

Thermochemistry of Uracils. Experimental and Computational Enthalpies of Formation of 5,6-Dimethyl-, 1,3,5-Trimethyl-, and 1,3,5,6-Tetramethyluracils

Rafael Notario,^{†,*} Vladimir N. Emel'yanenko,[‡] María Victoria Roux,[†] Francisco Ros,[§] Sergey P. Verevkin,[‡] James S. Chickos,[⊥] and Joel F. Liebman^{||}

[†]Instituto de Química Física "Rocasolano", CSIC, Serrano 119, 28006 Madrid, Spain

[‡]Department of Physical Chemistry, University of Rostock, Dr.-Lorenz-Weg 1, 18059 Rostock, Germany

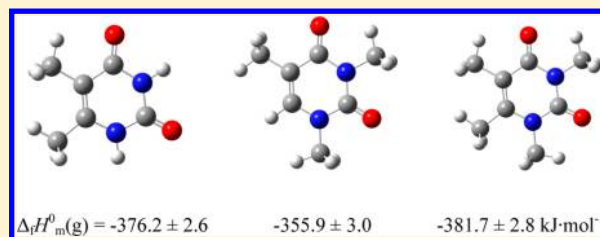
[§]Instituto de Química Médica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

[⊥]Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, Missouri 63121-4499, United States

^{||}Department of Chemistry and Biochemistry, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, Maryland 21250-1000, United States

S Supporting Information

ABSTRACT: We describe in the current paper an experimental and computational study of three methylated uracils, in particular, the 5,6-dimethyl-, 1,3,5-trimethyl-, and 1,3,5,6-tetramethyl derivatives. The values of the standard ($p^0 = 0.1$ MPa) molar enthalpies of formation in the gas phase at $T = 298.15$ K have been determined. The energies of combustion were measured by static bomb combustion calorimetry, and from the results obtained, the standard molar enthalpies of formation in the crystalline state at $T = 298.15$ K were calculated. The enthalpies of sublimation were determined using the transpiration method in a saturated N_2 stream. Values of $-(376.2 \pm 2.6)$, $-(355.9 \pm 3.0)$, and $-(381.7 \pm 2.8)$ $\text{kJ}\cdot\text{mol}^{-1}$ for the gas-phase enthalpies of formation at $T = 298.15$ K of 5,6-dimethyluracil, 1,3,5-trimethyluracil, and 1,3,5,6-tetramethyluracil, respectively, were obtained from the experimental thermochemical study. An extended theoretical study with the G3 and the G4 quantum-chemical methods has been carried out for all the possible methylated uracils. There is a very good agreement between experimental and calculated enthalpies of formation for the three derivatives studied. A Free–Wilson analysis on G4-calculated enthalpies of formation has been carried out, and the contribution of methylation in the different positions of the uracil ring has been estimated.



1. INTRODUCTION

Uracil (2,4(1*H*,3*H*)-pyrimidinedione) and many of its derivatives are well-known for their importance in biochemistry, molecular biology and medicine. In the particular, uracil and its 5-methyl derivative (more commonly called thymine) are primary components of nucleic acids (RNA and DNA respectively) while other methylation patterns of modified uracils (*O*-sugar and *N*-) and the *C*-nucleoside pseudouracil are minor, but indisputable, components of RNA.¹ Uracil, taken here as pyrimidine-2,4-dione, is a substructure of the three ring vitamin riboflavin and thereby numerous coenzymes, as well as part of the two ring non-nucleic acid purines, xanthine, uric acid, and their methylated counterparts theobromine, theophylline and caffeine. Substituted uracils of considerable medical import include the anticancer compound 5-fluorouracil, the anti-AIDS/HIV regimen, 5'-azido-5-deoxythymidine (more commonly known as AZT or zidovudine). Numerous benzouracils, more commonly known as quinazolinones, also exhibit diverse biomedical activity. Uracil derivatives,

including the aforementioned purines, long have also been of enthusiastic interest to calorimetrists.² Measurements of the enthalpy of formation of uric acid appear in the literature some 130 years ago and the earliest measurement for the parent barbituric acid and thymine are but 110 and 120 years old respectively.³ Bypassing results from the intervening century, we find calorimetric studies of diversely substituted uracils, e.g., refs 4–7, barbituric acid derivatives, e.g., refs 8–10, caffeine, e.g., ref 11, and the parent 2,4-quinazolinone, ref 12, were reported within this past decade. As members of this thermochemical community, we describe in the current paper our experimental and computational studies of methylated uracils, in the particular, the 5,6-dimethyl-, 1,3,5-trimethyl- and 1,3,5,6-tetramethyl derivatives, species 1, 2, and 3 respectively (See Figure 1).

Received: November 8, 2012

Revised: December 10, 2012

Published: December 10, 2012

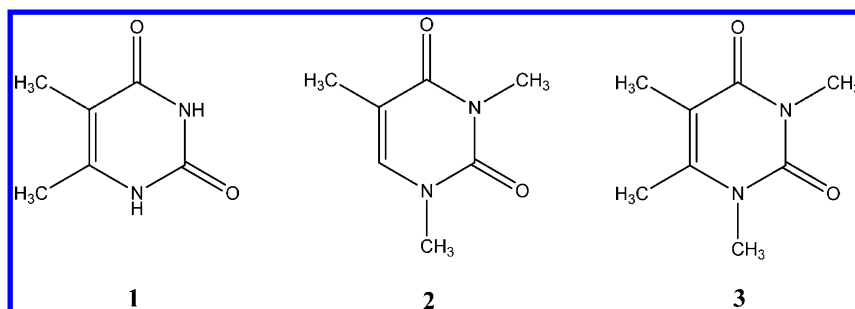


Figure 1. Structural formulas of 5,6-dimethyluracil (1), 1,3,5-trimethyluracil (2), and 1,3,5,6-tetramethyluracil (3).

Table 1. Results for Typical Combustion Experiments at $T = 298.15$ K ($p^\circ = 0.1$ MPa) of 5,6-Dimethyluracil^a

$m(\text{substance})/\text{g}^b$	0.35129	0.557738	0.349194	0.544652	0.56279	0.582406
$m'(\text{cotton})/\text{g}^b$	0.001042	0.001327	0.001347	0.001203	0.001255	0.001214
$m''(\text{polyethylene})/\text{g}^b$	0.310961	0.302507	0.374796	0.348888	0.313078	0.355321
$\Delta T_c/\text{K}^c$	1.4775	1.75051	1.67411	1.87528	1.78926	1.95001
$(\epsilon_{\text{calor}})(-\Delta T_c)/\text{J}$	−21980.7	−26042.2	−24905.6	−27898.4	−26618.6	−29010
$(\epsilon_{\text{cont}})(-\Delta T_c)/\text{J}$	−23.62	−28.87	−27.3	−31.05	−29.39	−32.64
$\Delta U_{\text{decomp}}(\text{HNO}_3)/\text{J}$	57.93	72.87	63.61	77.35	73.46	79.14
$\Delta U_{\text{corr}}/\text{J}^d$	9.65	13.09	10.65	13.6	13.32	14.41
$-m'\Delta_c u'/\text{J}$	17.66	22.49	22.82	20.38	21.27	20.57
$-m''\Delta_c u''/\text{J}$	14415.31	14023.41	17374.53	16173.51	14513.45	16471.72
$\Delta_c u^\circ(\text{cr})/(\text{J}\cdot\text{g}^{-1})$	−21360.5	−21406.5	−21367.1	−21380	−21369.4	−21388.6
$-\Delta_c u^\circ(\text{cr})/(\text{J}\cdot\text{g}^{-1})$						
						21378.7 ± 6.9

