551977

Theoretical study of tautomerization reactions for the ground and first excited electronic states of adenine

Latasha M. Salter[a,b] and Galina M. Chaban[*,c]

[a]Tougaloo College, 500 West County Line Road, Tougaloo, MS 39174; [b]Department of Chemistry and Computational Center for Molecular Structure and Interactions, Jackson State University, Jackson, MS 39217
[c]NASA Ames Research Center, Mail Stop T27B-1, Moffett Field, CA 94035-1000

Abstract

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 surfaces 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 states. It is found that the barrier heights and the shapes of the reaction paths are different for the ground and the excited electronic states, 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 should play an important role in the photochemistry of adenine.

---

[*] Corresponding author, e-mail address: chaban@pegasus.arc.nasa.gov

Introduction

Tautomerization processes that take place as a result of photoinduced hydrogen atom transfer reactions, are believed to be a first step in mutation of DNA. It is therefore of interest to study effects of electronic excitation on 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 states of adenine.

Schematic structures and conventional atom numbering for the four ground state tautomers of the amino (purine) form of adenine are shown in Fig. 1. Previous experimental and theoretical studies of adenine suggest that only one of these forms (the lowest 9H-adenine structure) is present in low-temperature matrix environments, while two tautomers (9H-adenine and 7H-adenine) coexist in polar solutions (due to the much higher dipole moment of 7H-adenine)[1]. All four tautomers (as well as the eight 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.

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[1,9,10], the excited state tautomerism is not well understood. Though excitation energies for all ground state tautomers (shown in Fig. 1) have been estimated[8], the energetic order of the tautomers in the excited states is not well known. 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 6-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 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[11]. 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 wavefunctions[12] with the Dunning-Hay double ζ + polarization (DZP) basis set[13]. 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 matrices were 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[14] with the second order Gonzalez-Schlegel algorithm[15] 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[16], that accounts for effects of dynamic correlation. The calculations were performed using the electronic structure package GAMESS[17].

The effects of the size of the MCSCF active space for one of the adenine tautomers (9H-adenine) are demonstrated in Fig. 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. While 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 a 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.

Results and Discussion

Geometries of the four ground state tautomers of adenine are shown in Fig. 3, those for the lowest excited state are shown in Fig. 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. Relative energies for all tautomers are presented in Table 1. The energetic order of tautomers in the ground state is: 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 6-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[11] 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 of that of the NH_2 group and 2π is the lone pair of the nitrogen in the rings). Orbitals 3π–6π are the π-bonds, while 7π–10π are the anti-bonding 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, while two of the anti-bonding π*-orbitals (7π and 8π) gain significant populations. The 5π and 6π orbitals correspond to π-bonds located mostly on the 6-membered ring, and 7π and 8π correspond to anti-bonding orbitals which also involve contributions from atoms of the 6-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 5-membered ring into the anti-bonding 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, since 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 lowest excited state of all adenine tautomers has π–π* character.

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). E.g., 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.

It can be seen from Table 1 that the excitation energies for the 9H, 7H, 3H, and 1H tautomers are 101, 105, 93, and 99 kcal/mol (4.4, 4.5, 4.0, and 4.3 eV), respectively (at the highest level of theory used here that also 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 two-photon ionization (R2PI) technique: 4.4 eV[9] and 4.5 eV[10]. Note, that while the excitation energies of 9H, 7H, and 1H tautomers are relatively similar, the excitation energy for the 3H-tautomer is significantly lower. If the 9→3 tautomerization process takes place on the excited potential energy surface, this could result in an emission band with a lower energy than that of the absorption excitation.

The transition state (TS) structures for the ground and excited state hydrogen atom transfer (9→3 tautomerization) reactions are shown in Fig. 5. While 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 5-membered ring. The energy of the transition state for the hydrogen transfer 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 in 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 Fig. 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. Comparison of Fig. 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[11], 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 kcalmol. 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 our belief 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 solvent. 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, while on the excited state surface this order is found to be different: 3H < 1H < 9H < 7H. While the tautomers with N-H fragments in the 5-membered ring are more stable in the ground state of adenine, the tautomers with N-H in the 6-membered ring have lower energies in the excited state. This is due to more stable "aromatic" electronic structure of both 6- and 5-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.

