confirms the formation of the 18C6 (or DB-18C6) complex with a single "exclusive" (or/and "inclusive") isomer with direct uranyl–macrocycle bonds.

In aqueous solutions the solvation of UO_2^{2+} is much more important and cannot be neglected. The existence of weak 1:1 complexes and 1:2 complexes with 18C6 and 15C5 seems to indicate that coordination occurs by hydrogen bond formation between hydrogens of water molecules of the hydrate shell of the uranyl ion and oxygen atoms of the crown ether. The 1:2 complexes formed could be "sandwich" type[31] with hydrogen bond intervention. These propositions agree with certain previous publications concerning the solid-state structure, which also propose hydrogen bond formation between water molecules coordinated in the equatorial plane of the uranyl ion and oxygen of the crown ether ligands.[8-10]

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Copper(II) Complexes of 2-(Trifluoromethyl)-L-histidine in Aqueous Solution[1]

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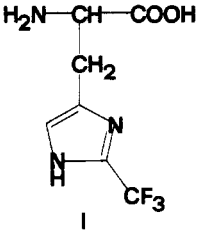
The coordination structures of various binary and ternary complexes of copper(II) and 2-(trifluoromethyl)-L-histidine have been investigated by circular dichroism and compared to the structures of the corresponding complexes of L-histidine. It has been found that 2-(trifluoromethyl)-L-histidine exhibits an exclusive tendency to assume a glycine-like mode of coordination in any binary or ternary system, even those where L-histidine largely prefers to bind histamine-like. This feature has been referred to the strong steric repulsion exerted by the 2-trifluoromethyl substituent of the imidazole ring in the copper equatorial plane, when the amino acid is bound histamine-like, toward any donor group in cis position. In acid medium the 2-(trifluoromethyl)-L-histidine ligand binds as bidentate and contains a protonated imidazole ring, while at neutral pH it binds as tridentate. Apical chelation to copper(II) by the imidazole group is characterized by weak CD activity near 350 and 230 nm (about 1 order of magnitude less intense than that corresponding to equatorial imidazole binding) that is assigned to $Im(\pi_1) \rightarrow Cu(II)$ and $Im(\sigma) \rightarrow Cu(II)$ LMCT, respectively. The third LMCT transition originating from the imidazole ring occurs in the same range as the LMCT transitions from amino and carboxylate groups and cannot be localized with certainty in the CD spectra.

Introduction

We have recently investigated the coordination structures of the major species existing in various pH ranges of the systems copper(II)–L-histidine (1:2),[2] copper(II)–L-N^{τ}-methylhistidine (1:2),[3] and copper(II)–L-N^{α},N^{α}-dimethylhistidine (1:2)[3] using CD spectroscopy. These studies complement previous investigations on copper(II)–L-histidine and related systems performed with various spectroscopic and potentiometric techniques,[4-9] since CD can easily differentiate the two basic coordination modes of L-histidine residues when apical binding to the metal by the donor atom on the side chain can occur.[10] However, as is usually the case when a potentially tridentate ligand binds a metal ion,[11] the physiologically important,[12] neutral bis(L-histidinato)copper(II) complex exists in solution as an equilibrium mixture of isomeric species and it is difficult to relate the CD features to the individual species. In order to gain an understanding of how each of these species contributes to the CD spectrum, we are extensively investigating the chiroptical properties of ternary systems containing L-histidine as well as those of systems containing appropriate derivatives of this amino acid. By introducing bulky substituents into the L-histidine molecule, we anticipate that a marked preference for a single species at the equilibrium can be imposed, thereby simplifying the appearance and interpretation of the corresponding CD spectrum. In this paper we present an investigation of the CD spectra of the binary systems of copper(II) and 2-(trifluoromethyl)-L-histidine (I) in various pH ranges, together with several related ternary systems at neutral pH. To our knowledge copper(II) complexes of 2-(trifluoromethyl)-L-histidine are reported here for the first time.