^aFor the definition of the symbols, see ref 24. $T_h = 298.15$ K; $V(\text{bomb}) = 0.32$ dm³; $p^\circ(\text{gas}) = 3.04$ MPa; $m^\circ(\text{H}_2\text{O}) = 1.00$ g. ^bMasses obtained from apparent masses. ^c $\Delta T_c = T^\circ - T^\circ + \Delta T_{\text{corr}}$; $(\epsilon_{\text{cont}})(-\Delta T_c) = (\epsilon_{\text{cont}})(T^\circ - 298.15 \text{ K}) + (\epsilon_{\text{cont}})(298.15 \text{ K} - T^\circ + \Delta T_{\text{corr}})$. ^d ΔU_{corr} , the correction to standard states, is the sum of items 81 to 85, 87 to 90, 93, and 94 in ref 24. $\Delta_c u^\circ(\text{polyethylene}) = -(46357.3 \pm 3.6)$ J·g^{−1}; $\epsilon = 14886.0 \pm 1.0$ J·K^{−1}.

2. EXPERIMENTAL DETAILS

2.1. Materials and Purity Control. Column chromatography was performed using Merck silica gel 60. Melting points were recorded on a capillary tube Mettler-Toledo MP70 instrument. ¹H NMR spectra were recorded on a Bruker Avance-300 spectrometer. The purity of the compounds was determined by HPLC on a Waters Alliance 2690 chromatograph using a reverse phase SunFire C18 column (3.5 μm , 4.6 \times 50 mm) and multiple wavelength detection (230–400 nm), and by differential scanning calorimetry (DSC), using the fractional fusion technique.¹³ The latter indicated that the mole fraction of impurities in the compounds was less than 0.0001. The standards used for DSC calibration were hexafluorobenzene, 99.9% purity, supplied by Aldrich; benzoic acid NIST standard reference sample 39j; and high-purity indium (mass fraction: > 0.99999) and tin (mass fraction > 0.99999) supplied by Perkin-Elmer.

5,6-Dimethyluracil (5,6-Dimethyl-2,4(1H,3H)-pyrimidinedione, CAS 26305-13-5, 1). A commercial sample was recrystallized twice from hot aqueous ethanol (90%): HPLC (MeCN/0.05% aq. TFA 2–95%, t_G 10 min) t_R 3.00 min, 100.0%.

1,3,5-Trimethyluracil (1,3,5-Trimethyl-2,4(1H,3H)-pyrimidinedione, CAS 4401-71-2, 2). It was prepared by a modification of a literature procedure.¹⁴ A mixture of 5-methyluracil (12.0 g, 95 mmol) and trimethyl phosphate (60 mL, 520 mmol) was heated under reflux (28 h). Excess trimethyl phosphate was removed under reduced pressure. A portion (8.3 g) of the crude product was chromatographed on a silica gel column (400 g) using dichloromethane and an increasing amount of methanol (0–1%) for elution and giving 1,3,5-trimethyluracil (5.5 g, overall 62%): mp 154.5–155.4 °C (lit.¹⁴ mp 153–155

°C); ¹H NMR (CDCl₃) δ 1.928 (d, 3 H, J 1.2 Hz), 3.360 (s, 3 H), 3.373 (s, 3 H), 6.985 (d, 1 H, J 1.2 Hz); HPLC (MeCN/0.05% aq. TFA 2–95%, t_G 10 min) t_R 3.58 min, 100.0%.

1,3,5,6-Tetramethyluracil (1,3,5,6-Tetramethyl-2,4(1H,3H)-pyrimidinedione, CAS 59264-09-4, 3). 5,6-Dimethyluracil (25.2 g, 180 mmol) was added to a solution of sodium ethoxide in ethanol, prepared from sodium (4.3 g, 190 mmol) and absolute ethanol (190 mL), and the mixture was vigorously stirred in a dry atmosphere (CaCl₂) at room temperature (30 min). Iodomethane (35 mL, 560 mmol) was then added and the mixture was heated under reflux (3 h). Ethanol and excess iodomethane were evaporated under reduced pressure at room temperature. To the remaining paste a fresh batch of sodium ethoxide solution (Na 4.3 g, abs. EtOH 190 mL) was added and the mixture was vigorously stirred (2 h). After adding a second portion of iodomethane (35 mL), the mixture was heated (4 h reflux) and the resulting slurry was further stirred overnight at room temperature, at which time a homogeneous solution was obtained. The solvent was removed and the remainder was dissolved in water (75 mL), repeatedly extracted with diethyl ether (10 \times 500 mL) and the combined ethereal extract was dried (Na₂SO₄). A portion (7.5 g) of the crude product was chromatographed on a silica gel column (350 g) using dichloromethane and an increasing amount of methanol (0–1%) for elution. Tetramethyluracil was isolated as a white solid (5.4 g, overall 42%): mp 136.7–137.5 °C (lit.¹⁵ mp 123–125.5 °C); ¹H NMR (CDCl₃) δ 1.990 (s, 3 H), 2.248 (s, 3 H), 3.359 (s, 3 H), 3.432 (s, 3 H); HPLC (MeCN/0.05% aq. TFA 2–95%, t_G 10 min) t_R 3.92 min, 100.0%.

2.2. Thermochemical Measurements. 2.2.1. Differential Scanning Calorimetry. The behavior of the samples as a function of temperature were studied by differential scanning calorimetry. A Perkin-Elmer Pyris 1 instrument equipped with

Table 2. Results for Typical Combustion Experiments at $T = 298.15$ K ($p^\circ = 0.1$ MPa) of 1,3,5-Trimethyluracil

$m(\text{substance})/\text{g}$	0.328719	0.424376	0.274175	0.568207	0.633139	0.7485
$m'(\text{cotton})/\text{g}$	0.001054	0.001148	0.00127	0.000992	0.001395	0.001395
$m''(\text{polyethylene})/\text{g}$	0.413174	0.36053	0.392924	0.26439	0.240166	0.275575
$\Delta T_c/\text{K}$	1.825	1.81826	1.67335	1.75277	1.78182	2.08101
$(\epsilon_{\text{calor}})(-\Delta T_c)/\text{J}$	-27167	-27066.6	-24909.5	-26091.7	-26524.2	-30977.9
$(\epsilon_{\text{cont}})(-\Delta T_c)/\text{J}$	-30.4	-30.23	-27.32	-28.85	-29.32	-35.45
$\Delta U_{\text{decomp}}(\text{HNO}_3)/\text{J}$	60.62	69.28	54.35	68.09	75.85	87.8
$\Delta U_{\text{corr}}/\text{J}$	10.98	11.7	9.68	12.58	13.25	15.97
$-m'\Delta_c u'/\text{J}$	17.86	19.45	21.52	16.81	23.64	23.64
$-m''\Delta_c u''/\text{J}$	19153.63	16713.2	18214.9	12256.41	11133.45	12774.91
$\Delta_c u^\circ(\text{cr})/(\text{J}\cdot\text{g}^{-1})$	-24197.9	-24231.4	-24205	-24228.3	-24177	-24196.4
$-\Delta_c u^\circ(\text{cr})/(\text{J}\cdot\text{g}^{-1})$				24205.9 \pm 8.5		

