Supporting Information

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

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TABLE S1. Formula, density ρ (T = 293 K), massic heat capacity c_p (T = 298.15 K), and expansion coefficients $(\delta V/\delta T)_p$ of the materials used in the present study

Compounds	Formula	ρ	c_p[a]	$10^{-6}\cdot(\delta V/\delta T)_p$[b]
		$g\cdot cm^{-3}$	$J\cdot K^{-1}\ g^{-1}$	$dm^3\cdot K^{-1}$
diphenylamine	$C_{12}H_{11}N_1$	1.22 [d]	1.20	0.1
N-phenylanthranilic acid	$C_6H_{10}O_4$	1.50 [e]	1.31	0.1
polyethene	$CH_{1.93}$	0.92	2.53	0.1
cotton[c]	$CH_{1.774}O_{0.887}$	1.50	1.67	0.1

[a] From d.s.c. measurements. [b] Estimated. [c] From 10 combustion experiments, $\Delta_c u^\circ = -(16945.2\pm4.2)\ J\cdot g^{-1}$. [d] Tewari, Brij, Bhushan; Revista de la Sociedad Quimica del Peru, **2005**, 71(4), 273-277. [e] Meassured with a picnometer.

TABLE S2. Results for combustion experiments at T = 298.15 K (p° = 0.1 MPa) of the diphenylamine [a]

m (substance) /g [b]	0.508503	0.495986	0.637361	0.43906	0.608113
m'(cotton) /g [b]	0.001193	0.001092	0.000983	0.001147	0.001122
m''(polyethene) /g [b]	0.176802	0.186719	0.149539	0.134378	0
ΔT_c /K[c]	1.85642	1.85613	2.10037	1.54668	1.5579
$(\varepsilon_{calor})\cdot(-\Delta T_c)$ /J	-27504.7	-27500.4	-31119.1	-22915.6	-23081.8
$(\varepsilon_{cont})\cdot(-\Delta T_c)$ /J	-29.52	-29.48	-33.78	-23.94	-23.83
ΔU_{decomp} HNO_3 /J	54.65	55.55	66.89	51.07	51.36
ΔU_{corr} /J[d]	13.36	13.2	15.98	10.97	12.75
$-m'\cdot\Delta_c u'$ /J	20.22	18.5	16.66	19.44	19.01
$-m''\cdot\Delta_c u''$ /J	8196.06	8655.79	6932.22	6229.4	0
$\Delta_c u°$ (liq) /(J·g^{-1})	-37856	-37877.8	-37845.3	-37873.3	-37858.9
$-\Delta_c u°$ (liq) /(J·g^{-1})	37862.3±5.9				

[a] For the definition of the symbols see reference 7, T_h = 298.15 K; V(bomb) = 0.32 dm^3; p^i(gas) = 3.04 MPa; $m^i(H_2O)$ = 1.00 g; [b] Masses obtained from apparent masses. [c] $\Delta T_c = T^f - T^i + \Delta T_{corr}$; $(\varepsilon_{cont})\cdot(-\Delta T_c) = (\varepsilon^i_{cont})\cdot(T^i - 298.15\ K) + (\varepsilon^f_{cont})\cdot(298.15\ K - T^f + \Delta T_{corr.})$. [d] ΔU_{corr}, the correction to standard states, is the sum of items 81 to 85, 87 to 90, 93, and 94 in reference 7 $\Delta_c u°$(polyethene) = -(46357.3±3.6) J·g^{-1}; [f] ε = 14816.0±0.9 J·K^{-1}.

TABLE S3. Results for combustion experiments at T = 298.15 K (p° = 0.1 MPa) of the N-phenylanthranilic acid

m (substance) /g	0.594592	0.816663	0.428892	0.443036	0.658887
m'(cotton) /g	0.001289	0.00105	0.000941	0.001017	0.001101
m''(polyethene) /g	0.128548	0	0.179582	0.192204	0.208641
ΔT_c /K	1.60613	1.65433	1.43099	1.49949	1.98682
$(\varepsilon_{calor})\cdot(-\Delta T_c)$ /J	-23796.5	-24510.5	-21201.5	-22216.4	-29436.8
$(\varepsilon_{cont})\cdot(-\Delta T_c)$ /J	-25.13	-25.59	-22.21	-23.41	-32.14
ΔU_{decomp} HNO_3 /J	49.57	71.67	41.21	46.59	60.32
ΔU_{corr} /J	13.91	16.65	11.07	11.56	16.78
$-m'\cdot\Delta_c u'$ /J	21.84	17.79	15.95	17.23	18.66
$-m''\cdot\Delta_c u''$ /J	5959.14	0	8324.94	8910.06	9672.03
$\Delta_c u°$ (liq) /$(J\cdot g^{-1})$	-29898	-29914.4	-29915.7	-29917.1	-29900.6
$-\Delta_c u°$ (liq) /$(J\cdot g^{-1})$	29909.0±4.1				