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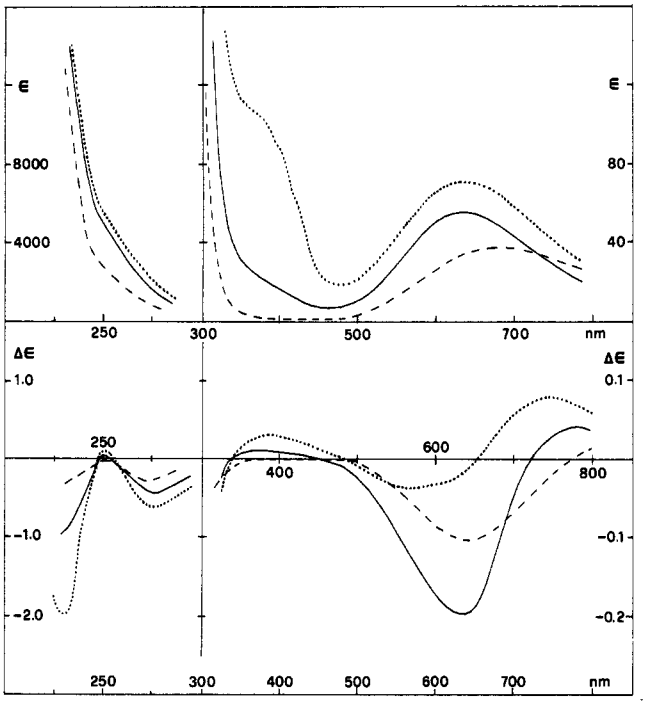

Figure 1. Electronic and CD spectra of 10^{-2} M aqueous solutions of copper(II)–2-(trifluoromethyl)-L-histidine (1:2): (---) at pH 4.5; (—) at pH 6.9; (···) at pH 9.0.

Experimental Section

The amino acids L-histidine, glycine, L-valine, and β-alanine and L-histidine methyl ester dihydrochloride, histamine dihydrochloride, L-histidinol dihydrochloride, 1,3-propanediamine, and copper(II) sulfate pentahydrate were reagent grade and were used as received. L-N^{α},N^{α}-Dimethylhistidine methyl ester dihydrochloride was prepared as described previously.[3] 2-(Trifluoromethyl)-L-histidine dihydrochloride was prepared from methyl (2*S*)-2,4,5-tribenzamido-(4*Z*)-pent-4-enoate[13] following a literature procedure:[14] UV (H_2O) λ_{max} 220 nm (ϵ = 7000); CD (H_2O) λ_{max} 208 nm ($\Delta\epsilon$ = +2.07).

The optical absorption and circular dichroism spectra were recorded at room temperature on 10^{-2} M aqueous solutions of copper(II)–2-(trifluoromethyl)-L-histidine (1:1 and 1:2) at various pH values and on 10^{-2} M neutral aqueous solutions of copper(II)–2-(trifluoromethyl)-L-histidine–glycine (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine–β-alanine (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine–L-valine (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine–histamine (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine-L-histidinol (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine–L-histidine methyl ester (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:1:1), copper(II)–2-(trifluoromethyl)-L-histidine–1,3-propanediamine (1:1:1), copper(II)–L-histidine–L-histidinol (1:1:1), copper(II)–L-valine–L-histidinol (1:1:1), copper(II)–L-histidinol (1:1 and 1:2), copper(II)–L-histidine methyl ester (1:1), and copper(II)–L-N^{α},N^{α}-dimethylhistidine methyl ester (1:1).[15] The pH values of the sample solutions were adjusted with concentrated sodium hydroxide. The ionic strength of the solutions was unadjusted. Spectral readings between 220 and 800 nm were taken immediately after preparation of the solutions using quartz cells of different path length between 0.01 and 1 cm in order to avoid any dilution of the solutions. Spectral data are given in terms of ϵ (molar extinction coefficient) and $\Delta\epsilon = \epsilon_l - \epsilon_r$ (molar differential extinction coefficient) in L mol^{-1} cm^{-1}. The electronic and circular dichroism spectra were recorded on a Perkin-Elmer Lambda-5 spectrophotometer and a Jobin-Yvonne Mark III dichrograph, respectively. Values of pH were measured with an Amel Model 328 pH meter.

