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Effects of Cu^+ on Proton Transfer Processes in Inosine-Cytosine Base Pair

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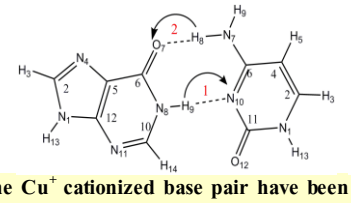
Abstract: **The influence of Cu^+ metal cation binded to different sites of inosine and cytosine on the proton-transfer reaction in inosine-cytosine (IC) base pair has been studied by B3LYP/6-311++G (d,p) method. Our results show that Cu^+ could react with inosine-cytosine base pair at various sites to form three stable adducts. For Cu^+ binded to N_{11} or N_4 of inosine, only the single proton-transferred process occur. The double proton-transfer has been found after Cu^+ coordinated to the O_{12} of cytosine. The proton-transfer processes about inosine-cytosine Cu^+ cationized base pair have been also investigated in water.**



Keywords: Proton-transfer; Base pair; Cu^+; DNA

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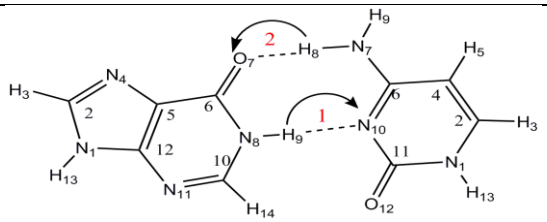
1. Introduction

As we all known, the double helix structure of DNA is stabilized by hydrogen bond. The importance of the proton-transfer in hydrogen bond is connected to the fact that it can contribute to the damage of DNA. The damage of DNA is the major cause of many disease such as cancer, genetic disease and metabolic disease [1-6], so it is important to study the proton-transfer processes of hydrogen bond.

It is well known that metal cations have a great influence on the stability of DNA [7-11]. Recently, an increasing number of people pay more attention to the interaction of various mental cations with base pairs. Gresh et al. investigated the binding of Zn^{2+} to guanine and adenine and to the guanine–cytosine and adenine-thymine base pairs using the SIBFA molecular mechanics and density functional theories approaches in 1999 [11]. In 2004, Noguera and co-workers studied the electrostatic and oxidative effects on intermolecular proton-transfer processes in guanine–cytosine Cu^{2+} cationized base pair using the method of B3LYP density functional [7]. Chunyang Yu et al. researched the interactions of Mg^{2+} and Ca^{2+} binding to adenine, cytosine, guanine, and thymine at different sites using a high-lever quantum chemical method in 2012 [12]. All this researches show that the influence of metal cation to base pairs is not negligible, the metal cation can modify the length of hydrogen bond or contribute to proton-transfer in base pairs.

In recent years, most of the researches focused on the interaction of metal cation binding to base pairs such as adenine-thymine or guanine–cytosine, fewer researches focused on the interaction of mental cation binding to inosine-cytosine base pair [13-20]. In this work, we will discuss the proton-transfer processes in IC (inosine-cytosine) Cu^+ cationized base pair.



Scheme1: Single Proton Transfer Processes for I-C Base Pair.

2. Method

Full geometries of considered structures have been optimized using the three-parameter B3LYP [21, 22] density functional. This approach has been shown to yield reliable geometries for many kinds of system, especially for studying transition-metal ligand systems [23, 24]. All calculations in this paper are carried out using 6-311G++ (d,p) basis set [25-27] for all atoms as implemented in the Gaussian 09 [28] set of program package. The vibrational frequencies of both resultant and reactant have been calculated at the same lever of theory used for their geometry optimization, so as to identify the optimized configuration is the minimum of potential energy surface [23].

Table 1. Total and Relative Energies of (GC + Cu^+) Base-Pair Radicals

	total energy (Eh)/relative energy (kcal/mol)		
	WC	DTS	DPT
$Cu^+(I_{N4}C)$	-2522.7/0.00	-2522.7/2.4	-2522.7/0.5
$Cu^+(I_{N11}C)$	-2522.7/20.3	-2522.7/22.3	-2522.7/20
$Cu^+(IC_{O12})$	-2522.7/24.3	-2522.7/40.2	-2522.7/39.3

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To examine solvent effects on the proton-transfer in IC Cu^{2+} cationized base pair, the polarizable continuum model (PCM) [29, 30] has been implemented and the same method and basis set used for gas phase species have been adopted.

