



Structural studies of cyclic ureas: 3. Enthalpy of formation of barbital

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ARTICLE INFO

Article history:

Received 26 May 2009

Received in revised form 20 June 2009

Accepted 22 June 2009

Available online 30 June 2009

Keywords:

Barbital
 Enthalpy of combustion
 Enthalpy of sublimation
 Enthalpy of formation
 Combustion calorimetry
 Knudsen effusion
 Vapour pressure
 Entropy of sublimation
 Gibbs energy of sublimation
 Differential scanning calorimetry
 Phase transitions
 Heat capacities
 G2 and G3 theories
 Complete basis set CBS-QB3
 Density functional methods B3P86 and B3LYP

ABSTRACT

A thermochemical and thermophysical study has been carried out for crystalline barbital [5,5'-diethylbarbituric acid]. The thermochemical study was made by static bomb combustion calorimetry, from which the standard ($p^\circ = 0.1$ MPa) molar enthalpy of formation of the crystalline barbital, at $T = 298.15$ K, was derived as $-(753.0 \pm 1.8)$ kJ · mol⁻¹. The thermophysical study was made by differential scanning calorimetry over the temperature interval (265 to 470) K. A solid–solid phase transition was found at $T = 413.3$ K. The vapour pressures of the crystalline barbital were measured at several temperatures between $T = (355$ and $377)$ K, by the Knudsen mass-loss effusion technique, from which the standard molar enthalpy of sublimation, at $T = 298.15$ K was derived as (117.3 ± 0.6) kJ · mol⁻¹. The combination of the experimental results yielded the standard molar enthalpy of formation of barbital in the gaseous phase, at $T = 298.15$ K, as $-(635.8 \pm 1.9)$ kJ · mol⁻¹. This value is compared and discussed with our theoretical calculations by several methods (Gaussian- n theories G2 and G3, complete basis set CBS-QB3, density functional B3P86 and B3LYP) by means of atomization and isodesmic reaction schemes.

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1. Introduction

The hexa-cyclic ureas formed by the reaction of urea with ethyl malonate are very well-known drugs, namely known as barbiturates, whose importance is significant in the treatment of diseases caused by central nervous system disorders. Barbiturates were first introduced for medical use a century ago and since then more than 2500 barbiturates have been synthesized, although just about 50 were marked for human use. Today, only about one dozen are still in medical use, producing a wide spectrum of effects on the central nervous system depression, from mild sedation to coma, having been prescribed as sedatives, hypnotics, anesthetics and anticonvulsants [1]. The first barbiturate commercially available was the

5,5'-diethylbarbituric acid, most known as barbital whose molecular formula is presented (5) in figure 1.

This compound was synthesized, in 1903, by Fischer and von Mering and in the following year, the German company Bayer placed it on the market, for human use, commercialized by the name of Veronal[®] with hypnotic, sedative, and anticonvulsant properties [2]. In a medical dictionary, barbital is classified as a long-acting barbiturate that depresses most metabolic processes at high doses and it is also used in veterinary practice for central nervous system depression [3]. Due to its low solubility in water, barbital was converted to its sodium salt that is easily soluble in water [4]. The hypnotic activity of barbiturate derivatives increases when are disubstituted by alkyl larger groups, at the C(5) ring position of the barbituric acid molecule, like ethyl, allyl, isoamyl, phenyl, or cyclohexyl groups [5,6].

The objective of this work is to determine the gas-phase enthalpy of formation of barbital (5). This paper is the third on a series of

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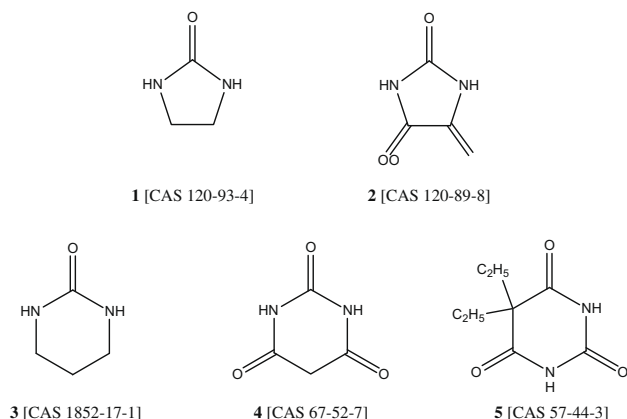


FIGURE 1. Molecular formula of cyclic ureas: (1) imidazolidine-2-one, (2) parabanic acid, (3) *N,N'*-trimethyleneurea, (4) barbituric acid, and (5) barbital.

papers concerned with the structural studies of cyclic ureas in which were presented the thermophysical and thermochemical studies of imidazolidine-2-one (1) and *N,N'*-trimethyleneurea (3) in the first paper [7] and of parabanic acid (2) in the second one [8]. As we have referred in the previous papers, the main purpose of these studies is to provide reliable data for this class of compounds that can be used both for the estimation of the thermochemical properties of related compounds that are not easy to study experimentally and also to understand the influence of steric, electrostatic, and stereo-electronic interactions produced by substituents on the thermochemical stability of these molecules. Some of us developed already a systematic study of host-guest complexes using biotin and cyclic urea derivatives of biological interest as guest, with the final purpose of mimicking the function of natural and artificial receptors by means of an iterative optimization approach [9–14].

