CH_3OCH_3 (0.78 mmol) were recovered.

Preparation of $CH_3CH_2OCH_2CH_3$. (a) $(CF_3)_2S(O)(OCF_3)_2$ (1 mmol) and CH_3CH_2OH (2 mmol) were condensed into a Pyrex glass vessel which contained excess NaF and reacted as above. The products isolated were $CF_3SO_2CF_3$ (0.92 mmol), CF_2O (1.91 mmol), and $CH_3CH_2OCH_2CH_3$ (0.91 mmol).

(b) As in the previous procedure, $(CF_3)_2S(OCF_3)_2$ (1 mmol) was used and $CF_3S(O)CF_3$ (0.89 mmol), CF_2O (1.82 mmol), and $CH_3CH_2OCH_2CH_3$ (0.80 mmol) were recovered.

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Registry No. **1**, 63465-11-2; **2**, 66632-46-0; **3**, 63441-15-6; **4**, 66632-47-1; CF_3SCF_3, 371-78-8; CF_3OCl, 22082-78-6; $CF_3S(O)CF_3$, 30341-37-8; tetrafluro-1,3-dithietane, 1717-50-6; $(CF_3)_2S{=}NH$, 60646-40-4; $(CF_3)_2S{=}NCH_3$, 60646-41-5; $(CF_3)_2S{=}NCH_2CH_3$, 60646-42-6; $(CF_3)_2S(O){=}NH$, 34556-22-4; $(CF_3)_2S(O){=}NCH_3$, 34556-25-7; $(CF_3)_2S(O){=}NCH_2CH_3$, 60646-44-8; $(CH_3CH_2)_2NSiMe_3$, 996-50-9; $C_6H_5OCF_3$, 456-55-3; *p*-$CH_3C_6H_4OCF_3$, 706-27-4; $CH_3CH{=}CH_2$, 115-07-1; $(CH_3)_2C{=}CH_2$, 115-11-7; $(CF_3)_2C{=}CH_2$, 382-10-5; CH_3OCH_3, 115-10-6; $CH_3CH_2OCH_2CH_3$, 60-29-7; $LiN{=}C(CF_3)_2$, 31340-36-0; phenol, 108-95-2; *p*-cresol, 106-44-5; isopropyl alcohol, 67-63-0; *tert*-butyl alcohol, 75-65-0; $(CF_3)_2C(CH_3)OH$, 1515-14-6; CH_3OH, 67-56-1; CH_3CH_2OH, 64-17-5; NH_3, 7664-41-7; CH_3NH_2, 74-89-5; monoethylamine, 75-04-7.

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Newly Synthesized Sulfhydryl- and Imidazole-Containing Tripeptides with a Specific Copper-Binding Site

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New tripeptides, *N*-mercaptoacetylglycyl-L-histidine (MAGH) and *N*-mercaptoacetyl-DL-histidyl-DL-histidine (MAHH), were synthesized as an artificial sulfhydryl-containing peptide with a histidine component in the third position of the molecular sequence. Their remarkably stable Cu(II) complexes were characterized by electronic, circular dichroism, electron spin resonance (ESR), and X-ray photoelectron spectra. The ESR spectra for the 1:1 Cu(II) complexes of MAGH and MAHH showed the seven and nine lines of nitrogen superhyperfine splitting, indicating clearly the coordination of three and four nitrogen atoms toward Cu(II), respectively. The ESR and bonding parameters estimated were as follows: $A_{\parallel} = 195 \times 10^{-4}$ cm^{-1}, $g_{\parallel} = 2.206$, $g_{\perp} = 2.099$, $A_N = 12.61 \times 10^{-4}$ cm^{-1}, $\alpha^2 = 0.81$, $\beta_1^2 = 0.67$, and $\beta^2 = 1.19$ for the MAGH–Cu(II) complex and $A_{\parallel} = 180 \times 10^{-4}$ cm^{-1}, $g_{\parallel} = 2.183$, $g_{\perp} = 2.060$, $A_N = 12.70 \times 10^{-4}$ cm^{-1}, $\alpha^2 = 0.75$, $\beta_1^2 = 0.65$, and $\beta^2 = 0.96$ for the MAHH–Cu(II) complex. These results support square-planar and square-pyramidal configurations for the Cu(II) complexes of MAGH and MAHH, respectively. In addition, proton nuclear magnetic resonance measurements for the 1:1 Cu(I) complexes of these peptides revealed that the sulfhydryl and imidazole groups participate in the coordination of Cu(I).

Introduction

The N-terminal portion Asp–Ala–His of human (or bovine) serum albumin coordinates Cu(II) ion strongly in a square-planar complex involving the amino group of the aspartic acid residue, an imidazole nitrogen of the histidine, and two intermediate peptide nitrogens.[1] Recent work by Sarkar and co-workers[1] has demonstrated that the tripeptide molecule glycylglycyl-L-histidine (GGH) contains the same potential metal-binding sites, is an adequate model for the specific Cu(II) transport site of human serum albumin, and may be

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quite useful in treating Wilson's disease. Wilson's disease is a copper-dependent disease of a peculiar metabolic defect characterized by excessive amounts of copper in the brain, liver, cornea, and urine. The high cupriuric activity of D-penicillamine, an artificial sulfhydryl-containing amino acid, has made this chelating agent the drug of choice for treating this disease.[2] Nevertheless, this agent leaves much to be desired as the patient's response is slow, a tolerance to the drug soon develops, and its nephrotoxicity is strong. Therefore, a new approach to this problem of removing copper has been initiated by designing suitable molecules which have the required specificity and affinity for copper.[1] From livers of patients with this disease, on the other hand, Porter[3] and Morell et al.[4] isolated and characterized a copper protein with high copper and sulfur content, hepatic mitochondrocuprein, and hepatic copper binding protein L-6-D. A common feature of these proteins is the tightly bound copper, probably copper coordinated with thiolate sulfur as observed in copper thionein.[5] It is well-known that a sulfur donor has a high binding affinity for Cu(I) ion. In any molecule designed specifically to bind copper, therefore, a sulfhydryl-containing peptide with a histidine component in the third position of the molecular sequence is specially suited to achieve the proper ligand geometry for copper binding and to counteract the copper accumulation.

