthalpy of fusion corresponded to 28.48 J g^{-1} (reference value 28.45 J g^{-1}). The melting temperature was 429.5 ± 0.1 K (determined from at least ten measurements). The enthalpy of melting at 298.15 K was calculated using Sidgwick's rule [27]:

$$\Delta^{l}_{cr}H^{o}_{m}(298.15\mathrm{K}) = \Delta^{l}_{cr}H^{o}_{m}(T_m) + 54.4(298.15 - T_m) \quad (1)$$

Vapor pressures measurements

Sublimation experiments were carried out by the transport method. This method consists in passing a stream of an inert gas over a sample at the constant flow rate and temperature, the rate being low enough to practically achieve saturation of the carrier gas with the substance's vapor. The vapor was condensed and the sublimated quantity was 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.

Details of the technique are given in the literature [28]. The inert gas (nitrogen) from tank flows through a column packed with silica to adsorb any water from the gas. The stabilization of the gas temperature occurs in a thermostated water bath. The stability of the gas flow with precision better than 0.01 % is realized by use of mass flow

Table 1 Source, CAS numbers, and purity of compounds studied

Compounds	Chemical names	CAS register no.	Source	Purification method	Purity /%	Analysis method
I	4-Aminobenzoic acid	150-13-0	Merck	Sublimation	≥99	GC
II	4-Aminobenzamide	2835-68-9	Acros organics	Sublimation	≥99	GC
III	4-Pyridinecarboxamide (Isonicotinamide)	1453-82-3	Acros organics	Sublimation	>99	GC
IV	3-Pyridinecarboxylic acid (Nicotinic acid)	59-67-6	Merck	Sublimation	>99	GC
V	*N*-(2-chloro-3-pyridinyl)-benzenesulfonamide	–	Synthesized	Recrystallization	>99	H_1 NMR
VI	4-Nitro-*N*-2-thiazolyl-benzenesulfonamide	–	Synthesized	Recrystallization	>99	H_1 NMR
VII	4-Amino-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide	–	Synthesized	Recrystallization	>99	H_1 NMR

GC—gas liquid chromatography; H_1 NMR—proton nuclear magnetic resonance

controller MKS type 1259CC-00050SU. The inert gas of constant temperature and velocity passes then to the glass tube, which is placed in the air thermostat. Three zones of the glass tube can be distinguished to starting zone for stabilizing of the inert gas; the transitional zone in which sublimation process occurs; ensuring slow sublimation of the substance investigated; the finishing zone in which the inert gas together with the sublimated substance is overheated by 4–5 K, controlled by platinum resistance thermometer. The temperature of the air thermostat is kept constant with a precision of 0.01 K by means of the temperature controller PID type 650 H UNIPAN equipped with a resistance thermometer. The finishing zone is coupled with the condenser built from glass helix, placed (outside the thermostat) located in a Dewar vessel filled with a liquid nitrogen. To avoid humidity adsorption from the air, a condenser is connected to a vessel filled with $CaCl_2$.

The equipment was calibrated using benzoic acid. The measured value of the vapor pressure at this apparatus is 0.962 Pa at $T = 317.15$ K. This value is in good agreement with the literature data: $p = 0.99$ Pa [29]. The standard value of the sublimation enthalpy obtained was $\Delta^{g}_{cr}H^{o}_{m} = 90.5 \pm 0.3\,\mathrm{kJ\,mol^{-1}}$. This is in good agreement with the value recommended by IUPAC ($\Delta^{g}_{cr}H^{o}_{m} = 89.7 \pm 0.5\,\mathrm{kJ\,mol^{-1}}$) [30].

From the experimentally determined pressure–flow rate relationship, the optimal flow rate of 1.2–1.8 dm3 h^{-1} has been identified. Under this flow rate, the saturated vapor pressure is independent of the flow rate, and thus, thermodynamic equilibrium is realized.

The saturated vapor pressures were measured five times at each temperature with the standard deviation no more than 5 %. Because the saturated vapor pressure of the compounds investigated is low, it may be assumed that the heat capacity change of the vapor with temperature is so small that it can be neglected. The experimentally determined vapor pressure data may be described in the following way:

$$\ln(p/\mathrm{Pa}) = A - B/T \tag{2}$$

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

$$\Delta^{g}_{cr}H^{o}_{m}(T) = -R\left(\frac{\partial(\ln p)}{\partial(1/T)}\right) \tag{3}$$

where universal gas constant $R = 8.3144598$ J $\mathrm{mol^{-1}\ K^{-1}}$.

The sublimation entropy at the given temperature T was calculated from the following relation:

$$\Delta^{g}_{cr}S^{o}_{m}(T) = \frac{(\Delta^{g}_{cr}H^{o}_{m}(T) - \Delta^{g}_{cr}G^{o}_{m}(T))}{T} \tag{4}$$

with $\Delta^{g}_{cr}G^{o}_{m}(T) = -\mathrm{RT}\ln(p/p_0)$, where p_0 is the standard pressure of $p_0 = 1.013 \times 105$ Pa.

