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Computational mechanistic investigation of radiation damage of adenine induced by hydroxyl radicals*

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The radiation damage of adenine base was studied by B3LYP and MP2 methods in the presence of hydroxyl radicals to probe the reactivities of five possible sites of an isolated adenine molecule. Both methods predict that the C8 site is the more vulnerable than the other sites. For its bonding covalently with the hydroxyl radicals, B3LYP predicts a barrierless pathway, while MP2 finds a transition state with an energy of 106.1 kJ/mol. For the hydroxylation at the C2 site, the barrier was calculated to be 165.3 kJ/mol using MP2 method. For the dehydrogenation reactions at five sites of adenine, B3LYP method predicts that the free energy barrier decreases in the order of H8 > H2 > HN62 > HN61 > HN9.

Keywords: DNA damage, radicals, adenine, dehydrogenation

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1. Introduction

Hydroxyl radicals (·OH), a highly reactive species, are generated indirectly by the photolysis/radiolysis of water surrounding cellular DNA. Normally, ·OH is present at low concentrations, due to the metabolism of oxygen. Higher concentrations can be caused by ionizing radiations or UVA solar light.[1,2] When living cells are exposed to ionizing radiations, DNA damage can be caused by ·OH. It is confirmed to be more heavily involved in the single/double-strand breaking of DNA than the other reactive oxygen species (ROS)[3,4] and may lead to mutations, carcinogenesis, cell aging and lethal lesions in biosystems.[5,6]

To understand the underlying mechanisms of the DNA damage, experimental and theoretical investigations have been carried out extensively in the past thirty years.[7–9] Previous investigations proposed that the reactivity of ·OH with DNA bases, including both purine and pyrimidine bases, is responsible for DNA damage.[10–12] At room temperature, some model systems constituted by aqueous solutions have been provided to investigate the reactions of ·OH with DNA components including nucleobases (nucleosides) and 2-deoxyribose.[13–16] Evidence shows that although the polarization of the water plays a vital role in the proton transfer, some similar structures and properties are inferred from the comparison of the distribution of the ·OH-mediated degradation in isolated nucleosides and cellular DNA.[17]

Nucleobases are the structural units which carry genetic information in DNA. There are four principal nucleobases in DNA: adenine (Ade), thymine (Thy), guanine (Gua), and cytosine (Cyt). A tremendous amount of experimental investigation confirms the probabilities that the different nucleobases are attacked by ·OH decreases in the order of Gua > Ade > Cyt > Thy.[18–21] Due to the exceptional stability, by far, guanine (Gua) has been verified to be most easily attacked by ·OH at the C4 site to produce mainly C4-OH·,[19,20] which was questioned by Chatgilialoglu *et al.* and a new mechanism was proposed.[21] Furthermore, the stabilization of Gua can be enhanced by cations.[22] Hazra *et al.* found that ·OH is attached to the C5 and C6 of Cyt by the ratio of 87% and 10%, respectively, due to the electron density of the C5 atom being much higher than that of the C6 atom.[18] A consistent conclusion has been drawn that the C5 site of Thy is favorably attacked by the ·OH.[18,19]

In comparison, Ade has lower radio-sensitivity than Thy[23] and a relatively less number of experimental observations have been carried out on the damage of Ade in the presence of ·OH. To our knowledge, Ade has only been observed experimentally sandwiched between two Guas.[24] Three reasons are responsible for the less reactivity of Ade toward ·OH.[18] Firstly, in the reaction products, the low density of the free radicals and the less reactivity of the free radicals toward oxygen mean that the free radicals cannot be caught and detected. Secondly, the oxidation and deoxidization of Ade is not stronger than pyrimidine, which make it difficult to study the damage of Ade using pulse radiolysis techniques. Thirdly, the instability of the reaction products causes easily the reconstitution and nonidentifiability of Ade radicals.

