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Research article

2,4-Ditellurouracil and its 5-fluoro derivative: Theoretical investigations of structural, energetics and ADME parameters

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ABSTRACT

2,4-Ditellurouracil exhibits keto-enol tautomerism via different pathways resulting in seven tautomers. These pathways were studied in the gas phase using density functional theory method. The functionals used were BLYP, B3LYP and BHLYP and the basis sets were 6–311++G(d,p) for all atoms except that LanL2DZ ECP was used for tellurium atom only. The results indicate that the diketo form is more stable as observed for uracil and its sulfur and selenium analogues. The effect of introducing fluorine at position 5 was also investigated and the energy difference between the diketo and dienol forms is reduced. 2,4-Ditellurouracil and its 5-fluoro analogue are expected to exist exclusively as the diketo form due to the high interconversion energy barrier. We extended the investigation to predict ADME parameters of the most stable diketo and dienol tautomers in view of understanding their biological properties. This research enlightens keto-enol tautomerism of 2,4-ditellurouracil and its 5-fluoro derivative with additional insights to biological functions.

1. Introduction

Nucleic acids represent one of the most outstanding breakthroughs in biology since the discovery of the structures of DNA and RNA. Uracil is one of the pyrimidine bases found in RNA which forms base pair with adenine and thereby, substituting thymine of DNA during the transcription mechanism. Uracil is important in the body as it aids in the production of enzymes and other proteins (Garrett and Grisham, 1997). It is also involved in the biosynthesis of polysaccharides (Brownt, 1998). Substituted nucleic bases have received considerable attention due to their various pharmacological, biochemical and biological capabilities (Novak and Kovač, 2005; Zhao and Meng, 2006; Rastogi et al., 2007, 2009; Palafox et al., 2007). Halogenated pyrimidines have been synthesised and used as potential anti-tumor (Presant et al., 1994; Nakajima, 1995), anti-bacterial (Chu et al., 1992a, 1992b) and anti-viral agents (Kim et al., 1992; Verheggen et al., 1995). Their incorporation into DNA and RNA increases the sensitivity of these biomolecules to ionising radiation such that the replication process in tumor cells is halted. Among the 5-monohalogenated derivatives of uracil, fluorine is similar in size to hydrogen and when it is substituted in uracil, 5-fluorouracil is formed and it was first introduced in medicine in 1957 (Heidelberger et al., 1957). This transformation alters the chemistry of uracil significantly and it inhibits enzymes from replicating. Consequently, it prevents the growth of cancerous cells and hence, 5-fluorouracil is a widely used drug in oncology and is also recognised as effective treatment of modalities (Katzung, 1998).

In 1965, Lipsett (1965) detected the presence of sulfur in natural tRNA and these substituted compounds possess biological activities. In view of this fact, substitution of oxygen by heavier atom in DNA has gained considerable attention (Wang et al., 2005) and several sulfur-substituted bases have been used as drugs (Lapinski et al., 1998). 2,4-Dithiouracil was found to be a melanoma-seeking agent owing to its specific incorporation in nascent melanin (Mars and Larsson, 1995). Sulfur-substituted purines and pyrimidines have also found applications in clinically useful drugs (Shefter and

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Mautner, 1967). Selenium is the other member of the chalcogen group which was regarded as highly toxic element until it was found in microorganisms and other species (Schwarz and Foltz, 1957). Selenocysteine was discovered as the 21st amino acid whereby it acts as a co-factor for reduction of anti-oxidant enzymes (Chambers et al., 1986; Hatfield and Gladyshev, 2002). Tellurium faced the same prejudice as selenium in terms of drugs capabilities until the biological activities of tellurium compounds were proven (Cunha et al., 2005, 2006). Tellurium compounds have been employed as drugs in the treatment of several diseases such as syphilis, leprosy, sickle cell anemia, AIDS. They are also used as anti-bacterial agents (Cunha et al., 2009).

Uracil is known to exhibit tautomerism and studies conducted both experimentally and theoretically to evaluate the relative stabilities of the keto-enol tautomerism (Jalbout et al., 2007; El-Gogary and El-Nahas, 2008; Shishkin et al., 2003; Kümmerle and Pomplun, 2009) as illustrated in Scheme 1. Tautomerism plays an important role from the medicinal and pharmacological point of views (Saenger, 1994) as it is useful in understanding mutation which may occur during DNA replication. Studies have been carried out in the gas phase, solid state and in solution in order to investigate the behaviours of uracil and its tautomers (Dougerty et al., 1976; Tsuchiya et al., 1988; Brown et al., 1988; Chin et al., 1984 Chin et al., 1984) during the proton transfer process. It was found that the diketo-form is the most stable tautomer (Jalbout et al., 2007; El-Gogary and El-Nahas, 2008). Similarly, tautomerism in thiouracils (Leszczynski and Lammertsma, 1991) and selenouracils (Trujillo et al., 2007) were investigated and in general the diketo form is more stable.

To the best of our knowledge, tautomerism involving 2,4-ditellurouracil has not been studied and this was the basis of our investigation of this compound and its 5-fluoro derivatives. The title compounds and their tautomers were studied in the gas phase using density functional theory (DFT) method so as to obtain their structural and spectroscopic parameters. Some of the physico-chemical and biological parameters for the most stable tautomers were also calculated. The findings of this research are hereby reported and compared with other uracil analogues.

