Absolute Affinities of α-Amino Acids for Cu^+ in the Gas Phase. A Theoretical Study

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Abstract: Ab initio calculations have been carried out on the [glycine−Cu]$^+$, [serine−Cu]$^+$, and [cysteine−Cu]$^+$ complexes. Investigation of several types of structures for each complex shows that the preferred binding site of Cu^+ involves chelation between the carbonyl oxygen and the amino nitrogen. With glycine, this leads to a complexation energy (best estimate of D_0) of 64.3 kcal/mol. Additional chelation with the alcohol group of serine or the thiol group of cysteine leads to larger binding energies, with cysteine binding more strongly than serine, in good agreement with a recent experimental scale of relative Cu^+ affinities of all α-amino acids present in natural peptides. Combining this scale to the accurate determination of the Cu^+ affinity of glycine from the present work leads to absolute values of Cu^+ affinities of all amino acids. Calculations were also carried out on the complexes of Cu^+ with water, ammonia, formaldehyde, and hydrogen sulfide. The geometrical and electronic structures of these complexes are used to analyze the binding of Cu^+ to amino acids.

I. Introduction

Copper is one of the most important transition metals involved in biochemical processes. Copper proteins are numerous, and some of them are involved in essential biological processes of living systems, such as dioxygen transport.[1] Understanding the details of local interactions between the metal ion and amino acids is therefore a matter of high interest.[2] The present work aims to add a step toward this goal.

There is also a special interest associated with the attachement of metal ions to amino acids and peptides in mass spectrometry. Characterizing fragile biomolecules as charged species in the gas phase has long been difficult. With the advent of recent ionization techniques, such as fast atom bombardment, the study of protonated peptides has become a routine task.[3] This provides a relatively straightforward access to the molecular mass of the molecule under study. Further analysis essentially aimed at deriving structural information, with ultimate goals such as peptide sequencing, is done *via* collisional activation (CA).[4] However, this technique is far from being universally useful. In recent years, formation of cation-bound biomolecules has emerged as a promising alternative for obtaining structural information for certain types of biomolecules. While most of the work to date has dealt with alkali cations,[5] their small binding interactions severely limit their ability to induce specific fragmentations of peptides. A potentially more useful strategy is to use transition metal ions, with which there is good hope to induce specific fragmentations without resorting to the energetic conditions used in CA.[6]

Thus there is currently a convergent need for a better grasp of the mechanism and energetics of metal−amino acid interactions.

The present theoretical work has been prompted by a recent experimental study[7] of the interaction of Cu^+ with the 20 α-amino acids which are present in natural peptides. The kinetic method was used to obtain a ladder of relative affinities for Cu^+ in the gas phase. Adding the knowledge of only one absolute affinity would enable one to obtain all 20 values at once. This is the essential motivation of this paper. For obvious reasons of computational tractability, we have chosen to study in detail the interaction of Cu^+ with glycine, the simplest of all α-amino acids. This case already represents a significant challenge to quantum chemical methods if high accuracy (ca. 1 kcal/mol) is required.

In an effort to go beyond this specific case study, we have used the [glycine−Cu]$^+$ case to assess the capabilities of various methods, including density functional theory (DFT). This enabled us to study the complexation of Cu^+ to two other amino acids, serine and cysteine. The good agreement with experiment obtained for the relative affinities of glycine, serine, and cysteine for Cu^+ lends further support to the reliability of both the theoretical and experimental procedures employed. Finally, a better understanding of the interaction of Cu^+ with neutral molecules has been obtained through the study of its complexes with NH_3, H_2O, H_2S, and formaldehyde. This is used to understand the fact that Cu^+ binding energies are much larger than those of alkali cations, and to explain the special affinity of Cu^+ for sulfur-containing amino acids.

II. Methods

Two different Gaussian basis sets have been employed:

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(1) All geometries have been optimized with the 6-31G* standard basis for the S, C, N, O, and H atoms and the Wachters basis [14s,11p,5d] contracted to (8s,6p,3d) for Cu.[8]

(2) For final energy calculations, the standard 6-311+G(2d,2p) basis for C, N, O, and H atoms, together with the MacLean−Chandler basis[9] for S and the same Wachters basis for Cu augmented with an s function ($\zeta = 0.0123$), the two p polarization functions uncontracted, a diffuse d function[10] and two f functions of exponents 2.88 and 0.72 was used. Overall, this basis can be written 6-311+G(2f,2d,2p). 5d and 7f sets were used throughout.

Four different types of wave function have been used:

(1) The Hartree−Fock (HF) method has been chosen for the initial geometry optimizations. Dipole moments were also computed at this level. Although the values might be overestimated at the HF level, they should be reliable enough for qualitative discussions.

(2) As electron correlation corrections may have a significant effect on the relative energies of the various structures, single point second order Moller−Plesset perturbation (MP2) calculations have been run using the HF geometries. In order to evaluate the reliability of this MP2//HF approach, geometries were also optimized at the MP2 level for all isomers of $[glycine-Cu]^+$ and for the most stable isomer of $[serine-Cu]^+$ and $[cysteine-Cu]^+$.

(3) In the case of the most stable structure of the $[glycine-Cu]^+$ complex, improved energies were obtained with the coupled cluster method including single, double, and a perturbative treatment of triple excitations (CCSD(T)). In order to obtain our best estimate of the complexation energy, some approximations have been derived from calculations on smaller complexes such as $[H_2O-Cu]^+$ and $[H_2S-Cu]^+$.

(4) Since the B3LYP hybrid density functional yields good results in the case of glycine conformers,[14b] it has also been used in order to test its reliability for both geometries and energies of some Cu^+ complexes.

In all correlated calculations, the frozen core approximation was used for the 1s electrons of C, N and O and for the 1s, 2s, and 2p electrons of S and Cu.

All geometry optimizations, at all wave function levels, were made without symmetry constraints, in order to avoid any bias in favor of structures of C_s symmetry since it is known for free glycine that several low-energy conformers are of C_1 symmetry.

In order to characterize the optimized structures for amino acids and their complexes with Cu^+ as minima on the potential energy surfaces (PES) and to calculate thermodynamical corrections, analytical frequency calculations have been carried out. For glycine, calculations were done at the MP2 and B3LYP levels for the most stable conformer. For $[glycine-Cu]^+$, calculations were performed on all optimized structures with B3LYP in order to confirm that all are minima on the PES. HF and MP2 frequencies were also computed for the lowest energy structure. For serine and cysteine and their Cu^+ complexes, frequency calculations were done for each isomer at the HF level and were restricted to the lowest energy structures at the B3LYP level. Comparison of the two levels with MP2 on the glycine case shows that the thermodynamical corrections are virtually insensitive to the type of wave function used.

Most calculations were run on an IBM RISC 6000 workstation, using the Gaussian94 package.[11] The largest calculations, such as MP2/6-31G* frequencies or CCSD(T)/6-31G* single point on $[glycine-Cu]^+$, had to be run on a Cray C98.

III. Results

A. Complexation of Glycine. There are two different forms of glycine: in the condensed phase the lowest energy form is the zwitterion while in the gas phase the neutral form is computed to be more stable by 17 kcal/mol and the zwitterion is no longer a minimum energy structure.[12]

Table 1. Relative Energies of Some of the Lowest Conformations of Glycine at Various Computational Levels (in kcal/mol)

computational levels	1S	2S	31	4S
MP2/6-31G*//HF/6-31G* [a]	0.0	1.7	1.5	6.5
MP2/6-31G*//MP2/6-31G* [b]	0.0	1.6	1.2	6.5
CCSD(T)/DZP//CCSD/DZP[c]	0.0	1.5	1.0	
MP4/6-311++G**//MP2/6-311++G** [d]	0.0	1.5	0.7	5.5
MP2/extended basis//MP2/6-311++G** [d]	0.0	1.7	0.4	4.9
B3LYP/DZP//B3LYP/DZP[e]	0.0	1.5	0.2	

[a] Reference 15c. [b] This work. [c] Reference 14c. [d] Reference 14d. [e] Reference 14b.

