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Structure-Energy Relationship in Barbituric Acid: A Calorimetric, Computational, and Crystallographic Study

María Victoria Roux,*,[†] Manuel Temprado,[†] Rafael Notario,[†] Concepción Foces-Foces,[†] Vladimir N. Emel'yanenko,[‡] and Sergey P. Verevkin[‡]

Instituto de Química Física "Rocasolano", CSIC, Serrano 119, 28006 Madrid, Spain, and Department of Physical Chemistry, University of Rostock, Hermannstrasse 14, D-18051 Rostock, Germany

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This paper reports the value of the standard ($p^o = 0.1$ MPa) molar enthalpy of formation in the gas phase at $T = 298.15$ K for barbituric acid. The enthalpies of combustion and sublimation were measured by static bomb combustion calorimetry and transference (transpiration) method in a saturated N_2 stream and a gas-phase enthalpy of formation value of $-(534.3 \pm 1.7)$ kJ·mol^{-1} was determined at $T = 298.15$ K. G3-calculated enthalpies of formation are in very good agreement with the experimental value. The behavior of the sample as a function of the temperature was studied by differential scanning calorimetry, and a new polymorph of barbituric acid at high temperature was found. In the solid state, two anhydrous forms are known displaying two out of the six hydrogen-bonding patterns observed in the alkyl/alkenyl derivatives retrieved from the Cambridge Crystallographic Database. The stability of these motifs has been analyzed by theoretical calculations. X-ray powder diffraction technique was used to establish to which polymorphic form corresponds to the commercial sample used in this study and to characterize the new form at high temperature.

1. Introduction

Two basic properties of chemical compounds are their structure and energy. These are intimately related because the energy associated with a particular structure depends on the atoms, types of bonds, bonds angles, and torsional angles that form the molecular framework.[1]

Thermodynamic data such as enthalpies of formation are often helpful in the understanding of the structural, conformational, and reactivity trends exhibited by molecules. The data are needed to estimate the amount of energy released or absorbed in a chemical reaction, in calculating other thermodynamics functions, and more importantly in assessing the relative stability of molecules. One of the purposes of thermochemistry is to derive the enthalpies of formation of compounds from their elements and to relate the energy to structure and chemical binding.[2,3]

Over the past years, we have been involved in the thermochemical study of the energetics of nitrogen containing compounds such as amides,[4–7] β-lactams,[8] azoles,[9–11] and cyclic ureas.[12] The fundamental interest in our work is to develop an understanding of structural effects on thermodynamic stabilities that are as reflected in the gas-phase enthalpies of formation of the compounds studied.

We are presently involved in the study of the thermochemistry of barbituric acid derivatives. The main purposes of this study are to provide some reliable data for the family of barbiturates that can be used for the estimation of the thermochemical properties of related compounds and also to contribute to the study of the influence of steric, electrostatic, and stereoelectronic interactions produced by substituents on the thermochemical stability of these molecules.

Barbituric acid (2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione, CAS number: 67−52−7) is a very well-known organic compound based on a pyrimidine heterocyclic skeleton.[13] It was synthetized for the first time in 1864 by von Baeyer,[14] and it is the parent compound of a large class of barbiturates that act as central nervous system depressants; by virtue of this they produce a wide spectrum of physiological effects. They are used in medicine as sedatives, hypnotics, soporifics, anticonvulsants, or as adjuncts in anesthesia.[15,16]

Barbituric acid itself is not pharmacologically active.[13] Barbital or barbitone (5,5-diethyl barbituric acid) was the first commercially available barbiturate, and it was used as a sleeping aid from 1903 until the mid-1950s. However, fatal overdoses of this slow-acting hypnotic were not uncommon. Phenobarbital (5-ethyl-5-phenyl barbituric acid), also called phenobarbitone, is the most widely used anticonvulsant worldwide and the oldest still in use. Other applications of barbituric acid derivatives comprise their use as antivirals,[17] in photochemical nanoscience,[18,19] as dyes, [20,21] polymers,[22] dental material,[23,24] and as polymerization catalysts.[25] Furthermore, it is an important precursor in the synthesis of riboflavin.[26]

In the context of a systematic study of the thermodynamic properties of this family of compounds and in spite of the important uses and applications of barbituric acid derivatives, reliable experimental thermochemical studies are scarce. To our knowledge, there is only one report[27] of the gas phase enthalpy of formation of the parent compound (barbituric acid), values for the enthalpies of formation in the condensed phase of the 5-nitro[28] and 5,5-dihydroxy[29] derivatives, and two very old reports of the enthalpy of combustion of the 5,5-diethyl derivative (barbital).[30,31] Moreover, there are three relatively recent determinations of the enthalpy of sublimation of barbituric acid that span a 13 kJ·mol^{-1} range.[27,32,33]

The current study provides a new and more reliable determination of the enthalpy of formation in the gas phase for barbituric acid. The approach selected is a combination of

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* To whom correspondence should be addressed: E-mail: victoriaroux@iqfr.csic.es.

[†] CSIC.

[‡] University of Rostock.

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experimental determination of the enthalpy of formation and high-level ab initio calculations. As this family of compounds is known to exist in several polymorphic forms in the solid state, the Cambridge Crystallographic Database[34] has been searched to identify the different hydrogen bonding networks present in the anhydrous 5,5-dialkyl/alkenyl derivatives as well as in the parent compound that have been reported.

2. Experimental Section

2.1. Material and Purity Control. Barbituric acid was commercially available from Fluka, (puriss >99.5%). The sample was carefully dried under vacuum and no further purification was performed. Determination of purity, assessed by HPLC and differential scanning calorimetry (DSC), using the fractional fusion technique,[35] indicated that the mole fraction of impurities in the compound was less than 0.0001.

2.2. Powder X-ray Diffraction. In the solid state, the barbituric acid exists in two anhydrous polymorphic forms and in two dihydrated forms as far as the Cambridge Crystallographic Database is concerned[34](CSD version 5.29 Jan. 2008 update; in the following refcodes in the CSD are given in capitals).

The X-ray powder diffraction technique was used to establish to which polymorphic form corresponds the commercial sample used in this study and to characterize the new polymorph observed by DSC (see Section 3.1.1). The X-ray powder diffraction patterns were measured on an XPert-PRO diffraction system equipped with a PW 3050/60 goniometer and Cu Kα radiation. The patterns were measured in the 2−60° θ range and the unit cell dimensions were determined with the indexing program INDEX1−2.[36]

According to the simulated powder patterns (program PLATON)[37] from the known polymorphic crystal structures (CSD refcodes: form i = BARBAC[38] and BARBAC01[39] and form ii = BARBAC02[39]) the commercial sample from Fluka corresponds to polymorph ii (Figure 1).