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

pH	UV-vis λ_{max},[a] nm (ϵ)	CD λ_{max},[a] nm ($\Delta\epsilon$)
	Cu(II)–L-CF_3His (1:1)	
2.6	795 (10)	690 (−0.005)
	250 sh (250)	270 (−0.04)
		220[b] (+0.75)
3.9	742 (24)	800[c] (+0.005)
		690 (−0.03)
	250 sh (1000)	272 (−0.26)
		250 (+0.01)
	223 (8400)	220[d] (−0.20)
6.9	658 (32)	800[c] (+0.02)
		640 (−0.07)
		360[d] (+0.005)
	250 sh (2400)	272 (−0.28)
		250 (+0.02)
	224 (9100)	220[e] (−0.70)
	Cu(II)–L-CF_3His (1:2)	
3.0	754 (22)	690 (−0.01)
	255 sh (800)	271 (−0.16)
	222 (14 400)	
4.5	681 (35)	800[c] (+0.01)
		645 (−0.11)
	250 sh (2500)	270 (−0.40)
	223 (16 000)	
5.5	644 (45)	800[c] (+0.02)
		640 (−0.18)
	250 sh (4000)	275 (−0.50)
	224 (16 700)	230[e] (−0.50)
6.9	631 (58)	780 (+0.04)
		635 (−0.20)
	360 sh (30)	360[d] (+0.01)
	260 sh (4500)	275 (−0.50)
		250 (+0.05)
	224 (17 300)	230[e] (−1.0)
9.0	630 (75)	740 (+0.08)
		630 sh (−0.03)
		570 (−0.04)
	420 sh (70)	380 (+0.03)
	390 sh (100)	
	360 sh (115)	
	250 sh (4500)	275 (−0.65)
		250 (+0.10)
	224 (17 400)	230 (−2.00)
11.8	640 (80)	740 (+0.15)
		630 (−0.05)
	460 sh (60)	550 sh (−0.02)
	400 sh (150)	400 sh (+0.03)
	350 sh (350)	360 (+0.10)
		315 sh (−0.05)
	250 sh (5000)	292 (−0.55)
		250 (+1.05)
	226 (16 000)	220[e] (−3.50)

[a] Shoulder = sh. [b] Maximum below 220 nm; $\Delta\epsilon$ in parentheses at 220 nm. [c] Maximum beyond the long-wavelength limit of the instrument; $\Delta\epsilon$ in parentheses at 800 nm. [d] Broad. [e] Position of the extremum not well-defined due to intense absorption of the solution; $\Delta\epsilon$ in parentheses at the wavelength given.

Results

The electronic and CD spectral data for the copper(II)–2-(trifluoromethyl)-L-histidine (1:2) system in aqueous solutions at various pH values are summarized in Table I, and representative examples are given in Figure 1. The corresponding 1:1 system was also investigated in acid and neutral medium (Table I). In general, as the pH of the solution is raised, the electronic spectra in the visible region of both these systems show a progressive shift

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(15) Abbreviations: 2-(trifluoromethyl)-L-histidinate anion, L-CF_3His; L-histidinate anion, L-His; L-N^{τ}-methylhistidinate anion, L-Me^{τ}His; L-N^{α},N^{α}-dimethylhistidinate anion, L-Me^{α}_2His; glycinate anion, Gly; β-alaninate anion, β-Ala; L-valinate anion, L-Val; amino acidato anion, aa; histamine, him; L-histidinol, L-HisOH; L-histidine methyl ester, L-$HisOCH_3$; L-N^{α},N^{α}-dimethylhistidine methyl ester, L-$Me^{\alpha}_2HisOCH_3$; 1,3-propanediamine, 1,3-pn; imidazole, Im. Binary and ternary complexes are abbreviated as Cu(L-CF_3His)$^+$, Cu(L-CF_3HisH)(L-CF_3His)$^+$, Cu(L-CF_3His)$_2$, Cu(L-CF_3His)(him)$^+$, Cu(L-CF_3His)(Gly), Cu(him)$_2^{2+}$, etc., according to the major species existing at the given pH.

