

The Ground and Excited State Hydrogen Transfer Potential Energy Surface in 7-Azaindole

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Multireference wave functions, augmented by second-order perturbation theory, are used to examine the hydrogen transfer process in the ground and first excited states of 7-azaindole and in the 1:1 7-azaindole: water complex. The presence of one water molecule dramatically reduces the barrier to proton transfer in both electronic states. In the excited state the order of the two tautomers is reversed, and the barrier for the hydrogen transfer from the (now higher energy) normal structure to the tautomer in the presence of one water is estimated to be ≤ 6 kcal/mol.

Introduction

Proton transfer and hydrogen atom transfer reactions are a key feature in many processes of biological importance. Since proton transfer reactions are frequently studied using optical spectroscopic techniques, the effect of electronic excitation on the proton transfer process is very important. Since the actual bioprocesses occur in solution (most typically aqueous solution), and most experimental probes of these processes are also carried out in solution, it is important to assess the impact of solvation on the proton-transfer process.

Petrich and co-workers¹ have demonstrated that 7-azatryptophan (7-AT) is a noninvasive in situ optical probe of protein structure and dynamics. Since 7-AT can be incorporated into bacterial protein, model proteins containing 7-AT, or its basic chromophore 7-azaindole (7-AI), can be synthesized. The most important and most interesting nonradiative process in these chromophores is solvent-assisted excited-state intramolecular hydrogen transfer. These hydrogen transfers, resulting in tautomerization, occur upon electronic excitation. The tautomerization does not occur on the ground-state surface.¹ Since 7-AI is the key chromophore in 7-AT, there have been several detailed experimental spectroscopic studies of 7-AI,^{1–3} and there has been a recent review of the experimental and theoretical studies of this important species.⁴

The two primary isomers of 7-azaindole are the normal form (the global minimum on the ground electronic potential energy surface, in which the six-membered ring is an aromatic pyridine structure) and the tautomer that is formed by transferring a hydrogen to the nitrogen on the six-membered ring. Experimental evidence indicates^{1–4} that, upon electronic excitation, the energy order of these two isomers inverts. In alcohols, the excited-state tautomerization occurs easily, with an observed activation energy that is on the order of 2–3 kcal/mol. The gas phase 0–0 excitation energy of normal 7-azaindole has very recently been measured in a beautiful series of experiments,⁵ in which successively smaller red shifts were observed as one, two and three water molecules were added. The effect of water on the electronic spectrum of 7-azaindole has recently been modeled by Shukla and Mishra.⁶

In a previous paper,⁷ the ground-state tautomerization process in 7-azaindole was studied without and with the presence of a mediating solvent (water and methanol) molecule, using Hartree–Fock geometries and second-order perturbation theory energies. As expected based on the experimental data, the

normal form of 7-AI was predicted to be more stable than its tautomer by about 14 kcal/mol, with a very large (59 kcal/mol) tautomerization barrier. Introduction of either solvent molecule dramatically decreased the barrier to a still substantial 19–23 kcal/mol. A preliminary qualitative probe of the lowest excited singlet state suggested (in agreement with experiment) that the order of stability of the two tautomers is reversed, but the level of theory used was not adequate for a reliable prediction of the associated energetics.

The present work focuses on the effect of electronic excitation on the relative energies of the two tautomers and the barrier separating these tautomers, using multireference wave functions.

