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Theoretical Study of Gas Phase Tautomerization Reactions for the Ground and First Excited Electronic States of Adenine

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Geometrical structures and energetic properties for different tautomers of adenine are calculated in this study, using multi-configurational wave functions. Both the ground and the lowest singlet excited-state potential energy surface are studied. Four tautomeric forms are considered, and their energetic order is found to be different on the ground and the excited state potential energy surfaces. Minimum energy reaction paths are obtained for hydrogen atom transfer (tautomerization) reactions in the ground and the lowest excited electronic state. It is found that the barrier heights and the shapes of the reaction paths are different for the ground and the excited electronic state, suggesting that the probability of such tautomerization reaction is higher on the excited state potential energy surface. This tautomerization process should become possible in the presence of water or other polar solvent molecules and may play an important role in the photochemistry of adenine.

Introduction

Tautomerization processes that take place as a result of photoinduced hydrogen atom transfer reactions are believed to be a first step in the mutation of DNA. It is therefore of interest to study effects of electronic excitation on the structure and relative energetics of different tautomers of DNA bases. Changes of reaction paths and barrier heights of hydrogen atom transfer reactions that take place in some DNA bases upon electronic excitation are of particular importance. Adenine is one of the DNA bases, for which excited state hydrogen atom transfer (tautomerization) reactions are possible and may play an important role in the photochemistry. In this study, we apply multi-configurational electronic structure techniques to investigate minimum energy paths of such reactions in both the ground and the lowest excited state of adenine.

Schematic structures and conventional atom numbering for the four ground state tautomers of the amino (purine) form of adenine are shown in Figure 1. Previous experimental and theoretical studies of adenine suggest that only one of these forms (the lowest energy 9H-adenine structure) is present in low-temperature matrix environments, whereas two tautomers (9H-adenine and 7H-adenine) coexist in polar solutions (due to the much higher dipole moment of 7H-adenine).[1] All four amino tautomers (as well as the tautomers of the imino form of adenine) were studied previously using ab initio methods with single-configurational (Hartree−Fock and second-order Møller−Plesset) wave functions.[2] These calculations showed that the energetic order of the conformers in the ground state is: 9H < 7H < 3H < 1H. Multi-configurational calculations (at the CASPT2 level of theory with (10,10) and (12,12) CAS active spaces) were performed to estimate vertical electronic excitation energies, oscillator strengths, and transition moment directions for two (9H and 7H) tautomers of adenine.[3,4] The relaxed geometries of the excited state 9H and 7H tautomers were obtained, and the 7H tautomer was found to be closer in energy to the 9H tautomer in the lowest excited state than in the ground state.[5] Proton transfer processes between amino and imino forms of the ground state 9H and 7H-adenine and the effect of a water molecule on these processes were also studied theoretically.[6] In addition, solvent effects on absorption and emission spectra and on relative energetics of the adenine and 2-aminopurine tautomers were studied using polarizable continuum model[7] and self-consistent reaction field approach.[8] It was found that water solvent significantly stabilizes the 7H tautomer of adenine, but 9H-adenine remains the lowest energy tautomer on the ground-state potential energy surface.

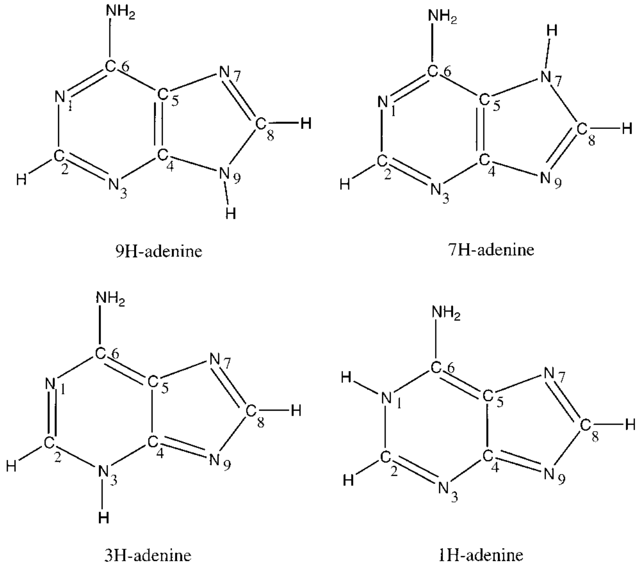

Figure 1. Schematic structure and atom numbering for adenine tautomers.

