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Thermochemistry of Drugs. Experimental and First-Principles Study of Fenamates

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S *Supporting Information*

ABSTRACT: This work has been undertaken to obtain new thermochemical data for diphenylamine and its derivatives to improve the group contribution methodology for the prediction of the thermodynamic properties of the biologically active compounds. Standard molar enthalpies of formation in the gaseous state of diphenylamine and *N*-phenylanthranilic acid have been obtained from combustion calorimetry and results from the temperature dependence of the vapor pressure measured by the transpiration method. To verify the experimental data, *first principles* calculations of all compounds have been performed. Enthalpies of formation derived from G3MP2 method and the bond separation procedure are in good agreement with the experimental results.

1. INTRODUCTION

One of the ways to develop new drug compounds is a modification of already known and proven drugs. However, at the beginning of the development a set of specific thermodynamic properties for already existing drug compounds have to be known. Such thermodynamic properties as the enthalpy of sublimation, the enthalpy of fusion, the enthalpy of vaporization, the enthalpy of formation in the condensed and in the gas phase are well-known as reliable descriptors for constructing various models predicting the biological activity. Sublimation and vaporization enthalpies are the key parameters for the estimation of the crystal lattices energies.[1] Enthalpies of fusion are involved in the assessment of solubilities of drugs. Enthalpies of formation are important parameters for the optimization of the drugs synthesis. Thus, the knowledge of reliable thermochemical properties of drugs is essential for the pharmaceutical industry.

Diphenylamine and *N*-phenylanthranilic acid are the basic structures for a well-known class of nonsteroidal anti-inflammatory drugs[2] called fenamates (see Figure 1). Thermodynamic data for these drugs are surprisingly scarce. In our previous work we studied enthalpies of sublimation and enthalpies of fusion of some fenamates.[3−5] In this work we have focused on determining enthalpies of formation of diphenylamine and *N*-phenylanthranilic acid as model compounds for energetics of fenamates. The thermochemistry of diphenylamine and *N*-phenylanthranilic acid including the sublimation enthalpies, $\Delta_{cr}^{g}H_m$, vaporization enthalpies, $\Delta_{l}^{g}H_m$, and the standard enthalpies of formation in the solid state, $\Delta_f H_m^o(cr)$, have been studied using experimental methods (combustion calorimetry and vapor pressure measurements). For a validation of the experimental data on these compounds, high-level first-principles calculations of $\Delta_f H_m^o(g)$ of these molecules have been performed using the GAUSSIAN-03 program package. Using the new experimental results, a group contribution methodology for predicting enthalpies of vaporization of compounds relevant to fenamates has been developed.

2. EXPERIMENTAL SECTION

2.1. Materials. Samples of diphenylamine (Sigma) and *N*-phenylanthranilic acid (Alfa) with purity of 99% were further purified by fractional sublimation at reduced pressures. The purity analyses were performed using a gas chromatograph (GC) with a flame ionization detector. A HP-5 capillary column (stationary phase cross-linked 5% PH ME silicone) was used in all our experiments. The column was 30 m long, 0.32 mm inside diameter, and had a film thickness of 0.25 μm. The flow rate of the carrier gas (nitrogen) was maintained at 7.2 $dm^3 \cdot h^{-1}$. The starting temperature for the GC was $T = 323$ K for the first 180 s followed by heating to $T = 523$ K at the rate of 10 $K \cdot min^{-1}$. No impurities greater than 0.02 mass percent were detected in all samples used in this work.

2.2. Combustion Calorimetry. An isoperibol bomb calorimeter was used for the measurement of energy of combustion of diphenylamine and *N*-phenylanthranilic acid. The substances were pressed into pellets of mass ≈500 mg and were burned in oxygen at a pressure 3.04 MPa with a mass of 1.00 g of water added to the bomb. We used small polyethylene peaces as the auxiliary material (Tables S1−S3, Supporting Information) to reach completeness of combustion. The detailed procedure has been described previously.[6] Combustion products were examined for carbon monoxide (Dräger tube) and unburned carbon, but none was detected. The energy equivalent of the calorimeter

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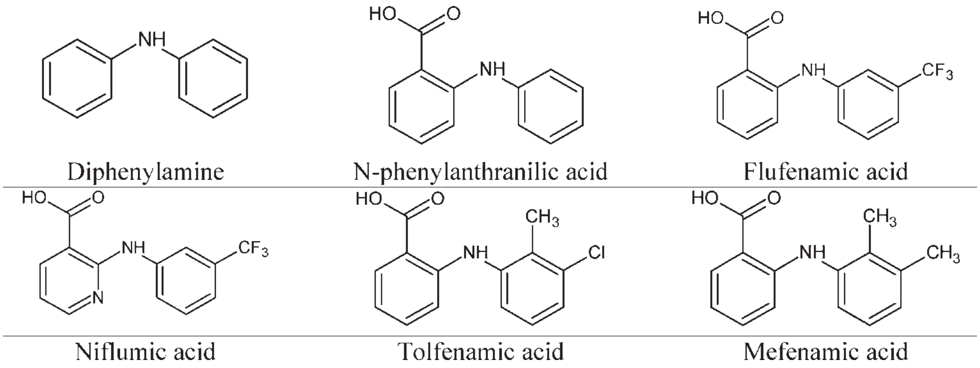


Figure 1. Structures of the molecules studied in this work.

