

# The Different Nature of Bonding in $\text{Cu}^+$ -Glycine and $\text{Cu}^{2+}$ -Glycine

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A comparative study of the metal–glycine bonding for the biologically relevant  $\text{Cu}^+$  and  $\text{Cu}^{2+}$  pair is presented. The structure and vibrational frequencies for several coordination modes of  $\text{Cu}^+$  and  $\text{Cu}^{2+}$  to glycine have been determined using the hybrid three-parameter B3LYP density functional approach. Single-point calculations have also been carried out at the modified coupled pair functional (MCPF) and single- and double- (triple) excitation coupled cluster (CCSD(T)) levels of theory and using larger basis sets. Calculations have shown that the metal–glycine bonding and the energy ordering of the different conformers are very different in  $\text{Cu}^+$ -glycine than in  $\text{Cu}^{2+}$ -glycine. Whereas for  $\text{Cu}^+$ -glycine, the ground state structure is found to have a bidentated  $\eta^2\text{-N,O}$  coordination in which  $\text{Cu}^+$  interacts with the nitrogen of the amino group and the carbonyl oxygen, the ground state structure of  $\text{Cu}^{2+}$ -glycine is the  $\eta^2\text{-O,O}$  ( $\text{CO}_2^-$ ) one, derived from the interaction of the metal cation with the  $\text{CO}_2^-$  terminus of the zwitterionic glycine. In this case, the results seem to indicate that glycine acquires an important radical character that changes the relative metal affinities of the different basic sites, which favors the interaction of the metal cation with the  $\text{CO}_2$  group compared with other coordinations.

## I. Introduction

Gas-phase transition metal ion chemistry has experienced a very important growth during the past two decades,<sup>1</sup> due to the importance of transition metal–ligand systems in several fields such as catalysis, atmospheric chemistry, or biochemistry. In particular, the study of metal binding affinities to biologically relevant molecules has attracted considerable attention both from an experimental<sup>2–11</sup> and theoretical<sup>11–18</sup> point of view. Thermodynamic information on metal ion–protein interactions is of great interest because it can help us understand the role of the metal in many essential biochemical processes. Moreover, such information can be very useful in interpreting the mass spectrometry experiments<sup>2,3</sup> used for the elucidation of the sequence of peptides cationized by alkali, alkaline earth-, and transition metal cations.

Previously, the relative  $\text{Cu}^+$  ion affinities of the 20 common  $\alpha$ -amino acids have been determined in the gas phase.<sup>7</sup> Prompted by this paper, Hoyau and Ohanessian have performed an extensive theoretical study<sup>17</sup> of  $\text{Cu}^+$  interacting with glycine, serine, and cysteine, which has allowed the determination of the absolute  $\text{Cu}^+$  affinities and the obtaining of structural information of these metal–amino acid systems. The results obtained indicate that the lowest energy structure of  $\text{Cu}^+$ -glycine has the metal ion interacting with the carbonyl oxygen and the amino nitrogen.

$\text{Cu}^{2+}$  also plays a very important role in many biochemical processes. Previously, an experimental gas-phase coordination study has found that the major fragmentations of  $\text{Cu}^{2+}$ -peptide complexes originate from the removal of  $\text{CO}_2$  and occur in the vicinity of the C terminus, suggesting that  $\text{Cu}^{2+}$  has some affinity to the C-terminal carboxylate group.<sup>9</sup>  $\text{Cu}^{2+}$  is an open shell system with a  $d^9$  ( $^2\text{D}$ ) ground state, whereas  $\text{Cu}^+$  has a closed shell  $d^{10}$  ( $^1\text{S}$ ) ground state. In addition to an enhanced electrostatic interaction in  $\text{Cu}^{2+}$ -glycine, and to a smaller metal–ligand repulsion, the radical character of  $\text{Cu}^{2+}$ , which can easily be reduced to  $\text{Cu}^+$ , can provide a very different chemistry

between the two cations. It is thus interesting to analyze the differences between  $\text{Cu}^+$  and  $\text{Cu}^{2+}$ . In this paper we determine different conformers of  $\text{Cu}^{2+}$  coordinating to glycine, the simplest amino acid, and compare them with those obtained for  $\text{Cu}^+$ . The results will show that whereas for  $\text{Cu}^+$  the most stable coordination is a bidentated  $\eta^2\text{-N,O}$  one (the cation interacts with the nitrogen and the carbonyl oxygen atoms), for  $\text{Cu}^{2+}$  the preferred coordination is the bidentated  $\eta^2\text{-O,O}$  one, in which the metal interacts with the  $\text{CO}_2^-$  group of the zwitterionic species.

## II. Methods

Full geometry optimizations and harmonic frequency calculations for different conformers of  $\text{Cu}^+$ -glycine and  $\text{Cu}^{2+}$ -glycine have been performed using the nonlocal three-parameter hybrid exchange B3LYP density functional method.<sup>19</sup> The adequacy of density functional methods for the study of the conformational behavior of glycine and other amino acids has been the subject of several recent papers.<sup>20–25</sup> It is shown that the hybrid methods, in particular the B3LYP one,<sup>20–23</sup> provide very similar structural parameters compared with MP2 and that the density functional vibrational frequencies and intensities are in excellent agreement with the experimental data.

Moreover, the hybrid scheme B3LYP has been shown to provide accurate results for many transition metal-containing systems.<sup>26–30</sup> However, it is always convenient to confirm the reliability of the B3LYP method applied to this kind of system by using highly accurate methods. Thus, we have performed single-point calculations, at the B3LYP geometries, using the essentially size-extensive modified coupled-pair functional (MCPF) method,<sup>31</sup> and the single- and double-excitation coupled cluster method<sup>32</sup> with a perturbational estimate of the triple excitations [CCSD(T)].<sup>33</sup> MCPF and CCSD(T) calculations have been carried out correlating the 3d electrons of the metal ion and all the electrons of glycine, except the 1s-like electrons of C, N, and O. Open shell calculations at the MCPF and CCSD-

(T) level are spin restricted. B3LYP calculations are based on a spin-unrestricted formalism.