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Despite the fact that the electronic structure and photochemistry of adenine has been studied extensively in the recent years both theoretically[1−8] and experimentally,[1,9−12] the excited-state tautomerism is not well understood. Though excitation energies for all ground-state tautomers (shown in Figure 1) have been estimated,[8] the energetic order of the tautomers in the excited states is not well established. In this study, we calculate geometric structures for all four tautomeric forms in the lowest excited state of adenine and find their energetic order, which differs significantly from the order of these tautomers in the ground state. We find that 3H and 1H tautomers (with six-membered ring nitrogens having N−H bonds), which are higher in energy on the ground-state potential surface, become lower in energy than the 9H and 7H tautomers in the excited state. In addition, we investigate in detail both the ground and the excited-state reaction paths (including barrier heights and shapes of minimum energy paths) for the hydrogen atom transfer that leads to tautomerization between the 9H and 3H tautomers. This helps to elucidate the differences in this reaction process upon electronic excitation to the lowest excited state. 9H → 3H tautomerization may take place in the polar solution upon electronic excitation and may be responsible for some photochemistry of adenine.[8] It was found that the barrier height for a similar tautomerization reaction in the excited state of 7-azaindole is very low in the presence of only one water molecule, and such reaction should proceed in water (or other polar) solutions upon electronic excitation.[13] In this paper, we investigate this tautomerization reaction for adenine using high level multi-configurational ab initio methods, and we plan a similar investigation for adenine−water complexes in a subsequent study.

Theoretical Approach

Stationary points on the ground and the lowest excited-state potential energy surfaces corresponding to different tautomers of adenine were located using multi-configurational MCSCF wave functions[14] with the Dunning-Hay double ζ + polarization (DZP) basis set.[15] This level of theory was also used to study reaction paths for tautomerization (hydrogen transfer) reactions. The MCSCF active space, denoted as (12,10), included all π electrons and π orbitals occupied in the single-configurational SCF (12 π electrons on 6 π orbitals, that included 4 π bonds and 2 π lone pairs on nitrogen atoms). In addition, the active space included 4 virtual π^* orbitals. A smaller active space, denoted as (8,8), that included 4 occupied and 4 virtual π orbitals and left lone pair orbitals doubly occupied and uncorrelated, was tested as well. Stationary points (minima and transition states) were optimized using analytic gradients of MCSCF energies. No symmetry constraints were imposed during geometry optimization. Second derivative (Hessian) matrices were calculated numerically using double differencing of analytical gradients. The Hessian matrix was calculated for each stationary point to verify that it has 0 (minimum) or 1 (transition state) negative eigenvalues. Minimum energy paths (MEPs) were followed using the intrinsic reaction coordinate (IRC) method[16] with the second-order Gonzalez−Schlegel algorithm[17] and a step size of 0.1 bohr•amu$^{1/2}$. More accurate energies for stationary points and selected points along the MEPs were calculated at the level of second-order multiconfigurational quasi-degenerate perturbation theory MCQDPT2,[18] that accounts for effects of dynamic correlation. The calculations were performed using the electronic structure package GAMESS.[19]

The effects of the size of the MCSCF active space for one of the adenine tautomers (9H-adenine) are demonstrated in Figure 2. It can be seen that geometries of both ground and excited-state structures are very close for the two MCSCF calculations with different, (12,10) and (8,8), active spaces (with the differences on the order of several thousandths of an Å). Similar results are found for other adenine tautomers. Although the geometrical parameters found with the (8,8) active space are in very good agreement with the (12,10) results, relative energies of different tautomers obtained with the smaller active space turned out to be unsatisfactory (see Table 1). Table 1 also shows that dynamic correlation (at the MCQDPT2 level of theory) has very significant effect on excitation energies, reducing them by almost 20 kcal/mol. The effect of dynamic correlation on relative energies is also very large, especially for the excited state (Table 1). Therefore, we conclude that it is necessary to use all π active space and to correct for dynamic correlation effects in order to obtain reliable energetics for this type of compounds.