Table II. Electronic and Circular Dichroism Spectra of Mixed Complexes of 2-(Trifluoromethyl)-L-histidine and Related Systems in Aqueous Solution (10^{-2} M)

system	pH	UV-vis λ_{max},[a] nm (ϵ)	CD λ_{max},[a] nm ($\Delta\epsilon$)
Cu(L-CF_3His)(Gly)	7.5	625 (50)	760 (+0.02)
			630 (−0.11)
		340 sh (10)	350[b] (+0.01)
			275 (−0.28)
		250 sh (4000)	250 (+0.05)
		223 (11 300)	230[c] (−0.50)
Cu(L-CF_3His)(β-Ala)	7.0	650 (50)	780 (+0.02)
			620 (−0.06)
		360 sh (40)	360[b] (+0.01)
			275 (−0.27)
		250 sh (4000)	250 (+0.02)
		224 (10 000)	230[c] (−0.50)
Cu(L-CF_3His)(L-Val)	7.2	625 (60)	760 (+0.05)
			610 (−0.24)
		360 sh (25)	360[b] (+0.03)
		250 sh (5000)	260 (−0.80)
		225 (12 400)	230[c] (−0.50)
Cu(L-CF_3His)(him)$^+$	7.1	612 (58)	720 (+0.02)
			590 (−0.21)
		330 sh (80)	350[b] (+0.005)
			293 (−0.07)
		250 sh (4000)	246 (+1.45)
		217 (12 400)	225 (−2.20)
Cu(L-CF_3His)(L-HisOH)$^+$	7.3	610 (72)	730 (+0.10)
			595 (−0.36)
			305 (−0.30)
		250 sh (4500)	250 (+3.00)
		218 (14 700)	225[c] (−3.30)
Cu(L-CF_3His)(L-$HisOCH_3$)$^+$	7.0	612 (66)	685 (+0.07)
			585 (−0.10)
		250 sh (4500)	280 (−0.45)
		218 (14 700)	225 (−4.10)
Cu(L-CF_3His)-(L-$Me^{\alpha}{}_2HisOCH_3$)$^+$	6.9	642 (72)	800[d] (−0.10)
		400 sh (20)	630 (+0.76)
		258 (4800)	265 (−4.50)
		217 (14 000)	224 (−6.00)
Cu(L-CF_3His)(1,3-pn)$^+$	7.1	604 (62)	760 (+0.01)
			625 (−0.04)
			550 sh (−0.03)
		370 sh (25)	370[b] (+0.005)
		250 sh (4800)	272 (−0.48)
			240 (−0.48)
		225 (10 300)	223 (−0.85)
Cu(L-His)(L-HisOH)$^+$	7.0	633 (91)	680 (+0.33)
			595 (−0.10)
		320 sh (160)	320 (−0.33)
		245 sh (4800)	265 (+0.45)
		215 (14 500)	223 (−12.60)
Cu(L-Val)(L-HisOH)$^+$	7.1	602 (68)	690 (+0.04)
			590 (−0.11)
			320 sh (−0.20)
		240 sh (6000)	270 (−0.55)
		215 (10 200)	225[c] (−1.30)
Cu(L-HisOH)$^{2+}$	7.0	654 (41)	780 (+0.01)
			685 (−0.005)
			595 (+0.04)
		330 sh (120)	318 (−0.14)
		240 sh (3000)	252 (+0.90)
		212 (9000)	223 (−1.50)
Cu(L-$HisOH)_2{}^{2+}$	7.1	602 (85)	642 (+0.35)
			540 (+0.20)
		330 sh (180)	318 (−0.52)
		240 sh (5000)	245 sh (−2.80)
		216 (15 900)	225 (−10.10)
Cu(L-$Me^{\alpha}{}_2HisOCH_3$)$^{2+}$	7.1	697 (53)	650 (+0.25)
		262 (2750)	264 (−1.60)
		208 (8100)	223 (−5.60)
Cu(L-$HisOCH_3$)$^{2+}$	7.4	631 (50)	640 (+0.11)
		330 sh (240)	330 sh (−0.04)
		280 sh (1000)	
		240 sh (3800)	245 sh (−1.00)
		212 (10 000)	225 (−3.30)

[a] Shoulder = sh. [b] Broad. [c] Position of the extremum not well-defined due to intense absorption of the solution. [d] Maximum beyond the long-wavelength limit of the instrument; $\Delta\epsilon$ in parentheses at 800 nm.