Geometry optimizations and frequency calculations have been performed using the following basis set. The Cu basis set is a [8s4p3d] contraction of the (14s9p5d) primitive set of Wachters<sup>34</sup> supplemented with two diffuse p and one diffuse d functions.<sup>35</sup> The final basis set is of the form (14s11p6d)/[8s6p4d]. For C, N, and O we used the (9s5p)/[4s2p] set developed by Dunning<sup>36</sup> from the primitive set of Huzinaga<sup>37</sup> supplemented with a set of diffuse sp functions ( $\alpha = 0.0438$  for carbon,  $\alpha = 0.0639$  for nitrogen, and  $\alpha = 0.0845$  for oxygen) and one 3d polarization function ( $\alpha = 0.75$  for carbon,  $\alpha = 0.80$  for nitrogen, and  $\alpha = 0.85$  for oxygen). For hydrogen, the basis set used is the (4s)/[2s] set of Dunning<sup>36</sup> supplemented with a diffuse function ( $\alpha = 0.036$ ) and a p polarization function ( $\alpha = 1.00$ ). Hereafter, this basis set will be referred as Basis1.

Single-point calculations have been carried out using a larger basis set for the metal ion that include a set of f polarization functions based on a three-term fit<sup>38</sup> to a Slater-type orbital of exponent 4.8. This enlarged basis set of the metal combined with the previous basis used for glycine will be referred as Basis2. When combined with the larger aug-cc-pVTZ,<sup>39</sup> in which one diffuse d and one diffuse f functions have been removed, this will be denoted as Basis3.

To analyze the nature of the bonding we have used the natural population analysis of Weinhold and Carpenter.<sup>40</sup> B3LYP calculations have been performed with the Gaussian94 package.<sup>41</sup> MCPF results have been obtained with the MOLCAS<sup>42</sup> program and the CCSD(T) ones with the MOLPRO 96 package.<sup>43</sup>

### III. Results and Discussion

In the gas phase, glycine is known to exist in the neutral form (NH<sub>2</sub>-CH<sub>2</sub>-COOH), the zwitterionic (NH<sub>3</sub><sup>+</sup>-CH<sub>2</sub>-COO<sup>-</sup>) structure not even being a minimum on the potential energy surface.<sup>44</sup> This zwitterionic structure, however, may be more stabilized through the interaction with metal cations than the neutral form, the two structures becoming competitive. Thus, the coordination of copper ions with both the neutral and the zwitterionic forms of glycine has been considered. For the neutral form of glycine, we have considered three different bidentated structures in which the metal ion is coordinating to the nitrogen and oxygen atoms, and one structure in which the metal is allowed to interact with the two oxygens of the carboxyl group. For the zwitterionic glycine, we have considered only the interaction of the metal ion with the CO<sub>2</sub><sup>-</sup> terminus.

Figures 1 and 2 show the obtained minima of Cu<sup>+</sup>-glycine and Cu<sup>2+</sup>-glycine. The computed relative energies are given in Table 1. Although the results obtained for Cu<sup>+</sup>-glycine are very similar to those reported by Hoyau and Ohanessian,<sup>17</sup> we have included them in the present work to compare Cu<sup>+</sup> and Cu<sup>2+</sup> by using exactly the same theoretical method and basis set. Moreover, we include an analysis of the bonding to understand the relative energies of the different conformers. This analysis has allowed us to get a deeper insight of the different behavior of the two metal cations.

**A. Cu<sup>+</sup>-Glycine.** Let us first analyze the Cu<sup>+</sup>-glycine system. All optimized structures have C<sub>1</sub> symmetry except the  $\eta^1$ -O(COOH), which has C<sub>s</sub> symmetry. Table 1 shows that the most stable structure corresponds to the metal ion interacting with the nitrogen and the carbonyl oxygen,  $\eta^2$ -N,O (1), as found previously.<sup>17</sup> The second most stable structure,  $\eta^2$ -N,O (2), lies 6.7 kcal/mol above and has the same type of chemical