For experimental reasons, sublimation data are obtained at elevated temperatures. However, in comparison with 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 estimated the heat capacities ($C^{o}_{p,m}(cr)$ value) of the crystals using the additive scheme proposed by Chickos et al. [31]. Heat capacity was introduced to adjust the enthalpy of sublimation to the temperature 298.15 K $\Delta^{g}_{cr}H^{o}_{m}(T_m)$ according to the equation:

$$\begin{aligned}\Delta^{g}_{cr}H^{o}_{m}(298.15\,\mathrm{K})/\mathrm{kJ\,mol^{-1}} &= \Delta^{g}_{cr}H^{o}_{m}(T_m)/\mathrm{kJ\,mol^{-1}} \\ &+ \Big[(0.75 + 0.15 \cdot C^{o}_{p,m}(\mathrm{cr})/\mathrm{J\,K^{-1}mol^{-1}}) \\ &\cdot (T_m/K - 298.15\,\mathrm{K})\Big]/1000\end{aligned} \tag{5}$$

The enthalpy of vaporization was calculated as

$$\Delta^{g}_{l}H^{o}_{m}(298.15) = \Delta^{g}_{cr}H^{o}_{m}(298.15\,\mathrm{K}) - \Delta^{l}_{cr}H^{o}_{m}(298.15\,\mathrm{K}) \tag{6}$$

where enthalpy of melting at 298.15 was calculated by Eq. (1).

Calculation procedure

Physicochemical descriptors were calculated with the program package HYBOT-PLUS (version of 2003) in Windows [32].

The root-mean-square error, RMSE, between the experimental and calculated vapor pressure values was obtained by the following equation:

$$\mathrm{RMSE} = \sqrt{\frac{\sum (\mathrm{Exp} - \mathrm{Calc})^2}{N}} \quad (7)$$

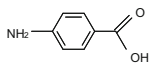
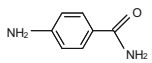
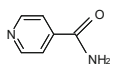
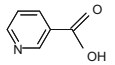
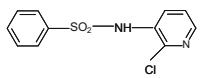
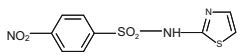
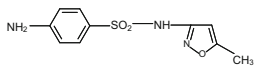
where Exp is the experimental lnp, Calc is the calculated lnp, and N is the number of observations in the prediction set.

Results and discussion

The melting temperatures and enthalpies of the investigated compounds were measured using the DSC technique, and the results are given in Table 2. The values of the obtained thermophysical parameters are in good agreement with the respective literature data. Thermophysical properties of sulfonamides V–VII have been investigated by us before and are indicated as literature data. The DSC curves profile indicates the stability of the substances and absence of the phase transitions in the studied temperature range. Rotich et al. [11] investigated the thermal behavior of the substituted aminobenzoic acids and established that 4-aminobenzoic acid is stable at the temperatures below the melting point as the experiment did not reveal any decarboxylation products.

The experimental vapor pressure values are shown in Table 3. The temperature ranges, coefficients of the Clausius–Clapeyron equation, and vapor pressure values of the compounds at $T = 376.15$ K are given in Table 4. The indicated temperature has been chosen as the most appropriate for comparative analysis of the results. The temperature ranges are caused by both the volatility of the substances and the specificity of the experiment. It was shown that at $T = 376.15$ K, the vapor pressure decreases in the following order: III > IV > I > V > II > VII > VI. The compound with the highest melting temperature VI appears to have the minimal vapor pressure value. For the benzene derivatives, the substitution of the amido-group in 4-aminobenzamide (II) by the hydroxyl one in 4-aminobenzoic acid (I) results in approximately tenfold vapor pressure growth. It is interesting to note that benzene and pyridine derivatives (excluding 4-aminobenzamide) were shown to have higher vapor pressure compared with sulfonamides.

Table 2 Structural formula, molecular mass, thermophysical parameters of melting, and descriptors for the compounds studied

Compounds	Structure	M/g mol^{-1}	T_m^a/K		$\Delta_{cr}^l H_m^o$ [b]/kJ mol^{-1}		α^c	ΣC_a [d]	ΣC_d [e]
			This study	Literature	This study	Literature			
I		137.14	460.4 ± 0.2	458.8–462.3[f]	25.4 ± 0.2	21.6[f] 24.5[g]	14.17	5.4	−5.81
II		136.15	455.5 ± 0.2	454–456[h]	30.4 ± 0.2	–	15.38	4.46	−6.94
III		122.12	429.8 ± 0.2	430[i]	23.6 ± 0.2	–	13.19	4.43	−4.16
IV		123.11	508.2 ± 0.2	509.9[j]	27.5 ± 0.2	28.2[j]	11.99	5.68	−3.15
V		268.72	–	426.2 ± 0.2	–	37.6 ± 0.5	26.63	4.82	−1.81
VI		285.29	–	529.8 ± 0.2	–	31.8 ± 0.5	25.76	5.34	−1.74
VII		253.28	–	441.3 ± 0.2	–	31.9 ± 0.5	24.74	7.77	−5.26

