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Solvent-mediated tautomerization of purine: single to quadruple proton transfer

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Abstract

We present calculations for the structures and the tautomerization reaction of purine and purine – $(H_2O)_n$ ($n = 1$–3) clusters. We find two pathways (via the carbene and the sp^3-type intermediate) for the $9 \leftrightarrow 7$ tautomerization of bare purine. The barrier heights for the $9 \rightarrow 3$ and $9 \rightarrow 7$ tautomerization of bare purine are calculated to be large (60–70 kcal/mol). Hydrogen bonding with the water molecule(s), however, dramatically lowers the $9 \rightarrow 3$ barrier by the concerted multiple proton transfer mechanism, favoring the formation of the conformer 3(H)- relative to the 7(H)-purine in the microsolvated environment, in contrast to the gas phase or the aqueous solution.

1. Introduction

Biomolecules may usually exist as a variety of conformers. Since the energy difference between the conformers is small (usually at most 5 kcal/mol), thermal energy may easily transform from one conformer to another in room-temperature solution phase. The biomolecule–solvent clusters [1–9] have been found to be very useful to study the effects of solvation on the structure and reactivity of biomolecules. Amino acid–water or nucleic acid base–water clusters are excellent examples. For example, the zwitterionic form of amino acids, which is not stable in the gas phase, may become kinetically stable (that is, thermodynamically less stable than other conformers, but stable enough with finite lifetime for the experimental observation) when at least two water molecules are binding [10–13]. Besides affecting the structures and the properties of biomolecules, the binding solvent molecules may also profoundly influence the reactivity by altering the environment around the solute, or they may directly participate in the dynamic processes as in solvent-mediated chemical reactions [14]. In some cases, the solvent molecules may even act as catalysts [14–16].

The cluster (or supramolecular) approach to study the solution phase is based on the assumption that they are intermediary system bridging the gas phase and the solution phase. In many studies the effects of microsolvation on the properties of the solute molecule were indeed found to change gradually as a function of the number of solvent molecules. In some cases, however, this transition from the gas phase to the solution phase via the cluster phase may not be smooth, and some peculiar properties of the cluster may appear. For example, the binding solvent molecules may lead to reactions that cannot occur either in the gas phase or the solution phase. In such case, the clusters may serve as useful system for providing novel properties and/or reactivity. In the present study, we report that the binding water molecules may dramatically alter the structure and reactivity of the purine molecule that are totally different from the gas phase or aqueous solution. We study the tautomerization processes of purine, which is the parent molecule for the DNA bases adenine [17–20] (6-aminopurine) and guanine (2-amino-6-oxypurine) [9,20–22] in the presence of the binding water molecule(s). We report the dynamic pathways between the

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7(H)- and 9(H)-purine. We also find that the hydrogen bonding with the water molecule(s) significantly affects the barrier heights for some tautomerization reactions. The water molecule(s) may directly participate, acting as catalyst, thereby drastically altering the kinetic stability of tautomers. The solvent-mediated mechanism, from the concerted double to quadruple proton transfer processes, is described in detail.

2. Computational methods

We employ the GAUSSIAN 94 and the GAUSSIAN 98W set of programs [23]. The MP2 and the density functional theory (B3PW91) [24,25] methods are employed with the 6-31G+(d,p) basis set. We find that the two methods give very similar results for the relative energies of the conformers and the barrier heights for isomerization. The stationary structures are confirmed by ascertaining that all the harmonic frequencies be real. The structure of the transition states are obtained by verifying that one the harmonic frequencies be imaginary, and also by carrying out the intrinsic coordinate analysis for the reaction pathway. We took zero point energies into consideration for calculating the energy, Gibbs function and the reaction barrier.