Acknowledgement

The authors would like to thank NASA Center for Computational Astrobiology and Fundamental Biology for sponsoring the Summer Students Internship Program that enabled LMS to spend time at the NASA Ames Research Center.

References

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*, 10051.

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

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

12. Schmidt, M. W.; Gordon, M. S. *Ann. Rev. Phys. Chem.* **1998**, *49*, 233 and references contained therein.

13. Dunning, T. H., Jr.; Hay, P. J. In *Methods of Electronic Structure Theory*, edited by Schaefer, H. F. III. Plenum, NY, 1977, Chap. 1, pp. 1–27.

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

15. Gonzalez, C., Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

16. Nakano, H. *J. Chem. Phys.* **1993**, *99*, 7983.

17. 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. Comp. Chem.* **1993**, *14*, 1347.

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)

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

Figure captions

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

Fig. 2. Comparison of bond lengths obtained using MCSCF wave functions with two different active spaces.

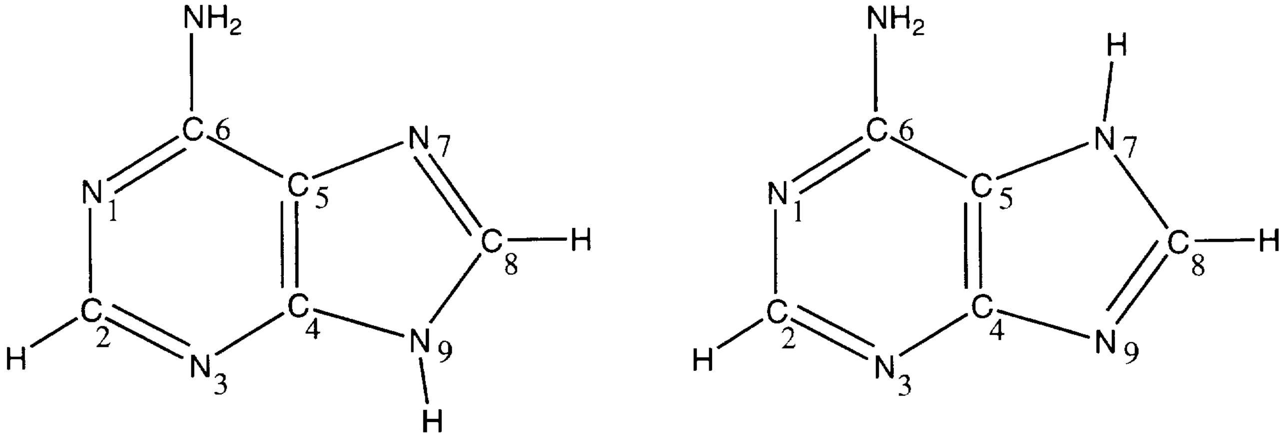
Fig. 3. Geometrical structure of the ground state tautomers of adenine, obtained at the MCSCF(12,10)/DZP level of theory.

Fig. 4. Geometrical structure of the lowest excited state tautomers of adenine, obtained at the MCSCF(12,10)/DZP level of theory.

Fig. 5. Geometrical structure of the transition states for 9→3 tautomerization reactions, obtained at the MCSCF(12,10)/DZP level of theory.

