A DFT Study of the Water-Assisted Intramolecular Proton Transfer in the Tautomers of Adenine

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High level quantum chemistry calculations have been applied in order to explore the intramolecular proton transfer process in the tautomers of adenine. The presence of hydration water stabilizes the imino form of the tautomers of adenine by approximately 2−3 kcal/mol. Inclusion of the bulk electrostatic interaction lowers the relative energy of $A_{am}N(7)H$ and $A_{am}N(7)H\cdot H_2O$ to only approximately 4 kcal/mol above $A_{am}N(9)H$ and $A_{am}N(9)H\cdot H_2O$. Consequentely, $A_{am}N(7)H$ might be present in a relatively large concentration in aqueous solutions and biological systems. The activation free energy for the transition of $A_{am}N(9)H\cdot H_2O$ to $TS1\cdot H_2O$ and for $A_{im}N(9)H\cdot H_2O$ to $TS1\cdot H_2O$ are 18.0 and 8.6 kcal/mol, while without water assistance, the free energy differences between $A_{am}N(9)H$ and TS1 as well as $A_{im}N(9)H$ and TS1 are 45.2 and 32.6 kcal/mol, respectively. The activation free energy for the N(7)H form is reduced to 16.1 kcal/mol for the transition of $A_{am}N(7)H\cdot H_2O$ to $TS2\cdot H_2O$ and is reduced to 9.7 kcal/mol for the transition of $A_{im}N(7)H\cdot H_2O$ to $TS2\cdot H_2O$. A lower activation energy barrier suggests that thermodynamics might control the tautomeric equilibrium. The inclusion of quantum mechanical tunneling effects in the calculations dramatically increases the proton transfer rate in adenine. The tunneling rates were evaluated to be 10^{10} times larger than the classical one for the gas phase and 10^3-10^4 times larger than for the classical proton transfer rate for the water-assisted process, suggesting the importance of the tunneling effect in the intramolecular proton transfer in the tautomers of adenine.

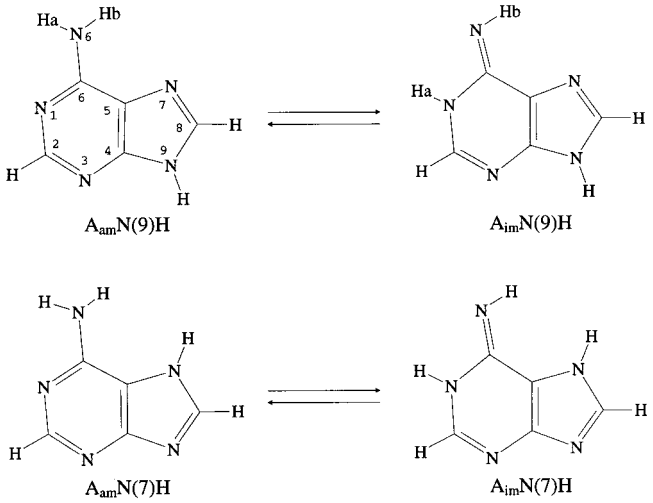
Introduction

The existence of "rare" tautomeric forms of DNA bases increases the possibility of mispairing of purines and pyrimidines that may lead to the spontaneous point mutations.[1−3] A large number of theoretical and experimental studies have been devoted to the tautomerism of DNA bases. Several factors such as excitation,[4] chemical modification,[5] metallic cation interaction,[6,7] electron attachment,[8] irradiation,[9] etc. have been found to be responsible for the tautomeric equilibrium between the "normal" and the "rare" forms of DNA bases. In addition, hydration plays significant roles in the tautomeric process. A water molecule may influence the stability of different tautomeric forms of DNA bases through hydrogen bonding interactions.[10,11] On the other hand, the water-assisted proton transfer has been shown to increase the populations of the minor tautomers greatly by lowering the activation energy barrier of the intramolecular proton transfer.[10−12]

Previous theoretical studies of intramolecular proton transfer in tautomers of guanine and its derivatives have revealed that the typical proton transfer barrier for the tautomeric oxo−hydroxo reactions is about 30−40 kcal/mol in the gas phase and is about 10 kcal/mol in the water-assisted process.[10,11]

A theoretical study of adenine has been focused on its structure,[13,14] IR spectrum,[14−16] and UV spectrum.[17] Recently, the stability of the tautomers of C8-oxidative adenine has been studied at different theoretical levels.[18] Several experimental studies for adenine in polar and nonpolar solvents show evidence for the existence of different tautomeric forms.[19,20]

SCHEME 1



As part of the research in our laboratory aimed at describing the intramolecular proton transfer process in the tautomers of DNA bases, this contribution is focused on the proton transfer between the amino and imino forms of tautomers of adenine. This study supplements the results of investigations of the similar processes between the oxo−hydroxo forms of bases.

