

Reactions of the OOH radical with guanine: Mechanisms of formation of 8-oxoguanine and other products

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ABSTRACT

The mutagenic product 8-oxoguanine (8-oxoGua) is formed due to intermediacy of peroxy (OOR) radicals in lipid peroxidation and protein oxidation-induced DNA damage. The mechanisms of these reactions are not yet understood properly. Therefore, in the present study, the mechanisms of formation of 8-oxoGua and other related products due to the reaction of the guanine base of DNA with the hydroperoxyl radical (OOH) were investigated theoretically employing the B3LYP and BHandHLYP hybrid functionals of density functional theory and the polarizable continuum model for solvation. It is found that the reaction of the OOH radical with guanine can occur following seven different mechanisms leading to the formation of various products including 8-oxoGua, its radicals, 5-hydroxy-8-oxoguanine and CO₂. The mechanism that yields 8-oxoGua as an intermediate and 5-hydroxy-8-oxoGua as the final product was found to be energetically most favorable.

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1. Introduction

Reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS) generated by a variety of endogenous and exogenous sources frequently react with DNA and other biomolecules altering their structures that can cause malfunctioning of cells, mutation, cancer and many other severe diseases [1–4]. Reactions of ROS and RNOS with guanine which is the most frequently attacked base of DNA yield several deleterious products including 8-oxoguanine (8-oxoGua), 8-nitroguanine (8-nitroGua), spiroiminodihydantoin (Sp) and guanidinodihydantoin (Gh) that are implicated in various pathological conditions including mutation and cancer [1–5]. 8-OxoGua is considered to be one of the most important oxidative DNA lesions due to its easy formation and high reactivity as well as due to its mispairing ability with adenine during DNA replication that causes GC to TA transversion mutation [3,4,6].

Peroxy (OOR) radicals belonging to the ROS family are important oxidants and are present abundantly in cells [7–10]. These radicals are known to play major roles in the lipid peroxidation and protein oxidation-induced DNA damage [11–13]. Peroxyl radicals are formed as intermediates due to decomposition of lipid hydroperoxides during both enzymatic and non-enzymatic lipid peroxidation. They are also formed due to decomposition of protein hydroperoxides in the presence of metal ions [8,11–16]. Peroxyl radicals are capable of reacting with DNA molecules far

away from the sites of their formation in biological media due to their long lifetimes [17]. Guanine has been found to be most reactive while adenine has been found to be least reactive with regard to oxidation of DNA bases by peroxy radicals [18]. Occurrence of 8-oxoGua due to oxidation of DNA by peroxy radicals has been observed experimentally [7,9,19]. Base level DNA damage caused by different environmental agents and prevention of the damage are subjects of great importance in chemistry, biology and medicine [20–28]. Further, study of mechanisms of formation of 8-oxoGua and other mutagenic products due to reactions involving ROS and RNOS is of immense current research interest [29–36]. However, the mechanisms of formation of the wide spectrum of products including 8-oxoGua due to oxidation of guanine in DNA by peroxy radicals remains to be elucidated.

The hydroperoxyl radical (OOH) which is a conjugate acid of the superoxide radical anion (O₂⁻) is the smallest and highly reactive peroxy radical [10,37–39]. OOH radicals are formed in a variety of ways involving those due to radiation and are known to play a significant role in the radiation-induced oxidation of different biomolecules including DNA [4,10]. Superoxide radical anion, a well-known ROS, is produced abundantly during oxidative stress and damages cells in a variety of ways [4,10]. 8-OxoGua and other oxidative products of guanine are known to form due to reactions involving O₂⁻ in biological media [40,41]. In view of the above-mentioned facts, we have investigated here theoretically the reaction of the OOH radical with the guanine base of DNA aiming to elucidate the mechanisms of formation of 8-oxoGua and other products. In addition to this, the present study is also expected

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to aid experiments in identifying different types of oxidative products of guanine that are formed due to intermediacy of peroxy (OOR) radicals in the lipid peroxidation and protein oxidation-induced DNA damage.

2. Computational details

Molecular geometries of reactants (guanine and OOH radical), intermediate and product complexes as well as those of the transition states involved in the different schemes of reaction between guanine and the OOH radical were obtained initially at the B3LYP/6-31G(d,p) level of density functional theory (DFT) [42–44] in gas phase. All the stationary points so obtained were relocated by full geometry optimization employing the B3LYP and BHandHLYP hybrid functionals [42,43,45] of DFT in conjunction with the Dunning's correlation consistent double zeta aug-cc-pVDZ basis set [46]. However, the transition state TS10 could not be relocated at the BHandHLYP/aug-cc-pVDZ level of theory in gas phase. Therefore, in this case, single-point energy calculation was performed at the BHandHLYP/aug-cc-pVDZ level of theory using the B3LYP/aug-cc-pVDZ optimized geometry. To treat the bulk solvent effect of aqueous media on the energetics of the reaction, single-point energy solvation calculations at the BHandHLYP/aug-cc-pVDZ level of theory were carried out employing the polarizable continuum model (PCM) of the self-consistent reaction field (SCRf) theory [47] as implemented in the Gaussian98 (G98 W) program [48] and the gas phase BHandHLYP/aug-cc-pVDZ optimized geometries.

