

Thermochemistry of organic molecules: The way to understand energy–structure relationships*

María Victoria Roux[‡], Concepción Foces-Foces, and Rafael Notario

Instituto de Química Física “Rocasolano”, CSIC, Serrano 119, 28006 Madrid, Spain

Abstract: The combination of experimental calorimetric measurements, particularly of the standard energies and enthalpies of combustion and formation, and theoretical examination of model molecules constitutes a powerful tool for the understanding of the conformational and chemical behavior of organic molecules.

In this article, several examples are provided where the synergy between experiment and theory made possible the comprehension of various fundamental interactions in oxygen- and sulfur-containing six-membered heterocyclic compounds, the determination of the strain energy in two C₈H₈ derivatives, dimethyl cubane-1,4-dicarboxylate and dimethyl cuneane-2,6-dicarboxylate, and the calculation of the enthalpies of formation of the parent compounds, cubane and cuneane, and the study of the energy–structure relationship in barbituric acid.

Keywords: energy–structure relationships; enthalpies of formation; phase transition; polymorphism; thermochemistry.

INTRODUCTION

Structure and energetics are two of the most fundamental concepts in chemistry. The concept of energetics arises as soon as one considers nuclei and electrons, and their assemblages, atoms, and molecules. Structure and energetics are intimately related because the energy associated with a particular structure depends on the atoms, types of bonds, bond angles, and torsion angles that form the molecular framework.

The aim of thermochemistry is the study of the enthalpy changes accompanying the reactions, but even more the determination of the enthalpies of formation of compounds from their elements. This fundamental thermodynamic property of a compound is defined as the enthalpy change that occurs in the formation of a compound from its component elements in their standard states, at a temperature of reference, usually 298.15 K, and a standard pressure, usually taken as 1 bar. Values of the enthalpies of formation provide a measure of the relative thermochemical stabilities of molecules, intimately related to their structures, and they are also helpful in the understanding of structural, conformational, electronic, and reactivity trends exhibited by molecules.

Comparison of the standard enthalpies of formation at $T = 298.15$ K of isomeric compounds is particularly useful because it shows their relative stabilities and provides evidence on the interactions

*Paper based on a presentation at the 20th International Conference on Chemical Thermodynamics (ICCT 20), 3–8 August 2008, Warsaw, Poland. Other presentations are published in this issue, pp. 1719–1959.

[‡]Corresponding author

that are responsible for the enthalpy of formation of each isomer. As an example, we can consider the enthalpies of formation of the three isomers of formula C_5H_{12} , pentane, 2-methylbutane, and 2,2-dimethylpropane determined and published by Good [1] and given in Table 1.

Table 1 Enthalpies of formation in the gas state at $T = 298.15$ K of the isomers of formula C_5H_{12} . All values in kJ mol^{-1} , taken from ref. [1].

Compound	$\Delta_f H_m^\circ(\text{g})$
Pentane	-146.8 ± 0.6
2-Methylbutane	-153.7 ± 0.6
2,2-Dimethylpropane	-167.9 ± 0.6

The three compounds are more stable (they have lower enthalpy) than five carbon atoms and six hydrogen molecules in their fundamental states. But the comparison of the results shows that 2-methylbutane is 6.9 kJ mol^{-1} more stable than pentane and the most branched hydrocarbon, 2,2-dimethylpropane, is 21.1 and 14.2 kJ mol^{-1} more stable than pentane and 2-methylbutane, respectively, showing that the stability increases with the branching of the hydrocarbon.

High-precision combustion calorimetry is considered to be the best method to determine the heat of formation of organic compounds. In combustion calorimetry, the energy of combustion in an oxygen atmosphere at high pressure is measured and there is a total breakdown of the carbon skeleton. The enthalpy of formation in the gas phase is the thermodynamic property related with the structure. To achieve this, it is necessary to eliminate the intermolecular and network energies; therefore, the determination of the vaporization or sublimation enthalpy is a determining step in obtaining the enthalpy of formation in the gas phase.

Nowadays, there is an increasing synergy between experimental and computational chemistry. The interplay between experiment and theory now has been joined by a new mode of inquiry, that of computational experiment, and after the spectacular advances in computing hardware and numerical algorithms, we now commonly speak of experiment, theory, and computation as the three principal elements of modern scientific research.

High-level ab initio calculations give information on molecular and electronic structures [2] of the different molecules and also permit one to obtain reliable enthalpies of formation [3] of the molecules to compare with the experimental values. The combination of experimental calorimetric measurements, particularly of the standard energies and enthalpies of combustion and formation, and theoretical examination of model molecules constitutes a powerful tool for the understanding of the conformational and chemical behavior of organic molecules.

The following account will provide several examples where the synergy between experiment and theory made possible the comprehension of various fundamental interactions in oxygen- and sulfur-containing six-membered heterocyclic compounds [4–7], the determination of the strain energy in two C_8H_8 derivatives: dimethyl cubane-1,4-dicarboxylate (dimethyl pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1,4-dicarboxylate) and dimethyl cuneane-2,6-dicarboxylate (dimethyl pentacyclo[3.3.0.0^{2,4}.0^{3,7}.0^{6,8}]octane-2,6-dicarboxylate), and the calculation of the enthalpies of formation of the parent C_8H_8 compounds, cubane (pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane) and cuneane (pentacyclo[3.3.0.0^{2,4}.0^{3,7}.0^{6,8}]octane) [8], and the study of the energy–structure relationship in barbituric acid [9].

OXYGEN- AND SULFUR-CONTAINING SIX-MEMBERED RINGS

Oxygen- and sulfur-containing six-membered heterocycles occupy a fundamental position in chemistry [10], but whereas the chemistry of pyrans constitutes a very large body of knowledge, that of thiopyrans has been less extensively investigated. The difference in size, electronegativity, and bond polarities as-

sociated with oxygen and sulfur, as well as the availability of $3d$ orbitals in sulfur is reflected in contrasting structural [11], conformational [12,13], and reactivity behavior [14] of the corresponding heterocycles. Thus, C–O–C bond angles are substantially larger (ca. 113°) than the corresponding C–S–C bond angles (ca. 97°), whereas C–O bonds are significantly shorter (ca. 1.43 \AA) than typical C–S bonds (ca. 1.81 \AA).

Regarding conformational behavior, O–C–C–O segments exhibit a preference for *gauche* arrangements [15], whereas S–C–C–S segments generally adopt *anti* conformations, as a consequence of repulsive *gauche* interactions (Fig. 1) [15].

