Copper(II)-Sulfur Interactions in Pyridine- and Imidazole-containing Disulfide Complexes. Syntheses, Spectra, and Solution Equilibria

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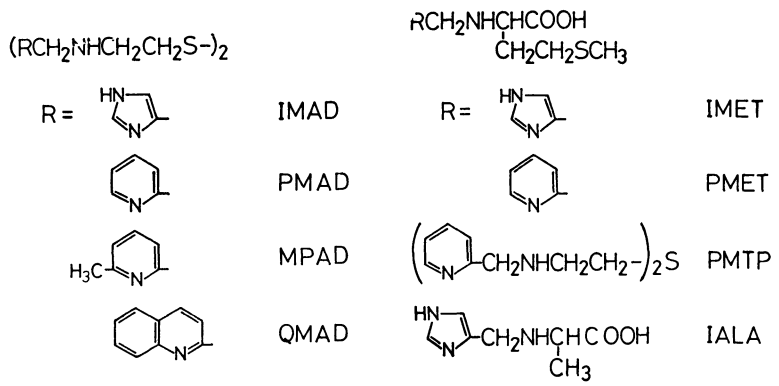
Synthetic, spectroscopic, and potentiometric studies on the copper(II) complexes of pyridine-, quinoline-, and imidazole-ring-containing disulfides and related compounds have been made with emphasis on copper(II)-sulfur interactions. In the presence of copper(II), disulfide ligands, $(RCH_2NHCH_2CH_2S-)_2$, where R=4-imidazolyl (IMAD), 2-pyridyl (PMAD), 6-methyl-2-pyridyl (MPAD), and 2-quinolyl (QMAD), are more stable in acid solution than in neutral-alkaline solution. A stable 1:1 copper(II) complex, $Cu(IMAD)(ClO_4)_2 \cdot H_2O$, was isolated as crystals from aqueous solution, whereas a binuclear complex, $Cu_2(PMAD)Cl_4$, was obtained as crystals in ethanol. The Cu(II)-IMAD systems exhibit a single d-d peak at 585 nm indicative of a CuN_4 chromophore but no charge transfer (CT) band in the region 300—900 nm. The other Cu(II)-disulfide systems exhibit d-d bands at 650 and $\approx$850 nm. A shoulder at 310—330 nm observed for the Cu(II)-PMAD and -MPAD systems at pH $\approx$4 and $>$6, respectively, is assigned to the S$\rightarrow$Cu(II) CT transition. Thioether ligands, *N*-(2-pyridylmethyl)-L-methionine and *N*-(4-imidazolylmethyl)-DL-methionine, show the S$\rightarrow$Cu(II) CT peak at $\approx$310 nm at pH 9 in the 1:1 Cu(II)-ligand systems. Equilibrium constants of the proton-ligand and Cu(II)-ligand systems were determined by pH titrations at 25 °C and I=0.1(KNO_3). The Cu(II)-disulfide systems were analyzed by considering monomeric species CuL, CuLH, and $CuLH_2$ (L=ligand; H=proton) and a binuclear species Cu_2L; the $\log \beta_{110}$ values for CuL are 13.38, 13.32, and 9.46 for L=IMAD, PMAD, and MPAD, respectively. Conductivity measurements showed that the Cu(II)-IMAD complex isolated as crystals is monomeric in aqueous solution. Comparison of the electronic absorption and electron spin resonance spectral data and stability constants for various systems suggests that Cu(II)-PMAD has a square-pyramidal CuN_4S chromophore with a sulfur atom in an equatorial position, whereas Cu(II)-IMAD has a planar CuN_4 chromophore. The stability of disulfide bonds in copper(II) complexes in aqueous solution is briefly discussed on the basis of the modes of coordination.

Sulfur as a soft Lewis base is an important ligand atom in various metal complexes and is now established as a constituent of the biological copper site in plastocyanin[1] and azurin,[2] where copper is bound to a thiolate and a thioether sulfur and two imidazole nitrogens. For the copper(I)/copper(II) redox systems, the binding site should have a proper affinity for both oxidation states, and combination of sulfurs and aromatic nitrogens around copper in the proteins may be a necessary consequence.

Disulfide sulfurs, on the other hand, have been postulated to be involved in the copper binding in stellacyanin.[3-5] Because of the coordinating ability of sulfur and the redox activities of copper and disulfide groups,[6-8] copper–disulfide systems may play a unique role in biological systems. Disulfide and thioether groups usually exhibit weak ligation toward copper (II)[9] unless effective neighboring donor groups force them to be in the vicinity of copper(II). The interactions of copper(I) and copper(II) with multidentate disulfide ligands are particularly intriguing because (i) the disulfide group involved in a multidentate ligand with aromatic nitrogens and other donor groups may coordinate to copper to form a binuclear or a dimeric complex of potential biological significance and (ii) it may participate in redox reactions with copper(I) and/or copper(II) upon complex formation. Lewis acids such as silver(I) and mercury(I) are known to cleave disulfide bonds.[10] Seff and his collaborators found that the reaction of copper(II) with di-2-pyridyl disulfide gives the corresponding copper(I)-disulfide complex as the main product and a small amount of the copper(II) complex of 2-pyridinesulfinate.[11] We have recently observed that a pyridine-containing disulfide, bis[2-(2-pyridylmethylamino)-ethyl] disulfide (PMAD), reacts with copper(II) under aerobic conditions to give the copper(II) complex of 2-(2-pyridylmethylamino)ethanesulfinate[12] and that the oxygen atoms from molecular oxygen are partly incorporated into the sulfinate moiety.[13] Since



such reactions of disulfide ligands depend much on their structures, the modes of copper(II)–disulfide interactions would have a crucial effect on the stability of the disulfide bond in aqueous solution.

In view of the potential importance of the structural and functional properties expected for copper–disulfide systems and the paucity of relevant information, we now investigated the properties of the copper(II) complexes of disulfide and related ligands involving pyridine, quinoline, and imidazole rings in order to acquire basic information of the modes of copper(II)–sulfur interactions and their effects on the complex and disulfide bond stabilities in solution. We initiated this study on the presumption that only the complexes with weak or no disulfide sulfur–copper(II) interactions are stable in aqueous solution, whereas those with strong interactions suffer disulfide bond cleavage.

