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단 신

DNA 염기의 구리(II) 착물에 대한 DFT 연구

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

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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 Wesdemiotis[8] 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 Ben[9] 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 bases[11-13] 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(B-Cu^{2+})] and the sum of the energies of the base [E(B)] and cupric cation monomer [E(Cu^{2+})] for the reaction

$$B + Cu^{2+} \rightarrow B\text{-}Cu^{2+}$$

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

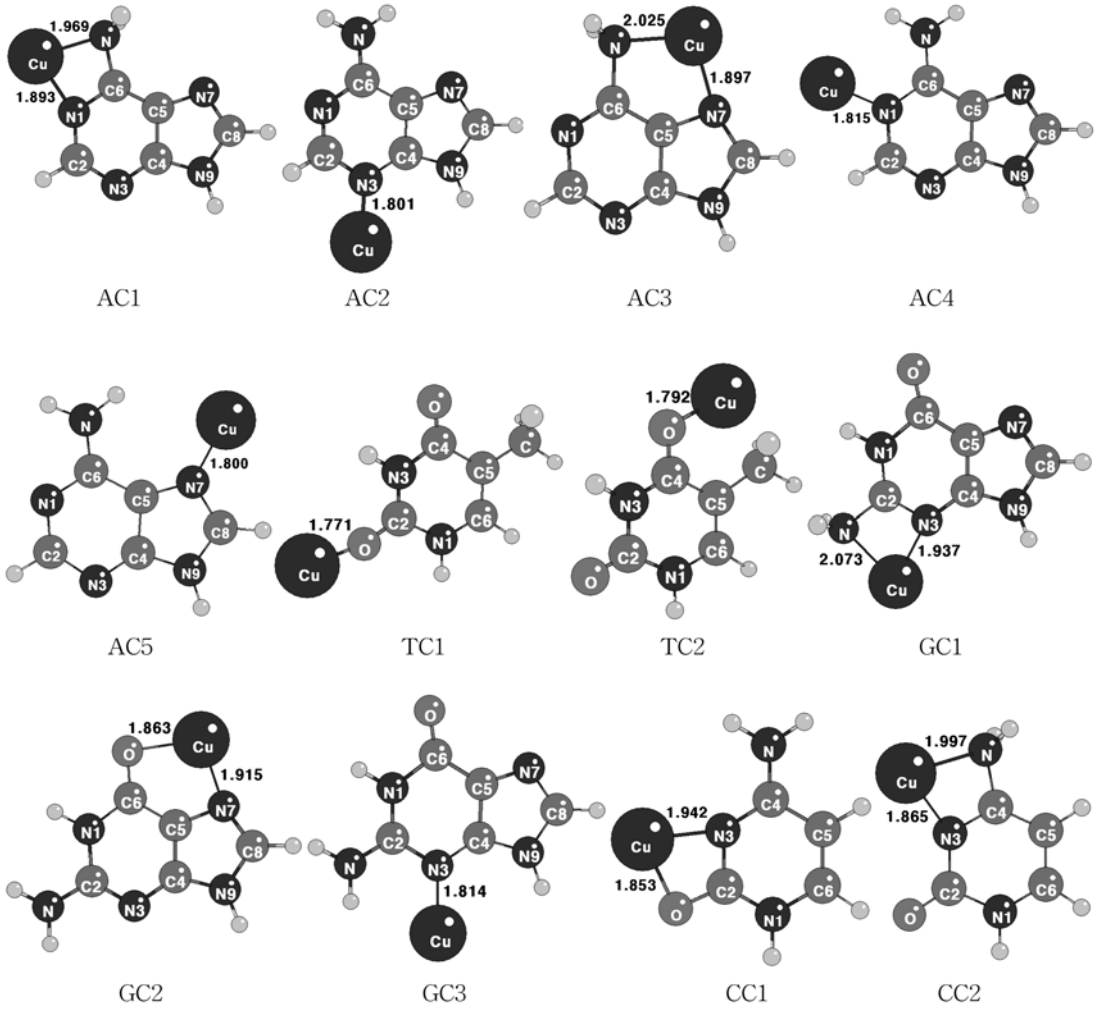

Fig. 1. B3LYP-optimized structures for Cu^{2+} complexes of AC) adenine, TC) thymine, GC) guanine, and CC) cytosine. Selected distances are in Å.