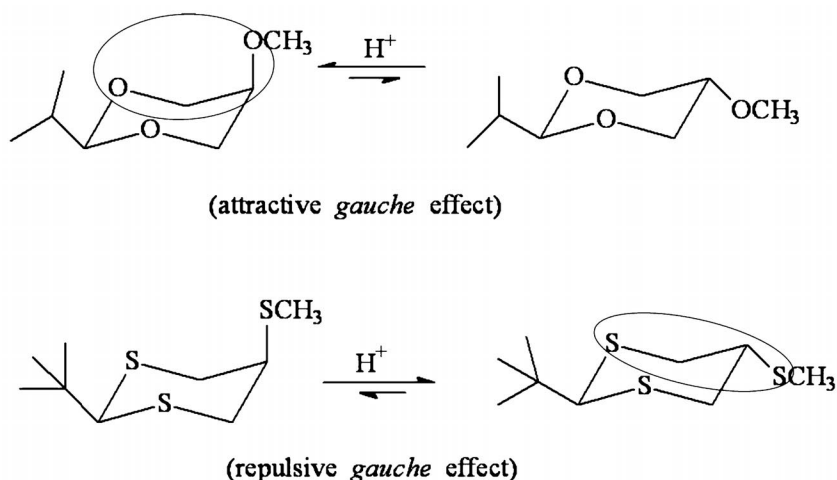


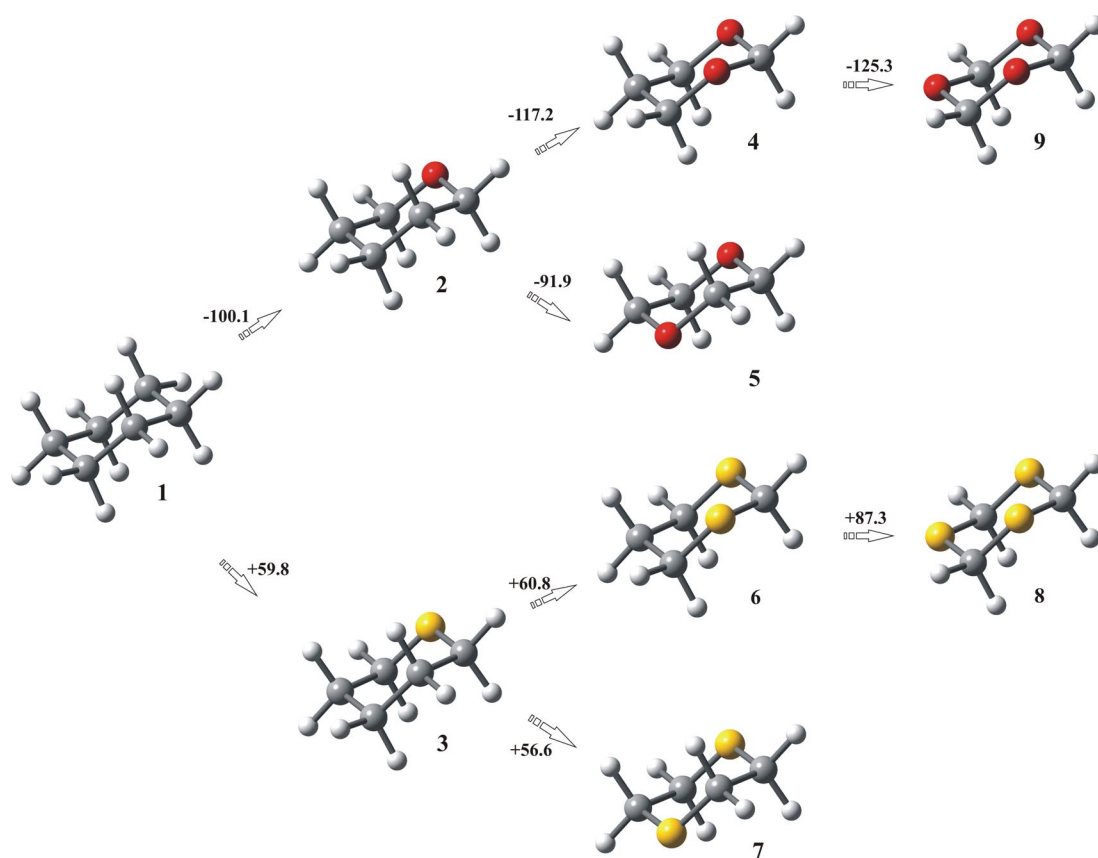
Fig. 1 Arrangements of O–C–C–O and S–C–C–S segments.

Furthermore, the anomeric effect [16] tends to be stronger in O–C–O relative to S–C–S. The enthalpies of formation in the condensed phase at $T = 298.15 \text{ K}$ of the sulfur-containing six-membered heterocycles, tetrahydrothiopyran (thiane), 1,3-dithiacyclohexane (1,3-dithiane), 1,4-dithiacyclohexane (1,4-dithiane), 1,3,5-trithiacyclohexane (1,3,5-trithiane) were determined in our laboratory by combustion calorimetry using a rotating bomb. The enthalpies of sublimation were evaluated by the Knudsen effusion technique. Values of $\Delta_f H_m^\circ(\text{g}, 298.15 \text{ K})$ were calculated from these measurements and are given in Table 2. This table also collects the enthalpies of formation of cyclohexane, and its oxygen-containing six-membered derivatives, tetrahydropyran (oxane), 1,3-dioxacyclohexane (1,3-dioxane), 1,4-dioxacyclohexane (1,4-dioxane), 1,3,5-trioxacyclohexane (1,3,5-trioxane) taken from the literature [17]. From this work, simpler synonyms will be used to facilitate comparative discussion.

The most stable form for all the oxygen- and sulfur-containing six-membered derivatives studied has the chair conformation with a structure similar to that of cyclohexane. In the sulfur derivatives, the chair structure is more puckered to accommodate the bond angles and bond lengths characteristic of sulfur. Figure 2 shows the differences in the enthalpies of formation $\Delta\Delta_f H_m^\circ$, in kJ mol^{-1} for the indicated conversions.

Table 2 Experimental enthalpies of formation in the gas state at $T = 298.15$ K in kJ mol^{-1} .

