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Coordination Modes of Histidine. 5.[1] Copper(II) Complexes of L-N^{τ}-Methylhistidine and L-N^{α},N^{α}-Dimethylhistidine in Aqueous Solution

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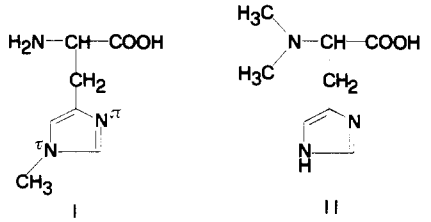
Received June 9, 1982

The coordination structures of various species in the copper(II)-L-N^{τ}-methylhistidine and copper(II)-L-N^{α},N^{α}-dimethylhistidine (1:2) systems in aqueous solution have been deduced by investigating the pH dependence of the circular dichroism spectra and compared to the structures of the corresponding complexes of L-histidine. The contributions of the CD spectra of the glycine-like binding mode of the L-histidine derivatives have been determined by recording the spectra of several ternary systems containing histamine or methyl esters of the L-histidine derivatives. The contributions to the CD spectra of the histamine-like binding mode of the L-histidine derivatives have been determined from the spectra of the ternary systems containing glycine or L-valine. In general, the structures of the binary and ternary complexes of L-N^{τ}-methylhistidine are similar to those of the corresponding complexes of L-histidine, while those of the systems containing L-N^{α},N^{α}-dimethylhistidine are often significantly different. Thus, while the species $Cu(HL)^{2+}$ (HL = L-N^{τ}-methylhistidine or L-N^{α},N^{α}-dimethylhistidine) contains the ligand bound glycine-like with an unbound imidazolium cation in both systems, the structures of the species $Cu(HL)L^{+}$ are different. The anionic ligand (L) is bound histamine-like in the case of L-N^{τ}-methylhistidine, while it is prevalently bound glycine-like in the case of L-N^{α},N^{α}-dimethylhistidine. Also the structures of CuL_2, the major species at neutral pH, reflect the higher preference of L-N^{α},N^{α}-dimethylhistidine than L-N^{τ}-methylhistidine or L-histidine to bind copper(II) in a glycine-like fashion. For bis(L-N^{α},N^{α}-dimethylhistidinato)copper(II) the main structure in solution appears to be that containing a glycine-like and a histamine-like bound ligand, whereas bis(L-N^{τ}-methylhistidinato)copper(II) exists in solution as an equilibrium mixture of a mixed-type chelation structure and structures containing both ligands bound histamine-like.

Introduction

The mode of histidine chelation in binary and ternary systems has been extensively investigated with a variety of spectroscopic and potentiometric methods[2-8] because of the many different geometric arrangements that are possible when one or two potentially tridentate ligands bind a metal ion.[9] We have recently found that circular dichroism can easily differentiate the two basic coordination modes of L-histidine residues (glycine-like and histamine-like) in a series of Schiff base chelates of copper(II) and zinc(II), since in these complexes the conformation of the amino acid chelate ring with an axial side chain is stereoselectively dictated and involves opposite chirality for the two L-histidine binding modes.[10] In metal complexes with simple amino acids, correlations between the signs of the Cotton effects and the conformations of the chelate rings are usually much less reliable because there is little preference for a particular conformation and other effects (e.g., vicinal effects)[11] become important. However, when the amino acid is tridentate, apical chelation by the donor atom on the side chain stabilizes the conformation with an axial side chain and correlations between CD and coordination structure may become reliable.

In a previous study of the copper(II)-L-histidine (1:2) system in aqueous solution we could relate the features of the CD spectra to the predominant species existing in various pH ranges.[1] The physiologically important[12] (neutral) bis(L-histidinato)copper(II) complex, however, exists in solution as an equilibrium mixture of isomeric species, and it was impossible to relate the CD data to the structures of each individual species. We report here a CD investigation of the binary systems of copper(II) and L-N^{τ}-methylhistidine (I) and



I

II

of copper(II) and L-N^{α},N^{α}-dimethylhistidine (II) in various pH ranges, together with several related ternary systems at neutral pH. A primary objective of the present study is to gain some clarification of the structure of the neutral bis(L-histidinato)copper(II) species by a comparison with the related copper(II) complexes derived from I and II.

Experimental Section

The amino acids glycine, L-valine, and L-histidine and L-histidine methyl ester dihydrochloride, histamine dihydrochloride, and cop-

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per(II) sulfate pentahydrate were of the highest grade commercially available. L-N^{τ}-Methylhistidine dihydrochloride[13] [UV (H_2O) λ_{max} = 214 nm (ϵ = 6350); CD (H_2O) λ_{max} = 212 nm ($\Delta\epsilon$ = +2.83)] and L-N^{α},N^{α}-dimethylhistidine hydrochloride[14] [UV (H_2O) λ_{max} = 213 nm (ϵ = 13800); CD (H_2O) λ_{max} = 211 nm ($\Delta\epsilon$ = +4.44); ^{1}H NMR (D_2O/DSS) δ 2.98 (s, 6 H, N–CH_3), 3.1–3.6 (m, 2 H, CH_2), 3.94 (dd, $J_1 + J_2$ = 14.2 Hz, 1 H, α-CH), 7.41 (s, 1 H, im 5-H),[15] 8.66 (s, 1 H, im 2-H)] were prepared according to literature procedures. L-N^{τ}-Methylhistidine methyl ester dihydrochloride was prepared by esterification of L-N^{τ}-methylhistidine in anhydrous methanol under a stream of dry hydrogen chloride. Anal. Calcd for $C_8H_{13}N_3O_2$·2HCl: C, 37.51; H, 5.90; N, 16.41. Found: C, 37.17; H, 5.90; N, 16.12. UV (H_2O): λ_{max} = 214 nm (ϵ = 5550). CD (H_2O): λ_{max} = 216 nm ($\Delta\epsilon$ = +2.98). ^{1}H NMR (D_2O/DSS): δ 3.44 (d, J = 6.8 Hz, 2 H, CH_2), 3.86 (s, 3 H, N^{τ}–CH_3), 3.90 (s, 3 H, OCH_3), 4.51 (t, 1 H, α-CH), 7.43 (s, 1 H, im 5-H), 8.67 (s, 1 H, im 2-H). L-N^{α},N^{α}-Dimethylhistidine methyl ester dihydrochloride was prepared similarly from L-N^{α},N^{α}-dimethylhistidine. Anal. Calcd for $C_9H_{15}N_3O_2$·2HCl·0.5H_2O: C, 38.72; H, 6.50; N, 15.05. Found: C, 38.87; H, 6.51; N, 15.23. UV (H_2O): λ_{max} = 213 nm (ϵ = 11900). CD (H_2O): λ_{max} = 214 nm ($\Delta\epsilon$ = +4.76). ^{1}H NMR (D_2O/DSS): δ 3.06 (s, 6 H, N–CH_3), 3.3–3.7 (m, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 4.58 (dd, $J_1 + J_2$ = 14.2 Hz, 1 H, α-CH), 7.49 (s, 1 H, im 5-H), 8.73 (s, 1 H, im 2-H). L-*N*,*N*-Dimethylvaline was prepared by catalytic hydrogenation (2 g of 10% Pd–C) of an aqueous solution (150 mL) of L-valine (5 mmol) and formaldehyde (10 mmol) at room temperature; after filtration of the catalyst and evaporation to dryness of the solution, the thick syrup was crystallized with ethanol–diethyl ether. Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.50; H, 10.20; N, 9.25. ^{1}H NMR (D_2O/DSS): δ 0.99 (d, J = 6.6 Hz, 3 H, CH_3–C), 1.08 (d, J = 6.9 Hz, 3 H, CH_3–C), 2.1–2.6 (m, 1 H, β-CH), 2.86 (s, 6 H, CH_3–N), 3.38 (d, J = 5.4 Hz, 1 H, α-CH).