Table 3. Results for Typical Combustion Experiments at $T = 298.15$ K ($p^\circ = 0.1$ MPa) of 1,3,5,6-Tetramethyluracil

$m(\text{substance})/\text{g}$	0.610827	0.309367	0.203329	0.83117	0.590984	0.460723
$m'(\text{cotton})/\text{g}$	0.001134	0.001096	0.001049	0.001077	0.001152	0.001106
$m''(\text{polyethylene})/\text{g}$	0.26126	0.340983	0.407843	0.189342	0.273258	0.312852
$\Delta T_c/\text{K}$	1.88676	1.60664	1.62871	2.04918	1.89	1.78447
$(\epsilon_{\text{calor}})(-\Delta T_c)/\text{J}$	-28086.3	-23916.4	-24244.9	-30504.2	-28134.5	-26563.7
$(\epsilon_{\text{cont}})(-\Delta T_c)/\text{J}$	-31.54	-25.94	-26.6	-34.79	-31.55	-29.53
$\Delta U_{\text{decomp}}(\text{HNO}_3)/\text{J}$	74.36	56.14	53.16	88.99	76.75	68.69
$\Delta U_{\text{corr}}/\text{J}$	13.22	9.35	8.7	15.85	13.05	11.47
$-m'\Delta_c u'/\text{J}$	19.22	18.57	17.78	18.25	19.52	18.74
$-m''\Delta_c u''/\text{J}$	12111.31	15807.05	18906.5	8777.38	12667.5	14502.97
$\Delta_c u^\circ(\text{cr})/(\text{J}\cdot\text{g}^{-1})$	-26029.9	-26024.8	-25994.3	-26033.8	-26040.1	-26027.2
$-\Delta_c u^\circ(\text{cr})/(\text{J}\cdot\text{g}^{-1})$				26025.0 \pm 6.5		

an intracooler unit was used to monitor purity, to study the fusion process and the possible existence of phase transitions in the solid sample. The apparatus was previously calibrated in temperature and energy with reference materials. Temperature and power scales were calibrated^{16–18} at heating rates of 0.04 and 0.17 K·s⁻¹. The temperature scales were calibrated by the melting temperature of the high-purity reference materials, hexafluorobenzene, tin, and indium.¹⁹ The power scales were calibrated with high-purity indium.¹⁹

Thermograms of samples hermetically sealed in aluminum pans were recorded in a nitrogen atmosphere. All masses were measured on a Mettler AT21 microbalance with a detection limit of 1×10^{-6} g, before and after the experiments to confirm that no product had volatilized. Experiments where any mass loss was observed were rejected.

After calibration, several runs with high-purity benzoic acid and indium were performed under the same conditions as the experimental determinations. The accuracies associated with measurements of temperature and enthalpy of fusion were calculated as the percentage deviation of the experimental data with respect to the values given in the literature;²⁰ in all cases the deviations were lower than 0.2 and 2.0% for temperature and enthalpy determinations, respectively.²⁰

For determination of purity, temperature, and enthalpy of fusion, a heating rate of 0.04 K·s⁻¹ was used, and seven samples weighing 1–2 mg were recorded. A fresh sample was used for each run. Different scans at heating rates of 0.04 and 0.17 K·s⁻¹ were performed to determine the possible existence of phase transitions in the sample over the temperature range from $T = 268$ K to its melting temperature.

2.2.2. Combustion Calorimetry. An isoperibol bomb calorimeter was used for the measurement of energy of combustion of the uracils studied. Results from combustion experiments are given in Tables 1 to 3. The detailed procedure

has been described previously.²¹ We used small polyethylene pieces as the auxiliary material (Table 1) in order to obtain complete combustion. The combustion products were examined for carbon monoxide (Dräger tube) and unburned carbon, but none was detected. The energy equivalent of the calorimeter 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).²² The sample masses were reduced to vacuum, using the densities of the sample and auxiliary compounds (Table S1 of the Supporting Information). The atomic weights used were those recommended by the IUPAC Commission in 2009.²³ Conventional procedures were applied for converting the energy of the actual combustion process to that of the isothermal process, and reducing to standard states.²⁴ To derive $\Delta_f H_m^\circ$ (l) from the molar enthalpy of combustion $\Delta_c H_m^\circ$, molar enthalpies of formation of H₂O(l), $-(285.830 \pm 0.042)$ kJ·mol⁻¹, and CO₂ (g), $-(393.51 \pm 0.13)$ kJ·mol⁻¹, have been used as assigned by CODATA.²⁵ The total uncertainty was calculated according to the guidelines presented by Olofsson.²⁶ The uncertainty assigned to $\Delta_f H_m^\circ$ is twice the overall standard deviation and includes the uncertainties from calibration, from the combustion energies of the auxiliary materials, and the uncertainties of the enthalpies of formation of the reaction products H₂O and CO₂.

2.2.3. Vapor Pressure Measurements. Vapor pressures and enthalpies of sublimation, $\Delta_{\text{cr}}^\circ H_m$, of the uracils were determined using the method of transpiration in a saturated stream of nitrogen. The method has been described in detail before^{27,28} and has proven to give results in agreement with other established techniques. The temperature dependence of vapor pressure was used to determine the enthalpies of sublimation of the pure substances. A sample of approximately 0.5 g of the sample was mixed with glass beads and placed in a

thermostated U-tube of length 10 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 in order 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 in order 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 $0.5 \text{ dm}^3 \cdot \text{h}^{-1}$. The upper limit for our apparatus was a flow rate of $10.5 \text{ dm}^3 \cdot \text{h}^{-1}$. Thus, we carried out the experiments in the using flow rates ranging from 4 to $9 \text{ dm}^3 \cdot \text{h}^{-1}$ 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 weighing ($\pm 0.0001 \text{ g}$).

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 Dalton's 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:

$$p_i^{\text{sat}} = m_i R T_a / V M_i; \quad V = V_{N_2} + V_i \quad (V_{N_2} \gg V_i) \quad (1)$$

where $R = 8.31447 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$; 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. Results from measurements of the vapor pressures using the transpiration method are collected in Table 4.

3. COMPUTATIONAL DETAILS

Standard *ab initio* molecular orbital calculations²⁹ were performed with the Gaussian 09 series of programs.³⁰ The energies of the compounds studied were calculated using two different theoretical model chemistry Gaussian-n methods, at the G3³¹ and G4³² levels. Details on these methods have been given in a previous paper.¹⁰

Energies at $T = 0 \text{ K}$ and enthalpies at $T = 298 \text{ K}$, for the three uracils studied, are collected in Table S2 of the Supporting Information.

