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Influence of the Oxygen at the C8 Position on the Intramolecular Proton Transfer in C8-Oxidative Guanine

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High-level quantum chemical calculation methods have been applied to explore the influences of the oxygen at the C8 position on the intramolecular proton transfer between the 6-oxo and 6-hydroxy forms of C8-oxidative guanine. The predicted order of relative stability of the tautomers of C8-oxidative guanine in the gas phase C8-OG1, C8-OG1* > C8-OG2, C8-OG2* is somewhat different from the stability of monohydrated C8-oxidative guanine: C8-OG1·H_2O > C8-OG1*·H_2O > C8-OG2·H_2O > C8-OG2*·H_2O. The inclusion of quantum mechanical tunneling in the calculation dramatically increases the proton-transfer rate in C8-oxidative guanine. The tunneling rates were evaluated to be 10^{-2} s^{-1} for the gas phase and 10^{9}−10^{10} s^{-1} for the water-assisted process. Our results suggest the importance of the tunneling effect and that it might dominate the tautomeric process in guanine and its derivatives at room temperature.

Introduction

Oxidative DNA damage has been believed to be closely related to the C8 modification of nucleobases.[1−4] C8-oxidative guanine is one of the most important products of the oxidative modification of DNA bases.[5] Under physiological conditions, the 6,8-dioxo form of C8-oxidative guanine has been found to be the most predominant form.[6] However, NMR experiments suggest the presence of about 15% of minor "rare" tautomers.[7] It has been believed that, in the case of guanine, the frequency of the mutation event is governed by the concentration of the free nucleotide triphosphate in its minor tautomeric forms in solution.[8] One can expect that 15% of the minor tautomers of C8-oxidative guanine would be significantly important in base-mispairing and in inducing spontaneous mutations. The contribution of C8-oxidative guanine to mutagenesis has been the subject of a number of investigations.[7,9,10]

The tautomerism of guanine and its sulfur substitution products have been studied both in the gas phase and in solution.[11−18] Also the effect of the oxo substitution at the C8 position on the molecular structure, energy properties, and biological activities has been studied using both experimental and theoretical methods.[6,7,19−27] Recently, the effect of guanine stacking on the oxidation of 8-oxoguanine in B-DNA has been investigated at the HF and the DFT levels.[28] However, the influence of the 8-oxo substituent on the intramolecular proton-transfer process is not clear.

Among the possible tautomers of C8-oxidative guanine, four different forms (6,8-dioxo (C8-OG1), 6-hydroxy-8-oxo (C8-OG1*), 6-oxo-8-hydroxy (C8-OG2), and 6,8-dihydroxy (C8-OG2*)) are the most important.[19] These four tautomers correspond to the four tautomers of guanine (7GUA, 7GUA*, 9GUA, and 9GUA*) as shown in Figure 1. The strong polarizability of the oxygen at the C8 position is expected to have important effects on the properties of the 6-oxo and 6-hydroxy forms.

In the comprehensive investigations of the 32 first-row compounds, Mebel, Morokuma, and Lin[30] demonstrated that the geometries and frequencies of the molecules calculated at the B3LYP/6-311G(d,p) level agree well with experiment. The absolute deviations for the bond lengths and angles are significantly smaller than those for the B-LYP or B-VWN density functional methods or even those for the ab initio MP2/6-31G* and QCISD/6-31G* levels of theory.[31] The studies of DNA bases and their derivatives has shown that even the B3LYP/6-31G(d,p) level reproduces the IR experimental spectra better than methods such as HF and MP2.[16−18,32−34] However, the B3LYP/6-31G(d,p) approach might have some deficiencies in estimating the tautomeric stability of DNA bases.[32]

From a biological viewpoint, the properties of DNA bases interacting with a polar solvent are more important than those of isolated species. Water-assisted proton-transfer mechanism studies have shown that the assistance of a water molecule significantly lowers the free energy barriers in the proton-transfer-related reaction.[12,32] On the other hand, the electrostatic interaction with a solvent represented by continuum models only slightly influences the activation barriers.[12,29] This suggests that the intramolecular proton-transfer process in an aqueous solution is mainly controlled through the assistance of a water molecule. The influence of the electrostatic interactions with the bulk is less important.

The purpose of our investigations is to reveal following aspects of the C8-oxo derivative of guanine: (1) How does the oxygen at the C8 position influence the intramolecular proton transfer between the 6-oxo and the 6-hydroxy forms of C8-oxidative guanine? (2) What are the effects of the oxygen at the C8 position on the water-assisted intramolecular proton-transfer process in the tautomers? (3) In what way does the oxygen at the C8 position change the nonplanar structure of the amino group in guanine?

