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Tautomerization of Adenine Facilitated by Water: Computational Study of Microsolvation

Ho-Sung Kim,[†] Doo-Sik Ahn,[†,‡] Sang-Yoon Chung,[†] Sang Kyu Kim,[‡] and Sungyul Lee*[,†]

College of Environmental Science and Applied Chemistry (BK21), Kyunghee University, Kyungki-do 449-701, Korea, and Department of Chemistry (BK21), Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

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We present calculations for the mechanism and the barrier heights of tautomerization of adenine. We find various pathways for the 9(H) ↔ 7(H) and 9(H) ↔ 3(H) tautomerization. One mechanism for the 9(H) → 7(H) tautomerization involves an sp^3- or carbene-type intermediate, whereas the other proceeds via imine intermediates. Tautomerization from the 9(H) tautomer to 7(H) or 3(H) is predicted to occur with a very large activation barrier (60−70 kcal/mol), indicating that the processes may not occur readily in the gas phase. Interactions with the water molecule(s) are found to lower the barrier tremendously. We suggest that dramatic lowering of the 9(H) → 3(H) and 9(H) → 7(H) barriers by microsolvating water molecules may facilitate the formation and observation of the 7(H) and 3(H) tautomers in the solution phase.

I. Introduction

Biomolecules[1−18] are known to exist as a variety of conformers with small energy differences (usually less than 5 kcal/mol). Since thermal energy may easily transform one conformer to another, a number of lower energy conformers may coexist in room-temperature solution phase. The solvent environment may profoundly affect the structures, relative stability, and reactivity of biomolecules, and the binding solvent molecules may also directly participate in the dynamic processes.[11,12,14]

Adenine−water clusters[15−22] received considerable attention recently. Coexistence of the 9(H), 7(H), and 3(H) tautomers in aqueous solution was reported by several groups[21,22] and was attributed to small differences in the relative energies of the tautomers in the solution phase. (For example, Hobza and coworkers[15] recently calculated that the relative free energy of 7(H) and 3(H) tautomers is only 2.5 and 2.8 kcal/mol above 9(H) tautomer in aqueous solution. Gu and Leszczynski[16] reported that the 7(H) tautomer is 4 kcal/mol above 9(H) in free energy under the influence of electrostatic interactions with bulk water.) In contrast to the numerous studies on the thermodynamic stability of the adenine tautomers both in the gas phase and in solution, much less focus has been paid on the dynamic aspects of tautomerization and the effects of solvent thereon. Gu and Leszczynski[16] examined the amine ↔ imine tautomerization of 9(H) and 7(H) tautomers by proton transfer from the amino group to the N1 atom, and they found that a water molecule may lower the barrier by as much as 27 kcal/mol. The detailed pathways of the 9(H) → 7(H) and 9(H) → 3(H) tautomerization, and the effects of solvent are of keen interest concerning the mechanism of formation of the higher energy tautomers in the solution phase. It is well known that the 7(H) and 3(H) tautomers are quite higher in energy (by 7−9 kcal/mol) than the most stable 9(H) tautomer in the gas phase and thus unfavorable for observation. Once these tautomers dissolve in water, however, they become close in energy to the 9(H) tautomer to be observed experimentally. In addition to the thermodynamic considerations, dynamic pathways and the magnitude of barrier for the 9(H) → 7(H) and 9(H) → 3(H) tautomerization under the influence of solvent (water) must be systematically studied to fully understand these experimental observations[21,22] of the 9(H), 7(H), and 3(H) tautomers in the solution phase.

In the present study, we report various mechanisms of adenine tautomerization. We predict that water molecules may dramatically (by more than 40 kcal/mol) lower the barrier of adenine tautomerization, thus facilitating the process. Our calculated results are discussed with regard to the observed coexsistence of several tautomers of adenine in the solution phase.

II. Computational Methods

We employ the GAUSSIAN 03 set of programs.[23] The density functional theory (B3PW91)[24,25] and MP2 methods are employed with the 6-311+G(d,p) basis set. The stationary structures are confirmed by ascertaining that all the harmonic frequencies are real. The structure of the transition states are obtained by verifying that one of the harmonic frequencies is imaginary and also by carrying out the intrinsic coordinate (IRC) analysis for the reaction pathway. The free energy of the adenine tautomers in aqueous solution is calculated by the B3PW91/6-311+G(d,p)/IEFPCM[26,27] method. We take the zero-point energies into consideration for calculating the energy, free energy, and the reaction barrier.