2.3. Procedure for Thermochemical Measurements. ***2.3.1. Differential Scanning Calorimetry.*** The behavior of the sample as a funtion of temperature was studied by differential scanning calorimetry. Two DSC apparatuses were used. For experiments at lower temperatures (from 150 to 298 K), a Mettler DSC30 was used. For experiments made in the temperature interval 260 to 530 K, a Pyris 1 instrument from Perkin-Elmer equipped with an intracooler unit was used. This last apparatus was used to monitor purity and to study the fusion process as well as the possible existence of phase transitions in the solid samples at temperatures above 260 K. Both apparatuses were previously calibrated in temperature and energy with reference materials. Temperature and power scales were calibrated[40−42] 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.[43] The power scales were calibrated with high-purity indium.[43]

Thermograms of samples hermetically sealed in aluminum pans were recorded in a nitrogen atmosphere. All the pans with the samples were weighed 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.

After calibration, several runs with high-purity benzoic acid and indium as reference materials[43] were performed under the same conditions as the experimental determinations. The accuracies associated with temperature and enthalpy of fusion measurements were calculated as the percentage deviation of the experimental data with regard to the values given in the literature;[43] in all the cases, these were lower than 0.2 and 2.0% for temperature and enthalpy determinations, respectively.[44]

For the determination of the purity and the temperature and enthalpy of fusion, a heating rate of 0.04 $K \cdot S^{-1}$ was used and five 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 $K \cdot s^{-1}$ were performed to determine the possible existence of phase transitions in the sample over the temperature range from $T = 150$ K to its melting temperature.

2.3.2. Combustion Calorimetry. An isoperibol calorimeter equipped with a static bomb was used for the measurements of the energy of combustion. The apparatus, technique, and procedure have been described.[45,46] Calorimetric temperatures of the calorimeter were measured within $\pm 1 \times 10^{-4}$ K by means of a 100 Ω platinum resistance thermometer, using a calibrated resistence bridge (Model F300, Automatic Sysytem laboratories, Ltd.) interfaced to a microcomputer programmed to calculate the adiabatic temperature change. The energy equivalent of the calorimeter, ε (calor), was determined from the combustion of benzoic acid, NIST standard reference sample 39j, having a specific energy of combustion, $\Delta_c u = -(26434 \pm 3)\ J \cdot g^{-1}$, under certificate conditions. From eight calibration experiments ε (calor) = $(14270.71 \pm 1.40)\ J \cdot K^{-1}$, where the uncertainty quoted is the standard deviation of the mean. Frequent calibration experiments were made throughout the series of combustion experiments. The energy of combustion of barbituric acid was determined by burning the solid samples in pellet form in oxygen under different conditions. In order to obtain complete reactions of combustion, benzoic acid or vaseline and polyethene were used as auxiliary substances. The combustion bomb was flushed and filled with oxygen, previously freed from combustible impurities, and an initial pressure of oxygen of 2.03 or 3.04 MPa was used. Details of the characterization and physical properties of barbituric acid and auxiliary substances used in this work are collected in Table 1.

After disassembly of the calorimeter the bomb gases were slowly let out and the absence of CO was confirmed with Dräger tubes (sensitivity level $\approx 1 \times 10^{-6}$ mass fraction). No traces of carbon residue were observed in the runs given as valid. The absence of NO_2^- was checked by calibrated ionic chromatography. The nitric acid content in the bomb liquid was determined by titration with 0.1 mol dm^{-3} NaOH(aq). The corrections for nitric acid formation[52] were based on the value of −59.7 $kJ \cdot mol^{-1}$ for the standard molar energy of formation of 0.1 mol dm^{-3} HNO_3(aq) from B_2(g), O_2(g), and H_2O(l). All samples were weighed with a Mettler AT-21 microbalance, sensitivity $\pm 1 \times 10^{-6}$ g, and corrections of apparent mass to mass were made. For these corrections, conversion of the energy of the actual bomb process to that of the isothermal process, and the correction to standard states, the values given in Table 1, were used. Corrections to the standard states were made according to Hubbard et al.[53] The atomic weights of the elements were those recommended by IUPAC in 2006.[54] The energy of solution of carbon dioxide in water at 298.15 K, $\Delta_{sol}U(CO_2)$, was taken as $-17.09\ kJ \cdot mol^{-1}$, and the solubility constant, $K(CO_2)$, as 0.03440 mol dm^{-3} atm^{-1} at 298.15 K.[55]

From the combustion energy, the enthalpy of formation in the condensed state at 298.15 K was calculated.

2.3.3. Vapor Pressure Measurements. Vapor pressures and the enthalpy of sublimation of barbituric acid were determined by using the method of transference in a saturated stream of nitrogen. The method has been described before[56,57] and has