The optical absorption and circular dichroism spectra were recorded at room temperature on 10^{-2} M aqueous solutions of copper(II)–L-N^{τ}-methylhistidine (1:2) and copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) at various pH values and on 10^{-2} M neutral aqueous solutions of copper(II)–L-N^{τ}-methylhistidine–glycine (1:1:1), copper(II)–L-N^{τ}-methylhistidine–L-valine (1:1:1), copper(II)–L-N^{τ}-methylhistidine–histamine (1:1:1), copper(II)–L-N^{τ}-methylhistidine–L-histidine methyl ester (1:1:1), copper(II)–L-N^{τ}-methylhistidine–L-N^{τ}-methylhistidine methyl ester (1:1:1), copper(II)–L-N^{τ}-methylhistidine–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:1:1), copper(II)–L-histidine–histamine (1:1:1), copper(II)–L-histidine–L-histidine methyl ester (1:1:1), copper(II)–L-histidine–L-N^{τ}-methylhistidine methyl ester (1:1:1), copper(II)–L-histidine–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:1:1), copper(II)–L-N^{α},N^{α}-dimethylhistidine–glycine (1:1:1), copper(II)–L-N^{α},N^{α}-dimethylhistidine–L-valine (1:1:1), copper(II)–L-N^{α},N^{α}-dimethylhistidine–histamine (1:1:1), copper(II)–L-N^{α},N^{α}-dimethylhistidine–L-histidine methyl ester (1:1:1), copper(II)–L-N^{α},N^{α}-dimethylhistidine–L-N^{τ}-methylhistidine methyl ester (1:1:1), copper(II)–L-N^{α},N^{α}-dimethylhistidine–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:1:1), copper(II)–L-histidine methyl ester (1:2), copper(II)–L-N^{τ}-methylhistidine methyl ester (1:2), copper(II)–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:2), and copper(II)–L-*N*,*N*-dimethylvaline (1:2).[15] The pH values of the samples solutions were adjusted with concentrated sodium hydroxide. The ionic strength of the solutions was unadjusted. Spectral readings between 220 and 780 nm were taken immediately after preparation of the solutions with use of quartz cells of path lengths varying between 0.01 and 1 cm so that dilution of the solutions was not required. Results are reported in terms of ϵ (molar absorption coefficient) and $\Delta\epsilon = \epsilon_l - \epsilon_r$ (molar CD coefficient), in L mol^{-1} cm^{-1}. Electronic spectra were recorded on a Beckman DK-2A spectrophotometer. Circular dichroism spectra were obtained by means of a Jobin-Yvonne Mark III dichrograph, calibrated with a solution of isoandrosterone in dioxane ($\Delta\epsilon$ = +3.31 at 304 nm). Values of pH were measured with a IL-259 pH meter.

Table I. Electronic and Circular Dichroism Spectra of Copper(II)–L-N^{τ}-Methylhistidine (1:2) in Aqueous Solution (10^{-2} M) at Various pH Values

pH	UV-vis, λ_{max}, nm[a] (ϵ)	CD, λ_{max}, nm[a] ($\Delta\epsilon$)
3.2	695 (39)	680 (+0.03)
	245 sh (4000)	250 (−1.22)
4.3	630 (63)	635 (+0.24)
		320 sh (+0.06)
	245 sh (5500)	248 (−3.15)
		225 (−5.40)
5.7	640 (94)	675 (+0.39)
		550 (−0.02)
		320 (−0.16)
		284 (+0.05)
	245 sh (5700)	245 sh (−3.90)
		225 (−9.90)
7.5	650 (110)	680 (+0.50)
		585 (−0.08)
		323 (−0.21)
		278 (+0.28)
	245 sh (5600)	245 sh (−4.50)
		225 (−11.80)
12.1	645 (82)	675 (+0.39)
		580 (−0.04)
		323 (−0.16)
		280 (+0.20)
	245 sh (5900)	245 sh (−3.60)
		224 (−12.20)

[a] sh = shoulder.

Table II. Electronic and Circular Dichroism Spectra of Copper(II)–L-N^{α},N^{α}-Dimethylhistidine (1:2) in Aqueous Solution (10^{-2} M) at Various pH Values

pH	UV-vis, λ_{max}, nm[a] (ϵ)	CD, λ_{max}, nm[a] ($\Delta\epsilon$)
3.5	800 (21)	690 (+0.02)
		560 (−0.005)
	245 (700)	262 (−0.10)
4.5	730 (52)	780[b] (+0.07)
		690 (−0.10)
		580 sh (−0.03)
		340 (−0.01)
		297 (+0.18)
	245 (2900)	262 (−0.48)
		238 (+0.24)
		220 (−1.50)
5.5	715 (72)	780[b] (+0.20)
		675 (−0.25)
		570 sh (−0.03)
		335 (−0.04)
		295 (+0.10)
	250 (3100)	262 (−0.39)
		240 (+0.38)
		220 (−3.90)
7.5	690 (106)	760 (+0.28)
		645 (−0.15)
		305 (−0.58)
	252 (4100)	245 (+0.99)
		220 (−3.90)
8.5	690 (108)	750 (+0.68)
		645 (−0.36)
		300 (−1.06)
	253 (4200)	245 (+1.15)
		222 (−2.30)
12.1	680 (90)	750 (+0.76)
		645 (−0.48)
		330 sh (−0.12)
		284 (−1.16)
	250 sh (4000)	245 (+0.65)
		230 (−0.80)

[a] sh = shoulder. [b] Maximum too close or beyond long-wavelength limit of instrument to be fully resolved. $\Delta\epsilon$ in parentheses is at 780 nm.

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(15) Abbreviations: L-N^{τ}-methylhistidinate anion, L-Me$^{\tau}$his; L-N^{α},N^{α}-dimethylhistidinate anion, L-Me$^{\alpha}_2$his; L-histidinate anion, L-his; glycinate anion, gly; L-valinate anion, L-val; L-*N*,*N*-dimethylvalinate anion, L-Me_2val; histamine, him; L-N^{τ}-methylhistidine methyl ester, L-Me$^{\tau}$hisOCH$_3$; L-N^{α},N^{α}-dimethylhistidine methyl ester, L-Me$^{\alpha}_2$hisOCH$_3$; L-histidine methyl ester, L-hisOCH$_3$; imidazole, im. Binary and ternary complexes are abbreviated as Cu(L-his)$_2$, Cu(L-his)(gly), Cu(L-his)(him)$^+$, Cu(him)$_2^{2+}$, Cu(L-hisH)(L-his)$^+$, etc. according to the major species existing at the given pH.

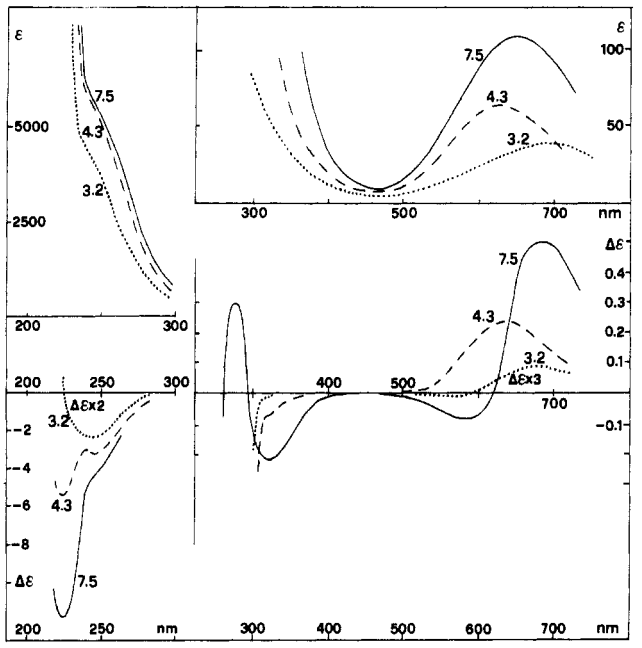


Figure 1. Electronic and CD spectra of 10^{-2} M aqueous solutions of copper(II)–L-N^{τ}-methylhistidine (1:2): (···) at pH 3.2; (- - -) at pH 4.3; (—) at pH 7.5.