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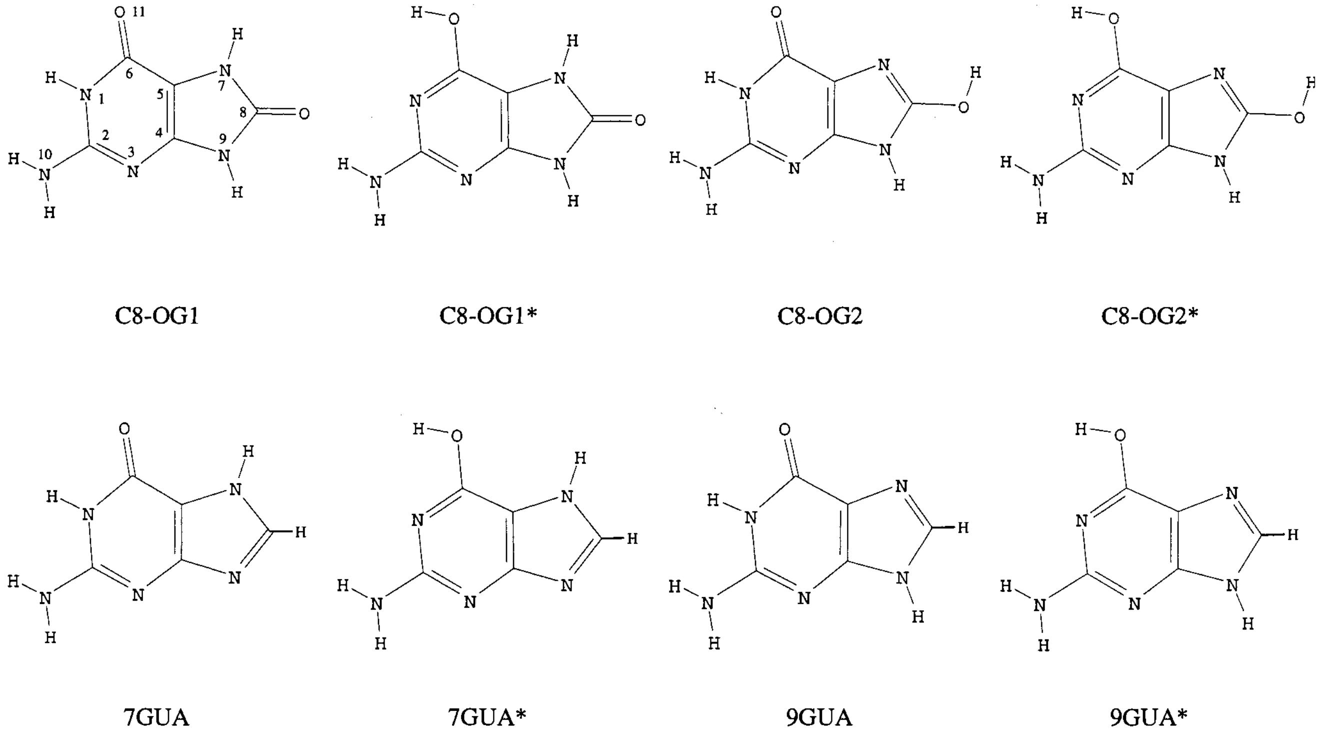


Figure 1. The four of C8-oxidative guanine tautomers 6,8-dioxo (C8-OG1), 6-hydroxy-8-oxo (C8-OG1*), 6-oxo-8-hydroxy (C8-OG2), and 6,8-dihydroxy (C8-OG2*), along with the four corresponding tautomers of guanine (7GUA, 7GUA*, 9GUA, and 9GUA*) according to whether hydrogen occupies the N7 position.

TABLE 1: Relative Energies, Free Energies, and Dipole Moments of the Tautomers of C8-Oxidative Guanine[a]

	ΔE		ΔE_0[b]	ΔG_{298}	μ	
	DFT	MP2	DFT	DFT	DFT	MP2
C8-OG1	0.00	0.00	0.00	0.00	6.5	7.3
C8-OG1*	0.82	−0.20 −0.80[c] −0.85[d]	0.77	0.88	4.0	4.3
C8-OG2	14.40	10.65	14.44	14.36	5.2	5.7
C8-OG2*	15.02	10.78	15.09	15.16	1.9	2.0
C8-OG1·H_2O	0.00	0.00	0.00	0.00	5.4	6.0
C8-OG1*·H_2O	2.00	0.83	2.03	2.15	4.3	4.6
C8-OG2·H_2O	14.49	10.77	14.55	14.70	4.1	4.4
C8-OG2*·H_2O	16.66	12.29	16.81	17.11	2.9	2.9

[a] Energies in kcal/mol; dipole moments (μ) in debyes. DFT: B3LYP/6-311G(d,p). MP2: MP2/6-31G(d,p). [b] Zero-point-corrected. [c] MP2/6-311G(d,p). [d] MP2/6-311G(d,p)//B3LYP/6-311G(d,p).

Method of Calculation

The local minimum structures and the transition state structures were fully optimized by analytic gradient techniques using the density functional theory with Becke's three-parameter (B3)[35] exchange functional along with the Lee−Yang−Parr (LYP) nonlocal correlation functional[36,37] (B3LYP) and the ab initio approach at the second-order Moller−Plesset level (MP2).[38−42] The standard valence triple-ζ basis set augmented with six d-type and three p-type polarization functions, 6-311G(d,p), was used in conjunction with the DFT method while the valence double-ζ basis set supplemented with d and p polarization functions 6-31G(d,p)[43] was used at the MP2 level. Frequency analysis was carried out at the B3LYP/6-311G(d,p) level. The intramolecular proton-transfer reaction path was determined by the B3LYP/6-311G(d,p) approach. The Gaussian 94 program package[44] was used. All optimizations were performed using the opt = tight option.

