

## 기체상에서 $\text{Cu}^+$ 및 $\text{Cu}^{2+}$ 이온과 Proline의 상호작용

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## Interaction of Proline with $\text{Cu}^+$ and $\text{Cu}^{2+}$ Ions in the Gas Phase

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**요 약.**  $\text{Cu}^+$  및  $\text{Cu}^{2+}$ 와 proline의 결합형태에 따른 구조 및 금속 친화도를 DFT(Density Functional Theory) 방법으로 조사하였다. 금속-proline의 결합과 여러 결합형태에 따른 에너지 순서는  $\text{Cu}^+$ -Proline 및  $\text{Cu}^{2+}$ -proline 착화합물에서 서로 매우 상이함을 알았다.  $\text{Cu}^+$ -Proline의 경우, 바닥상태의 구조는  $\text{Cu}^+$ 가 중성 proline의 카르보닐 산소 및 이미노기 질소에 배워진 두 자리 배위를 하며, 이에 비해  $\text{Cu}^{2+}$ -Proline의 바닥상태의 구조는 zwitter이온 형태 proline의 카르복시기의 두 산소 사이에 chelation을 형성하는 구조임을 확인하였다. 가장 안정한  $\text{Cu}^+$ -Proline 착화합물에서 proline의 금속 이온 친화도는 6-311++G(d,p) 수준에서 76.0 kcal/mol로 계산되었으며, proline의  $\text{Cu}^{2+}$  이온 친화도는 258.5 kcal/mol로 나타났다.

**주제어:** 구리, Proline, 금속이온친화도, 기체상, DFT계산

**ABSTRACT.** The structures and metal affinities of the binding configurations of  $\text{Cu}^+$  and  $\text{Cu}^{2+}$  to proline have been investigated using the hybrid three-parameter Density Functional Theory(DFT/B3LYP). We found that the metal-proline bonding and the energy ordering of several conformers were very different in  $\text{Cu}^+$ -proline and  $\text{Cu}^{2+}$ -proline. For  $\text{Cu}^+$ -proline, the ground state structure was found to have a bidentated coordination in which  $\text{Cu}^+$  was coordinated to the carbonyl oxygen and imino group nitrogen of neutral proline. On the contrary, the ground state structure of  $\text{Cu}^{2+}$ -proline involves chelation between the two oxygens of the carboxylate group in a zwitterionic proline. The metal ion affinity of proline of the most stable  $\text{Cu}^+$ -proline complex was calculated as 76.0 kcal/mol at 6-311++G(d,p) level, whereas the  $\text{Cu}^{2+}$  ion affinity of proline was calculated as 258.5 kcal/mol.

**Keywords:** Copper, Proline, Metal ion affinity, Gas phase, DFT calculation

## INTRODUCTION

Copper ions are the most important transition metals involved in several biological processes of living systems, including oxidation, dioxygen transport, and charge transfer.<sup>1</sup> The study of interactions between the metal ion and amino acids has attracted considerable attention from experimental<sup>2-6</sup> and theoretical<sup>6-11</sup> viewpoints. Thermochemical information on interactions between the metal ion

and biological molecules is essential as it can help us understand the role of the metal in several essential biochemical processes. The thermochemical properties can be obtained in the gaseous state where solvent effects are absent.

Proline is a constituent of collagen and plays an important role in enzymes and peptide hormone.<sup>12</sup> Proline has an imino group within the pyrrolidine ring, therefore making conformation more rigid than for other amino acids.

The binding energies for  $\text{Cu}^-$  complexes with 20 commonly found  $\alpha$ -amino acids in natural peptides have been determined in the gas phase.<sup>13</sup> Hoyau and Ohanessian have studied  $\text{Cu}^+$  ion affinities for glycine, serine, and cysteine by using an extensive theoretical method.<sup>14</sup> The results showed that the most favorable structure for  $\text{Cu}^+$ -glycine involves metal chelation between the carbonyl oxygen and amino nitrogen of glycine. The effects of metal ions ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$ ) on the structures and ion affinities of arginine-metal complexes have been studied by Remko *et al.*<sup>15</sup> The results confirmed that the strongest affinity to arginine is exhibited by the  $\text{Cu}^{2+}$  cation.

