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Thermochemical study of dichloromethylpyrimidine isomers

Piotr Szterner [a], Luísa M.P.F. Amaral [a,*], Victor M.F. Morais [a,b], Maria D.M.C. Ribeiro da Silva [a], Manuel A.V. Ribeiro da Silva [a]

[a] Centro de Investigação em Química, Department of Chemistry and Biochemistry, Faculty of Science, University of Porto, Rua do Campo Alegre, 687, P-4169-007 Porto, Portugal
[b] Instituto de Ciências Biomédicas Abel Salazar, ICBAS, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal

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ABSTRACT

The standard ($p^o = 0.1$ MPa) molar enthalpies of formation in the condensed phase, $\Delta_f H_m^o$, of 2,4-dichloro-5-methylpyrimidine, 2,4-dichloro-6-methylpyrimidine, 4,6-dichloro-2-methylpyrimidine and 4,6-dichloro-5-methylpyrimidine were derived from the standard molar energies of combustion, $\Delta_c U_m^o$, in oxygen, to yield CO_2 (g), N_2 (g) and $HCl{\cdot}600H_2O$ (l), at $T = 298.15$ K, measured by rotating bomb combustion calorimetry. The standard molar enthalpies of vaporization or sublimation, $\Delta_{cr,l}^{g} H_m^o$, for these compounds, at $T = 298.15$ K were determined by high temperature Calvet microcalorimetry. Combining these values, the following enthalpies of formation in the gas phase, at $T = 298.15$ K, were then derived: 2,4-dichloro-5-methylpyrimidine, (79.6 ± 4.1) kJ mol^{-1}, 2,4-dichloro-6-methylpyrimidine, (70.5 ± 3.0) kJ mol^{-1}, 4,6-dichloro-2-methylpyrimidine, (68.7 ± 3.3) kJ mol^{-1}, and 4,6-dichloro-5-methylpyrimidine, (78.1 ± 2.5) kJ mol^{-1}. The gas-phase enthalpies of formation were also estimated by G3 theoretical calculations, which were extended to the computation of gas-phase enthalpies of formation of the other dichloromethylpyrimidine isomers, namely, 2,5-dichloro-4-methylpyrimidine, 4,5-dichloro-2-methylpyrimidine and 4,5-dichloro-6-methylpyrimidine, whose experimental study was not performed.

1. Introduction

Pyrimidine is a six-membered heterocyclic molecule presenting two nitrogen atoms at positions 1 and 3 in the ring, whose great interest is due to the presence of this diazine in many natural and non-natural products, which, frequently, exhibit important biological activities and useful pharmacological applications [1,2]. As an example, it is possible to refer three types of nucleobases, cytosine, thymine, and uracil, which are pyrimidine derivatives and are also constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).

The literature review indicated that the pyrimidine nucleus is embedded in a large number of alkaloids, in different drugs, antibiotics, antitumor, antimicrobial, cardiovascular, antiparkinsonian agents, [3–10], and in agrochemicals, fungicides and herbicidal [10–12]. Pyrimidine skeleton is found in vitamins like thiamine (vitamin B1), riboflavin (vitamin B2) and folic acid (vitamin B9) [10,13].

Pyrimidine derivatives containing amino and chloro substituents have been used recently in more directed clinical studies: the 5-amino-2,4-dichloropyrimidine has been employed in the synthesis of piperidine-4-yl-aminopyrimidine derivatives, which are HIV-1 reverse transcriptase inhibitors [14]. On the other hand, 2,4-dichloro-5-(2-chloroethyl)pyrimidine was evaluated for cytostatic activity against human malignant tumor cell lines: acute lymphoblastic leukemia, colon carcinoma, breast carcinoma and lung carcinoma [15].