In addition, the histidine imidazole donor as well as the sulfhydryl group is one of the most important ligands for not only iron proteins but also copper proteins. In copper–zinc superoxide dismutase, the copper site has four histidine ligands.[6] Recent studies on the "blue" copper proteins plastocyanin and azurin revealed the coordinations of two histidine imidazole donors and one cysteine sulfur donor for the copper-active site.[7] Copper–imidazole(histidine) bonds have been also suggested for the copper environment of hemocyanin by resonance Raman studies.[8]

In this paper, *N*-mercaptoacetylglycyl-L-histidine (MAGH) and *N*-mercaptoacetyl-DL-histidyl-DL-histidine (MAHH) were newly synthesized as a designed peptide molecule with high affinity and specificity for copper. The unique Cu(II) and Cu(I) bindings of the new sulfhydryl- and imidazole-containing tripeptides were characterized mainly by electron spin resonance (ESR) and proton nuclear magnetic resonance (^{1}H NMR) spectra, and their bonding properties were compared with those of the glycylglycyl-L-histidine–copper(II) complex. MAGH and MAHH served as adequate ligands for not only Cu(II) but also Cu(I).

Experimental Section

Materials. New histidine-containing sulfur peptides, MAGH, MAHH, and *N*-mercaptoacetyl-β-alanyl-L-histidine (MAAH), were synthesized according to the previous method[9] with some modifications. Glycyl-L-histidine (or DL-histidyl-DL-histidine and β-alanyl-L-histidine; 0.1 M) was reacted with chloroacetyl chloride (0.12 M) in K_2CO_3 solution by making use of the Schotten–Bauman reaction. Sodium thiobenzoic acid (0.12 M) was then added to the reaction mixture and stirred overnight. The solution was brought to pH 1 with HCl. The precipitate was filtered and washed with cold water. The product, an *N*-benzoylmercapto compound, was then hydrolyzed in an ammonia solution for 30 min. After removal of benzamide by the extraction with ethyl acetate, the solution was evaporated under nitrogen. The white product was precipitated by addition of ethanol. The compound was recrystallized from water–ethanol and dried in vacuo over P_2O_5. The yield was approximately 30–40%. *N*-Mercaptoacetylglycylglycine (MAGG) and *N*-mercaptoacetylglycylglycylglycine (MAGGG) were also prepared using a previously reported method.[9] These new peptides were investigated by elemental analysis, iodometric titration, and infrared and ^{1}H NMR spectra. Satisfactory C, H, N, and S analyses were obtained.[10] All other reagents used were of commercial reagent grade. The 1:1 Cu(II) complexes of MAGH and MAHH were isolated in a manner similar to that described previously.[11] An aqueous solution (1 mL) of MAGH (or MAHH; 0.5 mol) containing NaOH was added to $CuCl_2 \cdot 2H_2O$ (0.5 mol) dissolved in 2 mL of ethanol. A red-brown precipitate formed in the reaction solution. The solid was filtrated and washed with ethanol. The product was recrystallized from water–ethanol. The yield was approximately 60%. The results of microanalysis and infrared measurement satisfied the molecular formulas $\{[SCH_2CONCH_2CONCH(CH_2)(C_3N_2H_3)COO]Cu\}Na_2 \cdot 2H_2O$ and $\{[SCH_2CONCH(CH_2)(C_3N_2H_3)CONCH(CH_2)(C_3N_2H_3)COO]Cu\}Na_2 \cdot H_2O$, respectively.[12]

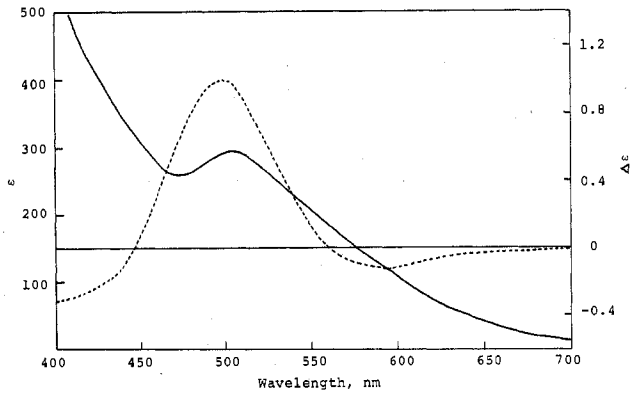


Figure 1. Visible (—) and circular dichroism (---) spectra of the 1:1 MAGH–Cu(II) complex.

Methods. Visible absorption and circular dichroism (CD) spectra were measured in an aqueous solution at 20 °C with a Shimadzu recording spectrophotometer, Model Double-40R, and a Jasco J-20 spectropolarimeter, respectively. X-Band ESR spectra were obtained at 77 and 293 K with a Jeol ME-3X spectrometer equipped with a gauss meter and frequency counter. The magnetic fields were calibrated by the splitting of Mn(II) in MgO (ΔH_{3-4} = 86.9 G). X-ray photoelectron spectra (XPS) of the isolated MAGH–Cu(II) complex were recorded at −100 °C on a Varian V-IEE 15 spectrometer equipped with 620L on-line computer. ^{1}H NMR spectra were recorded at 100 MHz on a Varian HA-100 NMR spectrometer. Sodium 3-(trimethylsilyl)propionate-d_4 was used as internal standard and/or as lock signal. All pD measurements were performed using a Hitachi-Horiba pH meter, Model F-5, equipped with a Toko combination electrode CE-103. The reading of the pH meter plus 0.4 was used to calculate pD according to the relationship pD = pH + 0.4.