4. RESULTS AND DISCUSSION

4.1. Molecular Structures. The crystal structure of 1,3,5-trimethyluracil was determined by X-ray diffraction,³³ but to our knowledge there are not experimental determinations of the molecular structures for the other two methylated uracils studied in this work. 1,3,5-Trimethyluracil crystallizes in monoclinic space group $P2_1/c$, $Z = 4$. In the crystals the molecules are hydrogen bonded to form infinite C–H \cdots O chains. The molecules in the crystal are 2-fold disordered.

There is only one theoretical study³⁴ on the geometry of 5,6-dimethyluracil, but at a very low level of theory, HF/4–21G. The B3LYP/6-31G(2df,p)-optimized structures of 5,6-dimethyluracil (1), 1,3,5-trimethyluracil (2), and 1,3,5,6-tetramethyluracil (3), are shown in Figure 2. In the three cases, the rings are planar. Bond distances and bond angles optimized for the

Table 4. Results from Measurements of Vapor Pressure p using the Transpiration Method

$T, ^\circ\text{K}$	$m, ^b \text{ mg}$	$V_{N_2}, ^c \text{ dm}^3$	gas-flow, dm^3/h	$p, ^d \text{ Pa}$	$(p_{\text{exp}} - p_{\text{calc}}), \text{ Pa}$	$\Delta_{\text{cr}}^{\text{g}} H_m, ^e \text{ kJ} \cdot \text{mol}^{-1}$
5,6-Dimethyluracil						
$\Delta_{\text{cr}}^{\text{g}} H_m (298.15 \text{ K}) = (132.4 \pm 1.4) \text{ kJ} \cdot \text{mol}^{-1}$						
$\ln(p/\text{Pa}) = \frac{334.01}{R} - \frac{140267.13}{RT} - \frac{26.4}{R} \ln\left(\frac{T}{298.15}\right)$						
416.0	6.4	491.6	5.54	0.23	−0.01	129.29
427.2	10.2	269.3	5.54	0.66	0.04	128.99
429.6	10.0	233.4	5.54	0.75	−0.02	128.93
436.5	10.1	129.0	5.54	1.37	0.01	128.74
440.8	17.2	156.8	5.75	1.93	0.00	128.63
446.6	16.6	93.8	5.54	3.11	0.07	128.48
450.9	29.2	122.5	5.75	4.19	−0.04	128.36
456.7	8.7	23.9	5.54	6.38	−0.14	128.21
1,3,5-Trimethyluracil						
$\Delta_{\text{cr}}^{\text{g}} H_m (298.15 \text{ K}) = (94.9 \pm 0.6) \text{ kJ} \cdot \text{mol}^{-1}$						
$\ln(p/\text{Pa}) = \frac{311.1}{R} - \frac{104038.1}{RT} - \frac{30.6}{R} \ln\left(\frac{T}{298.15}\right)$						
391.2	15.9	3.13	5.07	81.12	−3.03	92.07
386.9	17.4	4.61	5.32	60.25	−1.17	92.20
381.8	12.7	4.71	5.33	43.05	1.19	92.36
377.7	9.3	4.75	5.48	31.24	0.73	92.48
373.6	10.2	7.31	5.48	22.28	0.19	92.61
369.6	13.0	12.8	5.48	16.23	0.24	92.73
365.5	9.3	12.9	5.48	11.53	0.14	92.86
360.4	10.3	22.1	5.55	7.44	0.05	93.01
356.3	10.1	31.9	5.48	5.07	−0.10	93.14
352.3	18.6	83.4	5.55	3.57	−0.04	93.26
348.1	13.9	91.0	5.55	2.45	−0.01	93.39
1,3,5,6-Tetramethyluracil						
$\Delta_{\text{cr}}^{\text{g}} H_m (298.15 \text{ K}) = (101.7 \pm 0.9) \text{ kJ} \cdot \text{mol}^{-1}$						
$\ln(p/\text{Pa}) = \frac{328.1}{R} - \frac{111808.7}{RT} - \frac{33.9}{R} \ln\left(\frac{T}{298.15}\right)$						
369.7	10.1	16.6	3.96	8.92	−0.28	99.24
350.3	12.4	121.5	3.96	1.49	−0.03	99.90
361.5	21.8	70.5	3.96	4.52	0.10	99.52
364.6	11.2	28.0	3.96	5.84	−0.01	99.41
358.4	14.2	65.0	3.96	3.19	−0.12	99.62
366.6	10.0	20.1	3.96	7.27	0.24	99.34
374.0	10.8	11.8	3.96	13.38	0.04	99.09
371.4	43.9	56.4	3.96	11.39	0.72	99.18
377.9	10.4	8.11	3.96	18.75	0.22	98.96
382.0	11.1	6.20	3.96	26.18	0.21	98.82
386.2	13.0	5.34	3.96	35.58	−0.84	98.68
391.2	9.7	2.71	3.96	52.45	−1.49	98.51

^aTemperature of saturation. ^bMass of transferred sample condensed at $T = 293 \text{ K}$. ^cVolume of nitrogen used to transfer mass m of sample. ^dVapor pressure at temperature T calculated from m and the residual vapor pressure at the cooling temperature $T = 293 \text{ K}$.

three uracils are collected in Table S3 of the Supporting Information. Geometrical parameters for 5,6-dimethyluracil are compared in this Table with those obtained by X-ray diffraction for 5-ethyl-6-methyluracil that are available³⁵ in the literature.

4.2. Experimental Enthalpies of Formation in the Gas Phase. Table 5 summarizes the values of the standard molar enthalpies of combustion, $\Delta_{\text{cr}}^{\text{g}} H_m^0$, sublimation, $\Delta_{\text{cr}}^{\text{g}} H_m$, and formation in the crystalline, $\Delta_{\text{f}}^{\text{g}} H_m^0(\text{cr})$, and gaseous state, $\Delta_{\text{f}}^{\text{g}} H_m^0(\text{g})$ at $T = 298.15 \text{ K}$.

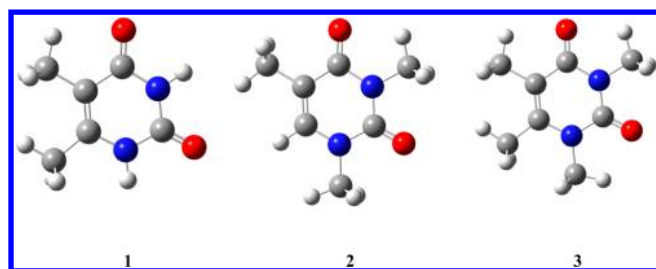


Figure 2. B3LYP/6-31G(2df,p)-optimized structures of 5,6-dimethyluracil (1), 1,3,5-trimethyluracil (2), and 1,3,5,6-tetramethyluracil (3).

