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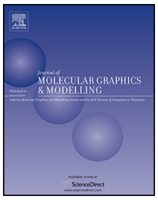

Controlled stabilization of anionic forms of the uracil derivatives: A DFT study

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ABSTRACT

Relative stabilities of the N1/N3/O5/O6 anions of 42 substituted uracils in gas phase and aqueous solutions have been theoretically studied using approximation IEFPCM (SMD) – TPSS/aug-cc-pVTZ. The specific solvation of uracil and its anions has been simulated with the first hydrate shell made up with 5 water molecules. The nonspecific solvation has been accounted in terms of the SMD model. We have found a series of relative stability under conditions of both specific and nonspecific hydration. The series is ranked according to the increase of the relative stability of the N3 anion. In gas phase, the N1 anion is significantly more stable than its N3 counterpart: the ΔG_{gas} values vary in the range from 19.54 (**5OH6**CH_3**U**) to 83.14 (**5NO$_2$6NH$_2$U**) kJ/mol that is caused by a more effective delocalization of the excess charge through the uracil framework in the N1 anion. The hydration pronouncedly diminishes $\mathbf{\Delta}G$ to the range from -0.02 (**5OH6**CH_3**U**) to 38.16 (**5Br6NO$_2$U**) kJ/mol due to the fact that the polar solvent is prone to stabilize more polar anionic states of uracils. Therefore, less polar uracil anions are more stable. We have defined the main factor influencing the N1/N3/O5/O6 distribution of anions, viz. the presence of the substituents in 5 and 6 positions of the pyrimidine ring. Herewith, the most favorable mechanism of the influence of 5-substituents has been previously defined as resonant whereas, as we found in this work, the inductive mechanism is more pronounced in the case of 6-substituents.

1. Introduction

Uracils are among the biologically important pyrimidines. Thymine (5-methyluracil) is a part of the DNA molecules, in which it forms a complementary pair with adenine (Fig. 1). Uracil itself (2,4-dioxypyrimidine) is complementary to adenine in the RNA molecules. Intriguingly, uracil can be formed from pyrimidine under vacuum, ultralow temperatures and hard radiation if water presents in the system [1]. Pyrimidine found in some meteorites is under the same conditions [1]. Obviously, the molecules close in their structures to thymine or uracil should reveal different properties resulted from their interaction with the DNA structures and involving by the replication processes. In the studies of uracils, a particular attention is paid to their aqueous solutions as these are closest to the natural biological media.

There are some difficulties for the experimental investigations of uracils. For example, under their ionization, it is impossible to define the exact position of the proton detachment. The use of the quantum chemistry methods allows solving such problems. These methods open opportunities to scrutinize each anionic form, ionization and transition states of this process. It should be noted that the application of quantum chemical methods to uracils has a long story starting when the simplest computers have been able to make rough and approximate calculations. However, the ongoing development of the computational facilities and improvement of quantum chemical methods allow deeper studying the above-mentioned problems using novel models and approximations.

The analysis of periodicals reveals a great number of the works [2–12] devoted to uracils as these substances are very effective drugs. Most of the works focus on the antioxidant properties of uracils underlying their biological activity [13,14]. At the same time, another property of uracils is also found significant, viz. their ionization. Indeed, ionization of nucleic bases is able to influence the replication processes and, herewith, the contents of the ionized forms increase [15]. This induces a continuing attention to

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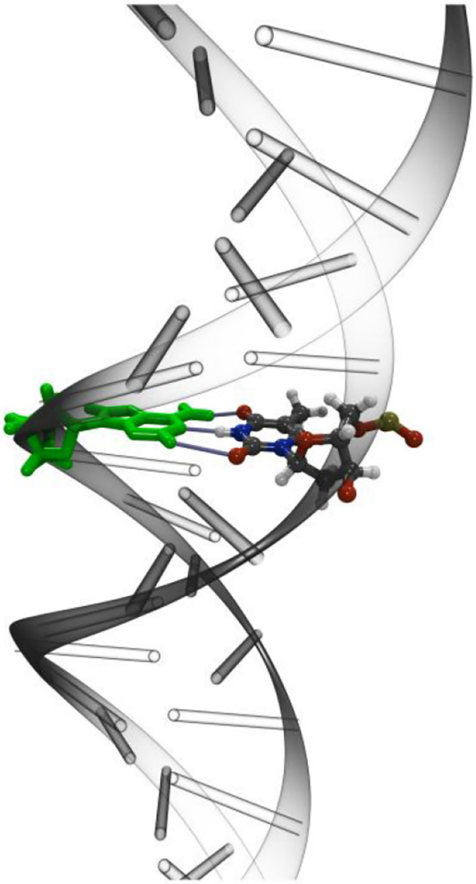