On the other hand, the interaction of proline with  $\text{Cu}^-$  has been investigated using *ab initio* methods by Hoyau and Ohanessian.<sup>16</sup> Marino *et al.*<sup>17</sup> have observed the  $\text{Cu}^+$  and  $\text{Cu}^{2+}$  preferred binding sites on  $\alpha$ -alanine and their affinity values for this amino acid by density functional theory calculations. The results showed that the two ions both demonstrate stable complexes with  $\alpha$ -alanine but stability order of the metalated complexes and the binding sites are different depending on the nature of the cation. Bertr n *et al.*<sup>18</sup> have reported the results of a study of the different nature in bonding of glycine with  $\text{Cu}^-$  and  $\text{Cu}^{2+}$  ions by theoretical calculations.

In spite of various theoretical studies of amino acid complexes of copper ions, no effort has been reported to estimate the different nature of bonding in  $\text{Cu}^-$  and  $\text{Cu}^{2+}$  with proline.

$\text{Cu}^-$  possesses a closed-shell system with a  $d^{10}$  ground state, while  $\text{Cu}^{2+}$  possesses an open-shell system with a  $d^9$  ground state. Therefore, these two copper ions are associated with very different chemistries. In this paper, we report the differences between  $\text{Cu}^-$  and  $\text{Cu}^{2+}$  with regard to their proline complexes.

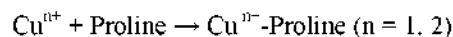
## COMPUTATIONAL METHODS

The Density Functional Theory (DFT) calculations were performed at the B3LYP level<sup>19,20</sup> with a

6-311++G(d,p) internal basis set for all atoms using the Gaussian 03 program.<sup>21</sup> It is shown that the density functional method provides accurate results for many transition metal-containing systems.<sup>22-24</sup> Unrestricted open shell methods were used to calculate the  $\text{Cu}^{2+}$  system

The equilibrium geometries for all the structures were fully optimized without any symmetry restrictions. Harmonic frequencies were also calculated to confirm that all the stationary points corresponded to true minima on the potential energy surface. The stationary structures were obtained by verifying that all of the harmonic frequencies are real. The natural atomic charges were calculated in order to analyze the nature of the bonding for complexes of copper with proline.

Copper ion affinities were calculated as the negative value of the enthalpy change ( $\Delta H$ ) associated with the following reaction:



## RESULTS AND DISCUSSION

The conformational behavior of amino acids is essential to understand their dynamic role in protein formation.<sup>25</sup> Therefore, extensive structural studies have been performed on amino acids in their natural solid state. However, amino acids have a zwitterionic structure in their solid state. Consequently, to obtain the neutral structure of amino acids, studies should be performed in the gas phase. Proline is the only natural amino acid that contains a secondary amino group as part of a flexible five-membered ring.

A number of experimental studies on the structure of the proline have been conducted in the condensed phase:<sup>26-28</sup> these studies include an x-ray diffraction analysis of the zwitterionic ring conformation, because of the high melting point of proline and associated low-vapor pressure. To date, no experimental structure of neutral proline has been reported. Ramek *et al.*<sup>29</sup> located 10 distinct conformers of proline at the 6-311++G\*\* RHF level, and Stepanian *et al.*<sup>30</sup> determined 15 stable minima on the PES of