Theoretical Approach

Parts of the ground and the lowest excited-state potential energy surfaces corresponding to hydrogen transfer reactions were studied using multiconfigurational MCSCF wave functions⁸ and Dunning–Hay double- ζ + polarization (DZP) basis sets.⁹ The MCSCF active spaces include all π electrons and π orbitals: four π bonds, four corresponding antibonding orbitals, and one nitrogen π lone pair. This results in an active space of 10 electrons in 9 orbitals and is denoted (10,9). Stationary points (minima and transition states) were optimized using analytic gradients of MCSCF energies. Numerical Hessians were calculated for each stationary point to verify that it has 0 (minimum) or 1 (transition state) negative eigenvalue. Minimum energy paths (MEPs) were followed using the intrinsic reaction coordinate (IRC) method with the second-order Gonzalez–Schlegel algorithm and a step size of 0.3 amu^{1/2} bohr. More accurate energies for stationary points and selected points along the MEPs were calculated using second-order multiconfigurational quasi-degenerate perturbation theory MCQDPT2.¹⁰ The effect of this dynamic correlation on isomerization energies and barrier heights is very significant, with corrections up to 20 kcal/mol. All calculations were performed using the GAMESS electronic structure program.¹¹

Results and Discussion

Isolated 7-Azaindole. MCSCF(10,9)/DZP geometries for the ground-state tautomers of 7-azaindole and the transition state for tautomerization between these isomers are shown in Figure 1. Also shown are energies (in kcal/mol) relative to the energy of the normal structure. Comparison with RHF geometries

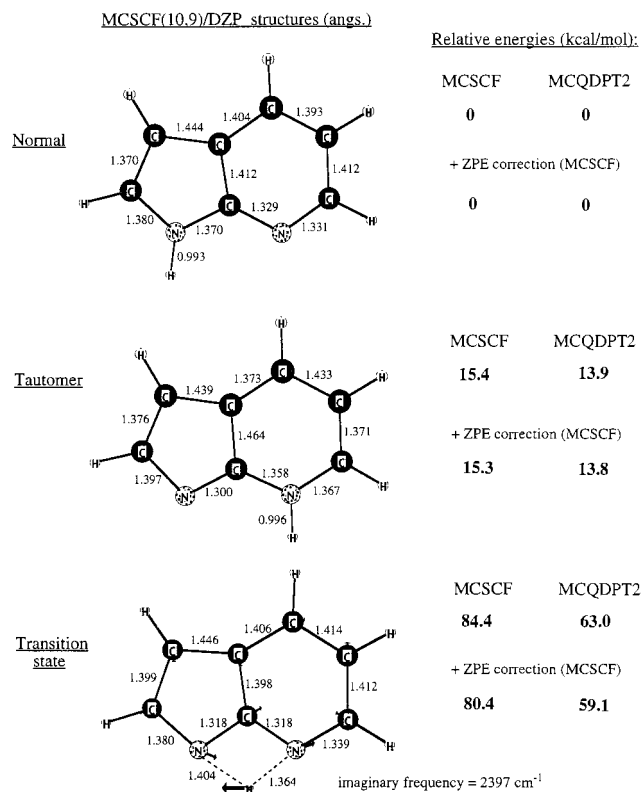


Figure 1. Structures and energetics for ground-state isomers and transition-state of 7-azaindole.

reported previously⁷ indicates that MCSCF ring bonds are slightly (≤ 0.015 Å) longer. The MCSCF and MCQDPT2 relative energies are nearly identical to those found at the RHF and MP2 levels, respectively.⁷ The tautomerization energy at the MCQDPT2 level of theory is 13.9 kcal/mol (vs 14.1 kcal/mol at the single-determinant MP2 level). The barrier height for the hydrogen transfer reaction is 63.0 kcal/mol relative to the lower energy (normal) structure (cf. MP2 barrier of 62.9 kcal/mol). This is reduced to 59.0 (58.7) kcal/mol when the vibrational zero point correction is included. The similarity of these multiconfigurational and single configurational results illustrates that the ground state is well described with single configuration wave functions.

