

5-Isopropylbarbituric and 2-thiobarbituric acids: An experimental and computational study



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ARTICLE INFO

Article history:

Received 30 October 2015

Received in revised form

27 November 2015

Accepted 17 December 2015

Available online 21 December 2015

Keywords:

Combustion calorimetry

Enthalpy of formation

Enthalpy of sublimation

5-Isopropylbarbituric acid

2-Thiobarbituric acid

G3 and G4 calculations

ABSTRACT

The standard ($p^\circ = 0.1$ MPa) molar energies of combustion, $\Delta_c U_m^\circ$, for the crystalline 5-isopropylbarbituric and 2-thiobarbituric acids were determined, at the temperature of 298.15 K, by static bomb or rotating bomb combustion calorimetry, respectively. For 5-isopropylbarbituric acid, the standard molar enthalpy of sublimation, $\Delta_{cr} H_m^\circ$, at $T = 298.15$ K, was derived by Calvet microcalorimetry. The standard molar enthalpy of sublimation, at $T = 298.15$ K, was derived by the Clausius–Clapeyron equation, from the temperature–vapor pressure dependence, measured by the Knudsen mass-loss effusion method. These experiments allowed the determination of the standard molar enthalpy of formation, in the gaseous phase, at $T = 298.15$ K for 5-isopropylbarbituric acid. For 2-thiobarbituric acid, the gas-phase enthalpy of formation was calculated combining the result derived for the crystalline phase with literature data for the enthalpy of sublimation, at $T = 298.15$ K.

These values were compared with estimates obtained from very accurate computational calculations using the G3 and G4 level theory composite methods.

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1. Introduction

Pyrimidines and its derivatives are integral part of DNA and RNA, being therefore associated with diverse biological activities, with a consequent increase of prominence due of their potential pharmaceutical interest. In particular, the barbituric acid (pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione) derivatives, known as barbiturates, [1] are a well-known class compounds with several pharmaceutical applications, being used, for example, in the synthesis of sedatives, hypnotics and anticonvulsants and also for anesthesia [2,3]. Barbiturates have been also widely used in the synthesis of new uracil derivatives, with the aim to discover more potent molecules, whose higher specificity and reduced toxicity improve their action [4–6]. In parallel, some 2-thiobarbituric acids (4,6-dihydroxy-2-mercaptopyrimidine) derivatives play also an important role due to their extensive biological activity, namely antimicrobial [7], antifungal [8], anticancer [9], anti-tubercular [10], antioxidant [11], anti-inflammatory [12], antiviral [13] and antidiabetic [14]. The thiobarbiturates differ from other barbiturates in having a sulfur atom in place of an oxygen atom at the

C-2 position, being their biological activity mainly related to the tautomerism and the nature of the substituent [15]. In addition, it was reported that the insertion of an aryl, amino, or a methyl moiety at 5-position of thiobarbituric acid enhances the antidepressant activities of the resulting compounds [16]. Thiobarbiturates are also widely used for the preparation of many complexes with various metals [17–19], being used in chemical analysis as a reagent for spectrophotometric determination of several metals (i.e., bismuth, ruthenium and rhodium) [20–22]. Other important applications of the 2-thiobarbituric acid derivatives have been investigated, namely as corrosion inhibitors for metal in acid environments [23,24]. The 2-thiobarbituric acid is a reagent with interest in chromatography [25] and is used for determination of the degree of oxidation of natural fats in food [26–30]. Industrially, barbituric and thiobarbituric acids have been investigated as thermal stabilizers for rigid poly(vinyl chloride) (PVC) at 180 °C, in air [31].

Due to the importance of these compounds in various industrial, clinical and pharmacological applications, the knowledge of the correspondent thermodynamic properties is relevant in order to contribute to the characterization of their chemical behavior.

Following our interest on the systematic study of pyrimidine [32–36], uracil [37–42] and thiouracil derivatives [43,44] we report herein an experimental and computational study of 5-isopropylbarbituric and 2-thiobarbituric acids, whose structural

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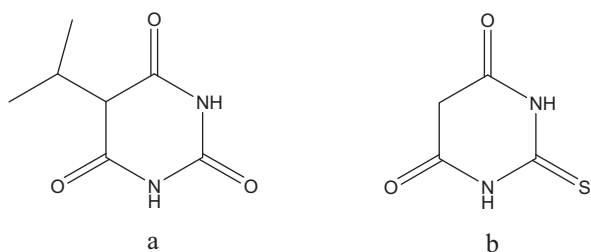


Fig. 1. Structural formula of 5-isopropylbarbituric acid (a) and 2-thiobarbituric (b) acid.

formulas are shown in Fig. 1. The standard molar enthalpies of formation of both compounds in the crystalline phase, at $T = 298.15$ K, were derived from their standard massic energy of combustion, in oxygen, at $T = 298.15$ K, measured by static bomb (5-isopropylbarbituric acid) or rotating bomb combustion calorimetry (2-thiobarbituric acid). The standard molar enthalpy of sublimation of 5-isopropylbarbituric acid was obtained either directly by high temperature Calvet microcalorimetry, or indirectly by applying the Clausius–Clapeyron equation to the temperature dependence of the vapor pressures measurements obtained by the Knudsen mass-loss effusion technique. Additionally, computational calculations of the gas-phase enthalpies of formation, at the G3 and G4 levels of theory, were also performed.