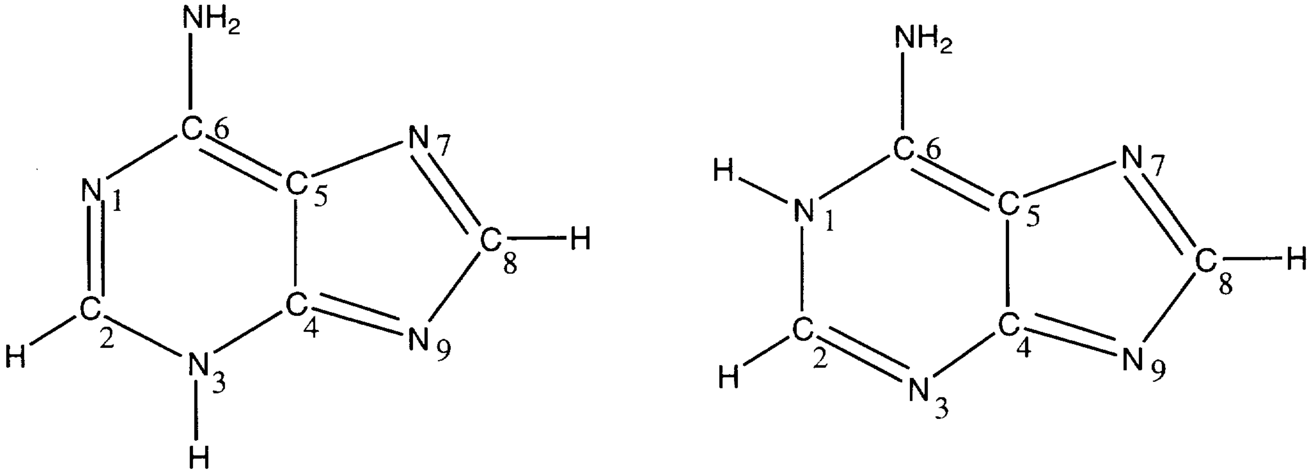
Fig. 6. Minimum energy path for 9→3 tautomerization reaction on the ground state potential energy surface of adenine.