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Available computational studies mainly concentrated on static geometries, relative energies, ionization potentials, and hyperfine coupling constants (HFCC) of the hydroxylated and dehydrogenated products of nucleobases using *ab initio* quantum chemistry methods.[7,8,10,25] A Monte Carlo (MC) simulation shows that the probabilities of suffering an initial ·OH attack for Gua, Ade, Thy, and Cyt are 36%, 24%, 22%, and 18%, respectively.[26] For example, the one-electron oxidation of Gua is of great interest in the presence of ·OH radicals. At the same time, the gas phase dehydrogenation reaction of Gua toward ·OH was investigated by using Car–Parinello molecular dynamics (CPMD),[27] and the amino group ($-NH_2$) is predicted to be the most favorable site for dehydrogenation. In our previous work,[28] B3LYP and MP2 methods are used to study the hydroxylation and dehydrogenation of thymine at different sites in the presence of ·OH. The calculated results are consistent with experimental data and the preference for the C5 site is due to the facility of ·OH in approaching the substrate. To understand electron attachment to DNA double helix, the oxidation pathways of the adenine–thymine (A–T) and guanine–cytosine (G–C) base pairs were studied both in the gas phase and in the aqueous solution.[29–31] For A–T base pairs, the results show that the hydrogen bonds have little effect on the hydroxylation and dehydrogenation happened at the sites, which are not involved in a hydrogen bond, while at the sites involved in hydrogen bond formation in the base pair, the reaction becomes more difficult, both in view of the free energy barrier and the exothermicity.[31] A recent study indicated that the dispersion-corrected density functionals such as BLYP-D are very well suited for describing hydrogen bonded A–T pair and stacked A–T dimers while the B3LYP functionals are not able to describe the stacked A–T dimers.[32]

For Ade, calculations at the B3LYP/DZP++ level show five possible dehydrogenation reaction pathways when attacked by ·OH and the barrier energies increase in the order of HN62 < HN9 < HN61 < H2 < H8.[25] Hydroxyl radicals are attached to the double bonds of Ade at the C4, C5, and C8 sites to yield C4–OH·, C5–OH· and C8–OH· radicals,[33–35] and the C4–OH· radicals adduct composes more than 81% of the products of hydroxylation. However, MC simulations above show Ade is the second highest species from the point of the probability of being attacked by ·OH, which is in disagreement with the previous experiments.[19,20]

Concerning the lack of a deep understanding on Ade in the presence of hydroxyl radicals, we concentrate in the present work on the reaction of ·OH with Ade at its different sites, using a density functional theory (B3LYP)[36,37] and a second-order Møller–Plesset perturbation theory (MP2) method.[38,39] It is worth mentioning that the density functional theory (DFT) is a computational quantum mechanical modelling method used in physics, chemistry and materials science to investigate the electronic structure of many-body systems. Using this theory, the properties of a many-electron system can be determined by using functionals, i.e., functions of another function, which in this case is the spatially dependent electron density.

2. Model and computational details

Density functional theory method, (U)B3LYP, and Møller–Plesset's second-order perturbation theory method were used, with all atoms treated at 6-311++G(d,p) level,[40,41] to study two possible mechanisms leading to the damage of Ade induced by ·OH radicals, i.e., the hydroxylation and the dehydrogenation. All stationary points reported here, including reactant states (RS), reactant complexes (RC), transition state (TS), and products (PC), have been fully optimized in gas phase, and vibrational frequency analysis was performed to verify the nature of these structures. Intrinsic reaction coordinate (IRC) calculations were also performed to confirm the RC and PC that TS connects. In order to check the importance to take into account a correction for dispersion interaction, B97D[42] functional has been also employed in the study on the hydroxylation reactions. The results are similar to those from B3LYP calculations, thus will not be discussed in this work.

All calculations were done with the Gaussian 09 suite of program, and GaussView 5.0 molecular modeling software was used for visualization of structures and vibrational modes.

3. Results and discussions

3.1. Hydroxylation

After the structure of Ade optimized at the level of 6-31G(d) basis set, it was found that three atoms (N1, N3, and N7) carry the negative charges and their electronegativity is almost as strong as hydroxyl radicals. Therefore, for the hydroxylation of Ade, we only consider five possible reaction pathways with the addition of ·OH happened at the C2, C4, C5, C6, and C8 sites (see Fig. 1 for the definition of reaction sites), respectively. Figure 2 describes the potential energy surface scanning at the B3LYP/6-311++G(d,p) level when an adenine is attacked by a hydroxyl radical. It is easily seen that their energy curves have a saddle point, except the C8 site. That is to say, the energy increases to a maximum and then begins to decrease with the reaction coordinate increasing when ·OH attacks the different C2, C4, C5, C6 sites. The corresponding distances (R_{OS}) between ·OH with target site is respectively 1.97 Å, 1.93 Å, 1.85 Å, and 1.93 Å when the energies reach their maximums. What is more, their energy curves almost trace a consistent track when the C4 and C6 sites are attacked by ·OH. For C8 site, the energy decreases with the reaction coordinate decreasing, and the lack of the saddle point indicates the absence of transition state.

