

## Ab Initio Molecular Orbital Study on the G-Selectivity of GGG Triplet in Copper(I)-Mediated One-Electron Oxidation

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**Abstract:** The G-selectivity for Cu(I)-mediated one-electron oxidation of 5'-TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3' and 5'-CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3' has been examined by ab initio molecular orbital calculations. It was confirmed that G<sub>1</sub> is selectively damaged by Cu(I) ion for both 5'-TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3' and 5'-CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3', being good agreement with experimental results. The Cu(I)-mediated G<sub>1</sub>-selectivity is primarily due to the stability of the Cu(I)-coordinated complex, [XG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-Cu(I)(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>. The Cu(I) ion coordinates selectively to N7 of G<sub>2</sub> of 5'-G<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3' rather than N7 of G<sub>1</sub>. The G<sub>2</sub>-selective coordination induces the G<sub>1</sub>-selective trap of a hole that is created by one-electron oxidation and migrates to GGG triplet. Therefore, the radical cation of G<sub>1</sub> is selectively created in both 5'-TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3' and 5'-CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3', giving the G<sub>1</sub>-selective damage of 5'-G<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3'.

### Introduction

Long-range guanine damage in DNA caused by one-electron oxidation of nucleobases has been extensively studied within the most recent decade.<sup>1-8</sup> Since guanine is the most easily oxidized base among DNA nucleobases, guanine radical cation

is the initial product of DNA one-electron oxidation in a wide variety of systems.<sup>4-7</sup> The hole created in DNA duplex by one-electron oxidation ultimately migrates to end up at guanine (G) base through the DNA  $\pi$  stack.<sup>9,10</sup> As is well-known, 5'-G of 5'-GG-3' sequences is selectively oxidized in the B-form DNA in the reaction systems using a variety of oxidizing agents.<sup>11-19</sup> The GG doublets are often used as a probe for the terminus in the long-range hole migration. 5'-GGG-3' triplets also act as a more effective trap in hole migration than 5'-GG-3' doublets.<sup>11b</sup>

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It has been confirmed experimentally for one-electron oxidation that  $G_2$  of  $5'$ -TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>T- $3'$  is more reactive than  $G_1$ , while for  $5'$ -CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>C- $3'$  the ordering of the selectivity is reversed; that is,  $G_1 > G_2$ .<sup>20</sup>

Ab initio molecular orbital calculations have been performed to elucidate the selectivity of  $5'$ -TGGG- $3'$  and  $5'$ -CGGG- $3'$  sequences toward one-electron oxidation.<sup>10d,20</sup> It was shown that the selectivity of the  $5'$ -TGGG- $3'$  sequence is primarily determined by the stability of neutral radical states produced through the radical cations by one-electron oxidation. Unlike  $5'$ -TGGG- $3'$ , it was suggested that the selectivity of the  $5'$ -CGGG- $3'$  sequence is not determined primarily by the stability of radical cations and neutral radicals and is determined by the reactivity of radical orbital localized on guanine radical in the neutral radical state of the  $5'$ -CGGG- $3'$  sequence.<sup>20</sup>

Recently, the site-specific oxidation at GG and GGG sequences in double-stranded DNA in the presence of transition metal ions has been investigated.<sup>21–32</sup> Kawanishi and co-workers have reported that, in the presence of Cu(I) ion and benzoyl peroxide (BzPO) in sodium phosphate buffer, preferential DNA damage is caused at the  $5'$ -site guanine of GGG and GG sequences in double-stranded DNA.<sup>22</sup> However, addition of Cu(II) ion instead of Cu(I) ion did not induce the DNA damage. Saito and co-workers have examined the site-selective oxidation of GGG and GG sequences in the presence of BzPO and Co(II) ion in sodium cacodylate buffer and observed preferential damage at the  $5'$ -site of guanine.<sup>24</sup> It was found that the relative rate of G-selective oxidation is well-matched with the distribution of the highest occupied molecular orbital (HOMO) of G-containing sequences. They have proposed that the Co(II) ion strongly coordinates to the N7 of guanine base according to a HOMO control process.<sup>24</sup> Relevantly, it was also reported by Hentle and co-workers that the preferential cleavages occurred at the nucleotide located  $5'$ -site to the sequence  $5'$ -XGGG- $3'$  under the condition of Fe(II) ion and a high concentration of H<sub>2</sub>O<sub>2</sub>.<sup>23</sup> Although it is apparent that a free radical generated by BzPO or H<sub>2</sub>O<sub>2</sub> plays an important role for oxidative DNA cleavage, the mechanism of oxidation by transition metal ions is not yet well-understood.

Recently Sletten and co-workers have shown, from <sup>1</sup>NMR spectroscopic study of the coordination of the Co(II) ion to the N7 of G in DNA oligomers, that the binding selectivity of the Co(II) ion toward  $5'$ -CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>C- $3'$  sequence follows the order  $G_1 > G_2 \gg G_3$  while holding a high  $5'$ -G selectivity for GG doublet.<sup>25</sup> Crystallographic<sup>26–29</sup> and experimental<sup>30–32</sup> studies

have indicated that the Mn(II), Ni(II), Co(II), and Cu(II) ions bind preferentially to the N7 of G by coordination.

Theoretical calculations of the coordination of the transition metals to the N7 of G are scarcely found except for Pt(II) ion, that is, cisplatin (*cis*-Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>).<sup>33–35</sup> Pt(II) ion simultaneously coordinates to both the N7 and O6 sites of a guanine.<sup>34</sup> However, the molecular and electronic structures of a guanine coordinated to the N7 site by Cu(I) ion are not clearly understood, leading to poor elucidation of metal-mediated site selective oxidation of GGG and GG sequences.