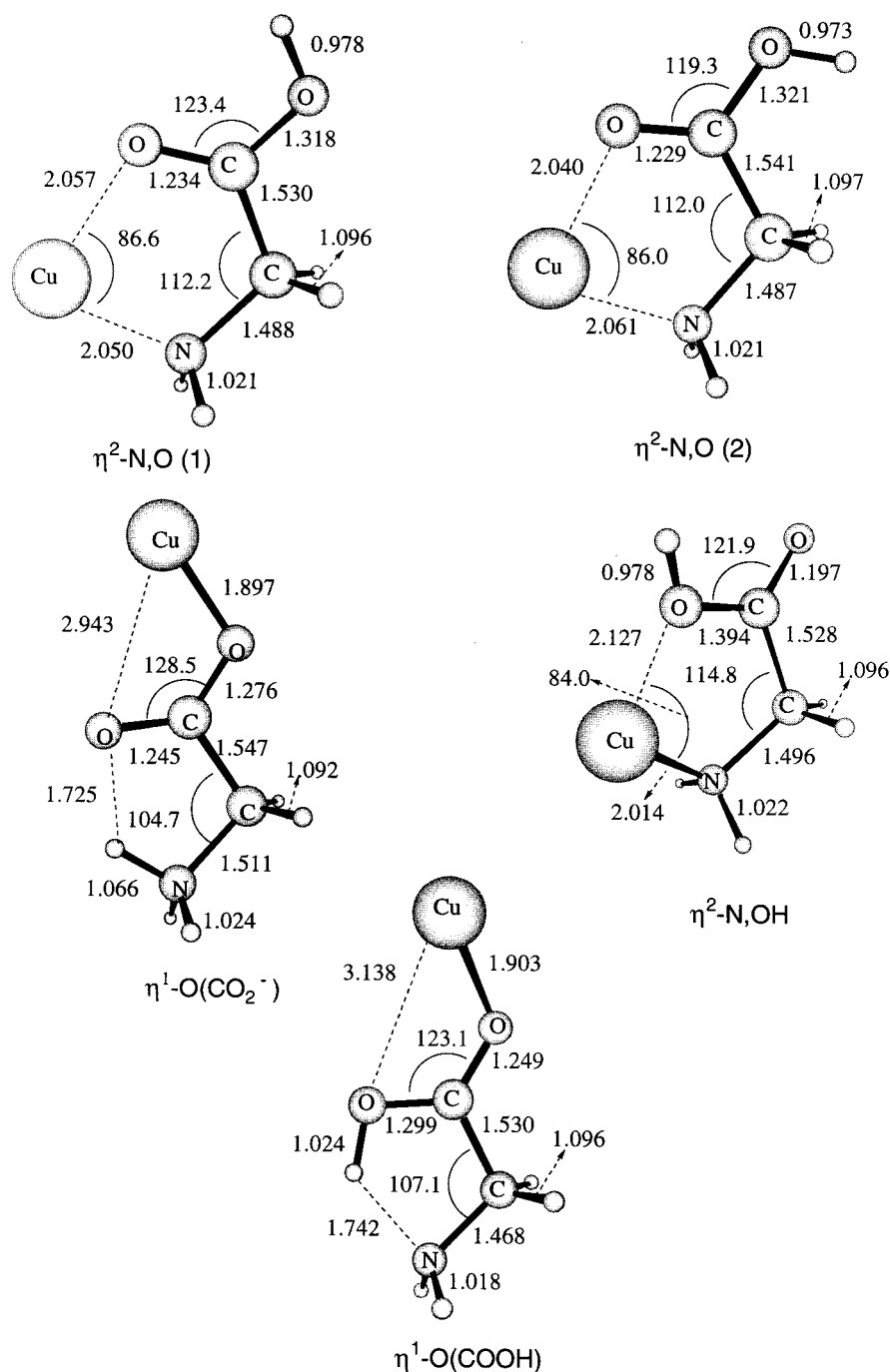
coordination, but has the OH group rotated. This isomer was not considered in the paper of Hoyau and Ohanessian.<sup>17</sup> For these two structures the geometric changes observed upon coordination of the metal ion are very similar and mainly correspond to a bond length increase of the CN and the interacting CO, whereas the other CO bond length decreases.

The remaining three structures lie very close in energy (within 1.6 kcal/mol) and follow the order  $\eta^1$ -O(CO<sub>2</sub><sup>-</sup>) <  $\eta^2$ -N,OH <  $\eta^1$ -O(COOH). For the  $\eta^1$ -O(CO<sub>2</sub><sup>-</sup>) coordination, Figure 1 shows that the Cu<sup>+</sup>-O distances are quite different (1.90 and 2.94 Å), so that glycine is acting as a monodentate ligand. This unsymmetrical coordination was also found at the MP2/6-31G\* level of calculation and was attributed to the strong local dipoles on the N-H bonds that lead to a global dipole moment pointing toward the opposite oxygen.<sup>17</sup> However, the analogous M<sup>+</sup>-CO<sub>2</sub><sup>-</sup> coordination with alkali metal cations show very similar distances between the cation and the two oxygens.<sup>18</sup> Thus, we attribute the difference between Cu<sup>+</sup> and the alkali metal cations not to the orientation of the total dipole moment, which is similar in both cases, but to the fact that Cu<sup>+</sup> prefers an unsymmetrical interaction to minimize the repulsion between the occupied d shell of the metal and the lone pairs of oxygens (see below). Similar arguments hold for the  $\eta^1$ -O(COOH) structure, which shows very different M<sup>+</sup>-O distances for Cu<sup>+</sup> but similar for alkali metal cations.<sup>8</sup> The differences between the two M<sup>+</sup>-O distances are now larger compared with those obtained for the  $\eta^1$ -O(CO<sub>2</sub><sup>-</sup>) structure because of the different chemical nature of the two oxygens.

Table 1 shows that B3LYP results are in good agreement with the MCPF ones, which indicates the reliability of B3LYP for studying these kind of systems. The previous MP2 results<sup>17</sup> show the same energy ordering, although the relative energies are somewhat smaller than those determined at the B3LYP or MCPF level of theory.

Several factors can determine the relative energy of these structures. The main ones are: the deformation energy of glycine when coordinating to the metal cation, the electrostatic interaction, the metal-ligand repulsion, and the charge transfer, which reflects the electronic delocalization between the metal and the ligand. To gain further insight into the observed trend we have computed the binding energy of glycine to a point charge for each coordination in two steps. First, we have calculated the deformation energy of glycine by determining the energy difference between glycine at the geometry of the complex and free glycine in its ground-state structure. Second, we have computed the electrostatic interaction, that is, the energy lowering of the deformed glycine in the presence of a single point charge at the same metal-glycine distance. In this calculation we allow the electronic relaxation of glycine, and so this lowering also includes the polarization term.

Table 2 shows the deformation and the electrostatic contributions to the binding energy of glycine to a point charge. First, it can be observed that the computed relative energies of the  $\eta^2$ -N,O (1),  $\eta^2$ -N,O (2), and  $\eta^2$ -N,OH structures using a point charge (0.0, 7.0, and 10.8) are very similar to those obtained for the Cu<sup>+</sup>-glycine system (0.0, 6.7, and 11.2). Table 2 shows that the energy difference between structures  $\eta^2$ -N,O (1) and  $\eta^2$ -N,O (2) mainly arises from the different deformation energy, the electrostatic interaction being almost the same for the two isomers. However, the difference between structures  $\eta^2$ -N,O (1) and  $\eta^2$ -N,OH mainly arises from the smaller electrostatic interaction in  $\eta^2$ -N,OH because of the fact that the hydroxyl oxygen is less basic than the carbonyl one. Given that the point charge model reproduces well the relative energies of these three



**Figure 1.** B3LYP-optimized geometries for the different minima of Cu<sup>+</sup>-glycine. Distances are in Å, and angles are in degrees.

structures, we can assume that the charge transfer and the metal–ligand repulsion contributions are almost constant in these cases. The net metal charges shown in Table 3 confirm that the charge transfer is constant in these Cu<sup>+</sup>-glycine structures.