The neutral form bears three internal rotational degrees of freedom, associated with the C−N, C−C, and C−O bonds. This leads to eight conformers of C_s symmetry. However, the balance of intramolecular hydrogen bonding, steric strain, and lone pair repulsions is such that not all of the C_s structures are minima, while several C_1 structures must be considered. The PES of neutral glycine has been investigated in details both experimentally[13] and theoretically[14] in the last 15 years. The three most stable conformers have been observed experimentally.[13] The main structural features so obtained are consistent with the structures and properties determined by *ab initio* calculations at several levels. Exploring the conformational space with experimental techniques is difficult. For instance, observing individual conformation by microwave spectroscopy requires that the dipole moment be non-negligible, which is the case for only some of the lowest conformers.

In such a difficult case for experiments, theoretical studies are particularly helpful since they allow a much more complete exploration of the PES. It has been possible to determine the structure and stability of conformers of higher energy than those observed experimentally. A selection of literature results for the relative energies of the most stable conformers is gathered in Table 1 and Figure 1. Conformers are numbered from 1 to 5, followed by "S" if the structure is of C_s symmetry, or "1" if there is no symmetry (C_1 group). From the many computational results described in the literature, the following conclusions can be drawn: (i) relative energies of the lowest conformations at the HF level can be in error by as much as several kilocalories per mole, and the ordering of structures is incorrect; (ii) the MP2 level captures the essentials of electron correlation corrections, and can be used to obtain accuracies of ca. 1 kcal/mol on the relatives energies; and (iii) for a precise description of the conformational curves which requires accuracies on the order of 1 kJ/mol, geometry optimization must be carried out at the MP2 level and a basis of better than DZP quality must be employed.

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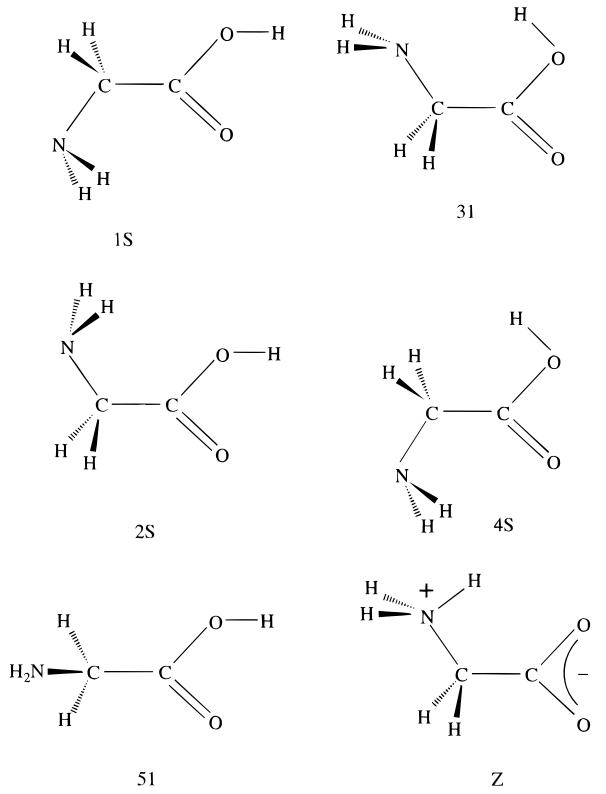

Figure 1. Conformers of neutral and zwitterionic glycine considered in this work.

(1) Selection of Starting Structures. Although there need not be a direct relationship between the lowest conformations of free glycine and the structure of glycine in the lowest forms of [glycine−Cu]$^+$, the former can be used as a guide for the selection of the set of starting structures for geometry optimization. The types of glycine conformation considered in this work (five neutral plus the zwitterion) are depicted in Figure 1. This choice is based on the combination of two criteria. On the one hand, binding of Cu^+ to a neutral molecule involves a sum of electrostatic and charge transfer interactions. The most favorable binding sites are therefore the electron rich nitrogen and oxygens. Thus the first criterion is the maximization of such interactions through polydentate binding. On the other hand, the lowest conformations of the free amino acids are partly determined by the strength of intramolecular hydrogen bonds. Therefore the second criterion is to retain hydrogen bonding as much as possible.

In the case of [glycine−Cu]$^+$, eight different initial structures have been chosen. Most of the structures involve complexation of Cu^+ to the neutral form of glycine because of its stability relative to the zwitterion. However, the strong ionic interaction between Cu^+ and the negatively charged end in the latter could be competitive and was therefore also considered.

The selected structures involve five different modes of complexation : (1) on all three basic sites of neutral glycine [if Cu^+ is placed above the OCO plane, it can interact with both oxygens and at the same time with nitrogen in a conformation such as 51]; (2) on nitrogen and one of the oxygens of neutral glycine [this corresponds to an in-plane approach of Cu^+ to either 1S (in which the carbonyl oxygen is involved) or to conformer 2S (in which the hydroxyl oxygen is involved); in either case, inversion of pyramidalization at nitrogen is required for efficient complexation]; (3) on both oxygens of neutral glycine [this is achieved through an in-plane approach of Cu^+ toward the carboxyl group of 31 or 4S]; (4) on both oxygens of zwitterionic glycine Z [if a N−H···O bond is maintained, this corresponds to a single structure]; (5) on a single basic site: if on nitrogen, this was done by attaching Cu^+ to N in the most stable conformation of glycine, i.e. 1S; if on oxygen, this was done by attaching Cu^+ to the carbonyl oxygen in the most stable conformation which does not bear a O−H···O bond, i.e. 31.