Experimental

Materials. 2-Pyridinecarbaldehyde was obtained from Tokyo Kasei Kogyo, and cystamine (bis(2-aminoethyl) disulfide) dihydrochloride and methyl L-alaninate hydrochloride from Nakarai Chemicals. Methyl L-methioninate was purchased from Sigma. 4-Imidazolecarbaldehyde was prepared from 4-(hydroxymethyl)imidazole hydrochloride by oxidation with nitric acid.[14] 1.9-Di-2-pyridyl-2,5,8-triazanonane (PDIEN) trihydrochloride[15] was prepared by reducing the Schiff base obtained from 2-pyridinecarbaldehyde and diethylenetriamine. All the materials used were of reagent grade, and distilled and deionized water was used throughout.

Syntheses.[16] *Bis[2-(4-imidazolylmethylamino)ethyl] Disulfide (IMAD)*: To a solution of cystamine dihydrochloride (11.26 g, 0.050 mol) in ethanol was added potassium hydroxide (5.61 g, 0.10 mol) dissolved in methanol, and the resulting inorganic salt (KCl) was removed by filtration. 4-Imidazolecarbaldehyde (9.60 g, 0.10 mol) in methanol was added to the filtrate, which was stirred for 30 min at 40—50 °C. A solution of $NaBH_4$ (3.8 g, 0.1 mol) in methanol was then added dropwise to the solution under cooling. The reaction mixture was neutralized with 1 M HCl (M= mol dm^{-3}), concentrated *in vacuo*, and extracted with methanol. Dry HCl gas was bubbled through the extract in methanol, when colorless crystals separated. These were filtered, washed with ethanol, and recrystallized from methanol to give IMAD·3HCl·H_2O in 80% yield. Found: C, 32.89; H, 5.73; N, 19.11; Cl, 24.18; S, 14.58%. Calcd for $C_{12}H_{23}N_6Cl_3S_2\cdot H_2O$: C, 32.89; H, 5.76; N, 18.94; Cl, 24.15; S, 14.56%.

Bis[2-(2-pyridylmethylamino)ethyl] Disulfide (PMAD):[17] This disulfide was obtained as tetrahydrochloride in the same manner from cystamine dihydrochloride (11.26 g, 0.050 mol) and 2-pyridinecarbaldehyde (10.8 g, 0.10 mol) in 70% yield. Mp 167 °C (decomp). Found: C, 38.28; H, 5.40; N, 11.39; Cl, 28.49; S, 12.84%. Calcd for $C_{16}H_{26}N_4Cl_4S_2\cdot H_2O$: C, 38.56; H, 5.66; N, 11.24; Cl, 28.46; S, 12.87%.

Bis[2-(6-methyl-2-pyridylmethylamino)ethyl] Disulfide (MPAD): This was prepared in methanol in the manner described for IMAD from cystamine dihydrochloride (4.68 g, 0.021 mol) and 6-methyl-2-pyridinecarbaldehyde (5.05 g, 0.042 mol) and recrystallized from methanol–ethanol. Yield, 25%; mp 191—193 °C. Found: C, 40.03; H, 6.30; N, 10.06%. Calcd for $C_{18}H_{30}N_4Cl_4S_2\cdot 2H_2O$: C, 39.71; H, 6.29; N, 10.29%.

Bis[2-(2-quinolylmethylamino)ethyl] Disulfide (QMAD): This was prepared in tetrahydrofuran–methanol in an analogous manner from cystamine dihydrochloride (5.54 g, 0.024 mol) and 2-quinolinecarbaldehyde (7.60 g, 0.048 mol) and recrystallized from ethanol. Yield, 10%; mp 199—200 °C. Found: C, 56.53; H, 5.56; N, 10.79%. Calcd for $C_{24}H_{28}N_4Cl_2S_2$: C, 56.79; H, 5.56; N, 11.04%.

Bis[2-(2-pyridylmethylamino)ethyl] Sulfide (PMTP):[18,19] To a solution of bis(2-aminoethyl) sulfide dihydrochloride (9.65 g, 0.050 mol) in anhydrous ethanol was added potassium hydroxide (5.6 g, 0.1 mol) in ethanol under N_2. After the inorganic salt was quickly removed by filtration, 2-pyridinecarbaldehyde (10.8 g, 0.1 mol) was added to the filtrate and the mixture was stirred for 10 min at room temperature. Reduction with $NaBH_4$ (3.8 g, 0.1 mol) and isolation as a hydrochloride were performed in the manner described for IMAD. Repeated recrystallization from ethanol gave PMTP·2HCl·H_2O as a pale yellow powder, mp 148 °C, in 60% yield. Found: C, 48.89; H, 6.20; N, 14.14; Cl, 18.95; S, 7.91%. Calcd for $C_{16}H_{24}N_4Cl_2S\cdot H_2O$: C, 48.85; H, 6.66; N, 14.24; Cl, 18.10; S, 8.15%.

N-(4-Imidazolylmethyl)-DL-methionine (IMET): A solution of methyl L-methioninate in methanol, prepared from the hydrochloride (11.75 g, 0.050 mol) and potassium hydroxide (2.81 g, 0.050 mol) in methanol, was added dropwise to a solution of 4-imidazolecarbaldehyde (4.80 g, 0.050 mol) in methanol. The mixture was stirred for 1—2 h at 30—40 °C, cooled, and treated with $NaBH_4$ (1.90 g, 0.050 mol) in methanol and then with 1 M HCl as described for IMAD. Sodium hydroxide (2.0 g, 0.05 mol) dissolved in water was added to the mixture, which was stirred for 30 min at room temperature, acidified with hydrochloric acid, and concentrated *in vacuo*. The residue was extracted several times with methanol and concentrated *in vacuo*. Recrystallization from methanol containing hydrochloric acid gave IMET·HCl as a colorless powder, mp 240—242 °C (decomp), in 80% yield. Found: C, 40.71; H, 6.12; N, 16.21; Cl, 12.61; S, 11.62%. Calcd for $C_9H_{16}N_3O_2ClS$: C, 40.68; H, 6.07; N, 15.81; Cl, 13.34; S, 12.06%. The Cu(II)–IMET systems did not give the expected circular dichroism (CD) spectral peaks in the d-d region, and accordingly IMET·HCl is described as a racemic mixture.

N-(2-Pyridylmethyl)-L-methionine (PMET): This was prepared in 80% yield in the manner described for IMET from methyl L-methioninate hydrochloride (11.75 g, 0.050 mol) and 2-pyridinecarbaldehyde (5.36 g, 0.050 mol). Recrystallization from ethanol gave PMET as a colorless powder, mp 219—220 °C (decomp). Found: C, 54.98; H, 6.72; N, 11.33; S, 13.34%. Calcd for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71; N, 11.66; S, 13.83%.