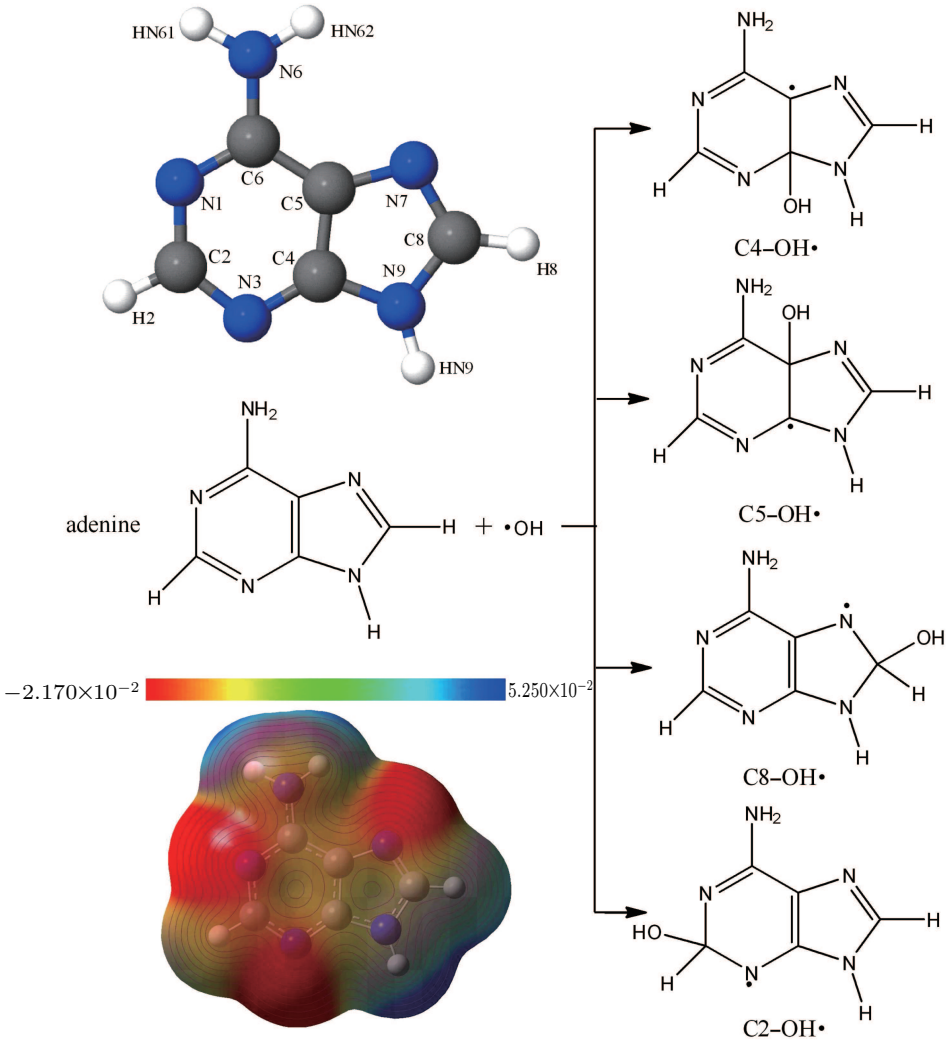


Fig. 1. (color online) The structures, labeling (upper), electron density (lower), and the primary intermediates proposed by experiments for the reactions between an adenine and an ·OH free radical.