Evaluation of ESR Parameters. Random motion of solute molecules at 293 K yields an isotropic spectrum from which g_0 and the nuclear hyperfine structure constant A_0 can be measured. The former parameter is the g value at the center of the four-line pattern, and A_0, expressed in cm^{-1}, is the spacing between the lines. In the vitreous state at 77 K, all orientations of the symmetry axis are present but fixed, and an anisotropic spectrum is obtained. From this, the values of $g_\parallel$ and $A_\parallel$ can be measured accurately. Using the approximate relations $3g_0 = g_\parallel + 2g_\perp$ and $3A_0 = A_\parallel + 2A_\perp$, we can obtain $g_\perp$ and $A_\perp$ values. The spectra could be fitted for $g_\parallel > g_\perp$ from which it can be deduced that the ground state for the cupric ion is $d_{x^2-y^2}$. Tetragonal distortion from octahedral symmetry by the Jahn–Teller effect splits the lower E_g doublet into two singlets (B_{1g} and A_{1g}) and the upper T_{2g} triplet into a singlet (B_{2g}) and a higher lying doublet (E_g). Therefore, two ligand electronic transitions ($B_{1g} \leftarrow E_g$ (E_{xz}) and $B_{1g} \leftarrow B_{2g}$ (E_{xy})) appear at lower wavelength. From the visible absorption and CD spectra, the following values were tentatively used as ligand field transition energies: E_{xz} = 19920 cm^{-1} and E_{xy} = 16950 cm^{-1} for the MAGH–Cu(II) complex, and E_{xz} = 19050 cm^{-1} and E_{xy} = 17200 cm^{-1} for the GGH–Cu(II) complex. In order to obtain additional detailed information about the bonding character, the following LCAO–MO scheme for D_{4h} symmetry was set up.

$$B_{1g} = \alpha(d_{x^2-y^2}) - \alpha'(-\sigma_x^{(1)} + \sigma_y^{(2)} + \sigma_x^{(3)} - \sigma_y^{(4)})/2 \quad \text{(A)}$$

$$B_{2g} = \beta_1(d_{xy}) - \beta_1'(P_x^{(1)} + P_y^{(2)} - P_y^{(3)} - P_x^{(4)})/2 \quad \text{(B)}$$

$$E_g = \beta(d_{xy}) - \beta'(P_z^{(1)} - P_z^{(3)})/2 \quad \text{(C)}$$

$$= \beta(d_{yz}) - \beta'(P_z^{(2)} - P_z^{(4)})/2 \quad \text{(D)}$$

The nomenclature in these antibonding wave functions is the same as used by Gersman and Swalen.[13] The LCAO–MO coefficients and

Table I. Visible Spectral Data of 1:1 Tripeptide-Copper(II) Complexes

Ligand	Donor set	λ_{max} (ϵ), nm (M^{-1} cm^{-1})
N-Mercaptoacetylglycylglycine	$S(N_p)_2O$	532 (210)
N-Mercaptoacetylglycyl-L-histidine	$S(N_p)_2N_{Im}$	502 (290)
N-Mercaptoacetyl-DL-histidyl-DL-histidine	$S(N_p)_2(N_{Im})_2$	513 (330)
N-Mercaptoacetylglycylglycylglycylglycine	$S(N_p)_3$	490 (330)
Glycylglycylglycine	$N(N_p)_2O$	555 (140)
Glycylglycyl-L-histidine	$N(N_p)_2N_{Im}$	525 (110)
Glycylglycylglycylglycine	$N(N_p)_3$	510 (160)

nitrogen superhyperfine coupling constants were computed by using relationships similar to those reported by Bryce.[14]

$$\alpha^2 = -\frac{A_\parallel}{P} + (g_\parallel - 2.0023) + \frac{3}{7}(g_\perp - 2.0023) + 0.04 \quad (1)$$

$$(P = -0.036\ cm^{-1})$$

$$\alpha^2 - 2\alpha\alpha' S + \alpha'^2 = 1 \quad (S = 0.093) \quad (2)$$

$$\beta_1^2 = (g_\parallel - 2.0023)/\left\{-\frac{8\lambda_0}{E_{xy}}(\alpha^2 - \alpha\alpha' S)\right\} \quad (3)$$

$$(\lambda_0 = -828\ cm^{-1})$$

$$\beta^2 = (g_\perp - 2.0023)/\left\{-\frac{2\lambda_0}{E_{xz}}(\alpha^2 - \alpha\alpha' S)\right\} \quad (4)$$

$$A_N = -\frac{4\pi}{9}\gamma_N\beta_0\beta_N(\alpha')^2|P_N(0)|^2 \quad (5)$$

$$(\gamma_N = 0.4036,\ |P_N(0)|^2 = 33.4 \times 10^{24}\ cm^{-3})$$

$$A_N = \frac{8\pi}{3}\frac{\mu_I\beta_I}{I}(1 - n^2)\frac{\beta^2(\alpha')^2}{4}|\psi(0)|^2 \quad (6)$$

$$(n^2 = \frac{2}{3}, \frac{8}{3}\pi\frac{\mu_I\beta_I}{I}|\psi(0)|^2 = 550\ G)^{15}$$

If the electron distribution on the ligand atoms is described in terms of an sp^2 hybrid orbital directed toward the cupric ion, the electronic-nuclear(^{14}N) coupling energy can be estimated by equation 5 or 6.