Combustion experiments with 5,6-dimethyluracil (1), 1,3,5-trimethyluracil (2), and 1,3,5,6-tetramethyluracil (3) have been performed for the first time. There are in the literature some experimental determinations of vapor pressures for 1,3,5-trimethyluracil³⁷ and 1,3,5,6-tetramethyluracil.³⁸ In Figures 3 and 4 we have compared our values with the previous ones. Unfortunately the temperature ranges of ours and the literature studies are too different for a proper comparison, but at least the vapor pressures for both compounds agree qualitatively.

In our work we used the following equation:

$$R \ln p_i^{\text{sat}} = a + \frac{b}{T} + \Delta_{\text{cr}}^{\text{g}} C_p \ln \left(\frac{T}{T_0} \right) \quad (2)$$

for fitting to the experimental p, T data using a and b as adjustable parameters. T_0 appearing in eq 2 is an arbitrarily chosen reference temperature (which in this case is 298 K). Consequently, from eq 3 the expression for the enthalpy of sublimation at temperature T is:

$$\Delta_{\text{cr}}^{\text{g}} H_m(T) = -b + \Delta_{\text{cr}}^{\text{g}} C_p T \quad (3)$$

Values of $\Delta_{\text{cr}}^{\text{g}} C_p$ have been derived from the experimental isobaric molar heat capacities of the solid compounds, C_p^{cr} , calculated according to the group-additivity procedure in the similar way as in our previous works.^{8–10}

DSC studies with 5,6-dimethyluracil (1) and 1,3,5,6-tetramethyluracil (3) have been performed for the first time. No solid–solid phase transitions were observed over the temperature interval from $T = 268$ K to the melting temperature for the three uracils studied in this work. Experimental temperatures (taken as the DSC onset temperature) and enthalpies of fusion of the compounds are as follows: $T_{\text{fus}} = (574.0 \pm 0.3)$ K, $\Delta H_{\text{fus}} = (28.0 \pm 0.9)$ kJ·mol^{−1}, for 5,6-dimethyluracil; $T_{\text{fus}} = (427.5 \pm 0.3)$ K, $\Delta H_{\text{fus}} = (23.3 \pm 0.9)$ kJ·mol^{−1}, for 1,3,5-trimethyluracil; $T_{\text{fus}} = (409.7 \pm 0.3)$ K, $\Delta H_{\text{fus}} = (19.9 \pm 0.9)$ kJ·mol^{−1}, for 1,3,5,6-tetramethyluracil. Uncertainties were taken as the standard deviation of the mean. Enthalpy of fusion $\Delta H_{\text{fus}} = 16.1$ kJ·mol^{−1} at $T_{\text{fus}} = 428.65$ K, for 1,3,5-trimethyluracil (2), reported in ref 37, is significantly lower than our new experimental value. However, according to our experience, the uracil derivatives samples under study have

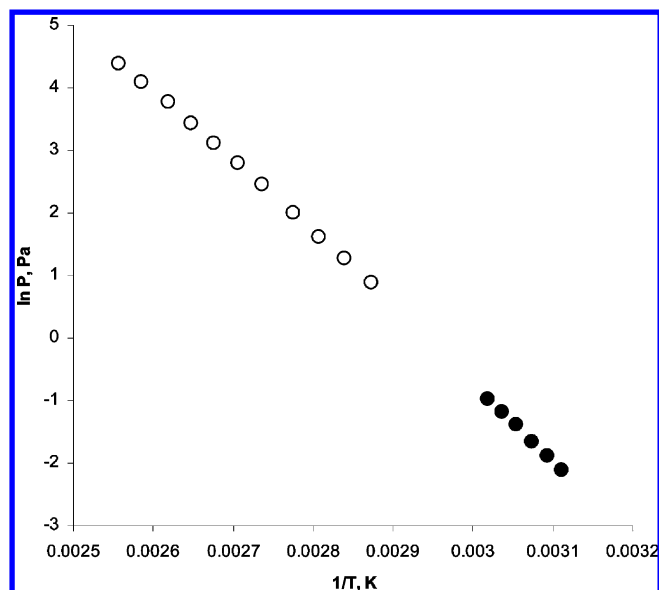


Figure 3. Comparison of experimental vapor pressures of 1,3,5-trimethyluracil: (○) this work; (●) ref 37.

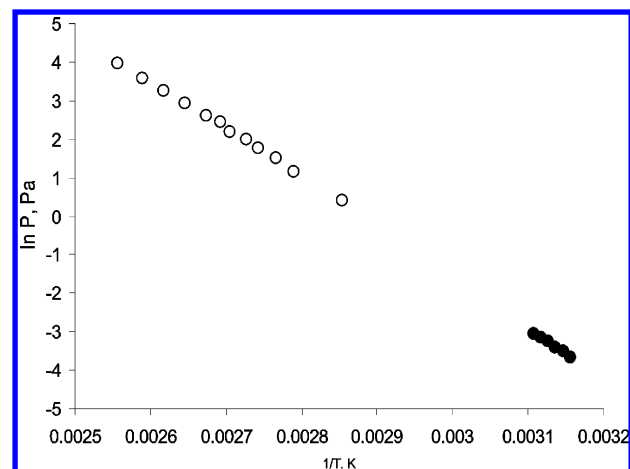


Figure 4. Comparison of experimental vapor pressures of 1,3,5,6-tetramethyluracil: (○) this work; (●) ref 38.

shown reproducible results only in the first melting run in the DSC. The second run with the sample usually resulted in a lower enthalpy of fusion, which perhaps due to incomplete recrystallization.

4.3. Theoretical Enthalpies of Formation in the Gas Phase. The standard procedure to obtain enthalpies of formation in Gaussian-n theories is through atomization reactions.^{39,40} The G3- and G4-calculated enthalpies of formation for the three uracils studied are collected in Table 6. As it can be seen, there is a very good agreement between experimental and G4-calculated enthalpies of formation for the

Table 5. Experimentally Determined Thermochemical Data at $T = 298.15$ K ($p^\circ = 0.1$ MPa) of the Uracils Studied (kJ·mol^{−1})

compounds	$\Delta_{\text{c}} H_m^\circ$ (cr)	$\Delta_{\text{f}} H_m^\circ$ (cr)	$\Delta_{\text{c}}^{\text{g}} H_m$	$\Delta_{\text{f}} H_m^\circ$ (g)
5,6-dimethyluracil	-2995.8 ± 2.0	-508.6 ± 2.2	132.4 ± 1.4	-376.2 ± 2.6
1,3,5-trimethyluracil	-3733.0 ± 2.7	-450.8 ± 2.9	94.9 ± 0.6 104.4 ± 1.5^a	-355.9 ± 3.0
1,3,5,6-tetramethyluracil	-4379.7 ± 2.4	-483.4 ± 2.6	101.7 ± 0.9 103.9^b	-381.7 ± 2.8

^aA value 103.5 ± 1.5 was reported in ref 37 and it was referred to the average temperature of experiment 326.4 K. We adjusted this value to the reference temperature 298.15 K. ^bValue measured over the temperature range 316.8–321.8 K, taken from ref 36.