ε_{calor} was determined with a standard reference sample of benzoic acid (sample SRM 39j, NIST). Correction for nitric acid formation was based on the titration with 0.1 mol·dm^{-3} NaOH(aq). The sample masses were reduced to vacuum, taking into consideration their density values (Table S1, Supporting Information). For converting the energy of the actual bomb process to that of the isothermal process, and reducing to standard states, the conventional procedure was applied.[7]

2.3. Measurements of the Vapor Pressures Using the Transpiration Method. Vapor pressures, enthalpies of sublimation, $\Delta_{cr}^{g}H_m$, and enthalpies of vaporization, $\Delta_{l}^{g}H_m$ of diphenylamine were determined using the method of transpiration in a saturated stream of nitrogen. The method has been described in detail before[8,9] and has proven to give results in agreement with other established techniques. The temperature dependence of the vapor pressures was used to determine the enthalpies of sublimation of the pure substances.

2.3.1. Experiments in Rostock. A sample of approximately 0.5 g of the sample was mixed with glass beads and placed in a thermostated U-tube of length 40 cm and diameter 0.5 cm. Preheated nitrogen stream was passed through the U-tube at constant temperature (±0.1 K). The flow rate of the nitrogen stream was measured using a soap film bubble flow meter (±0.2−0.3%) and optimized to reach the saturation equilibrium of the transporting gas at each temperature under study. We tested our apparatus at different flow rates of the carrier gas to check the lower boundary of the flow, below which, the contribution of the vapor condensed in the trap by diffusion becomes comparable to the transpired one. In our apparatus the contribution due to diffusion was negligible at flow rates down to 0.5 dm^3·h^{-1}. Very high flow rates could lead to incomplete saturation of the carrier gas. The upper limit for our apparatus was a flow rate of 13.5 dm^3·h^{-1}. Thus, we carried out the experiments in the using flow rates ranging from 1.7 to 11 dm^3·h^{-1} which ensured that transporting gas was in saturated equilibrium with the coexisting solid phase in the saturation tube. The material transported was condensed in a cold trap. The amount of condensed product was determined by using GC equipped with capillary column HP-5 or SE-30. The saturated vapor pressure p_i^{sat} at each temperature T_i was calculated from the amount of product collected within a definite period of time. Assuming that Daltos law of partial pressures when applied to the nitrogen stream saturated with the substance i of interest is valid, values of p_i^{sat} were calculated:

$$\begin{aligned} p_i^{sat} &= m_i \cdot R \cdot T_a / V \cdot M_i \\ V &= V_{N_2} + V_i \qquad (V_{N_2} \gg V_i) \end{aligned} \tag{1}$$

where $R = 8.31447$ J·K^{-1}·mol^{-1}, m_i is the mass of the transported compound, M_i is the molar mass of the compound, and V_i is its volume contribution to the gaseous phase. V_{N_2} is the volume of transporting gas and T_a is the temperature of the soap film bubble flow meter. The volume of transporting gas V_{N_2} was determined from the flow rate and time measurements.

2.3.2. Experiments in Ivanovo. The inert gas (nitrogen) at constant temperature was passed through to the thermostated glass tube (L = 1000 mm long, with a diameter d = 30 mm) filled with the glass beads covered by substance under study. A temperature of the experiment is maintained to ±0.01 K. The stability of the gas flow with precision better than 0.01% is maintained using the mass flow controller MKS type PR 4000. The only important difference to procedure applied in Rostock was the measurements of the mass of the transported material.[5] The amount of sample condensed in the cold trap (liquid nitrogen) was dissolved in a defined volume of solvent V_{sol}. The determination of the mass of the substance was based on the measuring of absorbance A of its solution by means of CARY 50 UV−visible spectrophotometer, Varian. According to the Lambert−Beer law the absorbance A is proportional to the concentration:

$$A = \varepsilon \cdot c \cdot l \tag{2}$$

and with the value of the extinction coefficient ε (in dm^3 mol^{-1} cm^{-1}) of the compound under study dissolved in the solvent one can calculate the concentration of the solution c (in mol dm^{-3}), and the mass of the transported compound:

$$m = c \cdot V_{sol} \cdot M \tag{3}$$

where l is an absorbing path length and M is a molar mass of compound under study. Mass of the compound derived from eq 3 was used in eq 1 for calculation of the vapor pressure according to eq 1 in the same way as in Rostock.

2.4. Computations. Standard first-principles molecular orbital calculations were performed with the Gaussian 03 Rev.04 series of programs.[10] Energies were obtained at the G3(MP2) level of theory. G3 theory is a procedure for calculating energies of molecules containing atoms of the first and second row of the periodic chart based on ab initio molecular orbital theory. A modification of G3 theory that uses reduced orders of Moller−-Plesset perturbation theory is G3(MP2) theory.[11,12] This method saves considerable computational time compared to G3 theory with some loss in accuracy but is much more accurate than G2(MP2) theory. For all the species included in this study, full geometry optimizations were carried out at the

Table 1. Thermochemical Data at T = 298.15 K (p° = 0.1 MPa) for Compounds Studied in This Work, kJ·mol^{-1}

compound	$-\Delta_c H_m^\circ$(cr)	$\Delta_f H_m^\circ$(cr)	$\Delta_{cr}^{g} H_m$	$\Delta_f H_m^\circ$(g)
diphenylamine	6424.7 ± 1.9[14,a]	130.5 ± 1.9[14,a]	95.2 ± 0.6[b]	213.7 ± 3.0[b]
	6411.6 ± 2.1[15,a]	117.4 ± 2.1[15,a]		
	6424.2 ± 1.4[16,a]	130.0 ± 1.5[16,a]		
	6412.7 ± 2.5[b]	118.5 ± 2.9[b]		
N-phenylanthranilic acid	6380.7 ± 2.3[b]	−307.0 ± 2.8[b]	126.0 ± 1.3[5]	−181.0 ± 3.1[b]

[a] Original experimental data were reanalyzed in compilations.[17,18] [b] This work.