Fig. 1. A complementary pair thymine–adenine in the DNA molecule.

the anionic equilibria of nucleic bases and their derivatives. On the one hand, ionization produces defects under the transmission of genetic information, which may further lead to cancer deceases. On the other hand, such spontaneous mutations in combination with natural selection lead to advanced organisms. Thus, the studies of formation of minor tautomeric and ionic forms of nucleic bases remain relevant.

In the present work, the relative energies of the uracil derivatives and their anions with all possible combinations of substituents in positions 5 and 6 (in total, 42 compounds) have been theoretically studied in gas phase and water shell

2. Computational details

The quantum chemical calculations were performed in the Gaussian09 Revision D program package [16]. The computational results were visualized using the VMD program [17]. The wave-functions of all molecules and ions were described using the restricted Kohn–Sham method (the wave-functions of the closed electronic shells). The calculations correspond to the standard conditions (298.15 K, 1 atm).

The optimization of the structures under study and solvation of the vibrational task were performed by the exchange τ-dependent TPSS density functional with gradient correction [18]. We used it in combination with the flexible and moderately time-cost basis set with triple valence split, augmented by *d*- and *p*-type polarization and diffuse functions, aug-cc-pVTZ [19–24]. All the found structures correspond to the minima of the potential energy surfaces that was confirmed by the presence of only positive vibration frequencies in the hessians.

Hydration has a pronounced influence on the anionic forms of uracils [25–29]. Herewith, both specific and nonspecific hyrdations are significant. Efficiency of the nonspecific hydration depends on the polarity of the molecule, which is characterized with the dipole moment. The specific hydration includes the formation of hydrogen bonds between the uracil and solvent molecules. To take it into account, we used the supermolecule approximation. A detailed analysis of the solvation model used is expounded in the work [25]. The nonspecific solvation were accounted in terms of the SMD model [30].

3. Results and discussion

3.1. Structures of uracil anions

All studied compounds have been divided into 7 groups for convenience (Fig. 2).

The structural parameters of the studied uracils and their anions, computed with and without the hydrate surrounding, are shown in Supplementary information. Uracils are weak acids, hence increasing pH leads to the proton detachment from one of the nitrogen atoms of the pyrimidine ring that results in one of four possible anions (Fig. 3).

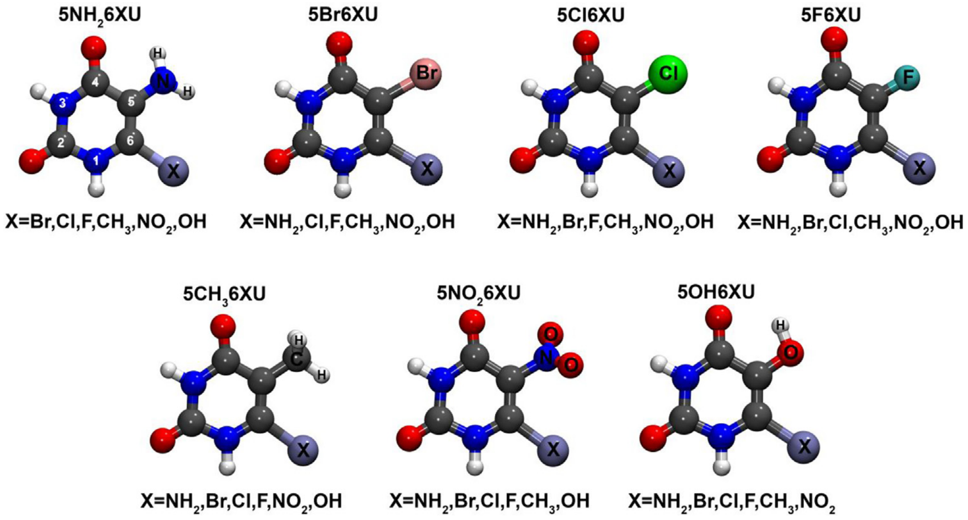

Fig. 2. Structures of the compounds under study.