For the  $\eta^1\text{-O(CO}_2^-)$  and  $\eta^1\text{-O(COOH)}$  structures, the obtained relative energies using the point charge model (12.8 and 15.5 kcal/mol) are somewhat larger than those of Cu<sup>+</sup>-glycine system (10.0 and 11.6 kcal/mol). This is probably due to the smaller metal–ligand repulsion in the  $\eta^1\text{-O(CO}_2^-)$  and  $\eta^1\text{-O(COOH)}$  structures than in the  $\eta^2\text{-N,O (1)}$ , which is not taken into account in the point charge model. The analysis of the molecular orbitals shows that for the  $\eta^1\text{-O(CO}_2^-)$  and  $\eta^1\text{-O(COOH)}$  coordinations the highest d orbital is the  $d_{z^2}$  orbital (the C–C bond lies on the z-axis), which mainly hybridizes with the 4s orbital of the metal (see Figure 3). This polarization reduces the electron

density on the metal–oxygen direction, which minimizes the repulsion with the ligand, mainly with the lone pair of the carbonyl oxygen. However, for the  $\eta^2\text{-N,O}$  structures the highest d orbital (assuming that the O–Cu–N atoms lie on the xz plane) is the  $d_{xz}$  orbital slightly hybridized with the  $4p_z$  orbital to reduce repulsion. Since the 4p orbitals of the metal cation lie higher in energy than the 4s orbital, polarization in this second case is less effective. Moreover, in this structure  $\eta^2\text{-N,O}$  repulsion is larger because the two lone pairs of the O and N are pointing to the metal cation.

Previous calculations at the MP2/DZP++//RHF/6-31G\* level have shown that the zwitterionic form of glycine in the gas phase lies 17 kcal/mol higher than the neutral conformation.<sup>44</sup> The present work shows that the interaction with the metal cation reduces this difference. At the B3LYP level the relative energy between the neutral  $\eta^2\text{-N,O (1)}$  and the zwitterionic  $\eta^1\text{-O(CO}_2^-)$

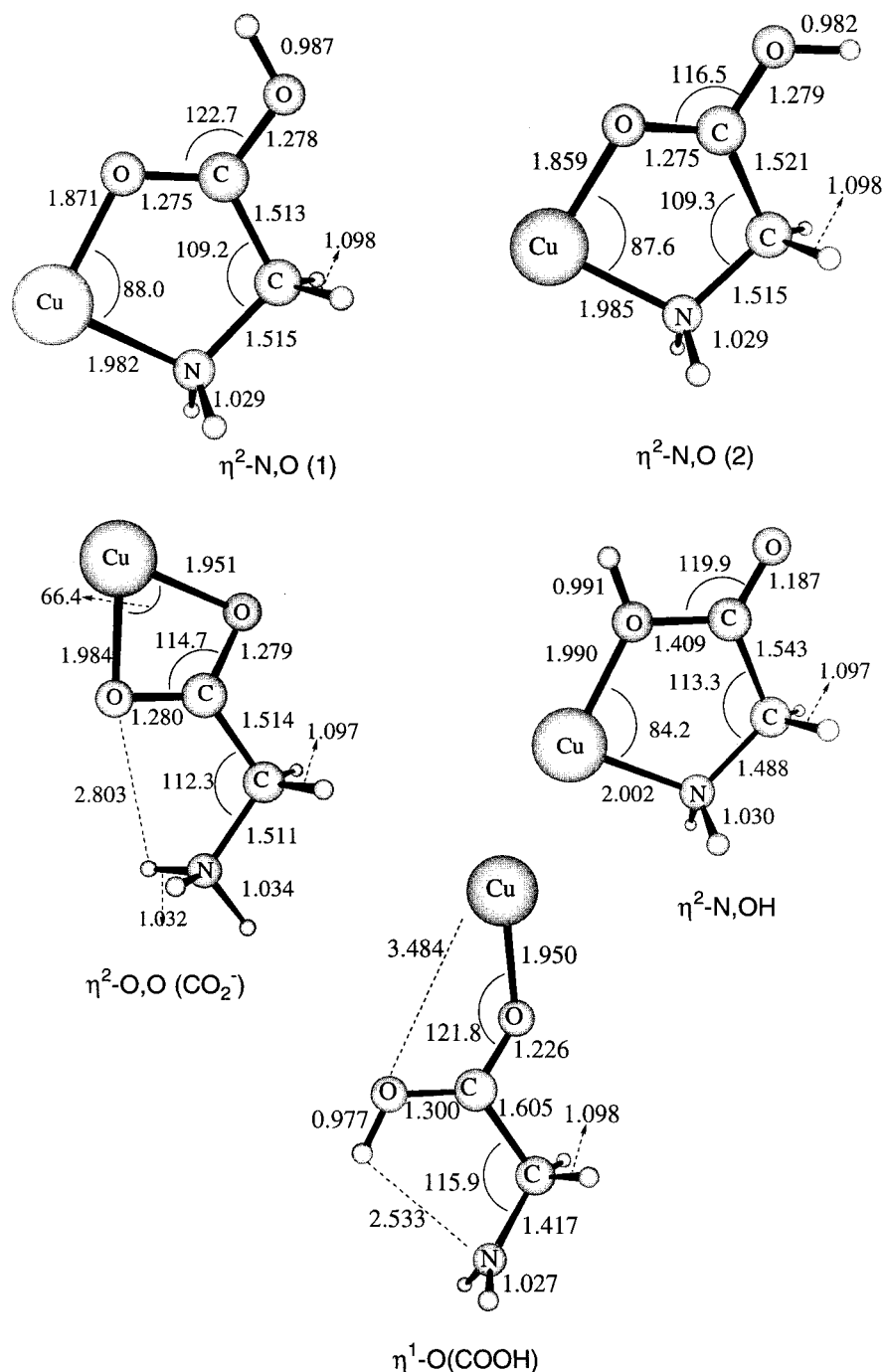


Figure 2. B3LYP-optimized geometries for the different minima of Cu<sup>2+</sup>-glycine. Distances are in Å, and angles are in degrees.