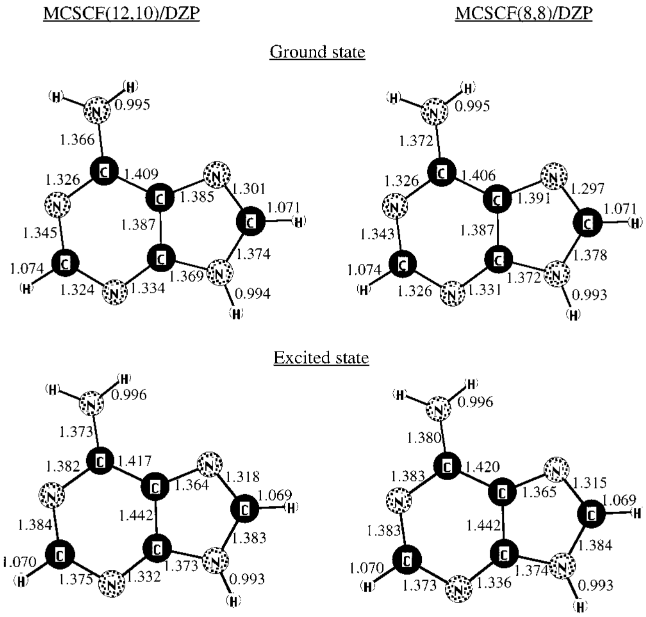

Figure 2. Comparison of bond lengths (in angstroms) obtained using MCSCF wave functions with two different active spaces.

Results and Discussion

Geometries of the four ground state tautomers of adenine are shown in Figure 3, those for the lowest excited state are shown in Figure 4. All minimized geometries slightly deviate from C_s symmetry, with NH_2 group forming an angle from 5° to 20° with the plane of the rings in the ground state and up to 50° in the excited state tautomers. This agrees with previously obtained nonplanarity of the amino group in the ground-state adenine.[5,8] However, we find that the extent of the nonplanarity increases for all tautomers when going from the ground to the lowest excited state. Relative energies for all tautomers are presented in Table 1. The energetic order of tautomers in the ground state is as follows: 9H < 7H < 3H <1H, and the relative energies obtained at the MCSCF(12,10) and MCQDPT2/MCSCF(12,10) levels of theory are close to those obtained previously with the single-configurational RHF and MP2 methods.[2] The relative energies of 7H, 3H, and 1H tautomers are 8.5, 8.8, and 20.1 kcal/mol above the lowest (9H) tautomer, respectively, at the highest level of theory used in this study (MCQDPT2/MCSCF(12,10) including zero point energy (ZPE) corrections). The energetic order in the excited state is different, it is: 3H <1H < 9H < 7H. The relative energies in the excited state are 0.0, 6.1, 8.0, and 12.1 kcal/mol for 3H, 1H, 9H, and 7H, respectively. The two tautomers with N−H bonds in the six-

TABLE 1: Relative Energies (kcal/mol) of the Ground and Excited State Tautomers of Adenine, and the Transition States for 9→3 Tautomerization Reaction, with Respect to the Most Stable Ground State Tautomer 9H (the numbers in parentheses correspond to relative energies with respect to the most stable excited-state tautomer 3H)