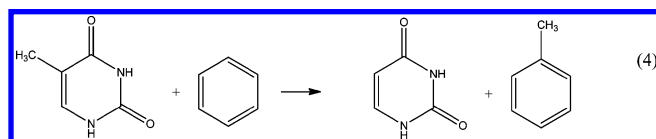
Table 6. Calculated and Experimental Enthalpies of Formation, $\Delta_f H_m^0(\text{g})$, for All Methyl-Substituted Uracils (All values in $\text{kJ}\cdot\text{mol}^{-1}$)

substituent	G3	G4	Free–Wilson	experimental
H	−299.2	−299.5	−299.8 ^a	−298.6 ± 1.2, ^b −298.7 ± 4.4, ^c −303.1 ± 2.3 ^d
1-Me	−308.9	−308.0	−306.6	—
3-Me	−310.1	−308.9	−308.3	—
5-Me	−338.1	−337.9	−336.7	−319.7 ± 4.3, ^e −328.7 ± 4.3 ^d
6-Me	−346.7	−346.3	−345.9	−342.3 ± 7.1 ^e
1,3-di-Me	−319.7	−317.4	−316.2	−313.6 ± 1.5, ^f −320.0 ± 2.1 ^b
1,5-di-Me	−347.5	−345.0	−344.6	—
1,6-di-Me	−347.9	−346.0	−344.0	—
3,5-di-Me	−349.2	−347.7	−346.3	—
3,6-di-Me	−357.5	−355.9	−355.5	—
5,6-di-Me	−377.4	−376.5	−375.3	−376.2 ± 2.6 ^g
1,3,5-tri-Me	−358.2	−355.6	−354.2	−355.9 ± 3.0 ^g
1,3,6-tri-Me	−358.1	−355.1	−353.6	—
1,5,6-tri-Me	−376.9	−374.7	−373.4	—
3,5,6-tri-Me	−389.2	−387.2	−384.9	—
1,3,5,6-tetra-Me	−386.4	−382.8	−383.0	−381.7 ± 2.8 ^g

^aValue of the Y-intercept in the adjusted Free–Wilson eq 6. ^bTaken from ref 41. ^cValue obtained from the enthalpy of formation in the condensed phase taken from ref 42, and the enthalpy of sublimation taken from ref 43. ^dTaken from ref 42. ^eTaken from ref 5. ^fTaken from ref 44. ^gThis work.

three studied compounds: 5,6-dimethyluracil, 1,3,5-trimethyluracil, and 1,3,5,6-tetramethyluracil.

We have also carried out calculations of the enthalpies of formation for all the methyl-substituted uracils. The agreement between experimental and G4-calculated values is very good in the case of the parent compound, uracil, and also for 6-methyluracil and 1,3-dimethyluracil, but not in the case of 5-methyluracil (thymine) where there is a difference of 9 $\text{kJ}\cdot\text{mol}^{-1}$ with the value measured by Sabbah et al.⁴² and 18 $\text{kJ}\cdot\text{mol}^{-1}$ with the value recently measured by Ribeiro da Silva et al.⁵ (see Table 6). We can also use the following homodesmotic reaction to estimate the enthalpy of formation of thymine:



A value of $-336.6 \text{ kJ}\cdot\text{mol}^{-1}$ is obtained at the G4 level, that agrees with the value obtained from atomization. These results suggest possible experimental errors in the two experimental determinations of the enthalpy of formation of thymine.

4.4. Analysis of the Substituent Effects in Uracil Derivatives. We can analyze the data in Table 6 using a simple statistical device called Free–Wilson matrices in medicinal chemistry^{45,46} or absence-presence matrices in other fields.^{47,48} This approach has been satisfactorily applied in chemistry by Elguero et al.⁴⁹ Free–Wilson analysis is based upon eq 5

$$\log\left(\frac{1}{C}\right) = \sum_{i=1}^n a_i x_i + \mu \quad (5)$$

where a_i = contribution of substituent i , with $a_H = 0$ (by definition); $x_i = 1$ or 0 depending upon the presence or absence of the i th substituent; and $\mu = \log(1/C)_{\text{calc}}$ for the unsubstituted compound.

Using the statistical Free–Wilson method, the enthalpies of formation of methylated uracils, calculated at the G4 level, have been correlated with the presence or absence of methyl groups in the different positions of the ring. We have also taken into account the possible interactions between two contiguous methyl groups, in positions 1,6 and 5,6 in the ring. Their corresponding coefficients represent the amount of further stabilization or destabilization relative to the two individual predicted effects, i.e., these coefficients should somewhat represent the synergistic effect of two contiguous methyl substituents. Free–Wilson matrix and regression analysis can be found in the Supporting Information, Tables S4 and S5.

The equation adjusted is:

$$\begin{aligned} \Delta_f H_m^0(\text{kJ}\cdot\text{mol}^{-1}) = & -7.9(\pm 0.7)[1\text{-Me}] - 9.6(\pm 0.5) \\ & [3\text{-Me}] - 38.0(\pm 0.7)[5\text{-Me}] \\ & - 47.2(\pm 0.9)[6\text{-Me}] \\ & + 9.8(\pm 0.9)[1,6\text{-di-Me}] \\ & + 8.6(\pm 0.9)[5,6\text{-di-Me}] \\ & - 299.8(\pm 0.8) \end{aligned} \quad (6)$$

The Y-intercept of the regression, $-(299.8 \pm 0.8) \text{ kJ}\cdot\text{mol}^{-1}$, is in very good agreement with the experimental enthalpy of formation of unsubstituted uracil (see Table 6). The regression coefficients provide an idea of the relative weight of the presence of the methyl groups in the different positions of the uracil ring (see Table 7). So, the methylation at C_5 or C_6

Table 7. Main Effects on $\Delta_f H_m^0(\text{g})$ of Methyl-Substituted Uracils, in $\text{kJ}\cdot\text{mol}^{-1}$

1-Me	−7.9 ± 0.7	1,6-di-Me	+9.8 ± 0.9
3-Me	−9.6 ± 0.5	5,6-di-Me	+8.6 ± 0.9
5-Me	−38.0 ± 0.7		
6-Me	−47.2 ± 0.9		

stabilizes the uracil derivatives by 38.0 and 47.2 $\text{kJ}\cdot\text{mol}^{-1}$, respectively, whereas the introduction of a methyl group attached to N_1 or N_3 produces a smaller stabilization (7.9 and 9.6 $\text{kJ}\cdot\text{mol}^{-1}$, respectively). The stabilizations calculated for the introduction of methyl groups in positions 5 and 6 of the uracil ring have been corroborated with the very recent experimental determinations of enthalpies of formation of thioracils by Ribeiro da Silva et al.⁷ They obtain values of $-(37.9 \pm 1.7)$ and $-(49.3 \pm 1.6) \text{ kJ}\cdot\text{mol}^{-1}$, for the introduction of methyls in positions 5 and 6, respectively, of 2-thioracil, in perfect agreement with our calculated values, $-(38.0 \pm 0.7)$ and $-(47.2 \pm 0.9) \text{ kJ}\cdot\text{mol}^{-1}$. On the other hand, the attachment of two methyl groups in adjacent positions of the uracil ring produces a destabilization (9.8 $\text{kJ}\cdot\text{mol}^{-1}$ when the methyl groups are attached to N_1 and C_6 , and 8.6 $\text{kJ}\cdot\text{mol}^{-1}$ when they are attached to C_5 and C_6). Qualitatively these stabilizing and destabilizing terms make sense. N-methylation of amides is usually accompanied by a relatively small change to more