In this paper, we have performed ab initio molecular orbital calculations to elucidate the G-selectivity of GGG triplet toward Cu(I)-mediated one-electron oxidation. First, the molecular and electronic structures of [G-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>, in which [Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> coordinates to N7 of a guanine, are discussed to make construction of [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>, in which [Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> coordinates to N7 of a guanine of 5'-GGG-3' triplet. Second, the electronic structures of [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> are investigated. Last, the electronic structures of [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>2+</sup> which is the hole-captured state, are discussed to elucidate the Cu(I)-mediated G-selectivity. Thymine (T) and cytosine (C) bases are chosen as X. Without Cu(I)-mediation, the G-selectivity of damage is different among T and C, that is, G<sub>2</sub>-selective damage in 5'-TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3' and G<sub>1</sub>-selective damage in 5'-CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3'.<sup>20</sup>

### Computational Details

[5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> (X = T, C) and [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>2+</sup>, in which [-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> coordinates to the N7 site of a guanine of GGG triplet, were calculated to elucidate the G-selectivity of 5'-TGGG-3' and 5'-CGGG-3' triplets toward one-electron oxidation mediated by Cu(I) ion, using ab initio molecular orbital theory. As shown in a previous paper,<sup>20</sup> the geometries of 5'-TGGG-3' and 5'-CGGG-3' sequences double stranded of B-form structure were constructed using the Insight II program with standard B-form geometrical parameters which have been optimized by X-ray crystallographic analysis of relevant monomers and X-ray diffraction data of polymers.<sup>36</sup> All the sugar backbones of the duplex 4-mer were replaced by a methyl group. For the calculations of [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> and [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>2+</sup>, the distance between the Cu atom and the N7 atom was optimized by keeping other geometrical parameters fixed. The charge and spin densities are summed into every base of GGG triplet to distinguish which of the guanines has localized positive charge and spin densities in [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>2+</sup>.

The geometry of [-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> in [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>n+</sup> ( $n = 1$  and  $2$ ) was estimated by the geometry optimization of the complexes, [G-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>, at the HF/6-31G\* level. The geometry of [G-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> was performed by two procedures. One is a partial optimization of only part of [-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> in the complex [G-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>. The geometry of G is frozen at the same geometrical parameters as those of G in [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>n+</sup> ( $n = 1$  and  $2$ ) in the geometry optimization. The optimized geometry of [-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> was employed to construct the structure of [5'-XGGG-3',-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>n+</sup> ( $n = 1$  and  $2$ ). It was confirmed from three-dimensional graphics that 5'-XGGG-3' has an enough room for coordination of [-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> to N7 without steric repulsion from atoms of other nucleobases (see Figure 3). Another

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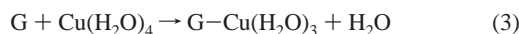
is a full optimization of all geometrical parameters of  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$  to investigate stability and electronic structure of the complex and to confirm applicability for constructing the complexes  $[5'-\text{XGGG}-3'-\text{Cu}(\text{H}_2\text{O})_3]^+$ .

The stability of  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$  was estimated by two procedures. One is a direct method as follows.



$$\Delta E_b = E(\text{G}-\text{Cu}(\text{H}_2\text{O})_3) - E(\text{G}) - E(\text{Cu}(\text{H}_2\text{O})_3) \quad (2)$$

$\Delta E_b$  presents directly the binding energy of G and  $[-\text{Cu}(\text{H}_2\text{O})_3]^+$  with their deformation. Another way to estimate the stability of the complex is given as follows,



$$\Delta E_{\text{rep}} = E(\text{G}-\text{Cu}(\text{H}_2\text{O})_3) + E(\text{H}_2\text{O}) - E(\text{G}) - E(\text{Cu}(\text{H}_2\text{O})_4) \quad (4)$$

$\Delta E_{\text{rep}}$  is equal to summation of the association energy of G and  $[-\text{Cu}(\text{H}_2\text{O})_3]^+$  and the dissociation energy of  $[\text{H}_2\text{O}-\text{Cu}(\text{H}_2\text{O})_3]^+$  and presents an index of a relative stability of  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$ . We call  $\Delta E_{\text{rep}}$  the H<sub>2</sub>O replacement energy hereafter.

All calculations were carried out using the Gaussian 94 program package.<sup>37</sup> Basis sets at the 6-31G\* level are employed for H-, C-, N-, and O atoms, and Wachters double- $\zeta$  basis set<sup>38</sup> is employed for Cu atom.

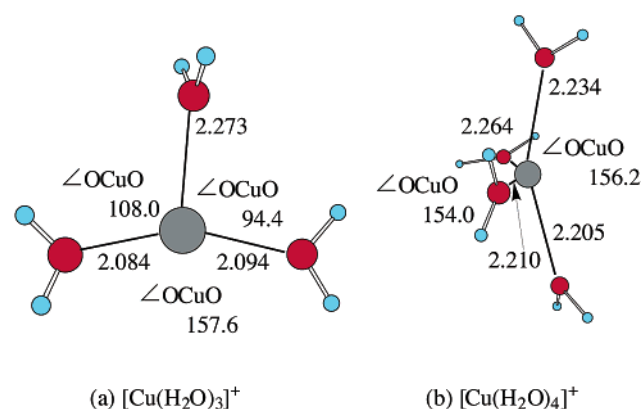
### Geometry and Electronic Structure of $[\text{G}-\text{Cu}(\text{H}_2\text{O})_n]^+$ ( $n = 3, 4$ )