TABLE S4. G3MP2 Total Energies at 0 K and Enthalpies at 298.15 K (in Hartree) of the Molecules Studied in This Work

Compounds	G3MP2		$\Delta_f H^{\circ}_{m}$ exp.gas
	E_0	H_{298}	
N-phenylanthranilic acid	-706.138053	-706.123769	---
tolfenamic acid	-1204.540973	-1204.523693	---
flufenamic acid	-1042.885038	-1042.867069	---
niflumic acid	-1058.931519	-1058.913800	---
diphenylamine	-517.761460	-517.749828	---
benzene	-231.829758	-231.824309	82.6±0.7
benzoic acid	-420.200783	-420.192542	-294.0±2.2
2-aminobenzoic acid	-475.489945	-475.480351	-296.0±1.3
aniline	-287.113824	-287.106878	87.1±1.1
toluene	-271.068985	-271.061629	50.5±0.5
chlorobenzene	-690.992623	-690.986059	52.0±1.3
(trifluoromethyl)benzene	-568.576824	-568.567832	-581.0
1,3-di-chlorobenzene	-1150.154362	-1150.146619	25.7±2.1
chloromethane	-499.573650	-499.569671	-81.9±0.5
1-fluoropropane	-218.043288	-218.037136	-285.9±2.2
methane	-40.422100	-40.418284	-74.9±0.4
ethane	-79.651199	-79.646714	-83.8±0.3
ammonia	-56.470142	-56.466333	-46.0±0.4
methanol	-115.552221	-115.547932	-201.5±0.2

Experimental data from:

Pedley, J. P.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*, 2nd Ed. Chapman and Hall: London. **1986**.

Cox, J.D.; Wagman, D.D.; Medvedev, V.A., *CODATA Key Values for Thermodynamics*, Hemisphere Publishing Corp., New York, **1984**.

TABLE S5. Reactions involved for determination of enthalpies of formation of compounds studied in this work.

We calculated enthalpies of formation of diphenylamine and fenamates using atomization reactions:

N-phenylanthranilic acid	$C_{13}H_{11}O_2N$ = 13 C + 11 H + N2
tolfenamic acid	$C_{14}H_{12}Cl_1N_1O_2$ = 14 C + 12 H + 1 Cl + 1 N + 2 O
flufenamic acid	$C_{14}H_{10}F_3N_1O_2$ = 14 C + 12 H + 3 F + 1 N + 2 O
niflumic acid	$C_{13}H_9F_3N_2O_2$ = 13 C + 9 H + 3 F + 2 N + 2 O
diphenylamine	$C_{12}H_{11}N$ = 12 C + 11 H + N

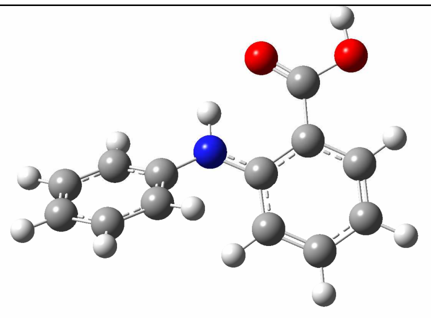
as well as on the basis of the selected bond separation reactions:

N-phenylanthranilic acid	$C_{13}H_{11}O_2N$ + 2 CH_4 = Benzoic acid + Aniline + C_2H_6
	$C_{13}H_{11}O_2N$ + 33 CH_4 = NH_3 + 2 CH_3OH + 22 C_2H_6
tolfenamic acid	$C_{14}H_{12}Cl_1N_1O_2$ + 2 Benzene + 2 CH_4 = Aniline + Benzoic acid + Toluene + ChloroBenzene + C_2H_6
	$C_{14}H_{12}Cl_1N_1O_2$ + 35 CH_4 = CH_3Cl + NH_3 + 2 CH_3OH + 23 C_2H_6
flufenamic acid	$C_{14}H_{10}F_3N_1O_2$ + 2 CH_4 = Aminobenzoic acid + (Trifluoromethyl)benzene + C_2H_6
	$C_{14}H_{10}F_3N_1O_2$ + 31 CH_4 = 3 C_3H_7F + NH_3 + 2 CH_3OH + 17 C_2H_6
niflumic acid	$C_{13}H_9F_3N_2O_2$ + 32 CH_4 = 3 C_3H_7F + 2 NH_3 + 2 CH_3OH + 17 C_2H_6
diphenylamine	$C_{12}H_{11}N$ + CH_4 = Aniline + Toluene
	$C_{12}H_{11}N$ + 28 CH_4 = NH_3 + 20 C_2H_6

