Damage mechanism of hydroxyl radicals toward adenine–thymine base pair*

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The adenine–thymine base pair was studied in the presence of hydroxyl radicals in order to probe the hydrogen bond effect. 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. With a 6-311++G(d,p) level of description, both B3LYP and MP2 methods confirm that the C8 site of isolated adenine has the highest possibility to form covalent bond with the hydroxyl radicals, though with different energetics: B3LYP predicts a barrierless pathway, while MP2 finds a transition state with an energy of 106.1 kJ/mol. For the dehydrogenation reactions, B3LYP method predicts that the free energy barrier increases in the order of HN9 < HN61 < HN62 < H2 < H8.

Keywords: DNA damage, hydrogen bond effect, hydroxylation, dehydrogenation

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1. Introduction

The basis of the biological effects brought by radiations is DNA damage, which is closely related to free radicals, especially hydroxyl radicals (•OH) generated indirectly by the photolysis/radiolysis of water surrounding celluar DNA. Since the hydroxyl radical is a highly reactive species, which is confirmed to be more heavily involved in the single/double-strand breaking of DNA than the other reactive oxygen species (ROS)[1,2] and may lead to mutations, carcinogenesis, cell aging, and lethal lesions in biosystem,[3,4] a broad interest toward an understanding of the underlying mechanisms of the DNA damage[5–7] has been seen in the past thirty years. Previous investigations have proposed that the main causes for this are the dominant reactions of •OH with DNA bases, including both purine and pyrimidine bases.[8–11] Evidence has been provided that aqueous solutions at room temperature constitute relevant model systems to investigate the reactions of •OH with DNA components including nucleobases (nucleosides) and 2-deoxyribose.[12–15] Although the polarization of water plays a vital role in proton transfer,[16] it was still inferred from the comparison of the distribution of the •OH-mediated degradation in isolated nucleosides and cellular DNA, which shows extensive similarities.

Experimentally, a consistent conclusion has been drawn that the C5 site of thymine (Thy) is favorably attacked by the •OH.[17,18] The guanine (Gua) is verified to be most easily attacked by •OH at the C4 site to produce mainly C4–OH•,[18,19] which was questioned by Chatgilialoglu *et al.* and a new mechanism was proposed.[20] However, the C4–OH adduct in guanine was recently re-verified by Phadatare *et al.*[21] Hazra *et al.* found that •OH is attached to the C5 and C6 of cytosine (Cyt) by the ratio of 87% and 10%, respectively, due to the fact that the electron density of the C5 atom is much higher than that of the C6 atom.[17] In comparison, adenine (Ade) has lower radio-sensitivity than Thy[22] and a relatively lower number of experimental observations are carried out on the damage of Ade in the presence of •OH.

Available computational studies mainly concentrated on static geometries, relative energies, ionization potentials, and hyperfine coupling constants (HFCC) of the hydroxylated and

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dehydrogenated products of Ade and Thy using *ab initio* quantum chemistry methods.[5,6,8,23] A Monte Carlo simulation (MC) shows that the probabilities of suffering an initial •OH attack for Gua, Ade, Thy, and Cyt are 36%, 24%, 22%, and 18%, respectively.[24] Then, the one-electron oxidation of Gua is of great interest in the presentence of •OH radicals. At the same time, the gas phase dedydrogenation reaction of guanine with •OH was investigated by using Car–Parinello molecular dynamics,[25] and the amino group ($-NH_2$) is predicted to be the most favorable site for dehydrogenation. 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.[23] Hydroxyl radical is attached to the double bonds of Ade at the C4, C5, and C8 sites to yield C4–OH•, C5–OH•, and C8–OH• radicals,[26–28] and the C4–OH• radicals adduct composes more than 81% of the products of hydroxylation. However, MC simulations show that 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.[18,19] 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 in both the gas phase and in the aqueous solution.[29,30] A recent study indicated that the dispersion-corrected density functionals such as BLYP-D are very well suitable 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.[31]

