Inorganica Chimica Acta, 93 (1984) 173–178

Copper(I) and Copper(II) Complexes of Biologically Relevant Tridentate Ligands

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Received July 23, 1984

Abstract

The preparation of a series of tridentate ligands of formulae $X(CH_2C_7H_5N_2)_2$ (X = NH, S, O, S_2) is described. The ligands contain two benzimidazole moieties and one of NH, S, O, or S_2 as the donor groups. Cu(I) and Cu(II) complexes of these ligands are prepared and characterized. Spectroscopic and X-ray data imply that the geometric constraints of these ligands impose a distorted coordination geometry at copper. The implications and relevance of this chemistry to copper proteins is discussed.

Introduction

The preparation and study of inorganic compounds containing biologically relevant ligands is prompted by the importance of metal ions in a variety of biochemical processes [1–5]. Such model studies attempt to provide low molecular weight species which mimic both the structure and reactivity of metal ion sites in complex biochemical systems. Important considerations in model compound preparation include donor atom types and the resulting geometry at the metal centre. Studies related to copper proteins, in particular azurin, plastocyanin, stellocyanin and hemocyanin have drawn considerable attention of late [4–21]. X-ray crystallographic [6–8] and spectroscopic studies [9–14] have established that the Cu(II) atom in the 'copper blue' proteins resides in a pseudo-tetrahedral environment while the Cu(II) of hemocyanin has a pseudo-square pyramidal geometry. Despite these differences the presence of copper–imidazole binding is common to both types of proteins. Recent inorganic studies have focused on Cu(I) and Cu(II) complexes of imidazole containing ligands [15–21]. In this paper we report the synthesis of a series of tridentate ligands whose geometries are constrained so as to facilitate distorted environments at copper. The ligands contain two benzimidazole groups and one of NH, S, O or S_2 as the donors. Cu(I) and Cu(II) complexes of these ligands have been synthesized and characterized. The results and implications of this chemistry are considered below.

Experimental

The preparation of Cu(I) complexes was performed under an atmosphere of dry O_2-free N_2, employing both Schlenk-line techniques and a Vacuum Atmospheres inert atmosphere glove box. ^1H NMR spectra were recorded on a Bruker CXP100 spectrometer operating at 90 MHz using $Si(CH_3)_4$ as the reference. UV-vis spectra were recorded on a Shimadzu 240 spectrometer. X band EPR data were recorded on a Varian E-12 EPR spectrometer. IR data were recorded using a Beckman IR-12 spectrometer. Melting points are reported uncorrected. Combustion analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario, Canada. Iminodiacetic acid, *o*-phenylenediamine, thiodiglycolic acid, diglycolic acid, and mercaptoacetic acid were purchased from the Aldrich Chemical Co.

Ligands

Preparation of $NH(CH_2C_7H_5N_2)_2 \cdot 3HCl$, (L1·3HCl)

A 6 N HCl solution containing *o*-phenylenediamine (108.1 g, 2 mol) and iminodiacetic acid (133.1 g, 1 mol) was refluxed for 72 h. Upon slow cooling, blue needles are isolated by filtration. Recrystallization from hot H_2O/acetone yielded 108 g (28%) of L1·3HCl, m.p. 254–59 °C(d), ^1H NMR (CD_3OD) δ: 7.8 (4H, m), 7.7 (4H,m), 4.7 (4H, s). *Anal.* Calcd. for $C_{16}H_{18}N_5Cl_3$: C, 49.69; H, 4.69; N, 18.11. Found: C, 50.29; H, 5.09; N, 17.92%.

Preparation of $NH(CH_2C_7H_5N_2)_2$, (L1)

A hot solution of L1·3HCl in H_2O is treated with excess NH_4OH. Purple solid biproduct is filtered off**.

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**This purple biproduct has ^1H NMR and infrared spectra similar to L1. We have formulated it as the imidazolate-ammonium zwitterion. Analytical data: C, 69.84; H, 5.04; N 25.15; is consistent with this formulation. Treatment with HCl in methanol affords the isolation of L1·3HCl.