Results and Discussion

Cu(II) Complexes. The 1:1 MAGH–Cu(II) and MAHH–Cu(II) complexes were remarkably stable in an aqueous solution (pH 5–12), and Cu(I) and the disulfide were not readily produced. Figure 1 shows the visible and CD spectra of the 1:1 MAGH–Cu(II) complex which have an absorption maximum at 502 nm (ϵ 290) and CD extrema at 495 nm ($\Delta\epsilon$ +1.0) and 592 nm ($\Delta\epsilon$ −0.1). The λ_{max} shifts to a shorter wavelength than that of the 1:1 GGH–Cu(II) complex [525 nm (ϵ 110)]. Table I summarizes the visible absorption data of the 1:1 Cu(II) complexes of these new sulfhydryl-containing peptides and the corresponding glycine-containing peptides. The order of relative effectiveness in the magnitude of the ligand field around the central Cu(II), as reflected in the λ_{max} values, was presumed to be MAGGG > MAGH > GGGG > GGH > MAGG > GGG. The results in Table I reveal that (1) exchange of the terminal amino group by a sulfhydryl group gave a blue shift of 25 nm and (2) exchange of the terminal carboxyl group by an imidazole group gave a blue shift of 30 nm. The unique spectroscopic properties of blue copper proteins are similar to those [λ_{max} 598 nm (ϵ 830) and $A_\parallel$ = 93 G] of the 1:1 *N*-mercaptoacetyl-L-histidine (MAH)–Cu(II) complex which consists of two chelate rings[16] rather than those of the rigid MAGH–Cu(II) complex which has a strong ligand field by the formation of three chelate rings. In the 1:1 sulfhydryl-containing peptide–copper(II) complexes, a blue shift of about 90 nm was induced by exchanging the two chelate rings for three chelate rings.[9] The 1:1 MAH–Cu(II) complex also showed CD extrema at 405 ($\Delta\epsilon$ −1.67), 445 ($\Delta\epsilon$ −1.97), 545 ($\Delta\epsilon$ +1.58), and 630 nm ($\Delta\epsilon$ −0.64) which are considerably different from those of the 1:1 MAGH–Cu(II) complex. The high extinction coefficients of the visible and CD absorptions of the MAH–Cu(II) complex are probably due to the distortion from square-planar to tetrahedral configurations. On the other hand, the 1:1 MAHH–Cu(II) complex gave an absorption maximum at 513 nm (ϵ 330). It is of interest that here the λ_{max} shifted to a longer wavelength than is seen with the 1:1 MAGH–Cu(II) complex which has a Cu(II) binding site with a square-planar arrangement. The red shift (10 nm) of the λ_{max} is explained in terms of a pentacoordination effect.

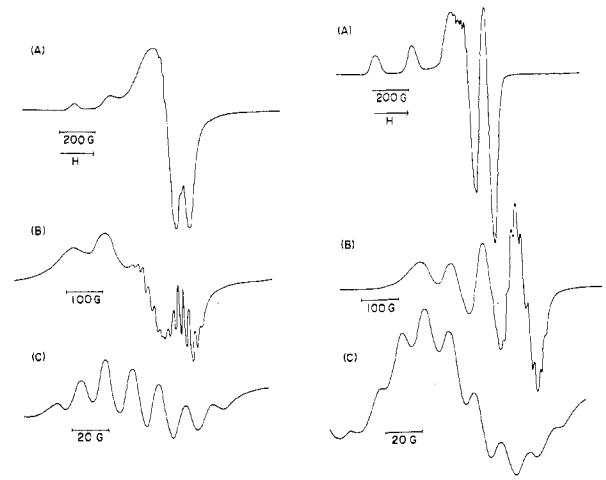


Figure 2. ESR spectra of the Cu(II) complexes of MAGH (left) and GGH (right) at 77 K (A) and 293 K (B, C). Spectra C show a nitrogen nuclear superhyperfine structure.

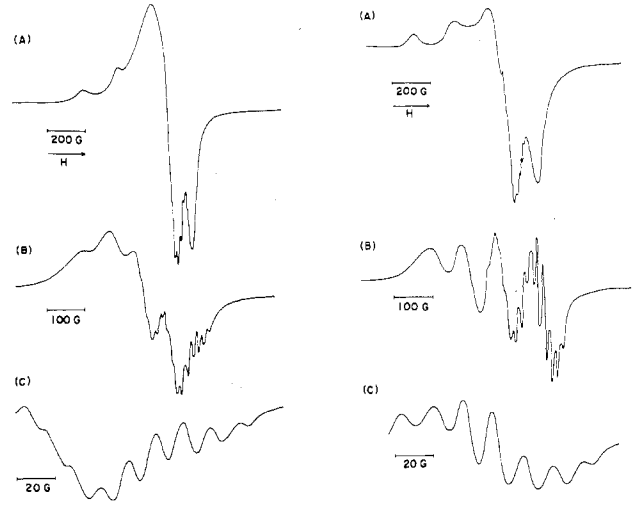


Figure 3. ESR spectra of the Cu(II) complexes of MAHH (left) and MAGGG (right) at 77 K (A) and 293 K (B, C). Spectra C show a nitrogen nuclear superhyperfine structure.

The ESR spectra of the MAGH–Cu(II) complex observed at 77 and 293 K are shown in Figure 2, in comparison with those of the corresponding GGH–Cu(II) complex. Figure 3 also shows the ESR spectra of the 1:1 Cu(II) complexes of MAHH and MAGGG at 77 and 293 K. The sample concentration was 0.01–0.001 M in an aqueous solution. All ESR spectra exhibit a typical copper hyperfine pattern with approximately axial symmetry ($g_x \simeq g_y$) and as such are characteristic of Cu(II) systems in local environments of C_{2v}

Table II. ESR and Bonding Parameters for Cu(II) Complexes of Sulfhydryl- and Imidazole-Containing Peptides

Ligand	$g_{\parallel}$	$g_{\perp}$	g_0	$10^4A_{\parallel}$, cm^{-1}	According to eq 1 from $A_{\parallel}$		10^4A_N, cm^{-1}	According to eq 6 from A_N		β_1^2	β^2
					α^2	$(\alpha')^2$		α^2	$(\alpha')^2$		
MAGH	2.206	2.079	2.099	195	0.82	0.27	12.61	0.81	0.28	0.67	1.19
GGH	2.172	2.065	2.109	206	0.81	0.28	12.46	0.79	0.30	0.57	0.94
MAHH	2.183	2.060	2.101	180	0.75	0.34	12.70	0.80	0.29	0.65	0.96
MAGGG	2.155	2.046	2.092	199	0.77	0.32	12.04	0.75	0.34	0.54	0.76