[a] Standard uncertainty of the fusion temperature determination is $u_r(T_m) = 0.2$ K

[b] Standard uncertainty of the melting enthalpy determination is $u_r(\Delta_{cr}^l H_m^o) = 0.5$ kJ mol^{-1}

[c] Polarizability, standard uncertainty of the polarizability determination is $u_r(\alpha) = 0.01$

[d] ΣC_a, standard uncertainty of the descriptor determination is $u_r(\Sigma C_a) = 0.01$

[e] ΣC_d, standard uncertainty of the descriptor determination is $u_r(\Sigma C_d) = 0.01$

Measured in Ref. [f][3]; [g][11]; [h][33]; [i][34]; [j][35]; all data for the compounds V–VII are taken from [36]

Table 3 Experimental values of vapor pressures of the compounds studied

I		II		III		IV		V		VI		VII	
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
347.15	0.046	373.15	0.052	351.15	0.263	362.15	0.555	357.15	0.021	451.55	0.010	378.65	0.0016
349.65	0.061	375.15	0.065	353.15	0.324	364.15	0.655	360.15	0.026	453.85	0.013	382.15	0.0021
352.15	0.081	377.15	0.084	354.15	0.375	365.15	0.792	365.15	0.048	455.15	0.014	386.15	0.0034
355.15	0.113	380.15	0.117	356.65	0.516	367.15	0.923	370.15	0.078	458.65	0.018	390.15	0.0046
358.15	0.167	384.15	0.184	359.15	0.675	369.15	1.099	373.15	0.091	461.15	0.020	394.15	0.0068
360.15	0.208	385.15	0.197	360.65	0.799	370.15	1.188	377.15	0.122	466.35	0.031	398.15	0.0085
361.15	0.232	386.15	0.213	362.65	0.938	371.15	1.310	380.15	0.186	468.75	0.034	403.15	0.0152
366.15	0.368	389.15	0.311	365.15	1.206	372.15	1.474	384.15	0.268	471.95	0.047	407.15	0.0193
369.15	0.483	391.15	0.353	365.65	1.260	374.15	1.806	386.65	0.327	476.75	0.060	414.15	0.0375
371.15	0.590	395.15	0.515	368.15	1.656	376.15	2.142	391.15	0.527	483.45	0.105	418.15	0.0599
373.15	0.747	396.15	0.571	370.15	2.083	378.15	2.595	395.15	0.657	485.55	0.113	424.15	0.0993
376.15	0.963	398.15	0.710	372.15	2.417	380.15	3.056	397.65	0.905	490.05	0.166	429.15	0.1401
379.15	1.338	400.15	0.893	374.15	3.022	382.15	3.692	402.15	1.311	495.45	0.266	436.15	0.2180
383.15	1.949	403.15	1.206	376.15	3.695	384.15	4.395	405.15	1.620	503.45	0.399		
386.15	2.665			377.65	4.473	385.15	4.854	407.15	2.141	509.55	0.658		
389.15	3.723					387.15	5.959						
392.15	5.032												

Standard uncertainty for temperature $u(T) = 0.01$ K; and relative standard uncertainty for pressure $u_r(p) = 0.05$

Table 4 Temperature ranges, coefficients of Clausius–Clapeyron equation, and saturated vapor pressure values of compounds studied at $T = 376.15$ K

Compounds	*T*range/K	*A*	*B*	*p*/Pa
I	347.15–392.15	37.2 ± 0.3	13,977 ± 29	0.963
II	373.15–403.15	38.6 ± 0.4	15,500 ± 147	0.074
III	351.15–377.65	38.3 ± 0.3	13,890 ± 122	3.695
IV	362.15–387.15	36.4 ± 0.3	13,399 ± 112	2.142
V	357.15–407.15	33.5 ± 0.4	13,371 ± 172	0.129
VI	451.55–509.55	31.6 ± 0.5	16,348 ± 222	7.06×10^{-6}
VII	378.65–436.15	31.5 ± 0.5	14,398 ± 202	1.14×10^{-3}

Figure 1 shows the temperature dependences of the saturated vapor pressure for all the investigated compounds. The thermodynamic sublimation parameters were calculated using the vapor pressure temperature dependences. The results are summarized in Table 5. The sublimation enthalpy change is a measure of intermolecular interactions in the crystal state and can be applied to the estimation of the crystal package characteristics. In turn, the chemical structure of the molecules in much largely determines the energy and packing architecture of the crystal lattice. The analysis of the results in Table 5 shows nicotinic acid (IV) to have the minimal value of the sublimation enthalpy and sulfonamide (VI)—the maximal one among the investigated compounds. Such differences of the sublimation enthalpies can be determined by their crystal structures. At that, the nicotinic acid molecules are linked in chains by hydrogen bonds between the oxygen atom and the nitrogen atom of the next molecule [42]. Unfortunately, the data of X-ray investigations for the above-mentioned sulfonamide are absent.

