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Theoretical Study of Tripeptides Complexes of Copper(II)

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The L,L-Phe-Gly-Phe-Cu(II), L,L-Phe-Phe-Gly-Cu(II), L,L-Phe-Gly-Phe-Cu(II) systems were studied using molecular modelling. The results obtained, are in good agreement with results obtained by potentiometric studies show a significant increase in stability of copper complexes, when one aromatic or two aromatic residues is located in C-terminal side (compared to the L,L-tripeptides containing the same amino acid residues). This phenomenon is attributed to the interaction between the *d*-orbital of copper(II) and the π-electrons of the aromatic ring and is observed in dipeptides and recently in tripeptides systems.

Key Words: Molecular modelling, Force field, Peptide, Copper(II), Interaction π-d.

INTRODUCTION

Copper is an essential element widely distributed in all parts of the body of the mammals. Among the principal ions of transition metal met in biology, Cu(II) is probably most effective[1] in chelation with peptides at physiological pH. In the body, the essence of copper is present under a non-labile form (for example: céruloplasmine). Labile copper is present in the form of complexes with amino acids or peptides[2].

Cu(II) forms very stable complexes with simple oligopeptides. The principal modes of coordination of the cupric ions with simple dipeptides and tripeptides are well established now[3].

At low pH, the species $[CuA]^+$ is formed with the tripeptide reacting like a bidentate ligand (**I**) [Fig. 1]. Towards pH = 5, peptidic hydrogen's can be deprotected in the presence of Cu(II), making it possible to rearrange the donors centres to form the structure (**II**) [Fig. 1], which is the $CuH_{-1}A$ species. In the zone of high pH (›9), one of the molecules H_2O dissociates to form a mono-hydroxylic complex whose formula is $[CuH_{-2}A]^-$ or $[CuH_{-1}(OH)A]^-$, which has the structure (**III**) shown in Fig. 1.

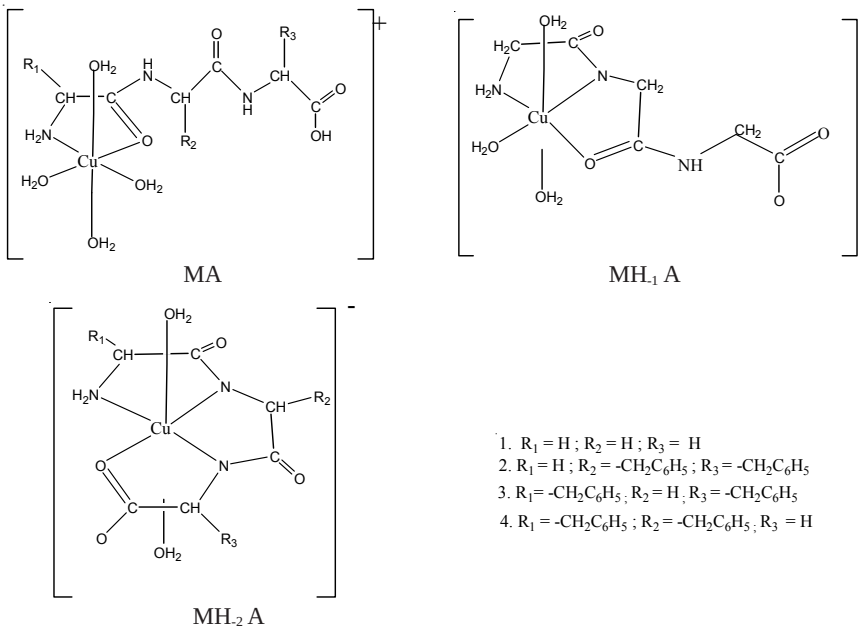


Fig. 1. Structural models of the cupric complexes with simple tripeptides

Sigel and Martin[1] indicate that there are great differences between the cupric complexes of the diglycine and the complexes with dipeptides where the residual glycyl is monosubstituted by coordinating side chains or not. A significant reduction in stability was observed in the cupric complexes with the dipeptides where the residual glycyl was substituted.