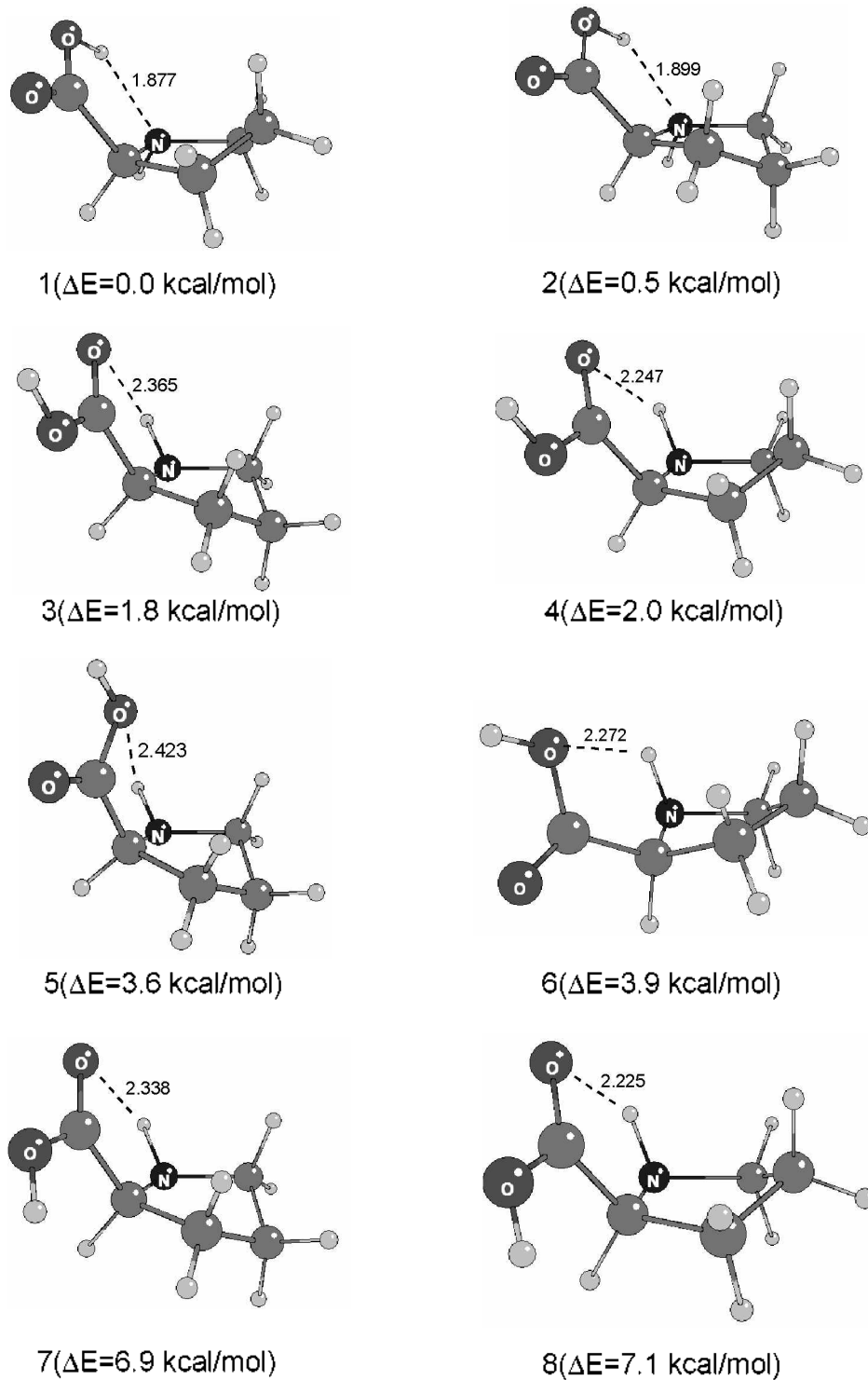


Fig. 1. Optimized structures at the B3LYP/6-311++G(d,p) level of eight neutral prolines numbered according to their relative energy order. Hydrogen bond lengths are in Å.

proline using DFT. Czinki and Csazar<sup>31</sup> reported that proline has 18 possible stable conformers at high levels of *ab initio* electronic-structure theory. Fig. 1 shows the numbering of the 8 conformers of neutral proline, which reflects the relative energies of the distinct conformers obtained at DFT optimized geometries in this study.