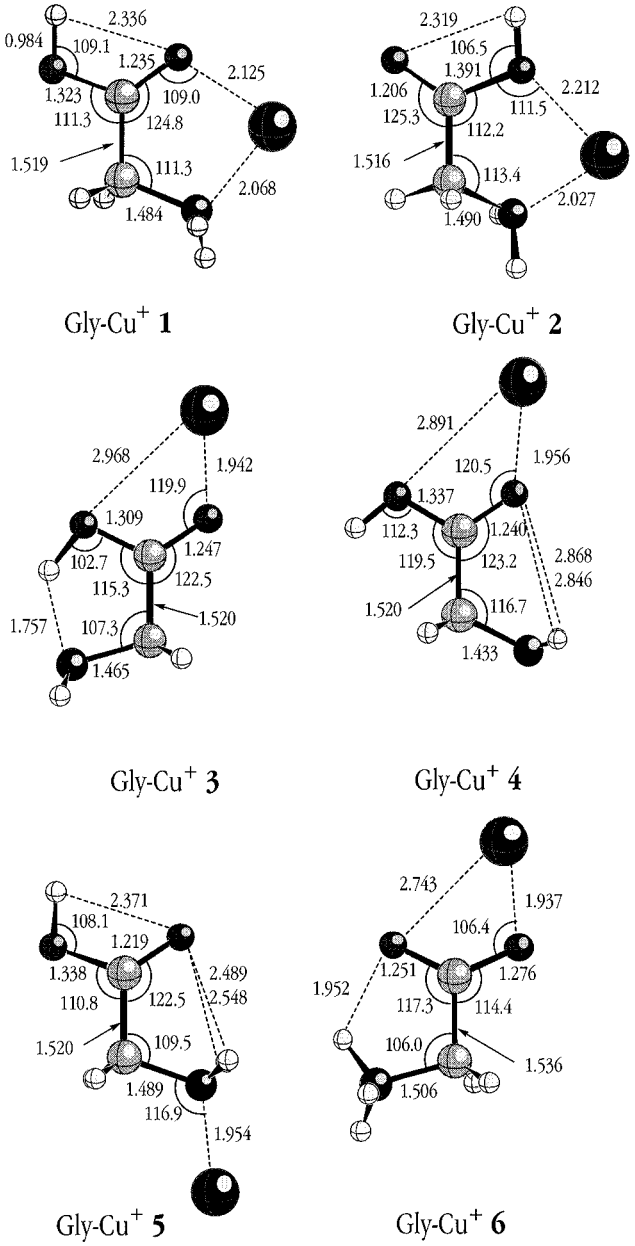

Figure 2. Main structural parameters of the optimized structures for [glycine−Cu]$^+$ at the MP2/6-31G* level. Distances are given in angstroms and angles in degrees.

(2) MP2 Results for [Glycine−Cu]$^+$ Complexes. Among the eight starting structures, not all lead to different optimized structures. Although interaction of Cu^+ with nitrogen and both oxygens might be *a priori* expected to lead to the strongest interaction, the associated 90° rotation around the C−C bond of glycine makes it a high-energy structure (ca. 40 kcal/mol above **1**), and geometry optimization slowly collapses it to **1** (see Figure 2) in which the glycine backbone is nearly planar (with a OCCN torsional angle of ca. 10°) and Cu^+ interacts in-plane with N and the carbonyl O. When attaching Cu^+ to the carboxyl group, the minima found correspond to one short (ca. 1.95 Å) and one long (ca. 2.90 Å) Cu^+−O bond to the carbonyl and hydroxyl oxygens, respectively. This is at variance

Table 2. Relative Energies (in kcal/mol) of [Glycine−Cu]$^+$ Optimized Structures

isomers	HF/6-31G*	MP2/6-31G*// HF/6-31G*	MP2/6-31G*	B3LYP/ 6-31G*
Gly−Cu^+ **1**	0.0	0.0	0.0	0.0
Gly−Cu^+ **2**	11.1	8.8	8.4	10.5
Gly−Cu^+ **3**	8.8	11.1	10.7	11.0
Gly−Cu^+ **4**	19.3	23.6	24.1	24.2
Gly−Cu^+ **5**	14.3	12.1	11.6	12.6
Gly−Cu^+ **6**	11.2	7.4	7.3	9.2

Table 3. Structural Parameters for Gly−Cu^+ **1**, the Lowest Energy Isomer of [Glycine−Cu]$^+$ (Restricted to Those Which Present a Significant Dependence upon the Method Used)

parameters	MP2/6-31G*	HF/6-31G*	B3LYP/6-31G*
Cu−O	2.125	2.139	2.073
Cu−N	2.068	2.207	2.037
CuOC	109.0	114.2	108.6
OCuN	83.8	77.0	86.6
C−O	1.323	1.298	1.316
C═O	1.235	1.203	1.230
C−N	1.484	1.467	1.488
O−H	0.984	0.957	0.980
N−H	1.022	1.004	1.021
COH	109.1	111.2	109.9

with complexation by alkali cations, for which complexation on both oxygens with more similar cation−oxygen distances have been obtained at several computational levels.[15] Overall, six different minima were obtained, as shown in Figure 2. Their relative energies, at all levels of computation used, are summarized in Table 2.

The most stable structure of [glycine−Cu^+] **1** involves formation of a five-membered ring in which Cu^+ chelates on nitrogen and the carbonyl oxygen. The large energy gap between **1** and the next most stable structure (7.3 kcal/mol at MP2/6-31G* level) leaves no doubt that further computational refinements would confirm that **1** is the lowest energy structure. Formation of five-membered ring chelates are well-known in the solution phase chemistry of copper−peptide complexes.[16] Complexation by Cu^+ induces only slight deformations in glycine. The CCO and CCN angles are slightly reduced (from 125.4° and 114.9° in free glycine to 124.8° and 111.3° in **1**, respectively) while the C═O and C−N bonds are lengthened (from 1.220 and 1.452 Å in free glycine to 1.235 and 1.484 Å in **1**, respectively), and the C−C bond remains unchanged. One might consider that the similarity is due to the NH···O bonds in 1S which confer to this structure a pseudo-cyclic character. However, if the hydrogen bonds are broken through inversion of pyramidalization at nitrogen, the glycine backbone is not significantly affected as shown by Csaszar (structures Ip and IVp in ref 14d). The second most stable structure of [glycine−Cu]$^+$ is **6** in which the cation interacts with the carboxylate group of glycine in its zwitteronic form. Given the high energy of the zwitterion relative to the lowest conformer of neutral glycine (17 kcal/mol at the MP2/DZP++//RHF/6-31G* level[12]), this is the most stabilizing type of interaction. This is not unexpected since a very strong ionic interaction between Cu^+ and RCO_2^- can be established in this case. Although both oxygens are equivalent in the zwitterion, Cu^+ binds in an unsymmetrical fashion with Cu−O bond lengths of 1.94 and 2.74 Å. The reason for the difference lies in the position of the amino group. The strong local dipoles on the N−H bonds lead to a global dipole moment for glycine (10.6 D at the HF/6-31G* level) pointing toward the opposite oxygen. Thus maximizing the charge-dipole interaction between Cu^+ and glycine leads to a non-symmetrical minimum.

The third structure **2** contains a five-membered ring but with Cu^+ chelating between nitrogen and the hydroxyl oxygen. Part of the energy difference with **1** arises from the glycine conformer being less favorable, but if conformations are considered with N pyramidalized outward as in **1** and **2**, the difference is only 0.5 kcal/mol (structures IVp and Vp in ref 14d). Thus, the higher stability of **1** mostly reflects the more favorable complexation of Cu^+ to the carbonyl than to the hydroxyl oxygen.

The next most stable structure is **3**, in which Cu^+ interacts with the carboxyl group of glycine 31. Since the hydrogen bond within the carboxyl group is now precluded, the most stable conformation of this type is obtained when the hydroxyl H binds to the amino nitrogen. This is realized in **3**. Contrary to alkali cations, which interact with both oxygens with similar distances,[15] Cu^+ makes unsymmetrical complexes with a short bond (ca. 1.95 Å) to the carbonyl oxygen and a long one (ca. 2.9 Å) to the hydroxyl oxygen. Calculations on H_2CO-Cu^+ (see section C) show that the interaction with formaldehyde includes a significant interaction of the metal cation with an oxygen lone pair, leading to a bent structure with a CuOC angle close to 140°. Reducing this angle to 120°, with a Cu^+−O bond distance nearly equal to that in H_2CO-Cu^+ (see Figure 5), allows the metal ion to lie on the O−H bond axis, thereby maximizing the ion−dipole interaction (see Gly−Cu^+ **3** and **4** in Figure 2).