Cu(I) ion is expected to be hydrated, as well as cisplatin,<sup>33–35</sup> in forming the complex coordinated to DNA in a cell. The hydrated complexes of Cu(II) ion,  $[\text{Cu}(\text{H}_2\text{O})_n]^{2+}$  ( $n = 3-8$ ), have been well-studied experimentally<sup>39</sup> and theoretically.<sup>40</sup> Density functional theory shows that  $[\text{Cu}(\text{H}_2\text{O})_n]^{2+}$  ( $n = 3-6$ ) are thermally stable and correctly describe the first solvation shell in solution.<sup>40</sup> The average binding energies of water molecules are nearly equal to 70 kcal/mol. It has also been shown that a square planar  $[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$  complex is a basic solvation unit in the formation of an extended second solvation.<sup>40</sup> As can be seen in Table 1, the average binding energies are given by 76.6 and 85.6 kcal/mol for  $[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$  and  $[\text{Cu}(\text{H}_2\text{O})_3]^{2+}$ , respectively, at the Hartree–Fock level, being comparable with those of density functional theory (DFT) calculations. However, the study of the hydrated complexes of Cu(I) ions,  $[\text{Cu}(\text{H}_2\text{O})_n]^+$ , are scarcely found. In our work to investigate Cu(I)-mediated G-selectivity of GGG triplet, we have tried to perform the geometry optimizations of  $[\text{Cu}(\text{H}_2\text{O})_3]^+$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  at the HF/6-31\* level. The optimized geometries are shown in Figure 1. The geometries of  $[\text{Cu}(\text{H}_2\text{O})_3]^+$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  are similar to those of  $[\text{Cu}(\text{H}_2\text{O})_3]^{2+}$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$

**Table 1.** Total Energies (au), Spin Angular Momentums, Average Binding Energies (kcal/mol) of  $[\text{Cu}(\text{H}_2\text{O})_n]^+$ , Binding Energies (kcal/mol), and H<sub>2</sub>O Replacement Energies (kcal/mol) of  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$

compd	$E_{\text{total}}$	$\langle S^2 \rangle$	$E_{\text{av}}^a$	$\Delta E_b^b$	$\Delta E_{\text{rep}}^c$
$[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$	-2445.214172	0.0		-38.6	-22.6
$[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$ (POpt) <sup>d</sup>	-2445.203592	0.0		-40.3	-24.3
$[\text{Cu}(\text{H}_2\text{O})_4]^+$	-1942.760544	0.0	-25.8		
$[\text{Cu}(\text{H}_2\text{O})_3]^+$	-1866.728600	0.0	-29.0		
$[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$	-1942.381569	0.7508	-76.6		
$[\text{Cu}(\text{H}_2\text{O})_3]^{2+}$	-1866.296111	0.7509	-85.6		
G	-578.424085	0.0			
G (not Opt)	-578.410753	0.0			
H <sub>2</sub> O	-76.006430	0.0			
Cu(I)	-1638.570498	0.0			
Cu(II)	-1637.867550	0.7501			

<sup>a</sup>  $E_{\text{av}} = \{E([\text{Cu}(\text{H}_2\text{O})_n]^+) - E(\text{Cu}(\text{I})) - nE(\text{H}_2\text{O})\}/n$ . <sup>b</sup>  $\Delta E_b = E([\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+) - E(\text{G}) - E([\text{Cu}(\text{H}_2\text{O})_3]^+)$ . <sup>c</sup>  $\Delta E_{\text{rep}} = E([\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+) + E(\text{H}_2\text{O}) - E(\text{G}) - E([\text{Cu}(\text{H}_2\text{O})_4]^+)$ . <sup>d</sup> POpt means a partial optimization of the  $[-\text{Cu}(\text{H}_2\text{O})_3]^+$  moiety in complex  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$ .

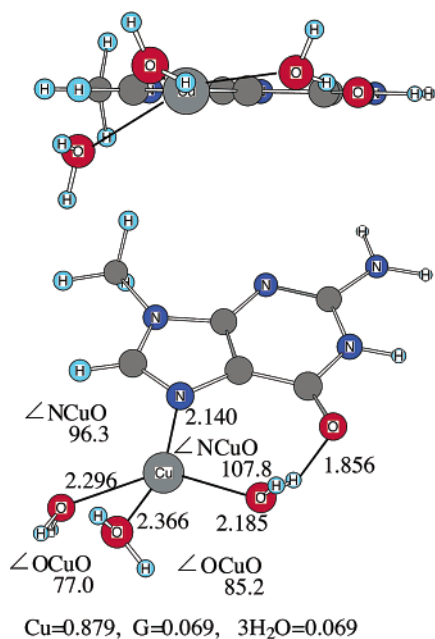


**Figure 1.** Optimized geometries of  $[\text{Cu}(\text{H}_2\text{O})_3]^+$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  with the selected geometrical parameters.

given by Bérces et al.<sup>40</sup> However, the distances between Cu(I) and O atom in complexes are longer by 0.16–0.31 Å, compared with 1.923–2.004 Å of  $[\text{Cu}(\text{H}_2\text{O})_3]^{2+}$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$ . The atomic charge densities on Cu atom in  $[\text{Cu}(\text{H}_2\text{O})_3]^+$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  are 0.900 and 0.897, respectively, showing that Cu atom has formally unit positive charge with slightly donating electron charge from water molecules. As can be found in Table 1,  $[\text{Cu}(\text{H}_2\text{O})_3]^+$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  have respectively average binding energies of 29.0 and 25.8 kcal/mol, that is, one-third of those of  $[\text{Cu}(\text{H}_2\text{O})_3]^{2+}$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^{2+}$ . The lowest vibrational frequencies are 14 and 4  $\text{cm}^{-1}$  in positive values, showing that the local minimum of  $[\text{Cu}(\text{H}_2\text{O})_3]^+$  and  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  are on the shallow potential energy surface.