TABLE 1: B3LYP/D95++(d,p) Relative Energies of Cu<sup>+</sup>-Glycine and Cu<sup>2+</sup>-Glycine (in kcal/mol)

structure	Cu <sup>+</sup> -glycine			structure	Cu <sup>2+</sup> -glycine	
	B3LYP	MCPF	MP2 <sup>a</sup>		B3LYP	MCPF
η <sup>2</sup> -N,O (1)	0.0	0.0	0.0	η <sup>2</sup> -N,O (1)	6.1	4.5
η <sup>2</sup> -N,O (2)	6.7	6.9		η <sup>2</sup> -N,O (2)	11.8	10.3
η <sup>1</sup> -O(CO <sub>2</sub> <sup>-</sup> )	10.0	9.9	7.3	η <sup>2</sup> -O,O(CO <sub>2</sub> <sup>-</sup> )	0.0	0.0
η <sup>2</sup> -N,OH	11.2	10.0	8.4	η <sup>2</sup> -N,OH	27.2	29.2
η <sup>1</sup> -O(COOH)	11.6	11.6	10.7	η <sup>1</sup> -O(COOH)	14.6	15.8

<sup>a</sup> Results taken from ref 17 at the MP2/6-31G\* level.

structures of Cu<sup>+</sup>-glycine is 10.0 kcal/mol. Using the point charge model the computed difference is 12.8 kcal/mol. It can be observed in Table 2 that the electrostatic contribution in the η<sup>1</sup>-O(CO<sub>2</sub><sup>-</sup>) zwitterion is only 2 kcal/mol larger than that of the neutral η<sup>2</sup>-N,O (1). This result indicates that the reduction

TABLE 2: Deformation and Electrostatic Contributions to The Total Interaction Energy of (+)-Glycine (See Text); ΔE are Relative Energies (in kcal/mol)

structure	E <sub>def</sub>	E <sub>elec</sub>	E	ΔE
η <sup>2</sup> -N,O (1)	7.1	-89.7	-82.6	0.0
η <sup>2</sup> -N,O (2)	13.6	-89.2	-75.6	7.0
η <sup>1</sup> -O(CO <sub>2</sub> <sup>-</sup> )	21.9	-91.7	-69.8	12.8
η <sup>2</sup> -N,OH	6.4	-78.2	-71.8	10.8
η <sup>1</sup> -O(COOH)	3.0	-70.1	-67.1	15.5

of this energy difference is not mainly due to an increase of the electrostatic interaction in the η<sup>1</sup>-O(CO<sub>2</sub><sup>-</sup>) conformer. The difference between the deformation energy of glycine in the zwitterionic η<sup>1</sup>-O(CO<sub>2</sub><sup>-</sup>) structure and in the neutral η<sup>2</sup>-N,O (1) one also contributes to the reduction. Note that in η<sup>2</sup>-N,O (1) the intramolecular hydrogen bond has been lost, whereas it is



**TABLE 3: Population Analysis. Net Atomic Charge and Spin Density of The Metal Cation in Cu<sup>+</sup>-Glycine and Cu<sup>2+</sup>-Glycine**

structure	Cu <sup>+</sup>	structure	Cu <sup>2+</sup>	
	charge		charge	spin
$\eta^2$ -N,O (1)	0.88	$\eta^2$ -N,O (1)	1.40	0.56
$\eta^2$ -N,O (2)	0.88	$\eta^2$ -N,O (2)	1.42	0.58
$\eta^1$ -O(CO <sub>2</sub> <sup>-</sup> )	0.87	$\eta^2$ -O,O(CO <sub>2</sub> <sup>-</sup> )	1.34	0.47
$\eta^2$ -N,OH	0.88	$\eta^2$ -N,OH	1.29	0.42
$\eta^1$ -O(COOH)	0.90	$\eta^1$ -O(COOH)	1.06	0.10

maintained in  $\eta^1$ -O(CO<sub>2</sub><sup>-</sup>), so that the destabilization of the neutral is larger than that of the zwitterionic form.

Overall, we could say that the point charge model reproduces fairly well the relative energy of the different conformers, the observed variations probably being due to changes in metal–ligand repulsion. Also, the decomposition of the total interaction energy of glycine to a point charge into the deformation and electrostatic contributions shows that both terms are needed to explain the relative stability of the different coordinations.

**B. Cu<sup>2+</sup>-Glycine.** The lowest electronic state of Cu<sup>2+</sup>-glycine of each coordination arises from ionizing the HOMO orbital of Cu<sup>+</sup>-glycine. In all cases except the  $\eta^2$ -N,OH, the optimized structures have *C<sub>s</sub>* symmetry and the lowest electronic state is a <sup>2</sup>A', that is, the open shell orbital lies on the symmetry plane. The  $\eta^2$ -N,OH isomer shows small deviations from the *C<sub>s</sub>* symmetry. It can be observed in Figure 3 that in general the HOMO orbital has an important contribution of both Cu<sup>+</sup> and glycine. As a result of that, the spin density is very delocalized all over the system, except for the  $\eta^1$ -OH, for which the spin density is mainly on the glycine fragment (see Table 3).

For the  $\eta^2$ -N,O and  $\eta^2$ -N,OH structures, ionization leads to smaller values of the Cu–O and Cu–N distances, due to an enhanced electrostatic interaction and to a smaller metal–ligand repulsion. Note that the HOMO orbital from which the electron is removed is an antibonding combination of a metal d orbital and the lone pairs atomic orbitals of the interacting heteroatoms (Figure 3). Consequently, the glycine becomes somewhat more distorted in Cu<sup>2+</sup>-glycine than in Cu<sup>+</sup>-glycine. In particular, it can be observed that the CN and the CO bonds interacting with the metal lengthen more than in the Cu<sup>+</sup>-glycine system.