The sublimation enthalpy value of 4-aminobenzoic acid (I) $\Delta_{cr}^{g}H_{m}^{o}(298.15) = 118.0\,\mathrm{kJ\,mol^{-1}}$ is very close to that of compound III (isonicotinamide). It is well known that in crystalline phase, dimers are structural units of the 4-aminobenzoic acid molecule.

As Gracin and Rasmuson [3] showed, the alfa-modification of this compound is based on dimers of molecules formed by strong hydrogen bonds between carboxylic acid groups, and twinning and disorder are common since an additional N–H···O–H bond is formed. The maximal

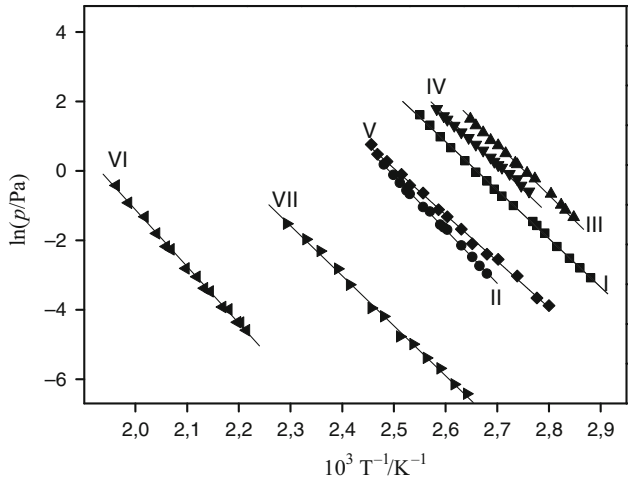


Fig. 1 Plots of lnp versus 1/*T* for: compounds I–VII

(among the benzene and pyridine derivatives) sublimation enthalpy value of 131.2 kJ mol^{-1} was revealed for 4-aminobenzamide, which has an acceptor amide group at the first carbon atom of the benzene and a donor amine group at the fourth carbon atom, offering the maximum eccentricity to the molecules and giving rise to a non-centro-symmetric crystal structure [12].

X-Ray experiments on the crystal structures of compounds V and VII show both similar and distinctive features [23]. As a consequence of the distinct features, the difference between the sublimation enthalpy values is of 9 kJ mol^{-1}. For compound V the simplest hydrogen bond network is observed, as only one hydrogen bond participates in their formation. It is caused by the fact that it is the sulfonamide group with an amide proton as a bond donor that becomes the only center of the hydrogen bond. The presence of the additional acceptor groups does not account for the growth of hydrogen bonds. For compound VII the presence of nitrogen in the ortho-position adjacent to an amide group of the ring is not enough for an imide tautomer to be formed. The adjacent molecule chains are linked with a hydrogen bond to form two-dimensional networks. The specific feature similar to compounds V and VII is having equally distant layers formed by infinite chains. The adjacent layers interact by means of van der Waals forces, while the way the molecule chains interact within the layer may vary.

Vaporization enthalpies $\Delta_l^g H_m^o(298.15\ K)$ shown in Table 5 were determined based on the sublimation and melting thermodynamic functions by using Eq. (6). There is a linear correlation between the sublimation and vaporization enthalpies (Fig. 2).

As the experimental procedure on the vapor pressure measuring is rather labor-consuming, we set a problem to calculate this parameter based on the thermodynamic and

Table 5 Heat capacities, standard molar enthalpy, entropy, Gibbs energy of sublimation, and enthalpy of vaporization at $T = 298.15$ K and $p0 = 105$ Pa of compounds studied