Table 2. Compilation of Data on Enthalpies of Sublimation $\Delta_{cr}^{g} H_m$ and Vaporization $\Delta_{l}^{g} H_m$ of Diphenylamine, kJ·mol^{-1}

phase	technique	temperature range, K	$\Delta_{cr}^{g} H_m/\Delta_{l}^{g} H_m$ at (T_{av})[a]	$\Delta_{cr}^{g} H_m/\Delta_{l}^{g} H_m$ at (298.15 K)[b]	ref
crystal	quartz fiber	298.2−324.8	91.3	91.6 ± 1.5	19
	n/a	298.2−324.8		96.9	20
	effusion			96.7 ± 2.5	21, 22
	transpiration	302.7−319.2		110.0 ± 1.0	5
	n/a	303.2−323.2	99.3	99.7 ± 3.8	25
	transpiration	293.1−325.2	94.6	**95.2 ± 0.6**	this work
liquid	n/a	381.4−575.0	75.0	77.0	23
	static	575−772	56.1	89.1 ± 0.4	24
	n/a	573−673		82.3	20
	transpiration	328.3−373.1	74.9	**79.5 ± 0.4**	this work

[a] Vapor pressure available in the literature were treated using eqs 2 and 3 to evaluate the enthalpy of vaporization at 298 K in the same way as our own results in Table 3. [b] According to the procedure developed by Chickos and Acree,[28,29] the value of ΔC_p = 29.5 J·mol^{-1}·K^{-1} (between the solid and the gas phase) has been estimated from the isobaric molar heat capacity of the solid compound C_p^{cr} = 191.7 J·mol^{-1}·K^{-1} (calculated according to procedure[28,29]) and the value of ΔC_p = 88.5 J·mol^{-1}·K^{-1} (between the liquid and the gas phase) has been derived from the isobaric molar heat capacity of the liquid, C_p^{l} = 299.6 J·mol^{-1}·K^{-1} (calculated according to procedure[28,29]).

HF/6-31G(d) level. The corresponding harmonic vibrational frequencies were evaluated at the same level of theory to confirm that the optimized structures found correspond to potential energy minima. All the minima found at the HF/6-31G(d) level were again fully reoptimized at the G3(MP2) method. G3(MP2) theory uses geometries from second-order perturbation theory and scaled zero-point energies from Hartree−Fock theory followed by a series of single-point energy calculations at the MP2(Full), QCISD(T), and MP2/GTMP2Large levels of theory (for details see ref 12). The enthalpy value of studied compound at T = 298 K, was evaluated according to standard thermodynamic procedures.[13]

3. RESULTS AND DISCUSSION

The enthalpy of formation in the gaseous phase of any compound is made up of two contributions:

$$\Delta_f H_m^\circ(g) = \Delta_{cr}^{g} H_m + \Delta_f H_m^\circ(cr) \tag{4}$$

where $\Delta_{cr}^{g} H_m$ is the enthalpy of sublimation and $\Delta_f H_m^\circ$(cr) is the enthalpy of formation in the solid state. There is surprisingly little known about the $\Delta_{cr}^{g} H_m$ and $\Delta_f H_m^\circ$(cr) of diphenylamine derivatives. Only thermochemical properties of diphenylamine itself were measured in the past.[14−25] Available data are collected in Tables 1 and 2. The data are in disarray. In this context, a systematic study of thermochemistry of diphenylamine and its derivatives seems to be highly desirable.

3.1. Enthalpies of Formation from Combustion Calorimetry.

Results of combustion experiments on diphenylamine and *N*-phenylanthranilic acid are summarized in Table 1 as well as in Tables S2−S3 (Supporting Information). Values of the standard specific energies of combustion, $\Delta_c u^\circ$, the standard molar enthalpies of combustion, $\Delta_c H_m^\circ$, and the standard molar enthalpies of formation in the crystalline state, $\Delta_f H_m^\circ$(cr) were based on the reactions

$$C_{12}H_{11}N(cr) + 14.75O_2(g) = 12CO_2(g) + 5.5H_2O(liq) + 0.5N_2(g) \tag{5}$$

$$C_{13}H_{11}O_2N(cr) + 15.75O_2(g) = 13CO_2(g) + 5.5H_2O(liq) + 0.5N2(g) \tag{6}$$

Values of the molar enthalpies of formation, $\Delta_f H_m^\circ$(cr) of compounds under study have been obtained from the enthalpic balance according to eqs 5 and 6 and Hess' law using the molar enthalpies of formation of H_2O(l) and CO_2(g) as assigned by CODATA.[26] The total uncertainties were calculated according to the guidelines presented by Olofsson.[27] The uncertainties assigned to $\Delta_f H_m^\circ$ are twice the overall standard deviation and include the uncertainties from calibration, from the combustion energies of the auxiliary materials, and the uncertainties of the enthalpies of formation of the reaction products H_2O and CO_2.