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From the cooled H_2O solution, a white product can be isolated.

Recrystallization from methanol and H_2O gives white needles, m.p. 250–51 °C (d). ^1H NMR (CD_3OD) δ: 7.62 (4H, m), 7.05 (4H, m), 4.03 (4H, s). *Anal.* Calcd. for $C_{16}H_{15}N_5$: C, 69.55; H, 5.47; N, 25.34. Found: C, 69.42; H, 5.34; N, 25.29%.

Preparation of $S(CH_2C_7H_5N_2)_2$, (L2)

6.91 g (46 mmol) of thiodiglycolic acid was combined with 10.0 g (93 mmol) of *o*-phenylenediamine in 250 mol of 4 N HCl. The solution was refluxed for 24 h. The resulting green solution was neutralized with 4 N NH_4OH. The white precipitate was collected, washed with ether and dried *in vacuo*. Yield 12 g (62%), m.p. 180–90 °C (d), ^1H NMR; ($(CD_3)_2SO$) δ: 7.6 (4H, m), 7.2 (4H, m), 4.05 (4H, s). *Anal.* Calcd. for $C_{16}H_{14}N_4S \cdot 0.25H_2O$: C, 64.30; H, 4.89; N, 18.75. Found: C, 64.35; H, 5.45; N, 18.93%.

Preparation of $O(CH_2C_7N_5N_2)_2$, (L3)

12.1 g (90 mmol) of diglycolic acid was combined with 19.5 g (180 mmol) of *o*-phenylenediamine in 250 ml of 4 N HCl. The solution was refluxed for 14 h. The resulting solution was neutralized with conc. NH_4OH. The white precipitate was collected, washed with ether and dried *in vacuo*. Yield 14.0 g (56%), m.p. 295 °C (d). ^1H NMR (CD_3OD) δ: 7.7 (4 H, m), 7.15 (4H, m), 4.95 (4H, s). *Anal.* Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.59; H, 5.11; N, 20.40%.

Preparation of $S_2(CH_2C_7H_5N_2)_2$, (L4)

L4 was prepared by a known method. 2-mercaptomethylbenzimidazole, prepared from mercaptoacetic acid and *o*-phenylenediamine, was oxidized by O_2 in methanol according to the method of Tulecki and Rafinski [22]. M.p. 181–85 °C. ^1H NMR (CD_3OD) δ: 7.7 (4H, m), 7.15 (4H, m), 4.0 (4H, s).

Complexes

Preparation of Cu(L1)BF_4, (1)

277 mg (1 mmol) of L1 was dissolved in dry, degassed acetonitrile under an inert atmosphere. To this solution was added $Cu(CH_3CN)_4BF_4$ (315 mg, 1 mmol). After stirring for 4 h, the white precipitate was filtered off and dried *in vacuo*. The compound is stable in air in the solid state but unstable in solution. ^1H NMR: (CD_3CN) δ: 4.11 (4H, s), 7.27 (4H, m), 7.54 (4H, m). *Anal.* Calcd. for $CuC_{16}H_{15}N_5BF_4$: C, 44.94; H, 3.59; N, 16.38. Found: C, 45.30; H, 3.72; N, 16.88%.

Preparation of Cu(L1)Cl, (4)

277 mg (1 mmol) of L1 was combined with 98 mg (1 mmol) of CuCl in dry degassed acetonitrile. Stirring for 4 h and filtration afforded a pale blue-white powder which is insoluble in common organic solvents. *Anal.* Calcd. for: $CuC_{16}H_{15}N_5Cl$: C, 51.11; H, 4.02; N, 18.63. Found: C, 51.03; H, 3.91; N, 18.58%.

Preparation of Cu(L2)BF_4, (2)

100 mg (0.34 mmol) of L2 was dissolved in dry degassed acetonitrile under an inert atmosphere ($Cu(CH_3CN)_4BF_4$) (125 mg, 0.34 mmol) was added. After stirring for 8 h the white precipitate was filtered off and vacuum dried. ^1H NMR (CD_3CN): 4.20 (4H, s), 7.30 (4H, m), 7.50 (4H, m). *Anal.* Calcd. for $CuC_{16}H_{14}N_4SBF_4$: C, 43.21; H, 3.17 Found: C, 41.78; H, 3.22%.