Due to the relevance of the pyrimidine derivatives in such a wide range of applications, the knowledge of their thermodynamic properties is important in order to develop energetic–structure–reactivity relationships and inherent characterization of the chemical behavior of such species. Recently, we have been involved in an extensive research project on the thermodynamic properties of pyrimidines [16–20], cytosine [21], uracil [22–28] thiouracil [29,30] and barbituric acid derivatives [31]. In this context, the present work complements the previous ones and reports the standard ($p^o = 0.1$ MPa) molar enthalpies of formation, at $T = 298.15$ K, of four dichloromethyl substituted pyrimidines: 2,4-dichloro-5-methylpyrimidine, 2,4-dichloro-6-methylpyrimidine, 4,6-dichloro-2-methylpyrimidine and 4,6-dichloro-5-methylpyrimidine. These values were calculated from the standard molar enthalpies of formation, in the crystalline phase, obtained by rotating bomb

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* Corresponding author at: REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal.

E-mail address: luisaamaral@fc.up.pt (L.M.P.F. Amaral).

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combustion calorimetry, and from their standard molar enthalpies of sublimation, determined by Calvet microcalorimetry. Additionally, computational thermochemistry was employed to calculate the gas-phase standard molar enthalpies of formation of all the dichlorometylpyrimidine isomers (presented in Fig. 1) using the G3 composite quantum chemical method, together with appropriate isodesmic or homodesmotic reactions.

2. Experimental details

2.1. Compounds and purity control

The compounds, 2,4-dichloro-5-methylpyrimidine, (2,4-dCl-5-MePyr), [CAS 1780-31-0], 2,4-dichloro-6-methylpyrimidine, (2,4-dCl-6-MePyr), [CAS 5424-21-5], 4,6-dichloro-2-methylpyrimidine, (4,6-dCl-2-MePyr), [CAS 1780-26-3] and 4,6-dichloro-5-methyl pyrimidine, (4,6-dCl-5-MePyr), [CAS 4316-97-6] were obtained commercially from Aldrich Chemical Co. The liquid 2,4-dichloro-5-methylpyrimidine was purified by repeated distillation under reduced pressure and the crystalline compounds 2,4-dichloro-6-methylpyrimidine, 4,6-dichloro-2-methylpyrimidine and 4,6-dichloro-5-methylpyrimidine, were purified by repeated sublimation under reduced pressure. Purity was checked by gas–liquid chromatography (GLC, HP-1890A), and found to be higher than 0.9990 (mass fraction) for each compound. Details of the origin and purification of the samples are presented in Table 1.

2.2. Combustion calorimetry measurements

The combustion experiments were performed with an isoperibol rotating-bomb calorimeter, firstly constructed at the University of Lund, Sweden according to the design of Sunner [32]. Detailed description can be found in literature [33,34]. The combustion experiments were carried out in a stainless steel platinum lined bomb, with the internal fittings machined from platinum, whose internal volume is 0.258 dm^3. In each experiment, the bomb is suspended from the lid of the calorimeter can, to which 5222.5 g of water, previously weighed in a Perspex vessel, is added.