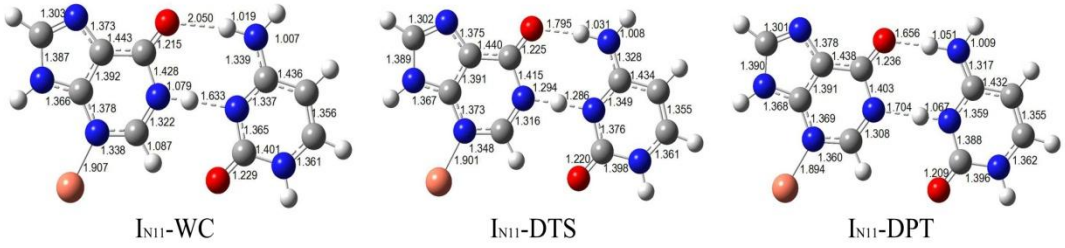

Figure 1. Optimized structures in the single proton-transfer process of Cu^{+}•I_{N11}-C.

3. Results and Discussion

Different single proton-transfer processes of IC base pair have been shown in Scheme 1. Figures 1-3 display the optimized structures about the different proton-transfer processes in the IC Cu^{2+} cationized base pair. The label Cu^{+}•I_{N11}-C means Cu^{+} has been coordinated to the N11 of inosine. For the explanation of other labels, we can refer to the label Cu^{+}•I_{N11}-C. In this paper, WC, DTS, DPT represent conventional state, transition state and transferred product repectively.

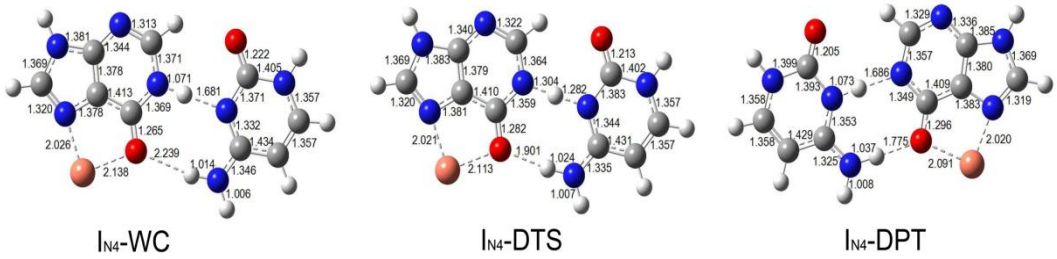

Figure 2. Optimized structures in the single proton-transfer process of Cu+•IN4-C.

3.1. Relative Energies

Total and relative energies of optimized structures about the various proton-transfer processes in (IC+Cu^{+}) base pair are displayed in Table 1. According table 1, we can define the energy of the traditional structure Cu^{+}•I_{N4}-WC as the zero of energy. Obviously, the structure I_{N4}-WC is the most stable and the constructure C_{O12}-WC is the most unstable according to the relative energies. The single proton transfer occur when Cu+ coordinated to N4 and N11 of inosine. The DPT energy (2.0 kcal/mol in I_{N4}-DPT) is higher than the corresponding WC energy (0.00 kcal/mol in I_{N4}-WC), so the WC is more stable. Compared with the isomers Cu^{+}•I_{N4}-C, the DPT energy (83.7 kcal/mol in I_{N11}-DPT) is lower than the corresponding WC energy (85.0 kcal/mol in I_{N11}-WC), the WC is less stable than the DPT. The double proton-transfer product is obtained only from the isomers I-Cu^{+}•C_{O12}. The DPT energy (164.5 kcal/mol in C_{O12}-DPT) is higher than the corresponding WC energy (101.5 kcal/mol in C_{O12}-WC). The energy barrier of reactants is 66.5 kcal/mol, and the DTS energy is higher than DPT energy by 3.5kcal/mol. Therefore, the single proton-transfer reaction may be more common in (IC+Cu^{+}) base pairs.