III. Results

Tautomers of adenine have been studied mostly focusing on the relative stability and abundance. It is well known that 9(H) adenine is the lowest-energy conformer in the gas phase and that the 7(H) and 3(H) tautomers are much higher in energy. In the solution phase, however, the 9(H), 7(H), and 3(H) adenine have been found to coexist,[21,22] suggesting that the 7(H) and 3(H) tautomers may be stable and abundant due to the effects of interactions with solvent. We calculate (Figure 1 and Table 1) that the 7(H) and 3(H) adenine are 8.4 (7.7) and 8.2

* To whom correspondence should be addressed. E-mail: sylee@khu.ac.kr.
† Kyunghee University.
‡ Korea Advanced Institute of Science and Tehcnology.

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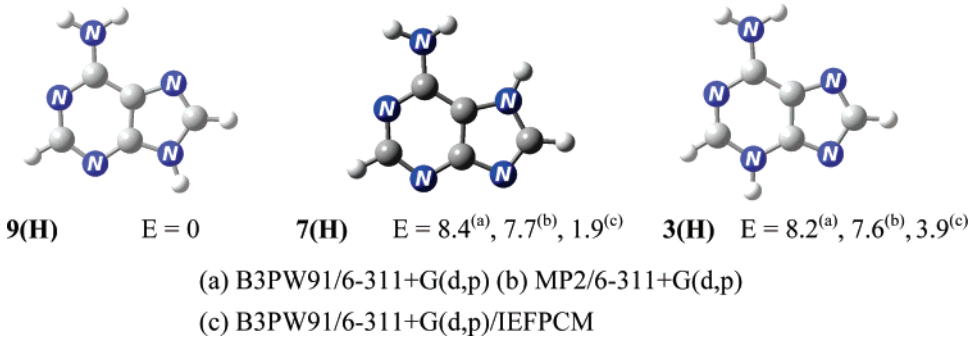

Figure 1. Structures and relative energies (kcal/mol) of adenine tautomers.

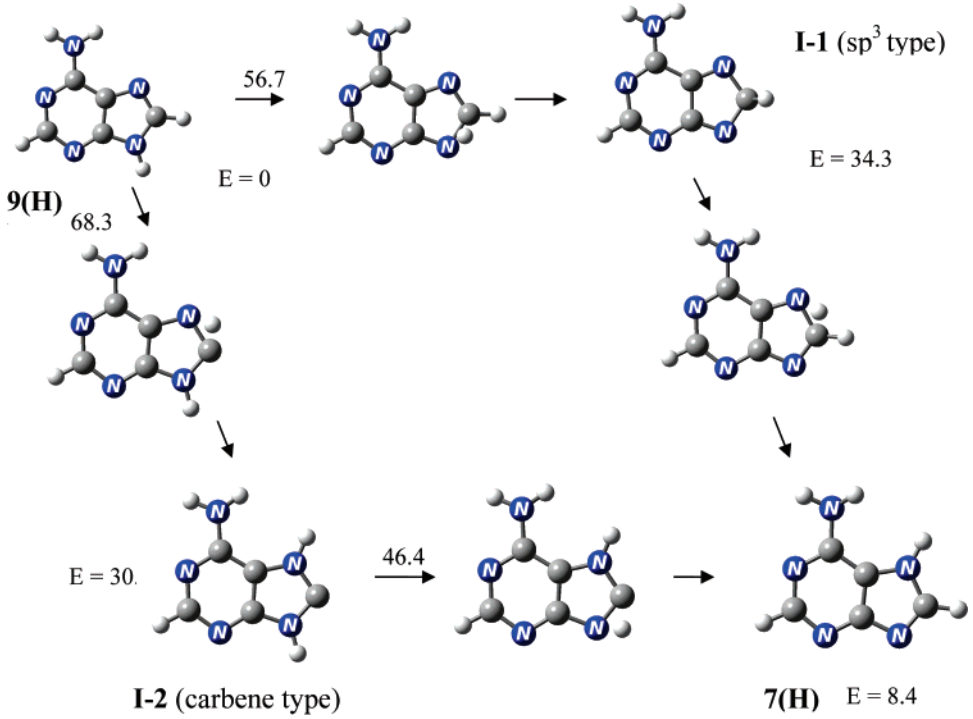

Figure 2. Mechanism of 9(H) ↔ 7(H) tautomerization via carbent-type and sp^3-type intermediates (B3PW91/6-311+G(d,p)). (Barriers and relative energies in kcal/mol.)