to shorter wavelengths of the d–d band, with a modest increase in intensity, while the absorptions in the UV region (a band near 220 nm with a shoulder near 250 nm) remain unshifted and undergo only a parallel increase in intensity. Additional absorptions appear as poorly defined shoulders between 300 and 400 nm at neutral pH and become somewhat better resolved above pH ~9. In acid or neutral medium the CD spectra of both the 1:1 and 1:2 systems display two-signed curves in the visible region, with a dominant negative component at higher energy, and resemble the CD spectra of copper(II) complexes with nonpolar L-amino acids.[16] Both components shift smoothly to shorter wavelengths and increase in intensity as the pH of the solution is raised. At neutral pH the negative CD band near 630 nm is nearly coincident with the position of the absorption maximum and additional weak, and featureless CD activity roughly centered near 360 nm can be detected. The CD band in the 300–400-nm region fully develops when the pH of the solution is raised to ~9, while above pH ~11 a complex pattern of CD bands can be observed in the same region. The presence of mixture of products above pH ~9 is confirmed by the appearance of several CD bands in the 500–800-nm region. The dominant Cotton effects within these bands, though, are of positive sign. The variation of pattern of the CD bands in the UV region with pH can be summarized as follows. Below pH ~3 only a negative band near 270 nm is present, while additional positive CD activity below 230 nm is at least partly due to unbound 2-(trifluoromethyl)-L-histidine. Between pH ~4 and pH ~5 the shape of the CD curve features a positive CD peak near 250 nm, even though the curve may not actually cross the zero line, while below 240 nm weak CD activity of negative sign is not well resolved due to the intense absorption of the solution. The positive CD peak at 250 nm becomes better defined in neutral medium but its intensity remains quite low, possibly because it is flanked on both sides and partly canceled by CD bands of opposite sign. At pH ~9, together with a growth of positive CD activity in the 300–400-nm region, a negative CD band near 230 nm becomes well-defined. At still higher pH the positive CD peak near 250 nm increases significantly in intensity, while the band at 270 nm is replaced by a negative band near 290 nm.

The CD spectra of neutral Cu(L-CF_3His)(Gly) and Cu(L-CF_3His)(β-Ala) solutions are similar to those of the copper(II)–2-(trifluoromethyl)-L-histidine (1:1 and 1:2) systems at pH ~7 (Table II; Figure 2). The CD spectrum of Cu(L-CF_3His)(L-Val) is also similar except for the absence of the weak positive peak at 250 nm. This is probably overshadowed by the stronger negative CD band typical for copper(II)–L-amino acid residues that occurs near the same wavelength.[17] In general, CD

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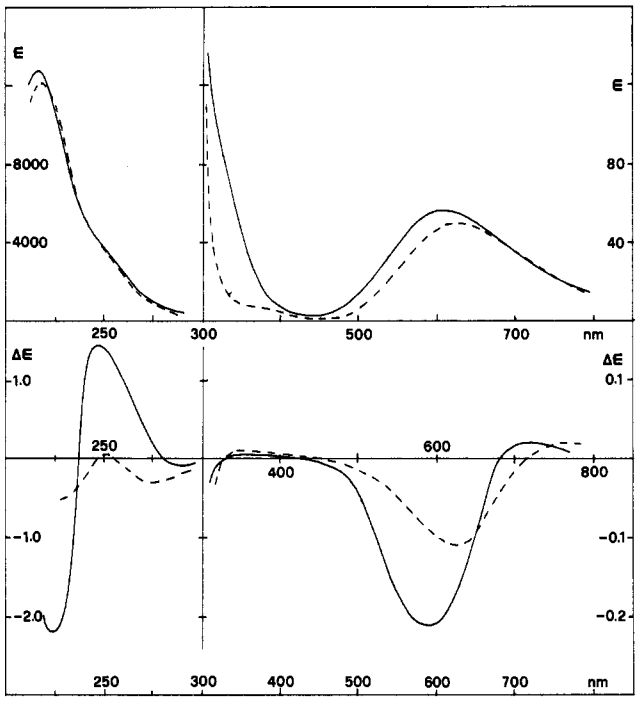

Figure 2. Electronic and CD spectra of 10^{-2} M aqueous solutions of (---) copper(II)–2-(trifluoromethyl)-L-histidine–glycine (1:1:1) at pH 7.5 and (—) copper(II)–2-(trifluoromethyl)-L-histidine–histamine (1:1:1) at pH 7.1.