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 200~260kcal/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).[13] 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 0.023Å compared to the parent base, whereas the C_5-C_6 bond length of 1.411Å is reduced to 1.373Å 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
	N_7	-2106.924456	-224.65
Thymine	O_2	-2093.709764	-207.74
	O_4	-2093.712008	-203.10
Guanine	N_2-N_3	-2182.155338	-221.01
	O_6-N_7	-2182.229118	-262.54
	N_3	-2182.158968	-226.31
Cytosine	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 C_6-N_6 distance. The $C_5C_6N_6$ 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 N_1-N_6 complex, respectively. This is due to the repulsion between the Cu^{2+} and amino hydrogen on the N_1 side of the C_6-N_6 bond. That is, the amino hydrogens rotate to reduce this repulsion. The N_1-Cu^{2+} and N_6-Cu^{2+} distances of this complex are calculated to be 1.893 and 1.969Å, respectively. When Cu^{2+} binds at N_3 (AC2 in *Fig*. 1), the N_1-C_2 bond length decreases by 0.051Å and the C_2-N_3 distance increases by 0.077Å. The N_3-Cu^{2+} distance is 1.801Å. All other bond distance and bond angle changes are small. For the bridging complex in which Cu^{2+} forms a five-membered ring (AC3 in *Fig*. 1), the N_7-Cu^{2+} distance is 1.897Å and the N_6-Cu^{2+} is 2.025Å. The $C_5C_6N_6$ angle changes considerably, decreasing by 8.2°. This large change is associated with bridging nature of the complex caused by interaction of Cu^{2+} with the N_6 and N_7 atoms. The N_1-Cu^{2+} distance in the N_1 complex(AC4 in *Fig*. 1) is calculated to be 1.815Å and N_7-Cu^{2+} distance in N_7 complex(AC5 in *Fig*. 1) is calculated to be 1.800Å.

The two association sites for Cu^{2+} complex with thymine have been found, one at each carbonyl group, as shown in *Fig*. 1. These features are similar to Zn^{2+} complex.[14] The association energies of these complexes are calculated to be -207.74 and -203.10 kcal/mol in the O_2 and O_4 complex, respectively. The O-Cu^{2+} 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 $N_1C_2N_3$ angle in the O_2 complex increases by 3.3° and the $N_3C_4C_5$ angle in the O_4 complex increases by 6.2°. The C=O bond distances increase upon complexation by 0.033 and 0.085Å in the O_2 and O_4 complex, respectively.

The three distinct complexes of Cu^{2+} with guanine have been found as shown in *Fig*. 1. The most stable guanine complex is the bridging complex in which Cu^{2+} forms a five-membered ring, interacting with the O_6 and N_7 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 O_6-N_7 five-membered ring complex of Cu^{2+} with guanine is the strongest of the Cu^{2+} complexes with the DNA bases as seen in *Table* 1. This tendency is similar to that obtained for the Zn^{2+} complex.[14] In five-membered ring complex, the $C_5C_6O_6$ angle decreases notably by 13.3° in comparison with parent base. This large change is also associated with the bridging nature of complex. The O_6-Cu^{2+} and N_7-Cu^{2+} distances of this complex are calculated to be 1.863 and 1.915Å, respectively. On the other hand, the two N-Cu^{2+} distances in four-membered ring complex are found to be 1.937 and 2.073Å. And N-Cu^{2+} distance in N_3 complex (GC3 in *Fig*. 1) is calculated to be 1.814Å.

The two bridged formations have been found in the cytosine complex in which Cu^{2+} forms four-membered ring with O_2-N_3 and N_3-N_4 as shown in *Fig*. 1. The O_2-N_3 bridging complex is more stable than N_3-N_4 complex. This result means that the carbonyl oxygen is preferred over the amino nitrogen. In the O_2-N_3 complex, notable changes occur in

bond distances and angles from N_1 to C_4. The N_1-C_2 distance decreases by 0.095Å 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 1.942Å, 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 1.997Å.

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^+).[8]

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.

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