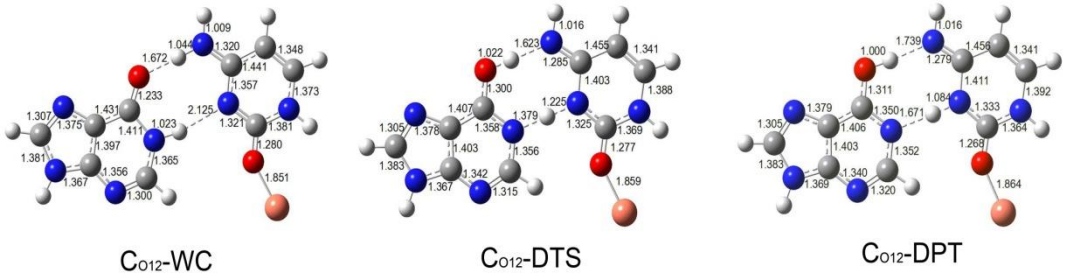

Figure 3. Optimized structures in the double proton-transfer process of Cu+•I−CO12.

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3.2. Geometries

All geometries in this paper have been optimized in B3LYP/6-311++G(d,p) method. Figure 1 shows the optimized structures in single proton-transfer processes of structure Cu^+•I_{N11}-C. As is shown in this figure, bonds (I)N_8–H_9 and (C)N_7–H_8 are increased by 0.625 and 0.032 Å, while bonds (I)O_7 ··H_8 and (C)N_{10} ··H_9 are decreased by 0.394 and 0.566 Å. The (I)O_7–C_6 and (C)N_{10}–C_6 bonds are lengthened, while the (I)N_8–C_6 and (C)N_7–C_6 bonds are shortened.

The Proton H_9 is transferred from inosine to cytosine through the N_8-H_9 ··N_{10} approach when Cu^+ is added to N_4 site of inosine(Figure 2). Bond distances (I)N_8–H_9 and (C)N_7–H_8 are increased, while bonds (I)O_7 ··H_8 and (C)N_{10} ··H_9 are shortened. The bonds (I)O_7–C_6 and (C)N_{10}–C_6 are lengthened, while (I)N_8–C_6 and (C)N_7–C_6 are shortened. The proton-transfer processes of the structure Cu^+•I_{N4}-C is similar to that of structure Cu^+•I_{N11}-C. In this proton-transfer process, hydrogen bonds are shortened, so the effects of Cu+ can make the structure of product more stable.

Concerted double proton-transfer occur when Cu^+ coordinates to O_{12} site of cytosine(Figure 3). The bonds (I)N_8–H_9 and (C)N_7–H_8 are significantly increased, while bonds (I)N_8–H_9 and (C)N_7–H_8 are shortened. At the same time, the bonds (I)O_7–C_6 and (C)N_{10}–C_6 are lengthened and bonds (I)N_8–C_6 and (C)N_7–C_6 are shortened. This result reveals the effects of Cu^+ can also solidify the structure of product in the concerted double proton-transfer processes.