Enthalpy of combustion of *N*-phenylanthranilic acid was measured for the first time (see Table 1). Previous calorimetric determinations of the standard molar enthalpy of formation, $\Delta_f H_m^\circ$(cr), of diphenylamine differ by 13 kJ·mol^{-1} (see Table 1). Our new result (118.5 ± 2.9) kJ·mol^{-1} is in close agreement with the value (117.4 ± 2.1) kJ·mol^{-1} reported by Anderson and Gilbert[15] and found in disagreement with the works[14,16] (see Table 1). We do not have any reasonable explanation for such a disagreement, but we intend to validate our value with help of our

Table 3. Results from Measurements of the Vapor Pressure p of Diphenylamine Using the Transpiration Method

T[a]	m[b]	$V_{(N2)}$[c]	gas-flow	p[d]	$(p_{exp} - p_{calc})$	$\Delta^{g}_{cr(1)}H_m$	T[a]	m[b]	$V_{(N2)}$[c]	gas-flow	p[d]	$(p_{exp} - p_{calc})$	$\Delta^{g}_{cr(1)}H_m$
K	mg	dm^3	dm^3/h	Pa	Pa	kJ·mol^{-1}	K	mg	dm^3	dm^3/h	Pa	Pa	kJ·mol^{-1}
Diphenylamine; $\Delta^{g}_{cr}H_m$ (298.15 K) = (79.54 ± 0.36) kJ·mol^{-1}													
$\ln(p/\mathrm{Pa}) = \frac{327.25}{R} - \frac{103984,58}{R\cdot(T,\ \mathrm{K})} - \frac{29.5}{R}\ln\left(\frac{T,\ \mathrm{K}}{298.15}\right)$													
293.1	0.34	131.7	10.59	0.04	0.00	95.11	318.7	0.66	11.11	11.11	0.85	−0.04	94.36
301.0	0.57^{e}	69.22	5.09	0.12	0.01	94.88	323.2	0.88	8.33	11.11	1.53	0.06	94.23
298.4	0.85	155.9	10.87	0.08	0.00	94.96	325.2	0.89	6.94	11.11	1.86	0.04	94.17
302.1	1.28	140.5	11.00	0.13	0.01	94.85	293.7	0.020^{f}	7.24	1.69	0.04	0.00	95.32
308.0	0.51^{e}	30.08	5.84	0.24	−0.01	94.67	296.2	0.017^{f}	4.20	1.69	0.06	0.00	95.25
308.0	0.69^{e}	39.75	2.93	0.25	−0.01	94.67	298.2	0.026^{f}	5.30	1.69	0.07	−0.01	95.19
302.7	0.83^{e}	82.05	5.84	0.15	0.01	94.83	300.2	0.026^{f}	4.00	1.69	0.10	0.00	95.13
309.1	0.86^{e}	44.09	5.84	0.29	−0.01	94.64	303.2	0.015^{f}	1.49	1.69	0.14	0.00	95.04
305.5	0.90	64.56	11.00	0.20	0.01	94.75	305.2	0.024^{f}	2.03	1.69	0.17	−0.01	94.98
309.3	0.80	38.51	11.00	0.30	0.00	94.64	308.2	0.032^{f}	1.83	1.69	0.26	0.00	94.89
313.0	0.49^{e}	15.48	5.84	0.45	−0.01	94.53	310.7	0.037^{f}	1.58	1.69	0.34	−0.01	94.82
315.0	0.43^{e}	11.62	5.09	0.54	−0.05	94.47	313.7	0.033^{f}	0.958	1.69	0.50	0.00	94.73
315.0	0.73^{e}	19.17	5.84	0.55	−0.04	94.47	315.7	0.049^{f}	1.21	1.69	0.60	−0.03	94.67
312.3	0.68	23.41	10.64	0.42	−0.01	94.55	316.7	0.046^{f}	0.958	1.69	0.70	−0.01	94.64
316.0	0.58^{e}	13.00	6.34	0.65	−0.01	94.44	317.2	0.052^{f}	1.01	1.69	0.75	0.00	94.63
318.0	0.80^{e}	14.00	6.00	0.83	0.00	94.38	318.2	0.066^{f}	1.10	1.69	0.86	0.02	94.60
315.4	0.78	18.45	10.80	0.61	0.00	94.46	320.7	0.059^{f}	0.789	1.69	1.10	−0.01	94.52
318.3	0.85	14.40	10.80	0.85	−0.01	94.37	323.2	0.058^{f}	0.592	1.69	1.43	−0.03	94.45
320.3	0.75	9.76	5.66	1.11	0.05	94.31	324.7	0.066^{f}	0.592	1.69	1.64	−0.08	94.41
324.1	0.89	7.59	5.66	1.69	0.07	94.20	326.7	0.109^{f}	0.789	1.69	2.03	−0.09	94.35
322.3	0.95	9.90	10.80	1.38	0.05	94.25							
Diphenylamine; $\Delta^{g}_{l}H_m$(298.15 K) = (79.54 ± 0.36) kJ·mol^{-1}													
$\ln(p/\mathrm{Pa}) = \frac{338.46}{R} - \frac{105926.10}{R\cdot(T,\ \mathrm{K})} - \frac{88.5}{R}\ln\left(\frac{T,\ \mathrm{K}}{298.15}\right)$													
328.3	0.96	5.66	5.66	2.45	0.06	76.88	358.2	0.90	0.551	3.15	23.55	−0.59	74.23
332.2	0.90	3.77	5.66	3.43	0.11	76.53	360.2	0.67	0.344	1.22	28.29	0.57	74.05
338.1	0.86	2.36	5.66	5.22	−0.16	76.01	363.0	1.76	0.788	3.15	32.20	−1.35	73.81
335.4	0.86	2.83	5.66	4.38	0.05	76.25	363.1	0.85	0.375	1.22	33.21	−0.55	73.80
341.2	0.68	1.44	3.32	6.84	−0.04	75.73	366.1	1.16	0.405	1.22	41.93	0.69	73.53
343.2	0.59	1.05	3.15	8.10	0.06	75.56	368.1	2.74	0.814	3.15	48.48	1.46	73.35
346.1	0.80	1.19	3.32	9.63	−0.40	75.30	368.3	0.93	0.284	1.22	47.91	0.27	73.34
348.2	0.90	1.10	3.15	11.74	0.00	75.11	373.1	3.62	0.788	3.15	66.21	1.43	72.91
353.1	0.93	0.788	3.15	16.98	0.15	74.68	371.9	1.27	0.304	1.22	61.08	1.04	73.02
357.2	0.56	0.375	1.25	21.81	−0.71	74.32							

