

단 신

DNA 염기의 구리(II) 착물에 대한 DFT 연구

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(2006. 10. 28 접수)

DFT Studies on the Copper(II) Complexes of DNA Bases

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(Received October 28, 2006)

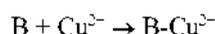
주제어: Cu^{2+} 착물, 금속이온친화도, DNA 염기, 다리 착물

Keywords: Cu^{2+} Complex, Metal ion Affinity, DNA Bases, Bridging Complex

The coordinated metal ions in metal complex of DNA bases play a significant role in the biological action of nucleic acids. Especially, metal cations interact with DNA bases, destroying the hydrogen bonding between the base pairs. The structure of DNA is changed as the result.^{1,2} Therefore, the metal cations affect syntheses, replication and cleavage of DNA. A number of experimental and theoretical studies have been reported for the metal cation interactions with DNA bases.³⁻⁷ Cerda and Wesdemiotis⁸ have reported the interaction of alkali metal ions (Li^+ , Na^+ and K^+) with DNA bases. However the binding sites were not suggested as the suitable to receive the metal cations. Del Ben⁹ have reported the results of a study for the Li^+ complexes of the DNA bases by *ab initio* calculations to determine the optimized structures and stabilization energies. Burda *et al.*¹⁰ have studied on the interaction of guanine and adenine with Zn^{2+} at the HF and MP2 level.

In the present paper, as a continuation of study on the binding of metal cations with DNA bases¹¹⁻¹³ we report a DFT investigation on the interaction of Cu^{2+} with DNA bases. DFT calculations are carried out at B3LYP level^{14,15} of theory with the 6-31G(d,p) basis sets using the Gaussian03 series of program.¹⁶ The metal binding sites for Cu^{2+} complexes were

taken from the previous theoretical data for the protonation sites of DNA bases proposed by Del Bene.¹⁷ The geometries of all structures are fully optimized without any constraint. The vibration frequencies of the optimized structures are also calculated at same level to determine the nature of the stationary points. All the conformers are found to be local minima, with all real harmonic frequencies and all positive Hessian eigenvalues. Zero point corrections are included in association energies. To obtain accurate association energies, basis set superposition errors(BSSE) are also subtracted from the calculated association energies in the full counterpoise(CP) approximation.^{18,19} The copper(II) cation association energies(ΔE) are calculated as the difference of the optimized energy of the base- Cu^{2+} complex [$E(\text{B-Cu}^{2+})$] and the sum of the energies of the base [$E(\text{B})$] and cupric cation monomer [$E(\text{Cu}^{2+})$] for the reaction



RESULTS AND DISCUSSION

In *Fig. 1*, the most significant geometrical parameters of stable Cu^{2+} -DNA bases complexes obtained by B3LYP/6-31G(d,p) computations are reported. The copper(II) cation association energies of DNA