Four possible tautomers of adenine that are related through an amino−imino equilibrium (Scheme 1) were selected (denoted as $A_{am}N(7)H$, $A_{im}N(7)H$, $A_{am}N(9)H$, and $A_{im}N(9)H$) in this study. Previous studies have demonstrated that in aqueous solutions the intramolecular proton transfer in tautomers of DNA

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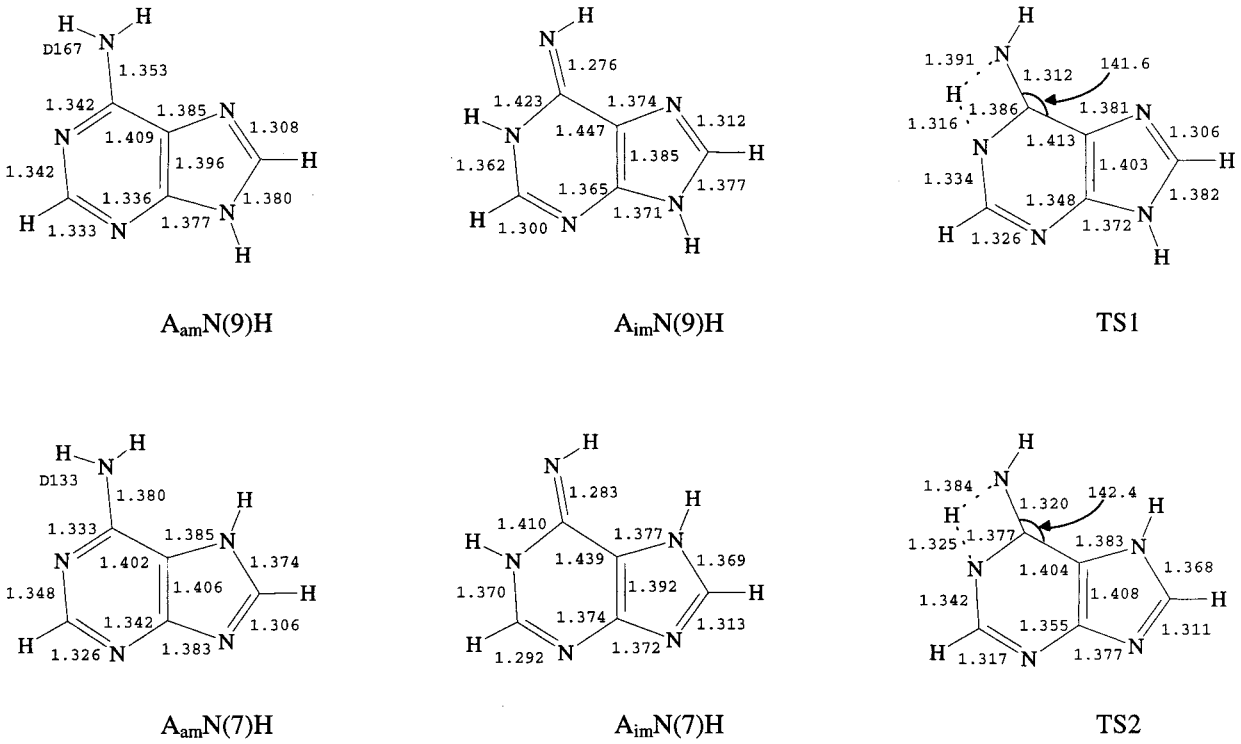

Figure 1. Optimized geometric structures of the tautomers and the related transition states of adenine in the isolated forms. Bond lengths in Ångstroms and bond angles in degrees. *D* represents the dihedral angle.

bases is solely controlled through the assistance of a hydrated water molecule, while the influence of the electrostatic interactions with the bulk is less important.[11,12] The hydrated tautomers of adenine were taken as models for direct interactions of adenine with polar solvents.

In this investigation we attempt to answer the following questions: (1) In what way does the hydration water influence the relative stability of the tautomers of adenine? (2) Is the intramolecular proton transfer in adenine different from that in guanine and its derivatives? (3) How important is the quantum tunneling effect in the intramolecular proton transfer process?