Preparation of Cu(L3)BF_4, (3)

106 mg (0.36 mmol) of L3 was dissolved in dry degassed acetonitrile under an inert atmosphere. 132 mg (0.36 mmol) of $Cu(CH_3CN)_4BF_4$ were added. After stirring overnight the white precipitate was isolated by filtration and vacuum dried. ^1H NMR (CD_3CN) δ: 4.10 (4H, s), 7.20 (4H, m), 7.50 (4H, m). *Anal.* Calcd. for $CuC_{16}H_{14}N_4OBF_4$: C, 44.83; H, 3.29. Found: C, 44.70; H, 3.30%.

Preparation of $Cu(L1)_2(ClO_4)_2 \cdot 2H_2O$, (5)

277 mg (1 mmol) of L1 was dissolved in CH_3OH (20 ml). To this solution was added 185 mg (0.5 mmol) of $Cu(ClO_4)_2 \cdot 6H_2O$. The solution was allowed to stand at room temperature for several hours and then cooled to 5 °C for 48 h. Blue crystalline blocks were isolated by filtration. UV-vis (CH_3OH) λ: 665 nm (ϵ =107 M^{-1} cm^{-1}). *Anal.* Calcd. for $CuC_{32}H_{34}Cl_2N_{10}O_{10}$: C, 45.05; H, 4.02; N, 16.42. Found: C, 44.79; H, 3.88; N, 16.44%.

Preparation of $Cu(L1)(C_4H_7N_2)(H_2O)_2(ClO_4)_2$, (6)

270 mg (1 mmol) of $Cu(ClO_4)_2 \cdot 6H_2O$ was added to a CH_3OH (20 ml) solution of 277 mg (1 mmol) of L1. N-methylimidazole (8.3 mg, 1 mmol) was added. Blue crystalline needles form in the solution on standing for 72 h. UV-vis (CH_3OH) λ: 640 nm (ϵ = 98 M^{-1} cm^{-1}). *Anal.* Calcd. for $CuC_{20}H_{25}Cl_2N_{12}O_{10}$: C, 36.51; H, 3.68; N, 14.90. Found: C, 37.17; H, 3.79; N, 14.94%.

Preparation of $Cu(L1)(C_5H_4N)(H_2O)_2(ClO_4)_2$, (7)

270 mg (1 mmol) of $Cu(ClO_4)_2 \cdot 6H_2O$ was added to a CH_3OH (20 ml) solution of 277 mg (1 mmol) of L1. 79 mg (1 mmol) of pyridine was added. On standing for several days dark blue prisms formed. The product was isolated by filtration. UV-vis (CH_3OH) λ: 660 nm (ϵ = 96 M^{-1} cm^{-1}). *Anal.* Calcd. for $CuC_{21}H_{24}Cl_2N_6O_2$: C, 39.62; H, 3.63; N, 12.60. Found: C, 39.63; H, 3.74; N, 13.07%.

TABLE I. Crystal and Data Collection Parameters for $Cu(L1)_2(ClO_4)_2 \cdot H_2O \cdot 2CH_3OH$, (9).

a, Å	9.576(3)
b, Å	10.123(3)
c, Å	11.628(5)
α, deg	83.31(3)
β, deg	80.93(3)
γ, deg	87.25(2)
crystal system	triclinic
space group	$P\bar{1}$
V Å^3	1105.0(6)
Z	1
$d_{calcd.}$, g/cm^3	1.37
μ abs. coeff cm^{-1}	6.32
radiation	MoKα (λ = 0.71069 Å)
scan speed, deg/min	2.0–5.09 ($\theta/2\theta$ scan)
scan range, deg	1.0 below $K_{\alpha 1}$, to 1.10 above $K_{\alpha 2}$
background/scan time ratio	0.5
data collected	$\pm h \pm k + l$ 2θ of 4.5–50°
unique data, $F_o^2 > 3\sigma(F_o^2)$	2421