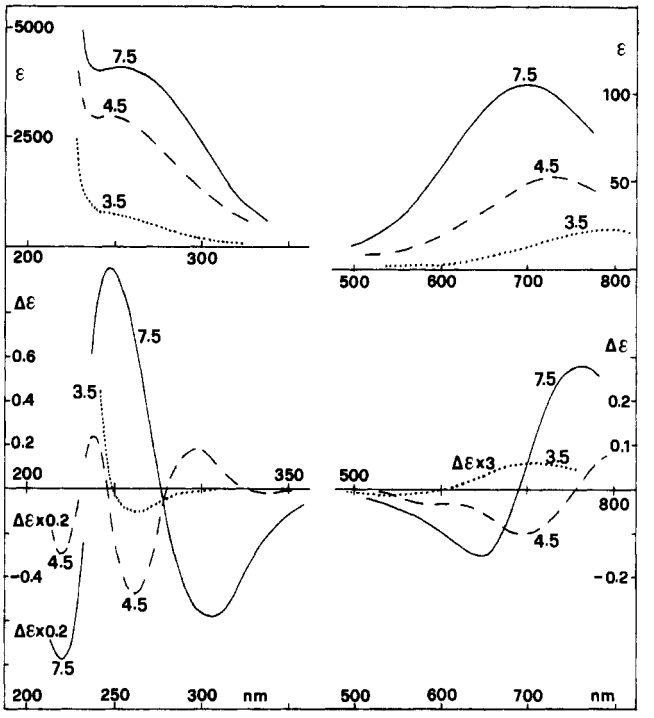


Figure 2. Electronic and CD spectra of 10^{-2} M aqueous solutions of copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2): (···) at pH 3.5; (- - -) at pH 4.5; (—) at pH 7.5.

Results

The electronic and CD spectral data for the copper(II)–L-N^{τ}-methylhistidine and copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) systems in aqueous solutions at various pH values are reported in Tables I and II, respectively, and representative examples are given in Figures 1 and 2. The variations of composition of these systems with pH are not known; therefore, the pH values were chosen with the assumption that the highest amounts of the individual species $Cu(HL)^{2+}$, CuL^{+}, $Cu(HL)L^{+}$, and CuL_2 (HL = L-N^{τ}-methylhistidine or L-N^{α},N^{α}-dimethylhistidine) exist in the same optimum pH range as their corresponding species in the copper(II)–L-histidine (1:2) aqueous system.[8e] For comparison purposes the systems Cu(L-Me$^{\tau}$his)(gly), Cu(L-Me$^{\tau}$his)(L-val), $Cu(L\text{-}Me^{\tau}his)(him)^{+}$, $Cu(L\text{-}Me^{\tau}his)(L\text{-}hisOCH_3)^{+}$, $Cu(L\text{-}Me^{\tau}his)(L\text{-}Me^{\tau}hisOCH_3)^{+}$, $Cu(L\text{-}Me^{\tau}his)(L\text{-}Me^{\alpha}{}_2hisOCH_3)^{+}$, $Cu(L\text{-}his)(him)^{+}$, $Cu(L\text{-}his)(L\text{-}hisOCH_3)^{+}$, $Cu(L\text{-}his)(L\text{-}Me^{\tau}hisOCH_3)^{+}$, $Cu(L\text{-}his)(L\text{-}Me^{\alpha}{}_2hisOCH_3)^{+}$, Cu(L-Me$^{\alpha}{}_2$his)(gly), Cu(L-Me$^{\alpha}{}_2$his)(L-val), $Cu(L\text{-}Me^{\alpha}{}_2his)(him)^{+}$, $Cu(L\text{-}Me^{\alpha}{}_2his)(L\text{-}hisOCH_3)^{+}$, $Cu(L\text{-}Me^{\alpha}{}_2his)(L\text{-}Me^{\tau}hisOCH_3)^{+}$, $Cu(L\text{-}Me^{\alpha}{}_2his)(L\text{-}Me^{\alpha}hisOCH_3)^{+}$, $Cu(L\text{-}Me_2val)_2$, $Cu(L\text{-}hisOCH_3)_2^{2+}$, $Cu(L\text{-}Me^{\tau}hisOCH_3)_2^{2+}$, and $Cu(L\text{-}Me^{\alpha}{}_2hisOCH_3)_2^{2+}$ in neutral aqueous solutions were also investigated (Figures 3–7, Table III; Figures 5–7 are included in the supplementary material).[15]

The electronic spectra of copper(II)–L-N^{τ}-methylhistidine (1:2) or copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) at various pH values display a weak d–d band between 600 and 800 nm, an intense UV band with a maximum below 220 nm, and a band or shoulder near 250 nm. Above pH ~5 an additional weak and poorly defined shoulder between 300 and 350 nm can be detected. Only the visible band undergoes appreciable changes in position and intensity with pH, while much more significant changes occur in the CD spectra with pH throughout the spectral range studied. For the copper(II)–L-N^{τ}-methylhistidine (1:2) system below pH ~3 the position of the visible absorption maximum is about ~700 nm and displays extremely weak Cotton effects (Figure 1). In the UV region a negative CD band occurs at 250 nm, while the additional positive CD activity below 220 nm is at least partly due to unbound L-N^{τ}-methylhistidine. When the pH is raised, the absorption and the positive CD bands in the visible region shift to higher energy and enhance their intensity, while a negative shoulder on the 250-nm CD band appears near 225 nm and rapidly increases in intensity. At pH 4.3 this negative 225-nm CD band dominates the UV region, and a weak but clearly discernible shoulder near 320 nm can also be detected. Above pH ~5 the absorption spectra remain approximately constant, while in the CD spectra the positive visible peak shifts toward longer wavelength and a negative band appears below 600 nm. A two-signed CD curve occurs also in the 300-nm region, with negative peak near 320 and positive peak near 280 nm. The behavior of the copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) system is similar to that of copper(II)–L-N^{τ}-methylhistidine (1:2) below pH ~4, though the CD spectra of the two systems become significantly different at higher pH (Figure 2). Between pH ~4 and ~6 CD bands of negative sign dominate the visible region, and five CD bands with apparent maxima near 330, 295, 260, 240, and 220 nm are clearly resolved in the UV region. Since each of these bands is flanked by CD bands of opposite sign, it is likely that they partially cancel each other. In particular, the asymmetric shape of the weak negative band near 330 nm indicates that the actual CD extremum lies at higher energy (Figure 2). When the pH is raised, CD bands of positive sign become increasingly important in the visible region, while disappearance of the CD bands near 295 and 260 nm simplifies the UV spectrum, leaving only CD bands near 300, 240, and 220 nm at neutral pH. These CD features remain substantially unchanged in basic solutions.

