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CO-ORDINATION ABILITY OF AN *N*-TERMINAL TETRAPEPTIDE FRAGMENT OF FIBRINOPEPTIDE A

Spectroscopic and potentiometric studies of the interaction of Cu(II) with an *N*-terminal fragment of fibrinopeptide A have shown considerable specificity of an aspartic acid residue (Asp-2) in metal ion binding. In the system Cu(II) — Ala--Asp-Ser(Bzl)-Gly four distinct species are formed involving all together the NH_2 group (Ala) and three amide nitrogens (see Fig. 1). Correlation of the spectroscopic and potentiometric data (Table I) allows assignment of the species CuL to co-ordination between Cu and NH_2(Ala) and the neighbouring peptide oxygen, $CuH_{-1}L$ to NN co--ordination (NH_2, N^-), $CuH_{-2}L$ to NNN co-ordi-

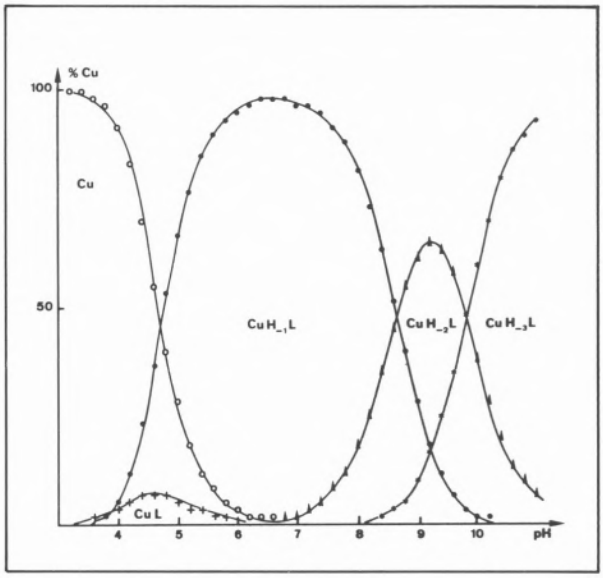

Fig. 1
The distribution of species as a function of pH for solutions containing Copper(II) and Ala-Asp-Ser(Bzl)-Gly with 1:1 metal to peptide molar ratio.

Table I
Formation constants and spectroscopic data of proton and Cu(II) complexes with Ala-Asp-Ser(Bzl)-Gly

Species	log β (or K)	Absorption spectra d-d $\lambda_{[nm]}(\epsilon 1.\ M^{-1}\ cm^{-1})$	CD spectra $\lambda_{[nm]}(\Delta\epsilon)$	EPR spectra $g_\parallel$	$A_\parallel$ (G)
LH	8.332(NH_3^+)				
LH_2	3.700(βCOOH)				
LH_3	2.510(αCOOH)				
CuL	6.18				
$CuH_{-1}L$	2.28	635(84)	618(+0.09)B+E [a]	2.245	192
			298(−0.78)N^-→Cu(II) [b]		
			264(+0.58)NH_2→Cu(II) [b]		
$CuH_{-2}L$	− 6.39	625(130)	590(−0.26)B+E		
			298(−0.48)N^-→Cu(II)		
			259(+1.9)NH_2→Cu(II)		
$CuH_{-3}L$	−16.2	510(180)	520(−1.8)B+E	2.179	210
			300(+0.84)N^-→Cu(II)		
			272(−0.4)NH_2→Cu(II)		

a) d-d transitions. b) charge transfer transitions.

nation (NH_2, N^-, N^-) and $CuH_{-3}L$ to NNNN co-ordination (NH_2, N^-, N^-, N^-).

Comparison of the formation constants of $CuH_{-1}L$ and $CuH_{-2}L$ complexes (Table I) with those of the comparable species in the Cu(II) — tetraglycine system shows the influence of Asp-2 in the system studied. For example the $CuH_{-1}L$ complex (log $\beta = 2.28$) is significantly more stable than with tetraglycine (log $\beta = -0.4$, ref. [1]). This comparison indicates clearly the involvement of COO^- of the Asp-2 residue in metal ion binding. The formation of the additional chelate ring when COO^- is bound to the Cu(II) ion in this NN species leads to the creation of a very stable complex with a maximum concentration reaching 100% around pH 7 (see Fig. 1).

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THERMODYNAMIC AND SPECTROSCOPIC STUDY OF METAL COMPLEX FORMATION WITH CYCLOPEPTIDES: Cu(II)- AND Zn(II)-CYCLO-L-HISTIDYL--L-HISTIDYL

Cyclic peptides can be very useful models for the study of protein-metal ion interactions. Cyclic peptides have the advantage over linear peptides that no free terminal amino and carboxylate groups are present to bind to the cation. Thus, cyclopeptide complexes of metal ions represent simple model compounds for the study of metal ion interaction with amido groups and side chains in proteins and polypeptides.

We have investigated copper(II) and zinc(II) complexation with cyclo-L-histidyl-L-histidyl (cyhis). Our interest in this type of ligand is well justified in light of work reported previously in the literature. LANGEBECK *et al.* [1] found that cyhis catalyzes the oxidation of DOPA and that the addition of Cu(II) to the reaction system accelerates the oxidation. HORI *et al.* [2] have obtained the crystal structure of $Cu(cyhis)_2(ClO_4)_2 \cdot 4H_2O$ by X-ray crystallography. On this basis it was proposed that cyhis may be a good model for elucidating interactions between metal ions and the imidazole group of the histidine residue of some enzymes.

In light of the problems associated with extrapolating solid state properties to solution species, we began an investigation of the coordination chemistry of the title ligand in aqueous solution. Specifically, we determined by potentiometric titration the stability constants of the species formed between the ligand and either copper(II) or zinc(II). The species $M(cyhis)^{2+}$ was present in the pH range 4.0 to 5.5 and was the principal complex species observed.

The ligand protonation constants determined potentiometrically were 6.53 and 5.49, for log K_1 and log K_2 respectively, at 25°C and I = 0.1 mol dm^{-3} (KNO_3).

Calorimetric measurements were also carried out to determine ΔH and ΔS values for the formation of the metal complexes. These data helped in ascertaining whether or not the imidazole nitrogen is involved in the complexation process.

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