Compound	$\Delta_f H_m^\circ(\text{g})$
Cyclohexane, 1	-123.3 ± 0.8^{17}
Oxane, 2	-223.4 ± 1.0^{17}
1,3-Dioxane, 4	-340.5 ± 4.2^{17}
1,4-Dioxane, 5	-315.3 ± 0.8^{17}
1,3,5-Trioxane, 9	-465.9 ± 0.4^{17}
Thiane, 3	-63.5 ± 1.0^{17}
1,3-Dithiane, 6	-2.7 ± 2.3^4
1,4-Dithiane, 7	-6.9 ± 2.4^5
1,3,5-Trithiane, 8	$+84.6 \pm 2.6^6$

**Fig. 2** Differences in the enthalpies of formation $\Delta\Delta_f H_m^\circ(\text{g})$ in kJ mol^{-1} for the indicated conversions in oxygen- and sulfur-containing six-membered derivatives. Red balls: O atoms; yellow balls: S atoms.

Relative to cyclohexane **1**, the enthalpy of formation of oxane **2** is much more negative, -123.3 and -223.4 kJ mol^{-1} , respectively (Fig. 2). By contrast, the enthalpy of formation of thiane **3**, is significantly less negative than that for cyclohexane, -63.5 kJ mol^{-1} (Fig. 2). These enthalpies of formation are all relative to the elements in their standard states; that is, 5 C , 5 H_2 , and $\frac{1}{2} \text{ O}_2$ for oxane **2** and 5 C , 5 H_2 , and $\frac{1}{8} \text{ S}_8$ for thiane **3**. Thus, the large negative enthalpy of formation of oxane indicates that formation of two C–O bonds more than compensates for the broken O–O bond. By contrast, the energy gained from two C–S bonds formed in thiane is less sizable, in principle, as a consequence of the higher energy cost involved in the dissociation of the S_8 molecule. These thermochemical data give evidence of the relative strength of the C–O and C–S bonds: the lower electronegativity of sulfur relative to oxygen results in diminished Coulombic attraction between the heteroatom and bonded carbon atoms, and thus weaker C–S bonds.

Comparison of the enthalpies of formation for oxane **2**, and 1,3-dioxane **4**, shows that introduction of the second heteroatom is significantly more exothermic than conversion of cyclohexane **1**, to oxane. Indeed, $\Delta_f H_m^\circ(\mathbf{2})$ is 100.1 kJ mol^{-1} more negative than $\Delta_f H_m^\circ(\mathbf{1})$ (Fig. 2), whereas $\Delta_f H_m^\circ(\mathbf{4})$ is 117.2 kJ mol^{-1} more negative than $\Delta_f H_m^\circ(\mathbf{2})$ [8,12]. Thus, the second substitution of $-\text{CH}_2-$ for $-\text{O}-$ (in $\mathbf{2} \rightarrow \mathbf{4}$) results in 17.1 kJ mol^{-1} further stabilization. This additional stabilization of 17.1 kJ mol^{-1} is not observed when the oxygen atoms are not geminal, as evidenced from examination of $\Delta_f H_m^\circ(\mathbf{5}) = -315.3$ kJ mol^{-1} , which is only 91.9 kJ mol^{-1} more negative than the enthalpy of formation of oxane **2** (Fig. 2). These results can be explained in terms of $n_{\text{O}} \rightarrow \sigma_{\text{C-O}}^*$ hyperconjugation (Fig. 3) [16] which provides “double bond–no bond” stereoelectronic stabilization to 1,3-dioxane **4**.

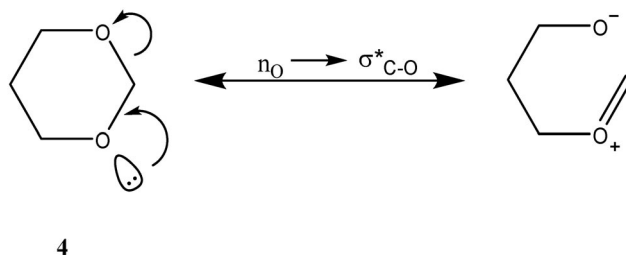


Fig. 3 Scheme of $n_{\text{O}} \rightarrow \sigma_{\text{C-O}}^*$ hyperconjugation in 1,3-dioxane **4**.

Dioxanes **4** and **5** are isomeric, and therefore comparison of their enthalpies of formation provides direct quantitative information on their relative energies.

We also can consider the case of 1,3-dithiane and 1,4-dithiane. In 1,3-dithiane **6**, the lack of stabilization in the geminal S–C–S segment present suggests that the “double bond–no bond” stereoelectronic interaction operative in the oxygen analog 1,3-dioxane is not effective here; the nonbonding orbitals at sulfur are less efficient in $n_{\text{S}} \rightarrow \sigma_{\text{C-S}}^*$ hyperconjugation. The more negative enthalpy of formation (increased stability) of 1,4-dithiane **7** relative to 1,3-dithiane **6** supported the existence of a repulsive interaction between sulfurs in a 1,3 arrangement. Such an effect should be more apparent in 1,3,5-trithiane **8**.

The experimental enthalpy of formation of 1,3,5-trioxane **9**, $\Delta_f H_m^\circ = -465.9$ kJ mol^{-1} , is 125.3 kJ mol^{-1} more negative (exothermic) than $\Delta_f H_m^\circ$ for 1,3-dioxane **4**: the third *meta* $\text{CH}_2 \rightarrow \text{O}$ substitution is 25.2 kJ mol^{-1} more stabilizing than the first substitution in cyclohexane \rightarrow oxane. In strong contrast, the experimental enthalpy of formation of 1,3,5-trithiane **8**, $\Delta_f H_m^\circ = +84.6$ kJ mol^{-1} , is 87.3 kJ mol^{-1} more *endothermic* than $\Delta_f H_m^\circ$ for 1,3-dithiane **6** (Fig. 2). These results are in line with the “anomeric” stabilization operative in the three O–C–O segments present in 1,3,5-trioxane, to be contrasted with through-space, lone pair–lone pair repulsion in 1,3,5-trithiane **8**.

CUBANE AND CUNEANE AND THEIR CARBOXYLATES

Cubane is a synthetic saturated polycyclic hydrocarbon of extraordinary geometry and strain formed by eight atoms of carbon placed at the corners of a cube, with one atom of hydrogen attached to each tertiary carbon. It is one of the platonic hydrocarbons, and for a long time it was considered that cubane could only exist theoretically due to the impossibility of synthesizing a compound with eight 90° C–C–C angles and therefore large strain energy (Fig. 4). It was synthesized for the first time in 1964 by P. Eaton [18]. Soon after the first synthesis of cubane, there were measurements of the enthalpies of combustion and sublimation [19], but the values of both measurements have been questioned [20–22]. Cuneane is a valence isomer of cubane of considerable lower symmetry and arises from cubane by Ag⁺-catalyzed rearrangement, suggesting that cuneane is more stable than cubane.