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



9H-adenine

7H-adenine



3H-adenine

1H-adenine

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

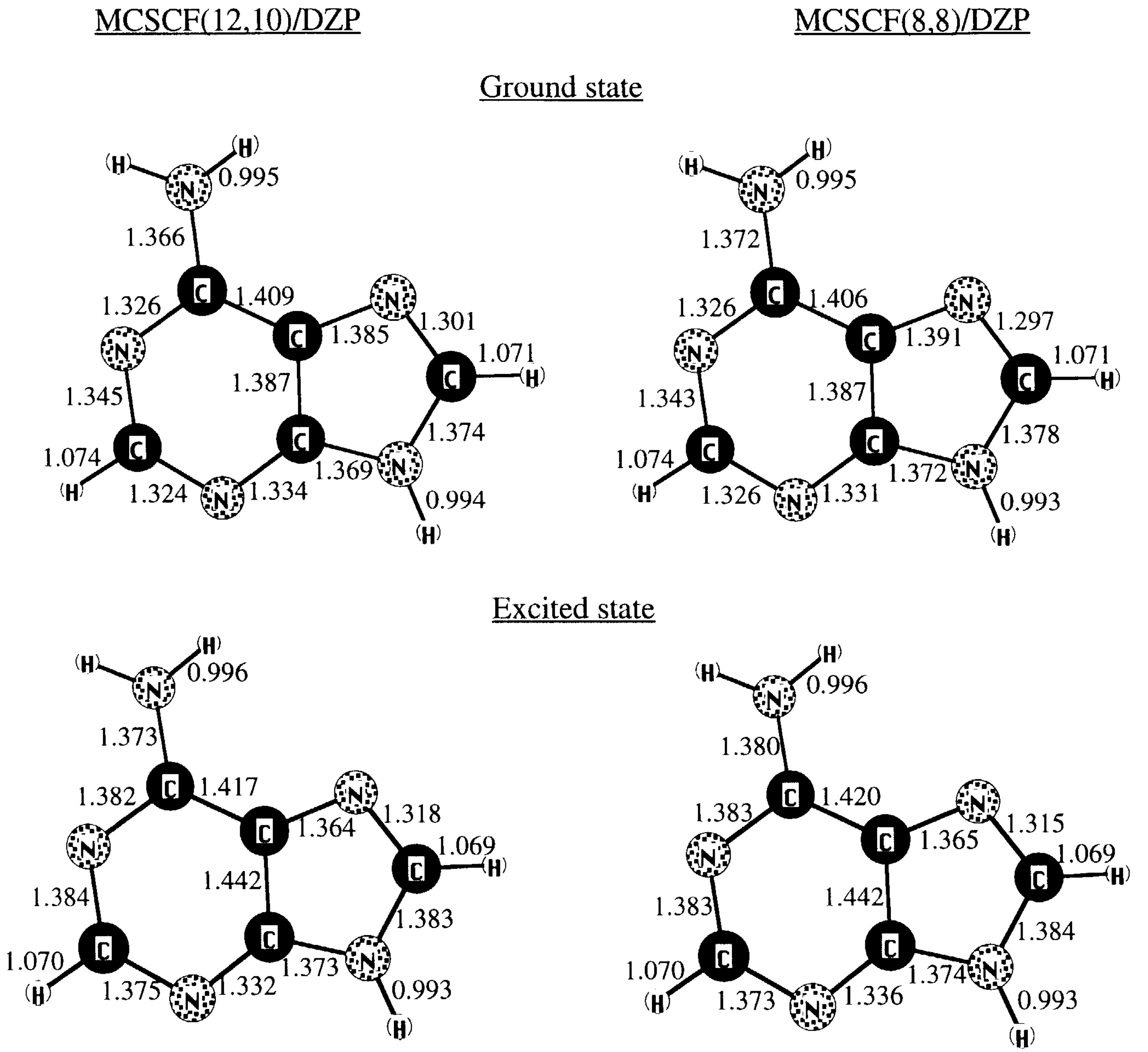


Fig. 2. Comparison of bond lengths obtained using MCSCF wave functions with two different active spaces.

