

## 단 신

### DNA 염기의 구리(II) 착물에 대한 DFT 연구

이 갑 용\*

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

Gab-Yong Lee\*

Department of Chemistry, Catholic University of Daegu, Gyeongsan 712-702, Korea  
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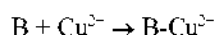
**주제어:**  $\text{Cu}^{2+}$  착물, 금속이온친화도, DNA 염기, 다리 착물

**Keywords:**  $\text{Cu}^{2+}$  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.<sup>1,2</sup> 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.<sup>3-7</sup> Cerda and Wesdemiotis<sup>8</sup> have reported the interaction of alkali metal ions ( $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{K}^+$ ) with DNA bases. However the binding sites were not suggested as the suitable to receive the metal cations. Del Ben<sup>9</sup> have reported the results of a study for the  $\text{Li}^+$  complexes of the DNA bases by *ab initio* calculations to determine the optimized structures and stabilization energies. Burda *et al.*<sup>10</sup> have studied on the interaction of guanine and adenine with  $\text{Zn}^{2+}$  at the HF and MP2 level.

In the present paper, as a continuation of study on the binding of metal cations with DNA bases<sup>11-13</sup> we report a DFT investigation on the interaction of  $\text{Cu}^{2+}$  with DNA bases. DFT calculations are carried out at B3LYP level<sup>14,15</sup> of theory with the 6-31G(d,p) basis sets using the Gaussian03 series of program.<sup>16</sup> The metal binding sites for  $\text{Cu}^{2+}$  complexes were

taken from the previous theoretical data for the protonation sites of DNA bases proposed by Del Ben.<sup>17</sup> 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.<sup>18,19</sup> The copper(II) cation association energies( $\Delta E$ ) are calculated as the difference of the optimized energy of the base- $\text{Cu}^{2+}$  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  $\text{Cu}^{2+}$ -DNA bases complexes obtained by B3LYP/6-31G(d,p) computations are reported. The copper(II) cation association energies of DNA