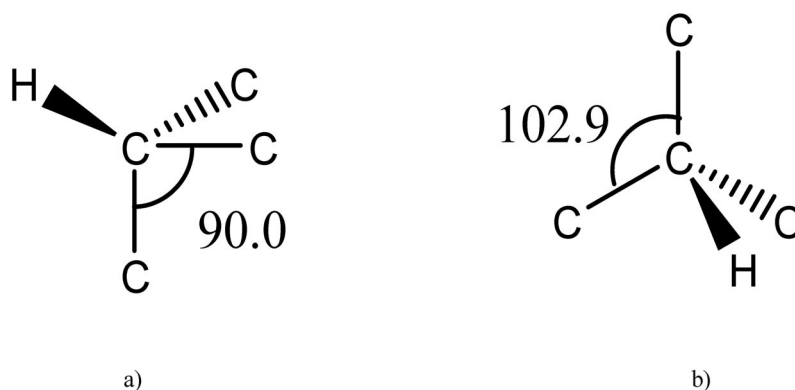


Fig. 4 Values in degrees of the C–C–C tertiary angles in (a) cubane and (b) no stressed compounds.

Our study was a combination of experimental and theoretical thermochemistry of dimethyl cubane-1,4-dicarboxylate (dimethyl pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1,4-dicarboxylate) and dimethyl cuneane-2,6-dicarboxylate (dimethyl pentacyclo[3.3.0.0^{2,4}.0^{3,7}.0^{6,8}]octane-2,6-dicarboxylate) and provided structural and thermochemical information about the rearrangement of these compounds [8]. The enthalpies of formation in the condensed phase at $T = 298.15$ K of dimethyl cubane-1,4-dicarboxylate and dimethyl cuneane-2,6-dicarboxylate were determined by combustion calorimetry. The enthalpies of sublimation were calculated by combining vaporization enthalpies evaluated by correlation gas chromatography and fusion enthalpies measured by differential scanning calorimetry. Values of $\Delta_f H_m^\circ(\text{g}, 298.15 \text{ K})$ were calculated from these measurements and are given in Table 3.

Table 3 Experimental standard enthalpies of formation in the condensed and gas phases and sublimation of dimethyl cubane-1,4-dicarboxylate and dimethyl cuneane-2,6-dicarboxylate at $T = 298.15$ K. All values in kJ mol^{-1} .

Compound	$\Delta_f H_m^\circ(\text{s})$	$\Delta_{\text{sub}} H_m^\circ$	$\Delta_f H_m^\circ(\text{g})$
Dimethyl cubane-1,4-dicarboxylate	-232.6 ± 5.8	117.2 ± 3.9	-115.4 ± 7.0
Dimethyl cuneane-2,6-dicarboxylate	-413.0 ± 5.2	106.8 ± 3.0	-306.2 ± 6.0

Dimethyl cubane-1,4-dicarboxylate and dimethyl cuneane-2,6-dicarboxylate are isomers. The combination of their enthalpies of formation gives an enthalpy of isomerization $\Delta_f H_m^\circ(\text{g}, 298.15 \text{ K})$ of -190 kJ mol^{-1} (Fig. 5).

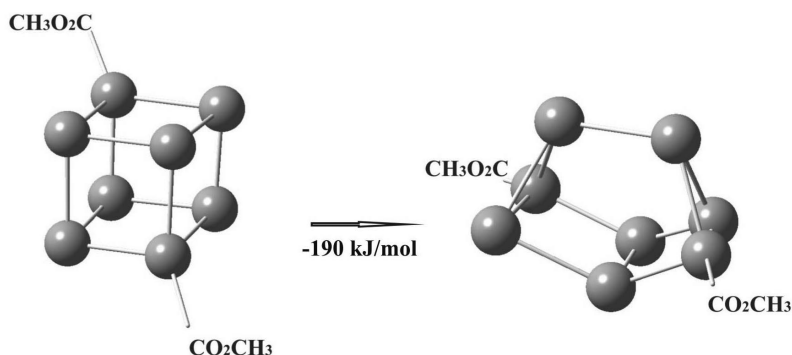


Fig. 5 Enthalpy of isomerization of dimethyl cubane-1,4-dicarboxylate to dimethyl cuneane-2,6-dicarboxylate.

One of the more interesting properties of cubane and its derivatives is their strain energy, defined as the difference between the enthalpy of formation of cubane and that of an unstrained reference material. We have chosen to use as our reference material for an unstrained quaternary carbon atom bearing a carbomethoxy group ($C-CO_2CH_3$), the difference in the experimental enthalpies of formation of methyl adamantane-1-carboxylate (methyl tricyclo[3.3.1.1^{3,7}]decane-1-carboxylate) and adamantane (tricyclo[3.3.1.1^{3,7}]decane), Fig. 6.

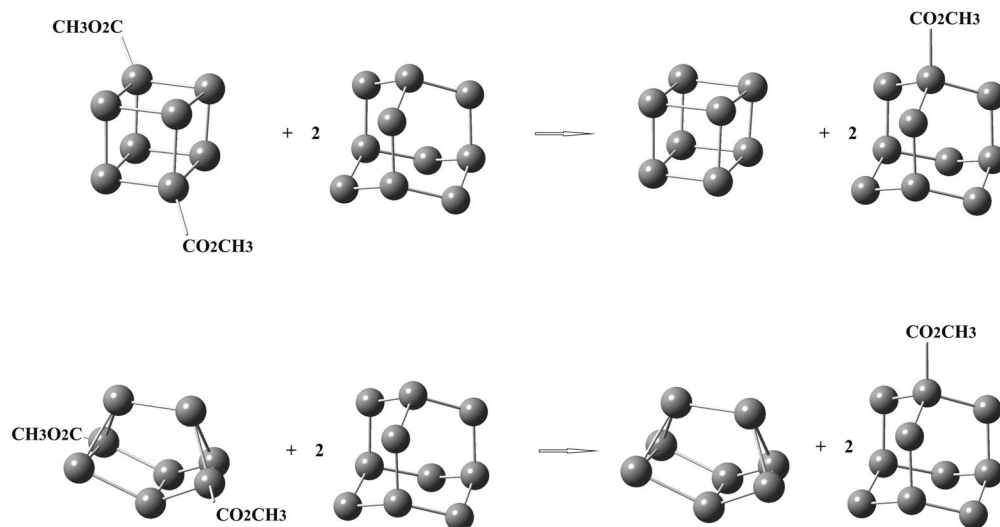


Fig. 6 Isodesmic reactions used for the calculation of the enthalpies of formation of cubane and cuneane.