	ground state				
	9H-adenine	7H-adenine	3H-adenine	1H-adenine	$TS_{9\to3}$
MCSCF(8,8)	0.0	14.0	18.6	29.8	92.8
MCQDPT2/MCSCF(8,8)	0.0	15.2	14.2	22.3	70.7
MCSCF(12,10)	0.0	7.4	12.3	20.2	89.9
MCQDPT2/MCSCF(12,10)	0.0	8.0	8.7	19.6	67.5
+ MCSCF ZPE correction	0.0	8.5	8.8	20.1	63.2
	excited state				
	9H-adenine	7H-adenine	3H-adenine	1H-adenine	$TS_{9\to3}$
MCSCF(8,8)	121.6 (28.6)	125.0 (32.0)	93.0 (0.0)	95.3 (2.3)	191.8 (98.8)
MCQDPT2/MCSCF(8,8)	102.2 (8.1)	107.7 (13.6)	94.1 (0.0)	97.8 (3.7)	157.9 (63.8)
MCSCF(12,10)	120.6 (26.2)	125.0 (30.5)	94.5 (0.0)	96.5 (2.0)	189.1 (94.7)
MCQDPT2/MCSCF(12,10)	104.2 (8.3)	108.2 (12.3)	95.9 (0.0)	100.2 (4.3)	151.6 (55.7)
+ MCSCF ZPE correction	100.8 (8.0)	104.9 (12.1)	92.8 (0.0)	98.9 (6.1)	144.0 (51.2)

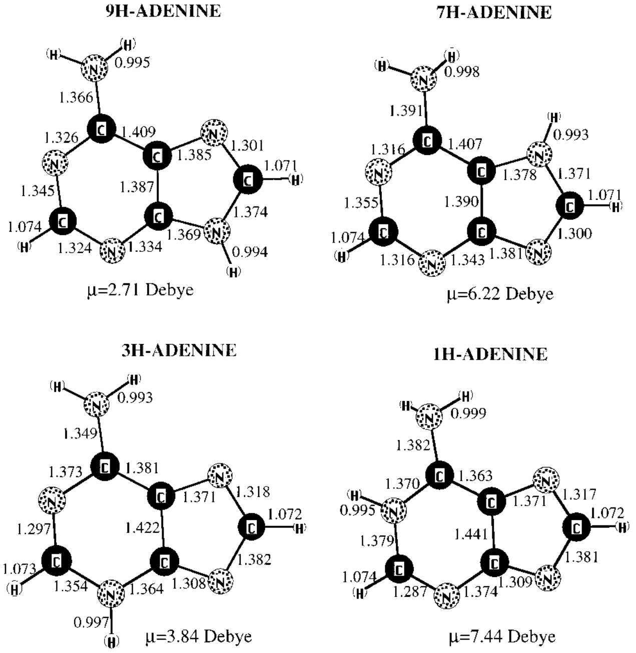

Figure 3. Geometrical structure and dipole moments of the ground-state tautomers of adenine, obtained at the MCSCF(12,10)/DZP level of theory (bond distances are given in angstroms).

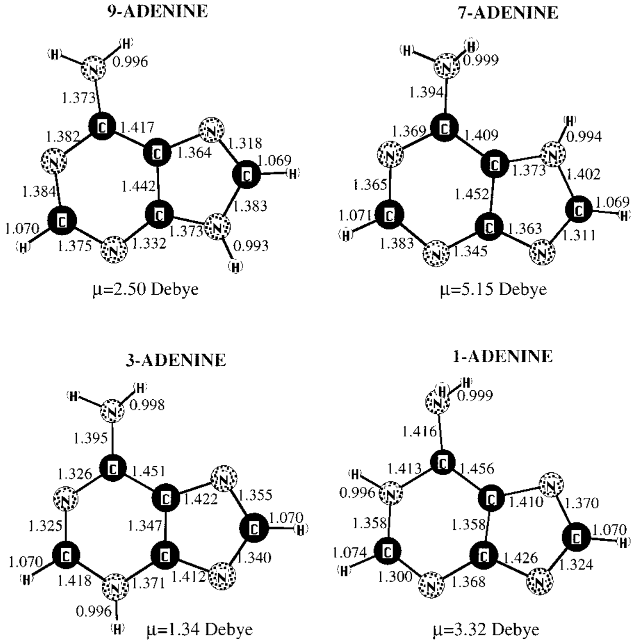

Figure 4. Geometrical structure and dipole moments of the lowest excited-state tautomers of adenine, obtained at the MCSCF(12,10)/DZP level of theory (bond distances are given in angstroms).

membered ring (3H and 1H) become more stable in the first exited electronic state. This is similar to the effect of electronic excitation in 7-azaindole[13] and can be explained qualitatively by the orbital character of the excitation.