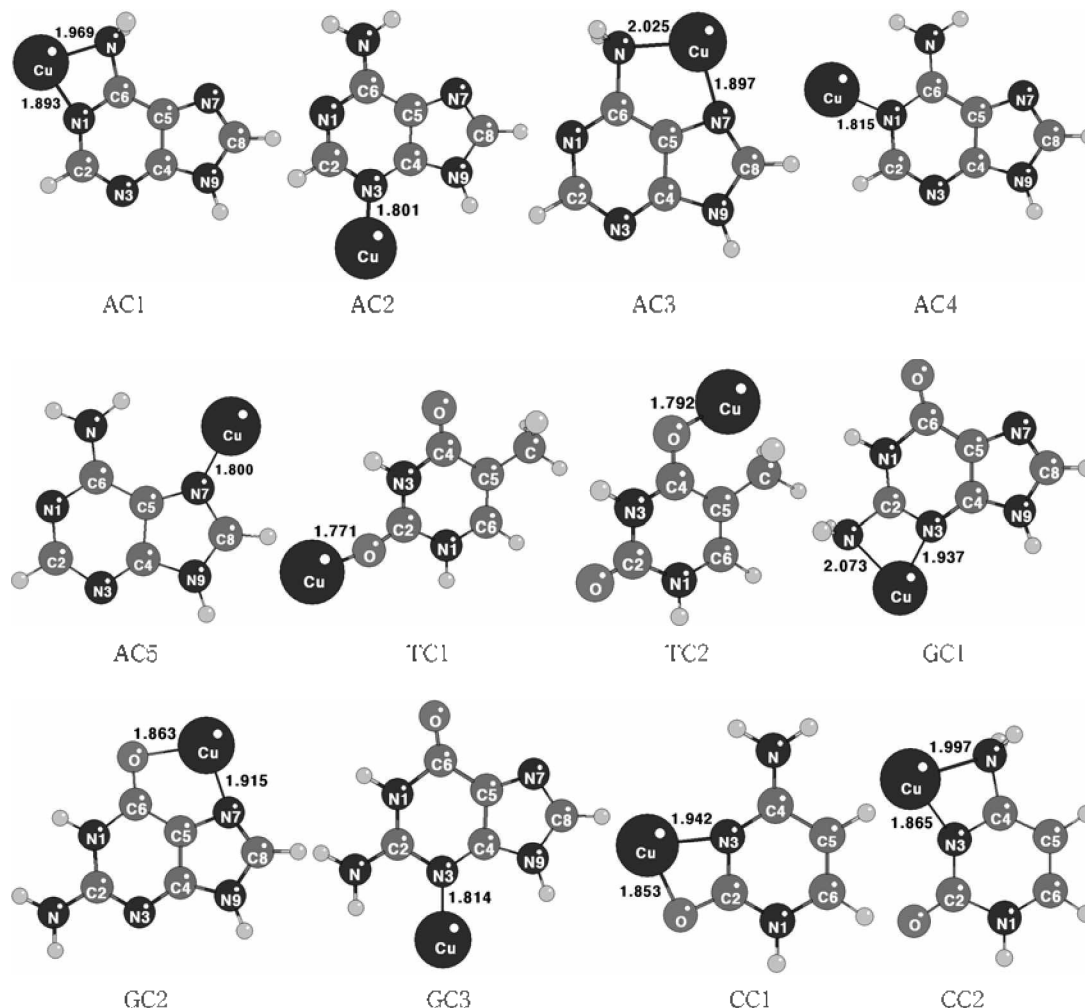


Fig. 1. B3LYP-optimized structures for  $\text{Cu}^{2+}$  complexes of AC) adenine, TC) thymine, GC) guanine, and CC) cytosine. Selected distances are in Å.

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  $\text{Cu}^+$  complexes (90–140 kcal/mol)<sup>14</sup> and are similar to that of  $\text{Zn}^{2+}$  complexes (180–250 kcal/mol).<sup>15</sup> This means that the association energy relates to charge of the metal ion.

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

of AC5 in the five complexes was not located in  $\text{Cu}^+$  complex.<sup>14</sup> The cupric cation association energies of these complexes are about 230 kcal/mol except  $\text{N}_7$  complex of about 225 kcal/mol as shown in Table 1.

Association of adenine with  $\text{Cu}^{2+}$  is accompanied by structural changes within the pyrimidine ring. When  $\text{Cu}^{2+}$  binds at the  $\text{N}_1$  and  $\text{N}_6$  atoms (AC1 in Fig. 1), the  $\text{N}_1$ - $\text{C}_2$  distance increases by 0.023 Å compared to the parent base, whereas the  $\text{C}_5$ - $\text{C}_6$  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 ( $\Delta E_c^a$  in kcal/mol) of DNA bases

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

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

increase of 0.103Å in the C<sub>6</sub>-N<sub>6</sub> distance. The C<sub>5</sub>C<sub>6</sub>N<sub>6</sub> 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<sub>1</sub>-N<sub>6</sub> complex, respectively. This is due to the repulsion between the Cu<sup>2+</sup> and amino hydrogen on the N<sub>1</sub> side of the C<sub>6</sub>-N<sub>6</sub> bond. That is, the amino hydrogens rotate to reduce this repulsion. The N<sub>1</sub>-Cu<sup>2+</sup> and N<sub>6</sub>-Cu<sup>2+</sup> distances of this complex are calculated to be 1.893 and 1.969Å, respectively. When Cu<sup>2+</sup> binds at N<sub>7</sub> (AC2 in Fig. 1), the N<sub>1</sub>-C<sub>2</sub> bond length decreases by 0.051Å and the C<sub>2</sub>-N<sub>3</sub> distance increases by 0.077Å. The N<sub>7</sub>-Cu<sup>2+</sup> distance is 1.801Å. All other bond distance and bond angle changes are small. For the bridging complex in which Cu<sup>2+</sup> forms a five-membered ring (AC3 in Fig. 1), the N<sub>7</sub>-Cu<sup>2+</sup> distance is 1.897Å and the N<sub>6</sub>-Cu<sup>2+</sup> is 2.025Å. The C<sub>5</sub>C<sub>6</sub>N<sub>6</sub> angle changes considerably, decreasing by 8.2°. This large change is associated with bridging nature of the complex caused by interaction of Cu<sup>2+</sup> with the N<sub>6</sub> and N<sub>7</sub> atoms. The N<sub>1</sub>-Cu<sup>2+</sup> distance in the N<sub>1</sub> complex (AC4 in Fig. 1) is calculated to be 1.815Å and N<sub>7</sub>-Cu<sup>2+</sup> distance in N<sub>7</sub> complex (AC5 in Fig. 1) is calculated to be 1.800Å.