Concerning the lack of a deep understanding on A–T pair and the Ade in the presence of hydroxyl radicals, we concentrate in the present work on the reaction of •OH with A–T pair and Ade at its different sites, using a density functional theory (B3LYP)[32–35] and a second-order Møller–Plesset perturbation theory (MP2) method.[36–38]

2. Model and computational details

To estimate the influence of intermolecular hydrogen bonds, which exist in DNA duplex, on the hydroxylation and dehydrogenation reactions, a base pair of A–T was prepared and studied using density functional theory method, (U)B3LYP, with all atoms treated by 6-311++G(d,p) basis set.[39] For comparison, (U)B3LYP and Møller–Plesset's second-order perturbation theory method (MP2) were used to study two possible mechanisms leading to the damage of Ade induced by •OH radicals, the hydroxylation, and the dehydrogenation. All stationary points reported here, including reactant state (RS), reactant complex (RC), transition state (TS), and product (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 a TS connects.

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

3. Results and discussion

3.1. Hydroxylation

Since bases always appear as pairs in DNA, to evaluate the influence of intermolecular hydrogen bond (Hbond) between two bases, we have investigated hydroxylation reactions in the A–T base pair at the C8 and C2 sites of Ade, the C5 and C6 sites of Thy (denoted as A^{C8}–T, A^{C2}–T, A–T^{C5}, and A–T^{C6}) and compared to corresponding reactions in monomers. In Watson–Crick base pair between Ade and Thy, there are two intermolecular Hbonds between the two bases contributed by O4 of Thy and HN61 of Ade, and by N1 of Ade and HN3 of Thy, respectively, as shown in Fig. 1. Due to the limit of computational resources, we have only carried out calculations of the base pair at the level of B3LYP/6-311++G(d,p), and the fully optimized stationary structures of hydroxylations in gas phase at the four different sites are shown in Fig. 1.

In the base pair, the two bases are bound together in a coplanar manner via the two hydrogen bonds between A—T^{O4} and A^{HN61}–T, A–T^{HN3}, and A^{N1}–T, and the distances between the two atoms of the atom pair in the two hydrogen bonds were calculated to be 1.93 Å and 1.84 Å, respectively. In the presence of •OH radicals, the configuration of A–T pair changes and the planar structure is distorted.

The strength of the intermolecular Hbonds has been affected by the hydroxylation, although it displays different dependences. As seen in Fig. 1, the hydroxylation at the A^{C2}, T^{C5}, and T^{C6} sites weekens the Hbond between A–$T^{O4}\cdots A^{HN61}$–T, with the former case due to the presence of a third intermolecular Hbond between the atom pair of T^{O2} and HO atom of •OH, while the latter two due to the charge shift from the carbonyl group $T^{C4=O4}$ to the sites where the •OH attaches. The Hbond A–$T^{HN3}\cdots A^{N1}$–T does not change much upon the hydroxylation except for the case where the •OH is attached to A^{C2} which leads to the formation of an additional Hbond, and staying in between two other Hbonds, the distance of the Hbond A–$T^{HN3}\cdots A^{N1}$–T is shortended.