3. Results

The thermodynamic stability (that is, relative Gibbs function) of the tautomers of purine is well known, and 9(H)-purine is the lowest-energy conformer in the gas phase [26,27]. We calculate that 7(H)-purine is higher in energy than 9(H)-purine by 3.9 (3.8) kcal/mol at MP2/6-31+G(d,p) (B3PW91/6-31+G(d,p)) level of theory (the relative Gibbs function at 298 K, $G_{298\ K}$, is calculated to be quite similar to the relative energy, as can be seen in Fig. 1). We focus on the tautomerization between the three lowest energy tautomers of purine, 9(H)-, 7(H)- and 3(H)-purine. By carrying out the intrinsic reaction coordinate (IRC) analysis employing the B3PW91 method, we find two competing reaction pathways for tautomerization from 9(H)- to 7(H)-purine as shown in Fig. 1. In the first pathway, the proton at the 9-N position first 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 is transferred to the 7-N atom. The ZPE-corrected barrier from 9(H)-purine to the intermediate (I-1) is calculated to be 57.09 (58.9) kcal/mol, with the (I-1) structure located 39.93 (40.0) kcal/mol higher above 9(H)-purine, by the MP2 (B3PW91) method. In the second pathway, the proton at 8-C position is first transferred to 7-N, forming a carbene

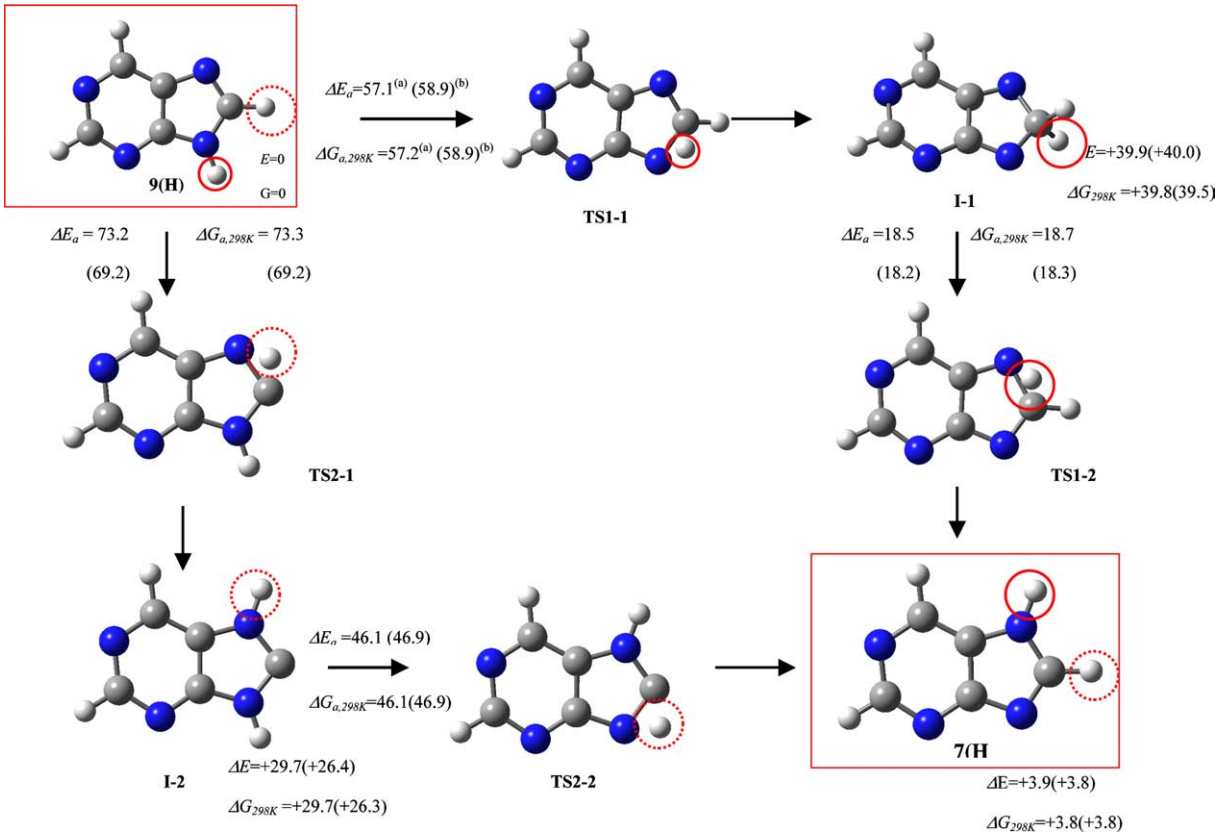

Fig. 1. Mechanism of tautomerization between 9(H)- and 7(H)-purine via sp^3-type intermediate (I-1) and via carbene intermediate (I-2). (a) MP2/6-31+G(d,p) (b) B3PW91/6-31+G(d,p).