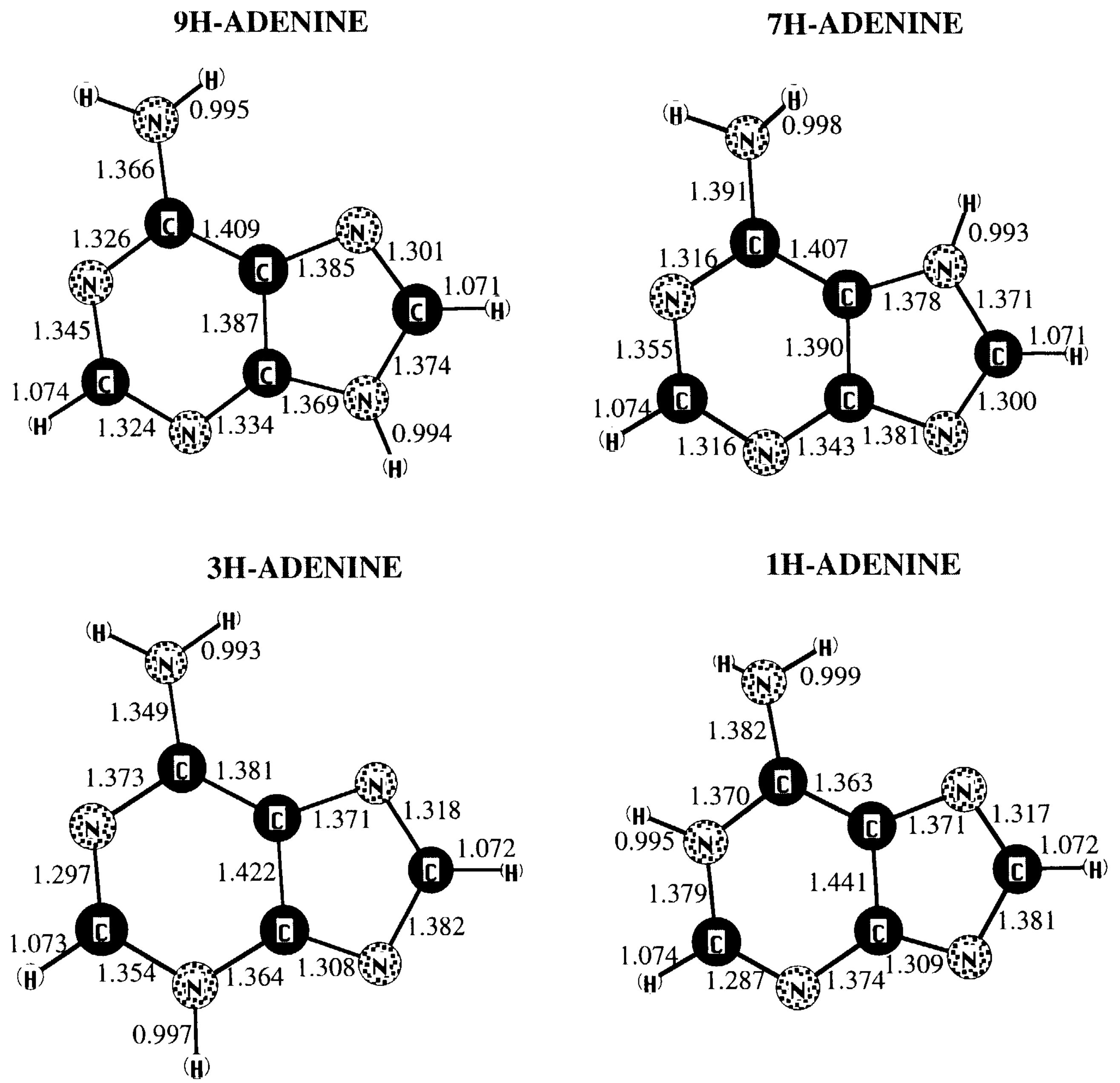


Fig. 3. Geometrical structure of the ground state tautomers of adenine, obtained at the MCSCF(12,10)/DZP level of theory.