N-(4-Imidazolylmethyl)-L-alanine (IALA): This was prepared similarly from methyl L-alaninate hydrochloride (4.00 g, 0.025 mol) and 4-imidazolecarbaldehyde (2.4 g, 0.025 mol) in 50% yield. Recrystallization from methanol gave IALA·HCl·H_2O as a colorless powder, mp 215 °C (decomp). Found: C, 37.59; H, 6.31; N, 18.79%. Calcd for $C_7H_{12}N_3O_2Cl\cdot H_2O$: C, 37.05; H, 6.06; N, 18.32%.

[Cu(IMAD)](ClO$_4$)$_2$·H$_2$O: A concd solution of Cu$(ClO_4)_2\cdot 6H_2O$ (3.7 g, 0.01 mol) in water was added to a solution of IMAD·3HCl·H_2O (4.4 g, 0.01 mol) in water, and the pH of the resulting solution was adjusted at ≈6.0 with 2 M NaOH. The deep blue solution was passed through a column packed with Amberlite IRA-410 ion exchange resin in the ClO_4^- form and stored at 10—15 °C, when dark violet crystals separated. Recrystallization from water gave pure crystals of [Cu(IMAD)]$(ClO_4)_2\cdot H_2O$. Found: C, 24.41; H, 3.89; N, 14.26%. Calcd for $C_{12}H_{20}N_6O_8Cl_2CuS_2\cdot H_2O$: C, 24.31; H, 3.74; N, 14.18%.

Attempts to isolate pure complexes from solutions containing Cu(II) and IMAD in the molar ratio of 2:1 were unsuccessful.

[Cu$_2$(PMAD)]Cl$_4$: To a solution of PMAD·4HCl·H$_2$O (5.0 g, 0.01 mol) in ethanol (50 ml) was added with stirring a solution of CuCl$_2$·2H$_2$O (3.4 g, 0.02 mol) in ethanol (20 ml). The pale blue precipitate which separated from the solution was filtered and washed with ethanol. Found: C, 31.56; H, 3.69; N, 9.31; Cl, 23.43; S, 10.57%. Calcd for $C_{16}H_{22}N_4Cl_4Cu_2S_2$: C, 31.85; H, 3.67; N, 9.29; Cl, 23.50; S, 10.67%.

[Cu(PMET)]ClO$_4$·H$_2$O: To a solution of PMET (2.4 g, 0.01 mol) in aqueous methanol was added a solution of Cu(ClO$_4$)$_2$·6H$_2$O (3.7 g, 0.01 mol) in methanol. The resulting solution was neutralized with 1 M NaOH and kept in a refrigerator, when greenish blue crystals separated. These were recrystallized from methanol. Found: C, 31.25; H, 4.19; N, 6.32%. Calcd for $C_{11}H_{15}N_2O_6ClCuS\cdot H_2O$: C, 31.43; H, 4.08; N, 6.66%.

[Cu(PDIEN)](ClO$_4$)$_2$: PDIEN·3HCl (3.9 g, 0.01 mol) and Cu(ClO$_4$)$_2$·6H$_2$O (3.7 g, 0.01 mol) were dissolved in water, and the pH of the resulting solution was adjusted at ≈7.0. The blue violet solution was passed through a column packed with Amberlite IRA-410 ion exchange resin in the ClO_4^- form and kept at room temperature, when blue violet needles separated. Found: C, 34.93; H, 4.10; N, 12.72%. Calcd for $C_{16}H_{23}N_5O_8Cl_2Cu$: C, 35.07; H, 4.24; N, 12.79%.

Spectroscopic Measurements. Absorption spectra were measured in water with a Hitachi 323 and a Union Giken SM-401 high-sensitivity recording spectrophotometer and CD spectra with a JASCO MOE-1 spectropolarimeter, the concentrations of samples being 1—4 mM for visible and 0.1—0.8 mM for ultraviolet spectral measurements. Electron spin resonance (ESR) spectra were measured for 4—5 mM solutions with JEOL FE-3X and FE-1X ESR spectrometers.

Conductivity Measurements. Conductivities of various copper(II) complexes were measured in water at 25 °C under N_2 with a Kyoto Denshi CM-07 conductivity meter calibrated with 0.01 M potassium chloride.

pH Titrations. *Reagents*: Carbonate-free 0.1 M KOH was prepared according to the method of Armstrong[20] and standardized against standard potassium hydrogen phthalate (Merck DIN 19226). Copper(II) nitrate (0.01 M) was prepared from Cu(NO$_3$)$_2$·3H$_2$O and standardized by chelatometry using metallic zinc (JIS primary standard) as standard.

Apparatus and Procedure: Measurements of pH were made with an Orion Research 901 ion meter equipped with an Orion 90-01-00 glass electrode and a 91-02-00 double junction reference electrode. The meter was calibrated with NBS standard buffer solutions (4.008, 7.413, and 9.180 at 25 °C). Conversion of pH meter reading (pH_M) to $-\log$ [H], where [H] refers to hydrogen ion concentration, was made by correcting the difference (0.060) between pH_M and $-\log$ [H] obtained by titrating 0.01 M HNO_3 with 0.1 M KOH at the ionic strength (I) of 0.1 M (KNO_3). The hydroxide ion concentration [OH] was calculated from the apparent ion product of water $pK_w' = 13.91$ ($= pH_M - \log$ [OH]) determined by titrating 0.1 M KNO_3 with 0.1 M KOH. Titrations were performed at 25±0.05 °C under N_2 for solutions containing a ligand only and those containing a ligand and Cu(II) in the molar ratio of 1:1, 1:2, and 2:1. Reproducibility was checked by multiplicate titrations.

Calculation of Equilibrium Constants. The equilibria in the present systems and the relevant equilibrium constants, β_{pqr}, are defined by Eqs. 1 and 2, respectively (charges are omitted for simplicity):

$$p\mathrm{Cu} + q\mathrm{L} + r\mathrm{H} \overset{\beta_{pqr}}{\rightleftharpoons} \mathrm{Cu}_p\mathrm{L}_q\mathrm{H}_r, \quad (1)$$

$$\beta_{pqr} = \frac{[\mathrm{Cu}_p\mathrm{L}_q\mathrm{H}_r]}{[\mathrm{Cu}]^p[\mathrm{L}]^q[\mathrm{H}]^r}, \quad (2)$$

where p, q, and r are the numbers of moles of Cu(II), ligand (L), and proton (H) in the complex $Cu_pL_qH_r$, respectively, and a negative value of r denotes the deprotonation from the complex. Calculation of β_{pqr} was made by the method of nonlinear least-squares with the use of the computer program MINIQUAD[21] where the function minimized is the sums of squares of the residuals in the mass balance equations for total hydrogen ion, total metal, and total ligand. A graphical method[22] was used for calculation of the stability constants for Cu(II)–PMET and –PMTP for which the least-squares treatment was not effective because of the small pH changes with the addition of alkali.