In agreement with Rabin[4], Sigel and Martin[1] conclude that stability increases with the lengthening of the side chains. This phenomenon was explained by the interactions between the non-covalent side chains[5,6]. Moreover certain authors proposed the existence of interaction π-d between the aromatic ring of the side chains and the metal ions in certain complexes[7,8].

Potentiometric studies (Table-1) on the mixed complexes of Cu(II) in the presence of several amino acids[9,10] showed that the most stable species are formed when one of the ligands is aliphatic and the other one is aromatic (*e.g.*, phenylalanine)[11-13].

TABLE-1
FORMATION CONSTANTS OF COPPER(II)-TRIPEPTIDE COMPLEXES AT 25 ºC, I = 0.2 mol dm^{-1} KNO_3

Tripeptide	log β_{1-11}
L,L-Gly-Phe-Phe	-0.38±0.01
L,L-Phe-Phe-Gly	-1.42±0.05
L,L-Phe-Gly-Phe	-1.58±0.07

All the tripeptides used in this study are of L,L conformation. The equilibria in metal ion-tripeptide systems and the stability constants of complexes are defined by the following equations (charges are omitted for simplicity):

$$pM + rA + qH \rightleftharpoons[\beta_{pqr}] M_pH_qA_r$$

$$\beta_{pqr} = [M_pH_qA_r]/[M]^p[H]^q[A]^r$$

where p,q and r are the stoechiometric numbers. A negative value for q denotes a deprotonated or hydroxylated from of species considered. The conjugated base of the ligand is noted A. HA is the zwitter ions form and M the metal ion.

THEORETICAL APPROACH

Molecular modelling is used to study the influence of the side chains in the tripeptides and especially those which contain a residue having one or two aromatic rings. We were interested to study the complexation of the Cu^{2+} close to the physiological pH, where the species (**II**) $MH_{-1}A$ is most predominant, with the three tripeptides according to: L,L-phenylalanyl-phenylalanyl-glycine (L,L-Phe-Phe-Gly), L,L-Glycyl-phenylalanyl-phenyl-alanine (L, L-Gly-Phe-Phe) and L,L-phenylalanyl-phenylalanyl-Glycine (L, L-Phe-Phe-Gly). Each tripeptide contains two aromatics side chain[14].

The $MH_{-1}A$ species is studied with the program EMO (energy of molecule) follow-up by semi empirical calculations by the SAM1/d method, in both three cases: (a) two phenyl group is located in C-terminal side (b) two phenyl group is located in N-terminal side (c) one phenyl is located in C-terminal side and the second is located in N-terminal side.

EMO was developed by B.Blaive in 1993 to treat the organic molecules.

The version of this program placed at our disposal is designed to function on PC[15-17]. This program uses the force field MM2, which is the force field of Allinger[18], which was conceived at the beginning for the simple molecules (alkanes, carbonyl compounds, sulphides, amines...). It is used to treat increasingly complex molecules.

The retained parameters, concerning structures of our complex ligands, are those proposed by the Professor B. Blaive completed by the statistical study done at the level of the CSD (Cambridge Structural Database 1995).

Several effects are often set forth in the interpretation of experimental results[19]. (a) side-chain donor effect, (b) hydrophobic side chain-side chain interaction, (c) Steric effects between the side chains, and (d) Effects from the surrounding solvent sphere.

Another effect was proposed by authors for copper(II)-dipeptide, nickel(II)-dipeptide, complexes containing aromatic side-chains[20,21]. It has been shown that the presence of an aromatic residue in a C-terminal site increases the stability of complexes[15,22-24].

Modelling of the Cu-ligand interactions: For reference bond length, the (Cu-N) and (Cu-O) bonds differ according to the type of atom of oxygen or nitrogen linked to the copper.

We interrogated the CSD and did a statistical study on more than 1000 cases having the same configuration of chromophor to these complexes. We chose values by taking the average values of those met at the time of this statistical study (Table-2).