Another important feature of the glycine−copper interaction emerges from the comparison of **3** and **4**. The difference between these structures is that in the latter, hydrogen bonding is no longer O−H···N between the hydroxyl and the amino groups, but rather N−H···O between the amino and the carbonyl groups. The energy difference between such conformations in free glycine is 4.1 kcal/mol (structures IIp and VIp in ref 14d). Inspection of the glycine structure in **3** and **4** shows that they are very similar to one another and also to the corresponding free glycine conformers. In fact, the energy difference between the free glycine fragments at their geometries in **3** and **4** is 5.0 kcal/mol. However, complexation of Cu^+ induces a large difference since **3** is higher in energy than **1** by 10.7 kcal/mol, while **4** lies 24.1 kcal/mol above **1**. This means that the Cu^+−glycine interaction is about 10 kcal/mol more stabilizing in **3** than it is in **4**. This occurs despite the very similar positions of Cu^+ relative to the carboxyl group in both structures. The reason for this large energetic difference arises from the global charge−dipole interaction between Cu^+ and glycine. In **3**, the local O−H and N−H dipoles add and lead to a large glycine moment of 6.9 D**.** This dipole is nearly exactly oriented in the direction of binding to Cu^+, leading to a strong stabilization. On the contrary in **4** the local dipoles partly cancel, with an overall glycine moment of only 3.8 D, which is no longer pointing in the direction of Cu^+.

Finally, one-site complexation on nitrogen was considered on the most stable conformation of glycine. This is found to be much less favorable than complexation on two sites since the resulting structure **5** lies 11.6 kcal/mol higher in energy than **1** while the corresponding conformer of glycine is 4.5 kcal/mol more stable than the one in **1** (due to inversion at N, see conformers Ip and IVp in ref 14d). The Cu^+−N distance of 1.95 Å is very similar to the one obtained at the same computational level in Cu^+-NH_3 (see section C).

(3) Final Calculations of Complexation Energy. In this section, improvements beyond MP2/6-31G* are considered in

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Table 4. Computed D_e Values for Gly−Cu^+ **1**, the Most Stable Isomer of [Glycine−Cu]$^+$ at Various Levels. The Best Estimate of D_e (Including Several Corrections for Further Computational Refinements; See Text), and the Best D_0, ΔU^{298}, ΔH^{298}, and ΔG^{298} [a]

MP2/6-31G*//MP2/6-31G* D_e	67.1
CCSD(T)/6-31G*//MP2/6-31G* D_e	64.9
MP2/6-311+G(2f,2d,2p)//MP2/6-31G* D_e	70.6
best estimate D_e	66.1
best D_0	64.3
best ΔU^{298}	−64.3
best ΔH^{298}	−64.9
best ΔG^{298}	−56.3

[a] Obtained by combining the best estimate of D_e with MP2/6-31G* vibrational frequencies.

order to obtain an accurate affinity of glycine for Cu^+. All calculations were performed at the MP2/6-31G* optimized geometries of **1** and glycine. In order to obtain the internal energy change at 0 K (D_0), the zero point vibrational energy (ZPVE) was calculated for glycine and **1** at the MP2/6-31G* level. These values were used in all further refinements of the complexation energy, and correspond to the difference between our best estimates of D_e and D_0 in Table 4.

Based on literature results on $Cu(H_2O)^+$ and related complexes,[17] it was expected that the use of the 6-31G* basis would lead to a significant basis set superposition error (BSSE) in the computed complexation energy. This is borne out by MP2 calculations with the counterpoise method, which indicate a large error of 10.9 kcal/mol. Test calculations show that this is mainly due to basis set incompleteness on the glycine fragment and that diffuse functions are mandatory in order to reduce the error significantly. Using the valence triple-ξ 6-311G basis, augmented with a set of diffuse s and p functions on all heavy atoms, plus two sets of polarization functions on all atoms instead of one on the heavy atoms only, as with 6-31G*, turned out to be the best compromise between accuracy and tractability. This final basis is denoted 6-311+G(2f,2d,2p). The MP2 value of D_e (i.e. dissociation energy ignoring ZPVE) with this basis is 70.6 kcal/mol, and the BSSE is strongly diminished to 2.8 kcal/mol. While this improvement is significant, the BSSE will still have to be taken into account for obtaining our best estimate of D_e (see below).

The fact that D_e is increased with the larger basis, despite the strong decrease in BSSE, means that the description of the Cu^+−glycine interaction has been significantly improved with this more flexible basis. It would therefore be desirable to re-optimize the geometry at this level. This is however untractable, because of the size of the system (245 basis functions). An estimate of this effect was obtained from the increase of D_e found in going from MP2/6-311+G(2f,2d,2p)//MP2/6-31G* to optimum MP2/6-311+G(2f,2d,2p) for complexes of Cu^+ with smaller molecules. This increase was found to be 0.3 kcal/mol for NH_3−Cu^+ and for H_2CO−Cu^+, leading to an estimated increase of 0.5 kcal/mol for glycine−Cu^+.

Finally, the limitations of MP2 as an approximate treatment of electron correlation must be evaluated. MP2 has been shown to perform well, compared to CISD and CCSD(T) methods, for the computation of the relative energies of glycine conformers.[14c,e] However, its accuracy must be re-evaluated in this case where a metal ion, albeit a closed shell one, is involved. For this purpose, the complexation energy in **1** was also computed at the CCSD(T)/6-31G* level. The results (see Table 4) show that the complexation energy is somewhat smaller than at the MP2/6-31G* level. Although small, this difference cannot be neglected. Thus the level of choice for the final calculation would be CCSD(T) with the extended basis set. This, however, is untractable. Therefore, an approximation scheme to this level was devised.

As described in section C, calculations were performed at the same levels on H_2O−Cu^+, H_2S−Cu^+, NH_3−Cu^+ and H_2CO−Cu^+, plus at our target level CCSD(T)/6-311+G(2f,2d,2p). A reduction of complexation energy, as for [glycine−Cu]$^+$, was observed from MP2 to CCSD(T) with the 6-31G* basis (1.9, 3.0, 3.3, and 1.5 kcal/mol for H_2O−Cu^+, H_2S−Cu^+, NH_3−Cu^+ and H_2CO−Cu^+, respectively). A reduction also occurs when the extended basis set is used, and it was found to be nearly exactly the same as that with 6-31G*. Therefore, a reasonable approximation to the true CCSD(T)/6-311+G(2f,2d,2p) value for [glycine−Cu]$^+$ can be obtained by subtracting to the MP2/6-311+G(2f,2d,2p) value the difference between CCSD(T)/6-31G* and MP2/6-31G*. Our best estimate of the D_e for [glycine−Cu]$^+$ was obtained from the MP2/6-311+G(2f,2d,2p)//MP2/6-31G* value of 70.6 kcal/mol by subtracting the counterpoise BSSE error of 2.8 kcal/mol, adding the 0.5 kcal/mol estimate of the effect that geometry re-optimization at the MP2/6-311+G(2f,2d,2p) level would have, and subtracting the estimate of 2.2 kcal/mol for the difference between MP2 and CCSD(T) levels. This leads to a best estimate of 66.1 kcal/mol. Vibrational frequencies computed at the MP2/6-31G* level were used to evaluate the ZPVE contribution to the 0 K binding energy. We thus obtain a best value of 64.3 kcal/mol for D_0 (see Table 4).