Also included in Fig. 6 is the homodesmotic reaction relating dimethyl cuneane-2,6-dicarboxylate to cuneane. The theoretical calculations indicate that both reactions are not exactly thermoneutral, resulting in enthalpies of reaction of 6.8 and 21.0 kJ mol^{-1} , in the case of cubane and cuneane, respectively. An uncertainty of $\pm 4 \text{ kJ mol}^{-1}$ in the calculated enthalpies of reaction has been estimated. Combining these results with the experimental enthalpies of formation of adamantane, $-134.6 \pm 2.2 \text{ kJ mol}^{-1}$ [17] and methyl adamantane-1-carboxylate, $-495.4 \pm 2.7 \text{ kJ mol}^{-1}$ [23], enthalpies of formation, $\Delta_f H_m^\circ(\text{g}, 298.15 \text{ K}) = 613.0 \pm 9.5$ and $436.4 \pm 8.8 \text{ kJ mol}^{-1}$, for cubane and cuneane, respectively, were obtained.

Strain enthalpies for cubane and cuneane were obtained using the isodesmic reactions and stoichiometry of Fig. 7, and the experimental enthalpies of formation of ethane and isobutane, -83.8 ± 0.3 and -134.2 ± 0.6 kJ mol⁻¹, taken from ref. [17].

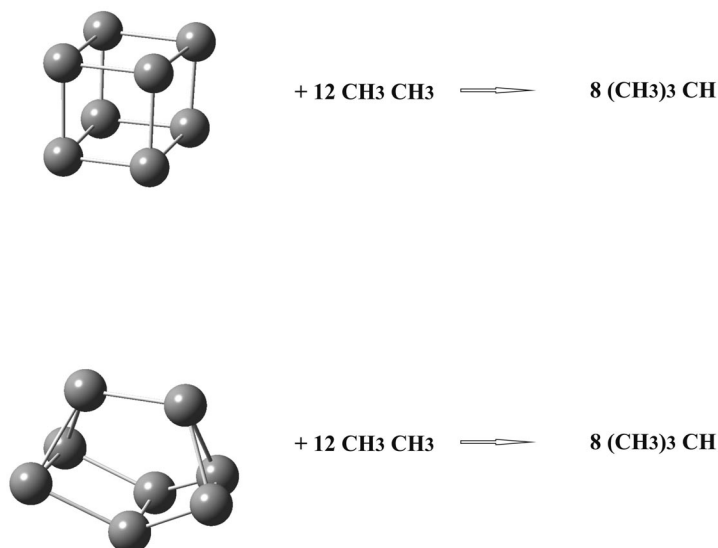


Fig. 7 Isodesmic reactions used for the calculation of the strain enthalpies of cubane and cuneane.

The calculated values for the strain enthalpies of cubane and cuneane were 681.0 ± 9.8 and 504.4 ± 9.1 kJ mol⁻¹, respectively. Strain enthalpies of 670.7 ± 9.4 and 509.2 ± 9.4 kJ mol⁻¹ were calculated using their enthalpies of formation derived from Gaussian-n calculations. Theoretically calculated values at the MP2(FULL)/6-31G(d) level are 685.3 and 505.7 kJ mol⁻¹, respectively.

BARBITURIC ACID

We are presently involved in the study of the thermochemistry of barbituric acid derivatives. The main purposes of this study are to provide reliable data for the family of barbiturates and 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 [(1*H*,3*H*,5*H*)-pyrimidine-2,4,6-trione, CAS number: 67-52-7] is a very well known organic compound based on a pyrimidine heterocyclic skeleton [24]. It was synthesized for the first time in 1864 by von Baeyer [25], and it is the parent compound of a large class of barbiturates that act as central nervous system depressants, and 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 [26,27].

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, reliable experimental thermochemical studies are scarce. To our knowledge, there is only one report [28] of the gas-phase enthalpy of formation of the parent compound (barbituric acid) and two very old reports of the enthalpies of combustion and formation in condensed phase [29,30]. Moreover, there are three relatively recent determinations of the enthalpy of sublimation of barbituric acid that span a 13 kJ mol⁻¹ range [28,31,32]. 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 experimental determination of the enthalpy of formation and high-level ab initio calculations.

A differential scanning calorimeter (DSC) was used to study the behavior of our commercial sample as a function of temperature. DSC scans show a solid–solid phase transition at $T = 516.0 \pm 0.4$ K having an enthalpy of 1.30 ± 0.04 kJ mol⁻¹, Fig. 8. This behavior was reproducible, being observed in all the runs performed with fresh samples. The temperature and enthalpy of fusion determined by DSC were $T_{\text{fus}} = 526.4 \pm 0.5$ K and $\Delta_{\text{fus}}H = 20.87 \pm 0.14$ kJ mol⁻¹, respectively.

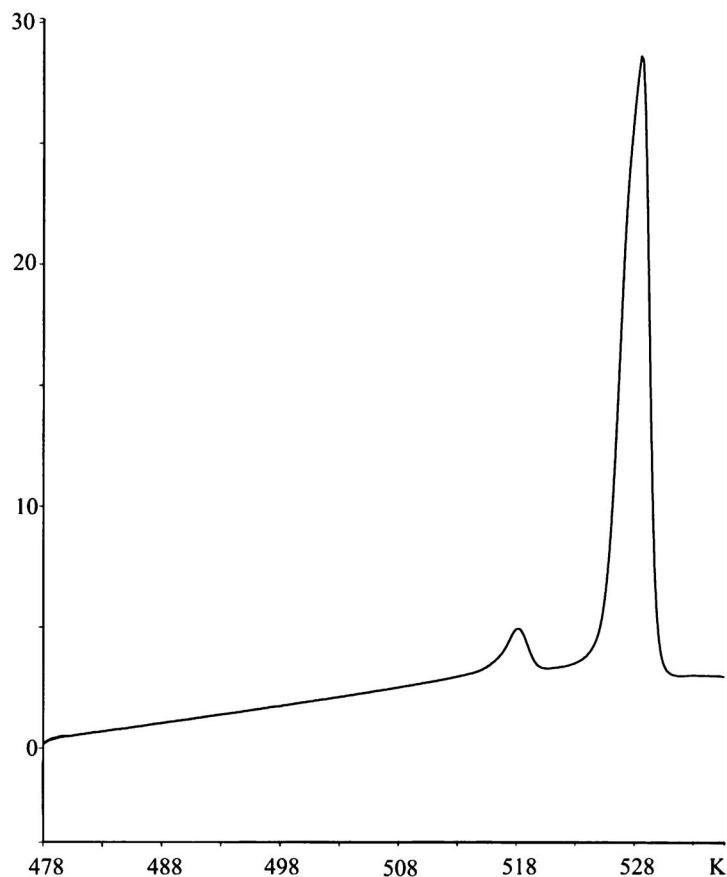


Fig. 8 Plot of the DSC scans obtained for barbituric acid in heating.