bands of negative sign dominate the visible spectra of these Cu(L-CF_3His)(aa) ternary systems; this behavior is exactly opposite to that exhibited by the corresponding ternary systems derived from L-histidine, Cu(L-His)(aa), or L-N^τ-methylhistidine, Cu(L-Me$^\tau$His)(aa).[2,3] With the single exception of Cu(L-CF_3His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$, the spectra of mixed complexes containing amine derivatives, i.e. Cu(L-CF_3His)(him)$^+$, Cu(L-CF_3His)(1,3-pn)$^+$, Cu(L-CF_3His)(L-HisOH)$^+$, and Cu(L-CF_3His)(L-HisOCH$_3$)$^+$, display dominant Cotton effects of negative sign within the visible, two-signed CD curve (Table II; Figure 2). Although these spectra bear a qualitative resemblance with the CD spectra of the corresponding mixed systems derived from L-histidine or L-N^τ-methylhistidine, they resemble those of the derivatives of histamine rather than those of the derivatives containing chiral amino esters.[2,3] In the UV region, the CD spectra of these positively charge mixed complexes display two negative bands, near 225 nm (rather intense) and between 265 and 305 nm. The latter band probably obscures the weak and broad CD activity of positive sign near 350 nm, that can be detected only in the spectra of the systems containing nonchiral amine derivatives, Cu(L-CF_3His)(him)$^+$ and Cu(L-CF_3His)(1,3-pn)$^+$. The CD spectra of Cu(L-CF_3His)(him)$^+$ and Cu(L-CF_3His)(L-HisOH)$^+$ display an additional positive peak near 250 nm of significant intensity, while this peak is completely absent in the spectra of Cu(L-CF_3His)(L-HisOCH$_3$)$^+$, Cu(L-CF_3His)(1,3-pn)$^+$, and also Cu(L-CF_3His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$. Interestingly, this positive 250-nm peak is a characteristic of the CD spectrum of Cu(L-HisOH)$^{2+}$, though it is absent in the spectra of either Cu(L-HisOH)$_2^{2+}$ or any other copper(II)–amino ester derivative, i.e. Cu(L-HisOCH$_3$)$^{2+}$, Cu(L-Me$^\alpha_2$HisOCH$_3$)$^{2+}$, Cu(L-HisOCH$_3$)$_2^{2+}$,[3] and Cu(L-Me$^\alpha_2$HisOCH$_3$)$_2^{2+}$[3] (Table II). The visible CD spectrum of Cu(L-CF_3His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$ bears a mirror-image relationship to those of the other ternary systems derived from 2-(trifluoromethyl)-L-histidine, since the two-signed CD curve displays a dominant positive component at shorter wavelength and seems related to the spectra of Cu(L-His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$ and Cu(L-Me$^\tau$His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$.[3] We also recorded the spectra of two other mixed complexes of L-Histidinol that were not reported previously: Cu(L-His)(L-HisOH)$^+$ and Cu(L-Val)(L-HisOH)$^+$. As expected,[3] these exhibit a pattern of CD bands of opposite sign in the visible region, while of the three UV bands only that near 270 nm has an opposite sign in the two systems.

Discussion

The CD spectra of the copper(II)–2-(trifluoromethyl)-L-histidine (1:2) system do not show the marked variations with pH observed for the corresponding copper(II)–L-histidine,[2] copper(II)–L-N^τ-methylhistidine,[3] and copper(II)–L-N^α,N^α-dimethylhistidine[3] (1:2) systems. This indicates that the introduction of the relatively bulky trifluoromethyl substituent at the 2-position of the imidazole ring produces the expected drastic reduction in the number of isomeric species that can be present at the equilibrium, particularly near neutral pH. The visible CD spectra clearly indicate that 2-(trifluoromethyl)-L-histidine exhibits a marked preference for a glycine-like mode of coordination. In acid medium the ligand is prevalently bound as bidentate and contains a protonated imidazole ring, while at neutral pH it can bind as tridentate. Apical binding by the imidazole nitrogen donor of the 2-(trifluoromethyl)-L-histidinate anion is characterized by weak CD activity near 360 nm (the actual extremum being probably at somewhat shorter wavelength, since this band is systematically flanked by a CD band of opposite sign at higher energy) and near 230 nm, that we assign to Im(π_1) → Cu(II) and to Im(σ) → Cu(II) LMCT transitions, respectively.[18] The positions of these transitions are not too different from those arising from equatorially bound imidazole rings,[2,3,18] though the magnitude of the Cotton effects within the corresponding CD bands is about 1 order of magnitude lower. The third LMCT transition originating from the imidazole ring, Im(π_2) → Cu(II), at intermediate energy between the other two,[18] occurs in the same range as the $NH_2(\sigma)$ → Cu(II) and COO(σ) → Cu(II) LMCT transitions[17,19] and cannot be localized with certainty in the spectra. The intensity of the electronic and CD bands related to LMCT from imidazole nuclei to copper(II) becomes significant only in basic medium, where deprotonated imidazole nuclei may replace the carboxylate groups coordinated in equatorial positions of neighboring molecules.