TABLE 1: Electronic Energy (*E*, hartree), Zero-Point Energy (ZPE, kcal/mol), Relative Energy (Δ*E*, kcal/mol), and Relative Free Energy at 298 K (ΔG_{298K}, kcal/mol) of Adenine Tautomers

	E	ZPE	Δ*E* (gas phase)	ΔG_{298K} (soln)
9(H)	−467.26904[a] (−466.17244)[b]	70.30439[a] (70.10261)[b]	0[a] (0)[b] (0)[c]	0[d]
3(H)	−467.25623 (−466.15832)	70.50209 (68.83330)	8.2 (7.6) (9.2)	1.9
7(H)	−467.25563 (−466.16020)	70.31103 (70.13395)	8.4 (7.7) (7.8)	3.9
I-1	−467.21276	69.31979	34.3[a]	
I-2	−467.22129	70.63746	30.3	
IM1	−467.24149	70.61531	17.6	
IM2	−467.22975	70.21440	24.6	
IM3	−467.19992	70.74306	43.8	
IM4	−467.24234	70.56086	16.6	

[a] B3PW91/6-311+G(d,p). [b] MP2/6-311+G(d,p). [c] MP2/aug-cc-pVDZ//RI-MP2/TZVPP (ref 15). [d] B3PW91/6-311+G(d,p)/IEFPCM.

(7.6)kcal/mol, respectively, above the 9(H) tautomer at B3PW91/6-311+G(d,p) (MP2/6-311+G(d,p)) level of theory. Our calculated relative energies are in good agreement with those obtained by Hobza and co-workers,[15] who employed the MP2/aug-cc-pVDZ//RI-MP2/TZVPP method (Table 1). Considering the high relative energy (8.2∼8.4 kcal/mol) of the 7(H) and 3(H) tautomers relative to the 9(H) adenine, it seems that they are thermodynamically less favorable for observation in the gas phase. The relative free energy of the 3(H) and 7(H) tautomers in the solution phase are also given in Table 1, calculated to be 1.9 and 3.9 kcal/mol higher than the 9(H) tautomer in aqueous solution.

By carrying out the IRC analysis, we find various competing reaction pathways for tautomerization from 9(H) to 7(H) adenine in the gas phase. The mechanism may or may not involve the amino group. Figure 2 depicts the pathway in which the amino group plays no role. We find two competing mechanisms: In the first pathway (sp^3-type), the proton at the 9-N position first