TABLE 2: Activation Energies, Activation Free Energies, and Dipole Moments of the Transition States of C8-Oxidative Guanine[a]

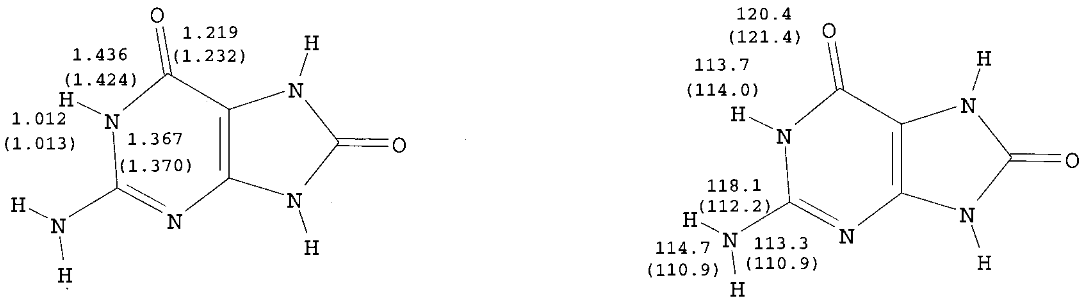
	ΔE		ΔE_0[b]	ΔG_{298}	μ	
	DFT	MP2	DFT	DFT	DFT	MP2
TS1 ⇔ C8-OG1	37.18	37.19	33.93	34.05	4.8	5.4
TS1 ⇔ C8-OG1*	36.36	37.39	33.17	33.17		
TS2 ⇔ C8-OG2	36.47	36.52	33.28	33.44	4.2	4.6
TS2 ⇔ C8-OG2*	35.85	36.39	32.63	32.63		
TS1·H_2O ⇔ C8-OG1·H_2O	14.62	14.64	10.84	11.84	4.9	5.7
TS1·H_2O ⇔ C8-OG1*·H_2O	12.62	13.81	8.80	9.70		
TS2·H_2O ⇔ C8-OG2·H_2O	14.90	15.28	11.07	12.14	3.6	3.7
TS2·H_2O ⇔ C8-OG2*·H_2O	12.73	13.76	8.81	9.73		

[a] Energies in kcal/mol; dipole moments in debyes. DFT: B3LYP/6-311G(d,p). MP2: MP2/6-31G(d,p). [b] Zero-point-corrected.

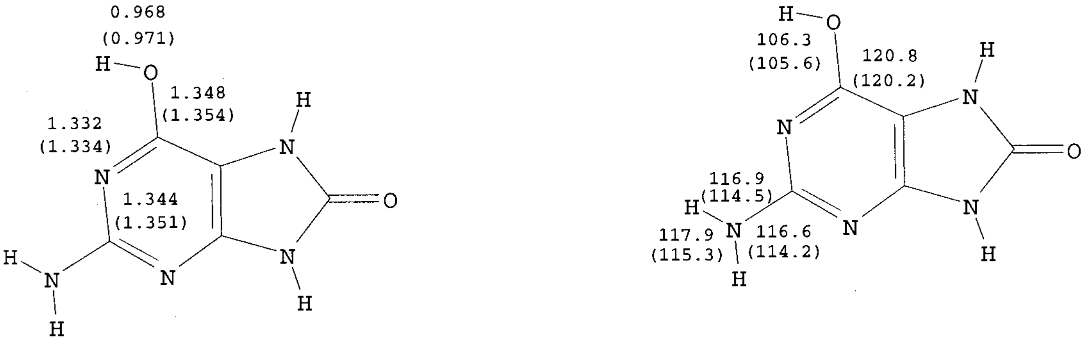
Results and Discussion

Relative Stabilities and Proton-Transfer Barriers. The relative energies, the free energies, and the dipole moments of the tautomers of C8-oxidative guanine are listed in Table 1. The relative stabilities of the tautomers predicted by the DFT method are similar to those obtained at the MP2 level except for those of C8-OG1 and C8-OG1*. At the B3LYP/6-311G(d,p) level, 6,8-dioxoguanine is 0.8 kcal/mol more stable than 6-hydroxy-8-oxoguanine, while this order reverses at the MP2/6-31G(d,p) level, and C8-OG1 is 0.2 kcal/mol less stable than C8-OG1*.

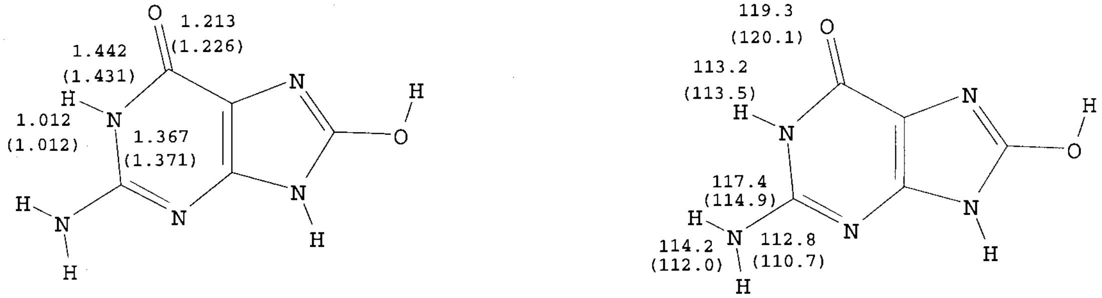
The previously reported HF calculations with the 3-21G and 3-21G(d) basis sets indicate that C8-OG1 is most stable in the gas phase.[19,20] However, the energy sequence changes with an increase of the basis set and the inclusion of the electron correlation at the MP2 level.[19] C8-OG1 becomes less stable than C8-OG1*. The energy of C8-OG1 is higher than that of C8-OG1* by 1.60 kcal/mol at the HF/6-31G(d,p) level, 0.2 kcal/mol at the MP2/6-31G(d,p) level, 0.56 kcal/mol at the