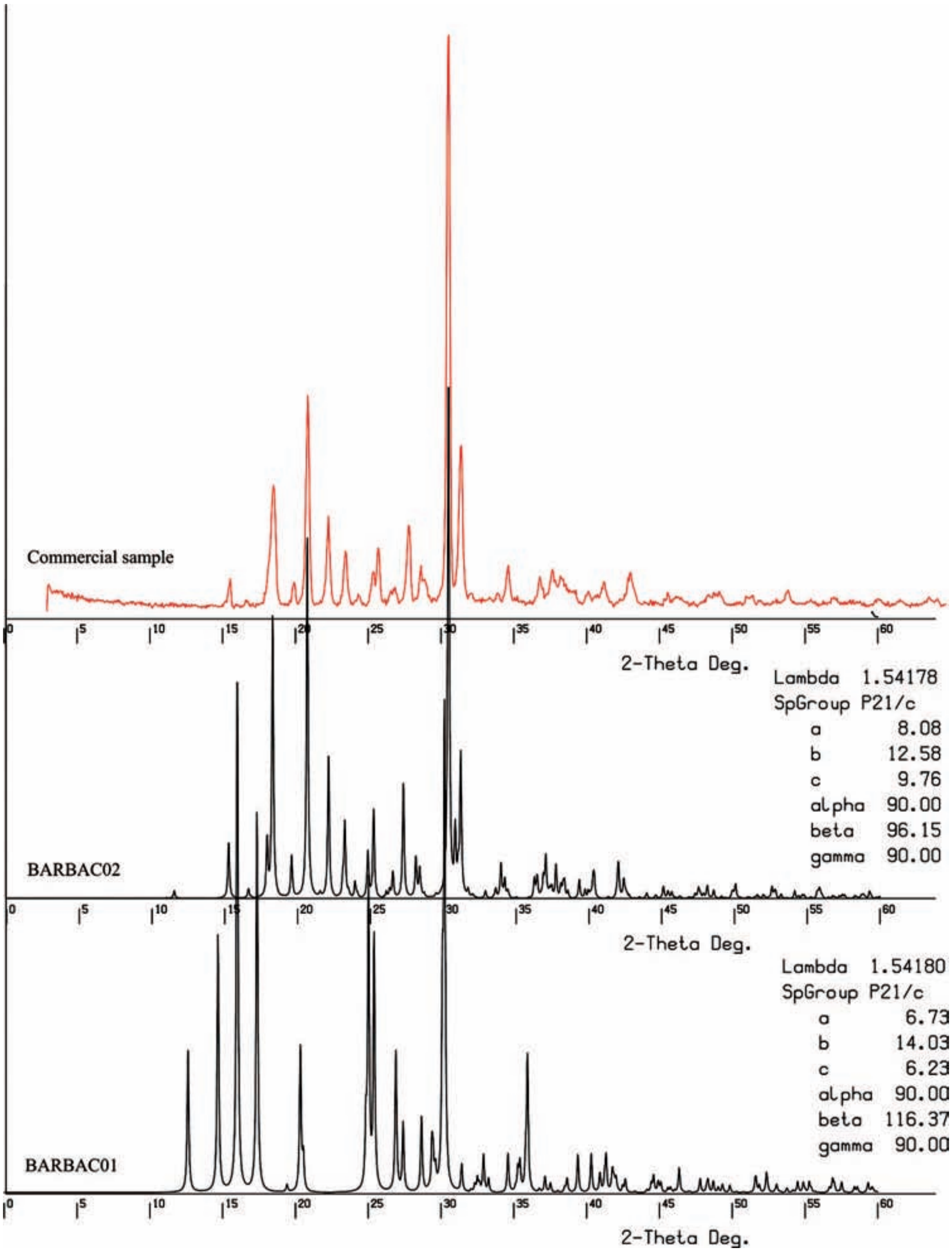

Figure 1. Comparison between the X-ray powder measured diffractograms of the commercial barbituric sample and the calculated on the basis of the single-crystal structures of the two anhydrous polymorphs.

TABLE 1: Properties at T = 298.15 K; the Value in Parentheses Was Estimated

compound	M g·mol^{-1}	ρ g·cm^{-3}	$(\delta V/\delta T)_P \times 10^{-7}$ dm^3·g^{-1}·K^{-1}	c_P J·K^{-1}·g^{-1}	$\Delta_c u°_m$(cr) J·g^{-1}
polyethene	13.5582[a,b]	0.918	7.650	1.99	−(46371 ± 4)[b]
vaseline	14.0266	0.870[c]	8.374[d]	2.22[e]	−(46086 ± 5)[c]
benzoic acid	122.1213	1.32	3.85	1.21	−(26434 ± 1)
cotton	27.700[f,b]	1.5	9.69[g]	1.48	−(17410 ± 37)[b]
barbituric acid	128.08616	1.589[h]	(3.354)	1.102[i]	

[a] Corresponding to an empirical formula of $C_{0.960}H_{2.000}$. [b] Determined in our laboratory. [c] Value taken from ref 47. [d] Value taken from ref 48. [e] Value taken from ref 49. [f] Corresponding to an empirical formula of $C_{1.000}H_{1.740}O_{0.871}$. [g] Value taken from ref 50. [h] Value taken from ref 27. [i] Value taken from refs 27 and 51.

proven to give results in agreement with other established techniques for determining vapor pressures of pure substances and enthalpies of vaporization from the temperature dependence of the vapor pressure.[58] About 0.5 g of the sample was mixed with glass beads and placed in a thermostatted U-tube of length 10 cm and diameter 0.5 cm. A 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 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. On the one hand, flow rate of nitrogen stream in the saturation tube should be not too slow in order to avoid the transport of material from U-tube due to diffusion. On the other hand, the flow rate should be not too fast in order to reach the saturation of the nitrogen stream with a compound. 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 a flow rate up to 0.5 $\mathrm{dm^3 \cdot h^{-1}}$. The upper limit for our apparatus where the speed of nitrogen could already disturb the equilibrium was at a flow rate of 9.0 $\mathrm{dm^3 \cdot h^{-1}}$. Thus, we carried out the experiments in the flow rate interval of (6 to 8) $\mathrm{dm^3 \cdot h^{-1}}$ which has ensured that the transporting gas was in saturated equilibrium with the coexisting solid phase in the saturation tube. The transported amount of material was condensed in a cooled trap. The amount of condensed product was determined by weighing (±0.0001 g).

The saturated vapor pressure $p_i^{\,\mathrm{sat}}$ 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 applied to the nitrogen stream saturated with the substance i of interest is valid, values of p_i^{sat} were calculated

$$p_i^{\mathrm{sat}} = m_i R T_a / V M_i; \qquad V = V_{\mathrm{N2}} + V_i; \qquad (V_{\mathrm{N2}} \gg V_i) \tag{1}$$

where $R = 8.31447\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$, m_i is the mass of transported compound, M_i is the molar mass of the compound, and V_i is its volume contribution to the gaseous phase. V_{N2} is the volume of transporting gas and T_{a} is the temperature of the soap bubble meter. The volume of transporting gas V_{N2} was determined from the flow rate and time measurements.

2.3.4. Computational Details. Standard ab initio molecular orbital calculations[59] were performed with the Gaussian 03 series of programs.[60] The energy of the compound studied was calculated using Gaussian-n theory at the G3 level.[61,62]

G3 corresponds effectively to calculations at the QCISD(T)/G3large level, G3large being a modification of the 6-311+G(3df,2p) basis set, including more polarization functions for the second row (3d2f), less on the first row (2df), and other changes to improve uniformity. In addition, some core polarization functions are added.[61] Single-point energy calculations are carried out on MP2(full)/6-31G(d) optimized geometries, incorporating scaled HF/6-31G(d) zero-point vibrational energies, a so-called higher-level correction to accommodate remaining deficiencies, and spin−orbit correction for atomic species only.

We have also reoptimized the geometry at the MP2(full)/6-31G(3df,2p) level to obtain a more reliable molecular structure for the compound studied.

According to the Cambridge Crystallographic Database[34] molecules of the anhydrous barbituric acid derivatives including the parent compound self-assemble into six hydrogen bonding networks. The corresponding models formed by six molecules (the minimum needed for the representation of the six motifs) idealized for the barbituric acid monomer have been optimized at different levels of calculation: semiempirical AM1, and DFT at two levels, B3LYP/6-31G(d) and B3LYP/6-31++G(d). In some cases the optimization was unsuccessful because of convergence problems.