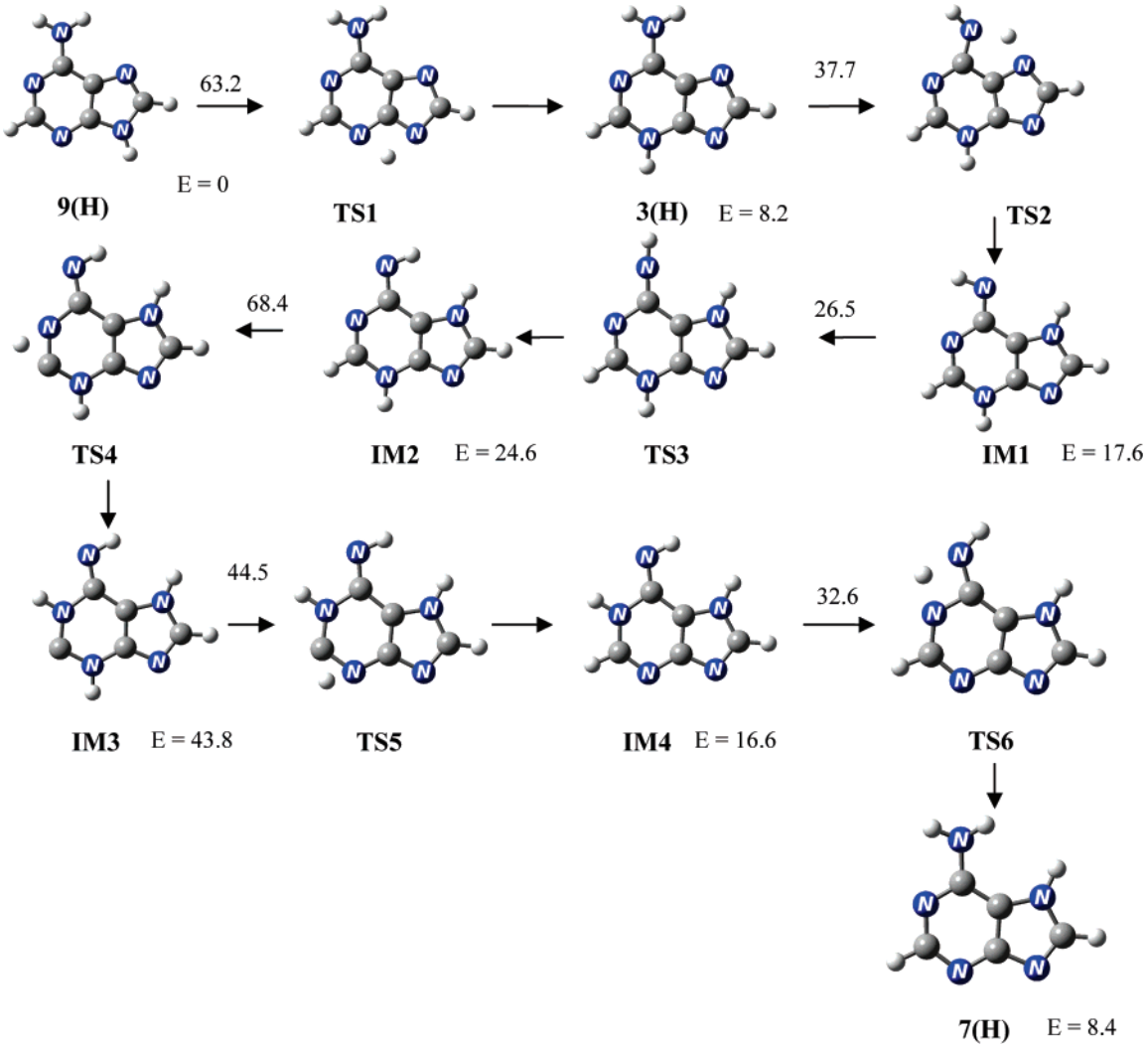

Figure 3. 9(H) ↔ 7(H) tautomerization via imine intermediates (B3PW91/6-311+G(d,p)). (Barriers and relative energies in kcal/mol.)

moves to the 8-C atom, forming an intermediate (I-1) with sp^3-type bonding at the 8-C atom. The proton is then transferred to the 7-N atom. The ZPE-corrected barrier from 9(H) adenine to the intermediate (I-1) is calculated to be large (~57 kcal/mol) by the B3PW91 method. In the second pathway (carbene-type), the proton at 8-C position is first transferred to 7-N, forming a carbene intermediate (I-2). Subsequently, the proton at 9-N moves to 8-C, producing the 7(H) adenine. The barrier (68 kcal/mol) from the 9(H) adenine to (I-2) is calculated to be larger (by 12 kcal/mol) than that to (I-1) in the first mechanism. It seems that the 9(H) tautomer would not easily transform to the 7(H) tautomer by these pathways due to the large barrier. Figure 3 shows that the amino group may be directly involved in the proton transfer processes and the tautomerization occurs via a series of imine intermediates. The mechanism initiates from the 9(H) → 3(H) tautomerization, followed by proton transfer from the amino group to 7-N atom. A series of proton transfer occurs between the neighboring C and N atoms, eventually regenerating the amino group and producing the 7(H) adenine. The barrier in the rate-determining step (IM2 → IM3) of the 9(H) → 7(H) tautomerization in the imine mechanism is especially high (68 kcal/mol), presumably because the process involves an awkward proton transfer between the neighboring N and C atoms. The large overall barrier in the imine mechanism depicted in Figure 3 may also make the 9(H) → 7(H) tautomerization very difficult to occur. The first step in the imine mechanism is the 9(H) → 3(H) tautomerization, and the process involves a transfer of a hydrogen atom from 9-N to 3-N with large barrier (63 kcal/mol). Thus, it seems that the 9(H) → 3(H) tautomerization would not proceed readily in the gas phase. Therefore, the presence of 7(H) and 3(H) tautomers in aqueous solution may be attributed to the effects adenine−water interactions.

