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Interaction of Cu⁺ and Cu²⁺ ions with α-alanine. A density functional study

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The Cu⁺ and Cu²⁺ preferred binding sites on α-alanine and their affinity values for this amino acid were determined at the density functional level using three different hybrid exchange correlation potentials and the 6−311++G** basis set. The results demonstrated that the two ions both give stable complexes with α-alanine but the stability order of the metalated species and the coordination sites are different depending on the nature of the cation. In particular, the Cu⁺−α-alanine ground-state structure is characterized by an η^2-N,O coordination with the nitrogen and oxygen atoms belonging to the amino and carbonyl groups, respectively. In contrast, the most stable complex of the Cu²⁺−α-alanine system has an η^2-O,O coordination with the cation bonded to the —CO₂⁻ moiety of the zwitterionic form of the amino acid. Comparison with the Cu⁺ and Cu²⁺ affinity values for glycine, computed at the same levels of theory, demonstrated that the relative values do not change significantly as different hybrid functionals are used, although the absolute affinities are strongly influenced by the choice of the hybrid potential. Copyright © 2002 John Wiley & Sons, Ltd.

INTRODUCTION

Oxidation, dioxygen transport and electron transfer are some of the biological processes in which the copper ions (Cu⁺ and Cu²⁺) play a fundamental role.[1–6] They can form numerous stable copper proteins bonding preferentially at the hydrophobic sites.[7] The knowledge of the copper ion coordination mode and of the binding energy is important for understanding not only the structure and the biological function of metal-containing proteins but also to help in the interpretation of the experimental data. In particular, such information can be useful in interpreting the mass spectrometric experiments[8–13] to understand the specific fragmentation of the peptides and then rationalize the sequence of peptides cationized by metal ions of different nature.

The gas-phase relative Cu⁺ affinities of the most common 20 α-amino acids have been determined experimentally by the kinetic method based on the unimolecular dissociation's of their Cu⁺-bound heterodimers.[14,15]

The interaction of Cu⁺ with glycine is the most studied reaction at both the MP2[16,17] and density functional[16] levels. To our knowledge, other theoretical investigations on the Cu⁺−amino acids interaction have been limited to an MP2 study[16] concerning serine and cysteine, to an *ab initio*

investigation of Cu⁺−proline complexes,[18] to a preliminary density functional determination of the Cu⁺−alanine metal affinity[19] and to a density functional study regarding the interaction of copper ions with some peptides containing basic residues for which also experimental data were reported.[20] Hoyau and Ohanessian,[16] combining the experimental scale of the relative Cu⁺ affinities of Ref. 14 with their theoretical determination of Cu⁺−glycine affinity, proposed the absolute values of copper(I) affinities for all the amino acids.

Much less work has been devoted to Cu²⁺−amino acid interaction, although this ion also plays a significant role in many biochemical processes. In an experimental gas-phase study[21] of a Cu²⁺−peptide complex, it was observed that Cu²⁺ binds preferentially to the C-terminal carboxylate group rather than the amino nitrogens which are generally the sites preferred by Cu⁺. This demonstrates that the two copper ions have a different chemistry essentially due to the different ground-state electronic configurations (open shell (d⁹) for Cu²⁺ and closed shell (d¹⁰) for Cu⁺), but also to the different charge. This situation was previously evidenced in an exhaustive theoretical study on the interaction of glycine with Cu²⁺ and Cu⁺ ions.[17]

Although the determination of the different coordination modes of Cu⁺ and Cu²⁺ ions with the most stable conformers of α-alanine is an important aspect in the metal–ligand interaction field and in our investigations, the main goal of this study was to develop a suitable theoretical tool for evaluating the absolute values of the affinity of copper ions

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for amino acids. Until now, experimental determinations allowed us to obtain only relative values for these quantities.

COMPUTATIONAL METHODS

Calculations for all the complexes, obtained by the interaction of the Cu$^+$ and Cu^{2+} ions on the different sites of the most stable α-alanine conformers, were performed with the Gaussian 98 package[22] using the Becke[23] three-parameter exchange and Lee–Yang–Parr[24] correlation functionals (B3LYP) in conjunction with the all-electron 6–311++G** internal basis set[22] for all atoms. This hybrid scheme was previously tested in a series of metal–ligand interaction studies including amino acid–and DNA bases–metal ions systems[19,25–32] and, although the results concerning the relative energies were found to be in good agreement with available experimental data, nevertheless, some discrepancy was evidenced in the reproduction of theoretical absolute values, especially in the case of the metal affinity determination for amino acids. For this reason, for the copper affinity estimation, we repeated the computations using two other hybrid exchange correlation potentials, namely B1LYP[24,33,34] and BHandHLYP,[24,35] characterized by a different mixture of Hartree–Fock exchange with DFT exchange correlation and the same LYP correlation functional. In this way, the overestimation of the self-interaction part of the exchange energy due to the delocalized electron hole should be alleviated.[36]