TABLE-2
REFERENCE BOND LENGTH L_0 FOR CU-LIGAND
(CAMBRIDGE STRUCTURAL DATABASE 1995)

Atomes chaining		L_0 (angstroms Tot. Obs).	
(Cu-O) (sp^3)	Axial	2.39 (2.38)	1117
(Cu-O) (sp^2)	Equatorial	1.96 (1.94)	1162
(Cu-O) (sp^3)	Equatorial	(2.03)	
(Cu-O) (sp^2)	Axial	(2.15)	
(Cu-N) (sp^3)	Equatorial	2.00 (2.04)	2279

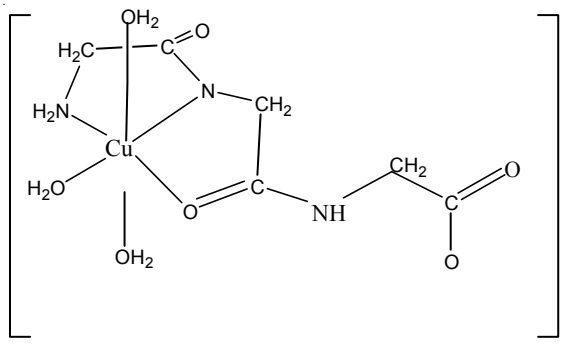
Values of reference bond length in brackets are taken from literature.

After having minimized the energy of the various peptidic complexes of Cu(II), an optimisation of energy is carried out by the SAM1/d method.

SAM1/d is a semi-empirical method which takes in consideration *d*-orbitals of transition metals.

RESULTS AND DISCUSSION

We studied the $MH_{-1}A$ species because it is the majority complex of the Cu(II)-tripeptide systems between pH = 4.5 and pH = 8[11] *i.e.* close to the physiological pH.



Structure of $CuH_{-1}A$

Steric energies of all the systems were minimized by the program EMO (version 2001). In order to avoid the local minima corresponding to unstable conformers, we carried out it with the option 'SCAN' which makes it possible to sweep the surface of potential energy (PES). This enabled us to eliminate the geometries having little chance to generate a whole of conformers probably stable. Energies of the found conformers are optimised by the semi empirical method SAM1/d. the results obtained are gathered in the Table-3.

TABLE-III
ENERGIES OF THE COMPLEXES CALCULATED
USING EMO AND SAM1/d

	L,L-Gly-Phe-Phe-Cu(II)	L,L-Phe-Phe-Gly-Cu(II)	L,L-Phe-Gly-Phe-Cu(II)
E_{EMO} (kj/mol)	-90.59	-87.21	-61.89
$E_{SAM1/d}$ (AMPAC)(ev)	-7176.72	-7176.66	-7176.52

In the light of the results obtained we noticed that the order of stability of the studied systems is as follows: L,L-Gly-Phe-Phe-Cu(II) > L,L-Phe-Phe-Gly-Cu(II) > L,L-Phe-Gly-Phe-Cu(II).

This gain of stability depends on the size of the side chain. This observation indicates that the interaction between the non-coordinating side chains exists and this interaction favours the stability of the complex. From the chemical point of view, the non-coordinating side chains should decrease the stability of the complex by steric effect. But an effect of interaction between the side chains assures the square planar structure favourable for the structure of the complex.

We also noticed a significant increase in the stability of the cupric complexes, when the aromatic groups is in C-terminal position for dipeptides[22] compared to the tripeptides containing the same amino acids, but the residue phenyl is into N-terminal. This phenomenon is attributed to the interaction between the *p*-electrons of the aromatic ring and the *d*-orbitals of the Cu(II).

Conclusion

The presence of one or tow aromatic rings in the C-terminal residues gives generally a more stable [$MH_{-1}A$] species. This stabilizing effect was attributed to an interaction between the metal ion and the aromatic ring. This interaction is found only when the aromatic ring is located in the C-terminal residue, because the (Cu-O) bond is weak and easily distorted. However, the rigid (Cu-N) bond formed when the aromatic ring is in the N-terminal residue does not favour this interaction[12].

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