The CD spectra of neutral Cu(L-Me$^{\tau}$his)(gly), Cu(L-Me$^{\tau}$his)(L-val), Cu(L-Me$^{\alpha}{}_2$his)(gly), and Cu(L-Me$^{\alpha}{}_2$his)(L-val) solutions (Figures 3 and 4) are very similar to those of the copper(II)–L-N^{τ}-methylhistidine (1:2) system at pH 4.5. The amount of ternary complex in these neutral mixed amino acid systems must be comparable with that of the related copper(II)–L-histidine–amino acid (1:1:1) systems (approximately 75%),[6a] since the CD features of Cu(L-Me$^{\tau}$his)(gly) or Cu(L-Me$^{\alpha}{}_2$his)(gly) differ markedly from those of the neutral copper(II)–L-N^{τ}-methylhistidine (1:2) or copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) systems, particularly in the

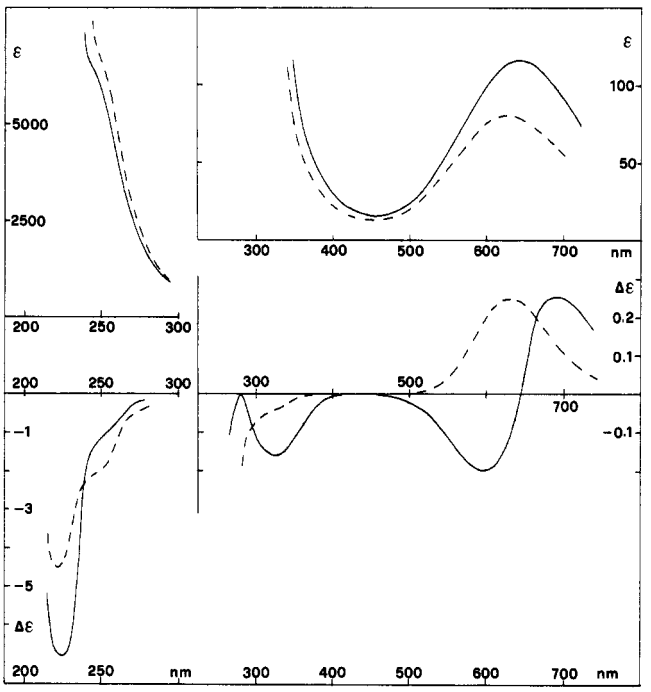


Figure 3. Electronic and CD spectra of 10^{-2} M aqueous solutions of (---) copper(II)–L-N^{τ}-methylhistidine–glycine (1:1:1) at pH 7.1 and (—) copper(II)–L-N^{τ}-methylhistidine–histamine (1:1:1) at pH 7.4.

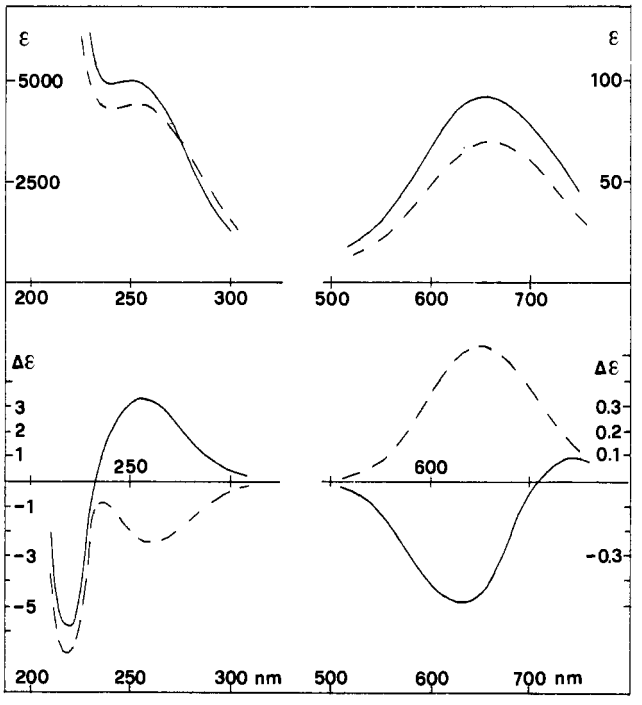


Figure 4. Electronic and CD spectra of 10^{-2} M aqueous solutions of (---) copper(II)–L-N^{α},N^{α}-dimethylhistidine–glycine (1:1:1) at pH 7.2 and (—) copper(II)–L-N^{α},N^{α}-dimethylhistidine–histamine (1:1:1) at pH 7.2.

visible and in the 250–300-nm regions. In the case of Cu(L-Me$^{\tau}$his)(L-val) the weak negative CD activity near 520 nm is most likely contributed by the small amount of Cu(L-val)$_2$ present in solution. The slight difference in the position of the visible absorption maximum observed for Cu(L-Me$^{\tau}$his)(gly) and Cu(L-Me$^{\tau}$his)(L-val) and for Cu(L-Me$^{\alpha}_2$his)(gly) and Cu(L-Me$^{\alpha}_2$his)(L-val) reflects the difference between Cu(gly)$_2$ (625 nm) and Cu(L-val)$_2$ (610 nm).[16]

(16) Hawkins, C. J.; Wong, C. L. *Aust. J. Chem.* **1970**, *23*, 2237–2246.

The CD spectrum of Cu(L-Me$^{\tau}$his)(him)$^+$ is largely dissimilar to that of the neutral copper(II)–L-N^{τ}-methylhistidine (1:2) system (Figure 3). The two-signed curve in the visible region displays positive (685 nm) and negative (595 nm) peaks of similar amplitudes while the positive CD peak near 280 nm has extremely reduced intensity. This indicates that the ternary complex is largely favored with respect to the individual bis complexes in the mixed system, as in the case of the related copper(II)–L-histidine–histamine (1:1:1) system.[6c] The CD spectra of Cu(L-Me$^{\tau}$his)(L-hisOCH$_3$)$^+$, Cu(L-Me$^{\tau}$his)(L-Me$^{\tau}$hisOCH$_3$)$^+$, and Cu(L-Me$^{\tau}$his)(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$ are similar in shape to that of Cu(L-Me$^{\tau}$his)(him)$^+$ but show a larger ratio of amplitude between the positive and negative peaks in the visible region (Figure 5,[17] Table III). The weak positive CD activity near 280 nm in the spectra of Cu(L-Me$^{\tau}$his)(him)$^+$, Cu(L-Me$^{\tau}$his)(L-hisOCH$_3$)$^+$, and Cu(L-Me$^{\tau}$his)(L-Me$^{\tau}$hisOCH$_3$)$^+$ may be partly contributed by small amounts of Cu(L-Me$^{\tau}$his)$_2$, while for Cu(L-Me$^{\tau}$his)(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$ this 280-nm CD peak is completely absent. In the CD spectra of the mixed complexes of L-histidine Cu(L-his)(him)$^+$, Cu(L-his)(L-hisOCH$_3$)$^+$, Cu(L-his)(L-Me$^{\tau}$hisOCH$_3$)$^+$, and Cu(L-his)(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$ the negative band near 590 nm has a lower amplitude than in the spectra of the corresponding complexes derived from L-N^{τ}-methylhistidine (Figure 6,[17] Table III). It can also be noted that for Cu(L-his)(L-hisOCH$_3$)$^+$ and Cu(L-his)(L-Me$^{\tau}$hisOCH$_3$)$^+$ the positive CD activity at 280 nm is significant, while the presence of a positive component at 280 nm can only be inferred from the shape of the CD curve near 300 nm in the case of Cu(L-his)(him)$^+$. It is difficult, therefore, to relate the CD activity at 280 nm to the presence of Cu(L-his)$_2$ in these cases, since the rather large stability constant found for Cu(L-his)(L-hisOCH$_3$)$^+$ indicates that the amount of ternary complex formed in neutral solution[5,18] is higher than that of Cu(L-his)(him)$^+$.[6c] For Cu(L-his)(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$, like Cu(L-Me$^{\tau}$his)(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$, the positive CD peak at 280 nm is absent.

The CD spectra of the mixed complexes Cu(L-Me$^{\alpha}_2$his)(him)$^+$ (Figure 4) and Cu(L-Me$^{\alpha}_2$his)(L-hisOCH$_3$)$^+$ and Cu(L-Me$^{\alpha}_2$his)(L-Me$^{\tau}$hisOCH$_3$)$^+$ (Figure 7[17]) differ remarkably from that of the neutral copper(II)–L-N^{α},N^{α}-dimethylhistidine system, particularly in the UV region, where the negative CD band near 300 nm is replaced by bands of positive sign between 250 and 280 nm. It can be noted that Cotton effects of negative sign largely dominate the visible CD spectrum of Cu(L-Me$^{\alpha}_2$his)(him)$^+$. This bears a qualitative resemblance with the CD spectra of copper(II) complexes of nonpolar L-amino acids.[11,16] The CD spectrum of Cu(L-Me$^{\alpha}_2$his)(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$ seems to result from overlap of the spectra of Cu(L-Me$^{\alpha}_2$his)$_2$ and Cu(L-Me$^{\alpha}_2$hisOCH$_3$)$_2^{2+}$ (Figure 7[17]). It is likely, therefore, that the amount of ternary complex in this mixed system is quite low.