Table 2 lists the MCSCF natural orbital occupation numbers for both the ground and excited-state tautomers. Orbitals 1π and 2π represent nitrogen lone pairs: 1π is that of the NH_2 group and 2π is the lone pair of the nitrogen in the rings. Orbitals $3\pi-6\pi$ are the π-bonds, whereas $7\pi-10\pi$ are the antibonding π^*-orbitals. It can be seen that in the 9H and 7H tautomers, the populations of the two π-bonds (5π and 6π) are significantly reduced upon the excitation, whereas two of the antibonding π^*-orbitals (7π and 8π) gain significant populations. The 5π and 6π orbitals correspond to π-bonds located mostly on the six-membered ring, and 7π and 8π correspond to antibonding orbitals which also involve contributions from atoms of the six-membered ring. In the 3H and 1H tautomers, there is a significant shift in population from 4π to 7π, with less significant change in the other orbitals. In these two structures, the electron is excited from the bonding π-orbital that is mostly localized on the five-membered ring into the antibonding π-orbital, which has contributions from atoms of both rings. Though all ground-state tautomers have aromatic 10 π-electron configurations, the 9H and 7H structures have more stable configurations, because both six-membered and five-membered rings in these structures have 6 π-electrons. Electron excitation of 9H and 7H tautomers involves the π-electrons of the six-membered ring, and therefore reduces its π delocalization and destabilizes these structures. In the 3H and 1H tautomers, the excitation mostly involves the electrons from the five-membered ring (which has 4 π-electrons and is not aromatic). As a result, these structures are less destabilized after the excitation and become more stable than the other two on the excited-state potential energy surface. Such reversal of the energetic order upon electronic excitation is not a unique feature of adenine, but should be characteristic for other compounds with the similar two-ring structure. It should be noted that π-lone pairs do not play a significant role in the excitation processes we considered here. It can be seen from Table 2 that the populations of lone pair orbitals (1π and 2π) practically do not change upon excitation. Therefore, our calculations show that the excitation

TABLE 2: MCSCF(12,10)/DZP Natural Orbital Occupation Numbers for Adenine Tautomers and the Transition States for 9→3 Tautomerization Reactions

	1π	2π	3π	4π	5π	6π	7π	8π	9π	10π
					9H					
ground	1.997	1.990	1.943	1.966	1.929	1.908	0.088	0.079	0.063	0.036
excited	1.995	1.988	1.924	1.881	1.470	1.405	0.542	0.603	0.118	0.075
					7H					
ground	1.998	1.991	1.943	1.963	1.916	1.909	0.093	0.087	0.064	0.037
excited	1.997	1.989	1.923	1.874	1.596	1.293	0.721	0.411	0.080	0.117
					3H					
ground	1.996	1.988	1.963	1.953	1.907	1.933	0.078	0.089	0.057	0.037
excited	1.998	1.994	1.937	1.914	1.865	1.046	0.962	0.123	0.102	0.059
					1H					
ground	1.998	1.989	1.964	1.943	1.928	1.901	0.094	0.084	0.060	0.039
excited	1.999	1.992	1.943	1.921	1.870	1.051	0.960	0.113	0.093	0.057
					$TS_{9\to3}$					
ground	1.996	1.981	1.952	1.967	1.917	1.940	0.081	0.077	0.055	0.034
excited	1.995	1.977	1.921	1.906	1.852	1.071	0.948	0.150	0.097	0.083

TABLE 3: Computed Excitation Energies (eV) of Adenine Tautomers

method	9H-adenine	7H-adenine	3H-adenine	1H-adenine
		adiabatic		
MCSCF(12,10)	5.23	5.10	3.56	3.31
MCQDPT2/MCSCF(12,10)	4.52	4.35	3.78	3.50
+ MCSCF ZPE correction	4.37	4.18	3.64	3.42
		vertical		
MCSCF(12,10)	5.51	5.43	4.43	4.48
MCQDPT2/MCSCF(12,10)	4.92	4.80	4.36	4.30

to the lowest excited state has $\pi\to\pi^*$ character for all adenine tautomers.