Figure 2 shows the optimized geometry of  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$ . Compared with the geometry of  $[\text{Cu}(\text{H}_2\text{O})_4]^+$  shown in Figure 1,  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$  has the geometry that one water molecule is replaced by a guanine molecule with distance of 2.140 Å between N7 and Cu atoms. This distance is smaller than those between Cu atom and O atoms of H<sub>2</sub>O molecules and comparable with 2.10–2.27 Å of Cu(II)-soaked CGCGTG given by the crystallographic study of Wang et al.<sup>26</sup> The planar geometry of a guanine is maintained in the complex. It is interesting that one water molecule in  $[-\text{Cu}(\text{H}_2\text{O})_3]^+$  forms a hydrogen bond to the O6 site of guanine, indicating that the binding bridge is constructed from N7 of a guanine, Cu atom, H<sub>2</sub>O to O6 of a guanine in the  $[\text{G}-\text{Cu}(\text{H}_2\text{O})_3]^+$  complex. From Table 1, the coordination of Cu(I) ion to N7 of a guanine gains

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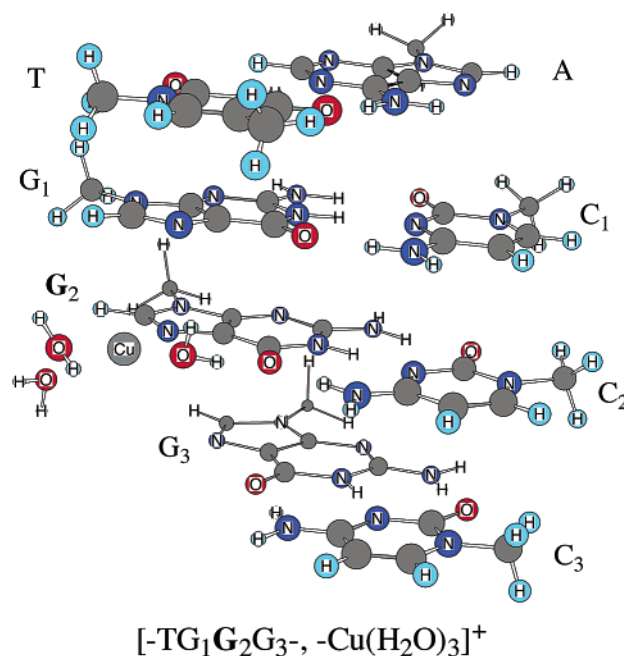
**Figure 2.** Optimized geometries of  $[G-Cu(H_2O)_3]^+$  with the selected geometrical parameters and charge densities of fragments.

the binding energy of 38.6 kcal/mol and the H<sub>2</sub>O replacement energy of 22.6 kcal/mol toward stable direction, showing that Cu(I) atom preferentially coordinates to N7 of a guanine. As shown in Figure 2, the charge densities summed into G, 3H<sub>2</sub>O, and Cu are given by 0.069, 0.052, and 0.879, respectively. Thus, the electronic structure of  $[G-Cu(H_2O)_3]^+$  is formally represented by  $[G-Cu(I)(H_2O)_3]^+$  with little charge donation from a lone paired electron on the N7 atom of guanine and O atoms of three water molecules to the unoccupied 4s orbital of the Cu atom.

### TGGG and CGGG Coordinated by $[-Cu(H_2O)_3]^+$

As shown in Table 1, partial optimization of  $[-Cu(H_2O)_3]^+$  in the complex  $[G-Cu(H_2O)_3]^+$  in which the geometry of a guanine is fixed with that in  $[XGGG-Cu(H_2O)_3]^+$  gives comparable results for the binding and H<sub>2</sub>O replacement energies with that of full optimization. In fact, the energy difference between optimized and partially optimized  $[G-Cu(H_2O)_3]^+$  is only 1.7 kcal/mol. The N7–Cu distance in partial optimization was estimated to be 2.140 Å, the same as that of full optimization of  $[G-Cu(H_2O)_3]^+$ . Thus, the geometry optimized partially is fairly applicable to the complex of  $[XGGG-Cu(H_2O)_3]^+$ . It is explored as a subsequent problem whether the N7 site of the GGG triple sequence has an enough space for coordination of  $[-Cu(H_2O)_3]^+$  or not. We constructed the complex  $[XGGG-Cu(H_2O)_3]^+$  using three-dimensional graphics software, Chem3D in CS ChemOffice. It was confirmed that  $[-Cu(H_2O)_3]^+$  has no steric repulsion to neighbor nucleic acid bases, showing that  $[-Cu(H_2O)_3]^+$  has the ability to coordinate to N7 of a guanine in the GGG triplet of B-DNA, as shown in Figure 3.

There are three possible coordinations of  $[-Cu(H_2O)_3]^+$  to N7 of G<sub>1</sub>, G<sub>2</sub>, and G<sub>3</sub> in 5′-G<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ triplet. Since G<sub>3</sub>-coordination to N7 gives much higher energy than G<sub>1</sub>- and G<sub>2</sub>-coordinations, G<sub>3</sub>-coordination was excluded from this work. Table 2 summarizes the total energies, optimized distances of N7–Cu, relative stabilities, and H<sub>2</sub>O replacement energy of G<sub>1</sub>-



**Figure 3.** Geometry of  $[-TG_1G_2G_3-, -Cu(H_2O)_3]^+$  in which  $[-Cu(H_2O)_3]^+$  coordinates to the N7 site of G<sub>2</sub> in the 5′-T G<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ double strand.