intermediate (I-2). Subsequently, the proton at 9-N moves to 8-C, producing 7(H)-purine. The barrier (73.23 kcal/mol, MP2) from 9(H)-purine to (I-2) is calculated to be larger (by 16.14 kcal/mol) than that to (I-1) in the first mechanism. The intermediate (I-2) in the latter mechanism, however, lies lower (by 13.26 kcal/mol) than (I-1). Since the barriers from 7(H)-purine either via the path (A) or the path (B) in Fig. 1 are so large, tautomerization from 9(H) to 7(H)-purine may not occur in the gas phase. We also checked if other indirect pathways (for example, the $9 \rightarrow 3 \rightarrow 1 \cdots \rightarrow 7$) for $9 \rightarrow 7$ tautomerization could exist. Since the proton transfer from 6-C to 7-N position is not feasible, however, it seems that the two pathways described in Fig. 1 are the only possible routes for $9 \leftrightarrow 7$ tautomerization in the gas phase. This large barrier of $9 \rightarrow 7$ tautomerization seems to be the reason that 9-(H) tautomer was found to predominate in low-temperature rare-gas matrices [26,27]. To our best knowledge, these pathways are reported for the first time.

We find that the dynamic pathways and the kinetic stability of the purine conformers are affected profoundly by the interactions with the water molecules. The proton transfer mechanism for the $9 \leftrightarrow 7$ tautomerization in the presence of binding water molecules via the carbene intermediate are depicted in Fig. 2. The process is very complicated, involving direct participation of two water molecules in the proton transfer processes. First, the water molecule binding to 7-N of 9(H)-purine – $(H_2O)_2$ induces transfer of a proton to 7-N, producing the carbene intermediate (I2-1) by the concerted double proton transfer mechanism. The barrier height for this first step is calculated to be about 41 kcal/mol (B3PW91), 28 kcal/mol lower than that for bare purine (Fig. 1), indicating that the water molecule catalyzes the process. The other water molecule bridging the 3-N and 9-H then moves rather violently and almost freely (notice the small barrier in Fig. 2), forming the intermediate (I2-2). The latter water molecule then mediates the transfer of a proton from 9-H to 8-C, again via the double proton transfer mechanism. We also carried out similar analysis for the effects of water molecules on the tautomerization via the sp^3-type intermediate, but we find very small differences from the case of bare purine, rather slightly increasing the barrier from 9(H)-purine – $(H_2O)_2$ to the transition state. Since the barrier height for the process catalyzed by two water molecules involving the carbene intermediate is significantly lower (by about 18 kcal/mol) than that via the sp^3-type intermediate, the probability of $9 \leftrightarrow 7$ tauto-