Preparation of Cu(L2)(H_2O)(ClO_4)$_2$, (8)

500 mg (1.6 mmol) of L2 was suspended in CH_2Cl_2 (25 ml), 630 mg (1.7 mmol) (of $Cu(ClO_4)_2 \cdot 6H_2O$) was dissolved in MeOH (25 ml) and added to the ligand solution. On standing green crystalline product precipitated. The product was isolated by filtration. UV-vis (CH_3OH) λ: 710 nm (br. ϵ = 46 M^{-1} cm^{-1}), 360 nm (ϵ = 368 M^{-1} cm^{-1}), 320 nm (ϵ = 507 M^{-1} cm^{-1}). (CH_3CN), λ: 640 nm (ϵ = 191 M^{-1} cm^{-1}), 330 nm (ϵ = 1241 M^{-1} cm^{-1}). *Anal.* Calcd. for $CuC_{16}H_{16}N_4SO_9Cl_2$: C, 33.43; H, 2.81. Found C, 33.67; H, 3.06%.

Reaction of L3 with Cu(II)

100 mg (0.36 mmol) of L3 was suspended in methanol and 133 mg (0.36 mmol) of $Cu(H_2O)_6(ClO_4)_2$ was added. The resulting pale green solution was monitored by UV-vis spectroscopy. Attempts to concentrate and isolate the Cu(II) complex failed because of the high solubility of these species. Vis (CH_3OH) λ: 820 nm (ϵ = 36 M^{-1} cm^{-1}), (CH_3CN) λ: 800 nm (ϵ = 50 M^{-1} cm^{-1}).

Reaction of L4 with Cu(II)

100 mg (0.31 mmol) of L4 and 113 mg (0.30 mmol) of $Cu(H_2O)_6(ClO_4)_2$ were combined in methanol. The dark green solution was examined by UV-vis spectroscopy. Concentration of the solution yielded no precipitate. The high solubility of this species precluded isolation. UV-vis (CH_3OH) λ: 720 nm (ϵ = 10 M^{-1} cm^{-1}), (CH_3CN) λ: 650 nm (ϵ = 100 M^{-1} cm^{-1}), 330 nm (ϵ = 906 M^{-1} cm^{-1}).

X-ray Data Collection, Reduction and Limited Structure Refinement

Crystallization of $Cu(L1)_2(ClO_4)_2 \cdot 2H_2O \cdot 2CH_3OH$ (9) was performed by slow cooling of a methanol solution. Removal of the crystals from the mother liquor resulted in immediate loss of crystallinity. Attempts to crystallize other salts of this cation yielded no materials of suitable crystalline form. Thus crystals of $Cu(L1)_2(ClO_4)_2 \cdot 2H_3OH$ were mounted in mother liquor in a capillary. Diffraction experiments were performed on a Syntex $P2_1$ four circle diffractometer with graphite-monochromatized Mo Kα radiation. Preliminary photographic work showed the symmetry of the crystals was consistent with space groups *P*1 and $P\bar{1}$. Crystal data are given in Table I. During data collection three standard reflections were recorded every 197 reflections; their intensities revealed an anisotropic decay of approximately 30%. Despite this problem a solution and refinement was attempted following the application of a decay correction.

Non hydrogen atomic scattering factors were taken from the tabulation of Cromer [23, 24]. The Cu position was fixed at the origin in space group $P\bar{1}$. From a difference Fourier calculation all of the non-hydrogen atoms of the cation were located. In subsequent such calculations however, the atoms of the anion and the solvent molecules were located only with difficulty. Disordering of the ClO_4 and CH_3OH was indicated. Attempts to model the disorders were in general unsatisfactory. In the best of the many models the atoms of the cation were