As shown in Fig. 1, the optimized geometries of proline are classified according to the type of intramolecular hydrogen bond( $\text{N}\cdots\text{H}-\text{O}$ ,  $\text{N}-\text{H}\cdots\text{O}=\text{C}$ , and  $\text{N}-\text{H}\cdots\text{O}-\text{H}$ ) and the nature of the bent configuration of the pyrrolidine ring(pucker-up and pucker-down).

Conformer 1 was found to be at the global minimum. The next stable structure is conformer 2. However, the energy difference between the global and first local minimum(2) is only 0.5 kcal/mol. Further, the only difference between conformers 1 and 2 is the pucker position of the pyrrolidine ring. These two conformers are stabilized relative to conformers 3 and 4 because the  $\text{N}\cdots\text{H}-\text{O}$  hydrogen bonds are more favorable to the secondary amine in proline (1.88 or 1.90 Å in conformers 1 and 2 versus 2.4 or 2.2 Å in conformers 3 and 4). This leads to conformers 1 and 2 being more stable than conformers 3 and 4. In contrast to simpler amino acids such as glycine and alanine, only a few low-energy conformers exist on the PES of neutral proline. Conformer pairs 1/2 and 3/4 are the only ones that have relative energies of less than 2 kcal/mol relative to the global minimum conformer 1. For the zwitterionic form, we have considered only the complexes formed by proline with the copper ion.

The optimized structures for eight low-energy conformers of  $\text{Cu}^-$ -proline and  $\text{Cu}^{2+}$ -proline are shown in Fig. 2 and 3, respectively. In addition, calculated energies, including the natural atomic charges of metal, are listed in Table 1.

Table 1 shows that the most favorable structure of  $\text{Cu}^+$ -proline corresponds to the  $\text{Cu}^+$  ion interacting with the imino nitrogen atom on the pyrrolidine ring with a pucker-down position and with the carbonyl oxygen on the carboxylate group, as observed in structure 3. In this conformer, the  $\text{Cu}^-$ -

O and  $\text{Cu}^-$ -N bond lengths are 2.090 and 2.043 Å, respectively. A similar result was found for the copper-glycine complex<sup>14,18</sup> and for the copper- $\alpha$ -alanine complex.<sup>17</sup> The second most favorable structure, complex 4, possesses 0.9 kcal/mol more energy and has the same type of chemical coordination, although it has the pucker-up form of a pyrrolidine ring. For the zwitterionic conformers (structure 1 and 2), Fig. 2 shows that the  $\text{Cu}^+-\text{O}$  distances are quite different(1.90 and 2.91 Å); thus, it can be deduced that proline acts as a monodentate ligand. This unsymmetrical coordination may be due to the hydrogen bond between the oxygen and the amino hydrogen. However, in the  $\text{Cu}^{2+}$ -proline complexes, the  $\text{Cu}^{2+}$ -O distances between the metal cation and the two oxygens are very similar(1.96 and 1.99 Å). This trend is also shown in analogous  $\text{M}^+-\text{COO}^-$  coordination with alkali metal cations.<sup>7</sup> Thus, we attribute the difference between  $\text{Cu}^-$  and  $\text{Cu}^{2+}$  cations to the fact that  $\text{Cu}^-$  tends to undergo an unsymmetrical interaction to minimize the repulsion between the occupied d orbitals of metal and the lone pairs of oxygens.

On the other hand, the most favorable structure of the  $\text{Cu}^{2+}$ -proline has a zwitterionic bonding arrangement, wherein binding occurs between the two carboxylate oxygens and the cation. To further investigate the nature of bonding, the natural population analyses were performed by the natural bond orbital(NBO) method. NBO calculations

Table 1. Relative energies of  $\text{Cu}^-$ -proline and  $\text{Cu}^{2+}$ -proline complexes(in kcal/mol) and natural atomic charges of the metal cation at B3LYP/6-311++G(d,p) level

Structures	$\text{Cu}^+$ -proline		$\text{Cu}^{2+}$ -proline	
	$\Delta E$	Charges	$\Delta E$	Charges
1	3.9	0.866	0.0	1.317
2	3.5	0.868	0.6	1.317
3	0.0	0.873	4.1	1.334
4	0.9	0.869	5.1	1.333
5	6.5	0.878	10.5	1.348
6	7.3	0.873	11.6	1.345
7	9.9	0.884	22.9	1.270
8	10.8	0.883	23.0	1.257