Geometries were fully optimized and characterized as minima structures on the basis of the vibrational analysis only at the B3LYP level. Ground-state structure binding energies of Cu$^+$–α-alanine (glycine) and Cu^{2+}–α-alanine (glycine) complexes were, instead, checked using B1LYP and BHandHLYP.

Metal ion affinity (MIA) was assumed to be the negative of the enthalpy variation ($-\Delta H$) for the processes

$$\text{amino acid} + Cu^+(Cu^{2+}) \longrightarrow \text{amino acid–} Cu^+ \, (Cu^{2+})$$
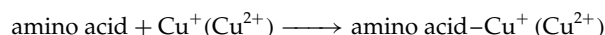
Thermochemical analysis at 298 K was carried out using the B3LYP force field.

RESULTS AND DISCUSSION

On the basis of previous gas-phase studies[16,19,25,37–41] on α-alanine performed at the B3LYP/6–311++G** level, the seven most stable conformers of the amino acid were chosen as ligands in the interaction process with the metal ions. These conformers have energy values included in a range of 7 kcal mol^{-1} (1 kcal = 4.184 kJ)[19,37] and suitable coordination sites that involve mainly the most negatively charged oxygen and nitrogen atoms. The zwitterionic structure of α-alanine, like that of glycine, although not stable in the gas phase,[16,17,19,25] is generally stabilized by the interaction with metal ions[17,25,42] and for this reason was considered in its complexed form.

The B3LYP/6–311++G** relative energies of the eight complexes originating from the interaction of Cu$^+$ and Cu^{2+} with α-alanine conformers are reported in Table 1, and the corresponding equilibrium geometries are depicted in Figs 1 and 2. A first glance at the results in Table 1 is sufficient for

Table 1. B3LYP/6–311++G** relative energies (ΔE) at 0 K for the Cu$^+$– and Cu^{2+}–α-alanine complexes[a]

Conformer	ΔE (kcal mol^{-1})	
	Cu$^+$–Ala	Cu^{2+}–Ala
1	0.0	5.6
2	9.6	0.0
3	6.9	12.2
4	12.5	9.1
5	9.2	21.6
6	25.6	0.8
7	24.5	4.5
8	15.5	24.4

[a] Absolute energy values at 0 K for the most stable conformers **1** (of Cu$^+$–α-alanine) and **2** (of Cu^{2+}–α-alanine) are −1964.040884 and −1963.549197 a.u., respectively.

underlining the differences between the coordination modes adopted preferentially by the two ions. The stability order of the Cu$^+$–α-alanine systems is **1** > **3** > **5** > **2** > **4** > **8** > **7** > **6**. In the absolute minimum **1**, the Cu$^+$ ion presents an η^2-N,O coordination involving the nitrogen and oxygen atoms of the amino and carbonyl groups. In this compound, the Cu$^+$—O and Cu$^+$—N bond lengths are 2.099 and 2.068 Å, respectively. A similar result was found for the copper–glycine complex by Bertrán *et al.*[17] and Hoyau and Ohanessian.[16]

In a range of ~10 kcal mol^{-1} three bidentated species (**3**, **5**, **2**), in which the copper ion is always linked to an oxygen and to a nitrogen atom, were found. In the complex **2**, Cu$^+$ shows a sort of η^2-O,O coordination with the amino acid in the zwitterionic form, but the values of the two Cu$^+$—O distances are very different (1.928 and 2.860 Å, see Fig. 1), indicating, more precisely, a situation of monocoordination. The systems **4**, **8**, **7** and **6** are instead resolutely monocoordinated and lie at higher energy (from about 12 to 25 kcal mol^{-1}) with respect to the most stable complex. In compounds **4**, **7** and **6**, the Cu$^+$ cation is bonded to one of the oxygen atoms of the amino acid whereas in system **8** it interacts with the amino nitrogen.

Although the geometric form of the corresponding Cu^{2+}–α-alanine complexes was similar to those of the Cu$^+$–α-alanine systems, we obtained for them a very different stability order: **2** > **6** > **7** > **1** > **4** > **3** > **5** > **8**. In fact, the interaction with Cu^{2+} determines an important radical character on the α-alanine with the unpaired electron delocalized essentially over the CO$_2^{2-}$ group.