The charge distribution has been analyzed using a population partition technique, the natural bond orbital (NBO) analysis of Reed and Weinhold.[63–65] The NBO analysis has been performed using the NBO program[66] implemented in the Gaussian 03 package.[60]

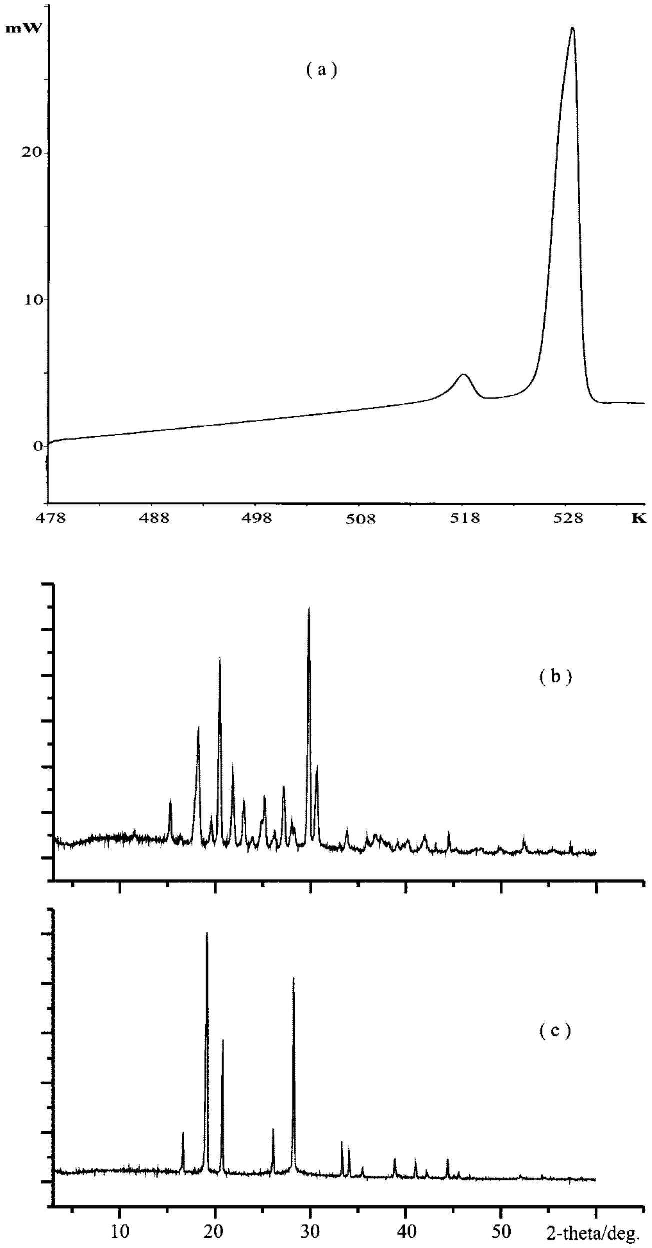

Figure 2. (a) Plot of the DSC scans obtained for barbituric acid in heating, (b) X-ray powder diffractogram at room temperature, and (c) X-ray powder diffractogram after the transition peak and before fusion.

3. Results and Discussion

3.1. Experimental Results. ***3.1.1. Phase Transitions.*** DSC scans for the sample studied (form ii) show a solid−solid phase transition at $T = (516.0 \pm 0.3)$ K having an enthalpy of (1.30 ± 0.04) $\mathrm{kJ \cdot mol^{-1}}$ (Figure 2a). This behavior was reproducible being observed in all the runs performed with fresh samples. The temperature and enthalpy of fusion determined by DSC were $T_{\mathrm{fus}} = (526.4 \pm 0.5)$ K and $\Delta_{\mathrm{fus}}H = (20.87 \pm 0.14)$ $\mathrm{kJ \cdot mol^{-1}}$, respectively.

The X-ray powder diffraction patterns at room temperature and after the phase transition are also shown in Figure 2. At room temperature (Figure 2b), the indexed[36] cell with the highest reliability factor is monoclinic with cell parameters in agreement with those reported by single crystal diffraction methods[39] (polymorphic form ii) as illustrated in Figure 1 ($a = 8.199$, $b = 12.613$, $c = 9.823$ Å and $\beta = 95.7°$ versus $a = 8.019$, $b = 12.479$, $c = 9.764$ Å and $\beta = 96.2°$, respectively). However,

TABLE 2: Results of a Typical Combustion Experiment on Barbituric Acid at $T = 298.15$ KP[a]

m' (compound)/g[b]	0.849911
m''(benzoic acid)/g[b]	0.268351
m'''(fuse)/g[b]	0.002628
ΔT_c/K = ($T_f - T_i + \Delta T_{corr}$)/K	1.2028
ε (calor) ($-\Delta T_c$)/kJ[c]	−17.1646
ε (cont) ($-\Delta T_c$)/kJ[d]	−0.0200
ΔU_{ign}/kJ[e]	0.0008
$\Delta U_{dec}(HNO_3)$/kJ[f]	0.0490
ΔU(corr to std states)/kJ[g]	0.0184
$-m'' \Delta_c u^o$ (benzoic acid)/kJ	7.0882
$-m''' \Delta_c u^o$ (fuse)/kJ	0.0458
$\Delta_c u^o$ (compound)/kJ·g^{-1}	−11.7451

[a] For a definition of the symbols see refs 53 and 67. $T_{th} = 298.15$ K; $V_{bomb} = 0.380$ dm^3; $p^i_{gas} = 3.04$ MPa; $m^i_{water} = 1.00$ g. [b] Masses obtained from apparent mass. [c] ε (calor), energy equivalent of the whole system less the content of the bomb. [d] ε (cont), energy equivalent of the contents of the bomb. [e] Experimental energy of ignition. [f] Experimental energy of formation of nitric acid. [g] Energy of correction to standard states.

TABLE 3: Experimental Conditions and Energies of Combustion of Barbituric Acid

auxiliary substance	$p(O_2)$ (MPa)	$-\Delta_c u^\circ$ kJ·g^{-1}
none	3.04	11.6917
none	2.03	11.6877
benzoic acid	3.04	11.7014
benzoic acid	3.04	11.6817
benzoic acid	3.04	11.7376
benzoic acid	3.04	11.7285
benzoic acid	3.04	11.7394
benzoic acid	3.04	11.7451
benzoic acid	3.04	11.7085
benzoic acid	2.03	11.6981
benzoic acid	2.03	11.6989
benzoic acid	2.03	11.7042
polyethene and vaseline	3.04	11.7209
polyethene and vaseline	3.04	11.7088
		(11.7109 ± 0.0054)[a]

[a] Mean and standard deviation of the mean.