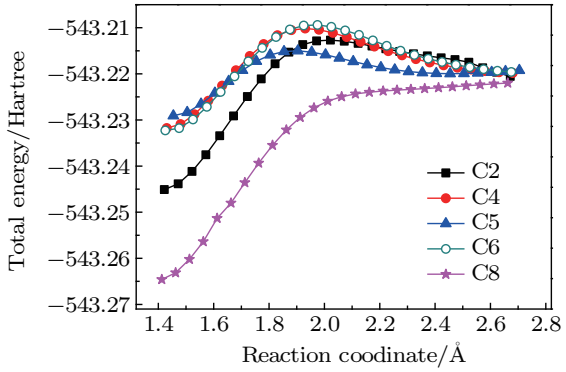


Fig. 2. (color online) Potential energy surface scanning at the B3LYP/6-311++G(d,p) level when an adenine is attacked by an ·OH free radical in gas phase.

The optimized structures of RC, TS, and PC in gas phase are shown in Fig. 3. The transition state along the pathway at the C2, C4, C5, and C6 sites are located by the B3LYP/6-311++G(d,p) levels, which is verified by the presence of a single imaginary frequency of 405i cm^{-1}, 445i cm^{-1}, 397i cm^{-1}, and 468i cm^{-1}, respectively. For C8 site, the corresponding geometrical structures and parameters, which are not given in Fig. 3, are obtained at the MP2/6-311++G(d,p), and the only imaginary frequency is 941i cm^{-1}.

In each pathway, the hydroxyl radical was placed in a manner such that its oxygen atom was located near the corresponding reaction sites, and was subjected to full optimization. The conformations of reactant complexes show that the approach of ·OH does not lead to a noticeable deformation of the six-membered ring of Ade, except the C4 and C5 sites. For the C4 and C5 sites, the dihedral angle is about 150° between the six-membered ring and the five-membered ring, accompanied by the breaking of the C4=C5 double bond and the disappearing of the π orbit. In the products, due to the formation of a C4–O or C5–O bond in the hydroxylation at C4 and C5 sites, these two atoms experience a reorganization of their electronic structures and geometrically transform from a planar sp^2 C to a tetrahedral sp^3 one. The corresponding products are C2–OH·, C4–OH·, C5–OH·, and C6–OH·, respectively. The calculations at the B3LYP/6-311++G(d,p) level show that the energy of isolated Ade is −467.34 Hartree (1 Hartree = 27.2114 eV), after experiencing the correction of zero point energy.

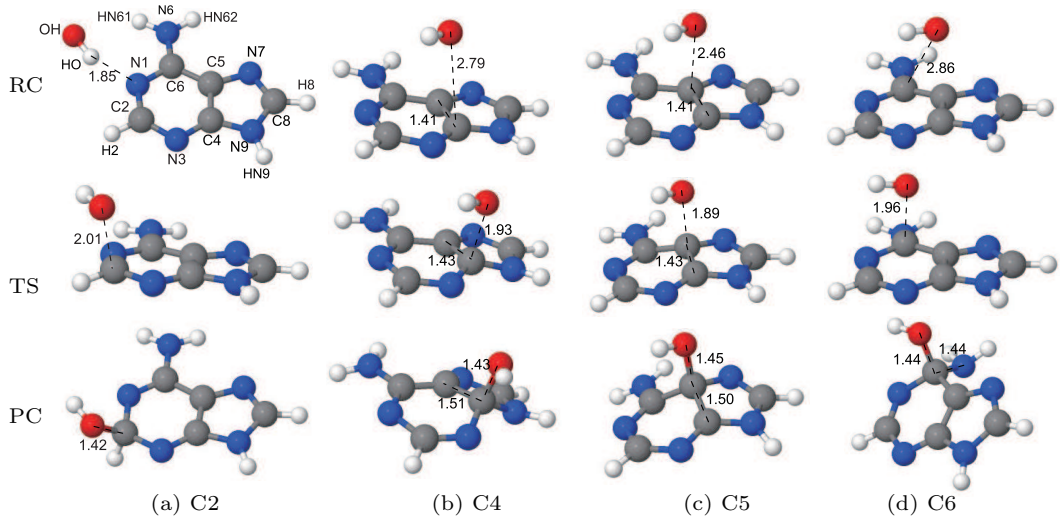


Fig. 3. (color online) Optimized structures (B3LYP/6-311++G(d,p)) with selected geometrical parameters (distances in unit Å) of reactant complexes (RC), transition states (TS), and products (PC) in the hydroxylation at C2 (a), C4 (b), C5 (c), C6 (d) of adenine by an ·OH free radical in gas phase, except for C8 site whose geometrical parameters are given by MP2/6-311++G(d,p) level (The plot is not given in Fig. 3).

