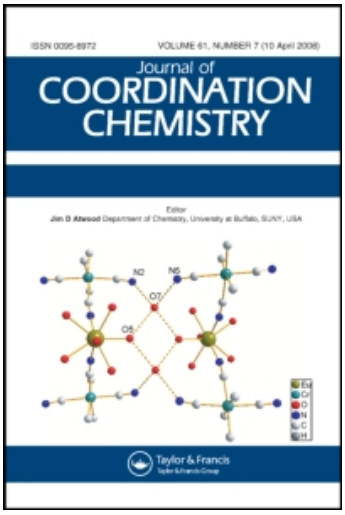

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SPECTROSCOPIC ANALYSIS OF BINARY AND TERNARY COPPER(II) COMPLEXES FORMED BY HISTIDINE AND GLUTAMIC ACID

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Ternary copper(II) complexes of the type [Cu(His)A] (HisH = *L*-histidine, A = glycinato, *L*-valinato, *L*-alaninato, *L*-threoninato, *L*-serinato, or *L*-asparaginato) and $[Cu(Glu)B]^{n-}$ ($GluH_2$ = *L*-glutamic acid, B = glycinato, *L*-alaninato, *L*-valinato ($n = 1$) or an amino-acid with positively charged protonated side chain such as *L*-asparagine, *L*-lysine, or *L*-ornithine ($n = 0$)) have been investigated in aqueous solution by means of ESR and absorption spectra. It is suggested that in the ternary species the histidinate ion adopts a histamine-like bonding mode giving rise to CuN_3O chromophores in the metal plane. Coordination in the bis-(glycine)-like mode is detected in the Glu-containing species. The spectral results have been used to postulate plausible structures for the bis-(histidinato)copper(II) complexes.

INTRODUCTION

Mixed-ligand complexes of copper(II) with imidazole, amino-acids and dipeptides are considered reliable models for understanding the nature of enzyme-metal ion-substrate interactions.[1-3] Histidine-containing ternary species are also involved in copper transport in blood.[4-5] Several ternary amino-acid copper(II) complexes have been described and characterized in both solution and the solid state.[6-15] However, in spite of increasing information provided even by X-ray analysis,[8,13,15] there is still uncertainty as to which of the coordination sites of potentially terdentate ligands are involved in the binding of metal ions.

The present study was undertaken to provide ESR information about the structure of representative ternary amino-acid copper(II) complexes.[11-14] In fact, with the exception of the histidine-threonine system,[9] for which conclusive results were not obtained, ternary amino-acid copper complexes have not been object of detailed ESR analysis. Two series of compounds have been examined in this work in an attempt to interpret their structure in view of the different donor ability of the ligands. In addition, based on spectral comparison with the ternary species, information has been obtained about the structure of the physiologically important bis-(*L*-histidanato)copper(II) complexes.

EXPERIMENTAL

The amino-acids such *L*-arginine, *L*-lysine monohydrochloride, *L*-histidine hydrochloride monohydrate, *L*-asparagine monohydrate, *L*-threonine, *L*-serine, *L*-ornithine monohydrochloride, *L*-glutamic acid, *L*-valine, *L*-alanine, and glycine were of Merck and B.D.H. biochemical grade. All other chemicals were of the highest grade available.

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The spectra of the ternary species were obtained on aqueous solutions containing copper(II) and the amino-acids in the ratio 1:1:1 (concentration: 5×10^{-3} M) at pH 7.5-8.0 according to previous reports.[11,14] The copper(II)-glutamic acid binary system was studied at a metal concentration of 5×10^{-3} M, L/M = 5 and pH 7.0. The spectra for the histidine-copper(II) binary system were run on 1:4-8 metal-ligand solutions ([Cu] 5×10^{-3} M) adjusted to pH 4.5 and 7.4 to give maximum concentrations of $[Cu(HisH)\ (His)]^+$ and $[Cu(His)_2]$, respectively.[16] First derivative ESR X-band (*ca.* 9.15 GHz) spectra were recorded with a Varian E-9 instrument. The g values were calibrated against diphenylpicrylhydrazyl (dpph). Glass spectra were obtained using g glycerol-water mixtures (3:2 ratio) at 133 K. Electronic spectra were measured with a Beckman Acta M IV spectrophotometer.

RESULTS AND DISCUSSION

At room temperature the ternary species in aqueous solution gave rise to ESR spectra exhibiting hyperfine splitting due to the copper nucleus. At 133 K typical glassy spectra were obtained, all characterized by three well-resolved hyperfine lines on $g_{\|}$ and the complex shape of the perpendicular region. An 'overshoot' signal at *ca.* 2.00, as is often the case in copper(II) complexes,[17] accounts for intermediate orientations relative to the external magnetic field. All the spectra are characterized by both $g_{\|}$ and $g_{\perp}$ values higher than 2.040, conforming to a ground state configuration with the unpaired electron in the $d_{x^2-y^2}$ orbital. Both the spin-Hamiltonian parameters listed in Table I, such as the large $A_{\|}$ values, and the shape of the perpendicular region in the glassy spectra are typical of tetragonal Cu(II) complexes with weak axial perturbation and strong in-plane ligands.