TABLE 4: Experimentally Determined Standard ($p^o = 0.1$ MPa) Molar Energy of Combustion and Standard Molar Enthalpies of Combustion and Formation in the Crystalline State at $T = 298.15$ K for Barbituric Acid; Values in kJ·mol^{-1}

$\Delta_c U^o_m$ (cr)	$\Delta_c H^o_m$ (cr)	$\Delta_f H^o_m$ (cr)
−1500.0 ± 1.5	−1496.3 ± 1.5	−649.4 ± 1.6

TABLE 5: Results from Measurements of the Vapor Pressure p of Barbituric Acid Using the Transpiration Method

T^a K	m^b mg	$V_{(N2)}{}^c$ dm^3	Gas-flow dm^3/h	p^d Pa	(p_{exp}-p_{calc}) Pa	$\Delta_{cr}^{g}Hm$ kJ·mol^{-1}
$\Delta_{cr}{}^{g}H_m$(298.15 K) = (115.11 ± 0.70) kJ·mol^{-1}						
ln(p/Pa) = (302.9/R) − [121643.7/R·(T,K)] − (21.9/R)ln(T,K/298.15)						
410.4	13.3	281.68	8.295	0.89	−0.05	112.65
413.6	21.1	336.45	8.295	1.19	−0.02	112.58
418.4	18.4	199.63	8.295	1.74	−0.02	112.48
423.3	28.0	207.65	8.295	2.55	−0.02	112.37
426.0	28.0	162.10	8.370	3.27	0.13	112.31
429.8	21.1	95.13	8.500	4.22	0.06	112.23
433.6	24.4	87.42	6.050	5.31	−0.16	112.14
438.4	16.0	38.95	8.530	7.80	0.08	112.04
445.1	18.5	28.72	8.530	12.26	−0.03	111.89
449.0	18.1	22.75	6.120	15.14	−0.74	111.81
452.8	15.7	13.98	8.470	21.30	0.88	111.72
457.6	16.8	10.73	8.470	29.75	1.87	111.62
464.5	17.3	7.34	8.470	44.85	1.74	111.47
468.1	18.7	6.33	8.530	56.25	2.20	111.39
474.3	18.7	4.41	8.530	80.74	2.53	111.25
478.2	17.1	3.21	6.120	101.27	2.83	111.17
483.2	16.3	2.45	6.120	126.70	−4.76	111.06
488.2	22.0	2.45	6.120	171.01	−3.46	110.95
492.2	21.3	1.84	6.120	220.76	2.30	110.86
497.3	23.4	1.63	6.120	272.84	−14.76	110.75
501.9	28.2	1.53	6.120	350.73	−16.87	110.65

[a] Temperature of saturation. [b] Mass of the transferred sample, condensed at $T = 299$ K. [c] Volume of nitrogen, used to transfer mass m of the sample. [d] Vapor pressure at temperature T, calculated from m and the residual vapor pressure at the temperature $T = 299$ K in a cold trap.

after the phase transition (Figure 2c), the powder pattern is consistent with two triclinic unit cells (1 and 2) with close reliability factors and cell volumes four times smaller than that at room temperature (1, $a = 9.394$, $b = 5.930$, $c = 4.635$ Å, $\alpha = 92.1$, $\beta = 94.2$ and $\gamma = 98.1°$; 2, $a = 8.558$, $b = 5.524$, $c = 5.479$ Å, $\alpha = 103.5$, $\beta = 85.3$ and $\gamma = 93.7°$). This suggests two molecules in the unit cell versus eight (two independent) in the monoclinic cell of form ii (see Section 3.4).

3.1.2. Experimental Enthalpy of Formation. Results for a typical combustion experiment on barbituric acid is given in Table 2 and corresponds to the reaction

$$C_4H_4O_3N_2(cr) + 7/2O_2(g) \rightarrow 4CO_2(g) + 2H_2O(l) + N_2(g) \qquad (2)$$

The individual values of $-\Delta_c u^o$, together with the conditions employed in the experiments, the mean value and its standard deviation, are given in Table 3.

Table 4 lists the derived standard molar enthalpies of combustion and formation in the crystalline state at $T = 298.15$ K. In accordance with normal thermochemical practice, the uncertainty assigned is twice the overall standard deviation of the mean and includes the uncertainties in calibration and in the auxiliary quantities used.[68] To derive $\Delta_f H^o_m$(cr) from $\Delta_c H^o_m$(cr), the CODATA values of the standard molar enthalpies of formation at $T = 298.15$ K of H_2O(l) and CO_2(g), −(285.839 ± 0.042) and −(393.51 ± 0.13) kJ·mol^{-1}, respectively, were used.[69]

3.1.3. Enthalpy of Sublimation. The enthalpy of sublimation was obtained from vapor pressure measurements by the method of transference in a saturated stream of nitrogen. Our experimental vapor pressures of barbituric acid have been measured in the broad temperature range below the phase transition point. The following equation

$$R \ln p_i^{sat} = a + \frac{b}{T} + \Delta_{cr}{}^{g}C_p \ln\left(\frac{T}{T_0}\right) \qquad (3)$$

was fitted to the experimental p, T data using a and b as adjustable parameters. T_0 appearing in eq 3 is an arbitrarily chosen reference temperature (which has been chosen to be 298.15 K). Consequently, from eq 3 the expression for the vaporization enthalpy at temperature T is derived

$$\Delta_{cr}{}^{g}H_m(T) = -b + \Delta_{cr}{}^{g}C_pT \qquad (4)$$

The value of $\Delta_{cr}{}^{g}C_p = 21.9$ J·mol^{-1}·K^{-1} has been derived from the experimental isobaric molar heat capacity of solid barbituric acid[27] C_p(cr) = 141.1 J·mol^{-1}·K^{-1}, according to a

TABLE 6: Experimentally Determined Thermodynamic Magnitudes at the Temperature T = 298.15 K for Barbituric Acid; all Values in kJ·mol^{-1}

$\Delta_c H°_m$(cr)	$\Delta_f H°_m$(cr)	$\Delta_{cr}{}^g H_m$	$\Delta_f H°_m$(g)	ref
−(1496.3 ± 1.5)	−(649.4 ± 1.6)	(115.1 ± 0.7)	−(534.3 ± 1.7)	this work
−(1511.1 ± 2.8)	−(634.7 ± 2.9)	(126.4 ± 0.9)[a]	−(508.3 ± 3.0)[a]	27
−1501.6	−644.2	(120.3 ± 1.2)[b]	−(514.4 ± 3.1)[b]	30
−1505.0	−640.8			31
		(113.6 ± 2.7)[a]		32
		(114.8 ± 0.9)[a]		33

[a] Obtained from experimental vapor pressures reported in the literature using eqs 3 and 4 in the same manner as our experimental results. [b] Experimental vapor pressures reported in ref 27 have been recalculated by Professor G. J. Kabo (private communication) according to the recent findings published in ref 73. These recalculated vapor pressures have been treated using eqs 3 and 4 in the same manner as our experimental results in order to derive the enthalpy of sublimation.