In the solid state, as far as the Cambridge Crystallographic Database (CSD version 5.29 Jan. 2008 update) is concerned [33], the barbituric acid exists in two anhydrous polymorphic forms: (i) [34,35] (CSD refcodes = BARBAC and BARBAC01) and (ii) [35] (BARBAC02).

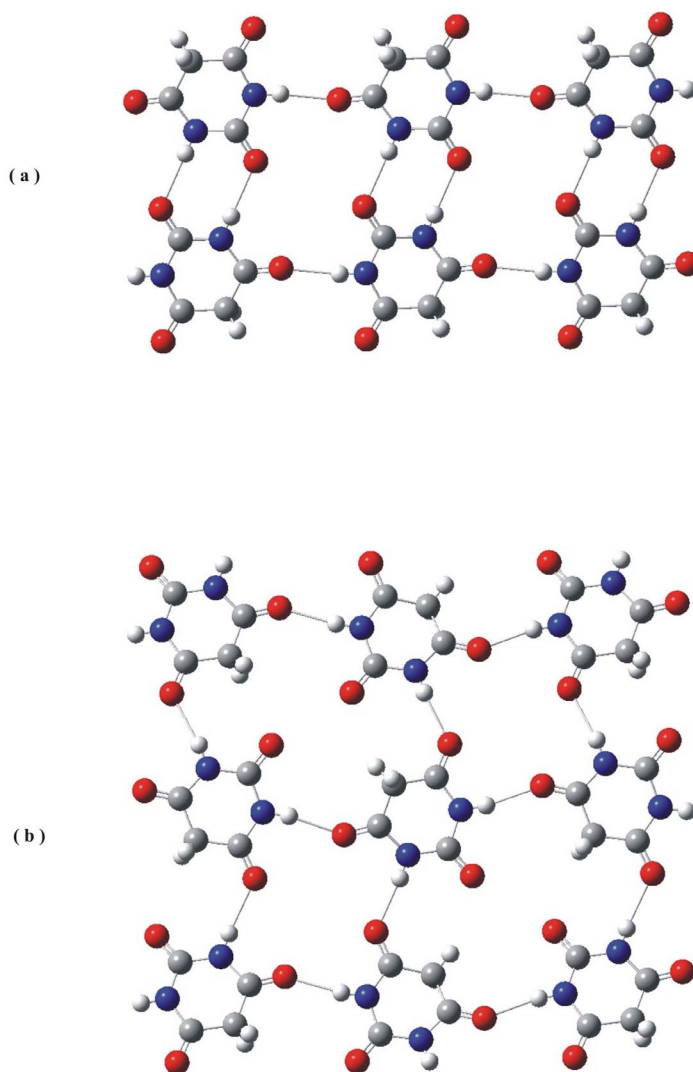


Fig. 9 Hydrogen-bonded molecular ribbon (a) and sheet (b) formed by the anhydrous barbituric acid polymorphs i and ii, respectively.

The X-ray powder diffraction technique was used to establish to which polymorphic form the commercial sample used in our study corresponds and to characterize the new polymorph observed by DSC. According to the simulated powder patterns (program PLATON) [36] from the known polymorphic crystal structures (Figs. 10a and 10b), the commercial sample from Fluka corresponds to polymorph ii (Fig. 10c). At room temperature, the indexed [37] cell with the highest reliability factor is monoclinic with cell parameters in agreement with those reported by single-crystal diffraction methods [35] for polymorphic form ii ($a = 8.199$, $b = 12.613$, $c = 9.823$ Å, and $\beta = 95.7^\circ$ vs. $a = 8.019$, $b = 12.479$, $c = 9.764$ Å, and $\beta = 96.2^\circ$, respectively). However, after the phase transition (Fig. 10d), 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 $\gamma = 98.1^\circ$; 2: $a = 8.558$, $b = 5.524$, $c = 5.479$ Å, $\alpha = 103.5$, $\beta = 85.3$, and $\gamma = 93.7^\circ$).