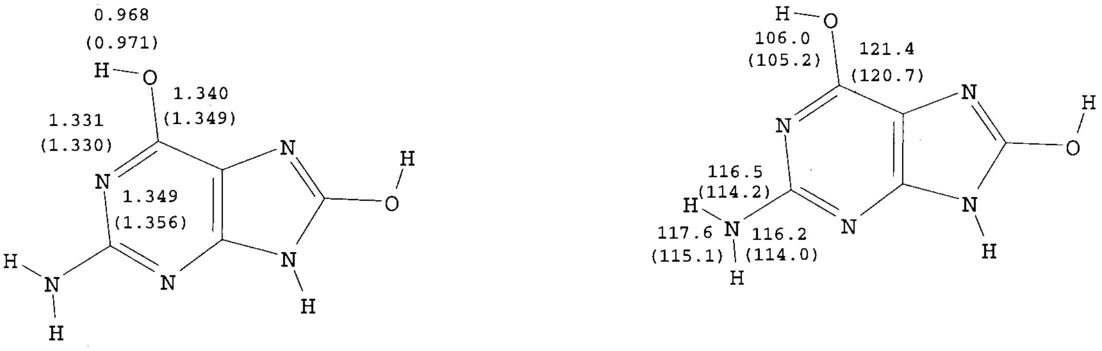
C8-OG1



C8-OG1*



C8-OG2



C8-OG2*

Figure 2. Geometric parameters of the local minima of C8-OG1, C8-OG1*, C8-OG2, and C8-OG2* obtained at the B3LYP/6-31G(d,p) and the MP2/6-31G(d,p) levels. The numbers in parentheses are the results at the MP2/6-31G(d,p) level.

MP2/MIDI level, 1.26 kcal/mol at the MP2/6-311++G(d,p)//HF/6-31G(d,p) level, and 1.03 kcal/mol at the MP2/6-311++G-(d,p)//MP2/6-31G(d,p) level.[19] Considering that the B3LYP/6-311G(d,p) approach yields better geometry than the MP2/6-31G(d,p) method, a further single-point MP2/6-311G(d,p) energy calculation was carried out for both B3LYP/6-311G-(d,p) and MP2/6-311G(d,p) reference geometries. The energy differences between C8-OG1 and C8-OG1* at these two levels are virtually the same; C8-OG1 is less stable by 0.85 and 0.80 kcal/mol at the MP2/6-311G(d,p)//B3LYP/6-311G(d,p) and MP2/6-311G(d,p)//MP2/6-311G(d,p) levels, respectively. It seems that the MP2 results stabilize the C8-OG1* form. However, the difference of the relative energies predicted by the MP4 and MP2 methods with different basis sets[12,45] for 9GUA, 9GUA*, and 7GUA suggests that the MP2 results may not be conclusive. The relative stability sequence of the tautomers of C8-oxidative guanine in the gas phase can be written as

C8-OG1, C8-OG1* > C8-OG2, C8-OG2*

For the hydrated species, the differences between the DFT and

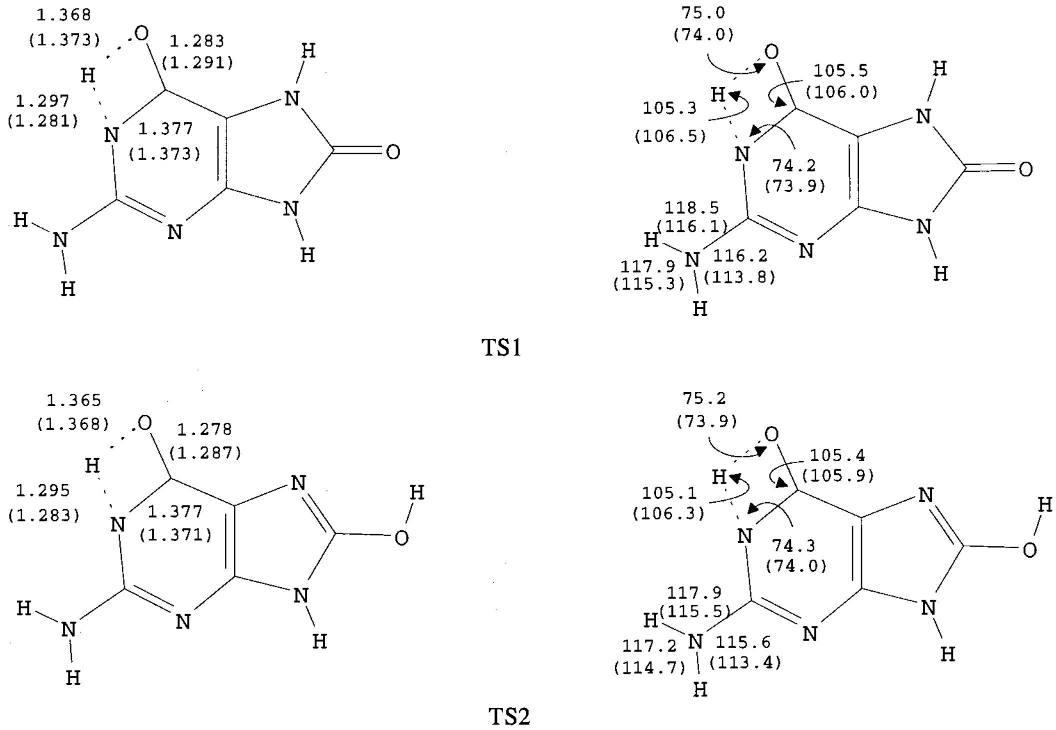


Figure 3. Geometric parameters of the transition states, TS1 and TS2, obtained at the B3LYP/6-311G(d,p) and the MP2/6-31G(d,p) levels. The numbers in parentheses are the results at the MP2/6-31G(d,p) level.