**Table 2.** Total Energies (au), Optimized Distances (Å) of N7–Cu, Relative Stabilities (kcal/mol), and H<sub>2</sub>O Replacement Energies (kcal/mol) of  $[5′-XG_1G_2G_3-3′, -Cu(H_2O)_3]^+$  (X = T and C)

complex <sup>a</sup>	$E_{total}$	$R_{N7-Cu}$	$E_{rel}$	$\Delta E_{rep}^b$
TG <sub>1</sub> G <sub>2</sub> G <sub>3</sub>	−5891.139 075	2.109	9.7	−36.8
TG <sub>1</sub> G <sub>2</sub> G <sub>3</sub>	−5891.154580	2.122	0.0	−46.5
CG <sub>1</sub> G <sub>2</sub> G <sub>3</sub>	−5907.135396	2.103	12.5	−34.5
CG <sub>1</sub> G <sub>2</sub> G <sub>3</sub>	−5907.155383	2.121	0.0	−47.0

<sup>a</sup> G means a guanine coordinated by  $[Cu(H_2O)_3]^+$ . <sup>b</sup>  $\Delta E_{rep} = E([XG_1G_2G_3-, Cu(H_2O)_3]^+) + E(H_2O) - E(XG_1G_2G_3) - E([Cu(H_2O)_4]^+)$ .

and G<sub>2</sub>-coordinations to 5′-TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ and 5′-CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ in  $[5′-XG_1G_2G_3-3′, -Cu(H_2O)_3]^+$ . The optimized distances of N7–Cu fall into the range of 2.103–2.122 Å, being slightly decreased from 2.140 Å of  $[G-Cu(H_2O)_3]^+$  shown in Figure 2. It is found that H<sub>2</sub>O replacement of  $[Cu(H_2O)_4]^+$  by TGGG or CGGG induced the stabilization energy by 35–45 kcal/mol. Compared with 24.3 kcal/mol of  $[G-Cu(H_2O)_3]^+$  shown in Table 1, these indicate enhancement of stabilization of GGG triplet. G<sub>2</sub>-coordination of  $[-Cu(H_2O)_3]^+$  to both 5′-TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ and 5′-CG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ is more stable by about 10 kcal/mol than G<sub>1</sub>-coordination, showing that Cu ion selectively coordinates to N7 of G<sub>2</sub> in 5′-XG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-3′ triplet.

To elucidate the electronic structure of the complexes, charge densities summed into nucleobases, Cu ion, and 3H<sub>2</sub>O in the complexes are summarized in Table 3. Charge densities of Cu fall into a small range of 0.872–0.874 for all cases of the coordinated complex  $[XGGG-Cu(H_2O)_3]^+$ . These values are quite similar to 0.879 of  $[G-Cu(H_2O)_3]^+$ , as shown in a previous section, with charge transfer to the unoccupied 4s orbital of Cu atom. The charge transfer from 3H<sub>2</sub>O is slightly suppressed compared with 0.052 of  $[G-Cu(H_2O)_3]^+$ . A guanine directly coordinated by Cu atom is positively charged and the hydrogen-bonded cytosines are also positively charged (0.030–0.040) with charge donation to Cu atom through the hydrogen bond. For example, in the case of -TG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-, G<sub>2</sub> and C<sub>2</sub> have charges of 0.030 and 0.030, respectively. However, qualitatively

**Table 3.** Charge Densities Summed into Fragments in  $[5'-TG_1G_2G_3-3',-Cu(H_2O)_3]^+$  and  $[5'-CG_1G_2G_3-3',-Cu(H_2O)_3]^+$ 

bases	$[TG_1G_2G_3,Cu(H_2O)_3]^+$		$[CG_1G_2G_3,Cu(H_2O)_3]^+$	
	$TG_1G_2G_3^a$	$TG_1G_2G_3^a$	$CG_1G_2G_3^a$	$CG_1G_2G_3^a$
T or C	-0.019	0.005	0.011	0.027
G <sub>1</sub>	0.030	-0.024	0.024	-0.032
G <sub>2</sub>	-0.005	0.030	-0.006	0.029
G <sub>3</sub>	-0.007	-0.008	-0.008	-0.008
C <sub>3</sub>	0.021	0.025	0.021	0.025
C <sub>2</sub>	0.013	0.030	0.013	0.030
C <sub>1</sub>	0.034	0.029	0.040	0.034
A or G	0.004	-0.006	-0.008	-0.023
Cu	0.873	0.874	0.872	0.874
3H <sub>2</sub> O	0.056	0.045	0.042	0.044

<sup>a</sup> G means a guanine coordinated by  $[Cu(H_2O)_3]^+$ .

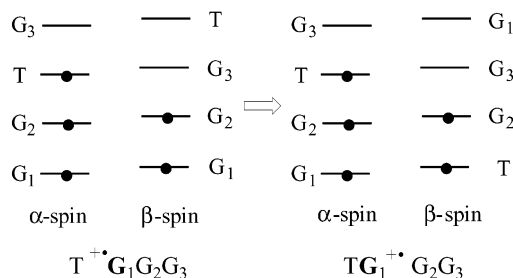
speaking, charge density on Cu atom is nearly equal to unity for all complexes, meaning that Cu atom has  $d^{10}$  electron configuration. Each base and water molecules are almost neutral, indicating formally  $[5'-XGGG-3',-Cu(I)(H_2O)_3]^+$ .