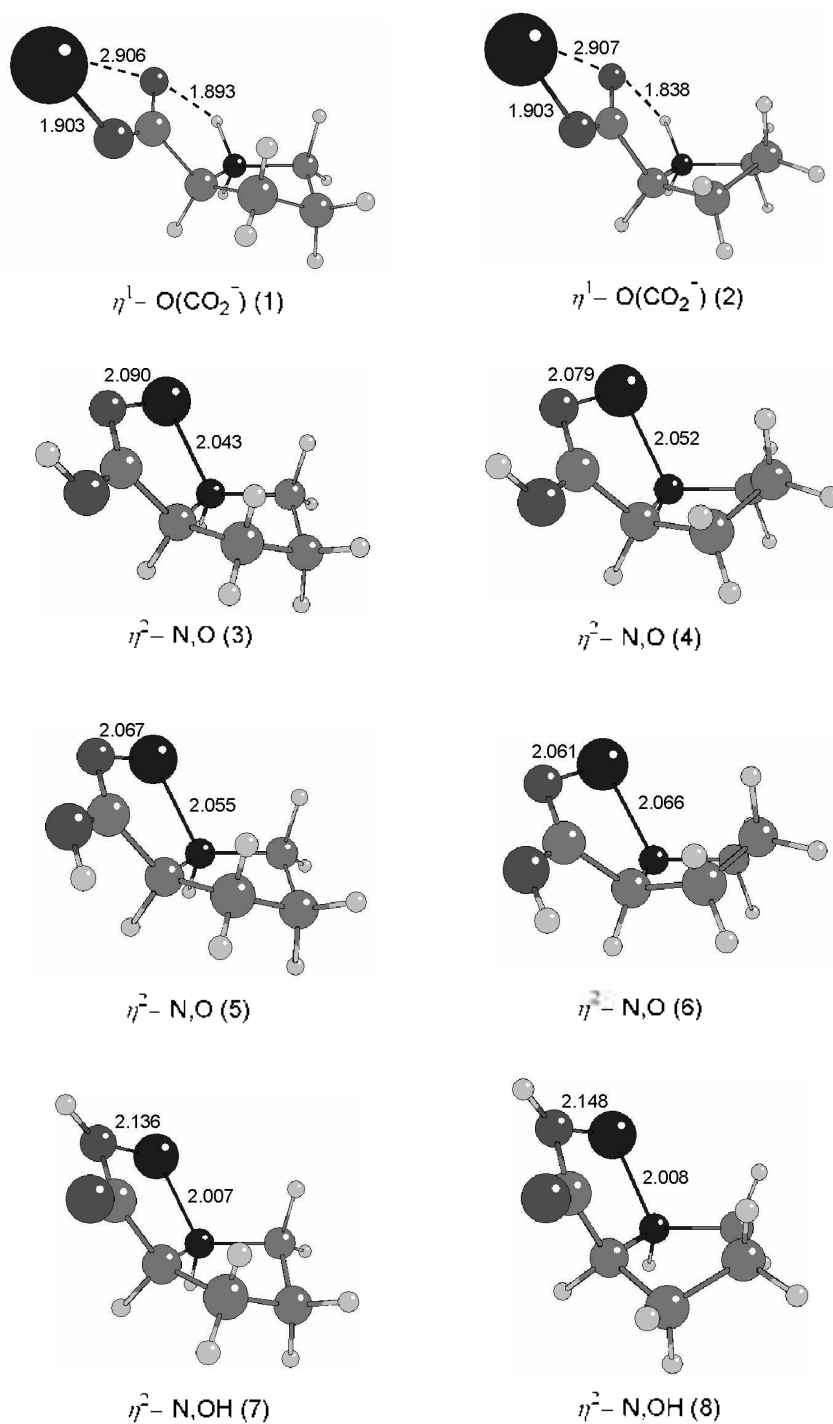


Fig. 2. Optimized structures at B3LYP/6-311++(d,p) level of theory of  $\text{Cu}^+$ -proline complexes. Distances are in Å.