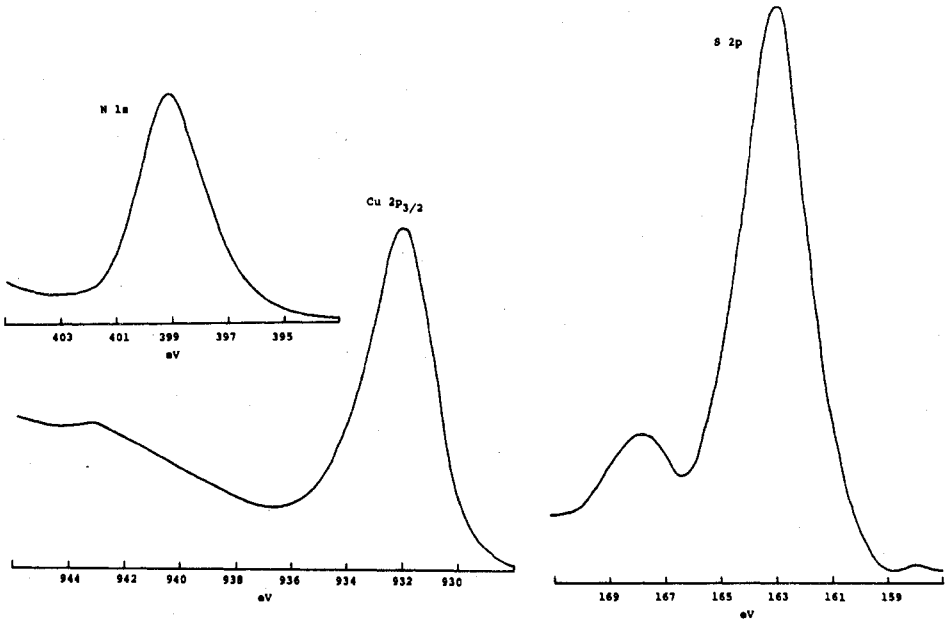
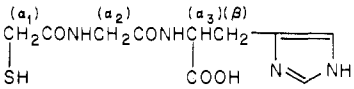
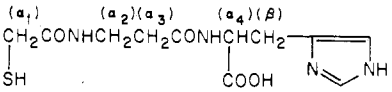
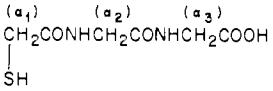
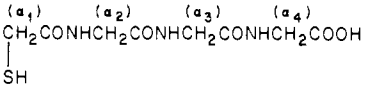
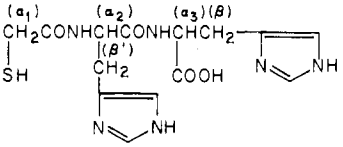


Figure 4. X-ray photoelectron spectra of the 1:1 MAGH–Cu(II) complex.

and D_{4h} symmetries as normally found in pseudo-square-planar environments. In addition, no ESR signals were detected at half-field, $g = 4$, resulting from the spin-forbidden $\Delta_m = 2$ transition in a spin-coupled Cu(II) dimer,[17] regardless of the experimental conditions. Hence, these peptide–copper(II) complexes are considered to be mononuclear in nature, and a dimer structure can be ruled out. Figures 2 and 3 indicate clearly that the ESR splitting of the perpendicular region is not due to the anisotropy in the x and y directions but rather to the superhyperfine interaction with neighboring nuclei, namely, nitrogen (^{14}N, $I = 1$) atoms. In the Cu(II) complexes of MAGH, GGH, and MAGGG, the well-defined seven, nine, and seven lines of nitrogen nuclear superhyperfine splitting support strongly the coordinations of three, four, and three nitrogen atoms toward Cu(II), respectively. The result reveals that their Cu(II) sites are in a square-planar environment with $S(N_p)_2N_{Im}$, $N(N_p)_2N_{Im}$, and $S(N_p)_3$ donor sets, respectively. In the MAGH–Cu(II) complex, the ratios of relative amplitudes of its seven lines were approximately 1:3:6:7:6:3:1. Comparison with the theoretical pattern of 1:3:6:7:6:3:1 suggests that the three nitrogen nuclei are magnetically equivalent. On the other hand, the nine nitrogen superhyperfine splittings of the MAHH–Cu(II) complex show clearly the coordination of four nitrogen atoms toward Cu(II) and suggest the formation of five-coordination species with $S(N_p)_2(N_{Im})_2$ donor set. The relative amplitude ratios of the nitrogen splittings in the MAHH–Cu(II) complex are appreciably different from the expected value (1:4:10:16:19:16:10:4:1) for four magnetically equivalent nuclei. The discrepancy is not due to noncoincidence of lines from the two isotopes ^{63}Cu and ^{65}Cu but to the presence of nonequivalent nitrogen atoms. The space-filling molecular model also supports a square-pyramidal configuration with axial imidazole coordination for the 1:1 MAHH–Cu(II) complex. Table II lists the values of the ESR and bonding parameters estimated for these peptide–copper(II) complexes. These Cu(II) complexes have similar $g_{\parallel}$, $g_{\perp}$, and g_0 values. In general, the copper hyperfine coupling constant ($A_{\parallel}$) in the parallel region decreases with introduction of a sulfur donor. Of special interest is that the $A_{\parallel}$ value of the MAHH–Cu(II) complex is quite similar to those of galactose oxidase ($A_{\parallel}$ = 176.5 G)[18] and the glutathione–copper(II) complex (177.2 G),[19] in which axial coordination by a π-bonding ligand is suggested. The small $A_{\parallel}$ parameter is indicative of reduced electron density along the perpendicular axial of the copper site. For these peptide–copper(II) complexes, on the basis of the bonding parameters estimated, the following bonding scheme is proposed: moderately covalent σ bonding with α^2 values of about 0.8, strongly covalent in-plane π bonding with β_1^2 values of about 0.6, and very weakly covalent out-of-plane π bonding with β^2 values of about 1.0. The small β_1^2 and β^2 values of the MAGGG–Cu(II) complex can be explained by attributing most of the covalent character of the in-plane and out-of-plane π bonding to the deprotonated peptide nitrogens. The bonding to amino- and pyridine-type nitrogens has been reported to be mostly ionic in character.[14] In general, these results suggest that σ-bonding character between Cu(II) and the ligand increases, and the bonding between Cu(II) and the ligand p orbital in the ligand plane decreases by exchange of the amino group for the sulfhydryl group.