Method of Calculation

The local minimum structures and the transitional state structures have been fully optimized by the analytic gradient techniques using the density functional theory with Becke's three-parameter (B3)[21] exchange functional along with the Lee−Yang−Parr (LYP) nonlocal correlation functional[22,23] (B3LYP). The standard valence triple-ζ basis set augmented with six d-type and three p-type polarization functions, 6-311G(d,p),[24] was used in conjunction with the DFT method. Frequency analysis and the intramolecular proton transfer reaction were also determined by the B3LYP/6-311G(d,p) approach. In the comprehensive investigations, Mebel, Morokuma, and Lin[25] 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 at the B3LYP/6-311G(d,p) level are smaller than those at the ab initio MP2/6-31G(d) and QCISD/6-31G(d) levels of theory.[26] Our previous study of the intramolecular proton transfer in C8-oxidative guanine also shows that the energy differences between the tautomers of guanine derivatives are basically the same for the B3LYP/6-311G(d,p) method and the MP2/6-31G-(d,p) approach.[10] The B3LYP/6-311G(d,p) approach used in this study ensures satisfactory predictions for the geometric parameters, the stabilities, and the vibrational spectra of the tautomers of adenine. To check the influence of the bulk electrostatic interactions, the solvent effects were calculated using the self-consistent isodensity polarized continuum model (SCI−PCM)[27] with the dielectric constant of 78.0 to simulate the water solvent. The Gaussian 94 program package[27] was used. All optimizations were performed using the opt = tight option.

Results and Discussion

Geometry. The optimized geometric parameters of the tautomers of adenine are depicted in Figure 1. To check the bond lengths of the single C−N and the double C=N bonds at the same theoretical level, two model molecules, H_3C-NH_2 and $H_2C=NH$, were also optimized at the B3LYP/6-311G(d,p) level. The bond lengths of N1−C6, N1−C2, N3−C2, and C4−N3 in $A_{am}N(9)H$ are around 1.34 Å, which is between the single C−N bond length of 1.47 Å in H_3CNH_2 and the double C=N bond length of 1.27 Å in H_2CNH. The C5−C6 and the C4−C5 bond lengths of 1.41 and 1.40 Å in $A_{am}N(9)H$ are also between the C−C single bond distance (1.53 Å for H_3C-CH_3) and the C=C double bond length (1.33 Å for $H_2C=CH_2$) at the same theoretical level.[25] From the viewpoint of bond length, the hex-ring in $A_{am}N(9)H$ forms a conjugated system. The bond length of N6−C6 (1.35 Å) implies that the amino group in $A_{am}N(9)H$ is also involved in the conjugated π electron system. On the other hand, the relatively shorter N7−C8 bond distance of 1.31 Å and the longer bond lengths of C5−N7, C8−N9, and C4−N9 of 1.38 Å in $A_{am}N(9)H$ suggest that the N7, C8, and N9 atoms are not included in the aromatic system.

In general, the bond lengths of $A_{am}N(9)H$ and $A_{am}N(7)H$ are similar. However, due to the influence of the hydrogen atom attached to N7, the nonplanarity of the amino group increases. The dihedral angle of $D_{C6N6HaHb}$ changes from 167° in $A_{am}N-(9)H$ to 133° in $A_{am}N(7)H$. As a result, N6 could not be involved in the conjugated π electron system with the hex-ring in $A_{am}N-(7)H$, as is indicated by the longer N6−C6 bond length of 1.38 Å.