The relative Gibbs free energies of RS, RC, TS, and PC in gas phase are shown in Fig. 4. Thermodynamically the reactions at the C8 and C2 sites are exothermic by 78.2 kJ/mol and 28.1 kJ/mol respectively, while those at the C5, C4, and C6 sites are endothermic by 13.0 kJ/mol, 8.5 kJ/mol, and 8.1 kJ/mol, respectively. These results experience a discrepancy with that of previous work,[25] in which the B3LYP method is adopted along with double-z quality basis sets with polarization and diffuse functions (denoted as DZP++).

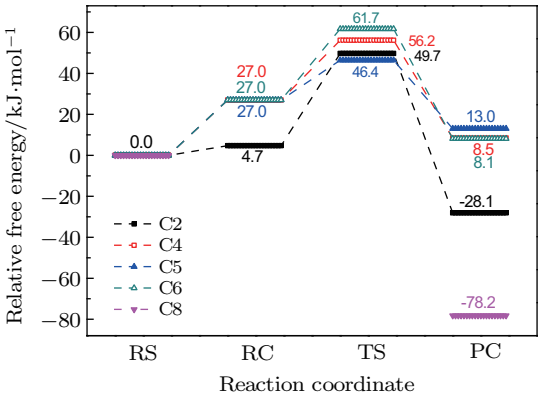


Fig. 4. (color online) The relative free energy profiles of RS, RC, TS, and PC in gas phase for the hydroxylation of Ade at C2, C4, C5, C6, and C8 sites at B3LYP/6-311++G(d,p) level.

According to our calculations, the free energy barriers inherent in the hydroxylation at C6 and C4 sites are as high as 61.7 kJ/mol and 56.2 kJ/mol respectively, suggesting that at ambient condition it is difficult for the hydroxylation to happen at the two sites either from a kinetic view or a thermodynamic view.

In contrast, the reactions at the C2 and C5 sites have a relatively lower free energy barrier (49.7 kJ/mol and 46.4 kJ/mol). In addition, the approach of the ·OH to the C2 site is relatively easier compared to that to the other sites, for the much lower relative free energy (4.7 kJ/mol). These data demonstrate that the reactivity of ·OH toward the C2 site is a more favorable process compared to that at the C4, C5 or C6 site. For the reaction at the C8 site, the B3LYP calculation did not locate a transition state, either by means of the potential energy surface scanning with the distance between C8 and O (hydroxyl) as the reaction coordinate, or through a full optimization for a first-order saddle point starting from a carefully prepared transition-state-like structure, and predicted the reaction as a barrierless process, suggesting a much higher reactivity of the C8 site. The result is different from that of the previous work,[34,35,43] the potential barriers are 23.7 kJ/mol (5.5 kcal/mol) and 4.6 kJ/mol (1.1 kcal/mol) respectively when ·OH adduct to the C4 and C8 sites. Experimentally, the percentage of C2–OH· product is only 2.0%,[35] and the reactivity of C2 site toward the attachment of ·OH ranks second only to C8 site is due to their distinct chemical environments.

As seen in Fig. 1, C2 is neighbored to two nitrogen atoms, and may thus shows stronger electrophilicity than C8 which is bonded to an amide group and a nitrogen atom and thus more nucleophilic. This may be seen from the relatively positive charge on C8 (0.22 e) and C2 (0.01 e) in Ade, thus stronger interaction between C8 and the electrophilic ·OH radicals than that between C2 and ·OH. The missing of a reactant complex and a transition state along the hydroxylation on C8 in B3LYP calculations is possibly due to the deficiency of the B3LYP functional.

For a better description of the interaction between an electrophilic radical and the positively charged C8 site, we have chosen MP2 method to re-optimize the stationary points along the reaction pathways. The calculated relative Gibbs free energies of RS, RC, TS, and PC in gas phase using MP2 method are shown in Fig. 5. At the MP2/6-311++G(d,p) levels, we located a transition state along each pathway, which is verified by the presence of a single imaginary frequency of 1311i cm^{-1}, 795i cm^{-1}, 584i cm^{-1}, 495i cm^{-1}, and 941i cm^{-1} at the C2, C4, C5, C6, and C8 sites respectively.