Saito and co-workers have performed  $^{15}N$  NMR spectroscopic study to elucidate the site-selective interaction of  $^{15}N$ -labeled GGG triplet with Mn(II) ion.<sup>42</sup> It was observed that Mn(II) ion is more strongly interactive with the N7 site of G<sub>2</sub> in the G<sub>1</sub>G<sub>2</sub>G<sub>3</sub> triplet than G<sub>1</sub> and G<sub>3</sub>. They concluded that G<sub>2</sub>-selective coordination is caused by HOMO distribution in GGG triplet. In fact, ab initio MO calculations give a fraction of 0.89 of electron density in HOMO on G<sub>2</sub> rather than G<sub>1</sub> and G<sub>3</sub>.<sup>43</sup> Our G<sub>2</sub>-selective coordination of Cu(I) ion is also in good agreement with the calculated HOMO distribution. It is found from Table 3 that C<sub>1</sub>, C<sub>2</sub>, and C<sub>3</sub> paired through hydrogen bonds with G<sub>1</sub>, G<sub>2</sub>, and G<sub>3</sub> are positively charged. Since G<sub>1</sub> and G<sub>2</sub> are polarized to be, respectively, negative and positive in G<sub>2</sub>-coordination of both  $-TG_1G_2G_3-$  and  $-CG_1G_2G_3-$ , the electrostatic interaction between G<sub>1</sub> and G<sub>2</sub> will be expected. It, therefore, seems that stability of G<sub>2</sub>-selective coordination could be enhanced by the charge donation from the G<sub>2</sub>-C<sub>2</sub> pair to the Cu ion and the electrostatic interaction of G<sub>2</sub>-G<sub>1</sub>-C<sub>1</sub>.

### Radical Cation States of the $[-TG_1G_2G_3-,-Cu(I)(H_2O)_3]^{2+}$ Complex

The hole generated by one-electron oxidation moves to end up at the GGG triplet by hole migration via a hopping mechanism through the DNA  $\pi$  stack.<sup>9,10</sup> The trapped hole, that is,  $(GGG)^+$ , will move forward and backward in triple G. In other words, there are three possible states such as  $-XG_1^+G_2G_3-$ ,  $-XG_1G_2^+G_3-$ , and  $-XG_1G_2G_3^+$  for the radical cation states,  $[-XG_1G_2G_3-,-Cu(I)(H_2O)_3]^{2+}$ . Assuming that the rates of damage of G<sub>1</sub><sup>+</sup>, G<sub>2</sub><sup>+</sup>, and G<sub>3</sub><sup>+</sup> are the same, the G-selectivity of damage will be proportional to the distribution of the hole in  $(GGG)^+$ . The distribution should be expected to be dependent on the stability of three possible radical cation states.

It is not so easy to obtain the electronic structures of three radical cation states from the SCF solution of  $[-XG_1G_2G_3-$

**Figure 4.** Schematic presentation of constructing an initial guess of the SCF procedure to get the radical cation state of  $TG_1^+G_2G_3$  from the SCF solution of  $T^+G_1G_2G_3$ .

$Cu(H_2O)_3]^+$ , because the removal of a single electron from the HOMO of  $[-XG_1G_2G_3-,-Cu(H_2O)_3]^+$  does not always correspond to the electronic structure of the desired state of the three radical cations. However, the desired state will be realized by an appropriate choice of the initial guess in the SCF procedure. As an example, an easy procedure of constructing the initial guess of  $TG_1^+G_2G_3$  radical cation state is schematically shown in Figure 4. As a first step, the SCF procedure is performed with an initial guess that one electron is removed from the HOMO of  $[-XG_1G_2G_3-,-Cu(H_2O)_3]^+$ . The SCF procedure converges to the  $T^+G_1G_2G_3$  state rather than one of three radical cation states. Fortunately, since most of the molecular orbitals in the  $T^+G_1G_2G_3$  state are localized on each nucleobase, we can easily assign the highest orbital localized on T and the highest orbital localized on G<sub>1</sub> in  $T^+G_1G_2G_3$ . The initial guess of the  $TG_1^+G_2G_3$  state can be constructed by altering the occupation of the highest  $\beta$ -spin-orbitals of T and G<sub>1</sub>. This initial function leads to the desired self-consistent field (SCF) solution of the  $TG_1^+G_2G_3$  radical cation state. SCF solutions of two other radical cation states were similarly obtained by alternation of  $\beta$ -electron occupation. After the desired state was obtained, the distance of N7-Cu was optimized.

Tables 4 and 5 show the charge and spin densities of every base, Cu ion, and H<sub>2</sub>O in  $[-TGGG-,-Cu(H_2O)_3]^{2+}$  and  $[-CGGG-,-Cu(H_2O)_3]^{2+}$ . It can be seen from Tables 4 and 5 that Cu atoms of the complexes have nearly positive unity charge and  $d^{10}$ -configuration, and radical orbital (singly occupied orbital) is localized on the desired base, meaning that our SCF solution exactly presents the desired radical states. For example, in  $[-TG_1^+G_2G_3-,-Cu(H_2O)_3]^{2+}$ , the Cu atom has a charge density of 0.880 and G<sub>1</sub> has 0.889. Radical spin is localized on G<sub>1</sub> with a value of 0.979. This confirms that the complex  $[-TG_1G_2G_3-,-Cu(H_2O)_3]^{2+}$  corresponds to  $[-TG_1^+G_2G_3-,-Cu(I)(H_2O)_3]^{2+}$ .