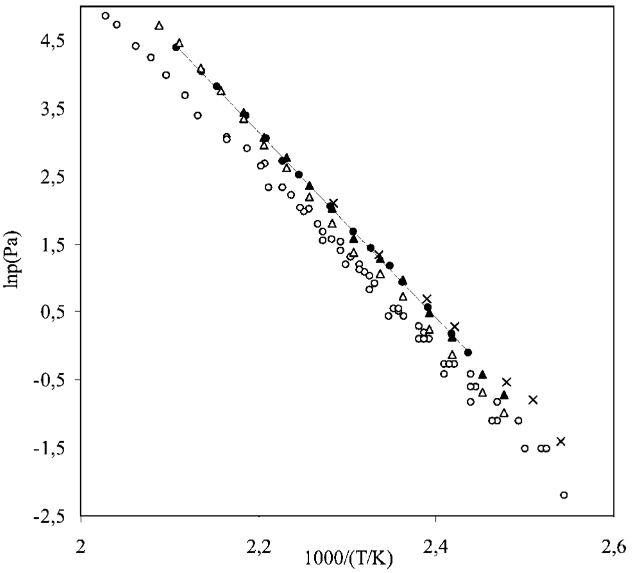

Figure 3. Experimental vapor pressure of the barbituric acid. •, This work; ○, Bruneti;[31] Δ, Soldatova;[27] ▲, Soldatova[27] (recalculated by Zaitsau and Kabo, see text and Supporting Information); ×, Zielenkiewicz.[30]

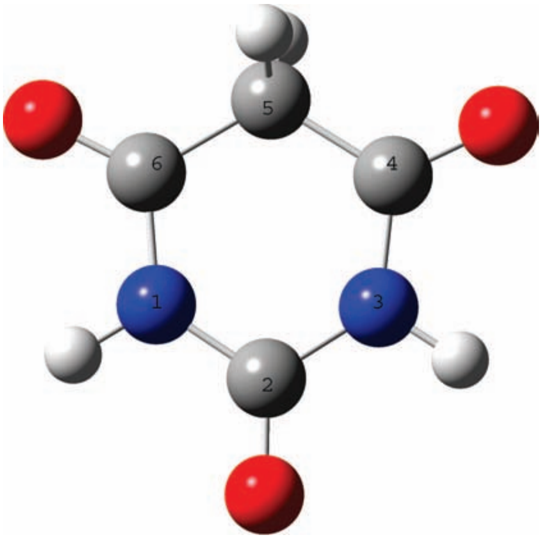

Figure 4. MP2(Full)/6-31G(3df,2p)-optimized structure of barbituric acid.

procedure developed by Chickos.[70–72] Value of $\Delta_{cr}{}^g C_p$ = 28.2 J·mol^{-1}·KP^{-1P} has been calculated according to a procedure developed by Chickos.[70–72]

Experimental results and parameters *a* and *b* are listed in Table 5.

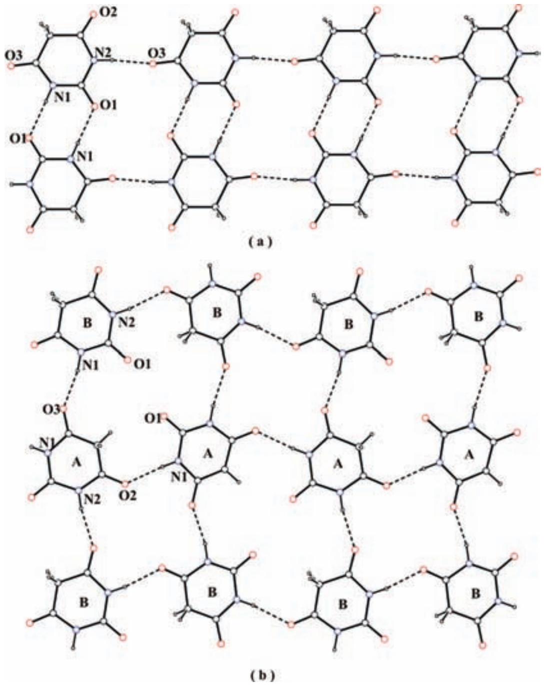

Figure 5. Hydrogen-bonded molecular ribbon (a) and sheet (b) formed by the barbituric acid polymorphs i and ii, respectively.

The standard molar enthalpy of combustion, $\Delta_c H°_m$(cr), sublimation, $\Delta_{cr}{}^g H_m$, and formation in the crystalline, $\Delta_f H°_m$(cr), and gaseous state, $\Delta_f H°_m$(g) at T = 298.15 K of barbituric acid are reported in Table 6.

Literature values for the enthalpies of combustion[27,30,31] and sublimation[27,32,33] of barbituric acid are also collected in Table 6. Figure 3 shows a comparison of the vapor pressure data available in the literature. None of these studies identified the polymorph used. Although the enthalpies of formation and sublimation of the condensed state depend on the polymorph used, the enthalpy of formation in the gas phase does not.

Experimental vapor pressure measurements for barbituric acid are available in the literature.[27,32,33] In these cases, the authors adjusted the enthalpy of sublimation to the reference temperature, T = 298.15 K, from the temperature dependence of vapor pressure in different ways. Therefore, we treated the original experimental results available from refs 27, 32, and 33 using eqs 3 and 4 and calculated the enthalpy of sublimation of barbituric acid at 298.15 K for the sake of comparison with our result (see Table 6). The vapor pressure data reported by Soldatova et al.[27] have been additionally corrected according to the isotropy failure theory (Professor G. J. Kabo, private communication) as was published elsewhere.[73] Some necessary additional details regarding these recalculations are given in the Supporting Information.