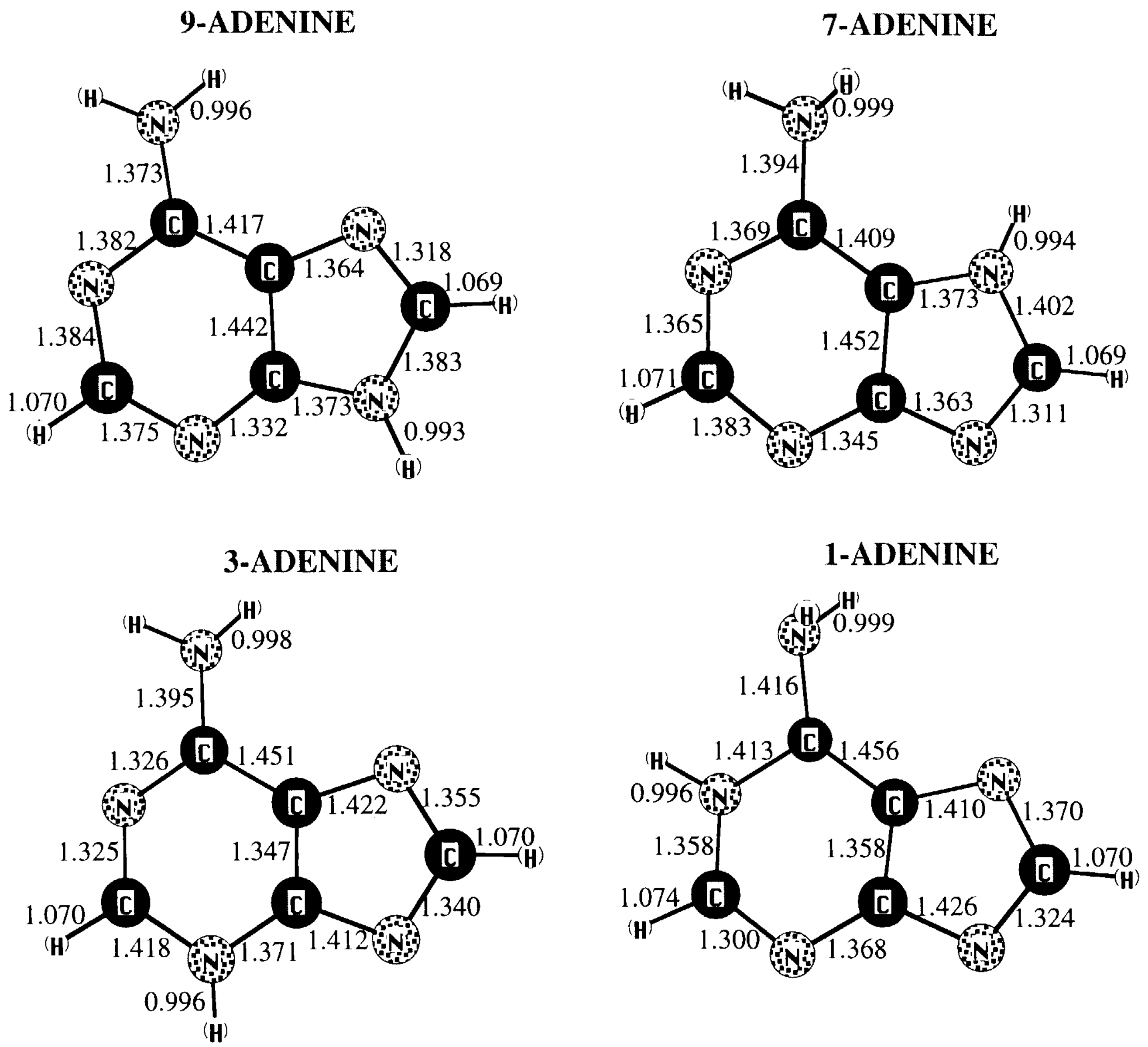
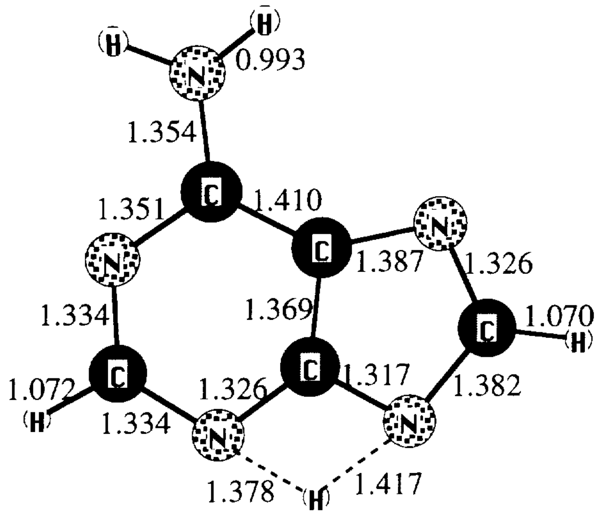


Fig. 4. Geometrical structure of the excited state tautomers of adenine, obtained at the MCSCF(12,10)/DZP level of theory.

ground state



excited state

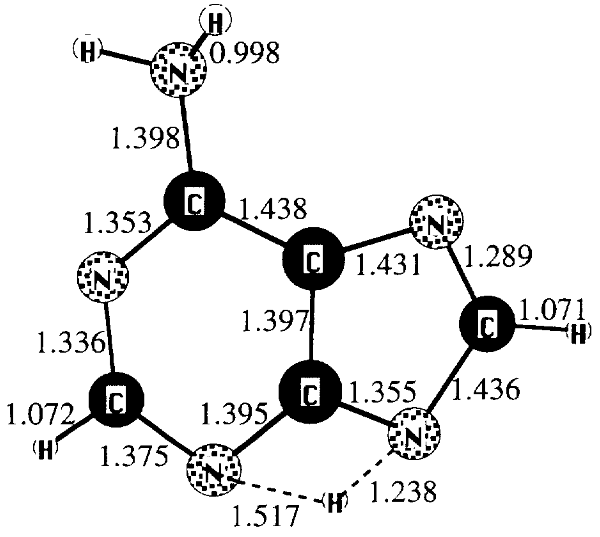


Fig. 5. Geometrical structure of the transition states for 9→3 tautomerization reactions, obtained at the MCSCF(12,10)/DZP level of theory.