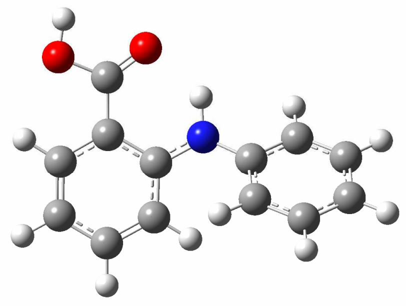
Table S6. Conformational population analysis of N-phenyl-anthranilic acid (in kJ/mol)

Conformer	ΔG	$\exp^{(-\Delta G/RT)}$	x_i	$\Delta_f H^o$ AT	$\Delta_f H^o$ BS$_1$	$\Delta_f H^o$ BS$_2$
k11	0.00	1.00	0.496394	-187.4	-178.8	-178.2
k12	0.00	1.00	0.496394	-187.4	-178.8	-178.2
k21	12.23	0.01	0.003568	-173.0	-164.4	-163.8
k22	12.23	0.01	0.003568	-173.0	-164.4	-163.8
k31	23.50	0.00	0.000038	-164.3	-155.7	-155.1
k32	23.50	0.00	0.000038	-164.3	-155.7	-155.1
				-187.3	-178.7	-178.1

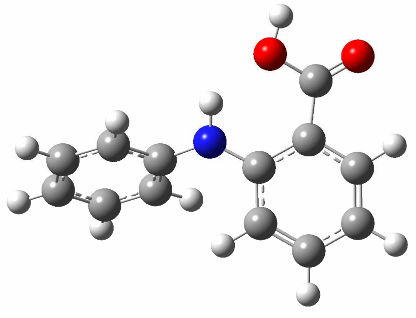
Most stable conformations of of N-phenyl-anthranilic acid and their relative stabilities (in kJ/mol)



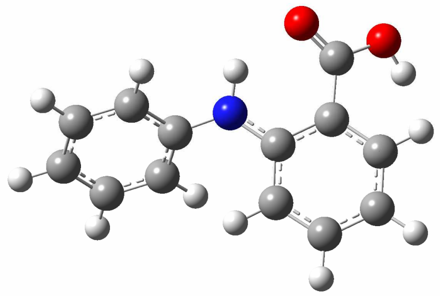
k11(0.00)



k12 (0.00)



k21 (14.4)



k31 (23.1)

TABLE S7. Thermochemical data at T = 298.15 K (p° = 0.1MPa) used for calculations of the grop contributions listed in Table 6, kJ·mol^{-1}

Compounds	$\Delta_{\mathrm{l}}^{\mathrm{g}}H_{\mathrm{m}}$ [a]	Ref.
Benzene	33.9	1
Methylbenzene	38.1	1
Pyridine	40.2	1
1,2-Dimethylbenzene	43.9	1
Chlorobenzene	41.0	1
1-Chloro-2-methylbenzene	46.1 ± 0.5	2
(Trifluoromethyl)benzene	37.7	1
Aniline	55.8	1
2-Methylaniline	57.9 ± 0.24	3
Benzoic acid[a]	75.1	4,5,6
2-Aminobenzoic acid	87.0 ± 0.8	2

[a] For the solid compounds the vaporization enthalpy was calculated by following equation:

$$\Delta_{\mathrm{l}}^{\mathrm{g}}H_{m}^{0} = \Delta_{\mathrm{cr}}^{\mathrm{g}}H_{\mathrm{m}}^{0} - \Delta_{\mathrm{cr}}^{\mathrm{l}}H_{\mathrm{m}}^{0}$$

(1) Majer, V.; Svoboda, V. *Enthalpies of Vaporization of Organic Compounds: A Critical Review and Data Compilation*, Blackwell Scientific Publications, Oxford, **1985**, 300.

(2) S. P. Verevkin. – paper in preparation.

(3) Steele, W.V.; Chirico, R.D.; Nguyen, A.; Knipmeyer, S.E. *J. Chem. Thermodyn.*, **1994**, *26*, 515-544.