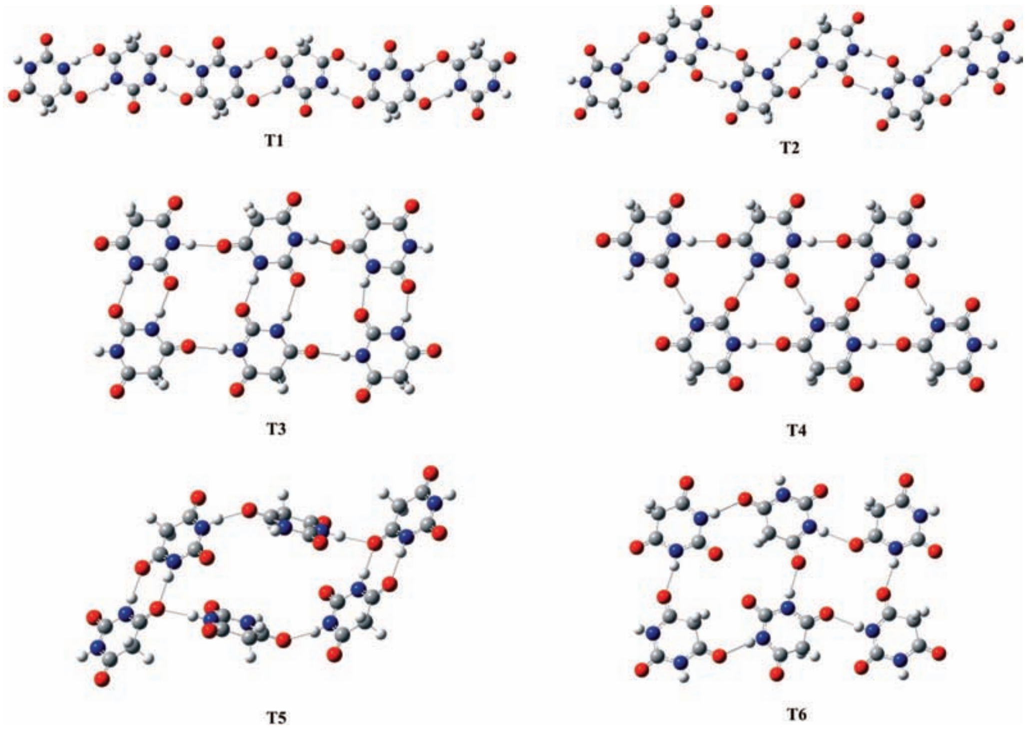

Figure 6. Hydrogen-bonded networks observed in the solid state by alkyl/alkenyl barbituric acid derivatives idealized for barbituric acid.

TABLE 7: Anhydrous 5-R-5-R′-Barbituric Acid Derivatives; R, R′=H and/Alkyl or Alkenyl Groups

R	R′	H-bond pattern	BARBAC, BARBAC01	polymorph	ref
cyclobutane		T1	CBUSPY		100
ethyl	ethyl	T1	DETBAA02,04,05	ii	101, 102, 103
ethyl	phenyl	T1	PHBARB	iii	104
allyl	isopropyl	T2	AIPBAR		105
ethyl	isoamyl	T2	AMYTAL10	i	106
ethyl	isoamyl	T2	AMYTAL11	ii	106
ethyl	but-2-enyl	T2	BEBWUA		107
ethyl	1,3-dimethylbut-1-enyl	T2	BEBWOU		108
ethyl	3-methyllbut-2-enyl	T2	BECLIE		109
allyl	allyl	T2	DALLBA		110
ethyl	n-pentyl	T2	ENPBAR		111
ethyl	butyl	T2	ETBBAR	i	112
ethyl	butyl	T2	ETBBAR01	[a]	113
ethyl	butyl	T2	ETBBAR02	ii	114
ethyl	cyclohexene-1-yl	T2	ETCYBA		115
ethyl	1,3-dimethylbut-2-enyl	T2	JIFRIZ		116
ethyl	1,3-dimethylbutyl	T2	MAOBAR		117
H	H	T3	BARBAC, BARBAC01	i	38, 39
ethyl	ethyl	T3	DETBAA01,06,10,11	i	101, 118, 119
H	ethyl	T3	ETBARB		120
methyl	phenyl	T3	MPBRBL		121
ethyl	3,3-dimethyl-n-butyl	T4	EMBBAR20		122
propenyl	1-methylbutyl	T4	TICFER		123
ethyl	1-cyclohepten-1-yl	T6	CHEBAR		124
ethyl	ethyl	T6	DETBAA03	iv	125
ethyl	1-methylbutenyl	T6	VINBAR		126
H	H	T6	BARBAC02	ii	39
ethyl	butyl	T3+T4	[b]	iii	127
ethyl	phenyl	T1+T5	PHBARB01,05	i	128, 129
ethyl	phenyl	T1+T5	PHBARB02,06	ii	128, 129

[a] Monoclinic form at low temperature, phase transition. [b] The polymorphic form of butobarbital has not yet in the CSD (5.29 version, Jan. 2008 update).

3.2. Molecular and Electronic Structure. Barbituric acid contains four mobile hydrogen atoms, and so it may exist in various tautomeric forms differing from each other by the position of the hydrogens, which may be bound to either nitrogen, carbon, or oxygen atoms. All ab initio and DFT theoretical calculations[74–80] report the triketo tautomer to be the most stable one in the gas phase, followed by the monohydroxy tautomers, 2,4-diketo-6-hydroxy and 2,6-diketo-4-hydroxy struc-

TABLE 8: Relative Energies Calculated at Different Computational Levels for the Six Idealized Idealized Hydrogen-Bonding Networks

	ΔE, kJ·mol^{-1}		
structure	AM1	B3LYP/6-31G(d)	B3LYP/6-31++G(d)
T3	0.0	10.3	0.0
T2	1.6	1.7	0.5
T1	5.8	0.0	1.7
T6	9.2	40.6	[a]
T4	11.8	[a]	[a]
T5	12.0	18.8	[a]

[a] The structures did not converge at this level of calculation.

tures. In the solid state, both the anhydrous compound and its dihydrated form exist only as the triketo form,[38,81,82] and from a kinetic study[83] it has been deduced that in most solvents, barbituric acid is present essentially in its triketo form. The higher stability of triketo form is associated with the much stronger double bond of C=O compared with the strength of C=C and C=N bonds. The high energy differences from the other tautomers suggest that the gas phase of barbituric acid consists of a single molecular species, in agreement with thermodynamic experimental data.[27,33]

Recently, Lewis et al.[39] have optimized the structure of barbituric acid at the MP2/6-31G(d,p) level, obtaining an envelope conformation. At this level, the planar structure is a transition state less than 1.2 kJ·mol^{-1} above the optimal envelope conformation. However, we have carried out the optimization using a higher-level basis set and taking into account all the electrons, at this level the envelope conformation is not a minimum. The calculation at this level of theory predicts a planar conformation. The MP2(Full)/6-31G(3df,2p)-optimized structure of barbituric acid is shown in Figure 4. The heavy atom skeleton is fully planar and the molecule possess C_{2v} symmetry. The calculated bond lengths and angles are in a good agreement with those of molecule B in polymorph ii as determined by X-ray diffraction[39] (CSD refcode BARBAC02).

Atomic charges have been calculated by the natural bond orbital (NBO) population analysis scheme. Positive charge is located at C atoms of the carbonyl groups (1.012 at C_2 and 0.851 at C_4 and C_6 atoms), whereas negative charge is located at N atoms (−0.785), O atoms (−0.698 at O atom bonded at C_2 and −0.672 at O atoms bonded at C_4 and C_6 atoms), and also at C_5 atom of the methylene group (−0.641). It is observed that the charge separation between the C_2 and O carbonyl group is higher than those on the other two carbonyl groups (1.710 versus 1.523).