Fig. 6. Minimum energy path for 9→3 tautomerization reaction on the ground state of adenine.

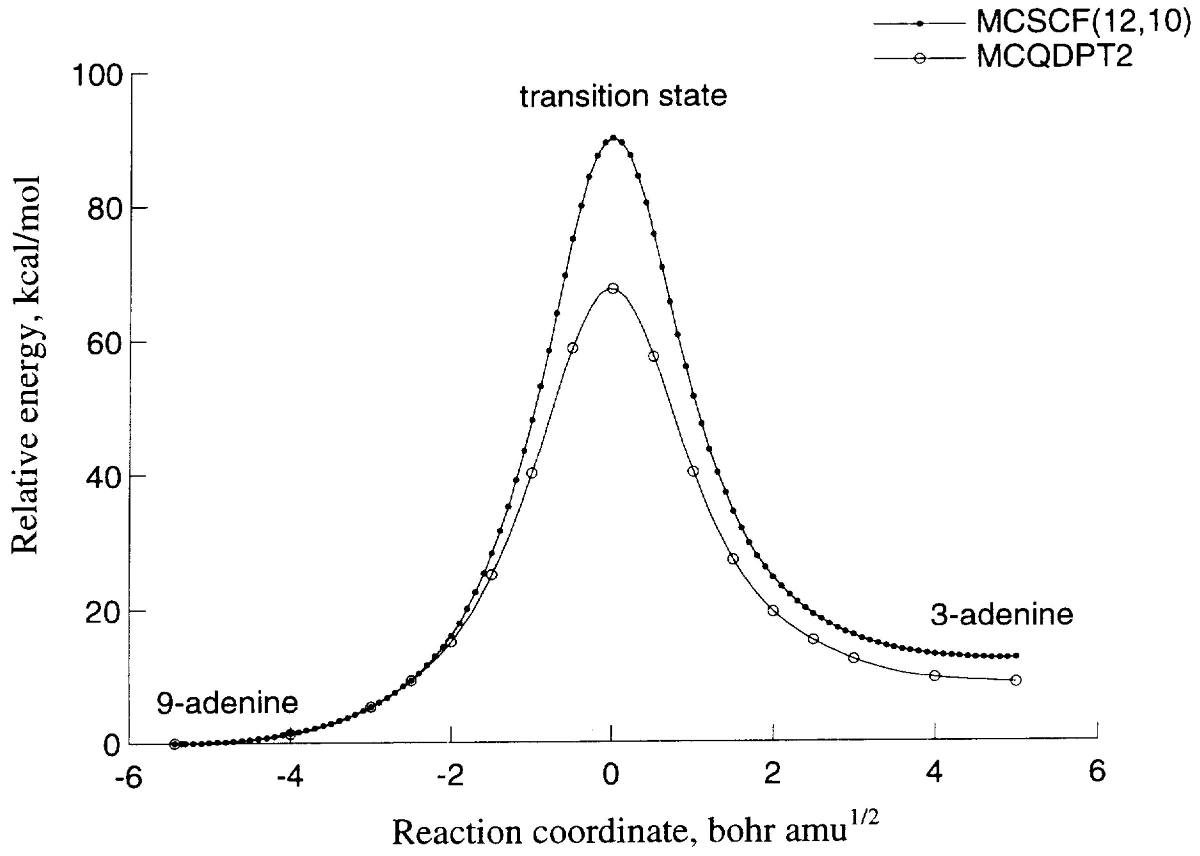


Fig. 7. Minimum energy path for 9→3 tautomerization reaction on the lowest electronic excited state of adenine.