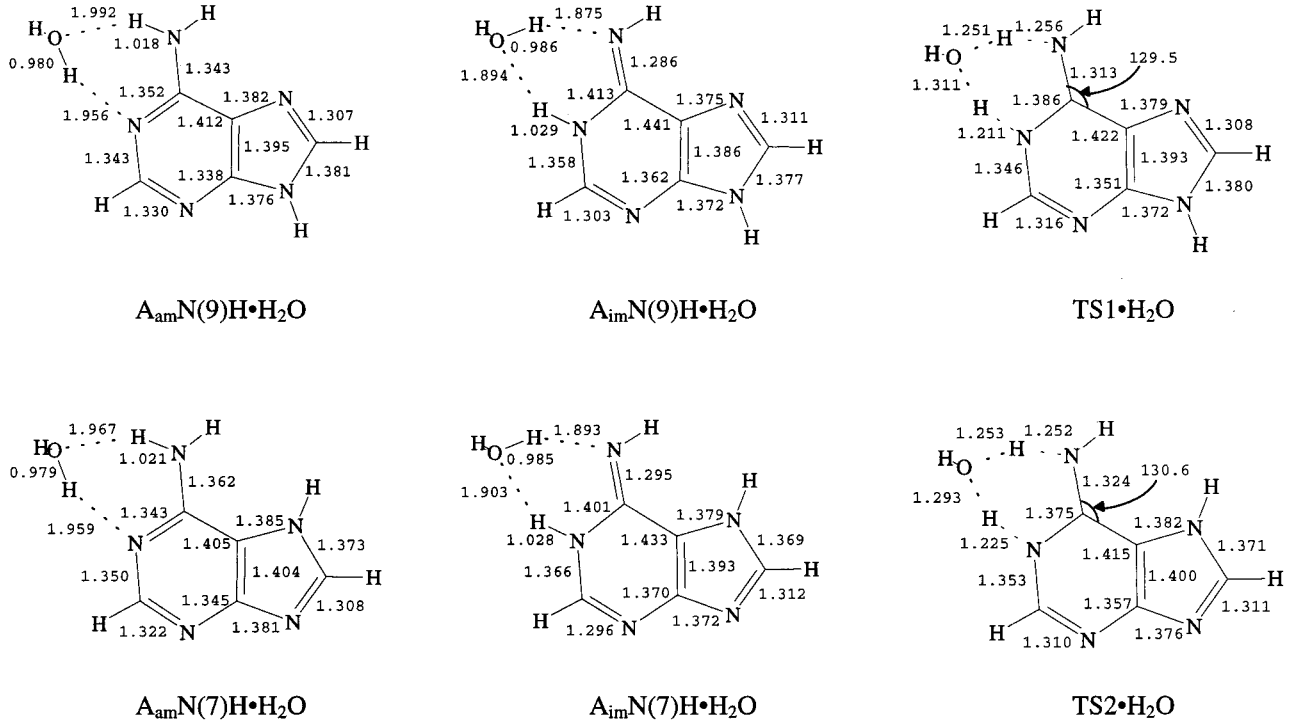

Figure 2. Optimized geometric structures of the tautomers and the related transition states of adenine in the monohydrated forms. Bond lengths in Angstroms and bond angles in degrees.

In the imino form, the longer bond distance of N1−C6 (1.42 Å) and C5−C6 (1.45 Å) and the short double bond character of N3−C2 (1.30 Å) and N6−C6 (1.28 Å) indicate that there is no conjugation in the six-member ring of A$_{im}$N(9)H. This is also true for A$_{im}$N(7)H. In addition, unlike the amino form, the two imino forms of adenine are planar.

The geometric parameters of the transition state of intramolecular proton transfer between the amino form and the imino tautomer (TS1 and TS2) are also shown in Figure 1. In TS1, except for the N1−C6 bond distance, which amouts to 1.39 Å (0.05 Å longer than that of A$_{am}$N(9)H), all other C−N and C−C bond lengths are closer to those in A$_{am}$N(9)H. The hydrogen atom at N7 in TS2 has little influence on the structure of the transition state. The geometric parameters of TS2 are very much similar to those of TS1. In the transition states of TS1 and TS2, the bond length character of conjugation suggests that these systems are stabilized by the conjugation. The conjugated π electron system seems to play an important role in the proton transfer process.

The optimized geometric parameters of monohydrated tautomers of adenine are listed in Figure 2 along with the molecular parameters of the water-assisted proton transfer transition states. The hydration water forms an Ow···Ha hydrogen bond of 1.99 Å and an Hw···N1 hydrogen bond of 1.96 Å with A$_{am}$N(9)H. The same hydrogen bonding appears in A$_{am}$N(7)H•H$_2$O. However, the Ow···Ha hydrogen bonding in the latter is slightly stronger than in the former, with a shorter H-bond length of 1.97 Å for Ow···Ha. The H-bonded water in the amino forms reduces the N6−C6 bond lengths by 0.01 Å in A$_{am}$N(9)H•H$_2$O and by 0.02 Å in A$_{am}$N(7)H•H$_2$O and increases the N1−C6 bond lengths by 0.01 Å in both A$_{am}$N(9)H•H$_2$O and A$_{am}$N(7)H•H$_2$O. The hydration water improves the conjugation in the amino form of adenine, especially the A$_{am}$N(7)H tautomer. The hydrogen bonding of water to the imino form of adenine is a little stronger than that to the amino form, as can be seen from the H-bond lengths of Ow···Ha at 1.89 Å in A$_{im}$N(9)H•H$_2$O and at 1.90 Å in A$_{im}$N(7)H•H$_2$O as well as the H-bond lengths of Hw···N2 at 1.88 Å in A$_{im}$N(9)H•H$_2$O and at 1.89 Å in A$_{im}$N(7)H•H$_2$O. The influence of hydrogen bonding on the geometries of the imino forms reduces the N1−C6 bond distance by 0.01 Å and enlarges the C6−N6 bond length by 0.01 Å in both imino forms. The influence of the water seems to be opposite to the corresponding effects in the amino forms. However, the driving forces of these effects are the same, that is, to enhance the conjugated π electron system in both amino and imino forms.