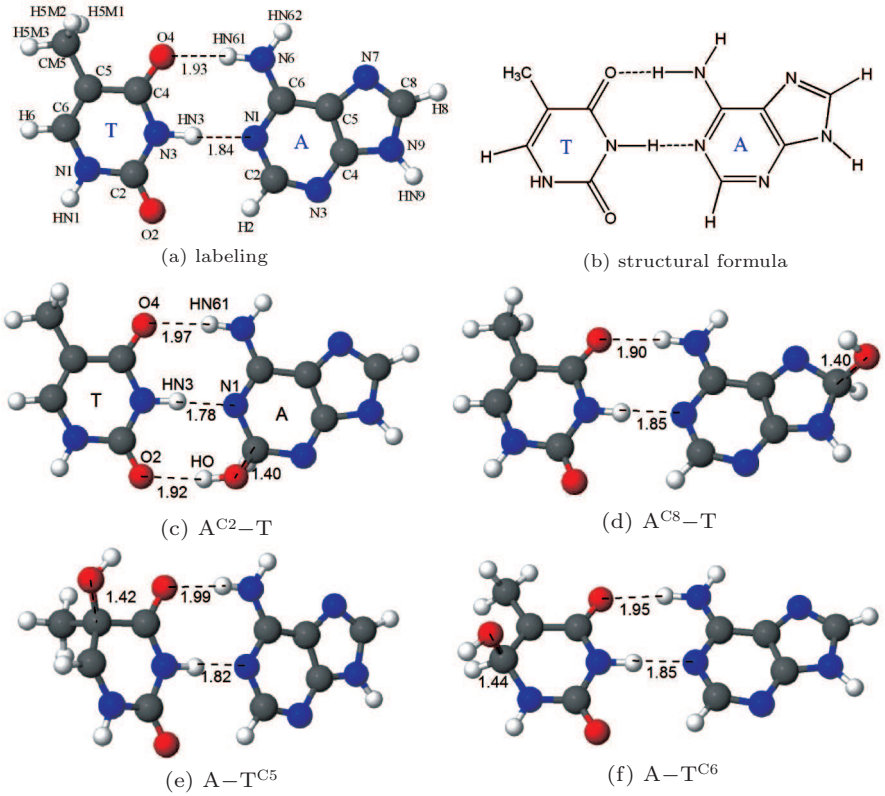


Fig. 1. (color online) The labeling (a), structural formula (b), and optimized structures at the B3LYP/6-311++G(d,p) level with selected geometrical parameters (distances in Å) of products (PC) in the hydroxylation at A^{C2}–T (c), A^{C8}–T (d), A–T^{C5} (e), and A–T^{C6} (f) by an •OH free radicals in gas phase.

The relative free energies of the hydroxylation reactions at the four different sites are listed in Table 1 in both A–T base pair and the single Ade or Thy base for comparison thermodynamically in the presentence of •OH.

Table 1. The relative free energies (kJ/mol) of RS, TS, and PC in the hydroxylation and dehydrogenation at different sites of Ade, Thy, and A–T at the B3LYP/6-311++G(d,p) level in gas phase.

A–T + •OH					Ade/Thy + •OH				
Site	RS	RC	TS	PC	Site	RS	RC	TS	PC
Hydroxylation									
A–T^{C5}	0.0	16.1	21.3	–37.8	T^{C5}	0.0	15.8	21.0	–35.3
A–T^{C6}	0.0	–	–	–66.4	T^{C6}	0.0	–	–	–68.9
A^{C2}–T	0.0	0.3	46.7	–40.1	A^{C2}	0.0	4.7	49.7	–28.1
A^{C8}–T	0.0	–	–	–88.3	A^{C8}	0.0	–	–	–78.2
Dehydrogenation									
A–T^{H5M3}	0.0	6.4	18.6	–106.8	T^{H5M3}	0.0	6.9	19.6	–108.0
A^{HN62}–T	0.0	15.3	26.8	–44.2	A^{HN62}	0.0	16.0	26.7	–51.8
A^{HN61}–T	0.0	15.3	40.3	–33.1	A^{HN61}	0.0	4.7	19.7	–49.9

Note: A^{HN61} represents the proton on N6 of Ade which forms an intermolecular hydrogen bond with Thy, and A^{HN62} denotes another proton on N6 of Ade.

At B3LYP/6-311++G(d,p) level, we have located the transition states only for the hydroxylation reactions at C5 site of Thy and C2 site of Ade in both A–T base pair and the corresponding single base, with energy barriers comparable to the reaction at the former site in both model systems, while moderately lower at the latter site in the base pair than in the single Ade base (46.7 kJ/mol versus 49.7 kJ/mol). For both reactions, the base pair brings more stabilization energy to the products than in the single base by 2.5 (C5 of Thy) kJ/mol and 12.0 (C2 of Ade) kJ/mol, respectively. This suggests that the intermolecular Hbonds between Ade and Thy favor the hydroxylation reaction thermodynamically.

For the reactions at the C6 site of Thy and the C8 site of Ade, the calculations did not find any transition state, and the pathway calculations with a reaction coordinate to mimic the bond formation between O atom of •OH and the C6 (Thy) or the C8 (Ade) atom always describe the energy profile as a downhill curve from the reactant state to the product, and *vice versa* from the product to the reactant state. Given these observations, we propose that the B3LYP method is probably inadequate to provide precisely a complete picture on the kinetics of the hydroxylation reactions of DNA.