the MP2 approaches disappear. Both methods predict the following relative order:

$$\text{C8-OG1}\cdot\text{H}_2\text{O} > \text{C8-OG1*}\cdot\text{H}_2\text{O} > \text{C8-OG2}\cdot\text{H}_2\text{O} > \text{C8-OG2*}\cdot\text{H}_2\text{O}$$

The relative energies and the dipole moments of the transition state forms are given in Table 2. Interestingly, the activation energy for C8-OG1 to TS1 predicted at the B3LYP/6-311G(d,p) level is almost the same as that at the MP2/6-31G(d,p) level. This also applies for the activation energies for C8-OG2 to TS2, C8-OG1·H_2O to TS1·H_2O, and C8-OG2·H_2O to TS2·H_2O. As expected, the assistance of a water molecule in the proton-transfer process greatly reduces the energy barrier. The activation free energies for C8-OG1·H_2O to TS1·H_2O and for C8-OG1*·H_2O to TS1·H_2O are 11.8 and 9.7 kcal/mol, while without water assistance, the free energy differences between C8-OG1 and TS1 as well as C8-OG1* and TS1 are 34.1 and 33.2 kcal/mol, respectively. The activation free energies for the 8-hydroxy forms are reduced to 12.1 kcal/mol for the transition of C8-OG2·H_2O to TS2·H_2O and to 9.7 kcal/mol for the transition of C8-OG2*·H_2O to TS2·H_2O.

Through a comparison with the zero-point-corrected energy barriers for 9GUA and 7GUA, we find that the presence of oxygen at the C8 position lowers the activation energy by about 1 kcal/mol in both directions of proton transfer. Consequently, one can expect that the proton-transfer process should be observable at room temperature in hydrated C8-oxidative guanine.

Since the dipole moments of C8-OG1 and C8-OG1·H_2O are much larger than those of the other forms, a polar medium such as an aqueous solution will further stabilize C8-OG1. The dipole moments of the 8-oxo tautomers and their hydrated complexes are larger than that of either the 9GUA or the 7GUA form. However, the dipole moment of the 8-hydroxy form is smaller than that of the corresponding 9GUA form. This tendency is also noticed for the transition states. We expect the aqueous solution will lower the energies of the tautomers of 8-oxoguanine more than those of 8-hydroxyguanine. On the basis of our predictions, the 6,8-dioxo form of the tautomer is the most stable one and 6-hydroxy-8-oxoguanine (C8-OG1*) predominates in the remaining 15% of rare tautomers observed in experiments.[7]

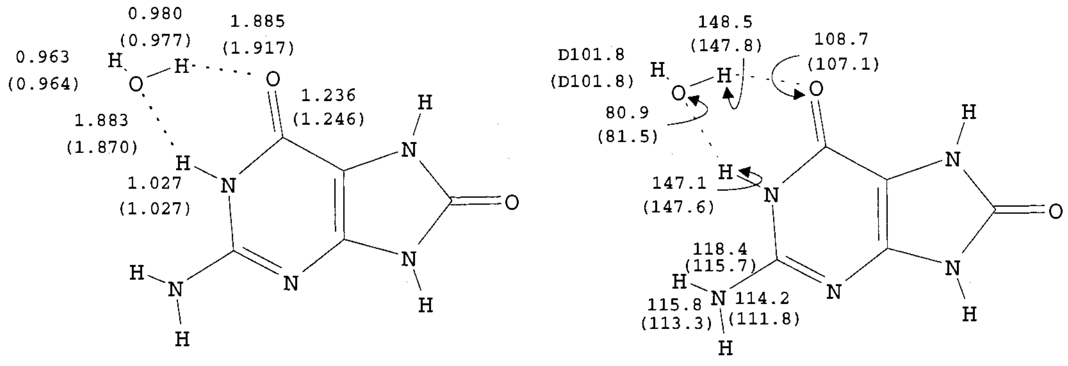
Geometries

The local minima of C8-OG1, C8-OG1*, C8-OG2, and C8-OG2* are located at the B3LYP/6-311G(d,p) and the MP2/6-31G(d,p) levels, and the optimized geometries are depicted in Figure 2. In general, the geometric parameters obtained at the B3LYP/6-311G(d,p) level do agree with the MP2/6-31G(d,p) results. The different forms of oxygen (oxo or hydroxy) at the C8 position of oxidative guanine lead to a small change in the C6−O11 bond lengths.

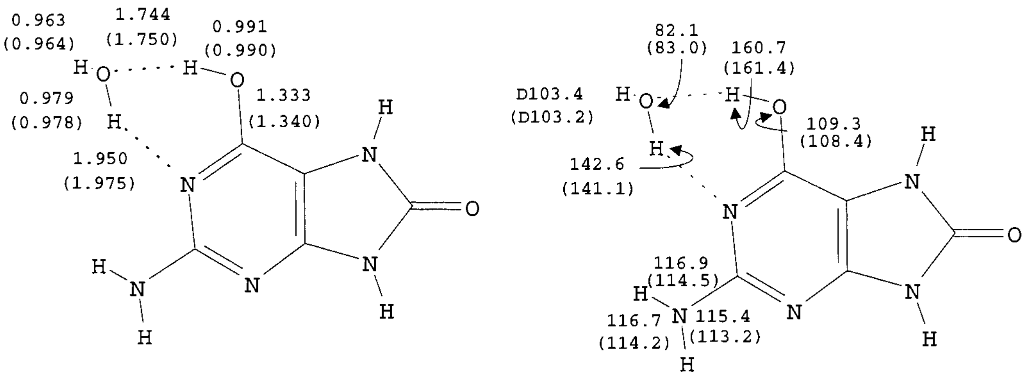
The most important geometrical parameters of the transition states between C8-OG1 and C8-OG1* (TS1) and between C8-OG2 and C8-OG2* (TS2) are given in Figure 3. No significant differences have been found between TS1 and TS2 except that the proton in transfer is slightly closer to the N1 atom in TS2.