The corresponding complexation enthalpy at room temperature can be obtained by adding the usual translational, rotational, and vibrational contributions (obtained from MP2/6-31G* frequency calculations) to the internal energy change at 0 K. In the absence of well-defined temperatures in the experimental setup used to obtain the relative Cu^+ affinities, we have computed the thermodynamical corrections at two different temperatures (298.15 and 500 K) and pressures (1 and 10^{-9} atm). These calculations have shown that whatever the pressure, both enthalpy and entropy changes are constant. When increasing the temperature from 298.15 to 500 K, the enthalpy change remains nearly constant (0.1 kcal/mol). Therefore, we have combined the experimental results with our best estimate of ΔH^{298} (−64.9 kcal/mol). Finally, the complexation entropy was computed to be 8.6 kcal/mol at the MP2/6-31G* level. This leads to a ΔG^{298} value of −56.3 kcal/mol. It is hoped that these values will prompt other experiments in order to obtain ΔH and ΔS values.

(4) MP2//HF and B3LYP Results. Geometry optimization was also carried out at the Hartree−Fock level. It is known for free glycine[14] that HF bond lengths are shorter than MP2 lengths by 0.001−0.002 Å, while valence angles differ by 0−2°. For the various isomers of [glycine−Cu]$^+$, we find that structural differences on the glycine fragment are slightly larger: bond lengths involving N and O are shorter (by 0.02−0.04 Å at most) at the HF level, while the largest differences in valence angles are in the 2−6° range. In most cases, dihedral angles are only slightly affected. Thus, the MP2 and HF geometries are in satisfactory agreement on the glycine fragment. There are, however, important differences related to the position of Cu^+. For all isomers, the lack of electron correlation leads to Cu−N and Cu−O distances which are too long, by as much as 0.15 Å in several cases. Illustrative examples are given in Table 3, in which the largest structural differences are gathered in the case of the most stable structure **1**. The differences within the glycine fragment appear to be due in part to the fact that complexation

(17) (a) Rosi, M.; Bauschlicher, C. W. *J. Chem. Phys.* **1989**, *90*, 7264. (b) Langhoff, S. R.; Bauschlicher, C. W.; Partridge, H.; Sodupe, M. *J. Phys. Chem.* **1991**, *95*, 10677.

by Cu^+ is stronger at the MP2 level. This tends to increase the distances between heavy atoms within glycine.

As for geometries, energetics at the HF level are in qualitative agreement with MP2, with some significant quantitative differences. The HF complexation energy in **1** is 56.0 kcal/mol, 11.1 kcal/mol less than the MP2 value. Differences also appear on the relative energies of the other isomers. The average absolute difference is 3.2 kcal/mol, and since some values are overestimated while others are underestimated, the energy ordering is incorrect. This is especially true for structure **6** involving zwitterionic glycine, which is found to be the fourth lowest isomer at the HF level, but the second with MP2. Therefore, accurate energetics cannot be based on HF wave functions. However, MP2/6-31G* energetics using HF/6-31G* geometries revealed much better quality, as shown in Table 2. The complexation energy in **1** is only 1.0 kcal/mol smaller than at the MP2 geometry, the ordering of isomers **1**−**6** is the same, and the average absolute difference in relative energies is only 0.4 kcal/mol. Therefore, MP2/6-31G*//HF/6-31G* is a very attractive level of computation for larger cases as a substitute to MP2/6-31G*, and it has been used for the calculations of [serine−Cu]$^+$ and [cysteine−Cu]$^+$ described below.

The performance of the B3LYP hybrid density functional, used in conjonction with the 6-31G* basis, was also studied. Agreement between B3LYP and MP2 geometries is excellent within the glycine fragment, with the largest differences being ca. 0.01 Å and 1°. Differences are greater for the position of Cu^+, which B3LYP places systematically closer to glycine than does MP2 for all structures (see Table 3 for the example of **1**). The differences in Cu−O and/or Cu−N distances lie in the 0.03−0.06 Å range. This seems to be a general feature of B3LYP.[22]

As a corollary to these structural differences, the B3LYP complexation energy is larger than the MP2 value by 11.9 kcal/mol (79.0 instead of 67.1 kcal/mol). The relative energies of the other isomers are in satisfactory agreement with MP2 values, with an average absolute error of 1.1 kcal/mol. This small error enables B3LYP to yield the correct energy ordering of all structures. Thus B3LYP is found to be another valuable alternative to MP2, especially for geometry optimization. Compared to HF, it provides geometries in better agreement with MP2, but at a significantly higher computational cost. A single optimization step (calculation of energy and of analytical first derivatives of energy with respect to nuclear coordinates) is about 3 times longer with B3LYP than it is with HF and is about as long as MP2 when the 6-31G* basis is used. Moreover, an initial guess of converged Hartree−Fock molecular orbitals is necessary for a better convergence with B3LYP. Given the very good agreement between MP2 and MP2//HF results, the latter method appears to be the best compromise between accuracy and computational demand for these types of systems.

B. Complexation of Serine and Cysteine. (1) Selection of Starting Structures. Structural studies are not as advanced for other amino acids as they are for glycine. Only recently did experiment[18] and theory[19,20] reach a high level for alanine. In the cases of serine and cysteine, there is currently no experimental information. However, we can take benefit from the recent comprehensive explorations of the conformational PES by Gronert and O'Hair.[20] The presence of the additional functional group introduces two new rotors (e.g. C−O and C−C in serine) in addition to the three rotors of glycine and thus renders the conformation space much more complicated. Both the alcohol group of serine and the thiol group of cysteine are found to participate as hydrogen bond donors to the carbonyl oxygen or to the amino nitrogen in a number of the most stable conformers. As a result, the three and five most stable conformers lie within 1 kcal/mol for serine and cysteine, respectively, and in both cases the first 33 conformations identified lie in a 4-kcal/mol range, at the highest level of calculations used.

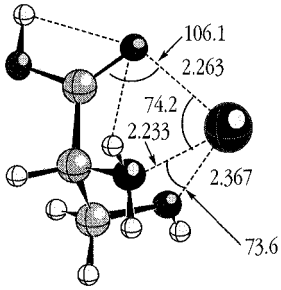
From these results, it is not possible to efficiently predict the most stable complexation modes of Cu^+ to serine and cysteine. The results previously obtained for [glycine−Cu]$^+$ appear to be a much better guide for the selection of starting structures. One criterion which seems firmly established is multidentate binding. Therefore no attempt was made to locate monodentate minima such as Gly−Cu^+ **5**. A second criterion is based on the particular stability found for Gly−Cu^+ **1**. Thus extensive exploration of the PES of [serine−Cu]$^+$ and [cysteine−Cu]$^+$ was made in the regions where Cu^+ is attached to the carbonyl oxygen and the amino nitrogen and/or the alcohol or thiol heteroatom. In cases where copper binding included the alcohol or thiol group but not the amino nitrogen, both N−H···O and O−H···N types of hydrogen binding were considered. Overall, this exploration led to four structures in each case, labeled Ser−Cu^+ (or Cys−Cu^+) **1**, **2**, **4**, and **6** (see Figures 3 and 4). Based on these results, only the tridentate binding site was investigated when Cu^+ is attached to the hydroxyl oxygen rather than the carbonyl oxygen within the carboxyl group, leading to structure **3** in both cases. As for glycine, complexation to all heteroatoms was also attempted. Starting from Ser−Cu^+ **1** and Cys−Cu^+ **1**, this is achieved through a 90° rotation around the C−C bond. Therefore the copper ion sits above the OCO plane in such a case. However, it was found, as for [glycine−Cu]$^+$, that such structures are of high energy, and that geometry optimization collapses slowly onto structures **3** or **4**. Finally, complexation of Cu^+ to the RCO_2^- end of the zwitterionic isomers of serine and cysteine was considered, leading to optimized structures Ser−Cu^+ **5** and Cys−Cu^+ **5**.