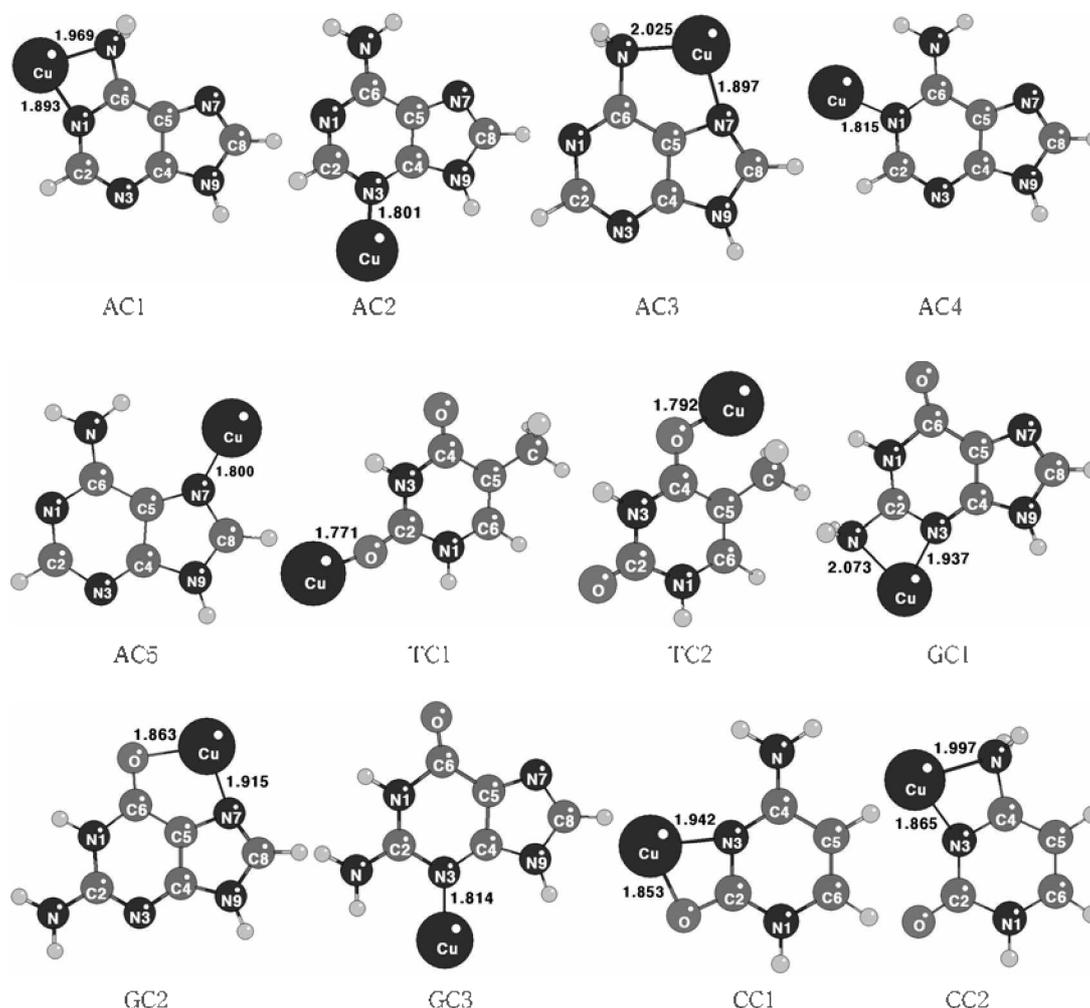


Fig. 1. B3LYP-optimized structures for Cu^{2+} complexes of AC) adenine, TC) thymine, GC) guanine, and CC) cytosine. Selected distances are in Å.

bases are summarized in Table 1.

All optimized structures in Fig. 1 have C_s symmetry except C_1 of the CC2.

On the other hand, the cupric cation association energies of DNA bases are calculated to be about 200–260 kcal/mol as shown in Table 1. These energies are larger than that of Cu^+ complexes (90–140 kcal/mol)¹⁴ and are similar to that of Zn^{2+} complexes (180–250 kcal/mol).¹⁵ This means that the association energy relates to charge of the metal ion.

As shown in Fig. 1, the five distinct complexes of Cu^{2+} with adenine have been found. The structure

of AC5 in the five complexes was not located in Cu^+ complex.¹⁴ The cupric cation association energies of these complexes are about 230 kcal/mol except N_7 complex of about 225 kcal/mol as shown in Table 1.

Association of adenine with Cu^{2+} is accompanied by structural changes within the pyrimidine ring. When Cu^{2+} binds at the N_1 and N_6 atoms (AC1 in Fig. 1), the N_1 - C_2 distance increases by 0.023 Å compared to the parent base, whereas the C_5 - C_6 bond length of 1.411 Å is reduced to 1.373 Å in the complex. The notable change in bond lengths is an

Table 1. B3LYP/6-31G(d,p) absolute energies (E in au) of the copper (II) complexes and cupric cation association energies (ΔE_c^a in kcal/mol) of DNA bases

Base	Association site	E	ΔE_c^a
Adenine	N ₁ -N ₆	-2106.938250	-229.03
	N ₃	-2106.934671	-231.28
	N ₆ -N ₇	-2106.942439	-230.40
	N ₁	-2106.929251	-228.11
Thymine	N ₇	-2106.924456	-224.65
	O ₂	-2093.709764	-207.74
Guanine	O ₄	-2093.712008	-203.10
	N ₂ -N ₃	-2182.155338	-221.01
Cytosine	O ₆ -N ₇	-2182.229118	-262.54
	N ₃	-2182.158968	-226.31
	O ₂ -N ₃	-2034.576717	-245.71
	N ₃ -N ₄	-2034.539214	-223.46

$$^a\Delta E_c = \Delta E + \Delta ZPE + BSSE$$

increase of 0.103Å in the C₆-N₆ distance. The C₅C₆N₆ angle also changes considerably, increasing by 8.7°. The two dihedral angles ($\angle N_1C_6N_6H$) of -10.0 and -170.1° by amino hydrogens in adenine change to 119.7 and -119.7° in N₁-N₆ complex, respectively. This is due to the repulsion between the Cu²⁺ and amino hydrogen on the N₁ side of the C₆-N₆ bond. That is, the amino hydrogens rotate to reduce this repulsion. The N₁-Cu²⁺ and N₆-Cu²⁺ distances of this complex are calculated to be 1.893 and 1.969Å, respectively. When Cu²⁺ binds at N₃ (AC2 in Fig. 1), the N₁-C₂ bond length decreases by 0.051Å and the C₂-N₃ distance increases by 0.077Å. The N₃-Cu²⁺ distance is 1.801Å. All other bond distance and bond angle changes are small. For the bridging complex in which Cu²⁺ forms a five-membered ring (AC3 in Fig. 1), the N₇-Cu²⁺ distance is 1.897Å and the N₆-Cu²⁺ is 2.025Å. The C₅C₆N₆ angle changes considerably, decreasing by 8.2°. This large change is associated with bridging nature of the complex caused by interaction of Cu²⁺ with the N₆ and N₇ atoms. The N₁-Cu²⁺ distance in the N₁ complex (AC4 in Fig. 1) is calculated to be 1.815Å and N₇-Cu²⁺ distance in N₇ complex (AC5 in Fig. 1) is calculated to be 1.800Å.