(4) Ribeiro Da Silva, M.A.V.; Monte, M.J.S. *Thermochimica Acta*, **1990**, *171*, 169.

(5) Andon, R.J.L.; Connett, J.E. *Thermochim. Acta*, **1980**, *42*, 241-247.

(6) Sorai, M.; Kaji, K.; Kaneko, Y. *J. Chem. Thermodyn.* **1992**, *24(2)*, 167-180.

Table S8. Group-additivity procedure for fenamates studied in this work.

The detailed summation of increments for each compound under study is given in Table S7. All group-additivity values (GAVs) were calculated based on the data given in Tables 6 and S6.

Diphenylamine.

N-$(Cb)_2$(H) increment have been calculated by difference between experimental vaporization enthalpy of diphenylamine determined in this work and ten Cb-$(Cb)_2$(H) increments determined earlier.

Γ_i (N-$(Cb)_2$(H)) = $\Delta_l^g H_m$ (exp)(diphenylamine) – 10× Γ_i (Cb-$(Cb)_2$(H))

$\Delta_l^g H_m$ (calc)(diphenylamine) = 1× Γ_i (N-$(Cb)_2$(H)) + 10× Γ_i (Cb-$(Cb)_2$(H))

N-Phenylanthranilic acid.

For the N-phenylanthranilic acid description three following increments have been introduced using experimental data (Table S7): Cb-$(Cb)_2$(COOH), ortho (NH_2-COOH), (Anthranilic) (Table 6). All fenamate molecules have intramolecular hydrogen bond between the carbonyl group of the carboxyl acid moiety and the imino group that bridges the two six-membered rings. This feature of the fenamate molecules have been taken into account by ortho (NH_2-COOH) increment. The last one increment is a fit parameter that includes all conformational strains in fenamate molecules. This increment has been applied for all compounds except diphenylamine.

Γ_i (Cb-$(Cb)_2$(COOH)) = $\Delta_l^g H_m$ (exp)(benzoic acid) – 5× Γ_i (Cb-$(Cb)_2$(H))

Γ_i (ortho (NH_2-COOH)) = $\Delta_l^g H_m$ (exp)(2-aminobenzoic acid) + $\Delta_l^g H_m$ (exp)(benzene) – $\Delta_l^g H_m$ (exp)(benzoic acid) – $\Delta_l^g H_m$ (exp)(aniline)

Γ_i (Anthranilic) = $\Delta_l^g H_m$ (exp)(N-phenylanthranilic acid) – 9× Γ_i (Cb-$(Cb)_2$(H)) – 1× Γ_i (N-$(Cb)_2$(H)) – 1× Γ_i (Cb-$(Cb)_2$(COOH)) – 1× Γ_i (ortho (NH_2-COOH))

$\Delta_l^g H_m$ (calc)(N-phenylanthranilic acid) = 9× Γ_i (Cb-$(Cb)_2$(H)) + 1× Γ_i (N-$(Cb)_2$(H)) + 1× Γ_i (Cb-$(Cb)_2$(COOH)) + 1× Γ_i (ortho (NH_2-COOH)) + 1× Γ_i (Anthranilic)

Flufenamic and niflumic acids.

To estimate the vaporization enthalpies of the flufenamic and niflumic acids one additional increment Cb-$(Cb)_2(CF_3)$ have been introduced. In niflumic acid the first benzene ring is replaced on pyridine ring thereby calculation of vaporization enthalpy for this compound have been corrected by Nb-$(Cb)_2$ increment.

Γ_i (Cb-$(Cb)_2(CF_3)$) = $\Delta_l^g H_m$ (exp)((trifluoromethyl)benzene) – 5× Γ_i (Cb-$(Cb)_2$(H))

Γ_i (Nb-$(Cb)_2$) = $\Delta_l^g H_m$ (exp)(pyridine) – 5× Γ_i (Cb-$(Cb)_2$(H))

$\Delta_l^g H_m$ (calc)(flufenamic acid) = 8× Γ_i (Cb-$(Cb)_2$(H)) + 1× Γ_i (N-$(Cb)_2$(H)) + 1× Γ_i (Cb-$(Cb)_2$(COOH)) + 1× Γ_i (ortho (NH_2-COOH)) + 1× Γ_i (Anthranilic) + 1× Γ_i (Cb-$(Cb)_2(CF_3)$)

$\Delta_l^g H_m$ (calc)(niflumic acid) = 7× Γ_i (Cb-$(Cb)_2$(H)) + 1× Γ_i (N-$(Cb)_2$(H)) + 1× Γ_i (Cb-$(Cb)_2$(COOH)) + 1× Γ_i (ortho (NH_2-COOH)) + 1× Γ_i (Anthranilic) + 1× Γ_i (Cb-$(Cb)_2(CF_3)$) + 1× Γ_i (Nb-$(Cb)_2$)

Mefenamic acid.