TABLE 1: Relative Energy, Solvent Effects Corrected Relative Energy, Free Energy, and Dipole Moments of the Tautomers of Adenine[a]

	ΔE	ΔE_{sol}	ΔE_0[b]	ΔG_{298}	μ
A$_{am}$N(9)H	0.00	0.00	0.00	0.00	2.4
A$_{im}$N(9)H	11.67	10.30	12.24	12.45	3.7
A$_{am}$N(7)H	8.59	3.96	8.56	8.79	6.8
A$_{im}$N(7)H	16.76	12.50	16.99	17.25	3.2
A$_{am}$N(9)H•H$_2$O	0.00	0.00	0.00	0.00	3.3
A$_{im}$N(9)H•H$_2$O	8.60	8.38	9.02	9.40	3.6
A$_{am}$N(7)H•H$_2$O	8.77	3.69	8.39	8.42	6.0
A$_{im}$N(7)H•H$_2$O	14.54	10.79	14.56	14.83	4.5

[a] Energy in kcal/mol, dipole moments (μ) in Debye. [b] Zero point corrected.

The transition states (TS1•H$_2$O and TS2•H$_2$O) of water-assisted proton transfer between the amino and imino forms have bond lengths very similar to those of TS1 and TS2. It is obvious that the water in the transition state forms a stable six-member ring structure with N1, C6, N6, and Ha in the proton transfer process. Consequently, the N6−C6−C5 bond angle in the hydrated systems is about 130° and has less tension than the highly bent bond angles of 142° in TS1 and TS2.

Relative Stabilities and Proton Transfer Barriers. The relative energies, the free energies, and the dipole moments of the tautomers of adenine are listed in Table 1. In both hydrated and nonhydrated systems the B3LYP/6-311G(d,p) method predicts A$_{am}$N(9)H to be the most stable form of the tautomers. This is consistent with the early experimental results[28] and the calculations of isolated adenine.[14,19] In the gas-phase condition

the imino forms have much higher energies than the amino forms. $A_{im}N(9)H$ is by 11.7 kcal/mol less stable than $A_{am}N(9)H$. $A_{im}N(7)H$ is by 8.2 kcal/mol less stable than $A_{am}N(7)H$. The stability of the amino form of adenine can be attributed to the better conjugated π electron system in the amino form tautomers, as discussed above. Also, the less conjugated amino group in $A_{am}N(7)H$ can partly account for the 8.6 kcal/mol higher energy than that of $A_{am}N(9)H$.

The interaction between a water and adenine stabilizes the imino forms by approximately 2−3 kcal/mol, as can be seen from Table 1. However, water does not change the relative stability of the amino form of adenine. $A_{am}N(7)H$ is still 8.8 kcal/mol less stable than $A_{am}N(9)H$ in the hydrated form. As a result, the relative stability of $A_{im}N(9)H\cdot H_2O$ and $A_{am}N(7)H\cdot H_2O$ are compatible. The inclusion of the bulk electrostatic interaction with a solvent does not significantly change the relative stability of the imino form of adenine as can be seen from Table 1. However, due to the larger dipole moments of $A_{am}N(7)H$ and $A_{am}N(7)H\cdot H_2O$, both of these forms are more stable in water solutions (4−5 kcal/mol lower in energy). Inclusion of the bulk electrostatic interaction is important for predicting the relative energies of systems with larger dipole moments.

At the B3LYP/6-311G(d,p) level, the relative stability sequence of the tautomers of adenine in the isolated form can written as

$$A_{am}N(9)H > A_{am}N(7)H > A_{im}N(9)H > A_{im}N(7)H$$

For the hydrated species, the difference between $A_{am}N(7)H$ and $A_{im}N(9)H$ disappears. Both of them have very similar stability. The relative stability sequence of the hydrated species is

$$A_{am}N(9)H\cdot H_2O > A_{am}N(7)H\cdot H_2O \approx A_{im}N(9)H\cdot H_2O > A_{im}N(7)H\cdot H_2O$$

Inclusion of the bulk electrostatic interactions changes the stabilities of $A_{am}N(7)H$ and $A_{im}N(9)H$. The relative stability sequence of the hydrated species is then

$$A_{am}N(9)H\cdot H_2O > A_{am}N(7)H\cdot H_2O > A_{im}N(9)H\cdot H_2O > A_{im}N(7)H\cdot H_2O$$

Inclusion of the bulk electrostatic interaction lowers the relative energy of $A_{am}N(7)H$ and $A_{am}N(7)H\cdot H_2O$ to only approximately 4 kcal/mol above $A_{am}N(9)H$ and $A_{am}N(9)H\cdot H_2O$. Consequentely, $A_{am}N(7)H$ might be present in a relatively large concentration in aqueous solutions and biological systems.