The two association sites for Cu²⁺ complex with thymine have been found, one at each carbonyl group, as shown in Fig. 1. These features are simi-

lar to Zn²⁺ complex.¹⁴ The association energies of these complexes are calculated to be -207.74 and -203.10 kcal/mol in the O₂ and O₄ complex, respectively. The O-Cu²⁺ distances are 1.771 and 1.792Å. In this complex, the notable change is an increase in the internal angle of the ring at carbon of the carbonyl binding site, and increase in the carbonyl C=O bond lengths. The N₁C₂N₃ angle in the O₂ complex increases by 3.3° and the N₃C₄C₅ angle in the O₄ complex increases by 6.2°. The C=O bond distances increase upon complexation by 0.033 and 0.085Å in the O₂ and O₄ complex, respectively.

The three distinct complexes of Cu²⁺ with guanine have been found as shown in Fig. 1. The most stable guanine complex is the bridging complex in which Cu²⁺ forms a five-membered ring, interacting with the O₆ and N₇ atoms. The cupric cation association energy of this complexes is -262.54 kcal/mol as shown in Table 1. The five-membered ring formation (GC2 in Fig. 1) is about 40 kcal/mol more stable than the four-membered ring formation (GC1 in the Fig. 1). This result shows that the five-membered ring formation is favored with respect to formation of four-membered ring because of the minor annular strain. This O₆-N₇ five-membered ring complex of Cu²⁺ with guanine is the strongest of the Cu²⁺ complexes with the DNA bases as seen in Table 1. This tendency is similar to that obtained for the Zn²⁺ complex.¹⁴ In five-membered ring complex, the C₅C₆O₆ angle decreases notably by 13.3° in comparison with parent base. This large change is also associated with the bridging nature of complex. The O₆-Cu²⁺ and N₇-Cu²⁺ distances of this complex are calculated to be 1.863 and 1.915Å, respectively. On the other hand, the two N-Cu²⁺ distances in four-membered ring complex are found to be 1.937 and 2.073Å. And N-Cu²⁺ distance in N₃ complex (GC3 in Fig. 1) is calculated to be 1.814Å.

The two bridged formations have been found in the cytosine complex in which Cu²⁺ forms four-membered ring with O₂-N₃ and N₃-N₄ as shown in Fig. 1. The O₂-N₃ bridging complex is more stable than N₃-N₄ complex. This result means that the carbonyl oxygen is preferred over the amino nitrogen. In the O₂-N₃ complex, notable changes occur in

bond distances and angles from N_1 to C_1 . The N_1-C_2 distance decreases by 0.095\AA and $N_1C_2O_2$ angle increases by 6.8° with complexation. These results lead to enhancement of the simultaneous interaction of Cu^{2+} with O_2 and N_3 . Similarly, the $N_3C_4N_4$ angle in the N_3-N_4 complex is reduced upon complexation to about 11.3° . In the O_2-N_3 complex, the O_2-Cu^{2+} and N_3-Cu^{2+} distances are 1.853 and 1.942\AA , respectively. In this complex, the $O-Cu^{2+}$ distance is longer than the corresponding ones in the thymine complexes. The association energy of this complex is -245.71 kcal/mol. On the other hand, the $N-Cu^{2+}$ distances in N_3-N_4 complex are calculated to be 1.865 and 1.997\AA .

In conclusion, there are five distinguishable Cu^{2+} complexes with adenine, two bridging complexes and the other three open structures at N_1 , N_3 and N_7 , respectively. There are two Cu^{2+} complexes with thymine, one at each carbonyl group. The three distinct complexes of Cu^{2+} with guanine are found, two bridging guanine- Cu^{2+} complexes and an open structure at N_3 . For the cytosine- Cu^{2+} complex, there are two bridging complexes, one at the O_2 and N_3 atoms, and the other at the N_3 and N_4 atoms.

In this study, structures and energetic aspects of the complexes of copper(II) with DNA nucleobases were investigated at B3LYP/6-31G(d,p) density functional level. The association energy values suggest that the most stable of the Cu^{2+} complexes with DNA bases are the bridging complexes with guanine and cytosine at the O and N atoms. This means that the coordination sites are the O and N atoms as the most suitable to receive the metal cations. The most favorable association energy values for each base suggest that the DNA bases reactivity order with Cu^{2+} is guanine > cytosine > adenine > thymine. This tendency of Cu^{2+} metal affinities is in agreement with the experimental results from kinetic method for the alkali metals (Li^+ , Na^+ , K^+).⁶

The results obtained in this study are the first theoretical consideration that concerned the Cu^{2+} interactions with DNA bases. These gas-phase results can be used with caution as a guideline for both the binding sites and association energies for the condensed phase.

Acknowledgement. This research was supported by the Catholic University of Daegu research grants in 2006.

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