In order to further elucidate the problem, we have studied five possible reaction pathways with the addition of •OH which happened at the C2, C4, C5, C6, and C8 sites of an isolated Ade at the 6-311++G(d,p) basic sets by using B3LYP and MP2 methods. The hydroxylation at the C2, C4, C5, and C6 sites of an isolated Thy using the above two methods have been studied in our previous work;[38] therefore, we need not discuss this point further.

The relative Gibbs free energies of RS, RC, TS, and PC in gas phase in the hydroxylation reactions of Ade at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) (in parentheses) levels are collected in Table 2. B3LYP calculation indicated that thermodynamical reactions at the C8 and C2 sites are exothermic by 78.2 kJ/mol and 28.1 kJ/mol, respectively, while those at the C4, C5, and C6 sites are endothermic by 8.5 kJ/mol, 13.0 kJ/mol, and 8.1 kJ/mol, respectively. According to our calculations, the free energy barriers inherent in the hydroxylation at C4, C5, and C6 sites are as high as 56.2 kJ/mol, 46.4 kJ/mol, and 61.7 kJ/mol, respectively, suggesting that at ambient condition it is more difficult to happen for the hydroxylation at the three sites either from a kinetic view or from a thermodynamic view.

Table 2. The relative free energies (kJ/mol) of RS, TS, and PC in the hydroxylation at different sites of Ade at the B3LYP/6-311++G(d,p) level in gas phase. For comparison, the corresponding stationary points energies at the MP2/6-311++G(d,p) level are given in parentheses.

Site	RS	RC	TS	PC
C2	0.0	4.7 (1.6)	49.7 (165.3)	–28.1 (37.8)
C4	0.0	27.0 (–1.4)	56.2 (120.1)	8.5 (31.0)
C5	0.0	27.0 (–2.4)	46.4 (103.7)	13.0 (48.1)
C6	0.0	27.0 (20.9)	61.7 (129.0)	8.1 (68.7)
C8	0.0	– (–1.4)	– (106.1)	–78.2 (–25.0)

The reaction at the C2 site has a free energy barrier (49.7 kJ/mol) slightly higher than that of the C5 site. However, the approach of the •OH to the C5 site is relatively more difficult in comparison with that to the C2 site due to the higher free energy by 27.0 kJ/mol than 4.7 kJ/mol, which makes it a more favorable process at the C2 site rather than at the C5 site. For the reaction at the C8 site, the B3LYP calculation did not locate any 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 it predicted the reaction as a barrierless process, suggesting a much higher reactivity of the C8 site.

The calculated results at B3LYP/6-311++G(d,p) level suggest that the C2 site is the second most easily site attacked by •OH. This is not in agreement with experimental observation[26] that the rate of output of the C2–OH• is only 2%, which means that statistically the •OH has a little chance to attach to C2.

Compared to the B3LYP results, as expected, MP2 method predicts much higher free energy barriers for the hydroxylated reactions, however, both methods suggest different trends in the activation free energy and thermicity. According to calculations, the hydroxylation at the C8 site is a barrierless process using B3LYP method while it has a substantial barrier of 106.1 kJ/mol with the MP2 method. For the hydroxylation at the C2 site, B3LYP predicted an exothermic process by 28.1 kJ/mol while MP2 predicted an endothermic process by 37.8 kJ/mol, and the free energy barrier is the highest by 165.3 kJ/mol. This indicates that the attacking •OH has little chance to attack the C2 site, which is in good agreement with the experimental observation.[26]

3.2. Dehydrogenation

The three typical dehydrogenation reactions in A–T base pair, that is, the hydrogen on the methyl group of Thy and the two hydrogen atoms of the amine group of Ade, with one involved in the intermolecular Hbond (HN61) while another one not (HN62), have been investigated to estimate the influence of the intermolecular hydrogen bonds. The relative free energies are collected in Table 1, and the optimized geometries of the products from the B3LYP/6-311++G(d,p) calculations are shown in Fig. 2 with key geometrical parameters.