We find that some tautomerization pathways are profoundly affected by the microsolvating water molecules (Figure 4). For example, we find that a binding water molecule dramatically lowers the 9(H) → 3(H) barrier from 63 to 16 kcal/mol, indicating that the water molecules may act as a catalyst. By carrying out the IRC analysis, we find that the mechanism of this solvent-assisted reaction is a concerted double proton transfer. Furthermore, binding of two water molecules may still lower the barrier to 9.7 kcal/mol, promoting the 9(H) → 3(H) tautomerization by a concerted triple proton transfer mechanism. This is very interesting, because this very low barrier for the 9(H) → 3(H) tautomerization under the influence of water molecules may suggest that the 9(H) adenine is prone to isomerization to produce the 3(H) tautomer in considerable amount, as observed experimentally in the solution phase.[21] Some steps in the imine mechanism depicted in Figure 3 may also be facilitated by water molecules, for example, the barrier of the 3(H) ↔ IM1 process decreases from 38 to 9.5 kcal/mol (Figure 4b). The rate-determining step (IM2 → IM3), in which a proton is transferred from nitrogen to neighboring carbon atom,

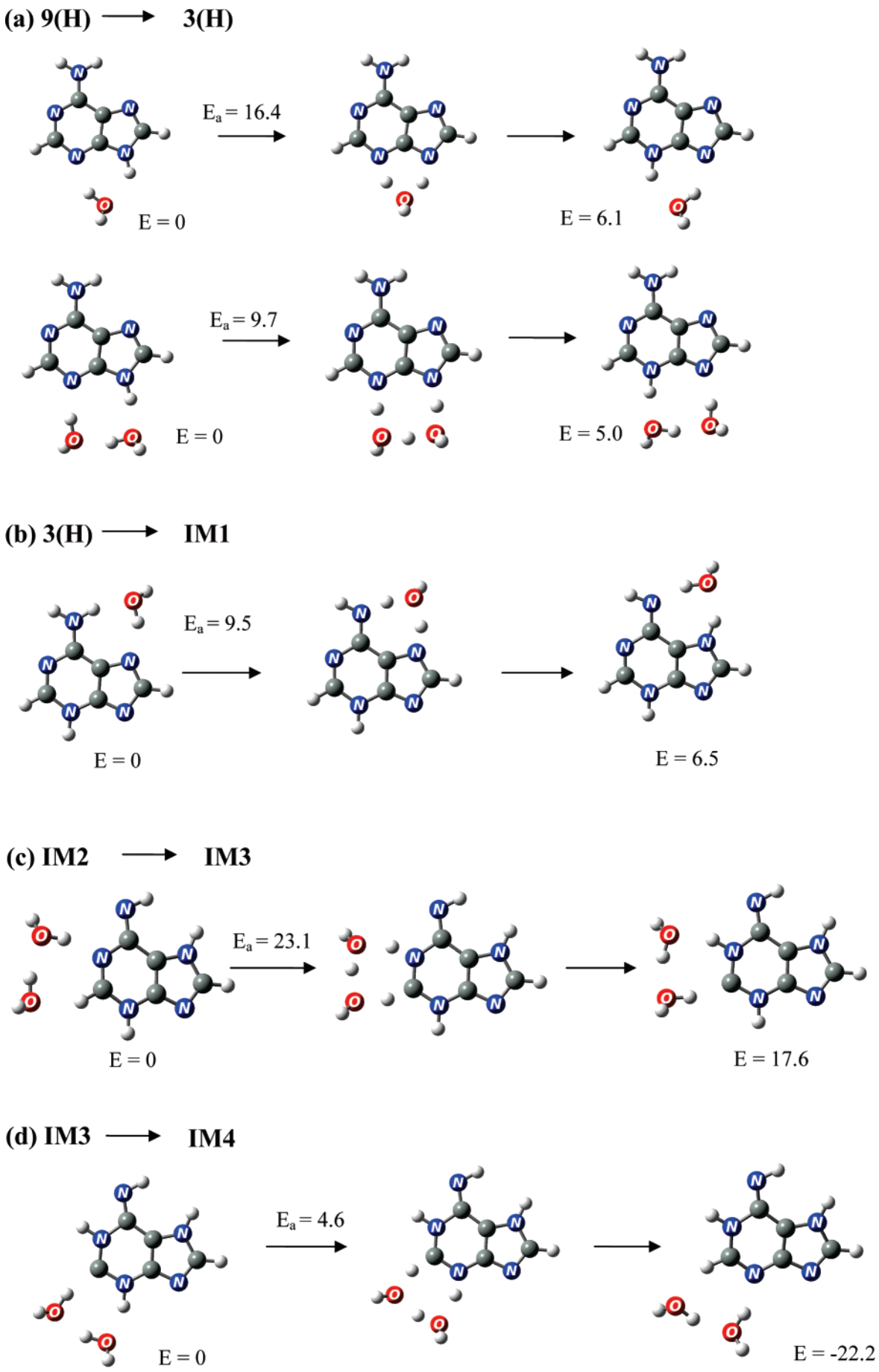

Figure 4. Part 1 of 2.