Before discussing the energetic aspects, it is worth noting that, in the bicoordinated species **1**, **3** and **5**, the Cu^{2+}—O and Cu^{2+}—N distances are shorter than the corresponding Cu$^+$—O and Cu$^+$—N lengths. This fact, together with the tendency of Cu$^+$ towards an asymmetric arrangement between the coordination sites, can be attributed to the major repulsion effect between a filled d orbital of Cu$^+$ and the lone pairs of the ligand heteroatoms. In contrast, in the monocoordinated species **4**, **6** and **7**, we can observe the opposite
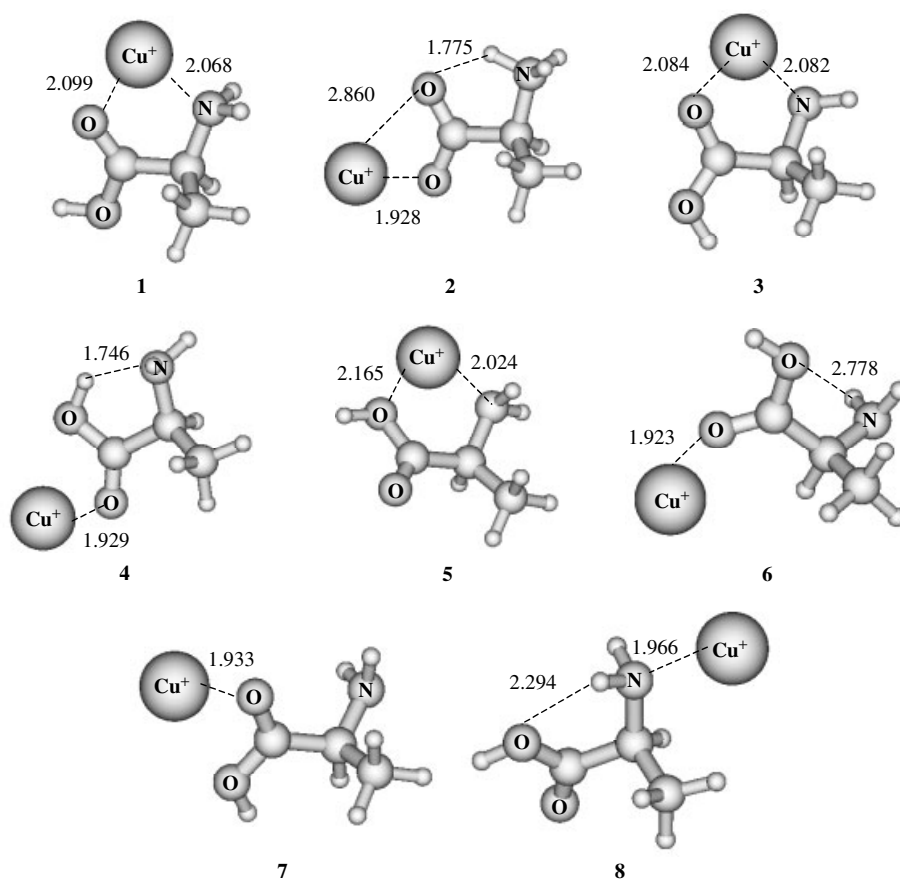
Figure 1. B3LYP/6−311++G** equilibrium geometries for the Cu⁺−α-alanine complexes. Distances are given in Å. Hydrogen bonds longer than 2.800 Å are not reported.

Figure 2. B3LYP/6−311++G** equilibrium geometries for the Cu²⁺−α-alanine complexes. Distances are given in Å. Hydrogen bonds longer than 2.800 Å are not reported.