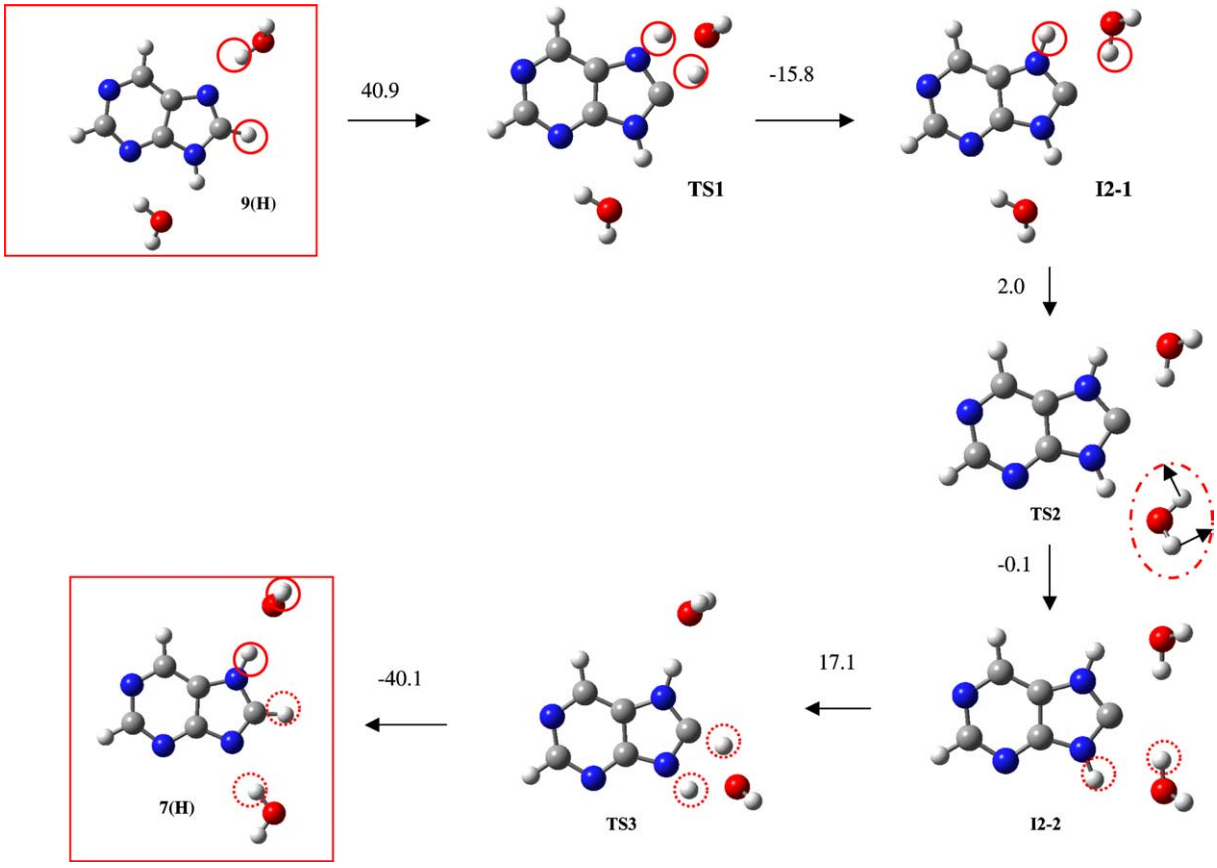

Fig. 2. Mechanism of solvent-mediated tautomerization between 9(H)- and 7(H)-purine via the carbene intermediate (I1-2) (B3PW91/6-31+G(d,p)). Reaction coordinate is shown for TS2.

merization in the gas phase cluster environment involving the carbene intermediate will be much larger than that via the sp^3-type intermediate structure, in contrast with the case of free purine.

The pathway from the bare 9(H)- to the 3(H)-purine is much simpler, as depicted in Fig. 3(1), with the proton transferring directly from 9-N to 3-N via a single transition state similarly to the case of adenine [16]. The barrier from the bare 9(H)-purine is calculated to be 66.9 (64.7) kcal/mol by the MP2 (B3PW91) method, more or less similar to those of the $9 \rightarrow 7$ tautomerization. Since the 3(H)-purine lies 6.9 kcal/mol (MP2) higher than the 7(H)-purine, the competition between the $9 \rightarrow 7$ and the $9 \rightarrow 3$ tautomerization processes would be thermodynamically determined, favoring the former. This implies that the thermodynamically more stable 7(H)-purine may be more abundant than the 3(H) tautomer in the gas phase in the absence of water molecules. The effects of microsolvation are, however, found to fundamentally alter the relative stability of the 9(H)- and the 3(H)-purine. As shown in Fig. 3(2), we find that a binding water molecule dramatically lowers the $9 \rightarrow 3$ barrier, from 66.9 (64.6) to 20.3 (16.7) kcal/mol by the MP2 (B3PW91) method, indicating that the water acts as catalyst. By carrying out the IRC analysis, we find that the mechanism of this *solvent-assisted* reaction is concerted double proton transfer. Furthermore, we find that the binding of two water molecules, depicted in Fig. 3(3), may still lower the barrier to 9.5 kcal/mol (B3PW91), catalyzing the $9 \leftrightarrow 3$ tautomerization by the concerted triple proton transfer mechanism. We also find that *three* water molecules may also catalyze the $9 \leftrightarrow 3$ tautomerization (Fig. 3(4)) with slightly larger barrier height (10.3 kcal/mol, B3PW91) by a *concerted quadruple proton transfer* mechanism, which is, to our best knowledge, reported for the first time. These latter findings clearly suggest that the competition between the $9 \leftrightarrow 7$ and the $9 \leftrightarrow 3$ tautomerization is now *kinetic* in the presence of binding water molecules, rendering the higher energy conformer 3(H)-purine more abundant than 7(H)-purine in the gas phase environment clustering with water molecules. This finding is very intriguing in relation to the experimental observation [28–31] that 9(H) and 7(H) tautomers of purine are more or less in equal amounts in aqueous solution at room temperature, while only 9(H) conformer is observed in the gas phase [32]. Thus, our present study clearly demonstrates that biomolecule–water clusters may not merely be intermediate system bridging the gas phase and the solution phase, but that biomolecules may behave in a fashion that is very different from either the gas phase or the solution phase. It will be extremely interesting to