In addition to 3H and 1H tautomers becoming more stable on the excited state potential energy surface, other changes in relative energetics take place upon the electronic excitation. In general, all tautomers are energetically closer to each other in the excited state (see Table 1). For example, energy separation between 9H and 7H tautomers is only about 4 kcal/mol in the excited state vs 8.5 kcal/mol in the ground state. Similarly, the separation between 3H and 1H tautomers decreases from 11 kcal/mol in the ground state to 6 kcal/mol in the excited state.

Adiabatic and vertical excitation energies for all tautomers obtained in our study are summarized in Table 3. The 0−0 excitation energies for the 9H, 7H, 3H, and 1H tautomers are 101, 96, 84, and 79 kcal/mol (4.4, 4.2, 3.6, and 3.4 eV), respectively (at the highest level of theory used in this study that includes the zero-point energy correction). The excitation energy for the lowest 9H-tautomer is in good agreement with the experimental 0−0 excitation energies obtained by the resonant multiphoton ionization techniques: 4.4−4.5 eV.[9−12] Note that the excitation energies of the 3H and 1H tautomers are significantly lower than those of the 9H and 7H ones. If the 9→3 tautomerization process takes place on the excited potential energy surface, this could result in accumulation of the 3H tautomer after the exposure of adenine to UV radiation. This would lead to observation of new absorption and emission bands with lower energies than those of the most dominantly present 9H tautomer. This effect was indeed observed and reported.[8] The reported absorption peak near 300 nm (4.1 eV) that has been suggested to correspond to 3H tautomer in aqueous solution of adenine[8] is however quite significantly higher than our calculated 0−0 excitation energy for 3H-adenine (3.64 eV) and is closer to our calculated value for 7H-adenine (4.18 eV). However, our present calculations do not include solvent effects, which makes the assignment of the observed bands difficult. Effects of complexation with water molecules (included in the calculation explicitly) on the excitation energies of the adenine tautomers will be considered in our future study and may shed more light on the assignment of this absorption peak observed by Mishra et al.[8]

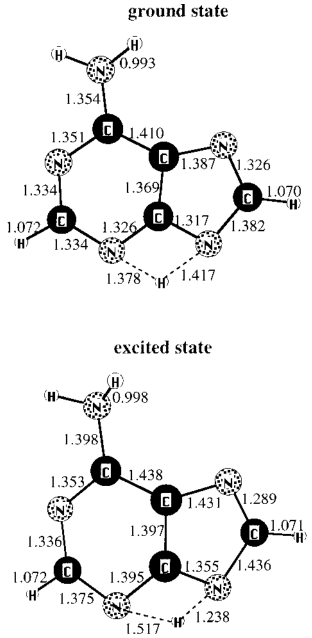

Figure 5. Geometrical structure of the transition states for 9→3 tautomerization reactions, obtained at the MCSCF(12,10)/DZP level of theory (bond distances are in angstroms).

The transition state (TS) structures for the ground and the lowest excited-state hydrogen atom transfer (9→3 tautomerization) reactions are shown in Figure 5. Whereas the ground-state TS structure is close to planar, the excited-state TS structure is bent, with two rings forming an angle of about 150 degrees with each other. Another difference between the ground and excited-state TS structures is that in the excited-state structure the transferring H is closer to the N in the five-membered ring. The energy of the transition state for the hydrogen transfer