The histamine-like mode of coordination is apparently inaccessible to the 2-(trifluoromethyl)-L-histidinate anion due to severe steric interaction arising between the imidazole trifluoromethyl substituent and any donor group coordinated in cis position in the copper square plane. This is particularly evident in the CD spectra of the mixed complexes of type Cu(L-CF_3His)(aa). These invariably show the pattern typical for glycine-like bound amino acid residues, in striking contrast with the behavior exhibited by the corresponding mixed complexes of L-histidine, L-N^τ-methylhistidine and L-N^α,N^α-dimethylhistidine, where the histamine-like binding mode was strongly preferred.[2,3] Therefore, unlike Cu(L-His)$_2$, Cu(L-Me$^\tau$His)$_2$, and Cu(L-Me$^\alpha_2$His)$_2$, the neutral Cu(L-CF_3His)$_2$ complex contains both ligand molecules bound glycine-like (II). Both the cis and trans isomers of Cu(L-CF_3His)$_2$ probably exist in solution, though only the cis isomer allows apical chelation by both imidazole rings. The conformation of each equatorial chelate ring in II has λ chirality; this is responsible for the dominant Cotton effects of negative sign within the d–d bands.[2,3] We note that the geometrical arrangement of the ligands depicted in II has been found in the crystal structure of bis(L-histidinato)cobalt(II).[20]

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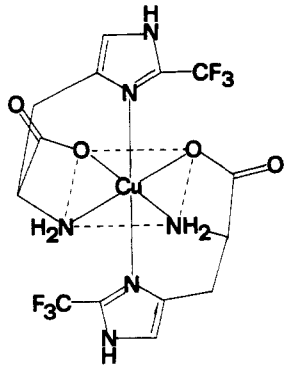
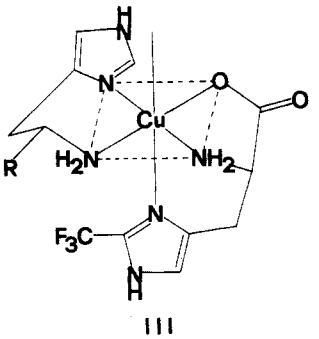


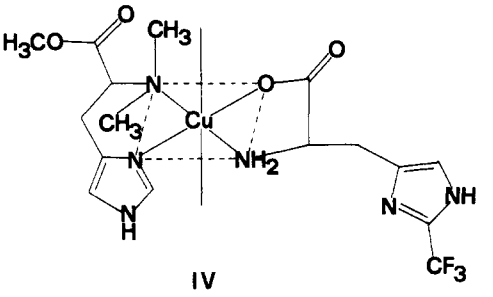
II

The necessity to assume a glycine-like mode of binding by the 2-(trifluoromethyl)-L-histidinate anion meets favorably the preference for the adoption of complementary chelate-ring types[21] in mixed complexes with amine or amino ester derivatives. Thus, while for ternary systems of the type Cu(L-His)(him)$^+$ or Cu(L-His)(L-HisOCH$_3$)$^+$ the CD spectra indicate an equilibrium mixture of a mixed-type chelation structure and a structure containing both ligands bound histamine-like,[2,3] the corresponding derivatives of 2-(trifluoromethyl)-L-histidine exhibit an exclusive tendency to assume the mixed-type chelation structure III (cis