The possible contribution by minor amounts of the binary species Cu(L-hisOCH$_3$)$_2^{2+}$, Cu(L-Me$^{\tau}$hisOCH$_3$)$_2^{2+}$, and Cu(L-Me$^{\alpha}_2$hisOCH$_3$)$_2^{2+}$ to the CD spectra of the ternary systems containing these methyl ester derivatives can be inferred from the spectra of copper(II)–L-histidine methyl ester (1:2), copper(II)–L-N^{τ}-methylhistidine methyl ester (1:2), and copper(II)–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:2) in neutral aqueous solution (Figure 8, Table III). The effect of N,N-dimethylation on the CD spectra of 2:1 complexes of nonpolar L-amino acids and copper(II) is exemplified by the behavior of Cu(L-Me$_2$val)$_2$ (Table III). As for 2:1 complexes of nonpolar L-amino acids and copper(II),[16] a broad negative CD band dominates the visible region while, in comparison with

(17) Supplementary material.
(18) (a) Hay, R. W.; Morris, P. J. *J. Chem. Soc. D* **1969**, 18–19. (b) Sigel, H.; Mackenzie, R. E.; McCormick, D. B. *Biochim. Biophys. Acta* **1970**, *200*, 411–413.

Table III. Electronic and Circular Dichroism Spectra of Mixed Complexes of L-N^{τ}-Methylhistidine, L-N^{α},N^{α}-Dimethylhistidine, and L-Histidine in Aqueous Solution (10^{-2} M)

syst	pH	UV-vis, λ_{max}, nm[a] (ϵ)	CD, λ_{max}, nm[a] ($\epsilon_l - \epsilon_r$)
Cu(L-Me$^{\tau}$his)(gly)	7.1	625 (80)	632 (+0.25)
			320 sh (−0.04)
		245 sh (7300)	250 sh (−1.95)
			222 (−4.50)
Cu(L-Me$^{\tau}$his)(L-val)	7.1	615 (74)	630 (+0.23)
			515 (−0.02)
			320 sh (−0.04)
		245 sh (7300)	245 (−3.30)
			223 (−5.65)
Cu(L-Me$^{\tau}$his)(him)$^+$	7.4	640 (116)	685 (+0.25)
			595 (−0.20)
			322 (−0.16)
			279 (0)
		245 sh (6400)	250 sh (−1.05)
			225 (−6.80)
Cu(L-Me$^{\tau}$his)-(L-hisOCH$_3$)$^+$	7.2	655 (120)	683 (+0.43)
			595 (−0.09)
			323 (−0.16)
			285 (+0.04)
		245 sh (6100)	250 sh (−2.85)
			225 (−12.30)
Cu(L-Me$^{\tau}$his)-(L-Me$^{\tau}$hisOCH$_3$)$^+$	7.2	655 (138)	685 (+0.43)
			595 (−0.11)
			323 (−0.16)
			283 (+0.02)
		245 sh (6500)	250 sh (−2.75)
			225 (−11.30)
Cu(L-Me$^{\tau}$his)-(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$	7.3	670 (122)	695 (+0.95)
			600 (−0.04)
			330 (−0.18)
		252 (4400)	250 (−4.40)
			225 (−12.40)
Cu(L-his)(him)$^+$	7.4	635 (82)	685 (+0.25)
			593 (−0.16)
			320 (−0.17)
		245 sh (4800)	245 sh (−2.00)
			223 (−8.10)
Cu(L-his)(L-hisOCH$_3$)$^+$	7.2	650 (121)	683 (+0.42)
			592 (−0.05)
			323 (−0.16)
			280 (+0.11)
		245 sh (6500)	245 sh (−2.60)
			223 (−13.60)
Cu(L-his)-(L-Me$^{\tau}$hisOCH$_3$)$^+$	7.1	650 (102)	680 (+0.43)
			590 (−0.06)
			325 (−0.15)
			281 (+0.07)
		245 sh (6500)	245 sh (−4.40)
			223 (−16.20)
Cu(L-his)-(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$	7.4	670 (114)	695 (+0.88)
			330 (−0.17)
		250 (4400)	250 (−4.40)
			225 (−12.50)
Cu(L-Me$^{\alpha}_2$his)(gly)	7.2	662 (70)	650 (+0.54)
			310 sh[b] (−0.30)
		252 (4400)	260 (−2.40)
			218 (−7.00)
Cu(L-Me$^{\alpha}_2$his)(L-val)	7.1	655 (80)	650 (+0.46)
			310 sh[b] (−0.40)
		252 (4600)	264 (−2.80)
			219 (−6.80)
Cu(L-Me$^{\alpha}_2$his)(him)$^+$	7.2	655 (92)	740 (+0.09)
			630 (−0.48)
		250 (5000)	255 (+3.30)
			220 (−5.80)
Cu(L-Me$^{\alpha}_2$his)-(L-hisOCH$_3$)$^+$	7.2	675 (98)	720 (+0.39)
			635 (−0.40)
			275 (+0.72)
		250 (4400)	245 sh (−0.30)
			222 (−10.80)
Cu(L-Me$^{\alpha}_2$his)-(L-Me$^{\tau}$hisOCH$_3$)$^+$	7.2	675 (96)	720 (+0.42)
			630 (−0.39)
			280 (+0.55)
		252 (4000)	255 (0)
			245 (+0.15)
			222 (−8.70)
Cu(L-Me$^{\alpha}_2$his)-(L-Me$^{\alpha}_2$hisOCH$_3$)$^+$	7.3	695 (100)	780[c] (+0.28)
			650 (−0.24)
			305 sh (−0.15)
			270 (−0.24)
		250 (3800)	242 (+0.38)
			220 (−4.50)
Cu(L-Me$_2$val)$_2$	7.2	625 (42)	615 (−0.29)
		245 (3000)	278 (+0.95)
			220[d] (+1.25)
Cu(L-hisOCH$_3$)$_2^{2+}$	7.1	633 (95)	657 (+0.42)
			560 sh (+0.07)
			335 (−0.08)
		245 sh (6100)	245 sh (−3.40)
			225 (−12.80)
Cu(L-Me$^{\tau}$hisOCH$_3$)$_2^{2+}$	7.0	635 (100)	664 (+0.46)
			540 (+0.03)
			335 (−0.10)
		245 sh (6200)	245 sh (−3.40)
			225 (−13.40)
Cu(L-Me$^{\alpha}_2$hisOCH$_3$)$_2^{2+}$	7.2	685 (70)	735 (+0.21)
			635 sh (+0.14)
			335 sh (−0.08)
		252 (3200)	261 (−1.66)
			222 (−4.90)

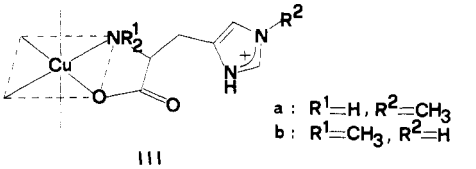
[a] sh = shoulder. [b] Poorly resolved. [c] Maximum too close or beyond long-wavelength limit of instrument to be fully resolved. $\Delta\epsilon$ in parentheses is at 780 nm. [d] Maximum below 220 nm. $\Delta\epsilon$ in parentheses is at 220 nm.

the above complexes, the CD band in the UV region is red shifted and displays Cotton effects of opposite sign.