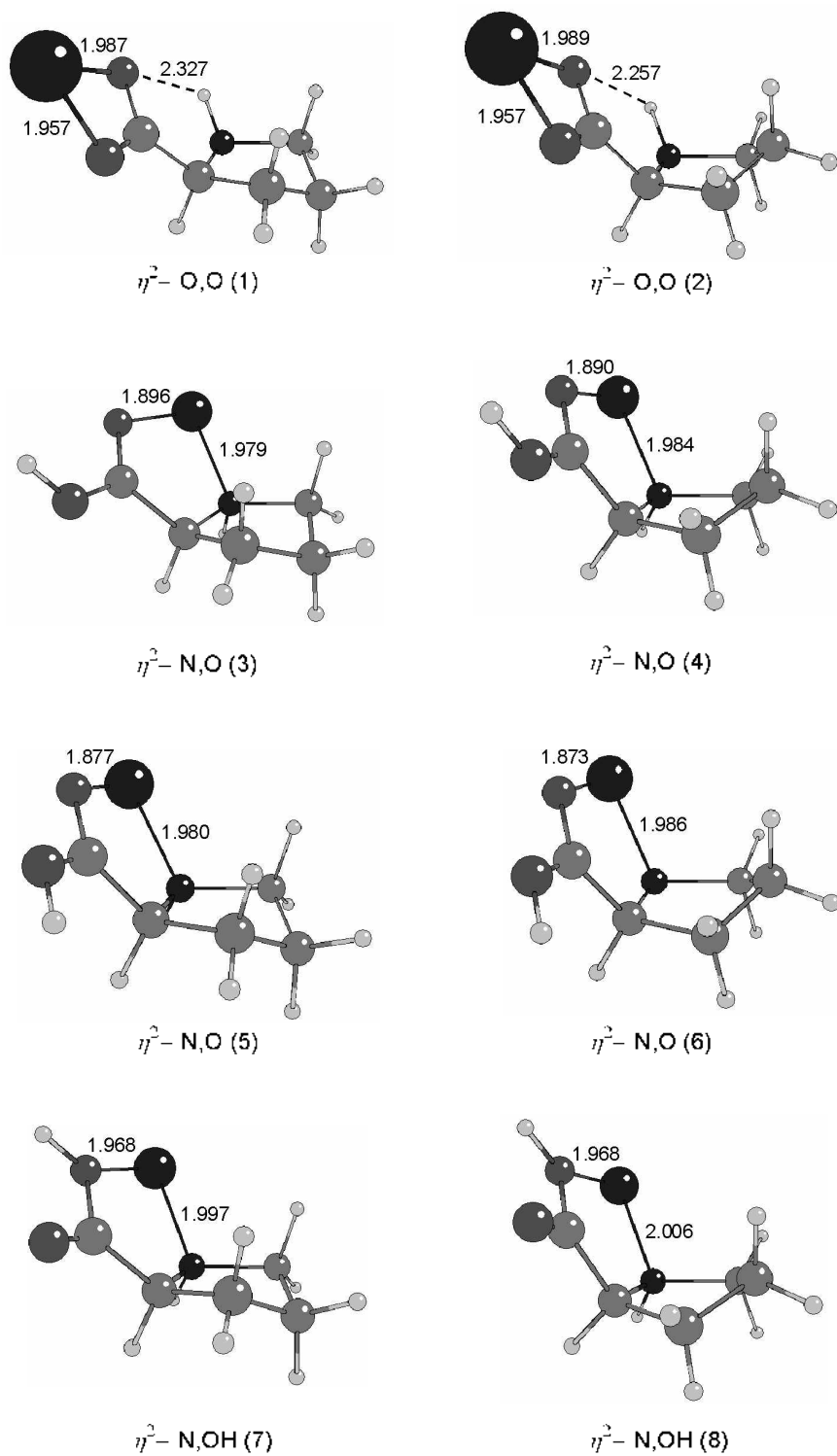


Fig. 3. Optimized structures at B3LYP/6-311++G(d,p) level of theory of  $\text{Cu}^{2+}$ -proline complexes. Distances are in Å.