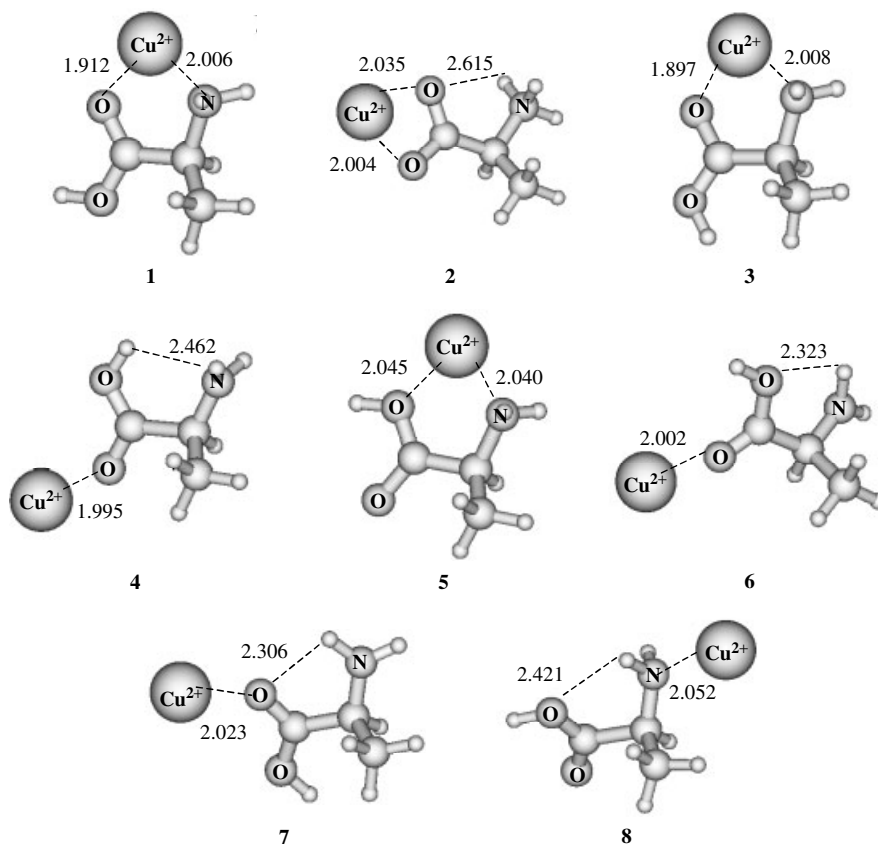**Table 2.** B3LYP/6−311++G** natural net charges (in |e|) on Cu^+ and Cu^{2+} ions and on α-alanine heteroatoms in the various conformers of the copper ion–amino acid complexes[a]

Conformer	Cu^+	N	O_1	O_2	Cu^{2+}	N	O_1	O_2
1	0.885	−0.934	−0.691	−0.630	1.344	−0.843	−0.612	−0.536
2	0.875	−0.710	−0.809	−0.694	1.278	−0.684	−0.521	−0.585
3	0.889	−0.929	−0.662	−0.613	1.351	−0.854	−0.571	−0.524
4	0.906	−0.876	−0.758	−0.648	1.031	−0.397	−0.663	−0.580
5	0.892	−0.939	−0.499	−0.799	1.225	−0.826	−0.274	−0.766
6	0.931	−0.815	−0.795	−0.618	0.990	−0.297	−0.723	−0.632
7	0.914	−0.819	−0.747	−0.650	0.968	−0.273	−0.724	−0.594
8	0.843	−0.930	−0.532	−0.711	1.009	−0.877	−0.162	−0.600

[a] O_1 = carbonyl oxygen (oxygen directly involved in the bond with Cu ion in the zwitterionic complex **2**); O_2 = hydroxyl oxygen.

situation. This is in contrast with the fact that, if we take into account the electronic configuration of the two ions, in the absence of the repulsion effect due to the lone pair of nitrogen atom, Cu^+ (closed shell) should form bonds with a major covalent character, whereas Cu^{2+} (which has an open shell) should add an ionic contribution, to the bonds giving rise to stronger interactions with the ligand. In other words the electron transfer from ligand to the metal ion should be stronger when the Cu^{2+} ion is involved. This fact is widely demonstrated by the natural charge analysis (see Table 2), which shows that, in the Cu^{2+}–α-alanine complexes, the total atomic net charge on the cation is always reduced by about 0.85 |e|, whereas in the Cu^+–α-alanine systems, the ligand transfers to the Cu^+ ion on average 0.10 |e|. Hence the explanation for this discrepancy must be sought elsewhere. Considering that many factors (electronic configuration of the ions, charge redistribution and structural rearrangements upon interaction) could influence the geometric parameters of the various complexes in a different manner, we focused our attention to the most accessible information deriving from the present computations (i.e. hydrogen bond presence and natural atomic charges) and tried to draw some partial conclusions.