Discussion

The electronic and CD spectra of the copper(II)–L-N^{τ}-methylhistidine (1:2) system recorded at various pH values show large similarities to those of the corresponding copper(II)–L-histidine (1:2) solutions.[1] This indicates similar composition and structure of the species involved in the two systems and shows that the introduction of a N^{τ}-methyl group has a minor effect on the structural preferences of coordinated L-histidine molecules. The only major difference is observed in the spectra recorded in basic solution, where the copper(II)–L-histidine (1:2) system contains a large fraction of ligand molecules with deprotonated imidazole nuclei. The spectral similarities between the copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) and copper(II)–L-histidine (1:2) systems, however, are confined within the acid pH range, while above pH ~4 the CD spectra of these two systems are significantly different.

Below pH ~3.5 the only major species in the copper(II)–L-N^{τ}-methylhistidine and copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) systems is $Cu(HL)^{2+}$, which contains the ligand bound as a substituted glycine with a protonated imidazole ring (III). This can be easily inferred from the position



III

(~250 nm) of the negative CD band in the UV region (Figures 1 and 2). Negative CD bands near this wavelength occur

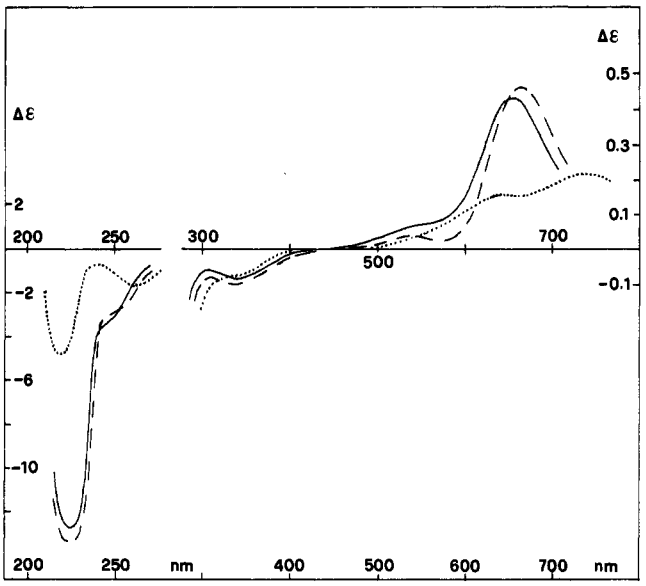
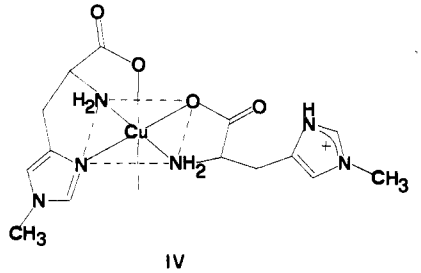


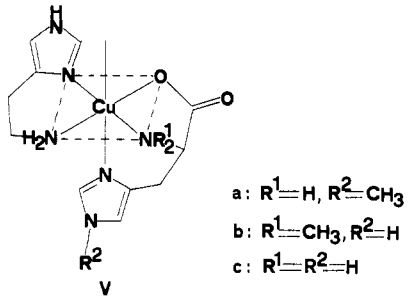
Figure 8. Circular dichroism spectra of 10^{-2} M aqueous solutions of (—) copper(II)–L-histidine methyl ester (1:2) at pH 7.1, (- - -) copper(II)–L-N^{τ}-methylhistidine methyl ester (1:2) at pH 7.0, and (···) copper(II)–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:2) at pH 7.2.

in the spectra of copper(II) complexes of L-amino acids with nonpolar side chains and result from overlap of charge-transfer transitions from amino and carboxylate groups to copper(II),[19] though the latter may occur at higher energy.[19c] Between pH ~3.5 and ~4.5 CuL^+ and $Cu(HL)L^+$ are the major species. However, by analogy with the copper(II)–L-histidine (1:2) system,[8e] we expect that the amount of CuL^+ is always exceeded by the amount of $Cu(HL)L^+$. In the CD spectra of copper(II)–L-N^{τ}-methylhistidine (1:2) in this pH range the appearance of bands near 220 and 320 nm, attributable to σ(im) → Cu(II) and π(im) → Cu(II) LMCT transitions, respectively,[20] indicates that the imidazole ring is involved in coordination to copper(II). Therefore, in Cu(L-Me$^{\tau}$his)$^+$ the ligand is probably tridentate, while in Cu(L-Me$^{\tau}$hisH)(L-Me$^{\tau}$his)$^+$, quite certainly the only major species near pH ~4.5, one ligand molecule binds copper(II) as a substituted glycine, with a protonated imidazole ring, and the other as a substituted histamine molecule (IV). The analogy between the CD



IV

spectrum of Cu(L-Me$^{\tau}$hisH)(L-Me$^{\tau}$his)$^+$ (Figure 1) and those of Cu(L-Me$^{\tau}$his)(gly) (Figure 3) and Cu(L-Me$^{\tau}$his)(L-val) suggests that the optical activity of Cu(L-Me$^{\tau}$hisH)(L-Me$^{\tau}$his)$^+$ is largely determined by the histamine-like bound L-N^{τ}-methylhistidinate ion. Apical binding by the carboxylate group of this amino acid residue is expected to stabilize the δ conformation of the chelate ring and is probably responsible for the positive visible CD band nearly coincident with the absorption maximum, while the optical activity contributed by the neutral ligand molecule bound glycine-like is almost negligible. Both the cis and the trans isomers of Cu(L-Me$^{\tau}$hisH)(L-Me$^{\tau}$his)$^+$ are likely to be present in solution, as is usually found for copper(II)–amino acid complexes.[8i,21] The CD spectra of copper(II)–L-N^{α},N^{α}-dimethylhistidine between pH ~4 and ~6 exhibit dominant Cotton effects of negative sign within the d–d bands (Figure 2). This pattern resembles that observed for Cu(L-Me$^{\alpha}_2$his)(him)$^+$ rather than that for Cu(L-Me$^{\alpha}_2$his)(gly) (Figure 4) and indicates that the structure of Cu(L-Me$^{\alpha}_2$hisH)(L-Me$^{\alpha}_2$his)$^+$ is different from those of Cu(L-Me$^{\tau}$hisH)(L-Me$^{\tau}$his)$^+$ and Cu(L-hisH)(L-his)$^+$.[1] Dominant Cotton effects of negative sign in the visible region are apparently associated with a glycine-like bound molecule of an L-histidine derivative provided the imidazole group of the side chain can bind copper(II) in an apical position and stabilize the λ conformation of the chelate ring. This effect is clearly visualized also in the CD spectra of Cu(L-Me$^{\tau}$his)(him)$^+$ (Figure 3) or Cu(L-his)(him)$^+$ (Figure 6), where the L-histidine derivative is largely bound as a substituted glycine[1,22] (V,cis and trans isomers). Therefore, we conclude that

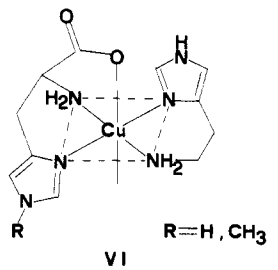


V

a: R^1=H, R^2=CH_3
b: R^1=CH_3, R^2=H
c: R^1=R^2=H

the L-N^{α},N^{α}-dimethylhistidinate ion in Cu(L-Me$^{\alpha}_2$hisH)(L-Me$^{\alpha}_2$his)$^+$ is bound glycine-like, while the contribution to the visible CD region by the neutral L-N^{α},N^{α}-dimethylhistidine molecule is negligible. This may be bound as a substituted glycine, with a protonated imidazole nucleus or act in monodentate manner, as recently proposed from stability constant measurements.[18] The complex pattern of CD bands observed for this complex in the UV region, associated with charge-transfer transitions from the donor groups to the metal center, seems to confirm the presence of several species.