The β_{110} value for Cu(II)–PMTP was calculated by Eq. 3 derived from the material balance equations and the electroneutrality of solution:

$$\beta_{110} = \frac{(A\alpha - C_L\beta)(3\alpha - \beta)}{[(3C_M - A)\alpha + (C_L - C_M)\beta](3C_L - A)}, \quad (3)$$

where

$$A = 3[\mathrm{CuL}] + 3[\mathrm{L}] + 2[\mathrm{HL}] + [\mathrm{H_2L}],$$

$$\alpha = 1 + [\mathrm{H}]/K_{a_3} + [\mathrm{H}]^2/K_{a_3}\cdot K_{a_2} + [\mathrm{H}]^3/K_{a_3}\cdot K_{a_2}\cdot K_{a_1},$$

and

$$\beta = 2[\mathrm{H}]/K_{a_3} + [\mathrm{H}]^2/K_{a_3}\cdot K_{a_2}.$$

The K_a values are acid dissociation constants. The equation for Cu(II)–PMET (Eq. 4) was derived in a similar way:

$$\beta_{110} = \frac{(2\alpha - \beta)(A\alpha - C_L\beta)[\mathrm{H}]^2}{[(2C_M - A)\alpha + (C_L - C_M)\beta](2C_L - A)}, \quad (4)$$

where

$$A = 2[\mathrm{CuL}] + 2[\mathrm{L}] + [\mathrm{HL}],$$

$$\alpha = 1 + [\mathrm{H}]/K_{a_2} + [\mathrm{H}]^2/K_{a_2}\cdot K_{a_1},$$

and

$$\beta = 2 + [\mathrm{H}]/K_{a_2}.$$

Results

Synthesis of Complexes. At pH>6 PMAD is decomposed by Cu(II) in the presence of dioxygen to give the Cu(II) complex of the sulfinate derived from PMAD.[12,13] Probably because of the cleavage and subsequent redox reactions, preparation of the Cu(II)–PMAD complex was not feasible in aqueous solution (pH≈7); in ethanol, however, PMAD·4HCl gave a binuclear complex of the composition, Cu$_2$(PMAD)Cl$_4$, as crystals. The imidazole-containing disulfide IMAD was less susceptible to the cleavage at pH 6—7, giving a 1:1 complex Cu(IMAD)(ClO$_4$)$_2$·H$_2$O which is stable in water. At higher pH it also affords the Cu(II)–sulfinate complex.[23] The methionine derivative PMET and the pyridine-containing diethylenetriamine derivative PDIEN gave the corresponding 1:1 complexes with Cu(II), but attempted isolation of the Cu(II)–PMTP and –IALA complexes was not successful under the conditions used.

Spectra. The Cu(II)–disulfide systems are relatively stable in acid solution. Figure 1 illustrates the absorption spectra of some 1:1 Cu(II)–ligand systems, and Tables 1 and 2 show the spectral data for various binary and ternary systems, respectively, in acid–neutral solution. The 1:1 and 2:1 Cu(II)–PMAD systems have an absorption peak at 650 nm and a shoulder at ≈330 nm at pH≈4, whereas the 1:1 and 1:2 Cu(II)–2-(aminomethyl)pyridine (ampy) systems have a peak at 650 and 585 nm, respectively. An additional band is observed at 850 nm as a shoulder for the 1:1 Cu(II)–PMAD system and the 2:1 system at pH<4.0. Interestingly, the peak at 650 nm of Cu(II)–PMAD remained unchanged on going from the 1:1 binary system to the 1:1:1 Cu(II)–PMAD–ampy ternary system. The isolated complex $Cu_2(PMAD)Cl_4$ exhibited a peak at 760 nm in dimethyl sulfoxide and at 660 nm in water (pH 4.2). The Cu(II)–MPAD and –QMAD systems show spectral behavior partly similar to those of Cu(II)–PMAD; the d-d peaks are observed at ≈650 nm, but the band in the region 300—350 nm appears only at pH>6 for the Cu(II)–MPAD system, while it is undetectable for the Cu(II)–QMAD

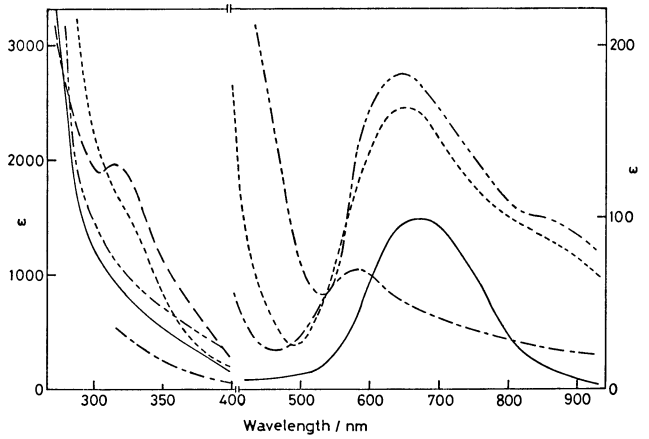


Fig. 1. Absorption spectra of 1:1 Cu(II)-ligand systems in water.
–––––: Cu(II)-IMAD (pH 5.0), ----: Cu(II)-PMAD (pH 4.5), ——–: Cu(II)-MPAD (pH 4.7), ——: Cu(II)-PMET (pH 7.0), — — —: Cu(II)-PMET (pH 8.9).