Compounds	${}_{cr}C_{p,m}^o$/J mol^{-1} K^{-1}	$\Delta_{cr}^g H_m^o(298.15K)/T$/kJ mol^{-1}	$\Delta_{cr}^g H_m^o(298.15K)$/ kJ mol^{-1}	$\Delta_{cr}^g H_m^o(298.15\ K)$/kJ mol^{-1}		$\Delta_{cr}^g S_m^o(298.15\ K)$/ J mol^{-1}K^{-1}	$\Delta_{cr}^l H_m^o(298.15K)$/ kJ mol^{-1}	$\Delta_l^g H_m^o(298.15K)$/ kJ mol^{-1}
				This study	Literature			
I	161.7	116.2 ± 0.9	52.5	118.0 ± 1.0	116.1 ± 3.7[a] 115.1 ± 1[b,c]	219.7 ± 6.1	16.6	101.4
II	163.0	128.9 ± 1.2	61.7	131.2 ± 1.2	131.0 ± 0,4[d]	233.1 ± 2.5	21.8	109.4
III	146.8	115.5 ± 1.0	49.1	117.0 ± 1.0	116.1 ± 1.5[e] 102.2[f,g]	227.7 ± 6.0	16.4	100.6
IV	145.5	110.0 ± 0.6	49.3	111.7 ± 1.2	112.1 ± 0.5[h] 123.9 ± 3.7[i] 105.17 ± 0.63[j]	209.3 ± 5.3	16.1	95.6
V	296.5	111.2 ± 1.4	56.7	115.0 ± 1.0	–	195 ± 6.0	30.6	84.4
VI	309.2	135.9 ± 1.8	86.2	144.0 ± 2.0	–	196.0 ± 6.0	19.2	124.8
VII	291.7	119.7 ± 1.7	70.2	124.0 ± 2.0	–	181.0 ± 6.0	24.1	99.9

Measured in Ref. [a][15] microcalorimeter Tian–Calvet of one effusion cell; [b,c][6, 37] torsion-effusion; [d][12] Knudsen mass-loss effusion technique; [e][13] static bomb calorimetry drop-sublimation Calvet microcalorimetry; [f,g][38, 39] mass-effusion method; [h][14] drop-sublimation Calvet microcalorimetry and Knudsen effusion method; [i][40] Calvet microcalorimetric technique; [j][41] sublimation calorimetry

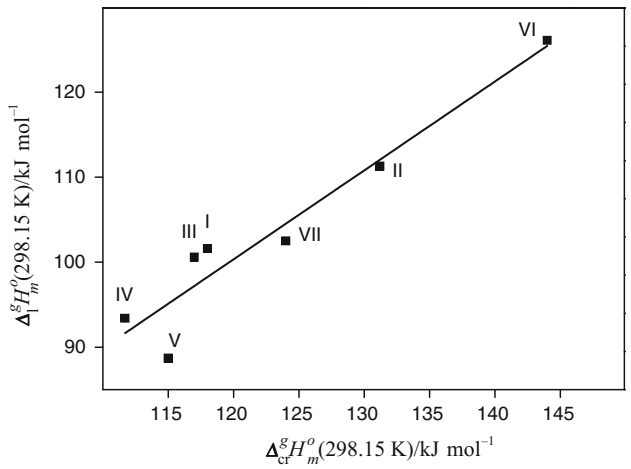


Fig. 2 Correlation between the vaporization enthalpy $\Delta_l^g H_m^o(298.15)$ and sublimation enthalpy for compounds studied I–VII ($R = 0.980$)

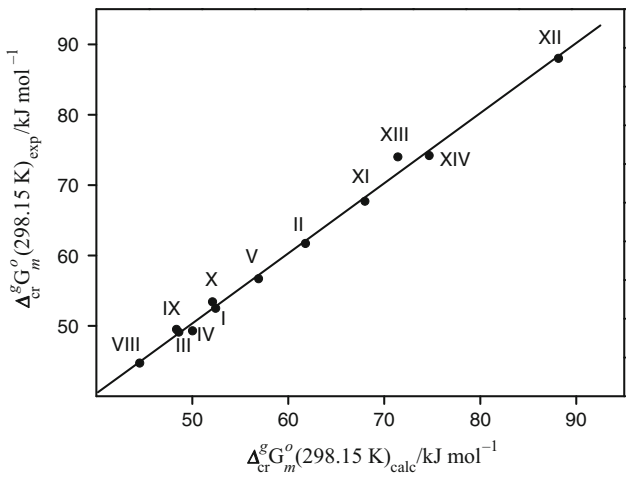


Fig. 3 Plot of experimental values $\Delta_l^g H_m^o(298.15)$ against calculated values $\Delta_{cr}^g G_m^o(calc)$ (Eq. 8) of compounds studied I–V, pyrazinamide—VIII and isoniazid—IX [43], *N*-phenyl-benzene-sulfonamide—X, *N*-(4-nitrophenyl)-benzene-sulfonamide—XI, and 4-amino-*N*-(4-cyanophenyl)-benzene-sulfonamide—XII [44], 4-amino-*N*-(4-chlorophenyl)-benzene-sulfonamide—XIII [26], 4-amino-*N*-(4-ethylphenyl)-benzene-sulfonamide—XIV [24]. ($R = 0.998$)

thermophysical parameters of the substances. The equation introduced by Monte et al. [37] for para-substituted benzoic acids was used to help establish the calculated values of the saturated vapor pressure with the help of $\Delta_{cr}^g G_m^o(298.15\ K)$ obtained from the following equation:

$$\Delta_{cr}^g G_m^o(298.15\ K) = -(39.4 \pm 1.8) + (0.65 \pm 0.02)\Delta_{cr}^g H_m^o(298.15K) + (0.035 \pm 0.006)T_m \quad (8)$$