III

and trans isomers). Following the criterion of taking the ratio of amplitude between the negative and positive components of the visible CD curve in the mixed complexes with histamine as a qualitative measure of the tendency by derivatives of L-histidine to assume a glycine-like coordination mode,[3] the following order is established: 2-(trifluoromethyl)-L-histidine > L-N^α,N^α-dimethylhistidine > L-N^τ-methylhistidine > L-histidine. This trend apparently follows that of the steric encumbrance of the substituent attached to the histidine molecule since it is reproduced in the ternary systems containing L-histidinol or methyl ester derivatives[3] (with the only exception of Cu(L-CF$_3$His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$) and also in the neutral Cu(L-His)$_2$, Cu(L-Me$^\tau$His)$_2$, Cu(L-Me$^\alpha_2$His)$_2$, and Cu(L-CF$_3$His)$_2$ complexes. The behavior of the mixed complex Cu(L-CF$_3$His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$ deserves comment since its CD spectrum cannot be accounted for in terms of the above scheme. The dominant positive CD activity within the d–d bands (rather intense, as is usually the case for mixed complexes of L-N^α,N^α-dimethylhistidine methyl ester)[3] cannot reasonably be associated with a structure containing the 2-(trifluoromethyl)-L-histidine anion bound histamine-like, since this would involve the bulky 2-(trifluoromethyl)imidazole group of the amino acid to be in cis position to either the dimethylamino or the imidazole group of the amino ester. The structure of Cu(L-CF$_3$His)(L-Me$^\alpha_2$HisOCH$_3$)$^+$ with minimal steric interaction is that containing trans amino and dimethylamino groups in the copper equatorial plane, IV. Also in this structure, however, the



IV

conformational mobility of the amino acidato ligand is probably confined within the narrow range attainable to conformations of δ chirality, containing the side chain in essentially equatorial disposition, while inversion to the λ conformation produces strong interaction between the trifluoromethyl and dimethylamino groups. We believe this imposed δ conformation of the amino acid chelate ring contributes Cotton effects of positive sign to the CD activity in the visible region; these add to those already involved in binding of L-N^α,N^α-dimethylhistidine methyl ester to copper(II).

In conclusion, the present investigation has shown that, without exceptions, the 2-(trifluoromethyl)-L-histidine molecule coordinates to copper(II) in a glycine-like fashion, either as bidentate or as tridentate, in every binary or ternary complex, even those where L-histidine exhibits a striking tendency to bind histamine-like. This enables establishment of the following order for the tendency to assume the glycine-like mode of coordination by derivatives of L-histidine: 2-(trifluoromethyl)-L-histidine > L-N^α,N^α-dimethylhistidine > L-N^τ-methylhistidine > L-histidine. The tridentate mode of binding of 2-(trifluoromethyl)-L-histidine gives the opportunity to spectrally characterize for the first time apical coordination of imidazole groups to copper(II). This result has some relevance for the interpretation of the spectral behavior of bioinorganic models of copper proteins.[22] Most of the stereochemical deductions were based upon consideration of the behavior of the visible CD spectra of the complexes, while we were unable to rationalize the CD spectra in the UV region. The range 250–300 nm comprises most of the LMCT transitions from the donor groups to copper(II) and appears too complex for interpretation at this stage, since it probably reflects both conformational equilibria and cis–trans isomerism in solution.

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Registry No. Cu(L-CF$_3$His)(Gly), 92397-52-9; Cu(L-CF$_3$His)(β-Ala), 92397-53-0; Cu(L-CF$_3$His)(L-Val), 92397-54-1; Cu(L-CF$_3$His)(him)$^+$, 92397-55-2; Cu(L-CF$_3$His)(L-HisOH)$^+$, 92397-56-3; Cu(L-CF$_3$His)(L-HisOCH$_3$)$^+$, 92397-57-4; Cu(L-CF$_3$His)(L-Me$_2^\alpha$HisOCH$_3$)$^+$, 92397-58-5; Cu(L-CF$_3$His)(1,3-pn)$^+$, 92397-59-6; Cu(L-His)(L-HisOH)$^+$, 92397-60-9; Cu(L-Val)(L-HisOH)$^+$, 92397-61-0; Cu(L-HisOH)$_2^{2+}$, 26920-85-4; Cu(L-CF$_3$His)$_2$, 92397-62-1.

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