Table 1. Absorption spectral data for binary systems in water[a)]

Ligand	Cu(II):Ligand	pH	λ_{max}/nm	ε / M^{-1} Cu^{-1} cm^{-1}
IMAD	1:1	3.4	720	21
		3.7	630	32
		4.4	592	63
		5.0	585	70
	2:1	4.0	600	40
PMAD	1:1	3.5	330sh	1370
			650	137
			850sh	74
		4.5	330sh	1400
			650	164
			850sh	89
	2:1	3.4	330sh	580
			650	73
			850sh	45
		4.1	330sh	770
			650	82
		4.5	330	1100
			650	101
			750sh	85
	2:1[b)]	(DMSO)	760	99
		4.2	660	85
MPAD	1:1	4.0	660	56
			850sh	36
		4.7	650	184
			850sh	100
		6.2—7.0	310	3700
			650	177
MPAD			850sh	90
	2:1	4.0	680	39
		5.1—5.3	300sh	1840
			650	127
QMAD[c)]	1:1	3.3	790	20
		4.0	670	72
		5.0	650	184
			850sh	95
	2:1	4.0	690	33
		5.2	650	107
PMTP	1:1	7.0	320	3500
			600	190
			850	81
PMET[d)]	1:1	7.0	680	100
		8.8	307	1750
			680	100
IMET	1:1	7.2	670	108
		9.0	308	1600
			670	110
IALA[d)]	1:1	7.4	660	83
ampy[e)]	1:1	6.8	650	47
	1:2	6.3	585	76
bimen[f)]	1:1	6.5	585	110

a) sh=Shoulder. b) $Cu_2(PMAD)Cl_4$ in dimethyl sulfoxide (DMSO) and in water. c) The CT peak at 300—350 nm is undetectable because of the quinoline band. d) The CD spectral data, λ_{max}/nm ($\Delta\varepsilon$), for these systems are as follows: Cu(II)-PMET, 635 (−0.11) at pH 7.0 and 325 (-0.62) and 615 (−0.22) at pH 8.8; Cu(II)-IALA, 580 (-0.11) and 720 (0.11) at pH 7.4. e) ampy=2-(Aminomethyl)pyridine. f) bimen=*N*,*N*′-Bis(4-imidazolylmethyl)ethylenediamine.

TABLE 2. ABSORPTION SPECTRAL DATA FOR TERNARY SYSTEMS IN WATER[a)]

System	pH	λ_{max}/nm	ε/M^{-1} Cu^{-1} cm^{-1}
1:1:1 Cu(II)-IMAD-bpy	7.1	700br	75
		870sh	51
2:1:2 Cu(II)-IMAD-bpy	7.1	700	70
		870sh	48
1:1:1 Cu(II)-PMAD-ampy	4.1—4.3	330sh	1400
		650	139
		850sh	65
2:1:2 Cu(II)-PMAD-ampy	3.9—4.3	330sh	900
		650	100
		850sh	46
1:1:1 Cu(II)-PMAD-bpy	4.1	680	107
		850sh	64
2:1:2 Cu(II)-PMAD-bpy	4.1	680	96
		850sh	65

a) sh=Shoulder; br=broad.

system because of the strong quinoline peaks.

In the region 300—900 nm the 1:1 Cu(II)–IMAD system at pH 5 has a single peak at 585 nm with a normal intensity. The wavelength and molar absorption coefficient of the peak are not affected by concentrations of the solution covering the range 10^{-4}—10^{-2} M, suggesting that the 1:1 Cu(II)–IMAD complex has a monomeric structure with an N_4 donor set analogous to that of 1:2 Cu(II)–ampy and of 1:2 Cu(II)–4-(aminomethyl)imidazole (amim). The ESR spectrum shows at least seven resolved superhyperfine structures due to nitrogen donors, the g values, $g_{//}$= 2.23 and $g_{\perp}$=2.06, being typical of a tetragonal structure with axial symmetry (Table 3).

The 1:1 Cu(II)–PMTP system, where a thioether sulfur replaces the disulfide sulfurs of PMAD, exhibits a strong peak at 320 nm (ε=3500) and well-resolved d-d bands at 600 and 850 nm. The 320-nm peak has been assigned to the S→Cu(II) charge transfer (CT) transition,[18)] which is compatible with the equatorial S–Cu(II) bonding. Because no CT band is observed for the five-coordinate complex of PDIEN which is the nitrogen analog of PMTP, the chromophore of Cu(II)–PMTP is described as CuN_4S with an axial nitrogen coordination. Complexes of analogous pyridine-containing thioethers with CuN_2S_2 chromophores have been reported to show the S→Cu(II) CT band at 340—380 nm.[24)] The 1:1 systems with PMET and IMET give a d-d band at 670—680 nm corresponding with a CuN_2O_2 chromophore, but an additional band appears at ≈310 nm with pH increase. The negative CD peak at 325 nm and its absence in 1:1 Cu(II)–IALA reveal that the 310-nm peak is due to the S→Cu(II) CT transition. The Cu(II)–methionine system in ethanol has been reported to give two S→Cu(II) CT peaks at 380 and 450 nm.[25)]

Solution Equilibria. Figure 2 shows the titration curves for some ligands in the absence and the presence of Cu(II). The overall proton-ligand stability constants, log β_{01r}, calculated from these data are listed in Table 4 and the stepwise dissociation constants (pK_a) in Table 5. The two lower acid dissociation steps of IMAD are assigned to the imidazole nitrogens, because the imidazole moiety of amim has the pK_a value of 4.73.[26)] As observed for PDIEN,[15)] the protonation of the least basic pyridine rings of PMAD and PMTP occurs only at pH<2.5.

Since the disulfide bonds are susceptible to cleavage in the presence of Cu(II) at neutral and alkaline pH, the stability constants were calculated from the data covering the pH ranges 2—3.5 for PMAD, 2.6—5.0 for MPAD, and 2.8—5.9 for IMAD. Considering

TABLE 3. ESR SPECTRAL PARAMETERS FOR 1:1 Cu(II)-LIGAND SYSTEMS AT 77 K

Ligand	pH	$g_{//}$	$g_{\perp}$	$\lvert A_{//}\rvert$/10^{-4} cm^{-1}
IMAD	7.0	2.23	2.06	202
PMAD[a)]	4.0	2.25	2.07	182
PMTP	7.0	2.20	2.07	175
PMET	7.0	2.28	2.05	185
	8.8	2.27	2.06	179
IMET	7.2	2.28	2.07	188
IALA	7.4	2.27	2.06	187
bimen[b)]	7.0	2.21	2.06	206

a) Parameters for the predominant species. b) bimen= *N,N'*-Bis(4-imidazolylmethyl)ethylenediamine.

Table 4. Stability constants, $\log \beta_{01r}$, of proton-ligand complexes, LH_r, at 25 °C and I=0.1(KNO_3)[a]

Ligand	$\log \beta_{011}$	$\log \beta_{012}$	$\log \beta_{013}$	$\log \beta_{014}$
IMAD	8.74(0.007)	16.59(0.006)	21.21(0.006)	25.10(0.005)
PMAD	7.88(0.006)	14.90(0.007)	16.77(0.006)	
MPAD	7.80(0.001)	14.81(0.001)	17.60(0.004)	19.76(0.006)
PMTP	8.01(0.001)	15.01(0.001)	16.79(0.002)	
PMET	7.60(0.003)	9.70(0.004)		

a) Values in parentheses are estimated standard deviations.