2. Experimental details

2.1. Compounds and purity control

5-Isopropylbarbituric acid [CAS 7391-69-7] and 2-thiobarbituric acid [CAS 504-17-6] were obtained from the Alfa Aesar Co. with the assessed value of mass fraction purity: 0.98. Both compounds were purified by sublimation under reduced pressure, recrystallization from water and further dried under reduced pressure. For 5-isopropylbarbituric purity was checked by the consistent results obtained from the combustion experiments, as well as by the closeness to unity of the carbon dioxide recovery ratios. The average ratio of the mass of the sample, together with the standard deviation of the mean was: (0.9998 ± 0.0003) . Purity control 2-thiobarbituric acid was assessed from gas–liquid chromatography, using a Hewlett-Packard 4890A gas chromatograph, on a HP5 column, using a mixture of nitrogen and compressed air as the carrier gas ($p = 3$ psi.); the purity was found to be greater than 0.999 (mass fraction).

The water content in the studied compounds was determined by coulometry (Karl Fischer titration), using a Karl Fischer coulometer, model XX (Metrohm, Herisau, Switzerland). There were no traces of water in any of the samples. Table 1 presents the origin and purification details of the samples used to perform the experiments.

2.2. Combustion calorimetry

The standard molar energies of combustion of 5-isopropylbarbituric and 2-thiobarbituric acids were determined in two isoperibol systems:

- i. The static bomb calorimeter used for 5-isopropylbarbituric acid comprises a twin valve bomb, type 1105, Parr Instrument Company, made of stainless steel, with an internal volume of 0.340 dm³. The apparatus and technique have been carefully described elsewhere [45,46]. Combustion of BCS-CRM 39j Thermochemical Standard Benzoic acid was used for calibration of the bomb. Its massic energy of combustion is $-(26434 \pm 3)$ J g⁻¹, under certificate conditions [47]. The calibration results were

corrected to give the energy equivalent of the calorimeter, ε_{cal} corresponding to the average mass of 3119.6 g of water added to the calorimeter. From six calibration experiments, ε_{cal} was found to be (15905.0 ± 0.8) J K⁻¹, where the uncertainty quoted is the standard deviation of the mean.

- ii. The rotating bomb calorimeter used to perform the 2-thiobarbituric acid measurements, formerly developed by Sunner at the University of Lund, Sweden [48], has been already described in the literature [49,50]. The bomb, whose internal volume is 0.258 dm³, is of stainless steel lined with platinum, and the internal fittings are machined from platinum. In each experiment, the bomb is suspended from the lid of the calorimeter can, to which an average mass of 5222.5 g of water is added. Benzoic acid NIST Standard Reference Material, sample 39j [47], was used for the calibration of the bomb. Calibration experiments were carried out in oxygen, in the conventional way, without bomb rotation, as suggested by Coops et al. [51], at the pressure of 3.04 MPa, with 1.00 cm³ of water added to the bomb. The calibration results were corrected to give the energy equivalent, corresponding to the average mass of water added to the calorimeter of 5222.5 g. From six calibrations experiments the value of energy equivalent of the calorimeter was found to be $\varepsilon_{\text{cal}} = (25146.35 \pm 1.3)$ J K⁻¹, where the uncertainty quoted is the standard deviation of the mean.

Samples in pellet form, were ignited in oxygen at a pressure $p = 3.04$ MPa, with a volume of 1.00 cm³ of deionized water added to the bomb for the combustion experiences of 5-isopropylbarbituric acid and 10.00 cm³ for 2-thiobarbituric acid. The procedure described by Waddington et al. [52] for combustion calorimetry of organosulfur compounds was followed. The rotating mechanism allows the simultaneous axial and end-over-end rotation of the bomb. Rotation of the bomb was started when the temperature rise in the main-period reached about 0.63 of its total value and was continued throughout the rest of the experiment. By adopting this procedure, described by Good et al. [53], the frictional work due to the rotation of the bomb is automatically included in the temperature corrections for the work of water stirring and for the heat exchanged with the surrounding isothermal jacket.

Calorimeter temperature was measured to $\pm(1 \cdot 10^{-4})$ K, at time intervals of 10 s, with a quartz crystal thermometer (Hewlett-Packard HP 2804A), interfaced to a PC programmed to compute the adiabatic temperature change. At least 100 readings were taken for the main period and for both the fore and after periods. Data acquisition and control of the calorimeter were performed using the LABTERMO program [54,55].

The electrical energy for ignition was determined from the change in potential difference across a 1400 μ F condenser discharge through a platinum wire of diameter 0.05 mm. For the cotton thread fuse whose empirical formula $\text{CH}_{1.686}\text{O}_{0.843}$, $\Delta_c u^0 = -16240$ J g⁻¹ was used [56], a value previously confirmed in our laboratory. *n*-Hexadecane (Aldrich, mass fraction >0.999), stored under nitrogen, was used as combustion auxiliary and its massic energy of combustion was measured, in our laboratory, as $\Delta_c u^0(l) = -(47136.7 \pm 2.3)$ J g⁻¹, where the uncertainty is the standard deviation of the mean

For the static bomb experiments, the amount of nitric acid produced was quantified by acid–base volumetry and for the rotating bomb, the nitric acid formed was determined using the Devarda's alloy method [57]. Corrections were based on -59.7 kJ mol⁻¹ for the molar energy of formation in which 0.1 mol dm⁻³ HNO_3 (aq) is formed from O_2 (g), N_2 (g) and H_2O (l) [58]. An estimated value of the pressure coefficient of massic energy: $(\partial u/\partial p)_T = -0.2$ J g⁻¹ MPa⁻¹ at $T = 298.15$ K, a typical value for most organic compounds [59] was assumed. For each compound, the corrections to the standard state to calculate the

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