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Enthalpy of formation of 5-fluoro-1,3-dimethyluracil: 5-Fluorouracil revisited

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ABSTRACT

In the present work, a re-determination of thermochemical data for 5-fluorouracil was performed and a new determination of thermochemical parameters for 5-fluoro-1,3-dimethyluracil are presented. The standard (p^o = 0.1 MPa) molar enthalpies of formation, in the crystalline phase, of 5-fluorouracil and 5-fluoro-1,3-dimethyluracil, at T = 298.15 K, were derived from the standard molar energies of combustion in oxygen, measured by rotating bomb combustion calorimetry. For these compounds, the standard molar enthalpies of sublimation, at T = 298.15 K, were determined from the temperature-vapour pressure dependence, obtained by the Knudsen mass-loss effusion method. Using the values for the heat capacity differences between the gas and the crystalline phases of the compounds studied, the standard (p^o = 0.1 MPa) molar enthalpies, entropies and Gibbs free energies of sublimation, at T = 298.15 K, were derived. From the experimentally determined values, the standard molar enthalpies of formation, in the gas phase, at T = 298.15 K, of 5-fluorouracil and 5-fluoro-1,3-dimethyluracil were calculated as $-(454.5 \pm 1.6)$ and $-(478.5 \pm 1.3)$ kJ · mol^{-1}, respectively. These values were compared with estimates obtained from very accurate theoretical calculations using the G3(MP2)//B3LYP composite method and appropriately chosen reactions.

1. Introduction

The chemical modification of nucleic bases is recognised as one of the most promising approaches for developing bioactive substances such as anticancer and antiviral agents [1]. The properties of fluorine as a substituent in many chemical reactions and especially its influence on hydrogen-bonding interactions, gives a strategic value to fluorine substitution in drug design [2]. 5-Fluorouracil is an anti-cancer chemotherapy drug. Although this antimetabolite is toxic, its efficacy makes it one of the most widely used agents against solid tumours. 5-Fluorouracil has antitumor activity against epithelial malignancies arising in the gastrointestinal tract and breast as well as the head and neck. [3–5]. One of the challenges of cancer research is the development of pro-drugs of 5-fluorouracil that decrease or circumvent some of its disadvantages: reduction of toxicity by avoiding certain routes of degradation (pro-drugs which are not a substrate for enzymatic degradation) or by targeting the tumor site (pro-drugs that liberate the active principle selectively in tumour cells) [6,7]; enhancement of activity by reducing catabolism (use of dihydropyrimidine dehydrogenase, DPD, inhibitors) [8,9] or by increasing anabolism, and improvement of the quality of life of the patient by developing oral pro-drugs. In addition, 5-fluorouracil has also been employed to enhance the therapeutic activity of other antineoplastic agents or modalities such as cisplatin and ionising radiation with which it can synergize [10,11].

The photoreaction of halogenated pyrimidines with benzenes and olefins has demonstrated that photoreaction is a useful method for the modification of the pyrimidine ring. In this respect, the photoreactions of 5-fluoro-1,3-dimethyluracil with various naphthalenes and its derivatives, were studied [12,13]. Also, oxidative modifications of 5-fluoro-1,3-dimethyluracil were also studied [14,15]. In any case for synthesis or for separation processes for this kind of compounds, knowledge of their thermodynamic properties would be very useful. Enthalpies of formation, enthalpies of vaporisation/sublimation, enthalpies of fusion and vapour pressures are needed for determination of reaction and process energies, for development of elementary reaction mechanisms, for evaluation of reaction pathways and for calculation of chemical equilibrium constants.

This paper reports our continued studies on the energetic effect caused by the introduction of different substituents in the uracil ring, which is one of our main research interests [16–19]. One of

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the purposes of this work was to compare the enthalpic increment of introducing a fluorine atom in the (5) position of 1,3-dimethyluracil with the same introduction in uracil and so, to study the energetic effect of this substitution in both molecules. We found an error in the calculation of the value for the enthalpy of formation of 5-fluorouracil in reference [18]. The recalculated value for the enthalpy of formation, in the crystalline state, for 5-fluorouracil is $-(582.2 \pm 1.1)\ \mathrm{kJ \cdot mol^{-1}}$, instead of $-(578.5 \pm 1.1)\ \mathrm{kJ \cdot mol^{-1}}$. This recalculated value combined with the standard molar enthalpy of sublimation in reference [18]gives for the standard molar enthalpy of formation of 5-fluoruracil, in the gaseous phase, a value of $-(449.0 \pm 2.9)\ \mathrm{kJ \cdot mol^{-1}}$.

The enthalpic increments for the introduction of a fluorine atom in the position (5) of uracil and 1,3-dimethyluracil (see scheme 1) seemed out of the line with each other, ($-150.3\ \mathrm{kJ \cdot mol^{-1}}$: uracil → 5-fluoruracil; $-164.9\ \mathrm{kJ \cdot mol^{-1}}$: 1.3-dimethyluracil → 5-fluor-1,3-dimethyuracil), prompting a re-investigation both experimentally and computationally of the enthalpies of formation of the two compounds.