The optimized local minimum structures of the monohydrated C8-oxidative guanines are shown in Figure 4. The only difference in the geometric parameters between the oxo and hydroxy forms of oxygen at C8 is the position of the hydrated water. At the B3LYP/6-311G(d,p) level, the Ow···H distance in C8-OG1*·H_2O amounts to 1.74 Å, about 0.03 Å shorter than that in C8-OG2*·H_2O (0.02 Å at the MP2 level). On the other hand, the Hw···N1 bond distance of 1.95 Å in C8-OG1*·H_2O is about 0.02 Å longer than that in C8-OG2*·H_2O. The Hw···O11 hydrogen-bond length of 1.89 Å in C8-OG1·H_2O is slightly reduced (to 1.87 Å) in C8-OG2·H_2O. The atomic distance of Ow···H in C8-OG1·H_2O is predicted to be 1.88 Å, 0.02 Å shorter than that in C8-OG2·H_2O. The water molecule is much closer to O11 in C8-OG1·H_2O and C8-OG1*·H_2O than in guanine.

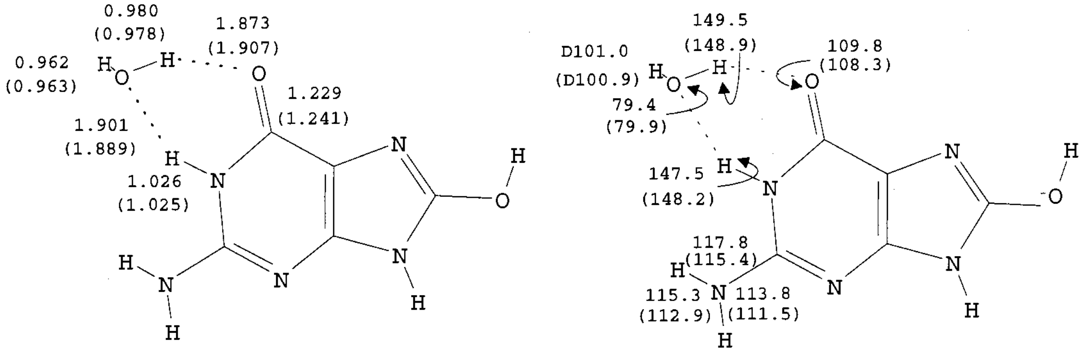
In TS1·H_2O, the two protons between the oxygen atom of the hydration water and O11 and N1 of the oxidative guanines