[a] Temperature of saturation. [b] Mass of transferred sample, condensed at T = 243 K. [c] Volume of nitrogen, used to transfer mass m of sample. [d] Vapor pressure at temperature T, calculated from m and the residual vapor pressure at the cooling temperature T = 243 K. [e] Validation experiment using the GC column SE-30 (see text). [f] Validation experiment using the determination of the transported mass using UV—vis (see text).

new result for sublimation enthalpy and a high-level first-principles calculations in the section 3.5.

3.2. Vapor Pressure and Sublimation Enthalpy. Experimental vapor pressures of diphenylamine have been measured in this work between 293 and 372 K over the solid and the liquid sample (see Table 3). The following equation:

$$R\cdot\ln p_i^{sat} = a + \frac{b}{T} + \Delta^{g}_{cr}C_p\cdot\ln\left(\frac{T}{T_0}\right) \qquad (7)$$

was fitted to the experimental p ,T data by using a and b as adjustable parameters. T_0 appearing in eq 7 is an arbitrarily chosen reference temperature (which in this case is 298.15 K). Consequently, from eq 7 the expression for the enthalpy of sublimation at temperature T is

$$\Delta^{g}_{cr}H_m(T) = -\mathrm{b} + \Delta^{g}_{cr}C_p\cdot T \qquad (8)$$

Values of $\Delta^{g}_{cr}C_p$ have been derived from the experimental isobaric molar heat capacities of the solid diphenylamine, C_p^{cr}, calculated according to the procedure developed by Chickos.[28,29] Experimental results and parameters a and b are listed in Table 3. We have checked the experimental and calculation procedures with measurements of vapor pressures of n-alcohols.[9] It turned out that vapor pressures derived from the transpiration method for diphenylamine were generally reliable within (3 to 5)% (see

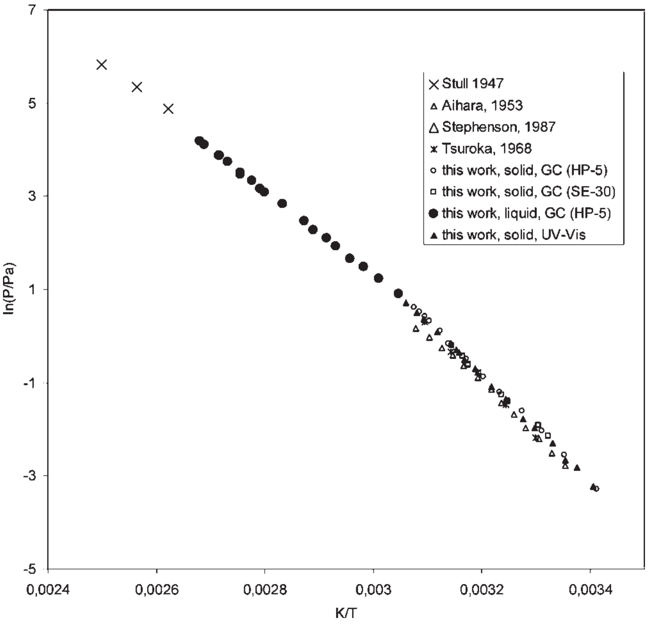


Figure 2. Experimental data of the vapor pressures of the diphenylamine.

Figures S1 and S2, Supporting Information) and their accuracy was governed by the reproducibility of the mass determination. To assess the uncertainty of the vaporization enthalpy, the experimental data were approximated with the linear equation $\ln(p_i^{\text{sat}}) = f\ (\text{T}^{-1})$, using the method of least squares. The uncertainties in the enthalpy of sublimation were assumed to be identical with the deviation of experimental $\ln(p_i^{\text{sat}})$ values from this linear correlation. Experimental results are presented in Table 3.