The charge densities of Cu ions fall into a small range of 0.873–0.882 for all radical cation states. These values coincide with 0.879 of  $[G-Cu(H_2O)_3]^+$  shown in Figure 2. Even in the case of  $Cu-G^+$ , for which the Cu ion directly coordinates to the radical cation of G, the charge density of Cu ion is similar to that of  $[G-Cu(H_2O)_3]^+$ . It seems that a little charge donation from the lone paired orbital on N7 of G to the 4s orbital of Cu ion is induced, indicating that the radical orbital in all radical cation states is a  $\pi$ -type orbital on G, not a  $\sigma$ -type orbital. Therefore, the Cu(I)-mediated degradation mechanism of a guanine in DNA is expected to be similar to that without Cu(I) coordination. The radical cation of a guanine will be damaged by addition of a singlet molecular oxygen or water molecule.<sup>41</sup>

Table 6 shows the energetics of the radical cation states. Interesting results are found in Table 6. In the case of  $TG_1G_2G_3$

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**Table 4.** Charge ( $\rho$ ) and Spin ( $\sigma$ ) Densities Summed into Fragments in  $[5'-TG_1G_2G_3-3', -Cu(H_2O)_3]^{2+}$ 

bases	$TG_1^+G_2G_3^a$		$TG_1G_2^+G_3^a$		$TG_1^+G_2G_3^a$		$TG_1G_2^+G_3^a$	
	$\rho$	$\sigma$	$\rho$	$\sigma$	$\rho$	$\sigma$	$\rho$	$\sigma$
T	-0.010	0.001	-0.012	0.001	0.011	0.000	0.010	0.000
G <sub>1</sub>	0.889	0.979	0.024	0.004	0.874	1.000	-0.017	0.008
G <sub>2</sub>	0.014	0.024	0.890	0.995	0.030	0.003	0.890	0.985
G <sub>3</sub>	-0.004	0.000	0.001	0.005	-0.004	0.000	0.006	0.011
C <sub>3</sub>	0.029	-0.000	0.038	-0.000	0.032	0.000	0.043	-0.000
C <sub>2</sub>	0.029	-0.000	0.062	-0.004	0.044	-0.000	0.076	-0.003
C <sub>1</sub>	0.082	-0.003	0.051	0.000	0.079	-0.004	0.045	0.000
A	0.014	-0.000	0.009	-0.001	0.005	-0.000	-0.002	0.000
Cu	0.880	0.001	0.874	-0.000	0.874	0.001	0.882	0.001
3H <sub>2</sub> O	0.077	-0.002	0.064	-0.000	0.054	0.001	0.066	-0.001

<sup>a</sup> G means a guanine coordinated by  $[Cu(H_2O)_3]^+$ .

**Table 5.** Charge ( $\rho$ ) and Spin ( $\sigma$ ) Densities Summed into Fragments in  $[5'-CG_1G_2G_3-3', -Cu(H_2O)_3]^{2+}$ 

bases	$CG_1^+G_2G_3^a$		$CG_1G_2^+G_3^a$		$CG_1^+G_2G_3^a$		$CG_1G_2^+G_3^a$	
	$\rho$	$\sigma$	$\rho$	$\sigma$	$\rho$	$\sigma$	$\rho$	$\sigma$
C	0.025	0.001	0.019	0.000	0.038	0.001	0.034	0.000
G <sub>1</sub>	0.879	0.977	0.017	0.004	0.864	0.998	-0.026	0.008
G <sub>2</sub>	0.013	0.023	0.889	0.995	0.030	0.003	0.890	0.985
G <sub>3</sub>	-0.004	0.000	0.001	0.005	-0.004	0.000	0.006	0.011
C <sub>3</sub>	0.028	-0.000	0.038	-0.000	0.032	0.000	0.043	-0.000
C <sub>2</sub>	0.029	-0.000	0.062	-0.004	0.044	-0.000	0.076	-0.003
C <sub>1</sub>	0.088	-0.003	0.056	0.000	0.085	-0.004	0.051	0.000
G	-0.001	0.003	-0.006	-0.000	-0.015	0.001	-0.021	0.000
Cu	0.880	0.001	0.873	-0.000	0.874	0.001	0.882	0.001
3H <sub>2</sub> O	0.063	-0.001	0.050	0.000	0.054	0.000	0.066	-0.001

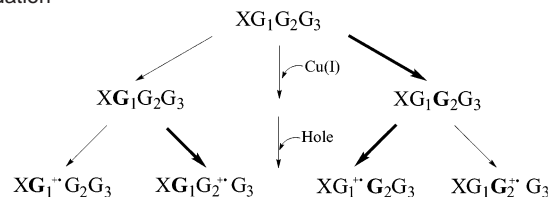
<sup>a</sup> G means a guanine coordinated by  $[Cu(H_2O)_3]^+$ .

**Table 6.** Total Energies (au), Spin Angular Momentums, Optimized Distances of N7–Cu (Å), and Relative Energies (kcal/mol) in Radical Cations,  $[5'-XG_1G_2G_3-3', -Cu(H_2O)_3]^{2+}$  (X = T and C)

complex	$E_{total}$	$\langle S^2 \rangle$	$R_{N7-Cu}$	$\Delta E_{rel}$
$TG_1^+G_2G_3$	-5890.852 664	0.9665	2.213	20.8
$TG_1G_2^+G_3$	-5890.885 842	0.9644	2.146	0.0
$TG_1^+G_2G_3$	-5890.880 206	0.9619	2.147	0.0
$TG_1G_2^+G_3$	-5890.866 513	0.9366	2.235	8.6
$CG_1^+G_2G_3$	-5906.851 192	0.9505	2.192	20.2
$CG_1G_2^+G_3$	-5906.883 392	0.9438	2.139	0.0
$CG_1^+G_2G_3$	-5906.883 706	0.9705	2.146	0.0
$CG_1G_2^+G_3$	-5906.868 847	0.9394	2.232	9.3

that G<sub>1</sub> is coordinated by Cu(I)(H<sub>2</sub>O)<sub>3</sub>, the  $TG_1G_2^+G_3$  state, in which G<sub>2</sub> next to G<sub>1</sub> is a radical cation, is more stable by 20.8 kcal/mol than the  $TG_1^+G_2G_3$  state in which G<sub>1</sub> is a radical cation. In the case of  $TG_1G_2G_3$  in which Cu(I)(H<sub>2</sub>O)<sub>3</sub> coordinates to G<sub>2</sub>, the state with the radical cation of G<sub>1</sub> at the 5'-site is more stable by 8.6 kcal/mol than the state with the radical cation of G<sub>2</sub>. Also, in both  $CG_1G_2G_3$  and  $CG_1G_2^+G_3$ , the state in which the neighbor G is the radical cation is more stable, being similar to the behavior of the radical cation state of TGGG. It is, therefore, concluded that ligand Cu(I)(H<sub>2</sub>O)<sub>3</sub> induces the radical cation state of XGGG in which the guanine neighbor to the guanine coordinated by Cu(I) ion has a positive charge and an unpaired spin.