Table 1 lists the MCSCF natural orbital occupation numbers for both ground and excited-state structures. In the normal conformation, the populations of two of the ground-state orbitals (4π and 5π) are significantly reduced upon excitation, while two of the previously virtual orbitals (6π and 7π) gain significant populations. The 4π and 5π orbitals correspond to π bonds located mostly on the six-membered ring, while 6π and 7π correspond to antibonding orbitals which also involve contributions from atoms on the six-membered ring. In the tautomer and the transition state, there is a significant shift in population

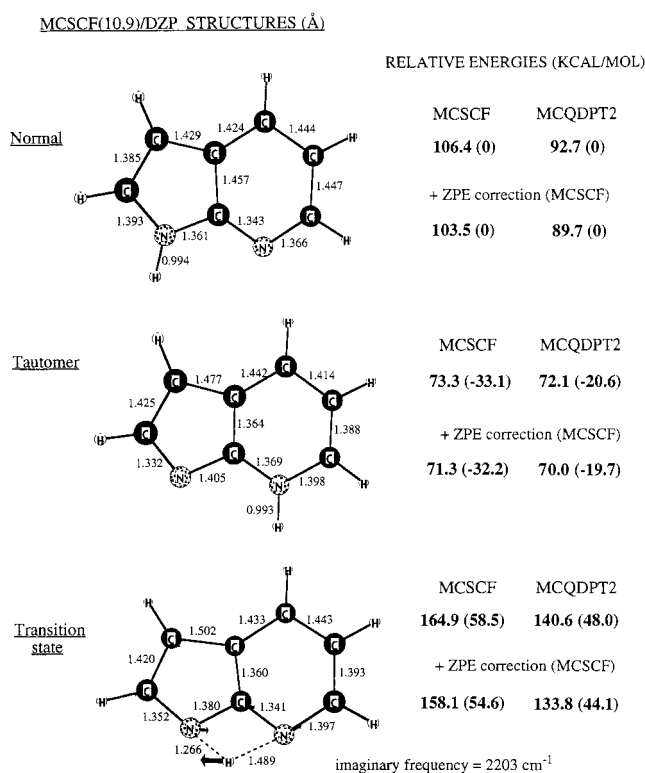


Figure 2. Structures and energetics for excited-state isomers and transition-state of 7-azaindole. Relative energies are given relative to the ground-state global minimum. Values in parentheses are relative to the normal excited state isomer.

from 4π to 6π , with little change in the other orbitals. In these two structures, the electron is excited from the π space of the five-membered ring into the antibonding π orbital which has contributions from atoms of both rings (mostly from the six-membered ring in the case of the transition state).

The orbital character of the excitation as described above can explain why the normal structure (which has the lowest energy on the ground state) becomes less stable than the tautomer after the excitation. In the ground state of the normal structure, both six-membered and five-membered rings have 6π electrons and can be considered to be quite stabilized by π delocalization ("aromatic"), whereas in the tautomer, the five-membered ring has only 4π electrons. This explains qualitatively the higher stability of the normal structure on the ground-state surface. For the normal structure, the excitation involves the π electrons of the six-membered ring, and therefore it reduces its π delocalization and destabilizes this isomer. In the tautomer, the excitation mostly involves the electrons from the five-membered ring (which is not aromatic in the tautomer ground state). As a result, the tautomer is less destabilized compared to the normal species after the excitation, giving rise to the reversed order of these isomers on the excited-state surface.

TABLE 1: MCSCF(10,9)/DZP Natural Orbital Occupation Values for Isolated 7-Azaindole

structure/orbital	1π	2π	3π	4π	5π	6π	7π	8π	9π
Normal									
ground state	1.991	1.963	1.940	1.914	1.892	0.113	0.085	0.065	0.037
excited state	1.987	1.883	1.922	1.258	1.620	0.771	0.372	0.076	0.111
Tautomer									
ground state	1.987	1.956	1.948	1.922	1.879	0.123	0.083	0.062	0.040
excited state	1.992	1.944	1.917	1.048	1.881	0.963	0.107	0.094	0.056
TS									
ground state	1.980	1.962	1.949	1.926	1.901	0.109	0.080	0.059	0.035
excited state	1.986	1.921	1.941	1.026	1.880	0.982	0.111	0.095	0.058