Based on the $g_{\|}$ and $A_{\|}$ values it appears that the mixed complexes are in two well-distinct groups: the mixed complexes with histidine are characterized by $g_{\|} \sim 2.24$ and $A \sim 190\text{-}200 \times 10^{-4}$ cm^{-1} whereas the ternary species involving glutamic acid exhibit higher $g_{\|}$ and lower $A_{\|}$ values. Likewise, the electronic spectra show absorption maxima (Table II) at energy values which are higher for the histidine than for the glutamic acid

TABLE I
ESR parameters for ternary and binary complexes.[a]

Complex	$g_{\|}$	$g_{\perp}$	$A_{\|}$	g_o	A_o
[Cu(His) (Gly)]	2.241	2.059	189	2.120	70
[Cu(His) (Ala)]	2.239	2.059	192	2.119	73
[Cu(His) (Val)]	2.239	2.062	190	2.118	74
[Cu(His) (Thr)]	2.238	2.058	197	2.119	72
[Cu(His) (Asn)]	2.238	2.060	197	2.120	73
[Cu(His) (Ser)]	2.242	2.059	194	2.119	73
$[Cu(HisH)\ (His)]^+$	2.245	2.060	191	2.119	74
$[Cu(His)_2]$	2.238	2.058	183	2.119	69
$[Cu(Glu)\ (Ala)]^-$	2.259	2.059	183	2.124	69
$[Cu(Glu)\ (Val)]^-$	2.260	2.059	181	2.123	70
$[Cu(Glu)\ (Gly)]^-$	2.263	2.060	182	2.125	69
[Cu(Glu) (Arg)]	2.256	2.059	182	2.124	69
[Cu(Glu) (Orn)]	2.259	2.062	182	2.124	69
[Cu(Glu) (Lys)]	2.257	2.060	180	2.123	69
$[Cu(Glu)]^{2-}$	2.258	2.061	183	2.123	70

[a] A values in units of 10^{-4} cm^{-1}.

TABLE II
Absorption maxima for ternary and binary complexes.[a]

Complex	λ (nm)
[Cu(His) (Gly)]	610 (58)
[Cu(His) (Val)]	610 (57)
[Cu(His) (Ala)]	610 (57)
[Cu(His) (Thr)]	610 (55)
[Cu(His) (Ser)]	610 (60)
[Cu(His) (Asn)]	605 (58)
[Cu(HisH) (His)]$^+$	615 (56)
[Cu(His)$_2$]	645 (82)
[Cu(Glu) (Gly)]$^-$	625 (51)
[Cu(Glu) (Val)]$^-$	625 (51)
[Cu(Glu) (Ala)]$^-$	625 (51)
[Cu(Glu) (Lys)]	625 (53)
[Cu(Glu) (Arg)]	620 (59)
[Cu(Glu) (Orn)]	620 (53)
[Cu(Glu)$_2$]$^{2-}$	620 (72)

[a]The molar absorption coefficients (M^{-1} cm^{-1}) are given in parentheses.

ternary complexes. These differences can be ascribed to unlike in-plane donor sets in the two series of compounds. Since the histidinate ion is a potential donor of two nitrogen atoms, it is likely that the ternary His complexes differ from those containing Glu in that CuN_3O rather than CuN_2O_2 chromophores are involved.

To assist the above interpretation, the binary species [Cu(Glu)$_2$]$^{2-}$, [Cu(HisH) (His)]$^+$, and [Cu(His)$_2$] have been investigated (see Figure 1 and Tables I and II). According to previous reports,[18] [Cu(Glu)$_2$]$^{2-}$ exhibits spectral parameters quite consistent with those

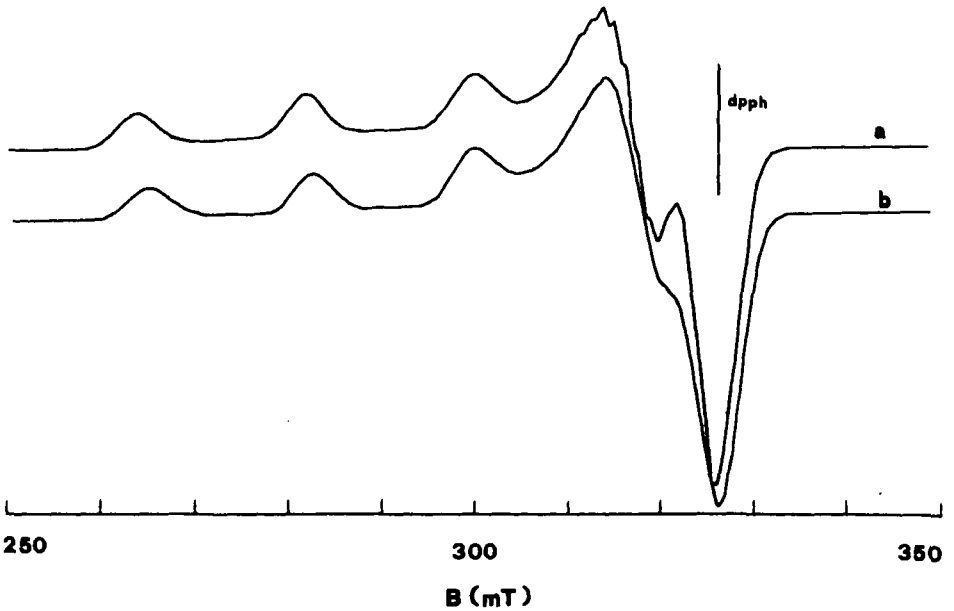

FIGURE 1 ESR spectra of the copper(II)-bis-(histidine) complexes in frozen solution: (a) [Cu(HisH) (His)]$^+$; (b) [Cu(His)$_2$].