Spectral experiments have suggested the existence of the $A_{am}N(7)H$ form of the tautomer in solution.[20,29−31] From the viewpoint of thermodynamics, the similar stabilities of $A_{am}N(7)H\cdot H_2O$ and $A_{im}N(9)H\cdot H_2O$ suggest the same possibility for the existence of both $A_{am}N(7)H$ and $A_{im}N(9)H$ in aqueous solutions.

The relative energies and the dipole moments of the transition state forms are given in Table 2. As expected, the assistance of a water molecule in the proton transfer process greatly reduces the energy barrier. The activation free energy for the transition of $A_{am}N(9)H\cdot H_2O$ to $TS1\cdot H_2O$ and for $A_{im}N(9)H\cdot H_2O$ to $TS1\cdot H_2O$ are 18.0 and 8.6 kcal/mol, while without water assistance, the free energy differences between $A_{am}N(9)H$ and TS1 as well as $A_{im}N(9)H$ and TS1 are 45.2 and 32.6 kcal/mol, respectively. The activation free energy for the N(7)H form is reduced to 16.1 kcal/mol for the transition of $A_{am}N(7)H\cdot H_2O$ to $TS2\cdot H_2O$ and is reduced to 9.7 kcal/mol for $A_{im}N(7)H\cdot H_2O$ to $TS2\cdot H_2O$.

TABLE 2: Activation Energy, Solvent Effects Corrected Activation Energy, Activation Free Energy, and Dipole Moments of the Transition States of Adenine[a]

	ΔE	ΔE_{sol}	ΔE_0[b]	ΔG_{298}	μ
$A_{am}N(9)H \rightleftharpoons TS1$	47.98	49.66	44.79	45.16	2.3
$A_{im}N(9)H \rightleftharpoons TS1$	36.31	39.36	32.55	32.60	
$A_{am}N(7)H \rightleftharpoons TS2$	46.00	48.26	42.37	42.32	5.3
$A_{im}N(7)H \rightleftharpoons TS2$	37.83	39.73	33.94	33.86	
$A_{am}N(9)H\cdot H_2O \rightleftharpoons TS1\cdot H_2O$	20.62	20.79	16.71	17.97	3.6
$A_{im}N(9)H\cdot H_2O \rightleftharpoons TS1\cdot H_2O$	12.02	12.41	7.69	8.57	
$A_{am}N(7)H\cdot H_2O \rightleftharpoons TS2\cdot H_2O$	19.04	20.14	14.98	16.07	5.4
$A_{im}N(7)H\cdot H_2O \rightleftharpoons TS2\cdot H_2O$	13.27	13.04	8.81	9.66	

[a] Energy in kcal/mol, dipole moments in Debye. [b] Zero point corrected.

TABLE 3: Lowest Vibrational Frequency of the Tautomers and the Transition States of Adenine at the B3LYP/6-311G(d,p) Level

	ω_{lowest}, cm^{-1}	
	isolated	hydrated
$A_{am}N(9)H$	138.6	44.7
$A_{im}N(9)H$	147.1	59.4
TS1	i1879.5	i1553.6
$A_{am}N(7)H$	158.1	54.2
$A_{im}N(7)H$	143.2	57.4
TS2	i1890.5	i1579.2

A lower activation energy barrier suggests that the thermodynamics might control the tautomeric equilibrium. Accordingly, because of the energy difference of 8 kcal/mol between $A_{am}N(9)H\cdot H_2O$ and $A_{im}N(9)H\cdot H_2O$, the hydration will favor the $A_{am}N(9)H$ form. From Table 2, one can see that inclusion of the bulk electrostatic interaction has no effects on the activation energy barriers.