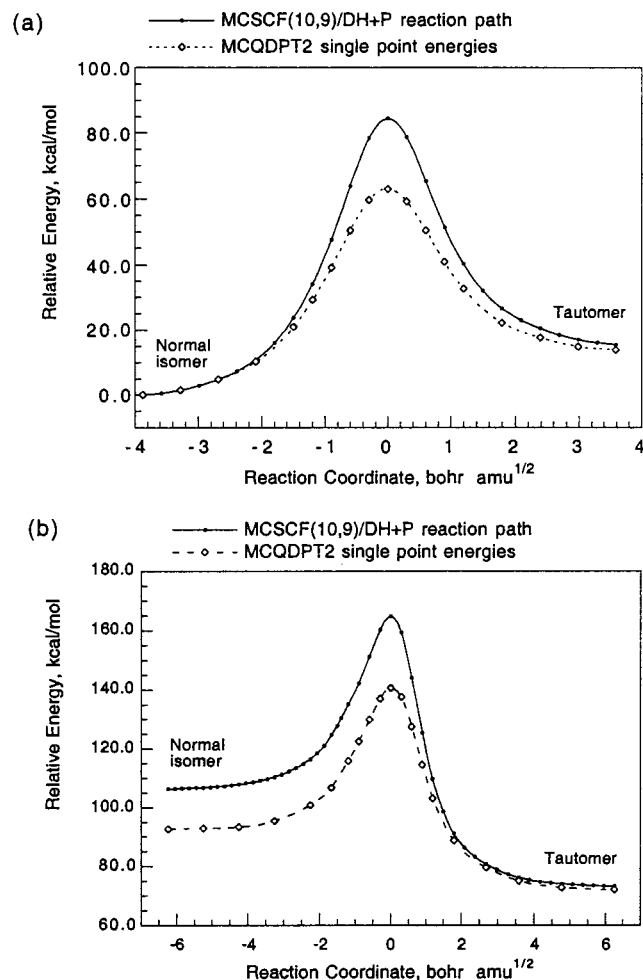


Figure 3. Reaction path for tautomerization of 7-azaindole: (a) ground and (b) excited state.

Geometries and energetics for the lowest singlet excited ($\pi \rightarrow \pi^*$) state of 7-azaindole are given in Figure 2. As noted above, the ground-state higher energy tautomer becomes lower in energy in the excited state. The normal isomer is 20 kcal/mol higher in energy at the MCQDPT2/DZP level of theory. The *adiabatic* MCQDPT2/DZP excitation energy for the normal species is 90 kcal/mol (3.9 eV). This may be compared with the experimental 0–0 excitation energies for normal 7-azaindole in the gas phase (4.29 eV) and complexed with one water (4.13 eV).¹² The transition state structure for the hydrogen transfer on the excited-state surface is also a four-membered ring, but the transferring H is closer to the N in the five-membered ring. The MCQDPT2 barrier height for this reaction on the excited-state surface is 48 kcal/mol relative to the higher energy (normal) isomer and 69 kcal/mol relative to the tautomer. When MCSCF vibrational zero point energies are included, these MCQDPT2 barrier heights become 44 and 64 kcal/mol, respectively.

TABLE 2: MCSCF(10,9)/DZP Natural Orbital Occupation Values for 7-Azaindole + H₂O

structure/orbital	1 π	2 π	3 π	4 π	5 π	6 π	7 π	8 π	9 π
Normal									
ground state	1.990	1.963	1.942	1.916	1.894	0.112	0.084	0.064	0.036
excited state	1.985	1.886	1.922	1.245	1.637	0.787	0.355	0.076	0.107
Tautomer									
ground state	1.984	1.959	1.950	1.925	1.884	0.119	0.081	0.060	0.038
excited state	1.991	1.944	1.919	1.038	1.882	0.972	0.106	0.094	0.056
TS									
ground state	1.981	1.965	1.948	1.928	1.897	0.109	0.078	0.059	0.035
excited state	1.983	1.929	1.948	1.019	1.888	0.991	0.099	0.089	0.053