The binding energy obtained for the 1:1 MAGH–Cu(II) complex was as follows: Cu $2p_{3/2}$ = 932.1 (main peak) and 943.5 (satellite), S 2p = 163.0 (main peak) and 167.4 (minor peak), N 1s = 399.2, and O 1s = 530.8 eV (see Figure 4). The result of XPS reveals that the sulfur has been polarized by an electron transfer from negative sulfur to copper, the electron is located near the copper, and the copper appears to be present in the oxidation state near +1. However, this

Table III. Proton Chemical Shifts of Tripeptides and Their Cu(II) and Ni(II) Complexes

Compd	Proton chem shift, ppm									
	α_1	α_2	α_3	α_4	β	β'	Im_4	Im'_4	Im_2	Im'_2
	3.21	3.90	4.40		3.07		6.93		7.70	
1:1 Cu(I) complex	3.99	3.92	4.43		3.19		7.16		8.31	
1:1 Ni(II) complex	3.40	4.12	4.29		2.96 2.70		6.64		6.95	
	3.23	3.40	2.48	4.44	3.14		6.96		7.77	
1:1 Cu(I) complex	3.81	3.45	2.52	4.47	3.20		7.21		8.45	
1:1 Ni(II) complex	Not resolved for broadening									
	3.28	4.00	3.79							
1:1 Cu(I) complex	3.94	4.05	3.81							
	3.29	4.02	4.02	3.78						
1:1 Cu(I) complex	3.96	4.08	4.05	3.80						
	3.26	4.50	4.32		3.10	3.21	7.00	7.06	7.90	8.07
1:1 Cu(I) complex	3.83	4.58	4.42		3.18	3.30	7.18	7.22	8.39	8.47

copper complex is actually ESR active and paramagnetic. Virtually all sulfur is detectable at 163.0 eV. Due to the polarization of the sulfur by the S–Cu(II) coordination, the somewhat elevated binding energy of the sulfur can be explained. The minor sulfur signal at 167.4 eV may be not due to some oxidized thiolate sulfur (RSO_3^-) but to a satellite of the S 2p signal. It has been a matter of argument as to whether or not the higher binding energy component in the S 2p levels of blue copper proteins arises from sulfur coordinated to copper or oxidized sulfur,[20] and further investigations are necessary to clarify this point. In general, the coordination of copper with a free amino group shifts the N 1s binding energies to higher values (399.9–400.4 eV), reflecting a decrease in electron density at the nitrogen atoms.[21] The N 1s binding energy (399.2 eV) of the MAGH–Cu(II) complex is close to that (398.9 eV) of the violet bis(biureto)–copper(II) complex in which copper is coordinated to four deprotonated amide nitrogen atoms. The present low binding energy of the N 1s is consistent with the structure of the Cu(II) complex coordinated by deprotonated peptide nitrogen atoms (see Figure 5). The O 1s binding energies of amino acid–copper(II) complexes and free amino acids are in the ranges of 531.2–532.2 and 530.5–531.0 eV, respectively.[21] The O 1s binding energy (530.8 eV) of the MAGH–Cu(II) complex suggests the presence of uncoordinated oxygen atoms.

From the result of a preliminary potentiometric titration of MAGH·HCl with KOH solution, the acid dissociation constants of the ligand were determined as follows: pK_{COOH} = 3.47, pK_{Im} = 7.10, and pK_{SH} = 8.65 (μ = 0.1 and 20 °C). The titration curve of the 1:1 MAGH·HCl–Cu(II) system gave a clear pH inflection at a = 5.0 (a = moles of base per metal). The finding strongly indicates deprotonations from two amide groups of the peptide linkage. The formation and ionization constants estimated for the 1:1 MAGH–Cu(II) complex were log K_1 = 8.03 and pK_{2c} = 11.41, respectively.[22] At a constant pH, the relative stability ($K_1K_{2c}/[H^+]^2$) of the MAGH–Cu(II) complex paralleled that of the 1:1 GGH–Cu(II) complex.[23]

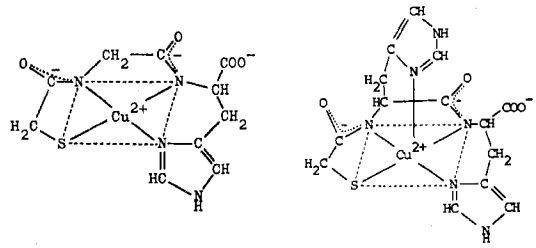


Figure 5. 1:1 Cu(II) complexes of MAGH (left) and MAHH (right).

For the 1:1 Cu(II) complexes of MAGH and MAHH, therefore, these experimental results and the molecular model support the structural assignment shown in Figure 5. MAGH has a Cu(II) binding site of a square-planar configuration and MAHH has that of a square-pyramidal configuration with axial imidazole coordination. The X-ray crystallographic studies of the 1:1 GGH–*N*-methylamide–Cu(II) and GGH–Cu(II) complexes show that the copper is tetradentately chelated by the terminal amino nitrogen, the next two peptide nitrogens, and a histidine nitrogen of the tripeptide molecules in a slightly distorted square-planar arrangement.[24]

The Ni(II) complex, prepared as its Cu(II) analogue using a 1:1 MAGH/Ni(II) molar ratio, was then investigated in order to confirm the structural information. The magnetic moment (diamagnetic) and visible absorption spectrum [317 (ϵ 650) and 430 nm (ϵ 290)] of the 1:1 MAGH–Ni(II) complex demonstrate that this complex possesses a square-planar geometry. The ^1H NMR spectral data of the MAGH–Ni(II) complex is shown in Table III. The histidine residual methylene protons (β) of MAGH only were observed as a single peak at 3.07 ppm. On the other hand, the methylene protons of the 1:1 MAGH–Ni(II) complex appeared as two signals at 2.96 and 2.70 ppm, indicating the formation of a complex with a rigid configuration. Similar

proton splitting of the methylene protons has already been observed in the Ni(II) complexes of several sulfhydryl-containing dipeptides.[16] In the potentiometric titration curve of the 1:1 MAGH·HCl–Ni(II) system, the pH inflection at $a = 5.0$ reveals deprotonations from two amide groups of the peptide linkages. For the 1:1 MAGH–Ni(II) complex, therefore, the coordination mode similar to the corresponding Cu(II) complex is reasonably proposed.