The thermophysical parameter of melting temperature is introduced in the equation as an independent variable along with the sublimation enthalpy, which allows calculating the sublimation Gibbs energy independently of the degree of orientational disorder in the crystalline package determined by the entropy term. We added a set of compounds investigated in the present work by a series of the related amido-derivatives that have been studied on the sublimation by us before [26, 43, 44]. Figure 3 presents the correlation between the experimental and calculated $\Delta_{cr}^g G_m^o(298.15K)$ values. It should be emphasized that non-aromatic heterocyclic compounds containing thiazolyl (VI) and isoxazolyl (VII) fragments were excluded from the correlation and further calculations due to a significant difference between the experimental and calculated values of the sublimation Gibbs energy.

The above calculated $\Delta_{cr}^g G_m^o(298.15K)$ values of the compounds I–V were used to help establish the saturated pressure values by the following equation:

$$\ln(p/10^5 Pa) = -\Delta_{cr}^g G_m^o(298.15K)/298.15R \quad (9)$$

The saturated vapor pressure data obtained by Eqs. 8, 9 are shown in Table 6.

Following the approach for the biologically active substances, we employ the model aspects based on the HYBOT descriptors to determine the correlation between the molecular structure and sublimation enthalpy. The equation, proposed by authors [45], where $\Delta_{cr}^g H_m^o(298.15K)$ is a dependent variable, and the physicochemical descriptors are independent ones, is represented below:

Table 6 Experimental and calculated vapor pressures of compounds studied at $T = 298.15$ K and $p_0 = 105$ Pa

Compounds	$\ln(p_{exp}/Pa)$	$\ln(p_{1calc}/Pa)$ (Eqs. 8, 9)	Res_1* (Eqs. 8, 9)	$\ln(p_{2calc}/Pa)$ (Eqs. 8–10)	Res_2* (Eqs. 8–10)
I	−9.68	−9.63	−0.05	−9.67	−0.01
II	−13.39	−13.41	0.02	−13.46	0.07
III	−8.34	−8.08	−0.26	−8.29	−0.05
IV	−8.40	−8.66	0.26	−8.65	0.25
V	−11.35	−11.43	0.08	−11.36	−0.01

* Resi = $\ln(p_{exp}/Pa)$—$\ln(p_{icalc}/Pa)$ ($i = 1, 2$)

$$\Delta_{cr}^{g}H_{m}^{o}(298.15\ \mathrm{K})_{calc} = (39.8 \pm 1.4) + (2.03 \pm 0.05)\alpha + (4.6 \pm 0.2)\Sigma C_a - (4.7 \pm 0.2)\Sigma C_d \quad (10)$$

The descriptors which best reflect the main types of interactions in the molecular crystals are the molecular polarizability (α), the sum of all H-bond acceptor factors (ΣC_a), and the sum of H-bond donor factors (ΣC_d). The polarizability parameter determines the impact of the non-specific interactions in the crystal lattice and the sums of donor/acceptor factors—the molecular ability to hydrogen bonding. The descriptor values are summarized in Table 2. The results of the calculation of the saturated vapor pressure based on Eqs. 8–10 are represented in Table 6.

In order to estimate the calculation methods, we used the residual data (Res) and derived the root-mean-square errors (RMSE) (Eq. 7). RMSE are equal to 0.17 when Eqs. 8, 9 are used and to 0.12 when Eqs. 8–10 are employed. Since the values of the saturated vapor pressures are rather low, both calculation approaches achieve the desired accuracy and are quite promising for the prediction of the volatility of the investigated compounds.

Conclusions

In the present paper, we measured the temperature dependences of the saturated vapor pressure of the seven biologically active substances and parent compounds: 4-aminobenzoic acid, 3-pyridinecarboxylic acid (nicotinic acid), 4-aminobenzamide, 4-pyridinecarboxamide, *N*-(2-chloro-3-pyridinyl)-benzenesulfonamide, 4-nitro-*N*-2-thiazolyl-benzenesulfonamide, and 4-amino-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide by using the inert gas transpiration technique. The temperatures and melting enthalpies of the compounds studied were obtained by differential scanning calorimetry. The analysis of the relationship between the vapor pressure values and the molecular structure of the substances has been performed. Benzene and pyridine derivatives (excluding 4-aminobenzamide) were shown to have higher vapor pressure compared with that of sulfonamides. The thermodynamic sublimation parameters: enthalpy, entropy, and Gibbs energy were derived from the temperature dependences of the saturated vapor pressure. The correlation equations proposed before were applied to calculating the saturated vapor pressure of the investigated compounds on the basis of the melting temperatures, sublimation enthalpies, and physicochemical descriptors HYBOT for biologically active compounds. The close values of the experimental and calculated parameters testify to the possibility of the prediction of the volatility of the investigated compounds using the proposed equations.