The two association sites for Cu<sup>2+</sup> complex with thymine have been found, one at each carbonyl group, as shown in Fig. 1. These features are simi-

lar to Zn<sup>2+</sup> complex.<sup>14</sup> The association energies of these complexes are calculated to be -207.74 and -203.10 kcal/mol in the O<sub>2</sub> and O<sub>4</sub> complex, respectively. The O-Cu<sup>2+</sup> 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<sub>1</sub>C<sub>2</sub>N<sub>3</sub> angle in the O<sub>2</sub> complex increases by 3.3° and the N<sub>3</sub>C<sub>4</sub>C<sub>5</sub> angle in the O<sub>4</sub> complex increases by 6.2°. The C=O bond distances increase upon complexation by 0.033 and 0.085Å in the O<sub>2</sub> and O<sub>4</sub> complex, respectively.

The three distinct complexes of Cu<sup>2+</sup> with guanine have been found as shown in Fig. 1. The most stable guanine complex is the bridging complex in which Cu<sup>2+</sup> forms a five-membered ring, interacting with the O<sub>6</sub> and N<sub>7</sub> 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<sub>6</sub>-N<sub>7</sub> five-membered ring complex of Cu<sup>2+</sup> with guanine is the strongest of the Cu<sup>2+</sup> complexes with the DNA bases as seen in Table 1. This tendency is similar to that obtained for the Zn<sup>2+</sup> complex.<sup>14</sup> In five-membered ring complex, the C<sub>5</sub>C<sub>6</sub>O<sub>6</sub> 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<sub>6</sub>-Cu<sup>2+</sup> and N<sub>7</sub>-Cu<sup>2+</sup> distances of this complex are calculated to be 1.863 and 1.915Å, respectively. On the other hand, the two N-Cu<sup>2+</sup> distances in four-membered ring complex are found to be 1.937 and 2.073Å. And N-Cu<sup>2+</sup> distance in N<sub>3</sub> 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<sup>2+</sup> forms four-membered ring with O<sub>2</sub>-N<sub>3</sub> and N<sub>3</sub>-N<sub>4</sub> as shown in Fig. 1. The O<sub>2</sub>-N<sub>3</sub> bridging complex is more stable than N<sub>3</sub>-N<sub>4</sub> complex. This result means that the carbonyl oxygen is preferred over the amino nitrogen. In the O<sub>2</sub>-N<sub>3</sub> complex, notable changes occur in

bond distances and angles from  $N_1$  to  $C_1$ . The  $N_1-C_2$  distance decreases by  $0.095\text{\AA}$  and  $N_1C_2O_2$  angle increases by  $6.8^\circ$  with complexation. These results lead to enhancement of the simultaneous interaction of  $Cu^{2+}$  with  $O_2$  and  $N_3$ . Similarly, the  $N_3C_4N_1$  angle in the  $N_3-N_4$  complex is reduced upon complexation to about  $11.3^\circ$ . In the  $O_2-N_3$  complex, the  $O_2-Cu^{2+}$  and  $N_3-Cu^{2+}$  distances are  $1.853$  and  $1.942\text{\AA}$ , 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  $1.997\text{\AA}$ .

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  $N_7$ . 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 ( $Li^+$ ,  $Na^+$ ,  $K^+$ ).<sup>6</sup>

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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