Cu(I) Complexes. In the present work, ^{1}H NMR techniques which give direct structural information on complexes containing a d^{10} ion such as Cu(I) were employed. Cu(I) complexes of the sulfhydryl- and imidazole-containing peptides were prepared by reduction of their Cu(II) complexes with sodium dithionite.[25] In a typical preparation, $CuCl_2 \cdot 2D_2O$ (0.1 M) was added to 2.0 mL of D_2O (pD 9.2) containing the ligand (0.1 M), and the red-brown Cu(II) complex obtained was reduced by the addition of powdered $Na_2S_2O_4$ (0.3 M). Part of the pale yellow solution was then transferred to an NMR tube and the remaining portion was used for pH measurement. ^{1}H NMR spectra of the free ligand plus sodium dithionite were examined in the absence of the metal ion as appropriate controls. The Cu(I) complexes showed no absorption maxima in the visible spectra and exhibited no positive signals in the ESR spectra. Table III summarizes the data of the proton chemical shifts for the sulfhydryl-containing tripeptides and their Cu(I) complexes, together with the 1:1 MAGH–Ni(II) complex. The fine structure of the peaks of the imidazole ring protons and the sharpness of the proton signals in the spectra of the Cu(I) complexes indicate that the concentration of Cu(II) in the solution is negligibly small. In the 1:1 Cu(I) complexes of MAGG and MAGGG, the only chemical shift appreciably affected by the complexation is that of the α_1 proton. These peptides probably form a linear μ-thiolato complex oligomer $[Cu^I SR]_n^-$ which is popularly observed in monodentate alkyl mercaptans.[26] In the 1:1 Cu(I) complexes of MAGH and MAAH, on the other hand, the peaks affected by complexation are those of the imidazole ring (Im_4 and Im_2) and α_1 protons. The large shift of the α_1 proton signal to low field indicates clearly the coordination of the sulfhydryl group toward Cu(I). In the values of their chemical shifts for the imidazole ring protons, Im_2 is closer to that of the protonated ligand (Im_2 = 8.63–8.67 ppm) than to that of the neutral ligand (Im_2 = 7.66–7.78 ppm), and Im_4 is intermediate between those of the protonated (Im_4 = 7.33–7.35 ppm) and neutral (Im_4 = 6.92–6.99 ppm) ligands.[25,27] The chemical shifts of the imidazole protons are known to be quite sensitive to changes of the net charge present on the ring. Therefore, the major cause of chemical shift differences among the imidazole ring protons in the protonated and neutral ligands and Cu(I) complexes is the influence of the positive charge from either H^+ or Cu^+. The present result is explained in terms of the sharing of one positive charge (Cu^+) by the imidazole (Im_2) nitrogen. The α_2, α_3, and α_4 proton chemical shifts of these ligands are affected little by Cu(I) complexation. Accordingly, the amide groups are not involved in the complexation of Cu(I) with MAGH and MAAH. In the 1:1 MAHH–Cu(I) complex, the large shift of α_1 to low field and the chemical shifts of all imidazole ring protons (Im_2, Im'_2, Im_4, Im'_4) to high field were observed. In addition, the α_2, α_3, β, and β' proton signals appreciably shifted to low field, although their chemical shifts were small. The result suggests that the amide groups together with one sulfhydryl and two imidazole groups participate in the coordination of Cu(I) in the 1:1 MAHH–Cu(I) complex. The presence of axial imidazole coordination may maintain five coordinations even in the Cu(I) state. In contrast with square-planar configuration, square-pyramidal arrangement is known to be favored in the Cu(I) complexes. Sulfhydryl sulfur and imidazole nitrogen are clearly good donor atoms not only for Cu(II) but also for Cu(I).

It is well-known that human (or bovine) albumin has a specific Cu(II) transport site with histidine as the third amino acid residue Asp–Ala–His,[28] and its Cu(II) complex is very similar to the 1:1 GGH–Cu(II) complex.[1] The peptide GGH approximates closely to albumin in total Cu(II)-binding ability and the tripeptide is able to compete with albumin for Cu(II).[29] In the 1:1 MAGH–Cu(II) complex, the terminal amino group of the GGH–Cu(II) complex is substituted by the sulfhydryl group. Furthermore, in MAHH the second glycine component in MAGH is substituted by histidine and MAHH forms a unique square-pyramidal Cu(II) complex with axial imidazole coordination. These artificial sulfhydryl-containing tripeptides with a histidine component in the third position of the molecular sequence are specially suitable to achieve the proper ligand geometry for copper binding and to counteract the copper accumulation. In fact, MAGH and MAHH, as well as GGH, are new synthetic peptides with an albumin-like binding site toward Cu(II). In addition, MAGH and MAHH, as well as D-penicillamine, can form stable complexes with not only Cu(II) but also Cu(I), whereas the chelators GGH and triethylenetetramine bind exclusively to Cu(II).[30] This versatility of MAGH and MAHH in chelation of the copper ion may result in a marked reduction of the tissue stores of copper in Wilson's disease.