were carried out for the optimized structures of copper-proline complexes. The calculated natural atomic charges are shown in *Table 1*. As shown in *Table 1*, the natural charge on the  $\text{Cu}^+$  ion is reduced by about 0.13|e|, whereas the charge on the  $\text{Cu}^{2+}$  is reduced by about 0.68|e|. This means that in the  $\text{Cu}^{2+}$ -proline complex, the ligand transfers a large amount of electrons to the cation. This result suggests that in comparison with the binding of  $\text{Cu}^-$  to proline, that of  $\text{Cu}^{2+}$  to proline involves a higher contribution of charge transfer rather than electrostatic effects.

For the zwitterionic isomers, namely, structures 1 and 2, the distances between the cation  $\text{Cu}^{2+}$  and the two oxygens are more similar than those obtained for  $\text{Cu}^+$ -proline. This difference is due to the smaller metal-ligand repulsion in the  $\text{Cu}^{2+}$ -proline system, which favors the symmetrical position of the metal cation. Moreover, the intramolecular hydrogen bond, present in  $\text{Cu}^+$ -proline; that is, the  $\text{O} \cdots \text{H}-\text{N}$  distance increases significantly. It is also noteworthy that, in the bicoordinated conformers 3 ~ 8,  $\text{Cu}^{2+}-\text{O}$  and  $\text{Cu}^{2+}-\text{N}$  distances were found to be shorter than the corresponding  $\text{Cu}^+-\text{O}$  and  $\text{Cu}^+-\text{N}$  distances. As mentioned above, this result is due to the repulsion effect between the filled d orbitals of  $\text{Cu}^-$  and the lone pairs of the ligand heteroatoms.<sup>17</sup>

*Table 1* shows that the energy ordering of the different conformers obtained for the  $\text{Cu}^{2+}$ -proline is very different from the ordering for  $\text{Cu}^-$ -proline. For the  $\text{Cu}^+$ -proline system, the order is structures  $3 < 4 < 2 < 1 < 5 < 6 < 7 < 8$ , whereas for  $\text{Cu}^{2+}$ -proline, the order is structures  $1 < 2 < 3 < 4 < 5 < 6 < 7 < 8$ . Thus, the ground state structure of  $\text{Cu}^{2+}$ -proline corresponds to that of conformer of zwitterionic structure 1 and not to that of structure 3 as found for  $\text{Cu}^-$ -proline. This observation is in good agreement with the experimental results that show that  $\text{Cu}^{2+}$  has some affinity to the C-terminal carboxylate group.<sup>32,33</sup> In other words, the most stable conformer comprises the  $\text{Cu}^{2+}$  ion interacting with zwitterionic proline through the carboxylate group in a bidentate manner, unlike the case of the  $\text{Cu}^+$  ion. A similar result is obtained for group 1

metal ions ( $\text{Li}^+$ ,  $\text{Na}^+$  and  $\text{K}^+$ ) binding with proline.<sup>34</sup>