(2) MP2//HF Results. Based on the comparison of methods described above for [glycine−Cu]$^+$, the MP2/6-31G*//HF/6-31G* level was used to compare the possible structures in [serine−Cu]$^+$ and [cysteine−Cu]$^+$. Results are summarized in Tables 5 and 6, and Figures 3 and 4. The types of structures and their relatives energies are very similar for [serine−Cu]$^+$ and [cysteine−Cu]$^+$ complexes, and therefore will be described together.

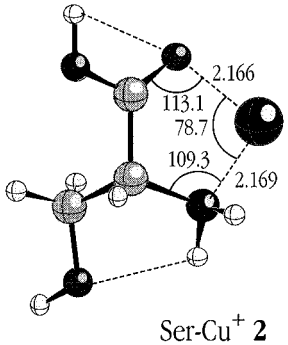
The most stable isomers are Ser−Cu^+ **1** and Cys−Cu^+ **1**. They involve interaction of Cu^+ to the carbonyl oxygen, the amino nitrogen, and the oxygen alcohol of serine, or the thiol sulfur of cysteine. Thus the favored binding mode is similar to that in [glycine−Cu]$^+$, with an additional site since the side chains, although small, are able to fold to approach the metal ion. The only noticeable difference between the structures of Ser−Cu^+ **1** and Cys−Cu^+ **1** involves the mode of complexation of the side chain. While the alcohol group approaches the metal in a locally planar fashion in Ser−Cu^+ **1** (i.e. Cu, O, C and the terminal H are close to being coplanar), this is far from being the case for thiol complexation in Cys−Cu^+ **1**, in which the CuSCH dihedral is 100.4° (see Figures 3 and 4). This difference parallels that observed between the optimum geometries of H_2O−Cu^+ and H_2S−Cu^+ (see section C), which can be attributed to a charge−dipole interaction in the oxygen case and to an interaction with polarizable and donating lone pairs in the sulfur case.

As for glycine, the significant energy gaps which separate

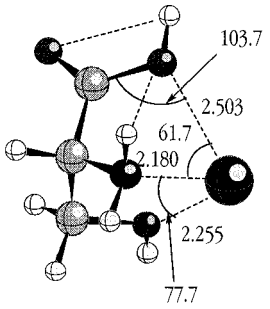
(18) Godfrey, P. D.; Firth, S.; Hatherley, L. D.; Brown, R. D.; Pierlot, A. P. *J. Am. Chem. Soc.* **1993**, *115*, 9687.
(19) Csaszar, A. G. *J. Phys. Chem.* **1996**, *100*, 3541.
(20) Gronert, S.; O'Hair, R. A. J. *J. Am. Chem. Soc.* **1995**, *117*, 2071.



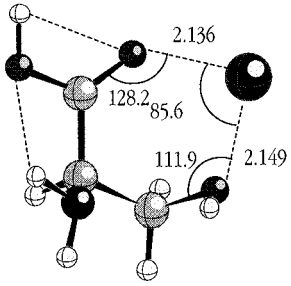
Ser-Cu$^+$ **1**



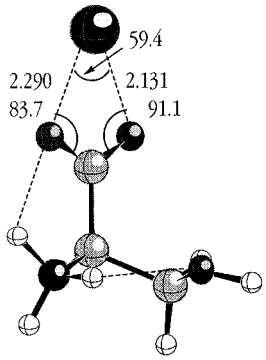
Ser-Cu$^+$ **2**



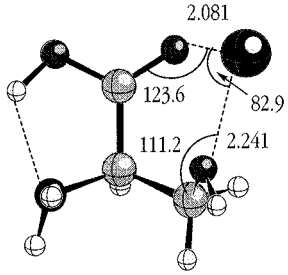
Ser-Cu$^+$ **3**



Ser-Cu$^+$ **4**

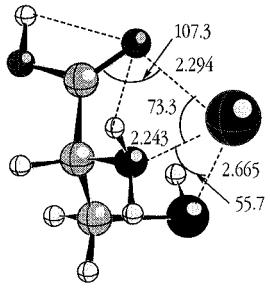


Ser-Cu$^+$ **5**

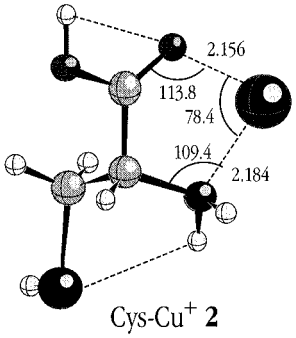


Ser-Cu$^+$ **6**

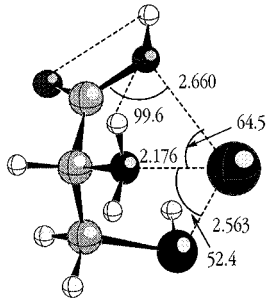
Figure 3. Some structural parameters of the optimized structures for [serine−Cu]$^+$ complexes at the HF/6-31G* level. Distances are given in angstroms and angles in degrees.



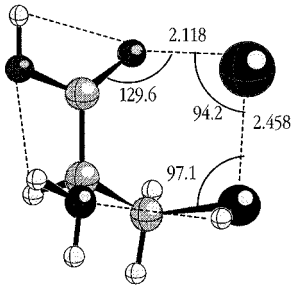
Cys-Cu$^+$ **1**



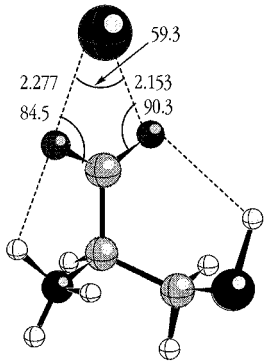
Cys-Cu$^+$ **2**



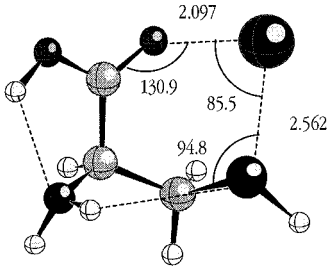
Cys-Cu$^+$ **3**



Cys-Cu$^+$ **4**



Cys-Cu$^+$ **5**



Cys-Cu$^+$ **6**

Figure 4. Some structural parameters of the optimized structures for [cysteine−Cu]$^+$ complexes at the HF/6-31G* level. Distances are given in angstroms and angles in degrees.

structures **1** from the next most stable make us confident that the former are the true equilibrium structures for [serine−Cu]$^+$ and [cysteine−Cu]$^+$.

Structures **2** differ from **1** by rotation around the side chain C−C bond, so that there is no longer interaction between the metal and the alcohol or thiol group. Accordingly, the amino acid structures are less distorted by complexation than they are in **1**: the geometry around Cu^+ is much more similar to that of Gly−Cu^+ **1**. Another favorable factor is that a hydrogen bond (O···H−N or S···N) can now be established. However, the relative energies gathered in Tables 5 and 6 show that reducing the number of complexation sites is destabilizing.

This is also found when the amino group, instead of the alcohol or thiol group, is moved away from Cu^+. Two resulting structures were optimized, **4** and **6**, with different types of hydrogen bonding. In **4** there is a O···H−O interaction within the carboxyl group, plus a O···H−N bond, while in **6** the hydroxyl H is oriented for interacting with the amino nitrogen. It may be that the greater stability of **4** relative to **6**, in both [serine−Cu]$^+$ and [cysteine−Cu]$^+$, is associated with the presence of two hydrogen bonds in the former and only one in the latter. However, it must also be noted that these different H binding modes influence the complexation geometry at Cu^+. Both **4** and **6** are of significantly higher energy than **2**. This is due to the much stronger interaction of Cu^+ to N than to O or S. At the same level of theory, the Cu^+-NH_3 bond is 15 and 22 kcal/mol stronger than the Cu^+-OH_2 and Cu^+-SH_2 bonds, respectively (see section C).