3.3. Theoretical Determination of the Enthalpy of Formation. The standard procedure in obtaining enthalpies of formation in Gaussian-n theories is through atomization reactions,[84,85] but there have been some suggestions[86–90] that there is an accumulation of errors in the application of this method to larger molecules. Glukhovtsev and Laiter[86] have shown that more accurate heats of formation can be derived using isodesmic or homodesmotic reactions[91] rather than atomization energies. As Raghavachari et al.[92] have pointed out, one of the deficiencies of the isodesmic reaction approach is that many different isodesmic reactions can be set up for the same molecule yielding different results. These authors have proposed using a standard set of isodesmic reactions, the "bond separation reactions",[59] where all formal bonds between nonhydrogen atoms are separated into the simplest parent molecules containing these same kinds of linkages, to derive the theoretical enthalpies of formation.

In this work, we have calculated the enthalpy of formation of barbituric acid, $C_4HN_2O_3$, using the atomization reaction, the bond separation isodesmic reaction (eq 5), and another isodesmic reaction (eq 6), taking urea and 2,4-pentanedione as references

$$C_4H_4N_2O_3(g) + 7CH_4(g) + 2NH_3(g) \rightarrow 2CH_3CH_3(g) + 4CH_3NH_2(g) + 3H_2CO(g) \quad (5)$$

$$C_4H_4N_2O_3(g) + 2CH_4(g) \rightarrow (NH_2)_2CO(g) + CH_3COCH_2COCH_3(g) \quad (6)$$

The G3-calculated enthalpies of formation obtained[93] from the atomization reaction, −532.3 kJ·mol^{-1}, and from the isodesmic reaction (eq 6), −531.1 kJ·mol^{-1}, are in very good agreement with the experimental value determined in this work, −534.3 ± 1.7 kJ·mol^{-1}. The value calculated using the isodesmic bond separation reaction (eq 5), −542.8 kJ·mol^{-1}, is higher than the experimental one with the difference probably arising because the large number of molecules (19 in all) included in the isodesmic reaction; this increases the error of the estimation.

3.4. Polymorphism and Hydrogen Bonding Networks. The crystal structure of the two different polymorphic forms of the barbituric acid has already been described (CSD refcodes: i = BARBAC and BARBAC01 and ii = BARBAC02).[38,39]

The presence of polymorphic forms in the barbituric acid family (i.e., barbituric acid, diethyl or 5-ethyl-5-phenyl derivatives) can be attributed to the different hydrogen-bonding possibilities, between the two primary NH sites and the three carbonyl groups. Two different combinations of these donor and acceptor groups are employed in both polymorphic forms in barbituric acid. In i, one C=O close to the CH_2 (O2 in Figure 5) and in ii the one between the NH groups (O1) are free of N−H···O hydrogen interactions.

The resulting packing motifs are quite different (Figure 5). In i, the secondary structure consists of a double strand of centrosymmetric dimers (C(6)R^2_2(8) graph set notation)[98] forming a "step-ladder" arrangement[99] with an interstrand O···O distance greater than the intrastrand one. These double strands are linked into a 3D network by weak C−H···O contacts. In ii, each independent molecule A and B, which differ in the planarity of the heterocyclic ring, forms chains that are further linked into sheets of alternating R^4_4(16) and R^4_4(20) rings (Figure 5). In the R^4_4(20) macroring, the O1 oxygen in both molecules is directed toward the inner part of the ring with a distance between them of 3.323(2)Å. Within the chain, this oxygen is involved in weak C−H···O1 interactions (C···O, H···O distances and C−H···O angles of 3.570(3), 2.72Å, 152° and 3.482(3), 2.87Å, and 127° for the A and B molecules, respectively). The crystal is built up of centrosymmetric sheets leading to a closer packing than in form i where the chains pack in a herringbone manner (packing coefficients = 0.703 and 0.750 for i and ii, respectively). In a recent study by Lewis et al.[39] where the crystal structure of form ii was reported, they found that ab initio calculations predict form ii to have lower lattice energy than form i. However, and in spite of the enormous computational and experimental efforts carried out by these authors looking for new polymorphic forms, only the new form ii was found even though there are several hypothetical crystal structures (with different hydrogen bonding motifs and crystal packing) between the global minimum and the lattice energy computed for form i.

Although the structure and properties of the barbituric acid derivatives have been the subject of numerous studies (viz. refs 39 and 13) the Cambridge Structural Database (CSD version

5.29 Jan. 2008 update),[34] was searched to identify the hydrogen-bonded patterns in anhydrous 5-R-5-R′-barbituric acid derivatives without any additional acceptor or donor groups, that is with R and R′═H and/or alkyl or alkenyl substituents. Six patterns were observed and these are represented in Figure 6 idealized for R═R′═H. Of them, four are 1D networks with two different chains of dimers ($C^2_2(10)[R^2_2(8)]$ graph set notation) labeled as T1 and T2 and two are double strands, T3 (centrosymmetric dimers through $R^2_2(8)$, $R^4_4(16)$ edge-fused rings) and T4 ($R^{3PB}_{3B}(12)$ rings). The remaining two motifs correspond to 2-D networks, T5 ($RP^{4PB}_{6B}(24)$ rings) and T6 ($R^4_4(20)$ and $R^4_4(16)$ edge-fused rings). In T5, the primary dimer motif is observed where one carbonyl group, responsible for the formation of the dimer, acts as a double acceptor of N−H···O hydrogen bonds resulting in the formation of $R^4_6(24)$ rings (Figure 6). The most commonly observed pattern, (Table 7) with eleven compounds is T2 whereas type T6 is less common with form ii of barbituric acid. This is probably due to the planarity of the macrorings and the short intraring O1···O1 distance. Weak C−H···O1 interactions probably do not allow the presence of substituents larger than H atoms without distortion of the sheet. Type T3 has been observed four times, and T1, T5, and T4 have been observed three times each (Table 7). The most striking feature was observed in the structures of form iii of the 5-ethyl-5-butyl barbituric acid[127] and in two out of three polymorphic forms of the 5-ethyl-5-phenyl barbituric acid (PHBARB05 and 06)[128] where two types are simultaneously observed (Table 7 and Figure 6).

The stability of the six hydrogen bonding networks, six molecules per motif (see Figure 6), has been analyzed at the semiempirical AM1 and DFT B3LYP/6-31++G(d) levels of theory (see Table 8). The stability order calculated at both levels is similar for structures T3, T2 (the most populated in the solid state), and T1; however, at the B3LYP/6−31++G(d) level it was impossible to optimize structure T6 (observed in form ii of barbituric acid), T4, and T5, after several attempts using different initial structures and also imposing constraints. We then tried to optimize the structures using a lower basis set, 6-31G(d), and in this case five of the structures were optimized but the stability order of T1, T2, and T3 obtained was different to that observed using the higher base set, probably because of the lack of diffuse functions that are appropriate to better reproduce the behavior of the hydrogen bonds.

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Supporting Information Available: Tables S1 and S2 and Figure S1 give details of the recalculation of vapor pressures and enthalpies of sublimation published in ref 27. This material is available free of charge via the Internet at http://pubs.acs.org.

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