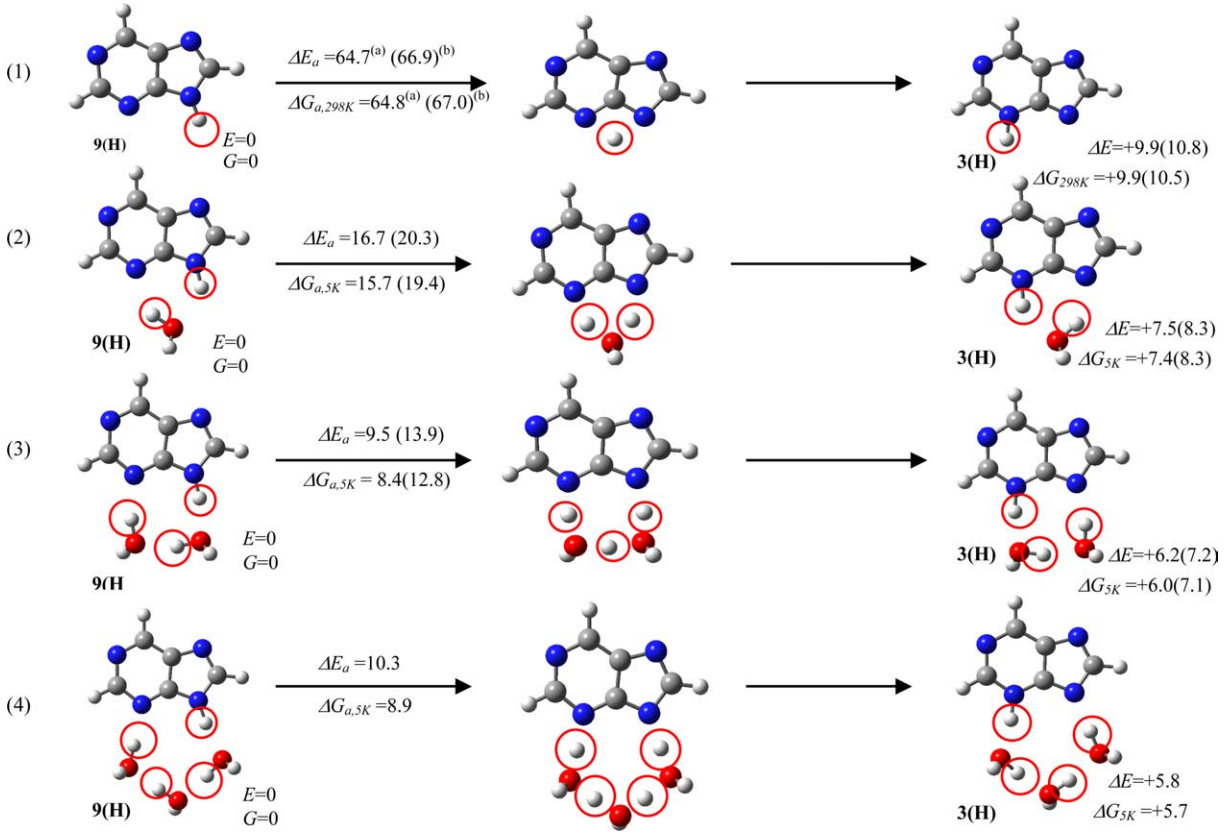

Fig. 3. Mechanism of tautomerization between 9(H)- and 3(H)-purine-$(H_2O)_n$ ($n = 0$–3) clusters by single, double, triple and quadruple proton transfer. (a) B3PW91/6-31+G(d,p) (b) MP2/6-31+G(d,p).

study the present findings for purine–water clusters experimentally.

Acknowledgements

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