



Theoretical study of the addition and abstraction reactions of hydroxyl radical with uracil

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ABSTRACT

The addition as well as abstraction reactions of hydroxyl radical ([•]OH) with the nucleic acid base, uracil (U), in the gas phase has been explored at the B3LYP/6-31+G(d,p) level of density functional theory (DFT). The energy barrier of the [•]OH addition to both the C5 and C6 positions of the uracil is less than 1 kcal/mol while the hydrogen abstractions (H-abstractions) from either the N1 or the N3 positions are ~9.5 kcal/mol. Further the energetics of these reactions are assessed by applying the effect of aqueous medium through the polarizable continuum model (PCM). Both the gas and the solution phase data established that the thermodynamic and kinetic factors are more favorable for the [•]OH addition to either C5 or C6 positions of the uracil than the H-abstraction reactions. Moreover, calculations at the MPW1K/6-31+G(d,p), CCSD(T)/6-31+G(d,p)//B3LYP/6-31+G(d,p) and CCSD(T)/6-31+G(d,p)//MPW1K/6-31+G(d,p) levels of theoretical methods qualitatively supported the B3LYP/6-31+G(d,p) results.

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1. Introduction

DNA is one of the main targets of cellular oxidants such as hydrogen peroxide, superoxide radical anion (O₂^{•-}), perhydroxyl radical (HO₂[•]), hydroxyl radical ([•]OH) and peroxy (RO₂[•]) radicals (von Sonntag, 2006; Sawyer, 1991). Significant information about the transients produced from the reactions of [•]OH with nucleic acid bases have been obtained by pulse radiolysis and laser photolysis experiments (von Sonntag, 2006). Mainly the [•]OH reacts with the nucleic acids through addition modes on the base units or by abstracting hydrogen atoms from the base and sugar lesions. In the case of pyrimidine bases, oxidation by the [•]OH leads to addition at the C5C6-double bond, which bring out a more complex product mixture (Burrows and Muller, 1998; Cadet et al., 1999). The [•]OH for all these reactions is produced by the activity of endogenous and exogenous agents on the solvent water, including ionizing radiation and UVA light. The DNA base-derived products are used as biomarkers of oxidative DNA damage (Dizdaroglu, 1991). Thus an understanding of the energetics of the reactions of [•]OH with nucleic acid bases is essential for the study of their oxidative degradation pathways.

Hydroxyl radical is a moderate electrophile (De Vleeschouwer et al., 2007) and shows high reactivity (von Sonntag, 2006) towards nucleic acid model compounds with nearly diffusion controlled rates (10⁹–10¹⁰ dm⁻³ mol⁻¹ s⁻¹). Previous studies showed that the [•]OH addition to the C5C6 double bond of pyrimidine nucleobases is more regioselective to the C5 atom than the C6 atom (Hayon and Simic, 1973; Fujita and Steenken, 1981; Al-Sheikhly and von Sonntag, 1983; Jovanovic and Simic, 1986; Steenken, 1989; Harza and Steenken, 1983). H-abstraction from the methyl group of thymine by [•]OH (ca. 10%) is also reported (Fujita and Steenken, 1981). Pulse radiolysis experiments on some substituted pyrimidines and their product analysis using HPLC with UV detection coupled to a mass spectrometer through an electrospray interface (HPLC-ES-MS) clearly demonstrated that [•]OH-addition to the C5C6 double bond is the major reaction pathway (Luke et al., 2002). Representative theoretical studies of [•]OH reactions with nucleic acid model compounds and their analogs revealed that the kinetic factors are more dominant than the thermodynamic factors (Ji et al., 2004, 2005; Pramod et al., 2006; von Sonntag, 2007). Based on DFT (Naumov and von Sonntag, 2008) and on experimental studies (von Sonntag, 2006), it was established that the distribution of the transients ([•]OH adducts) during the pulse radiolysis of nucleobases is primarily controlled by kinetic factors.