Vibrational frequency analysis in all the cases was performed at the B3LYP/6-31G(d,p), B3LYP/aug-cc-pVDZ and BHandHLYP/aug-cc-pVDZ levels of DFT using the respective optimized geometries in gas phase to ensure that the reactants, intermediate and product complexes had all real vibrational frequencies whereas the transition states had all except one real vibrational frequency each, and to obtain the zero-point energy (ZPE)-corrected total energies. The genuineness of all the transition states was ensured by visually examining the vibrational modes corresponding to the imaginary vibrational frequencies, and also by intrinsic reaction coordinate (IRC) calculations [49]. As an approximation, ZPE-corrections obtained at the BHandHLYP/aug-cc-pVDZ level of theory in gas phase were also applied to the single-point total energies obtained at the BHandHLYP/aug-cc-pVDZ level of theory in aqueous media. The calculations were performed employing the Windows versions of the Gaussian98 (G98 W) [48] and Gaussian03 (G03 W) [50] programs while molecular structures and vibrational modes were visualized employing the GaussView program [51].

3. Results and discussion

Reactions involving addition of an OOH radical at each of the five carbon (C2, C4, C5, C6 and C8) atoms of guanine were investigated at the B3LYP/6-31G(d,p) level of theory in gas phase. Relative ZPE-corrected total energies of transition states and adducts with respect to the sum of ZPE-corrected total energies of the reactants i.e. guanine and OOH radical are plotted in Fig. 1. It is evident from this figure that the barrier energies for addition of the OOH radical at the different carbon atoms follow the order $C8 < C2 < C4 < C5 < C6$, the difference between the barrier energies corresponding to the C8 and C6 sites being ~ 20 kcal/mol. It indicates that the OOH radical addition at the C8 site would be most probable. The same order is also followed by the relative stabilities of the different adducts (Fig. 1). The difference between the ZPE-corrected total energies of adducts at the C8 and C6 sites was found to be ~ 30 kcal/mol. The ZPE-corrected barrier energy and binding energy of the adduct involved in the OOH radical addition at the

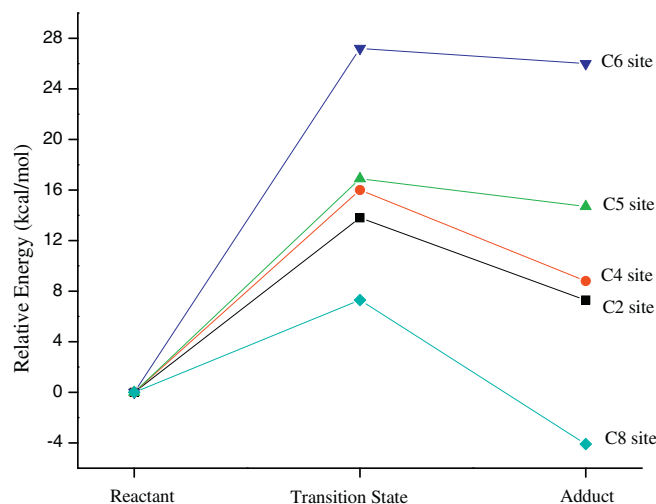


Fig. 1. ZPE-corrected relative total energies of transition states and adducts with respect to sum of the total energies of isolated reactants involved in the addition reaction of OOH radical at each of the C2, C4, C5, C6 and C8 sites of guanine obtained at the B3LYP/6-31G** level of theory in gas phase.

C8 site of guanine were found to be 7.3 and -4.1 kcal/mol at the B3LYP/6-31G(d,p) level of theory in gas phase respectively. The addition reaction of an OH radical was also found to be most probable and barrierless at the C8 site of guanine [21]. In view of the foregoing discussion, we have studied the reaction of an OOH radical at the C8 site of guanine in detail.

The reaction of the OOH radical with guanine at its C8 site can occur following seven different mechanisms and leads to the formation of six different product complexes denoted by PC1, PC1', PC2, PC3, PC4 and PC5 as shown in schemes 1–7 (Figs. 2–8). The schemes 1 and 2 yield PC1 (Figs. 2 and 3) while schemes 3, 4, 5, 6 and 7 yield PC1', PC2, PC3, PC4 and PC5 respectively (Figs. 4–8). PC1 is the complex of a water molecule with 8-oxoGua radical (Figs. 2 and 3) which may be denoted by [8-oxoGua(-H7)] as the hydrogen atom is absent from its N7 site. Similarly, PC1' is the complex of a water molecule with 8-oxoGua radical which may be denoted by [8-oxoGua(-H9)] as the hydrogen atom is absent from its N9 site (Fig. 4). PC2 and PC3 are 5-hydroxy-8-oxoGua and 4-hydroxy-8-oxoGua, respectively (Figs. 5 and 6). PC4 and PC5 are the product complexes involving CO and CO₂ as components, respectively (Figs. 7 and 8). Optimized structures along with certain geometrical parameters of the different species obtained at the BHandHLYP/aug-cc-pVDZ level of theory in gas phase as well as the ZPE-corrected barrier and released energies obtained at the same level of theory in aqueous media are given in Figs. 2–8. The ZPE-corrected barrier and released energies involved in the schemes 1–7 (Figs. 2–8), obtained at the different levels of theory in gas phase and aqueous media, are presented in Tables 1–7 respectively. It is observed that in going from the 6-31G(d,p) to the aug-cc-pVDZ basis set used along with B3LYP functional in gas phase, the barrier energies are usually changed only by 0–22% (Tables 1–7). Therefore, the results obtained using the aug-cc-pVDZ basis set would mainly be considered in the following discussion.

The reaction scheme 1 shows how starting from the reactants (guanine + OOH radical), the product complex PC1 is formed in three reaction steps involving the transition states TS1, TS2 and TS3, and the intermediate complexes IC1 and IC2 (Fig. 2) while the reaction scheme 2 illustrates formation of PC1 starting from IC1 through two different transition states TS4 and TS5 and an intermediate complex IC3 (Fig. 3). The schemes 1 and 2 are different only with regard to movement of the H8 atom after IC1 is

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