The NIST Chemistry Webbook (NIST Standard Reference Database Number 69) [15] reports two old values for the standard molar enthalpy of combustion of barbital, (-4126 and -4127.5) $\text{kJ} \cdot \text{mol}^{-1}$ given, respectively, by Fischer and Wrede [16] and Lemoult [17]. The present study presents a redetermination of the standard ($p^\circ = 0.1$ MPa) molar enthalpy of formation of barbital in the condensed phase together with the vapour pressures determination at different temperatures, to derive the standard molar enthalpy of sublimation at $T = 298.15$ K. The combination of these two parameters yielded the value of the standard molar enthalpy of formation in the gas-phase, at $T = 298.15$ K, of barbital.

2. Experimental

2.1. Sample preparation and characterization

Barbital (5,5'-diethylbarbituric acid) [CAS 57-44-3] was supplied from Fluka (mass fraction purity 0.99) and purified by crystallization in dichloromethane/hexane 3:1. The purity of the sample was checked by C, H, and N microanalysis and DSC, with the results, expressed in mass fraction, as follows: purity by DSC 0.9995; calculated for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3$, $10^2 w(\text{C}) = 0.5217$, $10^2 w(\text{H}) = 0.0657$, $10^2 w(\text{N}) = 0.1521$; found $10^2 w(\text{C}) = 0.5223$, $10^2 w(\text{H}) = 0.0652$, $10^2 w(\text{N}) = 0.1494$. The melting temperature determined by DSC is $T = (462.0 \pm 0.5)$ K (Caillet and Clavelier reported 463 K) [18].

2.2. Differential scanning calorimetry

A differential scanning calorimeter (Perkin Elmer, Pyris 1) equipped with an intra-cooler unit was used. Temperature and

power scales were calibrated [19–21] at heating rates of (0.04 and 0.17) $\text{K} \cdot \text{s}^{-1}$. The temperature scale was calibrated by the melting temperature of the high-purity reference materials: hexafluorobenzene, benzoic acid, tin, and indium [22]. The power scale was calibrated with high-purity indium [22].

Thermograms of samples hermetically sealed in aluminium 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 $\pm(5 \cdot 10^{-6})$ 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 [22] were performed under the same conditions as the experimental determinations. The accuracies associated with temperatures and enthalpies of fusion measurements were calculated as the percentage deviation of the experimental data with regard to the values given in the literature [22]; in all the cases this was lower than (0.2 and 2.0)% for temperature and enthalpy values, respectively [23].

For the determination of the temperature and enthalpy of fusion, a heating rate of $0.04 \text{ K} \cdot \text{s}^{-1}$ was used and seven samples weighing (1 to 2) mg were recorded. A fresh sample was used for each run.

Different scans were performed on heating and cooling to determine the possible existence of phase transitions or polymorphism in the sample, over the temperature range from $T = 268$ K to its melting temperature, at heating rate of $0.17 \text{ K} \cdot \text{s}^{-1}$.

Heat capacities were determined by the “scanning method” following the experimental methodology previously described [24–26] with synthetic sapphire (α -aluminium oxide) as reference material [22,24,25]. DSC is a commonly accepted method for the quantitative determination of heat capacities and it has been proven as a suitable technique to obtain reliable and accurate values [27,28]. To check the experimental method, heat capacity experiments were made with benzoic acid and synthetic sapphire as reference materials [22] over the temperature intervals (268 to 360) K and (268 to 410) K, respectively [23]. The relative percentage error of our measurements in comparison with those reported in the literature is less than 2% [23]. The mass of sapphire used in each run was 0.030345 g. For heat capacity determinations, three to four fresh samples weighing (10 to 25) mg were scanned for the solid compound within the temperature range from (265 to 405.15) K before the phase transition, and from $T = 430.15$ K to its melting temperature at a rate of $0.17 \text{ K} \cdot \text{s}^{-1}$. The complete temperature range for determination of the heat capacities was divided into intervals of approximately 40 K, overlapping by 5 K from one interval to another. The estimated uncertainty of the molar heat capacities is less than 2%. The experimental results were fitted to a third order polynomial in temperature.

2.3. Combustion calorimetry

An isoperibol calorimeter equipped with a twin valve static bomb, with an internal volume of 0.290 dm^3 , was used for the measurements of the energy of combustion of barbital. The apparatus and the detailed procedure have been previously reported [29–31] so only a short description will be presented here. The energy equivalent of the calorimeter $\epsilon(\text{calor})$ was determined using a sample of Standard Reference benzoic acid (sample NBS 39j) having a massic energy of combustion under standard bomb conditions of $-(26434 \pm 3) \text{ J} \cdot \text{g}^{-1}$ [32]. Calibration experiments were carried out in oxygen at $p = 3.04$ MPa with 1.00 cm^3 of desionized water added to the bomb. From 11 experiments $\epsilon(\text{calor}) = (15553.27 \pm 0.91) \text{ J} \cdot \text{K}^{-1}$, where the uncertainty quoted is the standard deviation of the mean. The calibration experiments, as well as the results of the combustion experiments of barbital were cor-

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