According to our calculations, the intermolecular Hbonds do not have a significant effect on the dehydrogenation reactions of T^{H5M3} and A^{HN62}, and the activation free energies to the two reactions are calculated to be 19.6 kJ/mol and 26.7 kJ/mol, respectively, in the corresponding single base, which change to 18.6 kJ/mol and 26.8 kJ/mol, respectively, in the base pair. In view of these values, the presence of the intermolecular Hbonds only moderately favors the abstraction of H5M3 by •OH radicals kinetically, while it brings destabilization energy to the products of the reactions at both sites by 1.2 kJ/mol and 7.6 kJ/mol.

For the abstraction of HN61, which is involved in an intermolecular Hbond in the base pair, it is much more difficult to proceed to the product in the base pair than in the single Ade base in view of both free energy barriers, which are 40.3 kJ/mol and 19.7 kJ/mol respectively, and the exothermicity, which are 49.9 kJ/mol and 33.1 kJ/mol, respectively. In addition, according to our calculations, it costs more energy for the •OH to access the HN61 atom in the base pair than in the single base (15.3 kJ/mol versus 4.7 kJ/mol). It is not surprising to concern that HN61 is hydrogen-bonded to O4 of Thy, and the abstraction of HN61 requires not only the breaking of the HN61–N6 bond, as in the single base, but also the overcoming of the repulsion from O4 atom and the breaking of the O4···HN61 hydrogen bond in the A–T base pair, leading to a much higher free energy barrier. The dehydrogenation of HN61 distorts the optimal conformation of the base pair, and although the broken Hbond between O4 and HN61 is replaced by two more Hbonds bridged by the newly formed water molecule shown in Fig. 2(b), this is not enough to compensate the loss in stabilization energy of the A–T base pair upon the dehydrogenation of HN61.

The distorsion of the planar conformation of the base pair does not happen in the dehydrogenation reactions of H5M3 (Fig. 2(a)) and HN62 (Fig. 2(c)).

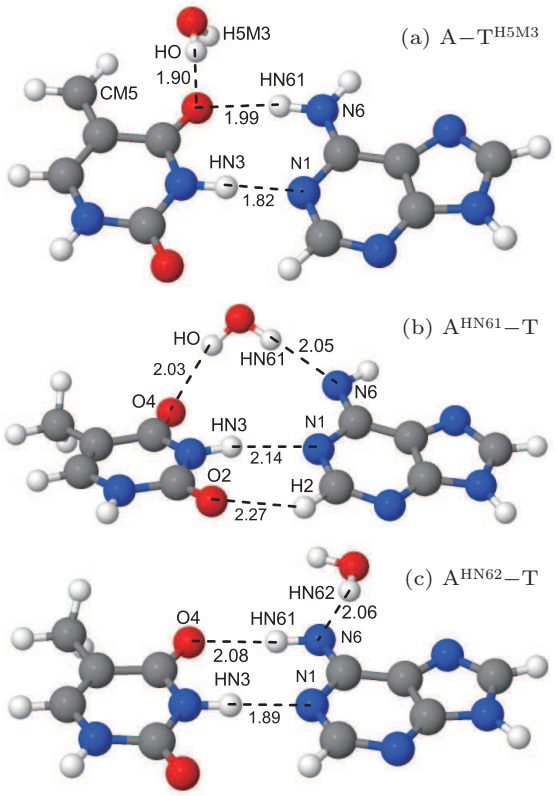


Fig. 2. (color online) Optimized structures (B3LYP/6-311++G(d,p)) with selected geometrical parameters (distances in Å) of products (PC) related to hydrogen abstraction of A–T^{H5M3} (a), A^{HN61}–T (b), and A^{HN62}–T (c) by an •OH free radicals in gas phase.