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References

1. Aromatic Hydrocarbons—Advances in Research and Treatment: 2013 Edition. Acton, A. Ed., ScholarlyEditions™: Atlanta, 2013
2. Akberova SI. Para-aminobenzoic acid and perspectives of its application in ophthalmology. Vestnic Ophthalmol. 2002;3:53–6.
3. Gracin S, Rasmuson ÅC. Polymorphism and crystallization of *p*-aminobenzoic acid. Cryst Growth Des. 2004;4:1013–23.
4. Olsen RA, Liu L, Ghaderi N, Johns A, Hatcher ME, Mueller LJ. The amide rotational barriers in picolinamide and nicotinamide: NMR and Ab initio studies. J Am Chem Soc. 2003;125:10125–32.
5. Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Atherosclerosis. 2010;210:353–61.
6. Maren TH. Relations between structure and biological activity of sulfonamides. Ann Rev Pharmacol Toxicol. 1976;16:309–27.
7. Owa T, Nagasu T. Novel sulphonamide derivatives for the treatement of cancer. Expert Opin Ther Pat. 2000;10:1725–40.
8. Winum J-Y, Scozzafava A, Montero J-L, Supuran CT. Sulfamates and their therapeutic potential. Med Res Rev. 2005;25:186–228.
9. De Kruif CG, Voogd J, Offringa JCA. Enthalpies of sublimation and vapour pressures of 14 amino acids and peptides. J Chem Thermodyn. 1979;11:651–6.
10. Domalski ES, Hearing ED. Estimation of the thermodynamic properties of C–H–N–O–S-Halogen compounds at 298.15 K. J Phys Chem Ref Data. 1993;22:805–55.
11. Rotich K, Glass BD, Brown ME. Thermal studies on some substituted aminobenzoic acids. J Therm Anal Calorim. 2001;64:681–8.
12. Almeida ARRP, Monte MJS, Agostinha M, Matos R, Morais VMF. Experimental and computational thermodynamic study of ortho- meta- and para-aminobenzamide. J Chem Thermodyn. 2013;59:222–32.
13. Ribeiro da Silva MDMC, Goncalves JM, Ferreira SCC, da Silva LCM, Sottomayor MJG. Experimental thermochemical study of the enthalpies of formation and sublimation of isonicotinamide, picolinamide, nicotinamide, isonicotinamide N-oxide, and nicotinamide N-oxide. The dissociation enthalpies of the N–O bonds. J Chem Thermodyn. 2001;33:1263–75.
14. Gonçalves EM, Bernardes CES, Diogo HP, Minas da Piedade ME. Energetics and structure of nicotinic acid (niacin). J Phys Chem B. 2010;114:5475–85.
15. Sabbah R, Chastel R, Laffitte M. Thermodynamics of nitrogen compounds. I. Calorimetric study of the enthalpies of sublimation of three aminobenzoic acids. Can J Chem. 1974;52:2201–5.
16. Aakeroy CB, Beatty AM, Helfrich BA. Do polymorphic compounds make good cocrystallizing agents? A structural case study that demonstrates the importance of synthon flexibility. Cryst Growth Des. 2003;3:159–65.
17. Lemmerer A, Bathori NB, Bourne SA. Chiral carboxylic acids and their effects on melting-point behaviour in co-crystals with isonicotinamide. Acta Crystallogr Sect B. 2008;64:780–90.
18. Vishweshwar P, Nangia A, Lynch VM. Molecular complexes of homologous alkanedicarboxylic acids with isonicotinamide: X-ray crystal structures, hydrogen bond synthons, and melting point alternation. Cryst Growth Des. 2003;3:783–90.
19. Fabian L, Hamill N, Eccles KS, Moynihan HA, Maguire AR, McCausland L, Lawrence SE. Cocrystals of fenamic acids with nicotinamide. Cryst Growth Des. 2011;11:3522–8.