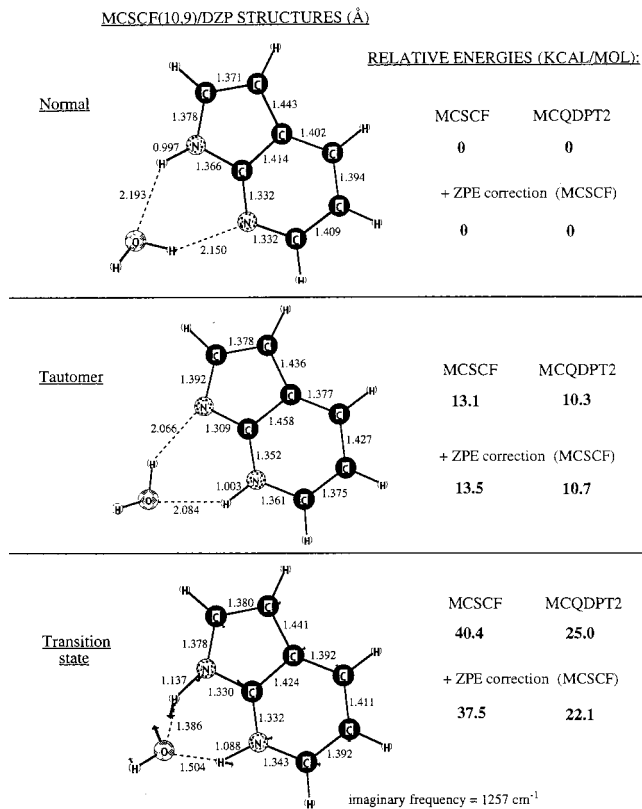


Figure 4. Structures and energetics for ground-state isomers and transition state of 7-azaindole + H₂O.

MCSCF minimum energy paths (and single point MCQDPT2 energies along these paths) for both ground- and excited-state hydrogen transfer reactions are shown in Figure 3.

7-Azaindole–H₂O Complex. The MCSCF natural orbital occupation numbers for 7-azaindole with one water present are given in Table 2. The addition of the water molecule has little effect on these populations and thus on the description of the excited states (cf. Table 1).

The geometries and energetics for the ground state 7-azaindole–water complex structures are shown in Figure 4. The ground-state geometries of the 7-azaindole rings are not changed much by complexation with water and are very close to those found at the RHF level.⁷ As was noted in the previous paper,⁷ the transition states of complexes with one solvent molecule present have less strained six-membered ring structures (the solvent molecule assists the transfer of the hydrogen). This has the effect of stabilizing the transition state and leads to much lower barriers to the hydrogen transfer when a solvent molecule is present. It can be seen from Figure 4 that the normal isomer is lower in energy (as it was for the isolated ground state 7-azaindole). The tautomer is 10.3 kcal/mol higher at the MCQDPT2 level of theory; this amounts to a 3.6 kcal/mol stabilization of the higher energy isomer due to the addition of

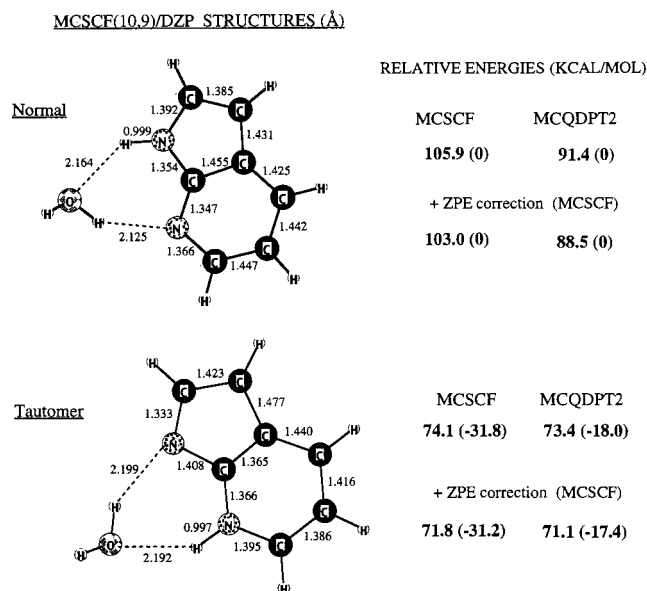


Figure 5. Structures and energetics for excited-state isomers of 7-azaindole + H₂O. Energies are relative to ground state normal tautomer. Values in parentheses are relative to excited state normal isomer.