In addition, we have calculated the relative reactivity of the four sites of isolated Ade toward the dehydrogenation invoked by the •OH radicals (i.e., C2, C8, N9, N6) where the hydrogen atoms may be abstracted by an •OH radical, leading to the formation of a water molecule and an Ade radical. These hydrogen atoms are denoted as H2, H8, HN9, HN61, and HN62, respectively, as shown in Fig. 1. Note that in DNA, the N9 atom forms a bond to the carbon atom of desoxyribose; thus, the dehydrogenation reaction does not happen at this site and the calculation of the dehydrogenation at N9 site is meaningful only for a single Ade base or Ade appears as the unprotected terminal group with a hydrogen atom on N9 atom, and is used here only for comparison.

Energetically, as seen in Fig. 3, compared to the other four reaction channels, the abstraction of H8 has the largest activation free energy (46.6 kJ/mol) and the lowest exothermicity (4.5 kJ/mol). This suggests a low possibility for the dehydrogenation to happen at the C8 site. The free energy barriers to the abstraction of H2, HN62, and HN61 were calculated to be 32.9, 26.7, and 19.7 kJ/mol, and the reaction free energies are –35.2, –51.8, and –49.9 kJ/mol, respectively. According to our calculations, compared to the abstraction of HN61, more energy is demanded for •OH to access HN62 (16.0kJ/mol versus 4.7 kJ/mol). In addition, a higher free energy barrier is inherent in the abstraction of HN62 than that of HN61, as seen in Fig. 3. These observations show that it is much easier for •OH to abstract HN61 than to abstract HN62.

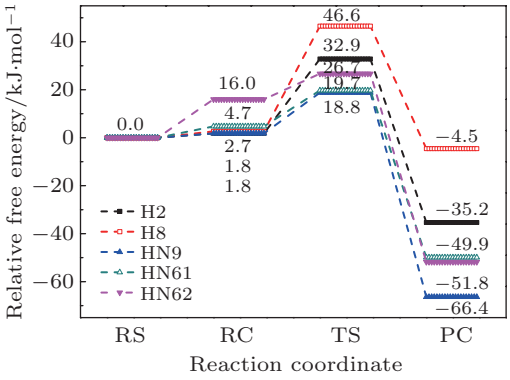


Fig. 3. (color online) Free energy profiles for the dehydrogenation reactions of Ade by an •OH radical at the sites of C2, C8, N9, and N6 at B3LYP/6-311++G(d,p) level.

We note that the dehydrogenation reaction of HN9 has a lower free energy barrier of 18.8 kJ/mol, which is larger than the value of 3.4 kcal/mol (14.1 kJ/mol) in previous results,[23] and is highly exothermic by 66.4 kJ/mol. In DNA, 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.

4. Conclusions

In the present work, the reactions of hydroxyl radicals with A–T base pair and Ade have been investigated in gas phase using B3LYP and MP2 methods at the 6-311++G(d,p) level.

Compared to the reactions in the single base, either Ade or Thy, the presence of intermolecular hydrogen bonds in the A–T base pair does not show much influence on the hydroxylation reactions at C5, C6, C2, and C8 sites, and the dehydrogenation reactions at the H5M3 and HN62 sites, but do make it difficult for the abstraction of HN61 to happen in view of the accessibility of •OH to HN61, which is involved in an intermolecular hydrogen bond, the activation free energy increasing by 20.6 kJ/mol, and the exothermicity of the reaction decreasing by 16.8 kJ/mol. The calculated results show that the hydrogen bonds have little effect on the dehydrogenation that has happened at those sites without hydrogen bonds. However, for those sites involved in hydrogen bond formation, the free energies of TS and PC increase.

For the hydroxylation of isolated Ade, both B3LYP and MP2 methods predict that the C8 site is the most probable site that the •OH radicals may attach to, although they describe different energetics for this process. At the B3LYP/6-311++G(d,p) level, the reaction at the C8 site is a barrierless process and strongly exothermic by 78.2 kJ/mol. Meanwhile, with the MP2 method we observed a transition state with a free energy of 106.1 kJ/mol relative to the reactants, the reaction is exothermic by 25.0 kJ/mol. For dehydrogenation, the B3LYP/6-311++G(d,p) calculations give results on the hydrogen abstraction in isolated Ade base; that is, the free energy barrier increases in the order of HN9 < HN61 < HN62 < H2 < H8.

Acknowledgments

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