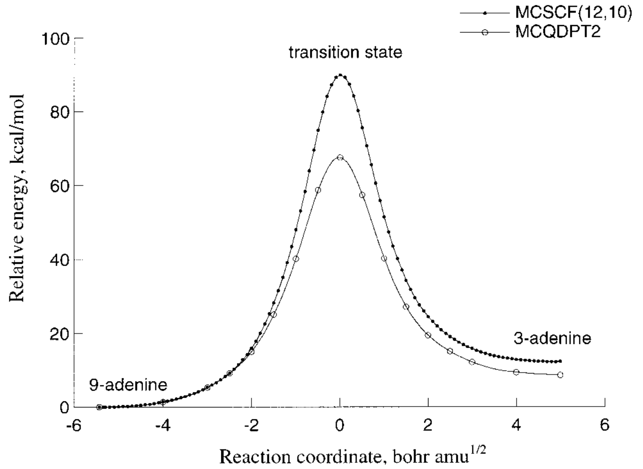

Figure 6. Minimum energy path for 9→3 tautomerization reaction on the ground-state potential energy surface of adenine.

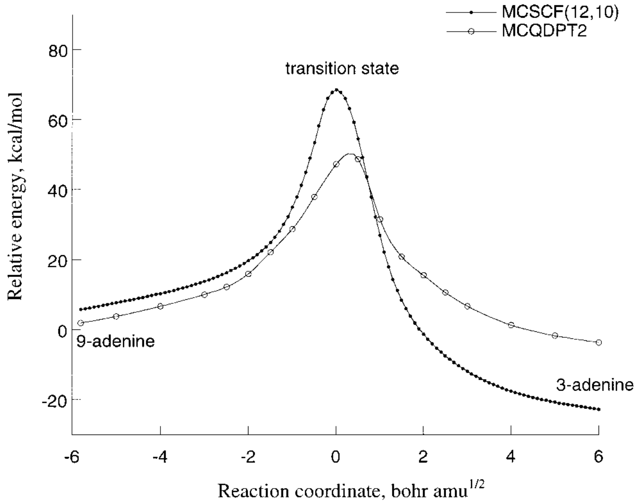

Figure 7. Minimum energy path for 9→3 tautomerization reaction in the lowest electronic excited state of adenine.

reaction in the ground state is 63.0 kcal/mol relative to the lower energy (9H) structure at the highest level of theory (see Table 1). The energy of the TS for this reaction on the excited-state surface is lower: 43 kcal/mol relative to the 9H (higher energy) tautomer and 51 kcal/mol relative to the 3H tautomer.

MCSCF minimum energy paths (and single point MCQDPT2 energies along these paths) for the ground and excited state hydrogen transfer reactions are shown in Figures 6 and 7, respectively. It can be seen from these figures that barrier heights, as well as shapes of the minimum energy paths for hydrogen atom transfer reactions are significantly changed when dynamic correlation is included at the MCQDPT2 level of theory. The barrier heights are reduced by about 20 kcal/mol, and the position of the barrier is slightly shifted on the excited state potential energy surface. A comparison of Figures 6 and 7 shows that the shape of the minimum energy path is much less "steep" in the excited state than in the ground state. The height of the barrier is also lower in the excited state. Both these findings suggest that the tautomerization reaction should proceed more easily on the excited-state surface than on the ground-state one. However, the barrier (about 45 kcal/mol) is still too high for this reaction to take place even in the excited state. The situation may change in the presence of water or other solvent. For the similar reaction paths of 7-azaindole,[13] it was found that complexation with just one water molecule leads to lowering the barrier heights for hydrogen atom transfer reactions very significantly, by about 40 kcal/mol. This is especially important for the 7-azaindole excited state reaction, where the barrier becomes low enough for the tautomerization reaction to take place very easily. It is likely that the same is true for the 9→3 tautomerization reaction in adenine and other similar molecules: such reactions should be facile in the lowest excited state in the presence of water or other polar solvents. We will consider the 9→3 tautomerization reaction for a complex of adenine with water in our future study.