Inspection of Figures 3 and 6[17] shows that substantial positive CD activity above 600 nm is present in the spectra of the ternary systems Cu(L-Me$^{\tau}$his)(him)$^+$ and Cu(L-his)(him)$^+$. Although small amounts of CuL_2 may give some contribution, this positive CD activity is mainly due to the ternary complexes containing both ligands bound histamine-like (VI), since it is known that the tendency of histidine to



VI

R=H, CH_3

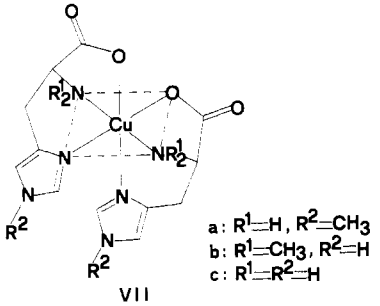
bind copper(II) in a glycine-like fashion is lower than that for

(19) (a) Tsangaris, J. M.; Chang, J. W.; Martin, R. B. *J. Am. Chem. Soc.* **1969**, *91*, 726–731. (b) Ibarra, C.; Soto, R.; Adán, L.; Decinti, A.; Bunel, S. *Inorg. Chim. Acta* **1972**, *6*, 601–606. (c) Phan, C. V.; Tosi, L.; Garnier, A. *J. Inorg. Nucl. Chem.* **1975**, *37*, 2385–2388. (d) Bunel, S.; Gil, L.; Bobadilla, H. *Ibid.* **1977**, *39*, 365–366. (e) Garnier-Suillerot, A.; Albertini, J.-P.; Collet, A.; Faury, L.; Pastor, J.-M.; Tosi, L. *J. Chem. Soc., Dalton Trans.* **1981**, 2544–2549.

(20) (a) Fawcett, T. G.; Bernaducci, E. E.; Krogh-Jespersen, K.; Schugar, H. J. *J. Am. Chem. Soc.* **1980**, *102*, 2598–2604. (b) Bernaducci, E.; Schwindinger, W. F.; Hughey IV, J. L.; Krogh-Jespersen, K.; Schugar, H. J. *Ibid.* **1981**, *103*, 1686–1691. (c) Amundsen, A. R.; Whelan, J.; Bosnich, B. *Ibid.* **1977**, *99*, 6730–6739. (d) Greenway, F. T.; Brown, L. M.; Dabrowiak, J. C.; Thompson, M. R.; Day, V. M. *Ibid.* **1980**, *102*, 7782–7784.

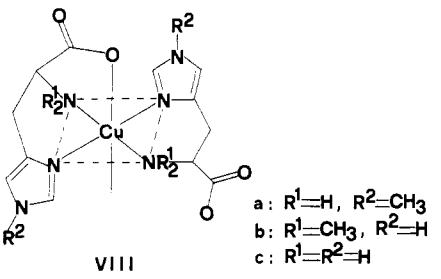
a histamine-like fashion.[2,22] The amplitude of the negative CD band near 600 nm in the mixed complexes with histamine can be taken as a qualitative measure of the tendency by derivatives of L-histidine to assume a glycine-like coordination mode and establishes the following order: L-N^{α},N^{α}-dimethylhistidine > L-N^{τ}-methylhistidine > L-histidine. This trend is exactly reproduced in the ternary systems containing L-histidine methyl ester, L-N^{τ}-methylhistidine methyl ester, or L-N^{α},N^{α}-dimethylhistidine methyl ester (Figures 5–7,[17] Table III). Also the spectra of these mixed complexes with methyl ester derivatives, however, display prominent CD bands of positive sign in the visible region, indicative of the presence of species with bis(histamine)-like structures like VI. In the case of Cu(L-his)(L-Me^{α}_2hisOCH$_3$)$^+$ and Cu(L-Me^{τ}his)(L-Me^{α}_2hisOCH$_3$)$^+$ the tendency by the amino acid anions to bind copper(II) in a glycine-like fashion is almost negligible, probably because the structure of mixed chelation type involves some steric interaction between one of the methyl groups of L-N^{α},N^{α}-dimethylhistidine methyl ester and the 2-H of the imidazole group of the amino acid bound in an apical position.

Major differences among the CD spectra of copper(II)–L-histidine (1:2), copper(II)–L-N^{τ}-methylhistidine (1:2), and copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2) solutions can be observed also in the neutral pH range, where the physiologically important CuL_2 species is largely dominant.[8e] Comparing the amplitude of the negative CD band near 600 nm in the three systems (Tables I and II and ref 1), we find that the fraction of the complexes containing the ligand bound in a glycine-like mode decreases in the order L-N^{α},N^{α}-dimethylhistidine > L-N^{τ}-methylhistidine > L-histidine. This order is in perfect agreement with that found for the mixed complexes with a derivative of histamine as the other ligand. The glycine-like-bound molecules of the L-histidine derivative is quite certainly part of a CuL_2 complex with a mixed chelation mode (VII), since the structure with both ligand mol-



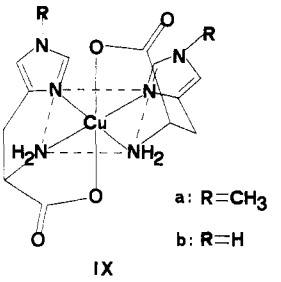
VII

ecules bound glycine-like has been recently excluded by ESR[8i] and Raman[8g] spectral investigations of copper(II)–L-histidine (1:2). The possibility of cis–trans isomerism in VII should also be excluded, because the cis isomer does not allow both ligand molecules to bind as tridentate ligands and, in the case of VIIb, involves severe steric hindrance between the bulky dimethylamino groups. From molecular models it appears that this steric hindrance between cis-dimethylamino groups is larger than those between the methyl groups of one ligand and the imidazole 2-H of the other ligand in the trans isomer. The visible CD spectrum of Cu(L-Me^{α}_2his)$_2$ displays positive and negative bands of comparable intensity. Thus, VIIb may be the only major structure for Cu(L-Me^{α}_2his)$_2$, while for Cu(L-Me^{τ}his)$_2$ and Cu(L-his)$_2$ Cotton effects of positive sign are largely dominant in the visible CD spectrum and suggest the presence in solution of other structures with histamine-like coordination modes besides VIIa and VIIc. We ascribe particular importance to the positive CD peak near 280 nm that seems peculiar to the neutral copper(II)–L-N^{τ}-methylhistidine (Figure 1) and copper(II)–L-histidine[1] (1:2) systems but that can be observed with reduced intensity also in the spectra of several ternary systems containing L-N^{τ}-methylhistidine or L-histidine and a histamine derivative (Table III). It is noteworthy that the 280-nm CD peak is absent in the spectra of any ternary system involving L-N^{α},N^{α}-dimethylhistidine methyl ester (Figures 5–7[17]) and in those of Cu(L-hisOCH$_3$)$_2^{2+}$, Cu(L-Me^{τ}hisOCH$_3$)$_2^{2+}$ and Cu(L-Me^{α}_2hisOCH$_3$)$_2^{2+}$ (Figure 8). This apparently rules out the possibility that the 280-nm CD peak is associated with a CuL_2 complex containing the ligands bound histamine-like with trans amino and imidazole groups (VIII), which appears to be the



VIII

only structure devoid of severe steric interactions available for Cu(L-Me^{α}_2hisOCH$_3$)$_2^{2+}$. Therefore, the 280-nm CD peak is associated with either a structure of mixed chelation type (VII) or a structure containing two L-histidine residues bound histamine-like with cis amino and imidazole groups (IX). A