Table 5. Relative Energies (in kcal/mol) of [Serine−Cu]$^+$ Optimized Structures

isomers	HF/6-31G*	MP2/6-31G*//HF/6-31G*
Ser−Cu^+ **1**	0.0	0.0
Ser−Cu^+ **2**	6.0	6.1
Ser−Cu^+ **3**	6.9	4.9
Ser−Cu^+ **4**	9.6	12.5
Ser−Cu^+ **5**	11.5	8.0
Ser−Cu^+ **6**	13.4	15.8

The results described above clearly show that the best complexation site of glycine, a cyclic structure in which the

Table 6. Relatives Energies (in kcal/mol) of [Cysteine−Cu]$^+$ Optimized Structures

isomers	HF/6-31G*	MP2/6-31G*//HF/6-31G*
Cys−Cu^+ **1**	0.0	0.0
Cys−Cu^+ **2**	5.8	7.4
Cys−Cu^+ **3**	6.9	4.2
Cys−Cu^+ **4**	9.5	12.0
Cys−Cu^+ **5**	11.4	9.1
Cys−Cu^+ **6**	11.8	14.4

metal interacts with the carbonyl oxygen and the amino nitrogen, will involve even stronger binding if the side chain of a larger amino acid folds toward the metal. We expect the same trend to hold true when Cu^+ interacts with the hydroxyl oxygen and the amino group. Since the latter type of complexation was found to be less favorable in [glycine−Cu]$^+$, the only structure considered was the tridentate binding mode. The optimized structures Ser−Cu^+ **3** and Cys−Cu^+ **3** are less stable than the **1** isomers by 4.9 and 4.2 kcal/mol, respectively.

Finally the interaction of Cu^+ with the negative end of zwitterionic serine and cysteine was considered. As in Gly−Cu^+ **6**, a O···H-N hydrogen bond can be formed with optimized structures shown as Ser−Cu^+ **5** and Cys−Cu^+ **5** in Figures 3 and 4. In addition, another N−H bond can interact with the side chain OH group in serine, while one of the S−H bonds of cysteine interacts with one of the carboxylate oxygens. Another noticeable difference with the glycine analog is that the Cu^+−O bonds are of roughly equal lengths in Ser−Cu^+ **5** and Cys−Cu^+ **5**, while a difference of 0.8 Å exists in Gly−Cu^+ **6**. The unsymmetrical structure in the latter is due to the orientation of the dipole moment of zwitterionic glycine, which is determined by the position of the positively charged ammonium group. In serine and cysteine, this is largely compensated by the local dipoles in the side chain alcohol or thiol group, leading to a much more symmetrical charge distribution. As a consequence, the optimum binding position of Cu^+ is displaced toward the symmetry plane of the CO_2^- group.

(3) Absolute Cu^+ Affinity Scale for All Amino Acids. The determination of the absolute affinity of glycine for Cu^+ was sufficient to transform the relative affinity scale of Cerda and Wesdemiotis[7] into an absolute affinity scale. Nevertheless, the above calculations for [serine−Cu]$^+$ and [cysteine−Cu]$^+$ provide a deeper insight into the binding modes of Cu^+ to amino acids in general. In order to obtain a meaningful comparison between the computed and experimental affinity differences between glycine, serine, and cysteine, higher level calculations were carried out on Ser−Cu^+ **1** and Cys−Cu^+ **1**. These included geometry optimization at the MP2/6-31G* level, and further single point calculations at the MP2/6-311+G(2f,2d,2p) level. B3LYP/6-31G* optimizations and single point B3LYP/6-311+G(2f,2d,2p) calculations were also run for comparison. The computed absolute and relative affinities are gathered in Table 7.

A significant difference found experimentally between the relative affinity scales of α-amino acids for Li^+ and Na^+ on one hand and for Cu^+ on the other is that the relative affinities of sulfur-containing amino acids, cysteine and methionine, are much higher for Cu^+ than they are for Li^+ and Na^+. As can be seen in Table 7, this effect is not reproduced at either HF or MP2 levels, when using the 6-31G* basis set. It turns out that the use of an extended basis set, together with the treatment of electron correlation, is necessary in order to reproduce the special affinity of Cu^+ for sulfur. As described below, this is already obtained for the complex between Cu^+ and H_2S. At our best *ab initio* level, our computed D_e is in satisfactory agreement with experimental values since no account was taken of residual BSSE, nor of ZPVE corrections. It may be noticed that the B3LYP values are also very satisfactory, and that this functional may even be more accurate than our best *ab initio* level for the relative energies. However, it leads to significant overestimations of the absolute values, especially when combined to the 6-31G* basis set. It should also be noted that the assumption of constant entropy change for the complexation of all amino acids may introduce small errors in the derived enthalpies. Indeed, our optimized structures indicate that three-site complexation of serine and cysteine is more structurally constraining than the two-site complexation of glycine. This should lead to more negative entropies of complexation in the former cases, leading to slightly larger differences in complexation enthalpies than in free enthalpies.

These results are very encouraging in that they lend support to the accuracy of both the computational and experimental procedures. Although the kinetic method has already been demonstrated to yield accurate relative affinity scales in a number of cases,[21] it was not *a priori* obvious that cationized heterodimers would involve the same metal−molecule binding interaction as cationized monomers. The optimized structures of [serine−Cu]$^+$ and [cysteine−Cu]$^+$ provide a hint in that direction: although multidentate binding is favorable, it involves three sites at most, and therefore there should remain enough coordination capability at the metal cation to bind a second amino acid molecule without significant structural perturbation.

Based on these results, we are now able to combine our best estimate for the Cu^+ affinity of glycine with the experimental relative scale of Cerda and Wesdemiotis. This is done in Table 8. These are ΔU^{298} values, which include thermal energy corrections but no ΔnRT corrections contrary to the ΔH^{298} values. We use ΔU^{298} instead of ΔH^{298} since the experimental pressures are negligible, so that the perfect gas model is irrelevant. The resulting absolute affinities are high, since they range from 64.3 kcal/mol for glycine to 77.6 kcal/mol for histidine. Even larger values are expected for lysine and arginine, but accurate relative affinities could not be obtained for these two highly basic molecules.