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Registry No. $[MAGG\text{-}Cu(II)]^{2-}$, 66523-77-1; MAGH-Cu(II)·2Na, 66523-79-3; MAHH-Cu(II)·2Na, 66552-51-0; $[MAGGG\text{-}Cu(II)]^{3-}$, 66523-82-8; $[GGG\text{-}Cu(II)]^{1-}$, 34803-37-7; $[GGH\text{-}Cu(II)]^{1-}$, 53554-01-1; $[GGGG\text{-}Cu(II)]^{1-}$, 57692-61-2; $[MAGH\text{-}Cu(I)]^{3-}$, 66523-85-1; $[MAAH\text{-}Cu(I)]^{3-}$, 66523-86-2; $[MAGG\text{-}Cu(I)]^{3-}$, 66523-87-3; $[MAGGG\text{-}Cu(I)]^{4-}$, 66552-52-1; $[MAHH\text{-}Cu(I)]^{3-}$, 66523-84-0; MAGH, 66516-06-1; MAAH, 66516-07-2; MAGG, 66516-08-3; MAGGG, 66516-09-4; MAHH, 66516-10-7.

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(MAGH); C, 34.32; H, 3.29; N, 17.15; Cu, 12.97 (MAHH). Found: C, 27.91; H, 3.48; N, 13.02; Cu, 15.14 (MAGH); C, 34.16; H, 3.47; N, 17.03; Cu, 13.11 (MAHH).
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(22) The K_1 and K_{2c} are defined as follows: $K_1 = [CuL]/[Cu^{2+}][L^{2-}]$ and $K_{2c} = [CuX^{2-}][H^+]^2/[CuL]$. The X represents the ligand form deprotonated from two peptide linkages.
(23) On the basis of similar potentiometric measurements, the acid dissociation and formation constants of GGH and its 1:1 Cu(II) complex were estimated: $pK_{COOH} = 2.84$, $pK_{Im} = 6.87$, $pK_{NH_3}{}^+ = 8.22$, $\log K_1 = 5.32$, and $pK_{2c} = 8.37$.
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Studies of the Cubane Cluster of Copper(I). A Modified Self-Consistent Charge and Configuration Molecular Orbital Investigation of the Cluster Containing the $Cu_8S_{12}{}^{4-}$ Core

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A molecular orbital study of the modified self-consistent charge and configuration type (SCCC) was performed on a model of a general class of cube copper clusters containing the nuclear core $Cu_8S_{12}{}^{4-}$, where the sulfur atoms are distributed (in a distorted cuboctahedral manner) above the edges of a cube formed by copper atoms. In the study the basis set was chosen to consist of copper 3d, 4s, and 4p and sulfur 3s and 3p atomic orbitals. The results of the calculations, which are compared with those of the observed electronic spectrum, show no net bonding Cu–Cu interaction with this model. The predicted lowest energy electronic transition is charge transfer, of the type S(3p) → Cu(4s, 4p). The highest filled molecular orbitals are sulfur in character and are antibonding. The lowest energy empty orbital is primarily a mixture of copper 4s and 4p and sulfur 3p orbitals. A cyclovoltammetric study of one tetraanionic cluster shows numerous high redox potential peaks. However, none are reversible and the cluster appears to decompose after repeated redox cycles, with the concomitant deposition of the oxidized ligand.

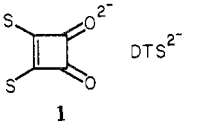
Introduction

The appearance of relatively short intermetallic separations in reported structures of copper(I) cluster complexes[1] has posed the intriguing question "Are there metal–metal bonds in such d^{10} systems?" A simple view which recognizes that closed-shell repulsions preclude attractive interactions suggests the absence of such bonds.[2] Yet at the 2.38-Å Cu–Cu separation found in (4-methyl-2-cupriobenzyl)dimethylamine,[1a] which is nearly 0.2 Å shorter than bond lengths in copper metal,[3] it seems likely that attractive interactions exist. However, given that all reported Cu clusters possess bridging ligands, it is not clear what role the stereochemical requirements of the ligands play in producing the apparent M–M interactions.

To improve our own understanding of the bonding in these multinuclear d^{10} systems, we performed a modified self-consistent charge and configuration (SCCC) molecular orbital study of one particular class of copper clusters,[4] those containing the core $Cu_8S_{12}{}^{4-}$. A study on copper(I) dimeric clusters has been recently performed by Mehrotra and Hoffmann.[5]

Slater and Johnson[21] briefly describe an Xα calculation on the neutral unit Cu_8. Since copper atoms in this case appear to have the configuration $d^{10}s$, some difficulty arises in direct comparison to our work. However, the general features of a closely spaced d band are similar.

The general class of octanuclear clusters which possess the Cu_8S_{12} core consists of at least three structurally characterized[6,7] members, $Cu_8(i\text{-MNT})_6{}^{4-}$, $Cu_8(DED)_6{}^{4-}$, and $Cu_8(DTS)_6{}^{4-}$, where i-MNT^{2-} = 1,1-dicyanoethylene-2,2-dithiolate, DED^{2-} = dicarboethoxy-2,2-ethylenedithiolate, and DTS^{2-} = dithiosquarate, **1**. In each of these complexes eight



1

copper(I) ions are arranged at the corners of a nearly perfect cube which is inscribed into a distorted cuboctahedron defined by the 12 sulfur atoms from six dithiolate ligands. In all cases the shortest Cu–Cu distances are approximately 2.8 Å. Since the central core Cu_8S_{12} can be viewed to have the point symmetry O_h (if one approximates the sulfur atoms to be situated directly above the edges of the cube), the theoretical study of such an esthetically intriguing class of compounds is considerably simplified by the use of group theory.

Hollander and Coucouvanis[7] presented an interesting structural view of the stability of such clusters. Presently, we will attempt to deal with the problem in the context of molecular orbital theory. In order to help visualize the Cu_8S_{12} geometry contained in these "cubane" clusters, an ORTEP stereodrawing of the $Cu_8(DTS)_6{}^{4-}$ with its approximate T_h symmetry is presented in Figure 1.

Method of Calculation

The bonding model to be discussed idealizes the clusters in the following way. The sulfur atoms are considered to be cuboctahedrally arranged above the edges of a cube of copper atoms, thus forming the hypothetical species $Cu_8S_{12}{}^{4-}$, of point group O_h, where the remaining portion of the ligand is ignored. The basis set consists of 120 atomic orbitals (AO), distributed

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