If we consider both the systems **4**, we can note that, in the case of Cu^+, a strong hydrogen bond $(O{-}H{\cdots}NH_2)$ occurs between the amino nitrogen and the hydrogen of the carboxylic group. This same bond is weakened in the corresponding complex of the Cu^{2+} ion (see Figs 1 and 2). The presence of such a strong hydrogen bond in the first system makes, through an inductive effect, the charge on the oxygen atoms more negative and hence the $Cu^+{-}O$ bond shorter than the $Cu^{2+}{-}O$ bond (see Table 2). In the Cu^{2+} complex **7**, a hydrogen bond $(NH{-}H{\cdots}O)$ (of different nature with respect to that occurring in system **4** because the donor–acceptor role of N and O atoms is now reversed), involving one of the H atoms of the amino group and the carbonyl oxygen, gives to the latter element a more positive charge so that its distance from Cu^{2+} ion becomes longer than in the corresponding complex with Cu^+ in which there is practically, no hydrogen bond. Similar arguments can be proposed to elucidate, even if only to some extent, the distances trend in the complexes **6** and **8**.

The most stable complex of Cu^{2+} is system **2** obtained starting from the zwitterionic conformer of α-alanine and deriving by the interaction of the copper ion with the $-CO_2^-$ moiety. In contrast to the Cu^+–α-alanine complex, **2** appears to be an η^2-O,O bicoordinated system with $Cu^{2+}{-}O$ bond lengths of 2.035 and 2.005 Å. These same conclusions about the preferred coordination mode of divalent copper ion were reached in previous studies on glycine.[17,21,43] At only 0.8 kcal mol^{-1} above **2** we found the monocoordinated complex **6** stabilized by hydrogen bond interaction between one of the amino hydrogens and the hydroxyl oxygen of the carboxylic group, and absent in the corresponding complex with the Cu^+ cation.

The next system **7** lies at 4.5 kcal mol^{-1} with respect to the absolute minimum; the complexes **1**, **4** and **3** follow at 5.6, 9.1 and 12.2 kcal mol^{-1}, respectively. Compounds **5** and **8** are strongly destabilized and lie at 21.6 and 24.4 kcal mol^{-1}.

In Table 3 we report the absolute (MIA) and relative (ΔMIA) values for the α-alanine–copper ion affinity. For the purpose of comparison, in Table 3 we have added some data, remeasured by us or taken from the literature,[14−17] relating to the Cu^+– and Cu^{2+}–glycine systems. The MIA values were computed taking as reference the most stable isomer of the free α-alanine,[25,37] because, although the absolute minimum of the Cu^{2+}–α-alanine system originates from the zwitterionic form of the amino acid, the latter isomer does not exist in the gas phase and is not a minimum on the computed potential energy surface.

First we can note that the affinity of α-alanine for the Cu^{2+} ion is decidedly greater than that for Cu^+. This fact is, however, perfectly in agreement with the different kinds of bond that the two ions form with the amino acid. The examination of the data concerning the Cu^+ cation shows that, notwithstanding the MIA absolute values obtained by different theoretical methods being slightly different, the discrepancies between the relative values referred to the two amino acids are more reasonable. The comparison of the BHandHLYP/6−311++G** absolute MIA of the Cu^+–glycine system with the previous highest level CCSD(T)/basis1 result,[17] taken as reference, proposes a complete coincidence, whereas differences of 4.8 and 3.3 kcal mol^{-1} with the B3LYP/6−311++G** and B1LYP/6−311++G** values were found, respectively.

Table 3. Absolute (MIA) and relative (ΔMIA) metal ion affinities (kcal mol^{-1}) for the Cu$^+$– and Cu^{2+}–glycine and the α-alanine systems

Method	Cu$^+$–Gly		Cu$^+$–Ala		Cu^{2+}–Gly		Cu^{2+}–Ala	
	MIA	ΔMIA	MIA	ΔMIA	MIA	ΔMIA	MIA	ΔMIA
B3LYP/6−311++G**	71.9	0.0	73.2	1.3	237.0	0.0	241.8	4.7
B1LYP/6−311++G**	70.4	0.0	71.8	1.4	230.5	0.0	244.3	13.8
BHandHLYP/6−311++G**	67.1	0.0	68.2	1.1	205.2	0.0	220.7	15.5
B3LYP/basis1[a]	75.2	—	—	—	243.0	—	—	—
B3LYP/basis2[a]	75.4	—	—	—	242.7	—	—	—
B3LYP/basis3[a]	74.2	—	—	—	240.2	—	—	—
MCPF/basis1[a]	66.5	—	—	—	214.2	—	—	—
MCPF/basis2[a]	67.5	—	—	—	218.5	—	—	—
CCSD(T)/ basis1[a]	67.1	—	—	—	210.5	—	—	—
CCSD(T)/ basis2[a]	68.1	—	—	—	214.8	—	—	—
MP2[b]	64.3	0.0	—	1.5	—	—	—	—
Exp.[c]	—	0.0	—	1.7	—	—	—	—

[a] From Ref 17; basis1, basis2 and basis3 correspond to the D95++(d,p), D95++(d,p) plus a polarization f function on Cu^{n+} ion and to the aug-cc-pVTZ sets, respectively.