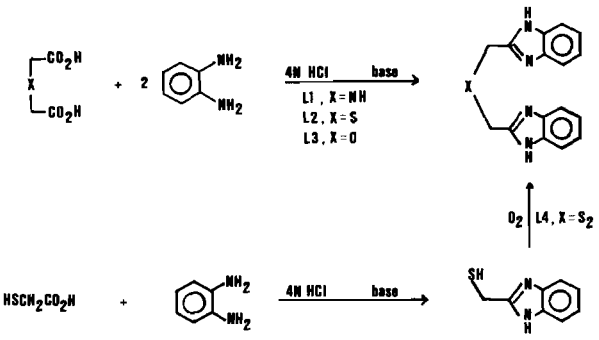

Fig. 1. Synthetic routes to L1, L2, L3 and L4.

described anisotropically, the ClO_4 group was constrained to two tetrahedral rigid groups of isotropic atoms with relative site occupancies of 0.4 and 0.6, the atoms of solvent molecules were described isotropically. Refinement of this model using 2421 reflections with $F_o^2 > 3\sigma(F_o^2)$ gave $R = 11.56\%$. Thermal parameters for the atoms of the cation were well behaved while those for the atoms of the anion and solvent molecules were large. Further attempts to improve the model were unsuccessful. At this point further refinement of the structure was abandoned.

Results and Discussion

Reactions of the appropriate acids with *o*-phenylenediamine are known to yield substituted benzimidazole functional groups [25]. Employing the appropriate diacids the tridentate ligands L1, L2, and L3 were readily prepared in good yields. These ligands contain two benzimidazole groups and either NH, S, or O as the central donor atom. L4, a similar ligand that has a central disulfide unit was prepared by the air oxidation of 2-mercaptomethylbenzimidazole [23] (Fig. 1).

Cu(I) complexes of the ligands L1, L2, and L3 were prepared by reaction of the appropriate ligand with $Cu(CH_3CN)_4BF_4$ in acetonitrile under strict anaerobic conditions. The resulting complexes were only sparingly soluble in organic solvents. Nevertheless the ^1H NMR and analytical data were consistent with the formulations, $Cu(Ln)BF_4$ (n = 1–3), (**1–3**). A three coordinate geometry is predicted for these Cu(I) salts. A four coordinate species was prepared by reaction of L1 with CuCl. This complex was totally insoluble and was formulated as Cu(L1)Cl (**4**) on the basis of combustion analysis data.

Cu(II) complexes were prepared by reaction of the ligands with $Cu(ClO_4)_2 \cdot 6H_2O$ in methanol. Complexes of L1 of formulae $Cu(L1)_2(ClO_4)_2 \cdot 2H_2O$ (**5**) and $Cu(L1)(L')(H_2O)_2(ClO_4)_2$ (L′ = N-methylimidazole, pyridine), (**6**, **7**) were isolated. These blue compounds (**5–7**) exhibited d–d bands in the range 640–665 nm with $\epsilon = 100\ M^{-1}\ cm^{-1}$. The UV-vis and analytical data were consistent with tetragonally distorted six coordinate Cu(II) species. An X-ray crystallographic study of $Cu(L1)_2(ClO_4)_2 \cdot 2H_2O \cdot 2CH_3OH$ (**9**) was performed. The space group, $P\bar{1}$ and a $Z = 1$ demand a crystallographically imposed centre of symmetry at the copper site. Thus for L1 to act as a tridentate ligand it must adopt a facial coordination mode. The limited nature of the refinement precludes a detailed characterization or discussion of the structure* however it is consistent with four benzimidazole nitrogens occupying the equatorial plane while two apical NH donors complete the coordination site. An ORTEP drawing [27] (Fig. 2) shows the expected Jahn-Teller distortion of the Cu environment. A further distortion caused by the tight geometrical constraints of L1 is also apparent.

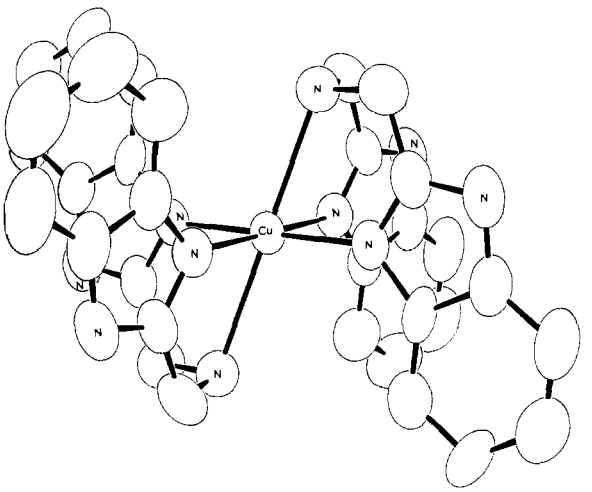

Fig. 2. ORTEP of the cation $Cu(L1)_2^{2+}$, 50% thermal ellipsoids are shown.