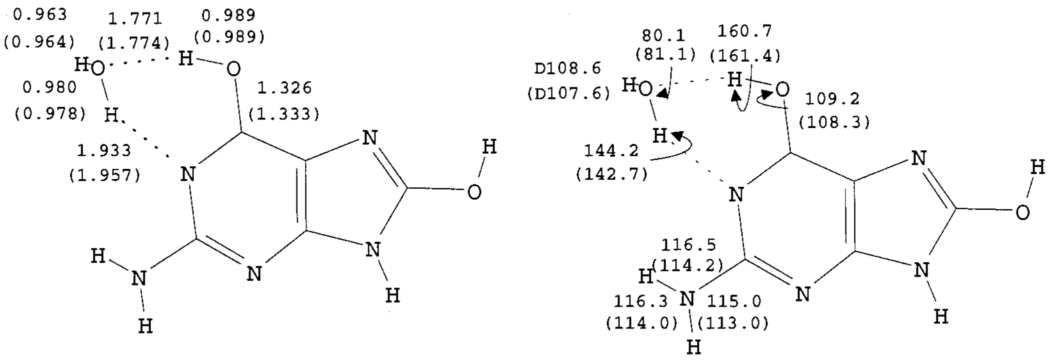
C8-OG1•H2O



C8-OG1*•H2O



C8-OG2•H2O

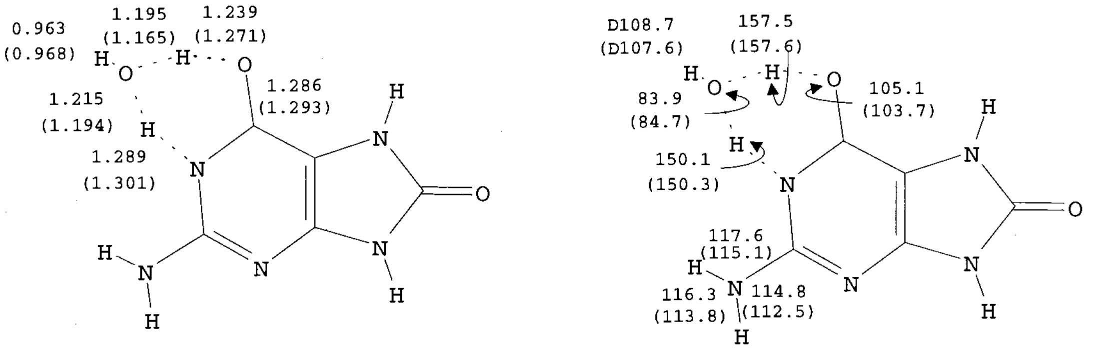


C8-OG2*•H2O

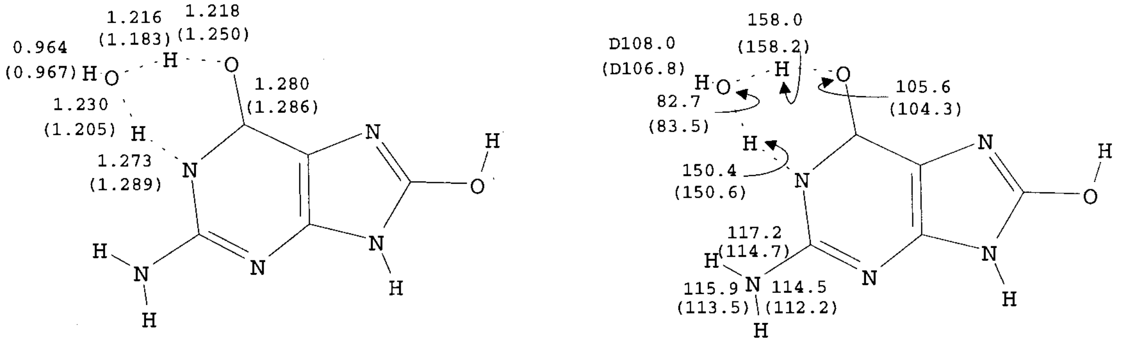
Figure 4. Geometric parameters of the local minima of monohydrated tautomers of C8-oxidative guanine, C8-OG1•H_2O, C8-OG1*•H_2O, C8-OG2•H_2O, and C8-OG2*•H_2O, obtained at the B3LYP/6-311G(d,p) and the MP2/6-31G(d,p) levels. The numbers in parentheses are the results at the MP2/6-31G(d,p) level. D indicates the dihedral angle HOHH with the first HOH in the C8-oxidative guanine molecular plane.

are closer to the oxygen of the hydration water than in TS2•H_2O as can be seen in Figure 5.

To explore the influence of the oxo and hydroxy substituents at the C8 position of oxidative guanine, a comparison was made between the two tautomers of the 8-oxo form (C8-OG1 and C8-OG1*) and the tautomers of 7GUA (7GUA and 7GUA*),[12] where a hydrogen atom is connected to N7. For the 8-hydroxy form, where there is no hydrogen at N7, a comparison was made to the tautomers of 9GUA.[12] No substantial change was found in the geometric parameters of the tautomeric related parts by



TS1•H_2O



TS2•H_2O

Figure 5. Geometric parameters of the transition states of the water-assisted proton transfer, TS1•H_2O and TS2•H_2O, obtained at the B3LYP/6-311G(d,p) and the MP2/6-31G(d,p) levels. The numbers in parentheses are the results at the MP2/6-31G(d,p) level. D indicates the dihedral angle of HOHH with the first HOH in the C8-oxidative guanine molecular plane.

a comparison between the tautomers of C8-oxidative guanine and guanine. However, the presence of oxygen at the C8 position leads to a stronger H-bond with the water in C8-OG1•H_2O, C8-OG2•H_2O, and C8-OG2*•H_2O in comparison with the 7GUA•H_2O, 9GUA•H_2O, and 9GUA*•H_2O systems.[12] The Hw•••O and Ow•••H bond lengths in C8-OG1•H_2O are 0.02 and 0.03 Å shorter than those in 7GUA•H_2O[12] (the MP2 level). The Hw•••N1 distance in C8-OG2*•H_2O and the Ow•••H bond in C8-OG2•H_2O are approximately 0.02 Å shorter than those in 9GUA*•H_2O and 9GUA•H_2O,[12] respectively. As a result, the hydration water is close to the C8-oxidative guanine.

The main geometric effect predicted for the transition states TS1 and TS2 due to the C8 oxidation is the reduction of the bond distance between the transferred hydrogen and the N1 atom. In TS1, the H•••N1 distance amounts to 1.28 Å, approximately 0.04 Å less than that in 7GUA-TS (the MP2/6-31G(d,p) level). The H•••N1 atomic distance of 1.28 Å in TS2 (the MP2 level) is 0.03 Å shorter than that in 9GUA-TS.[12] The H•••O11 atomic distances in TS1 and TS2 are also slightly shorter than those in 7GUA-TS and 9GUA-TS (0.01 Å less). Due to the presence of oxygen at the C8 position, the transferred proton is closer to the C8-oxidative guanine than it is in normal guanine.

The transition states for the forms of C8-OG1•H_2O (TS1•H_2O) and C8-OG2•H_2O (TS2•H_2O) (Figure 5) show the same trends as above. The Hw•••N1 bond distances in TS1•H_2O and TS2•H_2O are 0.04 and 0.03 Å shorter than those in 7GUA-TS•H_2O and 9GUA-TS•H_2O. Also, the O•••H bond lengths are 0.01−0.02 Å shorter in TS1•H_2O and TS2•H_2O compared to those in 7GUA-TS•H_2O and 9GUA-TS•H_2O.[12]

Vibrational Analysis

The IR spectra are predicted at the B3LYP/6-311G(d,p) level. The lowest vibrational frequencies of the minima and the imaginary frequencies of the transition states are listed in Table 3. The characteristic vibrational frequencies of the proton-transfer process are also listed in the table. The small lowest frequency for hydrated C8-oxidative guanine reflects weak bonding between water and C8-oxidative guanine.