The other two structures,  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) and  $\eta^1$ -O(COOH), show more important differences. For the derived zwitterionic isomer  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>), the distances between the metal cation Cu<sup>2+</sup> and the two oxygens are much more similar than those obtained for Cu<sup>+</sup>-glycine. We attribute this difference to the smaller metal–ligand repulsion and to the enhanced electrostatic interaction in the Cu<sup>2+</sup>-glycine system, which favors the symmetrical position of the metal cation. Moreover, the intramolecular hydrogen bond, present in Cu<sup>+</sup>-glycine, disappears in Cu<sup>2+</sup>-glycine; that is, the O···H–N distance increases significantly and the NH<sub>3</sub> group rotates. As it is shown in Figure 3, the ionized HOMO orbital has an important contribution of the lone pair of the proton acceptor oxygen, and so ionization decreases its proton acceptor character,<sup>45</sup> which weakens the hydrogen bond. In addition, this H-bond distance increase reduces the repulsive interaction between the metal cation and the NH<sub>3</sub><sup>+</sup> group of the zwitterionic glycine.

The  $\eta^1$ -O(COOH) isomer is the only structure that shows a larger metal–ligand distance for Cu<sup>2+</sup> than for Cu<sup>+</sup>. For this structure the population analysis shown in Table 3, spin density and metal charge, seems to indicate that the system behaves more as Cu<sup>+</sup>-glycine<sup>+</sup>. Thus, it is not surprising that the metal–O distance in this case is larger than in the Cu<sup>+</sup>-glycine system. The optimized geometric parameters also show an

important increase of the C–C bond length and of the intramolecular O–H···N hydrogen bond. The population analysis shows that the spin density on glycine mainly lies on the nitrogen atom. This is in agreement with the fact that the ionized HOMO orbital has an important contribution of the nitrogen lone pair orbital. As a consequence, the amino group becomes less basic after ionization and the intramolecular hydrogen bond is weakened.<sup>45</sup> The geometry optimization of the <sup>2</sup>A' state of the [NH<sub>2</sub>–CH<sub>2</sub>–COOH]<sup>+</sup> radical cation shows also an important increase of the C–C bond (1.70 Å) and of the H-bond (2.31 Å), compared with the values of 1.54 Å and 1.90 Å, respectively, obtained for the isolated neutral glycine, which confirms the radical character of glycine in the [Cu-glycine]<sup>2+</sup> complex.

Table 1 shows that the energy ordering of the different structures obtained for Cu<sup>2+</sup>-glycine is very different than the one determined for Cu<sup>+</sup>-glycine. For the Cu<sup>+</sup>-glycine system the ordering is  $\eta^2$ -N,O (1) <  $\eta^2$ -N,O (2) <  $\eta^1$ -O(CO<sub>2</sub><sup>-</sup>) <  $\eta^2$ -N,OH <  $\eta^1$ -O(COOH), whereas for Cu<sup>2+</sup>-glycine we obtain the following order:  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) <  $\eta^2$ -N,O (1) <  $\eta^2$ -N,O (2) <  $\eta^1$ -O(COOH) <  $\eta^2$ -N,OH. That is, the ground state structure of Cu<sup>2+</sup>-glycine is the derived zwitterionic  $\eta^2$ -O,O(CO<sub>2</sub><sup>-</sup>) isomer and not the  $\eta^2$ -N,O (1) structure as found for Cu<sup>+</sup>-glycine. This is in good agreement with the experimental results that suggest that Cu<sup>2+</sup> has some affinity for the C-terminal carboxylate group.<sup>9,10</sup>

To analyze the nature of the bonding in Cu<sup>2+</sup>-glycine we have also performed calculations using the point charge model. Table 4 shows the relative energies obtained when Cu<sup>2+</sup> is substituted by a double positive charge (+2). It can be observed that the computed energy ordering does not follow the ordering determined for Cu<sup>2+</sup>-glycine. According to this point charge (+2)-glycine model, the  $\eta^2$ -N,O structures should be more stable than the  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) zwitterionic one. The decomposition of these relative energies into the deformation and electrostatic contributions shows that this is mainly due to the much larger deformation energy of glycine in the  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) structure (+44.5 kcal/mol) than in the  $\eta^2$ -N,O (1) one (+15.4 kcal/mol). As expected, the electrostatic interaction is more stabilizing in the  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) coordination, although by only 1.7 kcal/mol. The fact that this point charge model does not reproduce the computed relative energies of Cu<sup>2+</sup>-glycine system implies that the charge transfer from glycine to the metal cation Cu<sup>2+</sup> is a very important factor that greatly contributes to determine the stability of the different isomers. This is confirmed by the population analysis given in Table 3, which shows that the net metal charge on the cation is much smaller than 2, especially for the  $\eta^1$ -OH coordination for which the computed value is 1.06.

If one considers that the ionization potential of Cu<sup>+</sup> (20.80 eV at the B3LYP level) is much larger than that of glycine (9.38 eV), one could expect that the ionization of Cu<sup>+</sup>-glycine system would mainly take place at the glycine fragment. If that is the case, the system would behave more as Cu<sup>+</sup>-glycine<sup>+</sup> than as Cu<sup>2+</sup>-glycine and thus, a point charge model (+)-glycine<sup>+</sup> should better reproduce the relative energies of the system. This model would represent the other limit situation in which one electron has been transferred from glycine to the metal cation. The computed relative energies of the <sup>2</sup>A' state of glycine<sup>+</sup> in the presence of a positive charge at the metal cation position are also given in Table 4. As can be observed, this limit situation does not reproduce the relative energies of the [Cu-glycine]<sup>2+</sup> system. However, in contrast to what was observed for the previous (+2)-glycine model, now the  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) structure appears clearly to be more stable than the  $\eta^2$ -N,O (1) one. This