In the previous papers,<sup>10d,20</sup> theoretical analyses of radical cations of 5'-TGGG-3' and 5'-CGGG-3' without Cu(I) mediation were examined. The 5'- $TG_1^+G_2G_3-3'$  state is more stable than the 5'- $TG_1G_2^+G_3-3'$  state but only by 1.3 kcal/mol. This means that the hole may be trapped by G<sub>1</sub> and G<sub>2</sub> with an equal probability in the radical cations of 5'-TGGG and the hole can reversibly move between 5'- $TG_1^+GG-3'$  and 5'- $TGG^+G-3'$ . On the other hand, in the case of the 5'- $CG_1G_2G_3-3'$  sequence, only

**Scheme 1.** Schematic Representation of G<sub>1</sub>-Selectivity of the GGG Triplet Sequence toward Cu(I)-Mediated One-Electron Oxidation

5'- $CGG^+G-3'$  state was found. This shows that the hole may be trapped at only G<sub>2</sub>. It was, therefore, concluded that the mechanism of G-selectivity of GGG triplets toward one-electron oxidation is different between 5'-TGGG-3' and 5'-CGGG-3'.<sup>20</sup>

However, in the present work, we can find all states of radical cations as shown in Tables 4–6. Both 5'- $CG^+GG-3'$  and 5'- $CGG^+G-3'$  are also obtained for both 5'-CGGG-3' and 5'-CGGG-3'. Furthermore, the difference of stability between G<sub>1</sub><sup>+</sup> and G<sub>2</sub><sup>+</sup> are significantly large, compared with those without Cu(I) coordination. This shows that the hole is trapped by one of G<sub>1</sub> and G<sub>2</sub> with high probability. In other words, Cu(I) coordination induces the condition in which the hole is selectively trapped by G<sub>1</sub> and G<sub>2</sub>.

### G<sub>1</sub>-Selectivity of XGGG Mediated by Cu(I) Ion

G<sub>1</sub>-selectivity of XGGG mediated by Cu(I) ion toward one-electron oxidation can be simply elucidated. Our present discussion on stability of  $[-XG_1G_2G_3-, -Cu(I)(H_2O)_3]^+$  and  $[-XG_1G_2G_3-, -Cu(I)(H_2O)_3]^{2+}$  leads to the schematic presentation shown in Scheme 1. Cu(I) ion selectively coordinates to G<sub>2</sub> of  $-XG_1G_2G_3-$ , rather than G<sub>1</sub>. The hole is selectively trapped on G<sub>1</sub> rather than G<sub>2</sub>, leading to G<sub>1</sub> being selectively damaged. In other words, G<sub>1</sub>-selectivity mediated by Cu(I) ion toward one-

electron oxidation is due to the G<sub>2</sub>-selective coordination of Cu(I) ion to -XG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-.

### Summary

The G-selectivity for Cu(I)-mediated one-electron oxidation of 5'-TGGG-3' and 5'-CGGG-3' has been examined by ab initio MO calculations. Our conclusions are summarized as follows: (1) The Cu(I)-mediated G-selectivity is primarily due to the stability of [-XG<sub>1</sub>G<sub>2</sub>G<sub>3</sub>-,Cu(I)(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup>; that is, Cu(I) ion coordinates selectively to N7 of G<sub>2</sub>. The electron-loss center created in duplex DNA ultimately moves to end up at GGG via hole migration through the π-stack. After the G<sub>2</sub>-selective coordination, the hole is trapped selectively at G<sub>1</sub>. The created G<sub>1</sub><sup>•+</sup> loses the N1 proton via transfer to N3 of cytosine of the base pair under the experimental condition of neutral pH, yielding the G<sub>1</sub><sup>•</sup> neutral radical without N1 proton. G<sub>1</sub><sup>•</sup> is damaged to give imidazolone by the attack of molecular oxygen to C5 of guanine. Briefly speaking, the conclusion is that G<sub>1</sub>-selectivity is due to G<sub>2</sub>-selective coordination of Cu(I) ion.

(2) The G<sub>2</sub>-selective coordination of Cu(I) ion is caused by the HOMO distribution that the middle G<sub>2</sub> of G<sub>1</sub>G<sub>2</sub>G<sub>3</sub> has the largest fraction of the electron density in HOMO of the GGG triplet. Stability of the G<sub>2</sub>-coordination will be enhanced by charge donation from the lone-paired electron orbital (σ-orbital) of N7 of G<sub>2</sub> to the unoccupied 4s orbital of Cu(I) ion.

(3) 5'-XGGG-3' has enough space for coordination of [-Cu(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> to yield [-XGGG-,Cu(I)(H<sub>2</sub>O)<sub>3</sub>]<sup>+</sup> with the stabilization energy by 35–45 kcal/mol as H<sub>2</sub>O replacement of [Cu(H<sub>2</sub>O)<sub>4</sub>]<sup>+</sup> by 5'-XGGG-3'.

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