The temperature dependence of vapor pressure for the diphenylamine is presented in Figure 2. As can be seen, our vapor pressures over the solid sample are somewhat higher in comparison with the data measured by the quartz fiber method[19] and by the Knudsen effusion method.[21] To prove our pressure values, two new series of experiments on the solid diphenylamine have been performed (see Table 3). In contrast to the first series, we deliberately used only a very moderate nitrogen flow of 3−6 $\text{dm}^3\cdot\text{h}^{-1}$ to ascertain the saturation conditions. We also used another GC device for determination of the mass of the transferred sample. This device was equipped with the 25 m long capillary column with SE-30 (the capillary column 25 m HP-5 was used in the first series). We have carefully performed the calibration of the system using the *n*-pentadecane as the internal standard. However, the results of the vapor pressures from both series have been indistinguishable and they were treated together (see Table 3). Additionally, we have performed the third series of the transpiration experiments in the temperature range 294−328 K and at very low nitrogen flow of 1.7 $\text{dm}^3\cdot\text{h}^{-1}$, and we have measured the mass of the transferred sample using the calibrated UV-Spectrometer (see the section 2.3.2). All three series of vapor pressures over the solid diphenylamine are very consistent. Thus, we have carefully proven reliability of our data and we would recommend our data set of vapor pressures instead the data available from refs 5 and 19−22. Some comments are required concerning our earlier results for diphenylamine[5] measured using the transpiration method. The disagreement between sublimation enthalpy obtained in those work with the current study is perhaps due to the temperature in the cold trap. All fenamates studied in ref 5 were crystals having very high melting points (from 405.3 K for flufenamic acid to 503.5 K for mefenamic acid). For such compounds the cold trap is usually kept at the ambient temperature. In the case with diphenylamine probably this temperature was not sufficient. In this work the trap was cooled to 243 K to decrease the residual vapor pressure at the condensation temperature.

Vapor pressures over the liquid diphenylamine reported by Stull[23] and by Glaser et al.[24] were measured at very high temperatures and it is hardly possible to perform any correct comparison with our new results, which were measured close to the melting temperature 326.2 K.

Sublimation enthalpy of diphenylamine derived in this work, $\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}(298.15\ \text{K}) = (95.2 \pm 0.6)\ \text{kJ}\cdot\text{mol}^{-1}$ is in agreement with most of the available data collected in Table 2; however, our result has smaller uncertainty. The set of available vaporization enthalpies of diphenylamine also shows a large spread in values, from (77 to 89) $\text{kJ}\cdot\text{mol}^{-1}$ (see Table 2). Vaporization enthalpy of diphenylamine derived in this work, $\Delta_{\text{l}}^{\text{g}}H_{\text{m}}(298.15\ \text{K}) = (79.5 \pm 0.4)\ \text{kJ}\cdot\text{mol}^{-1}$, fits to the average of these available results.

3.3. Enthalpies of Fusion of Diphenylamine and Fenamates. The melting temperatures and enthalpies of fusion of the diphenylamine and fenamates measured in the present work and those available from the literature are compiled in Table 4. No phase transitions other than melting (except for mefenamic acid) have been detected. Experimental enthalpies of fusion measured by DSC (see Table 4) are obtained at the melting temperature T_{fus}. Because of the differences in the reference temperatures, the experimental enthalpies of fusion were adjusted to $T = 298$ K. The adjustment was calculated from the equation:[30]

$$\begin{aligned}\{\Delta_{\text{cr}}^{\text{l}}H_{\text{m}}(T_{\text{fus}}/\text{K}) - \Delta_{\text{cr}}^{\text{l}}H_{\text{m}}(298\text{K})\}/(\text{J}\cdot\text{mol}^{-1}) \\ = \{(0.75 + 0.15C_p^{\text{cr}})[(T_{\text{fus}}/\text{K}) - 298\text{K}]\} \\ - \{(10.58 + 0.26C_p^{\text{l}})[(T_{\text{fus}}/\text{K}) - 298\text{K}]\} \qquad (9)\end{aligned}$$

where the isobaric molar heat capacities, C_p^{cr} and C_p^{l}, of the solid and the liquid fenamates are given in Table 4 and calculated according to procedure developed by Chickos and Acree[28,29]. With this adjustment (the uncertainty of the correlation was not taken into account), the molar enthalpies of fusion, $\Delta_{\text{cr}}^{\text{l}}H_{\text{m}}(298\ \text{K})$, were calculated (Table 4). Mefenamic acid exists in two polymorphic modifications, I and II, with the phase transition between 433 and 443 K.[5] Enthalpy of sublimation of the polymorph II was measured in our previous work[5] and given in Table 4.

3.4. Consistency Test of the Vaporization, Sublimation and Fusion Enthalpies of Diphenylamine. Since a significant discrepancy between available experimental data for diphenylamine have been found (see Table 2), additional arguments to support the reliability of our new vapor pressure measurements are required. A valuable test of consistency of the experimental data on sublimation and vaporization enthalpies measured for diphenylamine provides a comparison with an experimental value of enthalpy of fusion, $\Delta_{\text{cr}}^{\text{l}}H_{\text{m}} = (17.9 \pm 0.5)\ \text{kJ}\cdot\text{mol}^{-1}$ measured for this compound by DSC[31] (see Table 4). Indeed, in this work, the sample of diphenylamine was investigated by the transpiration method in both ranges, above and below its temperature of melting $T_{\text{m}} = 326.2$ K. The values $\Delta_{\text{cr}}^{\text{g}}H_{\text{m}}(298\ \text{K})$ and $\Delta_{\text{l}}^{\text{g}}H_{\text{m}}(298\ \text{K})$ were derived (see Tables 2 and 3). Comparison of the enthalpy of fusion, $\Delta_{\text{cr}}^{\text{l}}H_{\text{m}} = (15.7 \pm 0.9)\ \text{kJ}\cdot\text{mol}^{-1}$, calculated as the difference $\Delta_{\text{cr}}^{\text{g}}H_{\text{m}} - \Delta_{\text{l}}^{\text{g}}H_{\text{m}}$ (both values are referred to $T = 298$ K) from Table 2 and the enthalpy