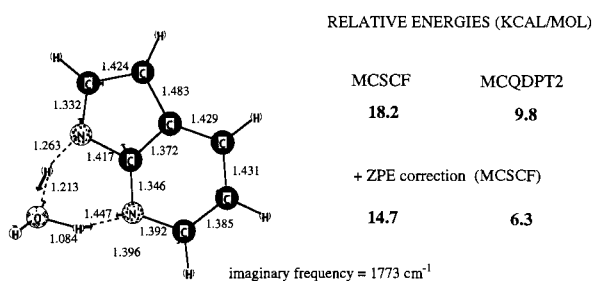


Figure 6. MCSCF structure and relative energetics for the transition state of tautomerization reaction on the excited state of 7-azaindole + H₂O. Energies are relative to the excited-state normal isomer shown in Figure 5.

the water molecule. The stabilization effect of a water molecule on the hydrogen transfer barrier height is about 37 kcal/mol, decreasing the MCQDPT2 barrier from 59 to 22 kcal/mol when MCSCF vibrational zero point corrections are included.

Structures and relative energies for excited-state tautomers are shown in Figure 5. The calculations for the *adiabatic* excitations predict a red shift in the excitation energy upon complexation with one water, in agreement with experiment, although the calculated MCQDPT2 red shift of 1.3 kcal/mol is somewhat smaller than the experimental value of 3.7 kcal/mol.^{5,12}

The tautomer (which is more stable in the excited state) is very slightly destabilized by the water molecule, so that energy difference between isomers becomes 18 kcal/mol, compared with 20 kcal/mol in the isolated structures as discussed above. The transition state for the tautomerization reaction (found at the MCSCF level) is shown in Figure 6. This transition state is connected by the IRC path to the tautomer structure in one direction, but the second IRC branch (toward the normal structure) ends at a slightly different minimum (isomer) with the N–H bond in the five-membered ring. This isomer (*n'*), shown in Figure 7, is about 4 kcal/mol higher in energy than the normal isomer (Figure 5), and it has a geometry that is rather different from those in Figures 4 and 5. At the MCSCF level of theory, the transition state that connects *n'* with the normal isomer is just 1 kcal/mol above *n'*, the higher of the two isomers (Figure 7). However, this transition state disappears when

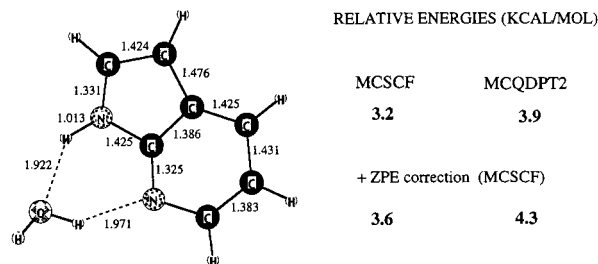


Figure 7. Geometry and energetics for the normal isomer structure obtained at the end of the IRC path. Energies are relative to the excited-state normal isomer shown in Figure 5.