The metal ion affinities (MIAs) were computed for the eight investigated binding arrangements of  $\text{Cu}^-$  and  $\text{Cu}^{2+}$ , as listed in *Table 2*. The MIAs were computed as the enthalpy difference between the corresponding complex and the sum of  $\text{Cu}^{2+}$  and the most stable conformer of the free proline. As shown in *Table 2*, there is a significant difference between the MIA values of  $\text{Cu}^-$  and  $\text{Cu}^{2+}$ . The MIA values of the  $\text{Cu}^{2+}$  ion are much larger than those of  $\text{Cu}^+$ . This large difference may be due to the  $\text{Cu}^{2+}$  ion possessing a greater charge than the  $\text{Cu}^-$  ion. No experimental value for  $\text{Cu}^{2+}$  ions is available in the literature for comparison with the value calculated in this paper. Cerda and Wesdemiotis<sup>13</sup> have reported experimental results on the affinity of copper(I) to various amino acids. However, no absolute values were reported. With regard to the theoretical studies performed thus far, Fleming *et al.*<sup>35</sup> have reported absolute MIAs for alkali earth metal ions ( $\text{Be}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ) bound to proline. With the DFT(B3LYP/6-311++G\*\*) method, these affinities were determined as follows:  $\text{Be}^{2+}=301.52$  kcal/mol,  $\text{Mg}^{2+}=184.29$  kcal/mol, and  $\text{Ca}^{2+}=139.95$  kcal/mol. As shown in *Table 2*, the MIAs of the  $\text{Cu}^{2+}$  ion are larger than those of  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$ , and are smaller than those of  $\text{Be}^{2+}$ . The MIA of the most stable  $\text{Cu}^-$ -proline conformer is calculated as 76.0 kcal/mol. This MIA value is larger than the values for alkali metal ions ( $\text{Li}^+=64.21$  kcal/mol,  $\text{Na}^+=47.32$  kcal/mol and  $\text{K}^+=34.62$  kcal/mol)<sup>34</sup> bound to proline.

On the other hand, the MIAs calculated in this

*Table 2.* Metal ion affinities of  $\text{Cu}^-$ -proline and  $\text{Cu}^{2+}$ -proline at B3LYP/6-311++G(d,p) level (in kcal/mol)

Structures	$\text{Cu}^-$ -proline	$\text{Cu}^{2+}$ -proline
1	71.6	258.5
2	72.1	258.0
3	76.0	255.4
4	75.1	254.5
5	69.6	248.9
6	68.8	248.0
7	66.3	237.7
8	65.5	227.7

study for the most stable  $\text{Cu}^+$ -proline and  $\text{Cu}^{2-}$ -proline are larger than the corresponding values for the copper-glycine complexes<sup>18</sup> ( $\text{Cu}^+=68.1$  kcal/mol and  $\text{Cu}^{2+}=214.8$  kcal/mol at CCSD(T) level) and for the copper- $\alpha$ -alanine complexes<sup>17</sup> ( $\text{Cu}^+=68.2$  kcal/mol and  $\text{Cu}^{2-}=220.7$  kcal/mol at BHandHLYP level). No experimental data have been reported absolute values of the copper ion affinity to amino acids. The only experimental study<sup>13</sup> shows that the relative  $\text{Cu}^+$  affinity of proline is larger than that of the glycine by 4.8 kcal/mol, and is larger than that of the  $\alpha$ -alanine by 3.1 kcal/mol. The result in this study is in good agreement with this experimental trend.

## CONCLUSION

A study of the metal-proline bonding for several modes of coordination of  $\text{Cu}^+$  and  $\text{Cu}^{2-}$  with proline is reported. The  $\text{Cu}^+$  ion has a tendency to bind to proline in a electrostatic interaction arrangement through the carbonyl oxygen and imino nitrogen atom. In contrast,  $\text{Cu}^{2-}$  tends to bind to proline by means of a charge-transfer mechanism through the two carboxylate oxygens of proline in a zwitterionic form. For the  $\text{Cu}^{2-}$ -proline, the obtained energy ordering of the different conformers is very different from that determined for the single positive  $\text{Cu}^+$ -proline system. The ground state structure of  $\text{Cu}^{2-}$ -proline is zwitterionic in nature, as observed from the interaction of the metal cation with the  $\text{COO}^-$  group of the zwitterionic proline. Thus, the proline favors the interaction of the  $\text{Cu}^{2-}$  cation with the carboxylate group as compared to other coordination modes. The calculated MIA shows that the  $\text{Cu}^+$  ion affinity is larger than the alkali metal ion affinity bound to proline and the affinity of  $\text{Cu}^{2+}$  ion is larger than that of  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$ , but smaller than that of  $\text{Be}^{2+}$ . The  $\text{Cu}^-$  ion affinity of proline is larger than that of the glycine and  $\alpha$ -alanine.

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