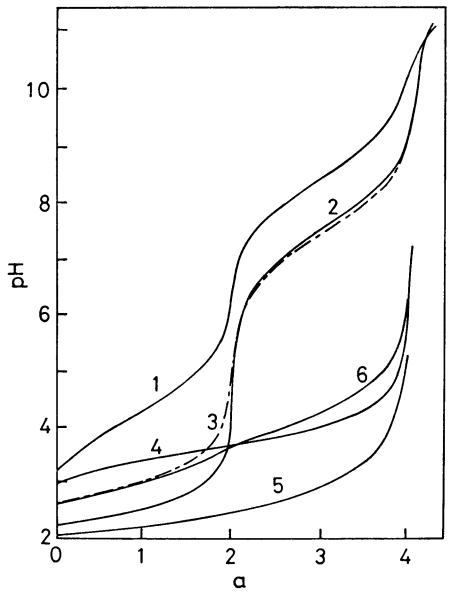


Fig. 2. Titration curves for proton- and Cu(II)-ligand systems at 25 °C.
a: Moles of KOH added per mole of ligand. 1: IMAD (0.004014 M), 2: PMAD (0.004000 M), 3: MPAD (0.002000 M), 4: Cu(II) (0.004027 M) and IMAD (0.004003 M), 5: Cu(II) (0.004027 M) and PMAD (0.004001 M), 6: Cu(II) (0.002029 M) and MPAD (0.002009 M).

that the absorption spectra of 1:1 and 2:1 Cu(II)-PMAD and -MPAD systems have a peak at 650 nm indicative of a monomeric species and that a complex with the composition Cu_2L (L=PMAD) was isolated, we attained convergence in the computer simulations by including the species $CuLH_2$ (for L=IMAD and MPAD), CuLH, CuL, and a binuclear species Cu_2L. The analysis of the 1:1 Cu(II)-IMAD system was possible either by the set of species $CuLH_2$, CuLH, and CuL, or by the set $CuLH_2$, CuLH, and Cu_2L_2, the sums of the squares of residuals being approximately the same. However, Cu_2L_2 was rejected in the simulation including both CuL and Cu_2L_2. From this fact and the absorption spectral behavior of the Cu(II)-IMAD systems, we preferred the set with monomeric species. This conclusion is further supported by the conductivity measurements of Cu(II) complexes (Fig. 3); $Cu(IMAD)(ClO_4)_2$ has the same molar conductivity as shown by $Cu(PDIEN)(ClO_4)_2$ and other

Table 5. Acid dissociation constants of ligands at 25 °C and I=0.1(KNO_3)

Ligand	pK_{a_1}	pK_{a_2}	pK_{a_3}	pK_{a_4}
IMAD	3.89	4.62	7.85	8.74
PMAD	a)	1.87	7.02	7.88
MPAD	2.16	2.79	7.01	7.80
PMTP	a)	1.78	7.00	8.01
	0.9[b]	1.9[b]	6.96[b]	7.98[b]
PMET	a)	2.10	7.60	

a) Not obtained. b) Ref. 19.

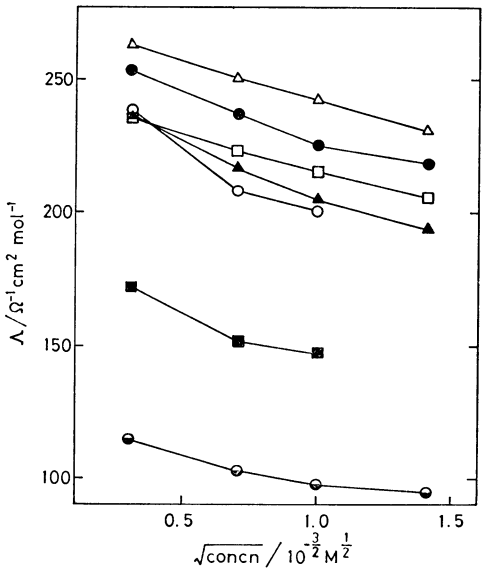


Fig. 3. Molar conductivities of copper(II) complexes in water at 25 °C.
△: $CuCl_2$, ●: $Cu(ClO_4)_2$, □: $Cu(bpy)(NO_3)_2$, ▲: $Cu(PDIEN)(ClO_4)_2$, ○: $Cu(IMAD)(ClO_4)_2$, ■: $Cu(PMET)ClO_4$, ◒: Cu(PMS)Cl (PMS=2-(2-Pyridylmethylamino)ethanesulfinate).

dipositive Cu(II) complex ions. The stability constants for Cu_2L were calculated from the data for the 2:1 Cu(II)-disulfide systems. Table 6 shows the overall stability constants for various complexes studied. The $\log \beta_{110}$ values for Cu(II)-PMAD and Cu(II)-IMAD are 13.32 and 13.38, respectively, which are much greater than those for 1:1 Cu(II)-ampy (=9.5)[27] and Cu(II)-amim (=9.22).[26] There is a drastic sta-

TABLE 6. STABILITY CONSTANTS, $\log \beta_{pqr}$, OF COPPER(II) COMPLEXES, $Cu_pL_qH_r$, AT 25 °C AND I=0.1(KNO_3)[a]

Ligand	Species pqr	$\log \beta_{pqr}$[b]
IMAD	112	20.51(0.02)
	111	17.22(0.007)
	110	13.38(0.006)
	210	16.30(0.04)[c]
PMAD	111	16.26(0.005)
	110	13.32(0.003)
	210	16.62(0.009)[c]
MPAD	112	16.75(0.018)
	111	13.54(0.005)
	110	9.46(0.003)
PMTP	110	16.3(0.1)[d]
		18.1(0.1)[e]
PMET	110	9.3(0.1)[d]
	11-1	0.5(0.06)
PDIEN	110	20.85(0.11)[f]
ampy[g]	110	9.5(0.2)[h]
	120	17.2(0.3)[h]
amim[i]	110	9.22(0.03)[j]
	120	17.17[j]

a) Values in parentheses are estimated standard deviations. b) Calculated for 1:1 Cu(II)-ligand systems. c) Calculated for 2:1 Cu(II)-ligand systems. d) Obtained by graphical methods. e) Ref. 19. f) Ref. 15. g) ampy=2-(Aminomethyl)pyridine. h) Ref. 27. i) amim=4-(Aminomethyl)imidazole. j) Ref. 26.

bility decrease in Cu(II)–MPAD due to the 6-methyl group, the $\log \beta_{110}$ value of 9.46 being as low as that of Cu(II)–ampy. The results imply that PMAD and IMAD behave as multidentate ligands coordinating through most of the available donor atoms, whereas MPAD coordinates to Cu(II) in the same way as ampy. We may compare the $\log \beta_{110}$ values for PMAD and IMAD with the $\log \beta_{120}$ values for ampy and amim: the $\log \beta_{110}$ values for the disulfides are smaller than these $\log \beta_{120}$ values, which could result from the difference in the ligand basicity and/or in the donor sets in the coordination plane.