Two additional interactions must be taken into account in mefenamic acid molecules. There are ortho interactions between two methyl groups in the second benzene ring and ortho interactions between methyl and amino groups. Thus the following additional increments have been introduced: ortho (CH_3- CH_3), ortho(NH_2- CH_3).

Γ_i (ortho (CH_3-CH_3)) = $\Delta_l^g H_m$ (exp)(1,2-dimethylbenzene) + $\Delta_l^g H_m$ (exp)(benzene) – 2×$\Delta_l^g H_m$ (exp)(methylbenzene)

Γ_i (ortho(NH_2-CH_3)) = $\Delta_l^g H_m$ (exp)(2-methylaniline) + $\Delta_l^g H_m$ (exp)(benzene) – $\Delta_l^g H_m$ (exp)(methylbenzene) – $\Delta_l^g H_m$ (exp)(aniline)

$\Delta_l^g H_m$ (calc)(mefenamic acid) = 7× Γ_i (Cb-(Cb)$_2$(H)) + 2× Γ_i (Cb-(Cb)$_2$(C)) 1× Γ_i (N-(Cb)$_2$(H)) + 1× Γ_i (Cb-(Cb)$_2$(COOH)) + 1× Γ_i (ortho (NH$_2$-COOH)) + 1× Γ_i (Anthranilic) + 1× Γ_i (ortho (CH$_3$- CH$_3$)) + 1× Γ_i (ortho(NH$_2$- CH$_3$))

Tolfenamic acid

The tolfenamic acid as the previous has two substituents in the second benzene ring located in ortho position. This ortho interaction also has been introduced by ortho (CH$_3$-Cl) increment.

Γ_i (ortho(CH$_3$-Cl)) = $\Delta_l^g H_m$ (exp)(1-chloro-2-methylbenzene) + $\Delta_l^g H_m$ (exp)(benzene) − $\Delta_l^g H_m$ (exp)(methylbenzene) − $\Delta_l^g H_m$ (exp)(chlorobenzene)

$\Delta_l^g H_m$ (calc)(tolfenamic acid) = 7× Γ_i (Cb-(Cb)$_2$(H)) + 1× Γ_i (Cb-(Cb)$_2$(C)) 1× Γ_i (N-(Cb)$_2$(H)) + 1× Γ_i (Cb-(Cb)$_2$(COOH)) + 1× Γ_i (ortho (NH$_2$-COOH)) + 1× Γ_i (Anthranilic) + 1× Γ_i (Cb-(Cb)$_2$(Cl)) + 1× Γ_i (ortho(NH$_2$-CH$_3$)) + 1× Γ_i (ortho(CH$_3$-Cl))