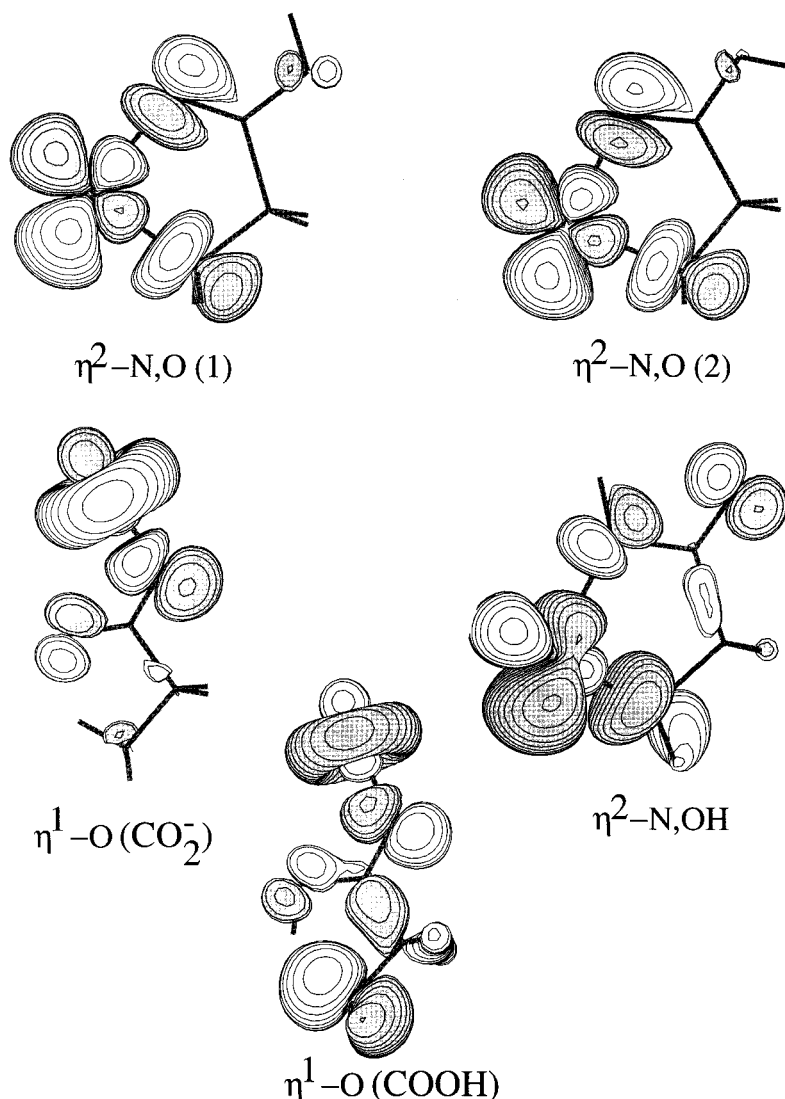


Figure 3. HOMO orbital of the different minima of Cu<sup>+</sup>-glycine.

TABLE 4: Relative Energies Using the Point Charge Model (in kcal/mol)<sup>a</sup>

structure	(+2)-glycine	(+)-glycine <sup>+</sup>
$\eta^2\text{-N,O (1)}$	-27.4	20.4
$\eta^2\text{-N,O (2)}$	-18.2	25.0
$\eta^2\text{-O,O(CO}_2^-)$	0.0	0.0
$\eta^2\text{-N,OH}$	14.5	17.7
$\eta^1\text{-O(COOH)}$	36.5	-6.4

<sup>a</sup> We have taken as reference the ground state  $\eta^2\text{-O,O}$  structure of [Cu-glycine]<sup>2+</sup>.

larger stability of the  $\eta^2\text{-O,O (CO}_2^-)$  coordination compared with the  $\eta^2\text{-N,O}$  one arises both from the deformation energy of glycine<sup>+</sup>, which is much smaller in  $\eta^2\text{-O,O (CO}_2^-)$  (+5.3 kcal/mol) than in  $\eta^2\text{-N,O (1)}$  (+14.9), and from the electrostatic contribution, which is 10.8 kcal/mol more destabilizing in  $\eta^2\text{-N,O(1)}$ . This is not surprising because in the [NH<sub>3</sub>-CH<sub>2</sub>-CO<sub>2</sub>]<sup>+</sup> conformation of glycine<sup>+</sup>, the positive charge is mainly located in the NH<sub>3</sub><sup>+</sup> fragment, the interacting CO<sub>2</sub> being almost neutral. However, in the [NH<sub>2</sub>-CH<sub>2</sub>-COOH]<sup>+</sup> conformer, the positive charge lies on the NH<sub>2</sub> and COOH groups that interact with the metal cation and thus, the electrostatic interaction is more unfavorable. That is, the ionization of glycine decreases the basicity of the interacting centers, especially that of the NH<sub>2</sub> group, which favors the  $\eta^2\text{-O,O (CO}_2^-)$  isomer.

As shown by the population analysis (see Table 3), the spin density is very delocalized over the molecule. It could be said that the electrostatic interaction between the metal cation and the ligand corresponds to an intermediate situation between the two limits considered. Moreover, the net metal charge values show that the charge transfer, and so the electronic delocalization, are not constant for all the isomers. The real interaction between the metal and the ligand is much more complex, and thus, it is not surprising that none of these too simplified models reproduces the relative energies of [Cu-glycine]<sup>2+</sup>. However, the performed analysis has allowed us to get a better understanding of the bonding. From the results obtained we can say that the fact that the  $\eta^2\text{-O,O (CO}_2^-)$  isomer is the ground state structure in [Cu-glycine]<sup>2+</sup> is not due to the larger electrostatic interaction between Cu<sup>2+</sup> and the CO<sub>2</sub><sup>-</sup> terminus, as one would have initially expected. The  $\eta^2\text{-O,O (CO}_2^-)$  coordination becomes more stable because glycine in [Cu-glycine]<sup>2+</sup> acquires an important radical character that changes the relative metal affinity of the different basic sites.

**C. Binding Energies.** The binding energies (*D<sub>e</sub>*) of Cu<sup>+</sup>-glycine and Cu<sup>2+</sup>-glycine computed at different levels of calculation are given in Table 5. As it is generally found,<sup>27,30,46</sup> the B3LYP binding energies are larger than the ones computed using conventional post-Hartree-Fock methods.