Vibrational Analysis. The IR spectra predicted at the B3LYP/6-311G(d,p) level are shown in Figure 3. The lowest vibrational frequency of the minima and the imaginary frequency of the transition states are listed in Table 3. The lowest frequency predicted for hydrated adenine reflects the weak bonding between water and adenine. The relatively large imaginary frequencies calculated for TS1 and TS2 are related to the sharp activation energy barrier in the proton transfer paths. Normal-mode analysis shows that the combined vibrations at 1663 cm^{-1} in $A_{am}N(9)H$ are changed to the combination of Ha−N1−C6 bending and ν(C6N6) at 1733 cm^{-1} in $A_{im}N(9)H$. The blue shift of 70 cm^{-1} from the amino form to the imino tautomer is consistent with the change in the bond length discussed above. A similar change can be observed for the $A_{am}N(7)H$ and $A_{im}N(7)H$ pairs in which the blue shift amounts to about 50 cm^{-1} due to the influence of H at the N7 position (see Figure 3). These vibrational modes are clearly related to the intramolecular proton transfer in the isolated form of adenine. As a comparison, the experimental frequency of this mode is recorded at 1626−1639 cm^{-1} for adenine in an Ar matrix.[14] An interaction between a water molecule and adenine also increases the frequency of the combined mode of $\beta(NH_2$ *scis*) and ν(C6N6) by 13 cm^{-1} in $A_{am}N(9)H\cdot H_2O$ and by 24 cm^{-1} in $A_{am}N(7)H\cdot H_2O$. However, this frequency is unaffected by the hydration water in the imino form. In the water-assisted proton transfer process the vibration mode related to the proton transfer is different from that in the isolated form. The proton transfer related vibrational mode in a water-assisted process has been found to be the combination of the ν(O−H) of water and the ν(N6−Ha) located at 3528 cm^{-1} for $A_{am}N(9)H\cdot H_2O$ and $A_{am}N(7)H\cdot H_2O$. This mode in the imino form is the combination of the ν(O−H) of water and the ν(N1−Ha) located at 3409 cm^{-1} for $A_{im}N(9)H\cdot H_2O$ and at 3445 cm^{-1} for $A_{im}N(7)H\cdot H_2O$.

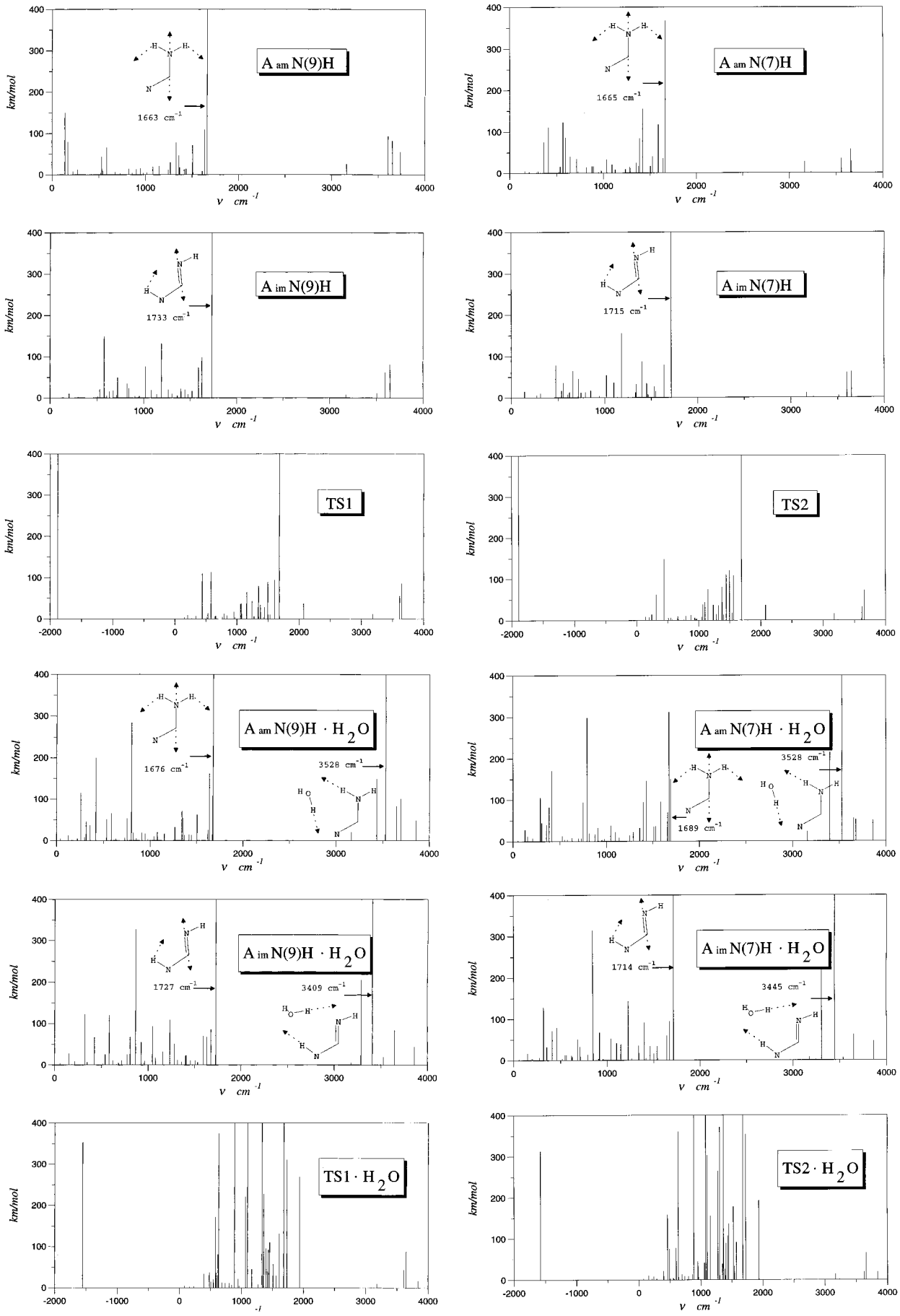

Figure 3. IR spectra of the tautomers and the related transition states of adenine, predicted at the B3LYP/6-311G(d,p) level.