Conclusions

Four possible tautomeric structures of the DNA base adenine are considered in this study using multi-configurational wave functions at the MCSCF(12,10) and MCQDPT2 levels of ab initio theory. Structural parameters and energetics are computed for all the tautomers in both the ground and the lowest singlet excited state. All four tautomers are found to correspond to minima on the potential energy surfaces. Their energetic order on the ground-state potential surface is 9H < 7H < 3H < 1H, whereas on the excited-state surface, this order is found to be different: 3H < 1H < 9H < 7H. Although the tautomers with N−H fragments in the five-membered ring are more stable in the ground state of adenine, the tautomers with N−H in the six-membered ring have lower energies in the excited state. This is due to more stable "aromatic" electronic structure of both 6- and five-membered rings in 9H and 7H-adenine in the ground state, which is significantly destabilized upon the electron excitation. Such destabilization and, as a result, the reversed order of tautomers in the lowest excited state should be a general feature characteristic for all compounds that possess similar two-ring structure. Minimum energy reaction paths are obtained for the hydrogen atom transfer (9→3 tautomerization) reactions in the ground and the lowest electronic excited states of adenine. The barrier height for this reaction is found to be lower and the shape of the reaction path to be more gently sloping for the excited state. This suggests a higher probability for such a reaction to take place on the excited-state potential energy surface than on the ground-state one. The barrier for this reaction in the excited state may become very low in the presence of water or other polar solvent molecules, and therefore, such tautomerization reaction may play an important role in the solution phase photochemistry of adenine.

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References and Notes

(1) Nowak, M. J.; Lapinski, L.; Kwiatkowski, J. S.; Leszczynski J. *J. Phys. Chem.* **1996**, *100*, 3527.

(2) Ha, T.-K.; Keller, M. J.; Gunde, R.; Gunthard, H. H. *J. Mol. Structure (THEOCHEM)* **1996**, *364*, 161.

(3) Fülscher, M. P.; Serrano-Andrés, L.; Roos, B. O. *J. Am. Chem. Soc.* **1997**, *119*, 6168.

(4) Broo, A.; Holmen, A. *J. Phys. Chem. A* **1997**, *101*, 3589.

(5) Broo, A. *J. Phys. Chem. A* **1998**, *102*, 526.

(6) Gu, J.; Leszczynski, J. *J. Phys. Chem. A* **1999**, *103*, 2744.

(7) Mennucci, B.; Toniolo, A.; Tomasi, J. *J. Phys. Chem. A* **2001**, *105*, 4749.

(8) Mishra, S. K.; Shukla, M. K.; Mishra, P. C. *Spectrochimica Acta Part A* **2000**, *56*, 1355.

(9) Kim, N. J.; Jeong, G.; Kim, Y. S.; Sung, J.; Kim, S. K. Park, Y. D. *J. Chem. Phys.* **2000**, *113,* 10 051.

(10) Nir, E.; Kleinermanns, K.; Grace L.; de Vries, M. S. *J. Phys. Chem. A* **2001**, *105,* 5106.

(11) Lührs, D. C.; Viallon, J.; Fischer, I. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1827.

(12) Plützer, Chr.; Nir, E.; de Vries, M. S.; Kleinermanns, K. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5466.

(13) Chaban, G. M.; Gordon, M. S. *J. Phys. Chem. A* **1999**, *103*, 185.

(14) Schmidt, M. W.; Gordon, M. S. *Annu. Rev. Phys. Chem.* **1998**, *49*, 233 and references contained therein.

(15) Dunning, T. H., Jr.; Hay, P. J. *Methods of Electronic Structure Theory*; Schaefer, H. F. III, Ed.; Plenum: New York, 1977, Chapter 1, pp 1−27.

(16) Baldridge, K. K., Gordon, M. S., Steckler, R., Truhlar, D. G. *J. Phys. Chem*. **1989**, *93*, 5107.

(17) Gonzalez, C., Schlegel, H. B. *J. Phys. Chem*. **1990**, *94*, 5523.

(18) Nakano, H. *J. Chem. Phys*. **1993**, *99*, 7983.

(19) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem*. **1993**, *14*, 1347.