The stability constants for Cu(II)–PMTP and Cu(II)–PMET were calculated by a graphical method. Both systems were analyzed by considering CuL only, and protonated species $CuLH_2$ and CuLH were negligible. The pyridine-containing thioether PMTP forms a 1:1 complex with $\log \beta_{110}$=16,3,[28] whereas PDIEN forms a complex with $\log \beta_{110}$=20.85.[15] The stability difference of 4.5 log unit is attributed to the difference in the coordinating ability of an amine nitrogen and a thioether sulfur, and further supports the conclusion derived from the spectra that Cu(II)–PMTP has an N_3S donor set in the coordination plane.

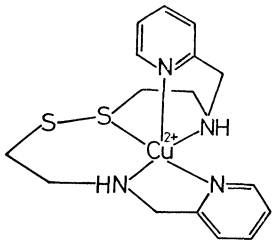
The amino acid derivative PMET forms a 1:1 complex with $\log \beta_{110}$=9.30, which is smaller than the value of 11.8 reported for *N*-(2-pyridylmethyl)glycine with higher pK_a values.[29] At pH>7 the complex liberates an additional proton probably from the coordinated water molecule, whose dissociation constant was calculated by assuming the following step:

$$CuL \rightleftharpoons CuL(OH) + H. \quad (5)$$

Discussion

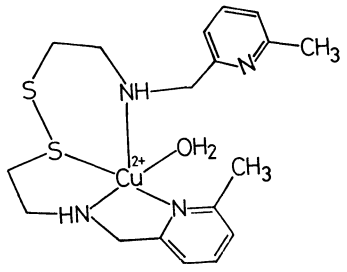
Structures of Complexes in Solution. The intensity and location of the S→Cu(II) CT band are affected by the mode of S–Cu(II) interactions.[30–32] The CT band due to equatorial thioether–Cu(II) bonding is strong, while the band due to apical bonding is sometimes too weak to be detected: the Cu(II) complex of an imidazole-containing thioether ligand, bis(4-phenyl-2-imidazolylmethyl) sulfide, has an apical S–Cu(II) bonding (2.824 Å) but shows no CT band.[32] The spectral properties of disulfide–Cu(II) bonding may be considered analogously, and the CT band arising from the apical disulfide–Cu(II) interaction may not be detected because of the poor overlap of the Cu(II) $d_{x^2-y^2}$ and S orbitals and the long axial S–Cu(II) bond as seen in the Cu(II) complexes of oxidized D-penicillamine (3.057 and 3.138 Å)[33] and glutathione (3.16 and 3.28 Å),[34] both of which apparently lack obvious S→Cu(II) CT bands. The Cu(II)···S separations in these complexes are much longer than the Cu(I)–S bonds (2.3—2.4 Å) in some Cu(I)–disulfide complexes.[35–38] Therefore, the 330-nm shoulder shown by Cu(II)–PMAD is assigned to the equatorial S→Cu(II) CT transition by analogy with the spectrum of the related system Cu(II)–PMTP.[18] The observed intensity (ε=1100) indicates that the S–Cu(II) interaction is weaker than that in Cu(II)–PMTP. For the system Cu(II)–tetramethylcystamine (=bis[2-(dimethylamino)ethyl] disulfide) Downes *et al.* observed three bands and suggested that both of the disulfide sulfur atoms are involved in the interactions with Cu(II).[39] Although a somewhat reduced $|A_{//}|$ value observed for Cu(II)–PMAD suggests sulfur coordination,[40] the ESR parameters do not explicitly point to the Cu(II)–S bonding. The splitting of the d-d band is ascribed to a square-pyramidal structure[41] with a donor group of PMAD occupying an apical position; in the 2:1 system the 850-nm band disappears at pH>4.1, indicating that the apical donor is used for forming a binuclear complex Cu_2L. The d-d band at 650 nm is remote from the band exhibited by 1:2 Cu(II)–ampy (585 nm) with a CuN_4 chromophore. Sterically PMAD may be coordinated to Cu(II) in the same way as ampy in 1:2 Cu(II)–ampy, but actually the maximum wavelength of 1:1 Cu(II)–PMAD is the same as that of 1:1 Cu(II)–ampy. Addition of ampy has no apparent effect on the spectrum of 1:1 Cu(II)–PMAD (Table 2), which may indicate either that the bonding by added ampy is similar to that by one of the two 2-pyridylmethylamino moieties of PMAD or that ampy does not coordinate to Cu(II) at all. With 2,2′-bipyridine (bpy), which probably

occupies two equatorial positions, the maximum at 650 nm shifts to 680 nm with concomitant loss of the 330-nm CT peak. An additional band is observed in both ternary systems at 850 nm as a shoulder. The 680-nm peak is close to the peak at 690 nm exhibited by 1:1:1 Cu(II)–ampy–bpy. This indicates that Cu(II)–PMAD–bpy and Cu(II)–ampy–bpy have a similar chromophore. Incidentally 1:2 Cu(II)–bpy complexes with various geometries often exhibit an electronic reflectance spectral peak at $\approx$650 nm.[42,43] From these considerations, the chromophore of 1:1 Cu(II)–PMAD in acid solution is best described as CuN_4S with apical coordination by a nitrogen donor, and we propose structure **1**, which is reminiscent of the probable structure of Cu(II)–PMTP.[18] Octahedral Ni(II)–PMAD complexes in the solid state have been reported to involve PMAD as a pentadentate ligand.[7,44]



1

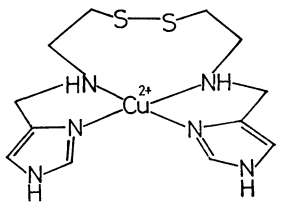
Another line of evidence is provided by the stability and the spectrum of the Cu(II)–MPAD system. In sharp contrast with the Cu(II)–PMAD system, it has the same stability constant as that of Cu(II)–ampy, which confirms an analogous mode of coordination in the square plane. The stability difference of 3.9 between Cu(II)–PMAD and Cu(II)–MPAD (Table 6) corresponds to the difference of one nitrogen donor in the plane, again indicating that at least three nitrogens are involved in the equatorial bonding in Cu(II)–PMAD. Space-filling molecular models show that, when MPAD is coordinated through the pyridine and amine nitrogens and the disulfide sulfur (structure **2**),



2

the methyl group severely interferes with the equatorial bonding by the rest of the donors. This is in accord with the lower stability and the lack of the S→Cu(II) CT band at pH<6.