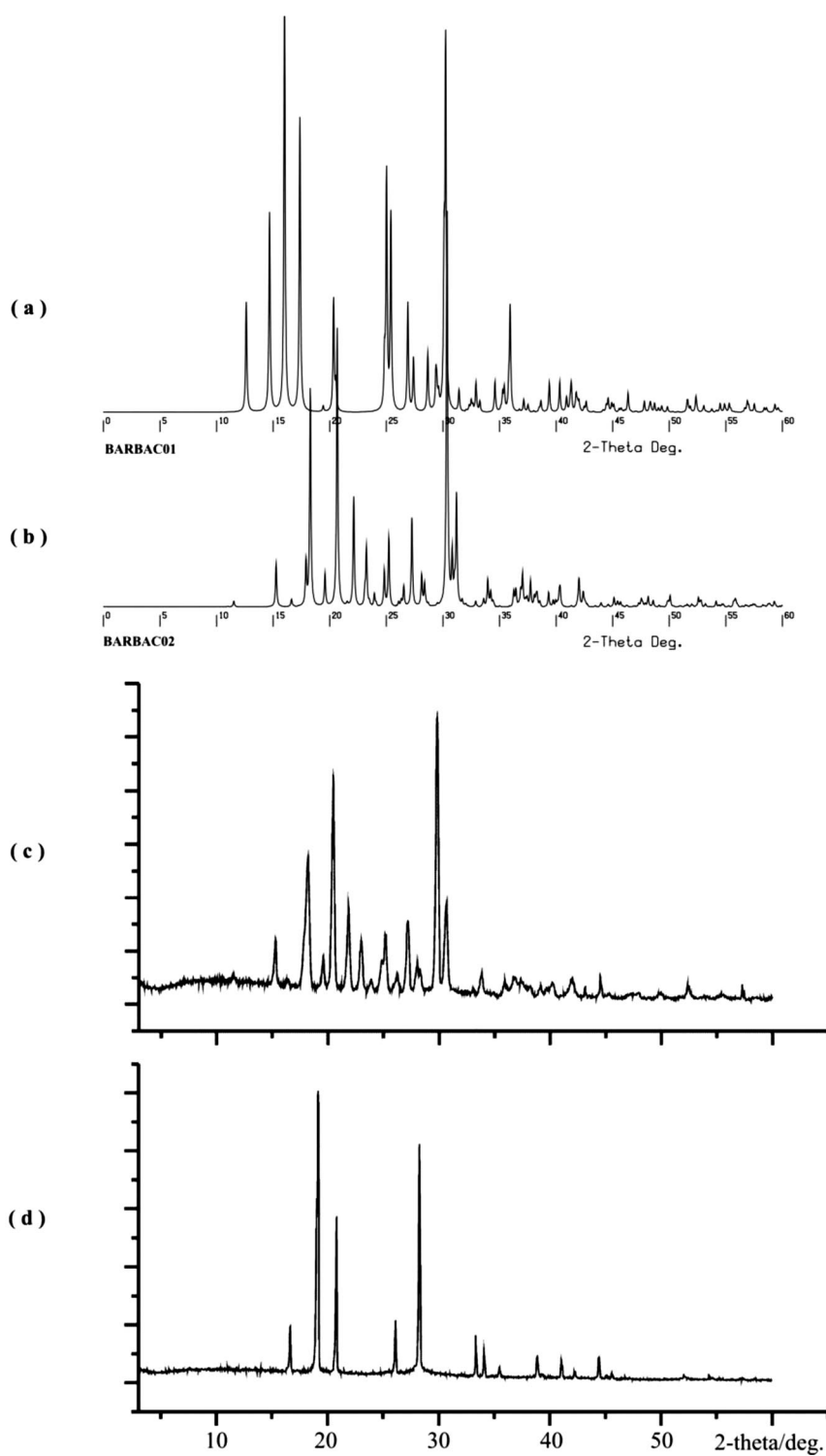


Fig. 10 X-ray powder diffraction pattern of the anhydrous barbituric acid. (a and b) simulated powder diffraction pattern based on the single-crystal structures of polymorphs i and ii. (c and d) experimental powder diffraction pattern of the commercial sample at room temperature and after the phase transition at $T = 516$ K.

This suggests two molecules in the unit cell vs. eight (two independent) in the monoclinic cell of form ii.

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 [38–44] report the triketo tautomer to be the most stable one in the gas phase. In the solid state, the anhydrous compound exists only as the triketo form [39,45,46]. 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 [28,32].

The enthalpies of combustion and sublimation were measured by static bomb combustion calorimetry and transference (transpiration) method in a saturated N₂ stream (Table 4), and a gas-phase enthalpy of formation value of -534.3 ± 1.7 kJ mol⁻¹ was determined at $T = 298.15$ K.

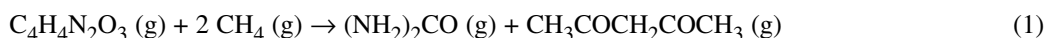
Table 4 Experimental enthalpies of combustion, sublimation, and formation in the solid and gas phases at $T = 298.15$ K for barbituric acid. All values in kJ mol⁻¹.

$\Delta_c H_m^\circ(\text{cr})$	$\Delta_f H_m^\circ(\text{cr})$	$\Delta_{\text{cr}}^\circ H_m^\circ$	$\Delta_f H_m^\circ(\text{g})$	Ref.
-1496.3 ± 1.5	-649.4 ± 1.6	115.1 ± 0.7	-534.3 ± 1.7	[9]
-1511.1 ± 2.8	-634.7 ± 2.9	$126.4 \pm 0.9^{\text{a}}$	$-508.3 \pm 3.0^{\text{a}}$	[28]
		$120.3 \pm 1.2^{\text{b}}$	$-514.4 \pm 3.1^{\text{b}}$	
-1501.6	-644.2			[29]
-1505.0	-640.8			[30]
		$113.6 \pm 2.7^{\text{a}}$		[31]
		$114.8 \pm 0.9^{\text{a}}$		[32]

^aObtained from experimental vapor pressures reported in the literature in the same manner as our experimental results, see ref. [9].

^bExperimental vapor pressures reported in ref. [28] have been recalculated by Prof. G. J. Kabo [47] and have been treated in the same manner as our experimental results in order to derive the enthalpy of sublimation, see ref. [9].

G3-calculated enthalpies of formation of barbituric acid, C₄H₄N₂O₃, were obtained using the atomization reaction, and one isodesmic reaction taking urea and 2,4-pentanedione as references:



The G3-calculated enthalpies of formation obtained [48] from the atomization reaction, -532.3 kJ mol⁻¹, and from the isodesmic reaction (1), -531.1 kJ mol⁻¹, are in very good agreement with the experimental value determined in this work.

ACKNOWLEDGMENT

The support of the Spanish Ministerio de Ciencia e Innovación under Projects CTQ2006-12745 and CTQ2007-60895/BQU is gratefully acknowledged.

REFERENCES

1. W. D. Good. *J. Chem. Thermodyn.* **2**, 237 (1970).
2. C. J. Cramer. *Essentials of Computational Chemistry. Theories and Models*, John Wiley, Chichester (2002).