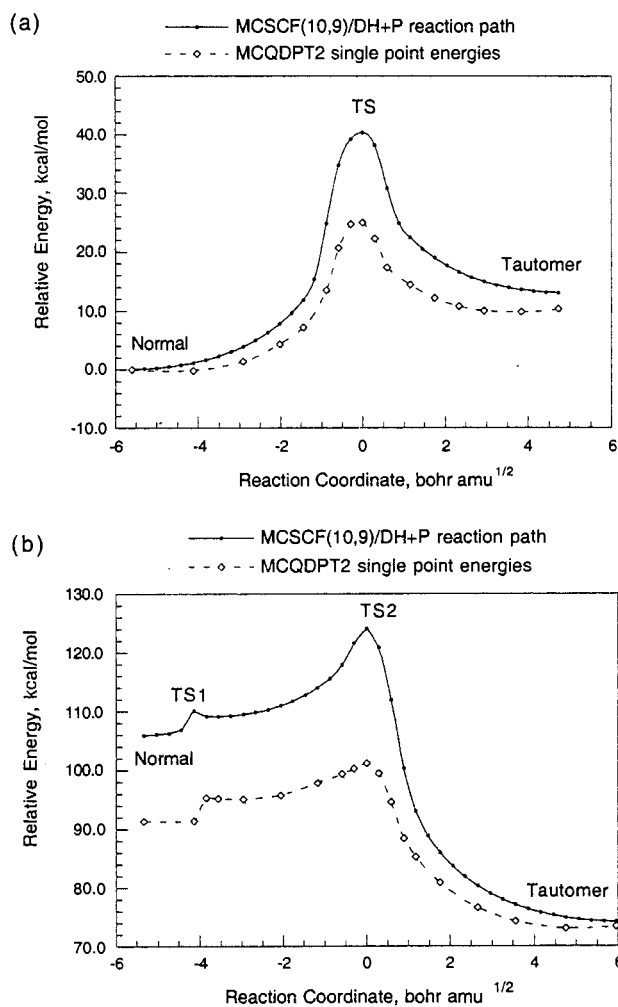


Figure 8. Reaction path for tautomerization of 7-azaindole+H₂O: (a) ground and (b) excited state.

dynamic correlation is included at the MCQDPT2 level, suggesting that the only normal isomer in the excited state of the 7-azaindole + H₂O complex is the structure shown in Figure 5 and that *n'* may not be a minimum on the excited-state potential energy surface. Use of a larger active space that included contributions from σ , as well as π , orbitals could also result in the disappearance of this local minimum.

A composite minimum energy path for the tautomerization process in the excited state of 7-azaindole-water is shown in Figure 8. The normal structure (Figure 5) is connected with the tautomer (Figure 5) via a transition state (Figure 6). The MCQDPT2 energy (including vibrational zero point corrections) that corresponds to this transition state is about 6 kcal/mol above that of the normal structure. Therefore, 6 kcal/mol is the estimated upper limit for the tautomerization barrier on the

excited state surface. This estimate is slightly larger than the experimental value of 2–3 kcal/mol for the excited-state barrier in aqueous solution.^{1,4} It is likely that this barrier would decrease if the geometry optimizations and reaction path were performed at the MCQDPT2 level of theory. The incorporation of additional water molecules, accounting for tunneling, and the use of higher levels of theory are all expected to reduce the calculated activation energy further. Therefore, these results suggest that the tautomerization reaction should occur very easily on the lowest excited state of 7-azaindole in the presence of water or another polar solvent. It was shown previously that the addition of a methanol molecule has the same stabilizing effect on the ground-state reaction barrier as a water molecule.⁷

Conclusions

The calculations presented in this work predict that complexation of 7-azaindole by one water molecule dramatically reduces the barrier for tautomerization on the ground-state potential energy surface and introduces a small red shift in the electronic absorption, in agreement with experiment. Most importantly, it is found, again in agreement with experiment, that the normal and tautomeric structures reverse their energetic order and that the barrier for the tautomerization on the excited electronic state surface is quite small. Consequently, the excited state tautomerization should be facile. Of course, the present work includes just one water molecule and therefore relates most directly to the gas-phase cluster experiments of Miller and co-workers.⁵ At this time, it is not possible to directly compare these cluster studies with the simulations of excited states in the bulk;^{3,6} however, future calculations will incorporate the effective fragment potential model for water¹³ and molecular dynamics models¹⁴ with the ab initio methods presented here to simulate bulk behavior.

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