20. Perlovich GL, Volkova TV, Manin AN, Bauer-Brandl A. Extent and mechanism of solvation and partitioning of isomers of substituted benzoic acids: a thermodynamic study in the solid state and in solution. J Pharm Sci. 2008;97:3883–96.
21. Manin AN, Voronin AP, Perlovich GL. Acetamidobenzoic acid isomers: studying sublimation and fusion processes and their relation with crystal. Thermochim Acta. 2014;583:72–7.
22. Ol'khovich MV, Blokhina SV, Sharapova AV, Perlovich GL, Proshin AN. Thermodynamics of sublimation and solvation for bicycloderivatives of 1,3-thiazine. Thermochim Acta. 2013;569:61–5.
23. Perlovich GL, Ryzhakov AM, Tkachev VV, Hansen LK, Raewsky OA. Sulfonamide molecular crystals: structure, sublimation thermodynamic characteristics, molecular packing, hydrogen bonds networks. Cryst Growth Des. 2013;13:4002–16.
24. Perlovich GL, Tkachev VV, Strakhova NN, Kazachenko VP, Volkova TV, Surov OV, Schaper KJ, Raevsky OA. Thermodynamic and structural aspects of sulfonamide crystals and solutions. J Pharm Sci. 2009;98:4738–55.
25. Perlovich GL, Strakhova NN, Kazachenko VP, Volkova TV, Tkachev VV, Schaper KJ, Raevsky OA. Studying thermodynamic aspects of sublimation, solubility and solvation processes and crystal structure analysis of some sulfonamides. Int J Pharm. 2007;334:115–24.
26. Perlovich GL, Strakhova NN, Kazachenko VP, Volkova TV, Tkachev VV, Schaper KJ, Raevsky OA. Sulfonamides as a subject to study molecular interactions in crystals and solutions: sublimation, solubility, solvation, distribution and crystal structure. Int J Pharm. 2008;349:300–13.
27. Chickos JS, Hosseini S, Hesse D, Liebman JF. Heat capacity corrections to a standard state: a comparison of new and some literature methods for organic liquids and solids. Struct Chem. 1993;4:271–8.
28. Zielenkiewicz W, Perlovich G, Wszelaka-Rylik M. The vapour pressure and the enthalpy of sublimation. Determination by inert gas flow method. J Therm Anal Calorim. 1999;57:225–34.
29. Ribeiro da Silva MAV, Monte MJS, Santos LMNB. J Chem Thermodyn. 2006;38:778–87.
30. Cox JD, Pilcher G. Thermochemistry of organic and organometallic compounds. London: Academic Press; 1970.
31. Chickos JS, Acree WE. Enthalpies of sublimation of organic and organometallic compounds. J Phys Chem Ref Data. 2002;2:537–698.
32. Raevsky OA, Grigor'ev VJ, Trepalin SV. HYBOT program package, Registration by Russian State Patent Agency No. 990090 of 26.02.99.
33. Eccles KS, Elcoate CJ, Maguire AR, Lawrence SE. Unzipping the dimer in primary amides by cocrystallization with sulfoxides. Cryst Growth Des. 2011;11:4433–9.
34. Habgood M, Deij MA, Mazurek J, Price SL, Horst JH. Carbamazepine co-crystallization with pyridine carboxamides: rationalization by complementary phase diagrams and crystal energy landscapes. Cryst Growth Des. 2010;10:903–12.
35. Joseph A, Bernardes CES, Minas da Piedade ME. Heat capacity and thermodynamics of solid and liquid pyridine-3-carboxylic acid (nicotinic acid) over the temperature range 296 to 531 K. J Chem Thermodyn. 2012;55:23–8.
36. Perlovich GL, Kazachenko VP, Strakhova NN, Raevsky OA. Impact of sulfonamide structure on solubility and transfer processes in biologically relevant solvents. J Chem Eng Data. 2014;59:4217–26.
37. Monte MJS, Santos LMNBF, Fonseca JMS, Sousa CAD. Vapor pressures, enthalpies and entropies of sublimation of *para* substituted benzoic acids. J Therm Anal Calorim. 2010;100:465–74.
38. Acree W, Chickos JS. Phase transition enthalpy measurements of organic and organometallic compounds. Sublimation, vaporization and fusion enthalpies from,1880 to 2010. J Phys Chem Ref Data. 2010;39(2010):1–942.
39. Harutada N, Solubility phenomena of pyridine- and pyrazinemonocarboxamides. I. Heat of sublimation of picolinamide, nicotinamide, isonicotinamide, and pyrazinecarboxamide. Takamine Kenkyusho Nempo. 1959; 11:66–75
40. Ribeiro da Silva MDMC, Goncalves JM, Acree WE Jr. Standard molar enthalpy of sublimation of crystalline 3-pyridinecarboxylic acid. J Chem Thermodyn. 2000;32:1071–3.
41. Sabbah R, Ider S. Thermodynamics of intermolecular and intramolecular bonds in three carboxypyridinic acids (picolinic, nicotinic and isonicotinic acids). Can J Chem. 1999;77:249–57.
42. Wright WB, King GSD. The crystal structure of nicotinic acid. Acta Cryst. 1953;6:305–17.
43. Blokhina SV, Sharapova AV, Ol'khovich MV, Volkova TV, Perlovich GL. Vapor pressures and thermodynamic sublimation of antitubercular drugs pyrazinamide and hydrazides isonicotinic acid. J Therm Anal Calorim. 2015;120:1053–60.
44. Perlovich GL, Ryzhakov AM, Tkachev VV, Hansen LK. Sulfonamide molecular crystals: thermodynamic and structural aspects. Cryst Growth Des. 2011;11:1067–81.
45. Perlovich GL, Raevsky OA. Sublimation of molecular crystals: Prediction of sublimation functions on the basis of HYBOT physicochemical descriptors and structural clusterization. Cryst Growth Des. 2010;10:2707–12.