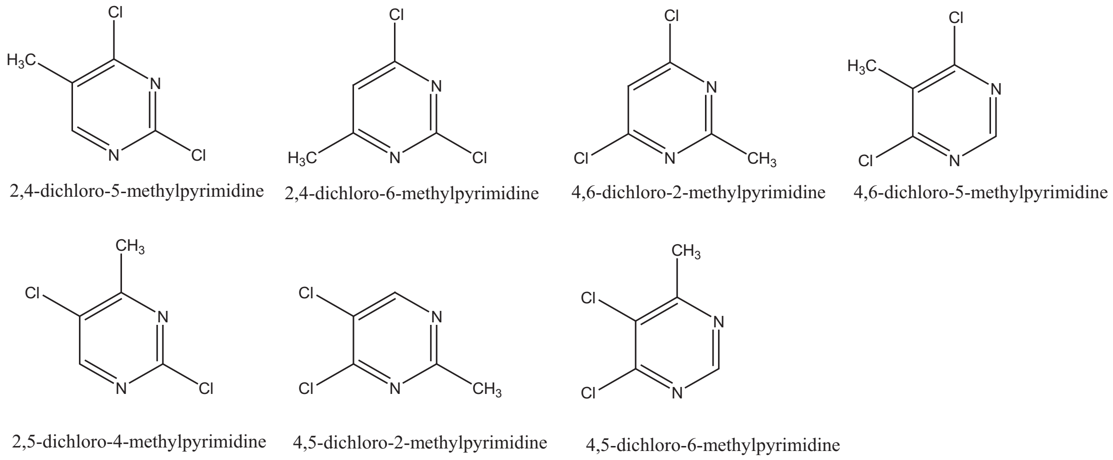
The calorimetric system was calibrated, in the conventional way, without bomb rotation, with benzoic acid (NBS Standard Reference Material 39j), having a massic energy of combustion under bomb conditions of $-(26{,}434 \pm 3)\ J\ g^{-1}$ [35]. The calibration experiments were conducted in oxygen, at the pressure of 3.04 MPa, with 1.00 cm^3 of deionized water added to the bomb, according to the procedure recommend by Coops et al. [36]. Two different calibration constants were used: $\varepsilon_{cal} = (25161.3 \pm 1.5)\ J\ K^{-1}$, for the experiments with 2,5-dichloro-6-methylpyrimidine, and $\varepsilon_{cal} = (25166.1 \pm 1.5)\ J\ K^{-1}$, for the experiments with the other three compounds studied. The uncertainty quoted is the standard deviation of the mean. For each experiment, a correction to the energy equivalent was used for the deviation of the mass of water used to the reference mass of 5222.5 g.

Calorimeter temperatures were 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 program LABTERMO [37,38].

For each experiment, the ignition temperature was selected so that the final temperature would be close to $T = 298.15$ K, and the rotation of the bomb was started when the temperature rise of the main period reached about 63% of its total value and was continued throughout the rest of the experiment. By adopting this procedure, Good et al. [39] have shown that the frictional work due to the rotation of the bomb is automatically integrated in the temperature corrections for the work of water stirring and for the heat exchanged with the surrounding isothermal jacket. The rotating mechanism permits the simultaneous axial and end-over-end rotation of the bomb, which allows that the solution placed in the bomb wash completely all internal surfaces of the bomb, yielding a homogenous final solution.

The samples were burnt enclosed in polyester bags made from Melinex (0.025 mm thickness) using the technique described by Skinner and Snelson [40]. The combustion experiments were made in oxygen at the pressure of 3.04 Pa, in the presence of an aqueous solution of As_2O_3, in order to reduce to hydrochloric acid all the free chlorine produced during the combustion. At the end of each experiment, the remaining quantity of aqueous As_2O_3 was determined by titration with a standardized iodine solution. The energy of oxidation of aqueous As_2O_3 to As_2O_5, ΔU (As_2O_3), was calculated as described by Hu et al. [41], using the enthalpies of oxidation of As_2O_3(aq) by Cl_2 [42] and the thermal effects of mixing As_2O_5(aq) with strong acids [43]. The amount of H_2PtCl_6 (aq) was determined from the loss of mass of platinum of the crucible and the energy correction was based on $\Delta_f H^{o}_{m}$ (H_2PtCl_6, aq) = $-(676.1 \pm 0.1)\ kJ\ mol^{-1}$ [44].

The electrical energy for ignition was determined from the change in potential difference across a 1400 μF condenser discharged through a platinum wire ($\phi = 0.05$ mm, Goodfellow, mass fraction 0.9999).



2,4-dichloro-5-methylpyrimidine 2,4-dichloro-6-methylpyrimidine 4,6-dichloro-2-methylpyrimidine 4,6-dichloro-5-methylpyrimidine

2,5-dichloro-4-methylpyrimidine 4,5-dichloro-2-methylpyrimidine 4,5-dichloro-6-methylpyrimidine

Fig. 1. Structural formula of the dichloromethylpyrimidine isomers studied.