Ji et al. have studied theoretically the reaction of [•]OH with thymine (Ji et al., 2004) as well as cytosine (Ji et al., 2005), both in vacuum and aqueous phases. They found that the relative

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probabilities for the addition and H-abstraction reactions that $\cdot\text{OH}$ can induce in thymine/cytosine are similar in vacuum and aqueous phases. Therefore, they suggested that $\cdot\text{OH}$ reactions with nucleic acid bases can be modeled in vacuum phase. Theoretical studies from our group on the reaction of $\cdot\text{OH}$ with 5-azacytosine exposed the kinetic control over the thermodynamic stabilities of the transients to account for the pulse radiolysis experimental results (Pramod et al., 2006). An earlier theoretical study (Wetmore et al., 1998) based on the calculations of hyperfine coupling constants (HFCCs) of the transients in the reaction of $\cdot\text{OH}$ with U could shed some light on the relative stabilities of the transients and to a certain extent about the pertaining reaction mechanism during ESR experiments.

Pulse radiolysis in juxtaposition with the absorption spectroscopy and the redox titration methods provided sufficient experimental results for evaluating the absorption maximum (λ_{max}) and the percent allocation of the oxidizing/reducing transients formed in the reaction of $\cdot\text{OH}$ with U. The transient absorption spectrum recorded for the reaction $\cdot\text{OH}$ and U by pulse radiolysis technique at pH 3.15 and taken at 0.1 μs after the irradiation. It was characterized by λ_{max} at 380 nm and a second peak at around 295 nm (Hayon and Simic, 1973). Quantification of the oxidizing and reducing transients were determined using the redox titration method in the pulse radiolysis experiments, which showed that $\sim 20\%$ transients possess oxidizing characteristics while the rest showed reducing characteristics (Fujita and Steenken, 1981). The present study will focus on systematical analyzes on the energetics of the mechanism of the reaction of $\cdot\text{OH}$ with U using well accepted theoretical methods, which would give further insight into the thermodynamic as well as kinetic factors that control the reaction.

2. Computational methods

Electronic structure calculations have been performed using the Gaussian 03 series of programs (Frisch et al., 2004). The widely used density functional theory method B3LYP (Lee et al., 1988; Becke, 1993; Stephens et al., 1994) in conjunction with the split valence basis set incorporating polarization and diffuse functions, 6-31+G(d,p), was used for the geometry optimization of all the systems. The local minima were verified by frequency calculations. The Mulliken scheme was used to obtain spin density distribution. The transition states (TS) were located by the Synchronous Transit-Guided Quasi-Newton approach (QST3 method) (Peng and Schlegel, 1993; Peng et al., 1996). The genuineness of the transition states in each case was ensured by the presence of one imaginary frequency. Further, qualitative reliability of the B3LYP/6-31+G(d,p) level calculations is tested with MPW1K/6-31+G(d,p) level optimizations (Lynch et al., 2000). More accurate energetics is also obtained by single point energy calculations at CCSD(T)/6-31+G(d,p) (Pople et al., 1987) using the B3LYP/6-31+G(d,p) and MPW1K/6-31+G(d,p) level optimized geometries. The combination calculations are represented as CCSD(T)/6-31+G(d,p)//B3LYP/6-31+G(d,p) and CCSD(T)/6-31+G(d,p)//MPW1K/6-31+G(d,p). Solution phase optimizations were performed at B3LYP/6-31+G(d,p) level using the polarizable continuum model (PCM) (Mennucci and Tomasi, 1997). Finally, a time dependent density functional theory (TDDFT) (Stratmann et al., 1998) at B3LYP/6-31+G(d,p) level has been performed to get insight about absorption spectrum of the transient species formed during the pulse radiolysis experiments.