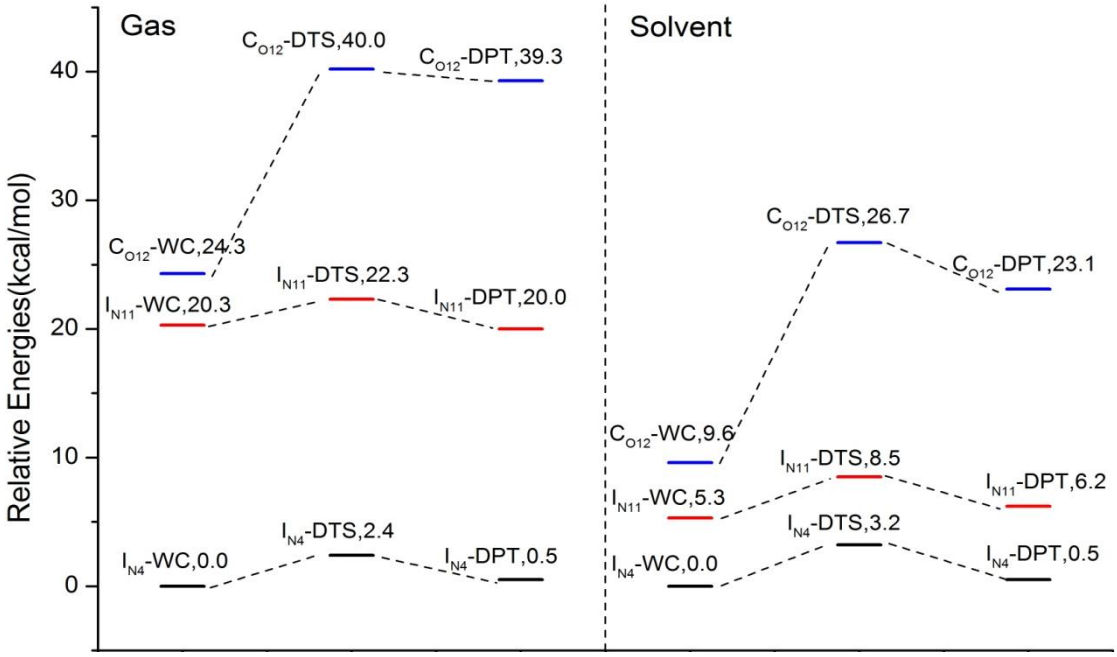

Figure 4. Energy profiles of the proton-transfer for the geometries I-Cu^+•C_{O12}, Cu^+•I_{N4}-C and Cu^+•I_{N11}-C in gas and water.

3.3. Proton Transfer Energy Profiles in the Gas Phase and in Water

The polarizable continuum model (PCM) has been implemented to study the influences of solvent on the proton-transfer processes in (IC+Cu^+) base pair. Figure 4 shows the energy profiles of structures I-Cu^+•C_{O12}, Cu^+•I_{N4}-C, and Cu^+•I_{N11}-C. Concerted double proton-transfer is obtained from the structure I-Cu^+•C_{O12} and single proton-transfer is founded from the structures Cu^+•I_{N4}-C and Cu^+•I_{N11}-C. The energy of the structure is the lowest when Cu^+ coordinates to IC base pair.

The energy of structure I_{N4}-WC lies 0.0 kcal/mol which lower than the energy of structure I_{N4}-DTS and I_{N4} -DPT, so the structure I_{N4}-WC is more stable. Compared with solvent, the energy barrier for single proton-transfer of the structure Cu^+•I_{N4}-C in gas phase is lower than those in water. For Cu^+•I_{N11}-C, I_{N11}-DPT with 20 kcal/mol is lower than the energy of I_{N11}-WC and I_{N11}-DTS in gas phase, the proton-transfer is easily obtained. But the I_{N11}-DPT with 6.2 kcal/mol is higher than the energy of structure I_{N11}-WC and lower than that of structure I_{N11}-DTS. As to the structure I-Cu^+•C_{O12}, C_{O12}-WC with 24.3 kcal/mol is lower than structure C_{O12}-DTS with 40 kcal/mol and C_{O12}-DTS with 39.3 kcal/mol in gas phase, so the structure C_{O12}-WC is more stable. In solvent, similarly to gas phase that the energy of structure C_{O12}-WC lower than those of structure C_{O12}-DTS and C_{O12}-DTS, but the energy barrier is higher than those in the gas phase.

4. Conclusion

The results show that only single proton-transfer

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occurs for N_4 and N_{11}, and the I_{N11}-DPT is more stable. For C_{O12}, the concerted double proton-transfer has been obtained, and the C_{O12}-DPT is less stable than C_{O12}-WC. Only one single proton-transfer has been obtained that the proton H_9 transfers from inosine to cytosine through N_8-H_9 ···N_{10} approach in this study.

Almost all of the structures lie the lower energy in solvent according to the energy profile, so the optimized structures about IC Cu^+ cationized base pair are more stable in solvent. The increase of energy barriers in solvent indicates that the proton-transfer reaction is more favorable in gas phase.

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