negative enthalpies of formation. For example, the gas phase enthalpy of formation of *N*-methylacetamide is $(-248.0 (\pm 5.5)) - (-238.3 (\pm 0.9)) \approx (10 \pm 6) \text{ kJ}\cdot\text{mol}^{-1}$ more negative than acetamide itself, while *N*-methylpyrrolidinone is $(-210.9 (\pm 0.6)) - (-197.4 (\pm 3.1)) \approx (13 \pm 3) \text{ kJ}\cdot\text{mol}^{-1}$ more negative than pyrrolidinone. By contrast, C-methylation is preceded to affect a much larger change. There is a ca. 30 $\text{kJ}\cdot\text{mol}^{-1}$ difference between the gas phase enthalpies of formation of *N,N*-dimethyl-*p*-toluamide⁵⁰ and *N,N*-dimethylbenzamide,^{50,51} a value shared by the parent *p*-toluic and benzoic acids, their corresponding acyl chlorides⁵⁰ and methyl esters.^{50,52} A nearly identical difference is found for comparably substituted benzoic acids, as well as for toluene compared to benzene. The reader will recall that an ca. 9 $\text{kJ}\cdot\text{mol}^{-1}$ repulsion was obtained between adjacent methyl groups. While we recognize the presence of three contiguous groups on the pyrimidine ring in the case of [1,6-di-Me] and [5,6-di-Me] substitution (if we include the keto oxygens), it is not clear how to quantify or even adequately mimic this destabilization. We note that gas phase 1,2-dimethylbenzene is less stable than its 1,3-isomer by $(19.0 (\pm 1.1)) - (17.2 (\pm 0.8)) = (1.8 \pm 1.3) \text{ kJ}\cdot\text{mol}^{-1}$.⁵³ Introduce a third methyl group and thus the possibility of three contiguous groups, we find 1,2,3-trimethylbenzene is destabilized relative to its 1,2,4-isomer by $(-9.6 (\pm 1.3) - (-13.9 \pm 1.0)) = (4.3 \pm 1.7) \text{ kJ}\cdot\text{mol}^{-1}$.⁵³ Consider 2-methylphenol. If a new methyl is introduced at the 3-position so the three groups are contiguous, the resulting dimethylphenol is less stable than when introduced in the 5-position by $(3.8 \pm 1.4) \text{ kJ}\cdot\text{mol}^{-1}$.⁵⁴

Taking $-298.7 \text{ kJ}\cdot\text{mol}^{-1}$ as the experimental value for the enthalpy of formation of uracil, and using the regression coefficients of the adjusted Free–Wilson eq 6 (see Table 7), values for the enthalpies of formation of the methylated uracils have been obtained and collected in Table 6. As can be observed, there is good agreement between these calculated values and the experimental ones (except in the case of thymine, see above), indicating that the statistical approach (Free–Wilson method) is a valuable tool in the identification of important stabilizing/destabilizing interactions, particularly in the case where a very large number of observations is available.

■ ASSOCIATED CONTENT

■ Supporting Information

Table S1, with physical constants of the materials used in the present study; Table S2, with G3- and G4-calculated energies at 0 K, E_0 , and enthalpies at 298 K, H_{298} , for methyl substituted uracils; Table S3, with B3LYP/6-31G(2df,p)-optimized bond distances, in Å, and bond angles, in degrees, for the three uracils studied; Tables S4 and S5, with the Free–Wilson matrix and the results of the analysis; and complete ref 30. This information is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rnotario@iqfr.csic.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The support of the Spanish Ministerio de Ciencia e Innovación under Project CTQ2010-16402 is gratefully acknowledged. We

thank Carlos Marco, from Instituto de Ciencia y Tecnología de Polímeros, CSIC, for his valuable help with DSC measurements.