A dark green Cu(II) complex of L2 was isolated and formulated as $Cu(L2)(H_2O)(ClO_4)_2$ (**8**) based on analytical and UV-vis data. In a crystallographic study of a copper complex of a similar ligand (*i.e.* $S(CH_2CH_2C_8H_7N_2)_2$) Reed [26] found a trigonal bipyramidal geometry; the coordination sphere consisted of the N_2S chelate, an H_2O and a coordinated perchlorate. On the basis of that result we propose a similar geometry for (**8**). The absorption spectrum of (**8**) shows a d–d band at 695 nm and charge transfer bands at 360 and 320 nm. These features are typical of Cu(II) complexes of thioether type ligands [27].

*Complete refinement of the model was unsuccessful thus no crystallographic parameters are reported. The ORTEP shown was drawn using parameters obtained in 'best' model. Further information will be supplied by the authors on request.

Reactions of L3 and L4 with $Cu(ClO_4)_2 \cdot 6H_2O$ were performed in CH_3OH and CH_3CN. Attempts to isolate the copper complexes of these ligands were unsuccessful due to the high solubility of these species. The reaction solutions were monitored by UV-vis spectroscopy. Figure 4 includes the spectra of 1:1 ligand to copper mixtures for L3 and L4 in CH_3OH. The $Cu(L3)^{2+}$ species in CH_3OH shows a weak d–d band absorption at 820 nm (ϵ = 36 M^{-1} cm^{-1}). In CH_3CN there is a shift of this peak to 800 nm (ϵ = 50 M^{-1} cm^{-1}). These spectra are consistent with the coordination of a weak field ligand, *i.e.* the etheral oxygen of L3. 1:1 solutions of L4 and Cu(II) in CH_3OH were not stable. The initially green solution (720 nm, ϵ = 10 M^{-1} cm^{-1}) faded to a pale color over a 1 to 4 h period depending on concentration. We presume that this represents cleavage of the disulfide bond by alkoxide with subsequent reduction of Cu(II) to Cu(I). This phenomenon has been studied in detail by Bosnich *et al.* [28]. Solutions of L4 and Cu(II) in CH_3CN were more stable. Absorptions at 650 nm (ϵ = 100 M^{-1} cm^{-1}) and 330 (ϵ = 906 M^{-1} cm^{-1}) are characteristic of a coordinated disulfide unit [28]. The nature of this species in solution is uncertain but is presumed to be $Cu(L4)(CH_3CN)_n^{2+}$ (n = 1 or 2 or 3).

The room temperature solid state X-band EPR spectra for (**5**) and (**9**) are shown in Fig. 3. The spectra are fairly typical of tetragonal distorted copper environments [16]. This is consistent with the weak axial coordination of S and NH in (**5**) and (**9**) respectively. A significant change in $g_{\|}$ would be expected if S were replacing N in the equatorial plane of (**5**). Fine structure over the low field side of the resonances is evident. Similar detail has been observed in other systems [16].

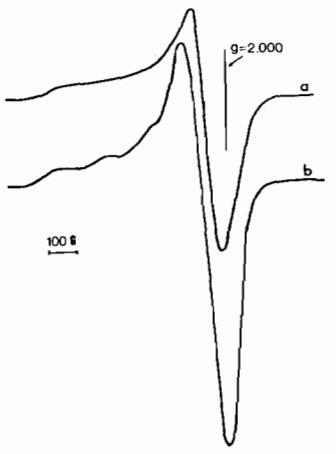

Fig. 3. X-band room temperature (25 °C), solid state EPR spectra of (a) $Cu(L2)(H_2O)(ClO_4)_2$; (b) $Cu(L1)_2(ClO_4)_2 \cdot 2H_2O$.