3. Results and discussion

The geometry of uracil, optimized at the B3LYP/6-31+G(d,p) level is depicted in Fig. 1 with selected bond lengths. The C5C6

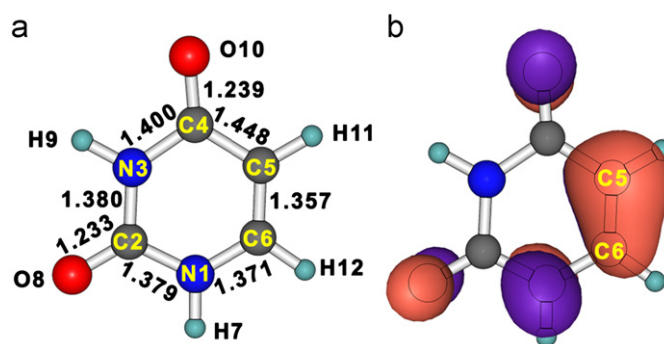


Fig. 1. (a) B3LYP/6-31+G(d,p) optimized geometry of uracil with selected bond lengths and (b) the HOMO (isocontour value = 0.055 a.u.) of uracil.

bond (1.357 Å) in the ring is substantially shorter than the rest, which indicates a localized double bond character for this bond. Indeed, the highest occupied molecular orbital (HOMO) is located on this bond (Fig. 1), which brings out that C5 and C6 are electron rich centers. Hence, the electrophilic additions of $\cdot\text{OH}$ would have a high preference on these atoms. In the present study, we have considered the energetics of OH addition to C5 giving rise to U_C5OH \cdot adduct as well as addition to C6 to yield the U_C6OH \cdot adduct. Further, the H-abstractions of $\cdot\text{OH}$, namely the H7 from N1 and H9 from N3 atoms are also modeled. The H-abstractions from N1 and N3 leads to the formation of radical systems U_N1 \cdot and U_N3 \cdot , respectively. The relative energy values reported in the present study are with respect to the free uracil and $\cdot\text{OH}$, unless otherwise stated.

3.1. Addition reactions

The $\cdot\text{OH}$ addition occurs when the oxygen atom of the hydroxyl radical approaches the π -face of the uracil to form the weak complex, U... $\cdot\text{OH}_{(1)}$. The stabilization of 5.9 kcal/mol observed for this complex is in the higher range of a typical value (~ 3.5 kcal/mol) of a weak closed shell non covalent OH- π interactions (Suresh et al., 2009; Mohan et al., 2010). Compared to the closed shell systems wherein the site of 'H' interacts with the π -region, the open shell U... $\cdot\text{OH}_{(1)}$ shows the interaction of 'O' with the π -bond. Due to this interaction, the C5C6 bond of length 1.357 Å in uracil is activated to 1.366 Å in the weak complex and paves the way for a facile addition reaction. Two addition pathways are observed from U... $\cdot\text{OH}_{(1)}$, one leading to the adduct U_C5OH \cdot via transition state TS1 and the other to adduct U_C6OH \cdot via TS2 (Fig. 2).

The energetics in Fig. 2(b) suggests that the activation energy (E_{act}) for first pathway is 0.4 kcal/mol while E_{act} of the second pathway is 0.2 kcal/mol, which means that both the reactions are nearly barrierless. U_C6OH \cdot is thermodynamically 1.2 kcal/mol more stable than U_C5OH \cdot . These results indicate that the product U_C6OH \cdot is thermodynamically the most favored addition product. Though both the reactions are nearly barrierless, the observed small difference in the activation barriers indicates some amount of regioselectivity. During the formation of the π -complex, significant amount of the spin density from the O of the $\cdot\text{OH}$ is transferred to the ring carbon atom and this spin distribution change is further enhanced in the transition state as well, suggesting strong coupling between the π and the unpaired electron densities.

The MPW1K/6-31+G(d,p) level calculations showed that compared to the B3LYP/6-31+G(d,p), the energy barriers are substantially higher for the formation of both the adducts U_C5OH \cdot (2.2 kcal/mol) and U_C6OH \cdot (1.5 kcal/mol). The E_{act} obtained at the CCSD(T)/6-31+G(d,p)//B3LYP/6-31+G(d,p) level

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