We have used the G3(MP2)//B3LYP composite method and appropriately chosen reactions to derive the enthalpy of formation of both 5-fluorouracil and 5-fluoro-1,3-dimethyluracil. The computational estimates obtained are in very good agreement with the experimental value for 5-fluoro-1,3-dimethyluracil but the agreement for 5-fluorouracil, measured by us in 2012, is not good. Due to the importance of reliable thermochemical values, we have decided to re-determine the standard molar enthalpy of formation of 5-fluorouracil, in the gas-phase.

The standard molar enthalpies of formation of 5-fluorouracil and 5-fluoro-1,3-dimethyluracil in the crystalline phase, at $T = 298.15$ K, were derived from its standard massic energies of combustion, in oxygen, at $T = 298.15$ K, measured by rotating bomb combustion calorimetry.

The standard molar enthalpies of sublimation of the compounds, at the mean temperature of the experimental temperature range, were obtained by the application of the Clausius–Clapeyron equation to the values of the vapour pressure, determined by the Knudsen mass-loss effusion technique at different temperatures. The value obtained for each compound was corrected for $T = 298.15$ K, using an estimated value for the heat capacity difference between the corresponding gas and crystal phases.

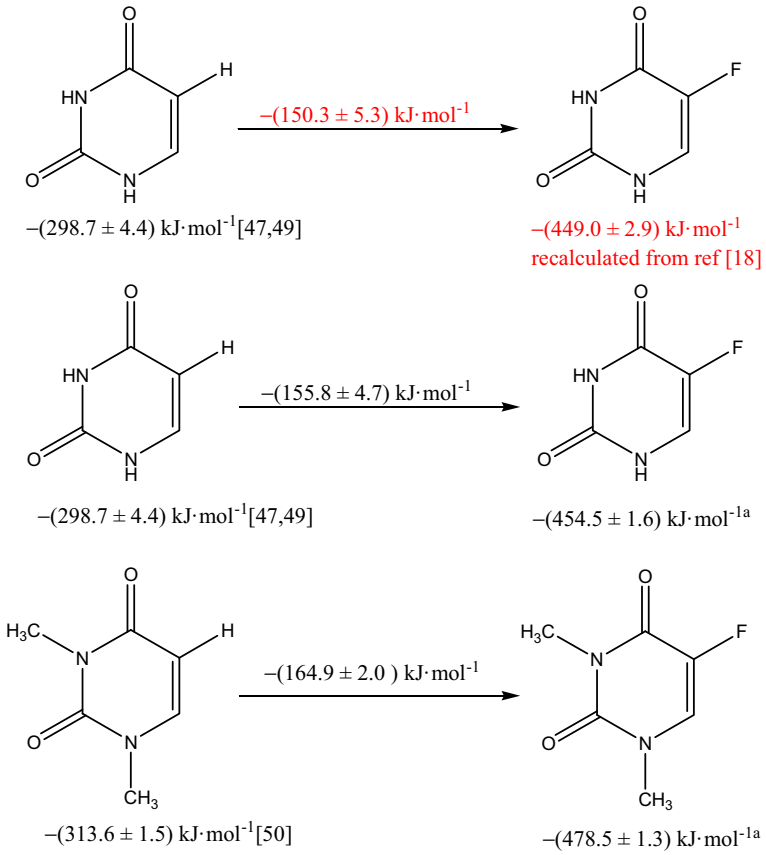
2. Experimental

2.1. Materials and purity control

5-Fluorouracil and 5-fluoro-1,3-dimethyluracil were purchased from Aldrich Chemical Co. with the assessed minimum value of mass fraction purity 0.99 and further purified by vacuum sublimation. The purity of the compounds was checked by gas–liquid chromatography, performed on an Agilent 4890D Gas Chromatography equipped with an HP-5 column, cross-linked, 5% diphenyl and 95% dimethylpolysiloxane ($15 \cdot 0.530$ mm i.d $\cdot$ 1.5 μm film thickness), and using nitrogen as carrier gas, with mass fraction $\geqslant 0.9998$. The origin and purification details of the samples used in this work are listed in table 1.

The specific densities were taken as, $\rho = 1.4593\ \mathrm{g \cdot cm^{-3}}$ [20] and $\rho = 1.37\ \mathrm{g \cdot cm^{-3}}$ [21] for 5-fluorouracil and 5-fluoro-1,3-dimethyluracil respectively.

The relative atomic masses used for the elements were those recommended by the IUPAC Commission in 2011 [22].



SCHEME 1. Enthalpic increments of the introduction of a fluorine atom in the position (5) of uracil and 1,3-dimethyluracil. [a]This work.