Table 4. Compilation of Experimental Data on Enthalpies of Fusion, $\Delta_{cr}^{l}H_m$, Enthalpies of Sublimation, $\Delta_{cr}^{g}H_m$, and Enthalpies of Vaporisation, $\Delta_{l}^{g}H_m$, of Diphenylamine and Fenamates

compounds	T_{onset} K	$\Delta_{cr}^{l}H_m$ at T_{fus} $kJ \cdot mol^{-1}$	C_p^{cr} [a] $J \cdot mol^{-1} \cdot$K-1	C_p^{l} [a] $J \cdot mol^{-1} \cdot$K-1	$\Delta_{cr}^{l}H_m$ [b] at 298 K $kJ \cdot mol^{-1}$	$\Delta_{cr}^{g}H_m$ at 298 K $kJ \cdot mol^{-1}$	$\Delta_{l}^{g}H_m$(exp) [c] $kJ \cdot mol^{-1}$	$\Delta_{l}^{g}H_m$(calc) [d] $kJ \cdot mol^{-1}$	Δ
1	2	3	4	5	6	7	8	9	10
diphenylamine	326.2[31]	17.9[31]	191.7	299.6	16.2	95.2 ± 0.6	79.0	79.7	−0.7
N-phenylanthranilic acid	458.2[5]	39.7[5]	235.8	380.5	27.7	126.0 ± 1.3[5]	98.3	98.3	0.0
mefenamic acid	503.5[5]	38.7[5]	291.0	437.3	22.2	132.6 ± 1.8[5]	110.4	105.7	4.7
tolfenamic acid	484.3[5]	38.6[5]	283.1	433.2	23.7	128.4 ± 0.8[5]	104.7	108.4	−3.7
flufenamic acid	405.3[5]	26.7[5]	296.2	436.6	18.2	121.2 ± 0.7[5]	103.0	102.2	0.8
niflumic acid	478.5[5]	36.5[5]	292.6	435.5	22.2	130.2 ± 0.8[5]	108.0	108.5	−0.5
								average:	±1.7

[a] Calculated according to procedure develpoed by Chickos and Acree.[28,29] [b] The experimental enthalpies of fusion $\Delta_{cr}^{l}H_m$ measured at T_{fus} and adjusted to 298.15 K (see text). [c] Calculated as the differences between enthalpies of sublimation (column 7, this table) and enthalpies of fusion (column 6, this table). [d] Calculated using group-additive values from Table 6.

Table 5. Results of Calculation of the Standard Enthalpy of Formation $\Delta_f H_m^o(g)$ for the Molecules Studied in This Work in the Gaseous Phase at 298.15 K, $kJ \cdot mol^{-1}$

compounds	AT	BS 1	BS 2	$\Delta_f H^o_{m\,exp,\,gas}$
N-phenylanthranilic acid	−187.4	−178.2	−181.2	−181.0 ± 3.1
tolfenamic acid	−257.0	−243.1	−249.8	
flufenamic acid	−869.6	−833.9	−845.5	
niflumic acid	−833.4		−813.1	
diphenylamine	206.2	213.5	214.7	213.7 ± 3.0

of fusion $\Delta_{cr}^{l}H_m$ = (16.2 ± 0.5) $kJ \cdot mol^{-1}$ (given in Table 4 and adjusted in this work to T = 298 K, according to eq 9) demonstrates an agreement that is very good within the boundaries of the experimental uncertainties of the methods used. Thus, our results for vaporization and sublimation enthalpy of diphenylamine given in Table 2 and 3 possess the internal consistency.

3.5. Calculation of the Gas Phase Enthalpies of Formation. Quantum Chemical Calculations. Values of sublimation enthalpies of compounds under study, derived in this work (Tables 2 and 3) can now be used together with the results from our combustion experiments for further calculation of the gas standard enthalpies of formation, $\Delta_f H_m^o(g)$ at 298 K according to the common eq 4. The resulting experimental values of $\Delta_f H_m^o(g)$ are given in the last column in Table 1 and they could be now compared with the theoretical results from quantum chemical calculations. First-principles molecular orbital methods for calculation of the enthalpy of formation of fenamates have not been yet reported in the literature. We have calculated using the G3(MP2) a total energy E_0 at T = 0 K and enthalpies H_{298} at T = 298.15 K (Table S4, Supporting Information). In standard Gaussian-*n* theories, theoretical standard enthalpies of formation, $\Delta_f H_m^o(g)$, are calculated through atomization reactions, bond separation reactions, or isodesmic reactions.[32] In this work we have applied the atomization procedure and selected reactions (see Table S5, Supporting Information) for calculation enthalpies of diphenylamine and fenamates. Results of calculations are given in Table 5. In all cases populations of the conformers have been taken into consideration (see Table S6, Supporting Information) for calculating of $\Delta_f H_m^o$(gas, 298 K). Results for *N*-phenylanthranilic acid from the bond separation reaction reactions are in good agreement with the experimental results (Table 5). Results from the atomization procedure are somewhat more negative, but they are still in acceptable agreement with the experimental value $\Delta_f H_m^o$(gas, 298 K) of *N*-phenylanthranilic acid (see Table 5). Results calculated from the atomization procedure and the bond separation reactions for diphenylamine are systematically less negative but also in acceptable agreement with the experimental value (see Table 5). Thus, the results of first principles calculations have helped to establish thermodynamic consistency of the experimental results from the transpiration and from the combustion calorimetry. The G3(MP2) method combined with the bond separation procedure could be recommended for reliable calculations of $\Delta_f H_m^o$(gas, 298 K) of fenamates.