C. Comparison with Complexes of Cu^+ with Small Molecules. As mentioned previously, complexes of Cu^+ with NH_3, H_2O, H_2S, and H_2CO were studied in order to help understand the mode of interaction of Cu^+ with amino acids. A detailed description of our calculations on these and other Cu^+ complexes of small molecules will be provided in a separate publication.[22] We provide in Figure 5 and Table 9 results using the MP2/6-31G* optimized geometries in order to be comparable with our results on amino acids complexes, and also at the MP2/6-311+G(2f,2d,2p) level for comparison. It should be noted that experimental binding energies exist for the Cu^+ complexes of NH_3,[23a] H_2O,[23b] and H_2CO,[23c] and that computations have been described for NH_3−Cu^+ and H_2O−Cu^+.[17] The appropriate comparisons and discussions will be given elsewhere.[22]

Our calculations show that binding in these small complexes is relatively strong, as already known except for H_2S−Cu^+ in which we predict a binding energy of 40.5 kcal/mol at the CCSD(T)/6-311+G(2f,2d,2p)//MP2/6-31G* level. The strongest interaction is with NH_3, which explains why a number of the low-energy isomers of [glycine−Cu]$^+$, [serine−Cu]$^+$ and

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Table 7. Complexation Energies (in kcal/mol) of the Most Stable Isomers of [Glycine−Cu]$^+$, [Serine−Cu]$^+$, and [Cysteine−Cu]$^+$ at Various Calculation Levels[a]

calculation levels	glyCu$^+$		serCu$^+$		cysCu$^+$	
HF/6-31G*//HF/6-31G*	−56.0	**0.0**	−62.9	**−6.9**	−59.9	**−3.9**
MP2/6-31G*//HF/6-31G*	−66.1	**0.0**	−73.6	**−7.5**	−72.5	**−6.4**
MP2/6-311+G(2f,2d,2p)//HF/6-31G*	−68.5	**0.0**	−73.8	**−5.3**	−77.5	**−9.0**
MP2/6-31G*//MP2/6-31G*	−67.1	**0.0**	−73.6	**−6.5**	−74.3	**−7.2**
MP2/6-311+G(2f,2d,2p)//MP2/6-31G*	−70.6	**0.0**	−75.6	**−5.0**	−82.3	**−11.7**
B3LYP/6-31G*//B3LYP/6-31G*	−79.0	**0.0**	−83.5	**−4.5**	−87.3	**−8.3**
B3LYP/6-311+G(2f,2d,2p)//B3LYP/6-31G*	−72.5	**0.0**	−75.5	**−3.0**	−82.2	**−9.7**
experimental[b]		**0.0**		**−3.1**		**−8.6**

[a] Relative energies are given in bold face. [b] Reference 7.

Table 8. Affinities for Cu$^+$ (in kcal/mol) of the 20 α-Amino Acids

amino acid	Cu$^+$ affinity	amino acid	Cu$^+$ affinity
glycine	64.3	glutamic acid	71.5
alanine	65.9	phenylalanine	72.2
serine	67.4	tyrosine	72.5
valine	67.9	cysteine	72.9
leucine	68.4	glutamine	74.0
isoleucine	68.6	methionine	74.6
threonine	68.8	tryptophane	75.7
proline	69.1	histidine	77.6
aspartic acid	69.3	lysine	>77.6
asparagine	70.9	arginine	>77.6

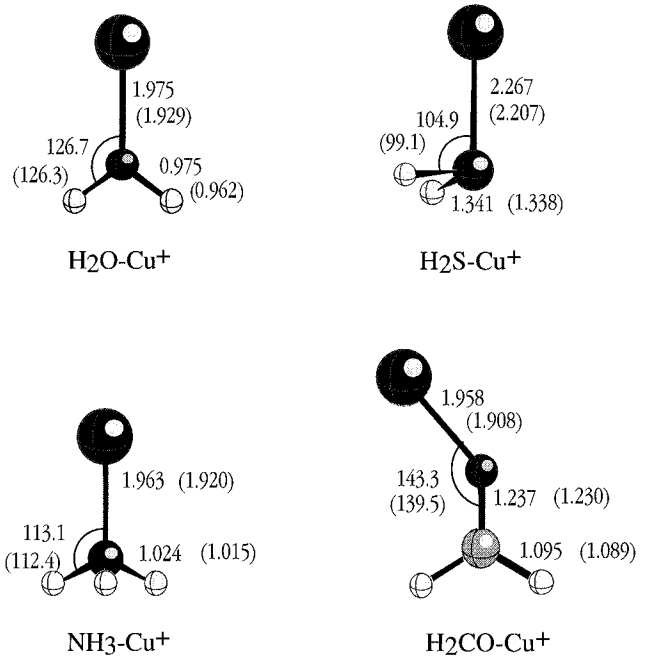

Figure 5. Optimized structures for H_2O-Cu^+, H_2S-Cu^+, NH_3-Cu^+, and H_2CO-Cu^+ at the MP2/6-31G* and MP2/6-311+G(2f,2d,2p) (in parentheses) levels. Distances are given in angstroms and angles in degrees.

[cysteine−Cu]$^+$ involve binding to the amino group. It is interesting to note that the Cu$^+$−N bond distances and energies are very close in NH_3-Cu^+ and GlyCu$^+$ **5**, despite the fact that glycine is more polarizable a species than is ammonia. In GlyCu$^+$ **5**, the glycine is more remote from the metal than in other [glycine−Cu]$^+$ isomers, and the larger molecular size does not bring increasing binding, 55.5 kcal/mol compared to 56.2 kcal/mol in NH_3-Cu^+ at the MP2/6-31G* level. The situation is much more favorable when bidentate binding is established, even if at the expense of non-optimal interaction with the amino group (as reflected in the longer Cu$^+$−N distance in Gly−Cu$^+$ **1** and **2**). The stronger interaction in **1** might be due to the fact that the binding of Cu$^+$ to the carbonyl group is optimal when nonlinear, as shown by the optimized structure of H_2CO-Cu^+ in Figure 5. It is likely that in this type of structure, Cu$^+$ interacts with an oxygen lone pair as a Lewis acid−base pair, since it differs from that in H_2CO-Na^+ where the C−O−Na backbone is linear, corresponding to a charge−dipole interaction which is typical for Na$^+$ binding.

Table 9. Complexation energies (D_e) for H_2O-Cu^+, H_2S-Cu^+, NH_3-Cu^+, and H_2CO-Cu^+ Using the MP2/6-31G* Geometries, Complexation Enthalpies (ΔH_{298}), and Experimental Values

method	H_2O-Cu^+	H_2S-Cu^+	NH_3-Cu^+	H_2CO-Cu^+
MP2/6-31G* D_e	−40.7	−34.6	−56.2	−37.0
CCSD(T)/-6-31G* D_e	−38.8	−31.6	−52.9	−35.5
MP2/6-311+G (2f,2d,2p) D_e	−38.6	-43.5	−57.3	−39.6
CCSD(T)/6 311+G (2f,2d,2p) D_e	−37.2	-40.5	−54.3	−38.3
MP2/6-311+G (2f,2d,2p)ΔH_{298}	−36.6	−41.3	−54.3	−37.2
experimental	-37.6 ± 1.8[a]		~ -60[b]	-34.7 ± 2.3[c]

[a] Reference 23b. [b] Reference 23a. [c] Reference 23c.

H_2O-Cu^+ and H_2S-Cu^+ show trends which parallel those in [serine−Cu]$^+$ and [cysteine−Cu]$^+$. Binding to oxygen centers appears to involve mainly charge−dipole interaction, leading to locally planar structures. On the other hand, interaction with the S lone pairs must be significant in shaping the interaction of Cu$^+$ with H_2S and thiols. This is a well-known structural effect in sulfur-containing peptides.[2a] This leads to a much higher computational demand for the description of the copper−sulfur interaction. In fact, the binding to H_2S is erroneously predicted to be weaker than that to H_2O, unless extended basis sets and correlation treatments are used. Again this effect is paralleled in the computed [serine−Cu]$^+$ and [cysteine−Cu]$^+$ binding energies.

The binding energies of Cu$^+$ to H_2O and H_2S, both close to 40 kcal/mol, are much larger than the binding energies of serine and cysteine relative to glycine. This shows that important structural distortions are required in order to achieve tridentate binding as in Ser−Cu$^+$ **1** and Cys−Cu$^+$ **1**. Longer side chains are required for reaching optimum interaction to a single metal center. However, this must be at the expense of more unfavorable entropies of complexation.

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