3. L. A. Curtiss, P. C. Redfern, D. J. Frurip. "Theoretical methods for computing enthalpies of formation of gaseous compounds", in *Reviews in Computational Chemistry*, Vol. 15, K. B. Lipkowitz, D. B. Boyd (Eds.), Chap. 3, Wiley-VCH, New York (2000).
4. M. V. Roux, J. Z. Dávalos, P. Jiménez, H. Flores, J. L. Saiz, J.-L. M. Abboud, E. Juaristi. *J. Chem. Thermodyn.* **31**, 635 (1999).
5. J. Z. Dávalos, H. Flores, P. Jiménez, R. Notario, M. V. Roux, E. Juaristi, R. S. Hosmane, J. F. Liebman. *J. Org. Chem.* **64**, 9328 (1999).
6. M. V. Roux, P. Jiménez, J. Z. Dávalos, R. Notario, E. Juaristi. *J. Org. Chem.* **66**, 5343 (2001).
7. E. Juaristi, R. Notario, M. V. Roux. *Chem. Soc. Rev.* **34**, 437 (2005).
8. M. V. Roux, J. Z. Dávalos, P. Jiménez, R. Notario, O. Castaño, J. S. Chickos, W. Hanshaw, H. Zhao, N. Rath, J. F. Liebman, B. Farivar, A. Bashir-Hashemi. *J. Org. Chem.* **70**, 5461 (2005).
9. M. V. Roux, M. Temprado, R. Notario, C. Foces-Foces, V. N. Emel'yanenko, S. P. Verevkin. *J. Phys. Chem. A* **112**, 7455 (2008).
10. A. R. Katritzky, C. W. Rees (Eds.), *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford (1984).
11. M. J. Cook. "Six-membered rings with more than one oxygen or sulphur atom", in *Comprehensive Heterocyclic Chemistry*, Vol. 3, A. R. Katritzky, C. W. Rees (Eds.), p. 943, Pergamon Press, Oxford (1984).
12. E. Juaristi (Ed.). *Conformational Behavior of Six-Membered Rings. Analysis, Dynamics, and Stereoelectronic Effects*, VCH, New York (1995).
13. M. B. Smith, J. March. *March's Advanced Organic Chemistry*, 5th ed., p. 172, John Wiley, New York (2001).
14. P. C. B. Page, M. B. van Niel, J. C. Prodger. *Tetrahedron* **45**, 7643 (1989) and refs. therein.
15. E. Juaristi. *Introduction to Stereochemistry and Conformational Analysis*, Chap. 18, John Wiley, New York (1991).
16. E. Juaristi, G. Cuevas. *The Anomeric Effect*, CRC, Boca Raton (1995) and refs. therein.
17. J. B. Pedley, R. D. Naylor, S. P. Kirby. *Thermochemical Data of Organic Compounds*, 2nd ed., Chapman and Hall, London (1986).
18. P. E. Eaton, T. W. Cole. *J. Am. Chem. Soc.* **86**, 962 (1964).
19. B. D. Kybett, S. Carroll, P. Natalis, D. W. Bonnell, J. L. Margrave, J. L. Franklin. *J. Am. Chem. Soc.* **88**, 626 (1966).
20. V. V. Diky, M. Frenkel, L. S. Karpushenkava. *Thermochim. Acta* **408**, 115 (2003).
21. A. Bashir-Hashemi, J. S. Chickos, W. Hanshaw, H. Zhao, B. S. Farivar, J. F. Liebman. *Thermochim. Acta* **424**, 91 (2004).
22. D. R. Kirklin, K. L. Churney, E. S. Domalski. *J. Chem. Thermodyn.* **21**, 1105 (1989).
23. J. L. M. Abboud, P. Jiménez, M. V. Roux, C. Turrión, C. Lopez-Mardomingo. *J. Chem. Thermodyn.* **24**, 1299 (1992).
24. J. T. Bojarski, J. L. Mokrosz, H. J. Barton, M. H. Paluchowska. "Recent progress in barbituric acid chemistry", in *Advances in Heterocyclic Chemistry*, Vol. 38, A. R. Katritzky (Ed.), Academic Press, New York (1985) and refs. therein.
25. A. von Baeyer. *Ann. Chem. Pharm.* **130**, 129 (1864).
26. B. Levine (Ed.). *Principles of Forensic Toxicology*, 2nd ed., p. 173, AACC Press, Washington, DC (2003).
27. M. Willow, G. A. R. Johnston. *Int. Rev. Neurobiol.* **24**, 15 (1983).
28. (a) T. V. Soldatova, G. Y. Kabo, A. A. Kozyro, M. L. Frenkel. *Zh. Fiz. Khim.* **64**, 336 (1990); (b) T. V. Soldatova, G. Y. Kabo, A. A. Kozyro, M. L. Frenkel. *Russ. J. Phys. Chem.* **64**, 177 (1990).
29. M. P. Lemoult. *Compt. Rend.* 663 (1904).
30. E. Fischer, F. Wrede. *Sitzungsber. Dtsch. Akad. Wiss. Berlin. Kl. Math. Phys. Tech.* 687 (1904).
31. W. Zielenkiewicz, G. L. Perlovich, M. Wszelaka-Rylik. *J. Therm. Anal. Calorim.* **57**, 225 (1999).
32. B. Brunetti, V. Piacente. *J. Chem. Eng. Data* **44**, 809 (1999).

33. F. H. Allen. *Acta Crystallogr., Sect. B* **58**, 380 (2002).
34. W. Bolton. *Acta Crystallogr.* **16**, 166 (1963).
35. T. C. Lewis, D. A. Tocher, S. L. Price. *Cryst. Growth Des.* **4**, 979 (2004).
36. A. L. Spek. *J. Appl. Crystallogr.* **36**, 7 (2003).
37. F. Kohlbeck, E. M. Hörl. *J. Appl. Crystallogr.* **9**, 28 (1976).
38. F. Raimondo, A. Pieretti, L. Gontrani, L. Bencivenni. *Chem. Phys.* **271**, 293 (2001).
39. S. Senthilkumar, P. Kolandaivel. *J. Comput.-Aided Mol. Des.* **16**, 263 (2002).
40. F. Zuccarello, G. Buemi, C. Gandolfo, A. Contino. *Spectrochim. Acta A* **59**, 139 (2003).
41. S. Ralhan, N. K. Ray. *J. Mol. Struct. (Theochem)* **634**, 83 (2003).
42. V. B. Delchev. *J. Struct. Chem.* **45**, 570 (2004).
43. L. I. Daskalova, I. Binev. *Int. J. Quantum Chem.* **106**, 1338 (2006).
44. Y. Ren, Y. Guo, B. Li. *Hainana Shifan Xueyuan Xuebao, Ziran Kexueban* **20**, 242 (2007) [CAN 148:214627].
45. G. A. Jeffrey, S. Ghose, J. O. Warwicker. *Acta Crystallogr.* **14**, 881 (1961).
46. A. R. Al-Karaghoul, B. Abdul-Wahab, E. Ajaj, S. Al-Asaff. *Acta Crystallogr., Sect. B* **33**, 1655 (1977).
47. G. J. Kabo. Personal communication (2007).
48. Experimental $\Delta_f H_m^\circ$ values for the reference compounds used inisodesmic reaction (1), methane, $-74.6 \text{ kJ mol}^{-1}$ has been taken from J. A. Manion. *J. Phys. Chem. Ref. Data* **31**, 123 (2002); $\Delta_f H_m^\circ$ value for urea, $-235.5 \text{ kJ mol}^{-1}$, has been taken from ref. [49]; and $\Delta_f H_m^\circ$ value for acetylacetone, $-358.9 \text{ kJ mol}^{-1}$, has been taken from ref. [50].
49. H. Y. Afeefy, J. F. Liebman, S. E. Stein. *Neutral Thermochemical Data in NIST Chemistry WebBook, NIST Standard Reference Database Number 69*, P. J. Linstrom, W. G. Mallard (Eds.), National Institute of Standards and Technology, Gaithersburg, MD, June (2005) <<http://webbook.nist.gov>>.
50. M. Temprado, M. V. Roux, P. Umnahanaut, H. Zhao, J. S. Chickos. *J. Phys. Chem. B* **109**, 12590 (2005).