■ REFERENCES

- (1) Carell, T.; Brandmayr, C.; Hienzsch, A.; Müller, M.; Pearson, D.; Reiter, V.; Thoma, I.; Thumbs, P.; Wagner, M. *Angew. Chem., Intl. Ed.* **2012**, *51*, 7110–7131.
- (2) Domalski, E. S. *J. Phys. Chem. Ref. Data* **1972**, *1*, 221–277.
- (3) As found in Domalski, op. cit. (ref 2), for uric acid: Stohmann, F.; von Rechenberg, C.; Wilaing, H.; Radatz, P. *Handw. Jahrb.* **1884**, *133*, 549–581. For barbituric acid: Matignon, C. *Ann. Chim. Phys.* **1893**, *28*, 289–294. For thymine: Fischer, E.; Wrede, F. *Sitzber. Preuss. Akad. Wiss. Math.-Phys. Kl.* **1904**, 687–715.
- (4) Ribeiro da Silva, M. A. V.; Amaral, L. M. P. F.; Szterner, P. *J. Chem. Thermodyn.* **2011**, *43*, 1763–1767.
- (5) Ribeiro da Silva, M. A. V.; Amaral, L. M. P. F.; Szterner, P. *J. Chem. Thermodyn.* **2011**, *43*, 1924–1927.
- (6) Ribeiro da Silva, M. A. V.; Amaral, L. M. P. F.; Szterner, P. *J. Chem. Thermodyn.* **2012**, *52*, 30–35.
- (7) Ribeiro da Silva, M. A. V.; Amaral, L. M. P. F.; Szterner, P. *J. Chem. Thermodyn.* **2013**, *57*, 380–386.
- (8) Roux, M. V.; Temprado, M.; Notario, R.; Foces-Foces, C.; Emel'yanenko, V. N.; Verevkin, S. P. *J. Phys. Chem. A* **2008**, *112*, 7455–7465.
- (9) Roux, M. V.; Notario, R.; Foces-Foces, C.; Temprado, M.; Ros, F.; Emel'yanenko, V. N.; Verevkin, S. P. *J. Phys. Chem. A* **2010**, *114*, 3583–3590.
- (10) Roux, M. V.; Notario, R.; Foces-Foces, C.; Temprado, M.; Ros, F.; Emel'yanenko, V. N.; Verevkin, S. P. *J. Phys. Chem. A* **2011**, *115*, 3167–3173.
- (11) See the conflicting measurements for caffeine: Pinto, S. S.; Diogo, H. P. *J. Chem. Thermodyn.* **2006**, *38*, 1515–1522. Dong, J.-X.; Li, Q.; Tan, Z.-C.; Zhang, Z.-H.; Liu, Y. *J. Chem. Thermodyn.* **2007**, *39*, 108–114. See also their reconciliation: Emel'yanenko, V. N.; Verevkin, S. P. *J. Chem. Thermodyn.* **2008**, *40*, 1661–1665.
- (12) Miranda, M. S.; Matos, M. A. R.; Morais, V. M. F.; Liebman, J. F. *J. Chem. Eng. Data* **2011**, *56*, 4516–4523.
- (13) Marti, E. E. *Thermochim. Acta* **1973**, *5*, 173–220.
- (14) Yamauchi, K.; Kinoshita, M. *J. Chem. Soc., Perkin Trans. I* **1973**, 391–392.
- (15) Kircher, W. *Lieb. Ann. Chem.* **1911**, *385*, 293–314.
- (16) Della Gatta, G.; Richardson, M. J.; Sarge, S. M.; Stølen, S. *Pure Appl. Chem.* **2006**, *78*, 1455–1476.
- (17) Gmelin, E.; Sarge, S. M. *Thermochim. Acta* **2000**, *347*, 9–13.
- (18) Gmelin, E.; Sarge, S. M. *Pure Appl. Chem.* **1995**, *67*, 1789–1800.
- (19) Sabbah, R.; Xu-wu, A.; Chickos, J. S.; Planas Leitão, M. L.; Roux, M. V.; Torres, L. A. *Thermochim. Acta* **1999**, *331*, 93–204.
- (20) Temprado, M.; Roux, M. V.; Jiménez, P.; Guzmán-Mejía, R.; Juaristi, E. *Thermochim. Acta* **2006**, *441*, 20–26.
- (21) Emel'yanenko, V. N.; Verevkin, S. P.; Heintz, A. *J. Am. Chem. Soc.* **2007**, *129*, 3930–3937.
- (22) Wagman, D. D.; Evans, W. H.; Parker, V. B.; Schumm, R. H.; Halow, I.; Bailey, S. M.; Churney, K. L.; Nuttall, R. L. *J. Phys. Chem. Ref. Data* **1982**, *11* (Suppl. 2), 1–58.
- (23) Wieser, M. E. Atomic Weights of the Elements 2009 (IUPAC technical report). *Pure Appl. Chem.* **2011**, *382*, 17–25.
- (24) Hubbard, W. N.; Scott, D. W.; Waddington, G. *Experimental Thermochemistry*; Rossini, F. D., Ed.; Interscience: New York, 1956; p 75.
- (25) Cox, J. D.; Wagman, D. D.; Medvedev, V. A. *CODATA Key Values for Thermodynamics*; Hemisphere Publishing Corp.: New York, 1989.
- (26) Olofsson, G. In *Combustion Calorimetry*; Sunner, S.; Mansson, M., Eds.; Pergamon: New York, 1979; Chapter 6.
- (27) Verevkin, S. P. *J. Chem. Eng. Data* **2000**, *45*, 953–960.
- (28) Verevkin, S. P. Pure Component Phase Changes Liquid and Gas: Chapter 1. In *Experimental Thermodynamics: Measurement of the*

thermodynamic properties of multiple phases; Weir, R. D., De Loos, Th. W., Eds.; 2005; Vol 7, pp 6–30.

(29) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. et al. *Gaussian 09, Revision A.02*; Gaussian, Inc.: Wallingford, CT, 2009.

(31) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764–7776.

(32) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **2007**, *126*, 084108.

(33) Khomenko, V. G.; Mitkevich, V. V.; Sukhodub, L. F. *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Khim. Biol. Nauki* **1986**, 30–33.

(34) Mastyukov, V. S.; Fan, K.; Boggs, J. E. *J. Mol. Struct.* **1995**, *346*, 173–186.

(35) Reeke, G. N., Jr.; Marsh, R. E. *Acta Crystallogr.* **1966**, *20*, 703–708.

(36) Zielenkiewicz, W.; Zielenkiewicz, A.; Wierzchowski, K. L. *Pure Appl. Chem.* **1994**, *66*, 503–507.

(37) Kamiński, M.; Zielenkiewicz, W. *J. Chem. Thermodyn.* **1996**, *28*, 153–158.

(38) Zielenkiewicz, W. *Bull. Pol. Acad. Sci.-Chem.* **1995**, *43*, 167–171.

(39) Notario, R.; Castaño, O.; Abboud, J.-L. M.; Gomperts, R.; Frutos, L. M.; Palmeiro, R. *J. Org. Chem.* **1999**, *64*, 9011–9014.

(40) Notario, R.; Castaño, O.; Gomperts, R.; Frutos, L. M.; Palmeiro, R. *J. Org. Chem.* **2000**, *65*, 4298–4302.

(41) Emel'yanenko, V. N.; Verevkin, S. P.; Achraimer, F.; Zipse, H. *Book of Abstracts*; 22nd International Conference on Chemical Thermodynamics and 67th Calorimetry Conference, August 5–10, Búzios, RJ, Brazil, 2012, .

(42) Nabavian, P. M.; Sabbah, R.; Chastel, R.; Laffite, M. *J. Chim. Phys.* **1977**, *74*, 115–126.

(43) Szterner, P.; Kamiński, M.; Zielenkiewicz, A. *J. Chem. Thermodyn.* **2002**, *34*, 1005–1012.

(44) Imamura, A.; Takahashi, K.; Murata, S.; Sakiyama, M. *J. Chem. Thermodyn.* **1989**, *21*, 237–246.

(45) Free, S. M. J.; Wilson, J. W. *J. Med. Chem.* **1964**, *7*, 395–399.

(46) Kubinyi, H. *QSAR: Hansch Analysis and Related Approaches In Methods and Principles in Medicinal Chemistry*, Mannhold, R., Krosgaard-Larsen, P., Timmerman, H., Eds.; VCH: Weinheim, Germany, 1993; Vol. 1.

(47) Gotelli, N. J.; McCabe, D. J. *Ecology* **2002**, *83*, 2091–2096.

(48) Miklós, I.; Podani, J. *Ecology* **2004**, *85*, 86–92.

(49) Alkorta, I.; Blanco, F.; Elguero, J. *Tetrahedron* **2008**, *64*, 3826–3836 and references therein..

(50) Guthrie, J. P.; Pike, D. C.; Lee, Y.-C. *Can. J. Chem.* **1992**, *70*, 1671–1683.

(51) Abboud, J.-L. M.; Jiménez, P.; Roux, M. V.; Turrión, C.; López-Mardomingo, C.; Podosenin, A.; Rogers, D. W.; Liebman, J. F. *J. Phys. Org. Chem.* **1995**, *8*, 15–25.

(52) Roux, M. V.; Temprado, M.; Dávalos, J. Z.; Jiménez, P.; Hosmane, R. S.; Liebman, J. F. *Phys. Chem. Chem. Phys.* **2002**, *4*, 3611–3613.

(53) Prosen, E. J.; Johnson, W. H.; Rossini, F. D. *J. Res. Natl. Bur. Stand. (U. S.)* **1946**, *36*, 455–461.

(54) Andon, R. J. L.; Biddiscombe, D. P.; Cox, J. D.; Handley, R.; Harrop, D.; Herington, E. F. G.; Martin, J. F. *J. Chem. Soc.* **1960**, 5246–5254.