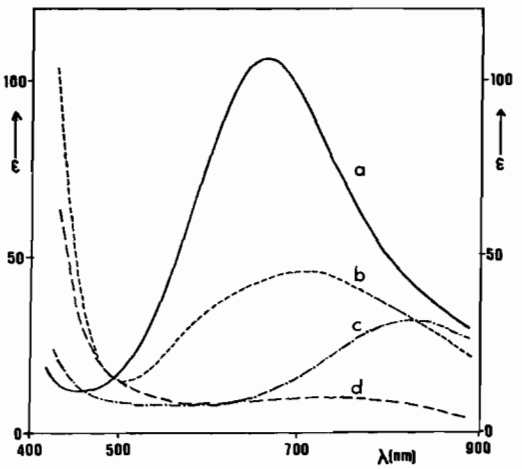

Fig. 4. Visible spectra of (a) $Cu(L1)_2(ClO_4)_2 \cdot 2H_2O$; (b) $Cu(L2)(H_2O)(ClO_4)_2$; (c) 1:1 solution of L3 and $Cu(ClO_4)_2 \cdot 6H_2O$; (d) 1:1 solution of L4 and $Cu(ClO_4)_2 \cdot 6H_2O$.

Relevance to Protein Systems

The ligands described herein provide a series of specific donor atom sets, yet maintain tight geometrical constraints on the relative positions of these donor atoms. Certainly these are features that a protein can offer to a metal center in a biological system. Of the complexes prepared several are particularly pertinent to specific protein systems.

The Cu(I) complexes (**1**, **3**) are related to the copper site in the protein hemocyanin. Two to four nitrogen or oxygen atoms are indicated by EXAFS in the linear or trigonal coordination sphere of Cu(I) in the deoxy-protein [11]. Our Cu(I) complexes (**1**, **3**) may indeed be appropriate models for the Cu(I) site of deoxyhemocyanin. The Cu(I) complexes are readily oxidized to Cu(II) in solution but we have yet to observe the reverse process. In the oxidized form of hemocyanin the Cu(II) site is dimeric. In the course of our work Suzuki *et al.* [29] have recently describe the specific alkylation of L1 thus providing a new facile route to binucleating ligands and model compounds pertinent to the oxy-form of hemocyanin.

The copper 'blue' protein sites have been the subject of many recent model [26, 30–33] studies. X-ray data [7] for plastocyanin reveals the coordination sphere of Cu to be a distorted tetrahedron containing two imidazoles, a methionine thioether and a cysteine thiolate. Stellacyanin, another copper 'blue' protein, has an electronic spectra similar to that of plastocyanin yet stellacyanin contains no methionine [34]. It has been suggested disulfide replaces thioether in the coordination sphere of copper [28]. Clearly, L2 and L4 provide three of the four donor atoms required for models for these pro-

tein sites. The short linkages between nitrogen and sulfur were contrived to attempt to facilitate a distortion to tetrahedral geometry. The Cu(II) complex (**9**) exhibits d–d bonds some 55 nm to higher energy than those found by Reed [26] with a similar but less strained ligand system. This is suggestive of a distorted geometry. A distortion from a 90° facial coordination mode similar to that seen for L1 in (**8**) is expected. Reaction of (**9**) with a bulky thiolate (2,6-dimethylthiophenol*) was performed in an attempt to sterically insure a tetrahedral geometry. However this yielded only reduction (Cu(I)) products above −77 °C. Ligand modification may enable us to stabilize a copper 'blue' model system.

The ligands described here offer a facile and direct route to a variety of biologically relevant compounds. Further work employing these ligands and their derivatives is underway. Accurate model compounds for both hemocyanin and the copper 'blue' proteins are our synthetic goals.

Acknowledgements

We thank NSERC of Canada for financial support of this work. Paul C. Kierkus is thanked for the preparation of L2 and 2,6-dimethylthiophenol.

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*2,6-dimethylthiophenol was prepared by a similar method to that described in reference 35.