TABLE 4: Classical and Quantum Tunneling Corrected Reaction Rate Constants of the Proton Transfer in Adenine

	$k_{classic}$, s^{-1}	$k_{quantum}$, s^{-1}
$A_{am}N(9)H \rightleftharpoons TS1$	4.7×10^{-21}	9.2×10^{-10}
$A_{im}N(9)H \rightleftharpoons TS1$	7.6×10^{-12}	1.6×10^{-3}
$A_{am}N(7)H \rightleftharpoons TS2$	5.7×10^{-19}	2.0×10^{-8}
$A_{im}N(7)H \rightleftharpoons TS2$	9.0×10^{-13}	3.8×10^{-4}
$A_{am}N(9)H{\cdot}H_2O \rightleftharpoons TS1{\cdot}H_2O$	4.0×10^{-1}	5.8×10^{3}
$A_{im}N(9)H{\cdot}H_2O \rightleftharpoons TS1{\cdot}H_2O$	3.2×10^{6}	1.9×10^{9}
$A_{am}N(7)H{\cdot}H_2O \rightleftharpoons TS2{\cdot}H_2O$	1.0×10^{1}	9.5×10^{4}
$A_{im}N(7)H{\cdot}H_2O \rightleftharpoons TS2{\cdot}H_2O$	5.1×10^{5}	4.9×10^{8}

Proton Transfer Rate. To evaluate the role of tautomerism of adenine 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 lower than 10^{-12} s^{-1} for the gas phase. However, when hydrated, the classical tautomeric rate constants are increased to 10^{-1}—10^{6} 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.[10,11,32,33] The inclusion of quantum mechanical tunneling in the calculations dramatically increases the proton transfer rate in adenine. Using the parabolic barrier approximation and one-dimensional model,[34,35] the tunneling rates were evaluated to be 10^{10} times larger than the classical one for the gas phase and $10^{3}-10^{4}$ times larger than the classical proton transfer rate for the water-assisted process. The characteristic frequencies used in the calculations are depicted in Figure 3. The computed classical and quantum tunneling rate constants for the proton transfer in adenine are listed in Table 4. Because the temperature dependence of the tunneling rate is negligible for temperatures up to about 300 K,[35] our results suggest the importance of the tunneling effect and indicate that it might dominate the adenine tautomeric processes in adenine at room temperature.

Conclusions

High level quantum chemistry calculations have been applied in order to explore the intramolecular proton transfer process in the tautomers of adenine. Based on an analysis of the geometric parameters, energies, proton transfer process, and vibrational modes, the following conclusions are reached in this investigation:

1. The presence of hydration water stabilizes the imino forms of adenine by approximately 2−3 kcal/mol. Consequently, the gas phase relative stability of

$$A_{am}N(9)H > A_{am}N(7)H > A_{im}N(9)H > A_{im}N(7)H$$

changes to

$$A_{am}N(9)H{\cdot}H_2O > A_{am}N(7)H{\cdot}H_2O \approx A_{im}N(9)H{\cdot}H_2O > A_{im}N(7)H{\cdot}H_2O$$

for the hydrated forms.

2. Inclusion of the bulk electrostatic interactions lowers the relative energy of $A_{am}N(7)H$ and $A_{am}N(7)H{\cdot}H_2O$ to only about 4 kcal/mol above $A_{am}N(9)H$ and $A_{am}N(9)H{\cdot}H_2O$. Consequently, $A_{am}N(7)H$ might be present in a relatively large concentration in aqueous solutions and biological systems.

3. The assistance of a water molecule in the proton transfer process reduces the energy barrier. The activation free energy for the transition from the hydrated amino to the imino tautomers is only half of that predicted for the isolated forms. The activation free energy of the inverse transition in the water-assisted process is as low as 9 kcal/mol, one-fourth of that calculated for the isolated form. Such a low activation energy barrier suggests that thermodynamics might control the tautomeric equilibrium.

4. Using the parabolic barrier approximation and one-dimensional model,[34,35] the tunneling rates were evaluated to be 10^{10} times larger than the classical one for the gas phase and $10^{3}\sim10^{4}$ times larger for the water-assisted process. This result suggests the importance of the tunneling effect in the intramolecular proton transfer in adenine.

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