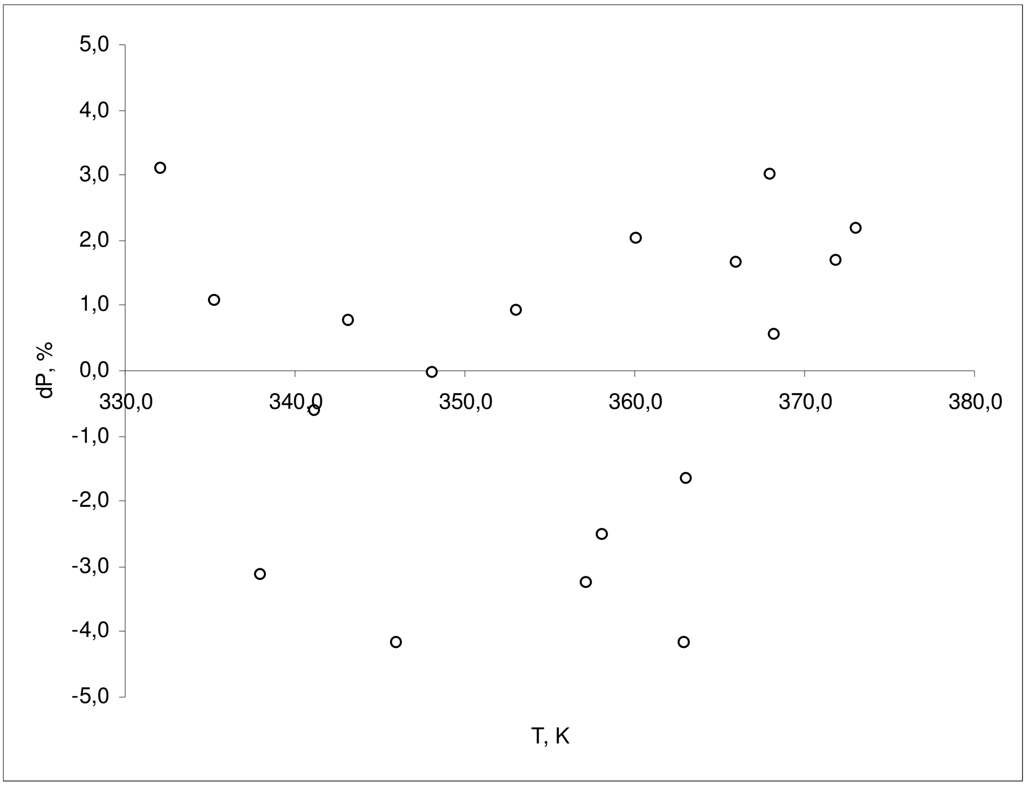


Figure S1. Fractional deviations (P-Pcalc) of the experimental vapor pressure P/Pa of the liquid diphenylamine from values Pcalc/Pa obtained by eq 2 as a function of temperature T/K.

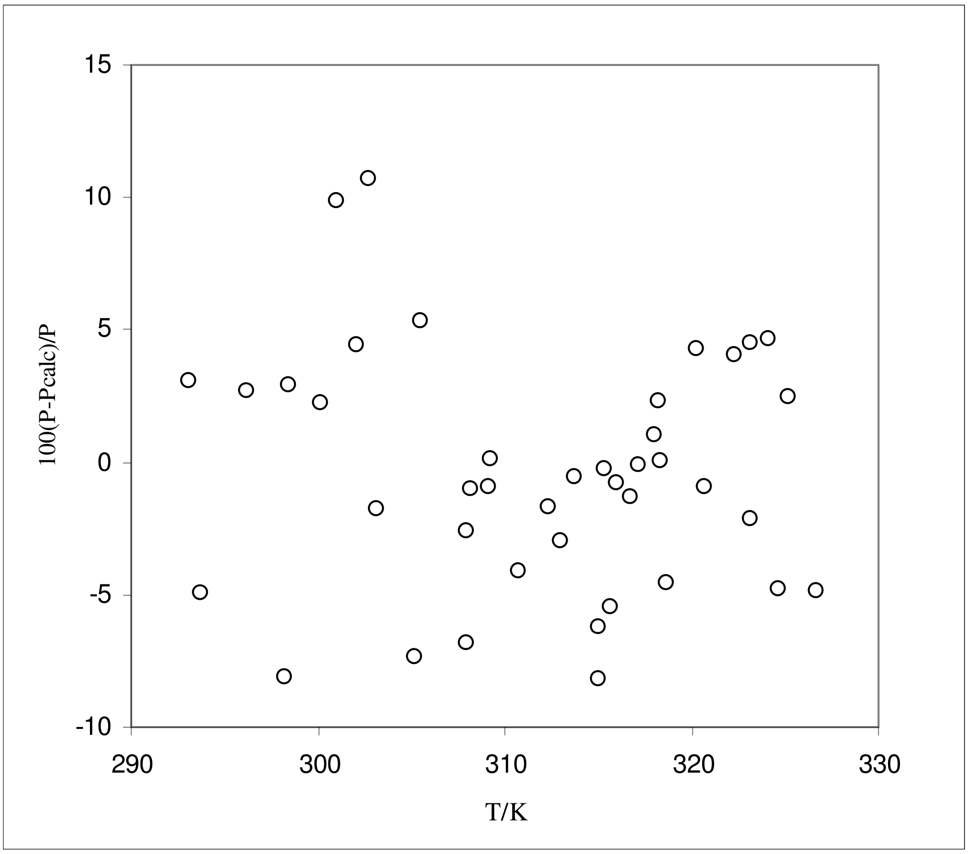


Figure S2. Fractional deviations (P-Pcalc) of the experimental vapor pressure P/Pa of the SOLID diphenylamine from values Pcalc/Pa obtained by eq 2 as a function of temperature T/K.