Compared to the B3LYP results, as expected, MP2 method predicts much higher free energy barriers for both types of reactions. It has been seen from Fig. 4 and Fig. 5 that the relative Gibbs free energies of TS and PC at the MP2/6-311++G(d,p) levels are higher than that of at the B3LYP/6-311++G(d,p) levels, while the contrary is the case to RC process. Compared to the reaction of C2, C4, C5, and C6, the relative Gibbs free energies of RC, TS, and PC are minimally 0.2 kJ/mol, 106.1 kJ/mol and −25.0 kJ/mol. It indicated that the C8 site is the most likely attacked by ·OH.

Then, CCSD(T) method was also a candidate to clarify the problem, while we could only afford the single point calculations rather than the gradient calculations. In Table 1 we collected the relative energies of the stationary points in the hydroxylation and hydrogen abstraction of Ade at the CCSD(T)//MP2/6-311++G(d,p) level. Both methods suggest similar trend in the activation free energy and exothermicity except for the hydroxylation at the C8 site, which is a barrierless process according to calculations using B3LYP method but has a substantial barrier of 106.1 kJ/mol with MP2 method and 0.3 kJ/mol with CCSD(T) method.

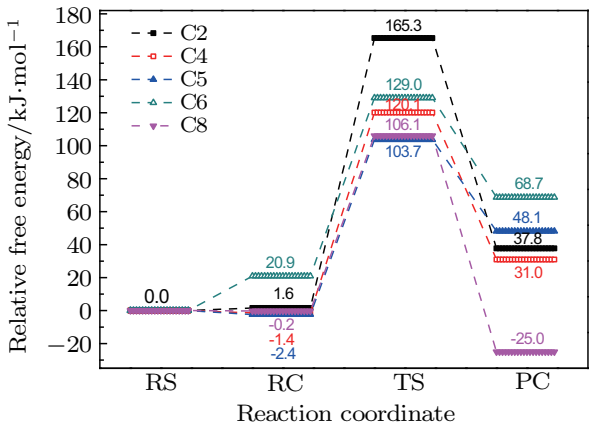


Fig. 5. (color online) The relative free energy profiles of RS, RC, TS, and PC in gas phase for the hydroxylation of Ade at C2, C4, C5, C6, and C8 sites at MP2/6-311++G(d,p) level.

Table 1. The relative free energies (in units kJ/mol) of RS, TS and PC in the hydroxylation and dehydrogenation at different sites of adenine at the CCSD(T)//MP2/6-311++G(d,p) levels in gas phase. For comparison, the corresponding energies at the CCSD(T)//B3LYP/6-311++G(d,p) levels are given.

Site	RS	CCSD(T)//B3LYP/6-311++G(d,p)			CCSD(T)//MP2/6-311++G(d,p)		
		RC	TS	PC	RC	TS	PC
C2	0.0	–39.7	21.1	–85.2	–39.0	32.0	–57.7
C4	0.0	–14.9	18.8	–57.8	–42.4	39.8	–49.8
C5	0.0	–14.9	1.1	–53.0	–16.8	26.6	–45.3
C6	0.0	–14.9	19.0	–67.9	–15.8	46.9	–51.6
C8	0.0	–	–	–125.1	–42.0	0.3	–117.2
H2	0.0	–42.8	31.6	–77.8	–42.6	33.9	–74.6
H8	0.0	-42.7	47.6	–47.2	–42.0	51.0	–43.2
HN61	0.0	-39.7	21.6	–78.7	–39.1	20.2	–43.4
HN62	0.0	-12.3	29.0	–88.6	–	–	–

However, to the reactivity of C2 site, B3LYP and MP2 methods gave two opposite conclusions. The reaction is exothermic and lower barrier (50.0 kJ/mol) using B3LYP method when the C2 site is hydroxylated by ·OH. Meanwhile MP2 calculations show that it is endothermic and higher barrier (165.3 kJ/mol). The results from MP2 calculations indicate that the C2 site is less likely attacked ·OH compared to the C8 site, which is consistent with the previous experimental investigation that the proportion of C2–OH· product is only 2%.[35] The conclusion is also verified by the CCSD(T) calculations, see Table 1.