On the other hand, the optical and ESR spectra (Tables 1 and 3) indicate that 1:1 Cu(II)–IMAD has a planar CuN_4 coordination structure with no strong Cu(II)–S bonding. Molecular models suggest that



3

both *cis* and *trans* structures are possible with respect to the imidazole nitrogens and that the dithio group apically approaches Cu(II) in the *trans* structure. Although the apical S–Cu(II) interaction is not incompatible with lack of S→Cu(II) CT bands, we prefer the *cis* structure (**3**) with negligible S–Cu(II) interactions on the basis of the stability of the 1:1 complex toward the disulfide bond cleavage as has been observed for PMAD.[12,13] It should be noted in addition that the 1:1 Cu(II) complex of *N,N'*-bis(4-imidazolylmethyl)ethylenediamine with an N_4 donor set shows the same absorption and ESR spectral parameters as those of the 1:1 Cu(II)–IMAD system (Tables 1 and 3). The ternary Cu(II)–IMAD–bpy systems show a broad peak at 700 nm and a shoulder at 870 nm, indicating a change from the square-planar to the square-pyramidal structure. Structures **1** and **3** are related to each other and may be determined by steric requirements for pyridine and imidazole rings in the *cis* coordination positions.

Effects of Sulfur Coordination on Stability Constants of Copper(II) Complexes. The difference of $\approx$4.5 between the $\log \beta_{110}$ values for PMTP and PDIEN is attributed to the difference in the complexing ability of a thioether sulfur and an amine nitrogen. An analogous stability difference exists between the Cu(II) complexes of diethylenetriamine ($\log \beta_{110}=15.9$) and bis(2-aminoethyl) sulfide ($\log \beta_{110}=9.07$).[27] The complex of PMAD is less stable than that of PMTP in spite of similar coordination structures of CuN_4S as inferred from absorption spectra. An explanation for this is the orbital overlap in the S–Cu(II) interaction, which is considered from the CT band intensities to be small in Cu(II)–PMAD and large in Cu(II)–PMTP. Steric effects due to the presence of two sulfur atoms in one of the chelate rings should also affect the stability. The $\log \beta_{110}$ value for PMAD is expectedly smaller than $\log \beta_{120}$ for 1:2 Cu(II)–ampy with an N_4 donor set by 3.9 log units. The low stability of Cu(II)–MPAD is ascribed to the bidentate nature of MPAD due to the steric hindrance arising from the 6-methyl group.

Although 1:1 Cu(II)–IMAD and 1:2 Cu(II)–amim probably have the same donor groups in the coordination plane, the difference between $\log \beta_{110}$ of Cu(II)–IMAD and $\log \beta_{120}$ of Cu(II)–amim is rather large ($\approx$3.8) and may be caused by lower basicity of IMAD and steric strains due to the disulfide bond.

The terdentate thioether ligand PMET forms a 1:1 complex ($\log \beta_{110}=9.3$), which is more stable than the Cu(II)–L-methioninate complex ($\log \beta_{110}=7.849$).[45] The stability enhancement is due primarily to the pyridine nitrogen, and contribution by the

thioether moiety may be negligible, because Cu(II)–ampy has approximately the same stability. In this connection, L-methionylglycine and *S*-methyl-L-cysteinylglycine form Cu(II) complexes CuL with significantly higher stability than expected from the basicity of the terminal amino group of various dipeptides; the thioether sulfur of glycyl-L-methionine has no effect on the stability of CuL owing to the inaccessibility of the side chain to Cu(II).[46]

Dependence of the Disulfide Bond Stability on the Coordination Structure. Disulfides are susceptible to heterolytic cleavage by Ag(I), Hg(I), and other soft Lewis acids, forming sulfinic acids and thiols by the reaction with water and subsequent disproportionation.[10] Formation of 2-pyridylsulfinate from di-2-pyridyl disulfide in the presence of Cu(II) has been interpreted as due to the same heterolytic cleavage reaction.[11] PMAD is readily converted to 2-(2-pyridylmethylamino)ethanesulfinate in the presence of Cu(II) and dioxygen at pH $\approx$7.[12,13] Although this reaction has been found to require dioxygen,[13] it must involve the heterolytic cleavage and the reaction with water, because the oxygens incorporated from dioxygen account for only 25—30% of the total sulfinate oxygens. The 2:1 Cu(II)–PMAD system at pH$\approx$7 exhibits a transient but resolved peak at 330 nm,[13] indicating that the Cu(II)–S interaction is stronger than in acid solution where the 330-nm peak appears as a shoulder. The Cu(II)–tetramethylcystamine system in acetonitrile, whose disulfide bond is more stable than that in the Cu(II)–cystamine system, gives strong S$\rightarrow$Cu(II) CT peaks and is rapidly decomposed by addition of a second equivalent of sodium methoxide.[39] On the other hand, the Cu(II)–penicillamine disulfide[33] and –glutathione disulfide[34] complexes, which were isolated from aqueous solution, have long Cu(II)$\cdots$S distances (3.0—3.3 Å) and show no CT bands. Also, the Cu(II)–IMAD system is more stable in aqueous solution and gives a 1:1 complex as crystals; in line with this, the system shows no band ascribable to the S$\rightarrow$Cu(II) CT transition. Since the stability constants of Cu(II)–disulfide and –thioether complexes are usually low,[47–50] neighboring effective Cu(II)-binding sites which bring the disulfide group close to Cu(II) would promote the cleavage reaction. These observations probably indicate that only those complexes which involve weak Cu(II)–S bonds are stable in aqueous solution.

The disulfide bond has been proposed as a copper binding site in stellacyanin[3–5] which lacks the methionyl residue established as a binding site in plastocyanin and azurin. While the proposal is attractive in view of the coordinating ability of the disulfide sulfurs, it becomes necessary to cope with the dichotomy between coordination and disulfide bond cleavage. We may infer from the present observations that the copper site should meet one of the following requirements for the stability of the bond in the vicinity of Cu(II): (i) the S$\cdots$Cu(II) separation is as large as 3.0 Å; (ii) water and other nucleophiles are excluded from the copper binding site. Just as the Cu(II)$\cdots$S(methionine) distance found in plastocyanin is unusually long (2.90 Å),[1] a disulfide group would be able to contribute to the copper binding in stellacyanin through weak interaction with a large Cu(II)$\cdots$S separation.

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