TABLE 3: Lowest Vibrational Frequencies and Proton-Transfer-Characteristic Vibrational Frequencies of the Tautomers and the Transition States of C8-Oxidative Guanine at the B3LYP/6-311G(d,p) Level

	ω_{lowest} cm^{-1}	ω_{transfer} cm^{-1}		ω_{lowest} cm^{-1}	ω_{transfer} cm^{-1}
C8-OG1	101	1559	C8-OG1•H_2O	52	3311
C8-OG1*	103	1713	C8-OG1*•H_2O	51	3306
TS1	*i*1859	*i*1859	TS1•H_2O	*i*1547	*i*1547
C8-OG2	113	1600	C8-OG2•H_2O	53	3328
C8-OG2*	115	1624	C8-OG2*•H_2O	53	3340
TS2	*i*1861	*i*1861	TS2•H_2O	*i*1563	*i*1563

Proton-Transfer Rate

To evaluate the importance of tautomerism of C8-oxidative guanine in inducing spontaneous mutations in DNA, the proton-transfer rate must be considered. The classical proton-transfer rate at room temperature (298 K) is calculated to be around 10^{-12} s^{-1} for the gas phase. However, upon hydration, the classical tautomeric rate constants are large enough for the reaction to be observed ($\sim 10^4$ s^{-1}) according to our calculated free energy barriers.

Previous studies have shown that the quantum tunneling effects cannot be ruled out in the formamide−water complex even at 300 K.[12,46,47] The inclusion of quantum mechanical tunneling in the calculation dramatically increases the proton-transfer rate in C8-oxidative guanine. Using the parabolic barrier approximation and the one-dimensional model,[48,49] the tunneling rates were evaluated to be 10^{-2} s^{-1} for the gas phase and 10^9−

TABLE 4: Classical and Quantum Tunneling Corrected Reaction Rate Constants for the Proton Transfer in C8-Oxidative Guanine

	k_{classic}, s^{-1}	k_{quantum}, s^{-1}
C8-OG1 → C8-OG1*	6.6×10^{-13}	6.5×10^{-3}
C8-OG1* → C8-OG1	2.9×10^{-12}	1.8×10^{-2}
C8-OG2 → C8-OG2*	1.9×10^{-12}	1.4×10^{-2}
C8-OG2* → C8-OG2	7.3×10^{-12}	2.8×10^{-2}
C8-OG1·H_2O → C8-OG1*·H_2O	1.3×10^{4}	1.5×10^{9}
C8-OG1*·H_2O → C8-OG1·H_2O	4.8×10^{5}	2.8×10^{10}
C8-OG2·H_2O → C8-OG2*·H_2O	7.7×10^{3}	1.3×10^{9}
C8-OG2*·H_2O → C8-OG2·H_2O	4.5×10^{5}	3.0×10^{10}

10^{10} s^{-1} for the water-assisted process. The characteristic frequencies used in the calculation are depicted in Table 3. The computed classical and quantum tunneling rate constants of the proton transfer in C8-oxidative guanine are listed in Table 4. Because the temperature dependence of the tunneling rate is negligible at temperatures up to about 300 K,[49] our results suggest the importance of the tunneling effect and indicate that it might dominate the tautomeric process in guanine and its derivatives at room temperature.

Conclusions

High-level quantum chemistry calculations have been applied to explore the influences of oxygen at the C8 position on the intramolecular proton transfer between the 6-oxo form and the 6-hydroxy form of C8-oxidative guanine. By analysis of the geometric parameters, energies, proton-transfer process, and vibrational modes, we can conclude the following as answers for the questions put forth in the beginning:

1. The presence of oxygen at the C8 position leads to the hydration water being closer to C8-oxidative guanine. The transferred protons are much closer to the molecule in hydrated C8-oxidative guanine than in normal hydrated guanine.

2. The stability of the monohydrated C8-oxidative guanine has been predicted to be

$$\text{C8-OG1}\cdot H_2O > \text{C8-OG1*}\cdot H_2O > \text{C8-OG2}\cdot H_2O > \text{C8-OG2*}\cdot H_2O$$

Due to the large dipole moments of 8-oxoguanine, we expect the aqueous solution will lower the energies of the tautomers of 8-oxoguanine more than those of 8-hydroxyguanine. As a result, the 6,8-dioxo form of the tautomer is the most stable form while 6-hydroxy-8-oxoguanine should predominate in the remaining 15% rare tautomers observed in the experiments.

3. The presence of oxygen at the C8 position lowers the activation energy barrier about 1 kcal/mol in both tautomeric directions. The activation free energies from C8-OG1·H_2O to TS1·H_2O and from C8-OG1*·H_2O to TS1·H_2O are 11.83 and 9.70 kcal/mol. The activation free energies in the 8-hydroxy forms is reduced to 12.14 kcal/mol for C8-OG2·H_2O to TS2·H_2O and 9.73 kcal/mol for C8-OG2*·H_2O to TS2·H_2O. Consequently, we expect the proton transfer to be observable at room temperature in hydrated C8-oxidative guanine.

4. The low barrier predicted in this study for tautomerism between the 6-oxo and 6-hydroxy forms along with the possible tunneling effects indicates that the tautomeric transition from the normal 6-oxo form to the 6-hydroxy form of C8-oxidative guanine should be a kinetically feasible process and might play a key role in mutagenic events.

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