3.2. Dehydrogenation

As a highly reactive species, it is possible for ·OH to abstract a hydrogen atom from Ade and give a molecule of water and an Ade radicals. In Ade, there are four sites bearing hydrogen atoms, i.e. C2, C8, N9, N6, where the corresponding hydrogen atoms are denoted as H2, H8, HN9, HN61, and HN62, respectively. Note that in DNA, the N9 atom of Ade is bonded to the carbon atom of desoxyribose, so the HN9 atom can hardly potentially be the target of ·OH radicals. For comparison, here we discuss our results on the relative reactivity of the four sites (C2, C8, N9, N6) toward the dehydrogenation invoked by the ·OH radicals. The fully optimized structures of the stationary points are shown in Fig. 6 with key geometrical parameters given, and the free energy profiles are plotted in Fig. 7.

As seen in Fig. 6, for all of the four reactions at the C2, C8, N6 sites, we located a transition state along each pathway, which is verified by the presence of a single imaginary frequency of 835i cm^{-1}, 1500i cm^{-1}, 1214i cm^{-1}, and 1032i cm^{-1} corresponding to the formation of H–OH bond and the cleavage of the C/N–H bond at the C2, C8, and N6 sites respectively. In the transition states, the reaction sites, the leaving hydrogen atom and the oxygen atom of the ·OH radicals are almost collinear, except the angle consists of N6, HN62 and ·OH, and the pyrimidine ring remains in its planar conformation.

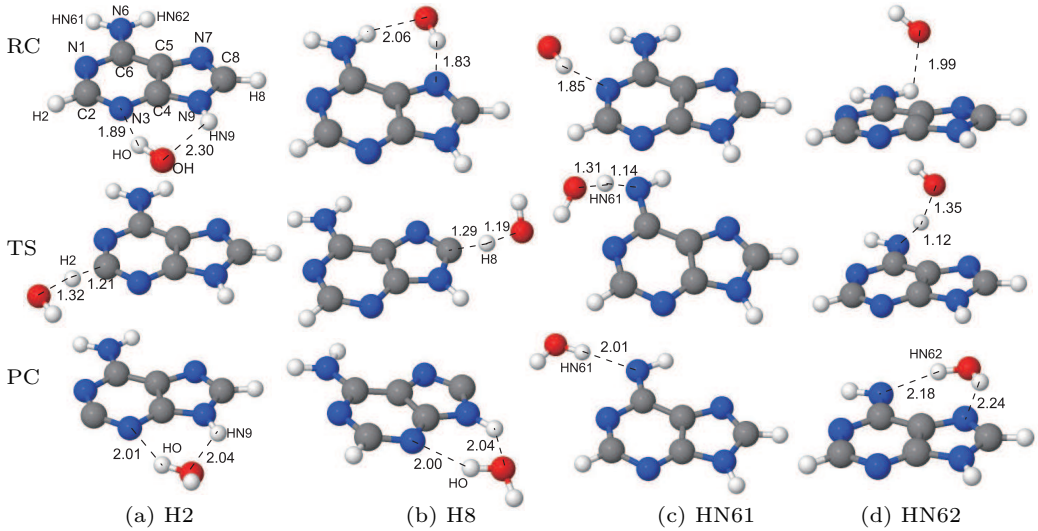


Fig. 6. (color online) Optimized structures (B3LYP/6-311++G(d,p)) with selected geometrical parameters (distances in unit Å) of reactant complexes (RC), transition states (TS), and products (PC) in the dehydroxylation at C2 (a), C8 (b), N6 (c, d) of adenine by an ·OH free radical in gas phase.

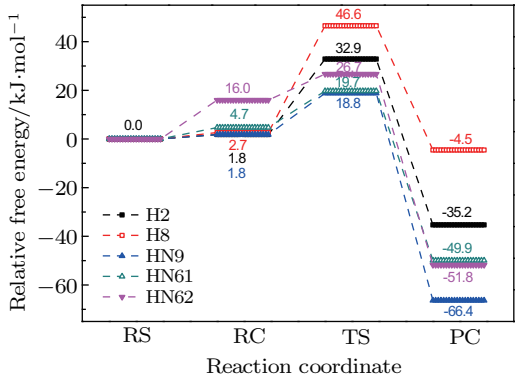


Fig. 7. (color online) The relative free energy profiles of RS, RC, TS, and PC in gas phase for the dehydroxylation of Ade at C2, C8, and N6 sites at B3LYP/6-311++G(d,p) level.