**TABLE 5: Interaction Energies ( $D_e$ ,  $D_0$ ,  $\Delta H^\circ_{298}$ , and  $\Delta G^\circ_{298}$ ) of Cu<sup>+</sup>-Glycine and Cu<sup>2+</sup>-Glycine (in kcal/mol)**

	Cu <sup>+</sup> -glycine	Cu <sup>2+</sup> -glycine
B3LYP/Basis1	75.2	243.0
B3LYP/Basis2	75.4	242.7
B3LYP/Basis3	74.2	240.2
MCPF/Basis1	66.5	214.2
MCPF/Basis2	67.5	218.5
CCSD(T)/Basis1	67.1	210.5
CCSD(T)/Basis2 <sup>a</sup>	68.1	214.8
$D_0^b$	66.2	212.7
$\Delta H^\circ_{298}^c$	66.9	213.4
$\Delta G^\circ_{298}^c$	58.7	203.4

<sup>a</sup> Estimated on the basis set dependence at the MCPF level.<sup>b</sup> Determined using the CCSD(T)/Basis2  $D_e$  value and the B3LYP unscaled harmonic frequencies. <sup>c</sup> After correction for translational, rotational, and vibrational energies determined at the B3LYP level.

For Cu<sup>+</sup>-glycine, the difference between the B3LYP (75.2 kcal/mol) and CCSD(T) (67.1 kcal/mol) values, using the smaller basis set, is 8.1 kcal/mol. The MCPF result (66.5 kcal/mol) is very similar to the CCSD(T) value. Because of that and for computational reasons, calculations with a larger basis set have only been performed at the MCPF level of calculation. Experience has shown that although basis sets of this size provide good results for B3LYP approach, larger basis sets are needed to converge the MCPF or CCSD(T) results. Adding an f function to the metal cation leaves the B3LYP value almost unchanged, whereas the MCPF binding energy increases 1 kcal/mol. Assuming the same basis set dependence, the binding energy at the CCSD(T) level with Basis2 would be 68.1 kcal/mol. Calculations with larger basis sets (Basis3) have only been possible at the B3LYP level, the obtained binding energy being 74.2 kcal/mol. At the CCSD(T) and MCPF levels the use of larger basis sets is expected to increase the binding energy somewhat. The estimated value of 68.1 kcal/mol at the CCSD(T)/Basis2 level is in good agreement with the best estimation of 66.1 kcal/mol provided by Hoyau and Ohanessian.<sup>17</sup>

For the Cu<sup>2+</sup>-glycine system, we observe the same trend on the binding energies at the different levels of calculation. However, the obtained differences are much larger. The difference between B3LYP (243.0 kcal/mol) and MCPF (214.2 kcal/mol) or CCSD(T) (210.5 kcal/mol) binding energies can partially arise from the nature of the bonding in this system. As mentioned, the open shell orbital mainly corresponds to the antibonding combination of a polarized d orbital of the metal and the HOMO orbital of glycine; that is, the system shows a three-electron interaction. This kind of interaction has recently been found to be overestimated by present density functionals<sup>47,48</sup> because of an overestimation by the exchange functionals of the self-interaction part of the exchange energy, due to the delocalized electron hole.<sup>48</sup> These studies have shown that the admixture of exact exchange reduces the error and that the density functional approach that better compares to post-Hartree-Fock calculations is the B3LYP method, for which the mixing is 50%. To analyze if the present system shows this kind of behavior, we have also computed the binding energy at the BLYP level (without exact exchange mixing) and at the B3LYP level (50% mixing), and we have compared it with the B3LYP value (20% mixing). The results obtained confirm the observed trends in previous three-electron interactions: The binding energy is greatly overestimated with the BLYP functional (264.0 kcal/mol); the error is reduced at the B3LYP level (243.0 kcal/mol); and the B3LYP method (215.2 kcal/mol) is the one that better compares with the MCPF (214.2 kcal/mol) and CCSD(T) (210.5 kcal/mol) ones. Adding an f function to

the metal basis set increases the MCPF binding energy to 218.5 kcal/mol. Assuming the same increase, the CCSD(T)/Basis2 value would be 214.8 kcal/mol.

In summary, B3LYP has been shown to provide good relative energies between the different conformers, both for Cu<sup>+</sup>-glycine and Cu<sup>2+</sup>-glycine. However, although the computed B3LYP binding energy is reasonably accurate for Cu<sup>+</sup>-glycine, it shows much larger errors for the Cu<sup>2+</sup>-glycine system because of the delocalized nature of the open shell. Because of that, the thermochemical information given in Table 5 has been determined by combining our best CCSD(T)  $D_e$  values for Cu<sup>+</sup>-glycine and Cu<sup>2+</sup>-glycine, and the B3LYP vibrational frequency calculations.

#### IV. Conclusions

A study of the metal-glycine bonding for the biologically relevant Cu<sup>+</sup>/Cu<sup>2+</sup> pair is presented. Several coordination modes of Cu<sup>+</sup> and Cu<sup>2+</sup> to glycine are considered. For the Cu<sup>+</sup>-glycine system, the ground state structure is found to be a bidentated  $\eta^2$ -N,O, in which Cu<sup>+</sup> interacts with the nitrogen of the amino group and the carbonyl oxygen. An analysis of the bonding shows that the relative energies of the different conformers can be understood considering the deformation energy of glycine and the electrostatic metal-ligand interaction.

For Cu<sup>2+</sup>-glycine, the obtained energy ordering of the different conformers is very different from that determined for the single positive Cu<sup>+</sup>-glycine system. The ground state structure of Cu<sup>2+</sup>-glycine is the  $\eta^2$ -O,O (CO<sub>2</sub><sup>-</sup>) one, derived from the interaction of the metal cation with the CO<sub>2</sub> group of the zwitterionic glycine. The bonding in Cu<sup>2+</sup>-glycine is much more complex than in Cu<sup>+</sup>-glycine. The population analysis show that glycine acquires an important radical character that changes the relative metal affinities of the different basic sites, which favors the interaction of the metal cation with the CO<sub>2</sub> group compared with the other coordinations.

For both systems, the B3LYP relative energies are in good agreement with those determined with the highly correlated MCPF method. However, the computed B3LYP binding energies show larger differences, especially for the open-shell Cu<sup>2+</sup>-glycine complex, for which the spin density is very delocalized over the system.

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