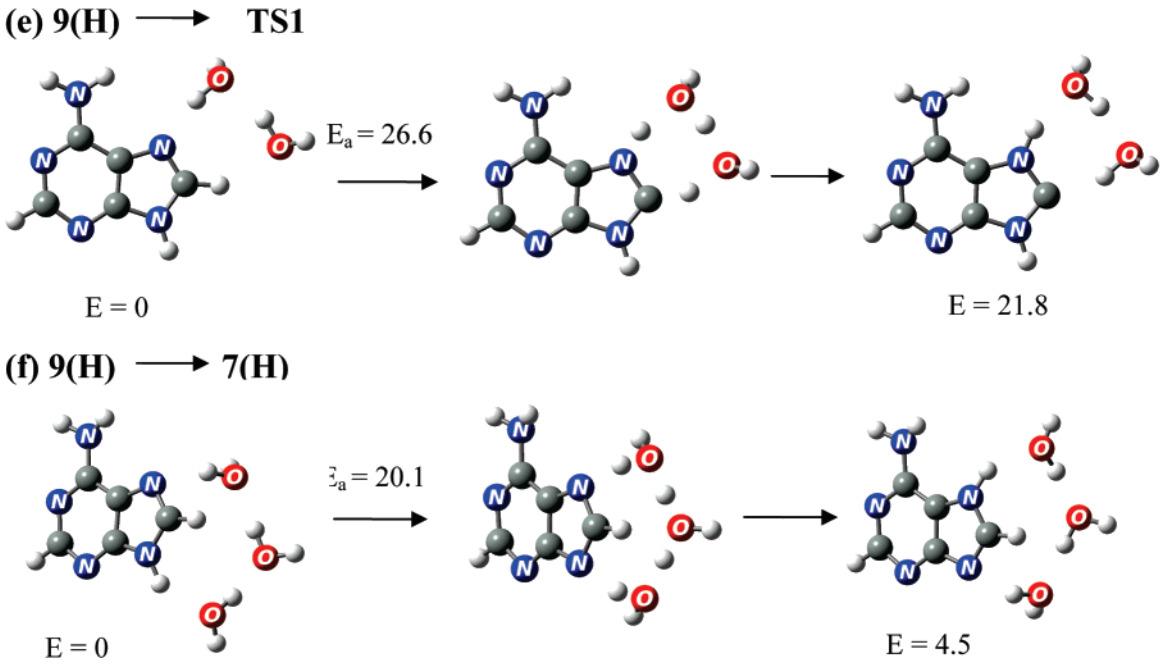

Figure 4. Part 2 of 2. Tautomerization processes facilitated by water. (Barriers and relative energies in kcal/mol.)

is not much affected by a single microsolvating water molecule presumably because the geometry of interacting −CH, H_2O, and −N is not ideal for cyclic proton transfer processes. The barrier height is, however, dramatically lowered from 68 to 23 kcal/mol by the intervention of *two* water molecules through a "proton wire"[28] for triple proton transfer (Figure 4c). Similarly, the IM3 → IM4 process is also accelerated by two water molecules lowering the barrier by ∼40 kcal/mol (Figure 4d). The last step of the imine mechanism (IM4 → 7(H)) was treated by Gu and Leszczynski,[16] of which the barrier was found to decrease by ∼27 kcal/mol as the result of interactions with a water molecule. This efficiency of water molecules for lowering the barrier is also seen in the mechanism depicted in Figure 2. Two water molecules interact to facilitate the proton transfer from the 8-C to 7-N in the first step of the 9(H) → 7(H) tautomerization via the carbine-type intermediate, lowing the barrier from 68 to 27 kcal/mol (Figure 4e).

Finally, we predict that the 7(H) ↔ 9(H) tautomerization may occur *directly* between 9-N and 7-N via three water molecules by a quadruple proton transfer process. The water molecules lying above the adenine ring again acts as a proton wire. The barrier of this process is calculated to be quite small (∼20 kcal/mol). These calculated results clearly indicate that the tautomerization between 7(H), 9(H), and 3(H) adenine is significantly promoted by the microsolvating water molecules. Considering that these tautomers are of similar relative free energy in aqueous solution,[15] our demonstrated solvent-assisted tautomerization processes may work as a key step producing the 7(H) and 3(H) tautomers in the solution phase. It would be of keen interest to experimentally examine the mechanism of adenine tautomerization predicted in this work.

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