Energetically, as seen in Fig. 7, the dehydrogenations at the C2, C8, N9, and N6 sites, are exothermic and low-barrier. To the N9 site, the dehydrogenation is highly exothermic by 66.4 kJ/mol with a free energy barrier of 18.8 kJ/mol. The two reactions at the N6 site have almost the same exothermicity of 49.9 kJ/mol and 51.8 kJ/mol thermodynamically, while the dehydrogenation of HN61 atom is kinetically more favorable with a free energy barrier of 19.7 kJ/mol than the dehydrogenation of HN62 atom by 26.7 kJ/mol. The reactions at the C2 and C8 sites are calculated with substantially high free energy barriers of 32.9 kJ/mol and 46.6 kJ/mol respectively, and the reaction free energies are respectively −35.2 kJ/mol and −4.5 kJ/mol. The trends of the different reaction sites toward the dehydrogenation are basically in agreement with the previous results.[25] To the dehydrogenation at different sites, the free energy barrier decreases in the order of H8 > H2 > HN62 > HN61 > HN9. These observations show that it is much easier for ·OH to abstract HN61 than HN62, suggesting low possibility for the dehydrogenation to happen at the C8 site. It is worth noting that the N9 site is used to bridge the deoxyribose and the base in DNA double-strand, thus it is less likely for the dehydrogenation to happen at the N9 site unless a DNA molecule is degraded at the N9 site in advance.

It is not difficult to find that the calculated results are almost the same as our previous works.[31] It indicates that the trend of the different reaction sites toward the dehydrogenation in isolated adenine base is nearly in agreement with that of adenine–thymine (A–T) base pairs. For simplicity, thus, the investigation of the reactivity in the isolated bases can be a substitute for the base pairs, although the isolated bases have a very low probability in vivo DNA.

4. Conclusions and perspectives

In the present work, the reactions of hydroxyl radicals with adenine were investigated in gas phase using density functional theory and MP2 methods. For the hydroxylation of Ade, B3LYP and MP2 methods give a different trend from free energy barrier. Calculations at B3LYP/6-311++G(d,p) level describe the reactions at the C2 site as processes with low free energy barriers of 49.7 kJ/mol and being strongly exothermic by 28.1 kJ/mol, while the reactions at the C8 site being simple — barrierless and highly exothermic by 78.2 kJ/mol. With MP2 method, the features of the reactions at C5, C4, and C6 sites are reproduced. However, for the hydroxylation at the C8 site, there exists a transition state with an energy 106.1 kJ/mol above the reactant state which is moderately higher than the energy of the transition state (103.7 kJ/mol) in the reaction at the C5 site, while the reaction at the C8 and C5 sites are exothermic by 25.0 kJ/mol and endothermic by 48.1 kJ/mol, respectively. It suggests that a more sophisticated treatment of the intermolecular interactions is necessary with precise description of the reaction at the C8 site. Though the reaction at the C8 site has a moderately higher barrier than the C5 site, it is more difficult for the ·OH radicals to approach the C5 site

than to the C8 site for the endothermic reaction at the C5 site. For the hydroxylation at the C2 site, the highest barrier is predicted by MP2 method. These explain the experimental results that there is larger chance for the hydroxylation to happen at the C8 site. The single point calculations at the CCSD(T) level confirms this explanation.

For dehydrogenation, the two methods give consistent results on the hydrogen abstraction thermodynamically, i.e., the free energy decreases in the order of H8 > H2 > HN62 > HN61 > HN9. Moreover, both B3LYP and MP2 methods predict the reaction at the N9 site superior over that at the sites of C2, C8, and N6. In DNA, however, the N9 site is used to bridge the deoxyribose and the base; thus, it is less likely for the dehydrogenation to happen at the N9 site unless a DNA molecule is degraded at the N9 site in advance.

The thermodynamic data for the hydroxylation and dehydrogenation of Ade in the presence of ·OH are refined at the levels of B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p). Using the newly obtained values with MP2 method, we are able to explain well the selectivity of the reaction sites in the ·OH-induced adenine damage.

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