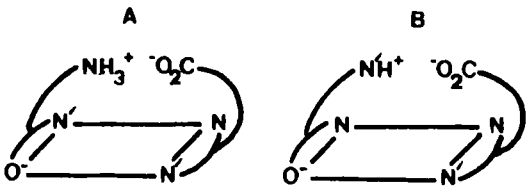

FIGURE 2 Proposed structures for the [Cu(HisH) (His)]$^+$ copper-histidine complex; N = amino nitrogen, N' = imidazole nitrogen

of the CuN_2O_2 series, indicating that glycine-like ligation behaviour takes place in both ternary and binary species. The ESR parameters of [Cu (HisH) (His)]$^+$ and [Cu(His)$_2$] are suggestive of chromophores of the CuN_3O type. This confirms that asymmetrical co-ordination of histidine molecules occurs in the bis-chelates.

The structures A and B in Figure 2 have been proposed for [Cu(HisH) (His)]$^+$,[16,18] which are both consistent with our results since CuN_3O in-plane coordination and weak oxygen axial bonding are involved. However, the close similarity of the ESR parameters with those of the [Cu(His)A] series, in which the second amino-acid adopts a glycine-like bonding mode, suggests that B is more probable

Great controversy has been centred on the structure of [Cu(His)$_2$)]. Based on spectral and thermodynamic data it was suggested that the copper(II) square planar coordination has been by: (*1*), amino-*N* and carboxyl-*O* atoms of two bidentate histidines (bonding in the bis-(glycine)-like mode);[19] (*2*), amino-*N* and carboxyl-*O* atoms of one histidine (bonding in the glycine-like mode) and amino- and imidazole-*N*-atoms of the other (bonding in the histamine-like mode);[20] (*3*) the amino- and imidazole-*N* atoms of both histidine molecules (bonding in the bis-(histamine)-like mode).[21-22] In interpreting the structure of [Cu(His)$_2$] the following observations seem meaningful. First, the ESR parameters are markedly different from those of the [Cu(Glu)B] series, thuse excluding a structure of type (*1*), and secondly, the absorption maximum value contrasts with the arrangement (*3*), as lower wavelength values should be expected for a CuN_4 chromophore with axial oxygen axial binding (see Table II in ref. 23).

Thus the ESR parameters, taken with the absorption data, seem more consistent with the apical coordination of a nitrogen atom, probably from the imidazole amino group of one glycine-like histidine bonded in the metal plane to a CuN_3O chromophore. The observation of a red shift upon replacement of *O*-donors by *N*-donors in the apical position of copper(II) complexes is well-known.[24-25] In addition such a hypothesis is substantiated by the $A_{\parallel}$ value which, being lower than for the other CuN_3O species, indicates stronger axial perturbation in [Cu(His)$_2$].[26] However, the decrease of $g_{\parallel}$ observed for [Cu(His)$_2$] with respect to [Cu(HisH) (His)]$^+$, indicates that the two species do not differ only with respect to the nature of the apical donor. Either changes in the covalency of the bonds or further structural rearrangements in the metal plane leading to a CuN_3O, N chromophore occur upon formation of [Cu(His)$_2$]. In conclusion, the two series of ternary complexes, [Cu(His)A] and [Cu(Glu)B], differ with respect to the in-plane donor set around the copper ion. Both ESR and absorption spectra of the ternary glutamato species agree with a bis-(α-aminocarboxylate) structure also found in the parent binary complex [Cu(Glu)$_2$]$^{2-}$. On the other hand, in [Cu(His)A], the histidine molecule exhibits 'histamine-like' behaviour, coordinating through the α-amino and δ-imidazole nitrogen atoms, whereas the second amino-acid is linked in a 'glycine-like' way.

Bis-(glycine)-like coordination for *L*-histidine has been detected in the solid complex [Cu(*L*-HisH)$_2$ (H$_2$O)$_2$] (NO$_3$)$_2$,[27] obtained at pH 3.7. Above pH 5 much evidence indicates that the imidazole group is involved in the copper coordination, but a

bis-(histamine)-like bonding mode has never been described. This agrees with our analysis, which shows that 'mixed' structures like those occurring in the [Cu(His)A] species are also strongly preferred when *L*-histidine is the second amino-acid. However, the involvement of the second imidazole group in the coordination to the copper(II) ion can occur in $[Cu(His)_2]$ but only in the axial position with respect to an in-plane 'mixed' structure.

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