IX

similar structure is not conceivable for Cu(L-Me^{α}_2his)$_2$ and is not usually considered even for Cu(L-his)$_2$ since it is believed that repulsive interactions can arise from cis imidazole rings. Molecular models show, however, that, if the imidazole rings are not coplanar with the copper square plane, as is usually found in the crystal structures of copper(II)–histidine–amino acid complexes, particularly when additional apical binding by the carboxylate group occurs,[8c,23] they can be easily accommodated in cis positions. We note that, in the spectra of the complexes where a single imidazole ring of L-histidine or L-N^{τ}-methylhistidine bound histamine-like occupies an equatorial coordination position, e.g., Cu(L-Me^{τ}his)(gly), Cu(L-Me^{τ}his)(L-val), and Cu(L-Me^{τ}hisH)(L-Me^{τ}his)$^+$, the dichroic absorption attributable to the π(im) → Cu(II) LMCT transition occurs near 320 nm. This negative 320-nm CD band is present also in the spectra of every binary and ternary system derived from L-histidine or L-N^{τ}-methylhistidine that exhibits the positive 280-nm CD band. Therefore, if the latter band is associated with a structure of mixed chelation type (like V or VII), it must characterize the apical imidazole binding of the glycine-like L-histidine or L-N^{τ}-methylhistidine residue, since both σ(NH$_2$) → Cu(II)[19,20c,24] and σ(COO) → Cu(II)[19,22]

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LMCT transitions occur at higher energy. Although a σ(imapical) → Cu(II) LMCT transition should be red shifted relative to that of equatorial imidazole near 220 nm, its intensity in both absorption and CD is expected to be very low, as shown by the recent characterization of extremely weak LMCT transitions for axial thioether–Cu(II) binding in both absorption[25] and CD,[26] in contrast to the prominent LMCT absorptions exhibited by equatorial thioether–Cu(II) units.[20c,27] This conclusion is supported by the observation of a 280-nm CD band in the spectra of ternary systems containing histamine or methyl ester derivatives with intensity much lower than in either Cu(L-his)$_2$ or Cu(L-Me$^\tau$his)$_2$, despite the fact the the latter systems contain a smaller fraction of the amino acid bound in a glycine-like mode, as judged from the amplitude of the negative CD band near 600 nm. In addition, while the intensity of the CD band at 280 nm in the ternary complexes of L-histidine, or L-N^τ-methylhistidine, and a derivative of histamine decreases in the order L-histidine methyl ester > L-N^τ-methylhistidine methyl ester > histamine, this order is simply inverted when the magnitude of CD activity near 600 nm is considered (Table III). Therefore, the intensity of the 280-nm CD band is not related to the amount of amino acid bound in a glycine-like mode and we are led to the conclusion that this CD activity near 280 nm must be associated with π(im) → Cu(II) LMCT transitions of cis imidazole rings in equatorial coordination positions. The different spectral location of the π(im) → Cu(II) LMCT transitions originating from imidazole rings that are in trans or cis equatorial positions probably arises from a different degree of distortion from coplanarity between the imidazole rings and the copper square plane.[20a] A considerable advantage of the cis structure IX for Cu(L-his)$_2$ and Cu(L-Me$^\tau$his)$_2$ is that it allows both L-histidine molecules coordinated histamine-like to bind as tridentate ligands, while only one can be tridentate and one bidentate in the trans structure VIII. In the mixed complexes of L-histidine and L-N^τ-methylhistidine with methyl ester derivatives or histamine the amount of the species with a bis(histamine)-like structure in a cis arrangement is clearly small, since a tridentate and a bidentate ligand molecule can be conveniently accommodated in a trans disposition. It should be noted that positive CD bands in the range 245–280 nm occur also in the spectra of binary and ternary systems containing L-N^α,N^α-dimethylhistidine bound in a glycine-like fashion (Figures 2, 4, and 7[17]). These moderately intense CD bands originate from σ(NMe$_2$) → Cu(II) LMCT transitions, since Cu(L-Me$_2$val)$_2$ (Table III) and a series of binary and ternary complexes of copper(II) and nonpolar L-N-methyl-amino acids[28] exhibit positive CD bands in the same spectral region. Interestingly, the sign of the CD bands associated with these σ(NMe$_2$) → Cu(II) transitions is reversed in the spectra of the systems where L-N^α,N^α-dimethylhistidine is bound in a histamine-like mode, i.e., Cu(L-Me$^\alpha_2$his)(gly) and Cu(L-Me$^\alpha_2$his)(L-val) (Figure 4). Although extensive overlap with CD bands of opposite sign often prevents the accurate location of the extrema in the near-UV spectra, CD bands that can be associated with charge-transfer transitions from imidazole to copper(II) in the systems containing L-N^α,N^α-dimethylhistidine occur near 300 nm, at slightly higher energy than in the corresponding systems of L-histidine or L-N^τ-methylhistidine.

In general, the magnitude of the CD band at 280 nm and, therefore, the ability to assume a cis histamine-like structure, is larger in the binary and ternary systems of L-histidine than in those of L-N^τ-methylhistidine, while, as stated above, the tendency to bind copper(II) glycine-like decreases in the order L-N^α,N^α-dimethylhistidine > L-N^τ-methylhistidine > L-histidine. The reason Cu(L-Me$^\tau$his)$_2$ has a higher preference than Cu(L-his)$_2$ for the mixed chelation structure VII and a lower preference for the cis bis(histamine)-like structure IX is that some steric hindrance between the N-methyl groups on cis imidazole rings in IXa may not be completely removed by twisting of the rings relative to the copper tetragonal plane. Although the amount of the trans bis(histamine)-like species VIII cannot be evaluated, the complementary preference exhibited by L-histidine and L-N^τ-methylhistidine in the neutral bis complexes according to VII or IX emphasizes the tendency by these ligand molecules to act as tridentate ligands in solution.

Acknowledgment. The authors thank the Italian CNR for support and Mrs. M. Bonfà for the recording of the NMR spectra.

Registry No. Cu(L-Me$^\tau$his)(gly), 83664-44-2; Cu(L-Me$^\tau$his)(L-val), 83664-45-3; Cu(L-Me$^\tau$his)(him)$^+$, 83664-46-4; Cu(L-Me$^\tau$his)(L-hisOCH$_3$)$^+$, 83664-47-5; Cu(L-Me$^\tau$his)(L-Me$^\tau$hisOCH$_3$)$^+$, 83664-48-6; Cu(L-Me$^\tau$his)(L-Me$_2^\alpha$hisOCH$_3$)$^+$, 83681-21-4; Cu(L-his)(him)$^+$, 83664-49-7; Cu(L-his)(L-hisOCH$_3$)$^+$, 83664-50-0; Cu(L-his)(L-Me$^\tau$hisOCH$_3$)$^+$, 83664-51-1; Cu(L-his)(L-Me$_2^\alpha$hisOCH$_3$)$^+$, 83664-52-2; Cu(L-Me$_2^\alpha$his)(gly), 83664-53-3; Cu(L-Me$_2^\alpha$his)(L-val), 83664-54-4; Cu(L-Me$_2^\alpha$his)(him)$^+$, 83664-55-5; Cu(L-Me$_2^\alpha$his)(L-hisOCH$_3$), 83664-56-6; Cu(L-Me$_2^\alpha$his)(L-Me$^\tau$hisOCH$_3$)$^+$, 83664-57-7; Cu(L-Me$_2^\alpha$his)(L-Me$_2^\alpha$hisOCH$_3$)$^+$, 83664-58-8; Cu(L-Me$_2$val)$_2$, 55722-79-7; Cu(L-hisOCH$_3$)$_2^{2+}$, 33271-66-8; Cu(L-Me$^\tau$hisOCH$_3$)$_2^{2+}$, 83664-59-9; Cu(L-Me$_2^\alpha$hisOCH$_3$)$_2^{2+}$, 83664-60-2; L-N^τ-methylhistidine methyl ester dihydrochloride, 4216-91-5; L-N^α,N^α-dimethylhistidine methyl ester dihydrochloride, 83664-43-1; L-N,N-dimethylvaline, 2812-32-0; L-N$^\tau$-methylhistidine, 332-80-9; L-N^α,N^α-dimethylhistidine, 24940-57-6.

Supplementary Material Available: Circular dichroism spectra of the ternary systems of methyl ester derivatives and L-N^τ-methylhistidine (Figure 5), L-histidine (Figure 6), and L-N^α,N^α-dimethylhistidine (Figure 7) (3 pages). Ordering information is given on any current masthead page.

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