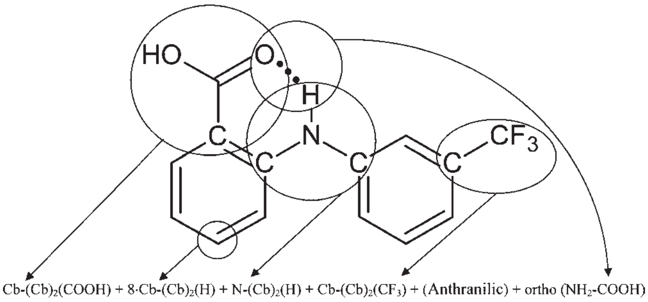
3.6. Additive Calculations of the Enthalpies of Vaporization of Compounds Relevant to Fenamates. Enthalpies of sublimation of fenamates are required for the drug properties modeling, but the experimental measurements of these values are very time-consuming. For this reason, any suitable method for prediction of sublimation enthalpies should be useful. Unfortunately, the prediction methods for sublimation enthalpy are very restricted. Sublimation enthalpies are not additive, because they consist of two contributions: vaporization enthalpy and fusion enthalpy. The fusion enthalpies are easy to measure using DSC. In contrast to the sublimation enthalpy, the enthalpy of vaporization is the additive property[33−35] and we are going to develop the group-additivity procedure for prediction enthalpies of vaporization of fenamates. Benson's group additivity method[36,37] seems to have the most widespread acceptance at present, and the overall best record for reliability of estimation techniques. However, the original work by Benson[36] and its updated compilation[37] do not provide group additivity values for the calculation of vaporization enthalpies, $\Delta_{l}^{g}H_m$, at 298 K. It seems to be logical to follow Benson's methodology for this thermodynamic property as well.[35] In this work, we have applied for the prediction of vaporization enthalpies of fenamates the same definition of groups and an evaluation procedure similar to those described by Benson.[36] The evaluation of the group-additivity values (GAVs) for predicting the vaporization enthalpies, $\Delta_{l}^{g}H_m$, was based on experimental data (see Supporting Information, Table S7). The group contribution values, which are specific for hydrocarbons are well established.[35] With these

Table 6. **Group Additivity Values, Γ_i, for the Calculation of the Enthalpy of Vaporization, $\Delta_l^g H_m$, for Fenamates[a] at T = 298 K, $kJ \cdot mol^{-1}$**

increment	Γ_i	increment	Γ_i
$C-(C)(H)_3$	6.33^b	$Cb-(Cb)_2(CF_3)$	9.5
$C-(C)_2(H)_2$	4.52^b	$Nb-(Cb)_2$	12.0
$Cb-(Cb)_2(H)$	5.65^b	*o*-(NH_2-COOH)	−10.0
$Cb-(Cb)_2(C)$	3.41^b	(anthranilic)	−12.6
		o-(CH_3-Cl)	1.0
$N-(Cb)_2(H)$	23.2	*o*-(CH_3-CH_3)	1.3
$Cb-(Cb)_2(COOH)$	46.8	*o*-(NH_2-CH_3)	−2.1
$Cb-(Cb)_2(Cl)$	12.8	($Cl-NH_2-Cl$)	−5.6

[a] For details see Table S8 (Supporting Information). [b] Increments were taken from our previous work.[35]

values fixed, we then turned to fenamates to derive GAVs necessary for those compounds. Group additivity parameters for prediction of vaporization enthalpies of these compounds are given in Table 6. For example, for the prediction of the vaporization enthalpy of flufenamic acid the following increments should be accounted:



There are several specific contributions introduced for improvement of the model. All fenamate molecules have an intramolecular hydrogen bond between the carbonyl group of the carboxyl acid moiety and the amino group that bridges the two aromatic rings. This feature of the fenamate molecules has been taken into account by a special contribution "anthranilic" in addition to the *o*-(NH_2-COOH) increment evaluated using experimental data for *o*-aminobenzoic acid (Table 6). The detailed composition of increments for each compound under study is given in Table S8 (Supporting Information). Comparison of the experimental and calculated enthalpies of vaporization is given in Table 4. The average deviation of ±1.7 $kJ \cdot mol^{-1}$ seems to be acceptable taking into account the combined experimental uncertainties of the sublimation and fusion experiments used for estimation of the GAVs. The compilation of the increments given in Table 6 could be used for prediction vaporization enthalpies of drugs with similar structural elements.

4. CONCLUSIONS

The purpose of this work was to establish a consistent set of experimental thermochemical quantities for diphenylamine and *N*-phenylanthranilic acid, which are parent compounds of the fenamate drugs. The data sets on thermodynamic properties were checked for internal consistency. The use of the modern first-principle calculations allowed the validation of the mutual consistency of the experimental data. The group-additivity method has been developed for prediction enthalpies of vaporization of fenamates and related biologically active compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Results from combustion calorimetry (Tables S1−S3); G3(MP2) total energies at 0 K and enthalpies at 298 K (in Hartree) of the molecules studied in this work (Table S4); reactions involved for determination of enthalpies of formation of compounds studied in this work (Table S5); conformational population analysis of *N*-phenylanthranilic acid (Table S6); data involved in the calculation of the group additivity values (Table S7); group-additivity procedure for fenamates studied in this work (Table S8). Deviations of the experimental vapor pressures of the liquid and solid diphenylamine as a function of temperature (Figures S1 and S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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