2. Computational methods

The notations used for the tautomers and rotamers of ditellurouracil, denoted as TeU, are based on Figs. 1 and 2. The name of tautomer is derived from the atom numbering connected to a hydrogen atom while for the rotamer, the position of the hydrogen of each OH group is distinguished by subscript "1" or "2" such as **$2_1,4_1$-TeU** and **$2_2,4_1$-TeU**. 2,4-Ditellurouracil (**1,3-TeU**), its possible tautomers (**$1,2_2$-TeU**, **2_1,3-TeU**, **$1,4_1$-TeU**, **$2_1,4_1$-TeU**, **$2_2,4_1$-TeU** and **$3,4_1$-TeU**) due to proton transfer and transition state structures (**TS($1,2_2 \rightarrow$1,3)**, **TS(2_1,3 $\rightarrow$ 1,3)**, **TS(1,3 $\rightarrow$ $1,4_1$)**, **TS($1,4_1 \rightarrow 2_1,4_1$)**, **TS($2_1,4_1 \rightarrow 2_2,4_1$)** and **TS($2_2,4_1 \rightarrow 3,4_1$)**) are illustrated in the energy profile of Fig. 1. The 5-fluoro analogues are also illustrated in Fig. 2 and the acronym F is added, signifying that fluorine is located at the 5-position. All the structures were fully optimised in the C_s symmetry in the gas phase. The transition states involved during tautomerisation were also modeled. The geometries were optimised using the hybrid DFT with three different functionals, namely;

(a) Becke (B) half and half exchange functional (H) with Lee-Yang-Parr's correlation functional (LYP) non-local correlation functional (BHLYP),
(b) Becke's three-parameter hybrid exchange (B3) with the LYP correlation functional (B3LYP),
(c) Becke's 1988 exchange functional with LYP correlation functional (BLYP).

The basis sets employed for all atoms were 6–311++G(d,p) except that LanL2DZ ECP was used for the tellurium atom only. All computations were carried out with the Gaussian 09 program (Frisch et al., 2009). Frequency computations were performed by the optimised structures in order to investigate the nature of the stationary points. All ground state structures do not have imaginary frequencies while transition states have one imaginary frequency. The energies were also corrected for zero-point energies (ZPE). The adiabatic electron affinity (EA) and the adiabatic ionisation energy (IE) were determined at their relaxed geometries as follows:

$$EA = [E(optimised\ neutral) + ZPE] - [E(optimised\ anion) + ZPE] \quad (1)$$

$$IE = [E(optimised\ cation) + ZPE] - [E(optimised\ neutral) + ZPE] \quad (2)$$

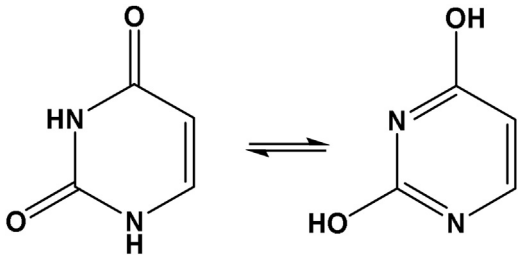
Optimised geometries were used to carry out conductor-like screening for real solvents (COSMO-RS) calculations using COSMOtherm program (Eckert and Klamt, 2005). ADME (Absorption, distribution, metabolism, excretion) parameters were investigated for potential drug activity. These parameters include solubility, lipophilicity, intestinal absorption, and blood brain coefficient.

3. Results and discussion

The results of the electronic computations on the structural parameters are reported and discussed. This is followed by analyses of the dipole moments, tautomer stability, electron affinity and ionisation potential, COSMO-RS calculations, physico-chemical and physiological properties.

3.1. Structural parameters

The interconversion of the tautomers of 2,4-ditellurouracil and its 5-fluoro derivatives are shown in Fig. 1(a) and (b). The structures and atom labelling of **1,3-TeU**, **$2_1,4_1$-TeU**, **1,3-TeU-F** and **$2_1,4_1$-TeU-F** are displayed in Fig. 2. The structural parameters of **1,3-TeU**, **$1,4_1$-TeU**, **$2_1,4_1$-TeU**, **2_1,3-TeU**, **1,3-TeU-F**, **$1,4_1$-TeU-F**, **$2_1,4_1$-TeU-F** and **2_1,3-TeU-F** are summarised in Tables SI1-2 (SI = Supplementary information). An analysis of the data from Tables SI1 and SI2 indicates that there is only a slight difference among the optimised structural data obtained from the three functionals used. It is worth pointing out that the structural features of the 2,4-ditellurouracil derivatives are in accordance with known experimental data of their analogous uracil (Parry, 1954), 2,4-dithiouracil (Shefter and Mautner, 1967) and 2,4-diselenouracil (Trujillo et al., 2007) except for those parameters where the tellurium atom is involved. The length of C-F bond is found to be longer in 5-fluoro-2,4-ditellurouracil compared to 5-fluorouracil where the experimental C-F bond length is 1.348 Å



Scheme 1. Tautomerism of uracil.