[b] From Ref. 15; the value refers to the best estimate obtained from a MP2/6−311+G(2f,2d,2p)//MP2/6−31G* computation.

[c] From Ref. 14

Although our B3LYP computations give absolute MIA lower than those obtained using other basis sets (see B3LYP/basis1, B3LYP/basis2 and B3LYP/basis3 in Table 3),[17] they still remain overestimated with respect to both CCSD(T)/basis1 and MCPF/basis2 data. This fact underlined the strong dependence of the MIA values on the basis set, but mainly on the exchange-correlation potential used. In particular, we can note that on increasing the percentage of exact exchange on going from B3LYP to BHandHLYP functionals, the MIA values become smaller like those obtained by the more expensive Hartree–Fock-correlated methods. The total absence of exact exchange, as in the B1LYP potential, provides, instead, results that are not easy to rationalize. In fact, following the previous arguments, they should be the largest values, but really this is true only for the Cu^{2+}–α-alanine complex. It is clear that the present behavior cannot be attributed to the different nature of the open or closed shell of the systems considered, so that its explanation must be deferred to a more detailed study involving a greater number of cases. The same trend of MIA was observed in the case of the Cu$^+$–α-alanine system. Because of the lack of other experimental and theoretical studies, no comparison was possible concerning the absolute values of the metal affinity. The only experimental indication[14] concerns the relative MIA value of the Cu$^+$–α-alanine system with respect to the Cu$^+$–glycine system. This value of 1.7 kcal mol^{-1} is not far from all the other results (the maximum deviation is 0.6 kcal mol^{-1}) also because the experimental uncertainty is estimated to be ±0.3 kcal mol^{-1}.

The differences between the MIA absolute values obtained with various methods in the case of Cu^{2+}–glycine and Cu^{2+}–α-alanine systems were much more substantial. As widely discussed in the work of Bertran *et al.*[17] on the different natures of bonding in glycine–Cu$^+$ and glycine–Cu^{2+}, the discrepancies between the density functional and the CCSD(T) or MCPF metal affinities depend essentially on the

fact that the first method overestimates the three-electron interaction energy like that occurring between the HOMO of glycine or α-alanine and the polarized half-filled d orbital of the metal ion. Also, this time the overestimation was alleviated by the use of the BHandHLYP exchange correlation potential in which the mixing of Hartree–Fock exchange with DFT exchange correlation is 50%. Our BHandHLYP value of 205.2 kcal mol^{-1} for Cu^{2+}–glycine is, however, higher by about 5 kcal mol^{-1} than that obtained with CCSD(T) (210.5 kcal mol^{-1}), but it is considerably lower than both MCPF results. Similar behavior can be observed for the MIA values of Cu^{2+}–α-alanine.

Hence the set of BHandHLYP values of MIA obtained for all systems considered seem to be the more coherent and this functional is the most appropriate one for the reproduction of the metal ion affinities.

CONCLUSIONS

Several complexes originating from the interaction between α-alanine and Cu$^+$ and Cu^{2+} ions were studied with the aim of evaluating, for the first time, the absolute metal ion affinities.

The equilibrium geometries, the preferred coordination sites for the cations and the stability orders of the complexes were discussed and rationalized on the basis of the different kinds of bond between the amino acid and the metal ions.

The most stable Cu$^+$–α-alanine and Cu^{2+}–α-alanine complexes have different structures with the former characterized by an η^2-N,O coordination of the metal and the latter by an η^2-O,O coordination with the cation bonded to the —CO$_2{}^-$ moiety of the zwitterionic form of the amino acid.

The results demonstrated that the absolute metal affinity values depend strongly on the exchange correlation potential

and the basis set used. Good results were obtained using the BHandHLYP/6–311++G** scheme, which, in a very short computational time, allowed a reliable evaluation of the metal affinities like that reachable only with the more expensive CCDS(T) method. The computed best values of the metal affinities were 68.2 and 220.7 kcal mol^{-1} for the Cu$^+$−α-alanine and Cu^{2+}−α-alanine systems, respectively.

Acknowledgements

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