

Reactivity of some cuprous salts towards ten-membered macrocyclic disulphides: A new route to the synthesis of Cu(II)-thiolates

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Abstract. Cuprous ion is found to be quite reactive towards disulphide present in a macrocycle. Thus, when $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ or $[\text{Cu}(\text{MeCN})_4]\text{ClO}_4$ is allowed to reflux in acetonitrile with a ten-membered macrocycle containing two amino nitrogens and one disulphide donor in an atmosphere of nitrogen, electron transfer takes place from the metal centre to the disulphide group. As a result, copper is oxidised to the + 2 state and the disulphide reduced to thiolates. The thiolates then bind the Cu(II) and form discrete and neutral CuN_2S_2 complexes. Syntheses of two new CuN_2S_2 complexes have been achieved following this route. The reactions take place smoothly and give the desired product in excess of 25% yield with respect to the macrocycle. Electronic absorption spectral results are consistent with a nearly square planar geometry. Each of the two complexes isolated exhibits quasi-reversible Cu(II)/Cu(I) couple with E_r near -0.3 V vs SCE. Both the complexes are further characterised by room temperature magnetic susceptibility, EPR spectroscopy at 298 and 77 K and elemental analyses.

Keywords. Cu(II)-thiolate; synthetic method; macrocycle; Cu-blue protein models.

1. Introduction

Interconversions between thiol and disulphide are important in chemistry as well as in biochemistry. Transition metal ions like Fe(II) (Koch *et al* 1975), Ti(III) (Akers *et al* 1987), Co(II) (Pattenden 1988) have been used to reduce disulphides to the corresponding thiolates which then coordinate the metal ion forming metal thiolates. In such reactions, the formal oxidation state of the metal ion increases by one with electron transfer from the metal to the disulphide. Also, specific thiols like propane-1,3-dithiol (Ranganathan and Jayaraman 1991) and dithiothreitol (Dabre 1986) have been used to reduce disulphide bonds in peptides. Besides, hydroxyl radicals generated by Cu(II)/ascorbic acid/ O_2 system can cleave disulphides present in small synthetic peptides (Inoue and Hirobe 1987). It is of interest to us to find out whether a Cu(I) salt can reduce a disulphide to thiolates and in the process a stable Cu(II)-thiolato complex can be formed. Synthesis of Cu(II)-thiolato complexes with different coordination geometries to model the active sites of copper proteins is an area of considerable current interest (Casella *et al* 1990; Kitajima *et al* 1990; Mandal and Bharadwaj 1992). Isolation of stable Cu(II)-thiolates is difficult due to the facile decomposition that takes place when a Cu(II) salt is allowed to react with a thiol (Davis *et al* 1983; Back *et al* 1985). However, surmounting this redox instability in different ways (Casella *et al* 1990;

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Kitajima *et al* 1990; Hughey *et al* 1979; Becher *et al* 1983), a number of Cu(II)-thiolato complexes have been isolated and characterised. Cu(I) salts when allowed to react with acyclic disulphides, do not lead to the desired product. Therefore, we started with the idea that if a Cu(I) ion could be anchored in a macrocycle by bond formation with donors that include two nitrogens and a disulphide, then this might facilitate electron transfer from Cu(I) to the disulphide to reduce it to thiolates. The Cu(II) ion, formed as a result of the electron transfer could then be bonded to the thiolates. Indeed, we were able to isolate two neutral CuN_2S_2 complexes by this method. Isolation and characterisation of the complexes are described here.

2. Experimental

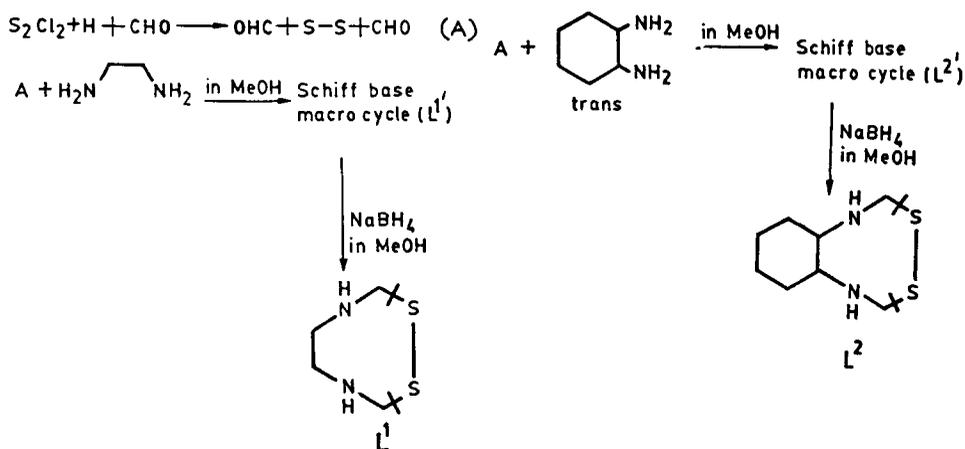
Materials: Reagent grade sulphur monochloride, isobutyraldehyde and *trans*-1,2-diaminocyclohexane (E Merck) were used as received. Ethylenediamine and all the solvents (Glaxo, India) were purified prior to use following standard procedures (Perrin *et al* 1966).

Measurements: Spectroscopic data were collected as follows. IR (KBr disc, $4000\text{--}400\text{ cm}^{-1}$), Perkin-Elmer model 1320; electronic absorption spectra (at 298 K, acetonitrile or dichloromethane as the solvent), Perkin-Elmer model Lambda-2; proton NMR (80 MHz, CDCl_3 , standard SiMe_4), Bruker WP 80 FT instrument; magnetic susceptibility (at 300 K, $[\text{CoHg}(\text{SCN})_4]$ standard), Cahn Faraday magnetic balance; EPR (X band, solid and solution, diphenylpicrylhydrazyl (DPPH) standard), Varian E-109 with solute concentrations of $1 \times 10^{-3}\text{ mol dm}^{-3}$ in acetonitrile or dichloromethane at 298 K as well as at 77 K. Solution electrical conductivity was measured with a model CM-82T Elico conductivity bridge (Hyderabad, India) with solute concentrations of $\approx 1 \times 10^{-3}\text{ mol dm}^{-3}$. Cyclic voltammetric measurements were performed on a PAR model 370-4 electrochemistry system: 174A polarographic analyzer; 175 universal programmer and RE 0074 x-y recorder. Potentials were recorded at 298 K of dinitrogen flushed solutions containing a complex ($1.0 \times 10^{-3}\text{ mol dm}^{-3}$) and NBu_4ClO_4 (0.15 mol dm^{-3}) as supporting electrolyte relative to a saturated calomel electrode (SCE) and are uncorrected for liquid junction potentials. The working electrode was a PAR model G0021 glassy carbon electrode. Under our experimental conditions, the reversible ferrocenium-ferrocene couple ($E_f = 0.40\text{ V}$ vs SCE in acetonitrile) has ΔE_p of 80 mV, which was used as the criterion for electrochemical reversibility (Weiner and Basu 1980) ($E_f = 0.5(E_{pc} + E_{pa})$; E_{pc} and E_{pa} are the cathodic and the anodic peak potentials respectively). Microanalyses were carried out at the Central Drug Research Institute, Lucknow.

3. Syntheses of ligands and complexes

The ligands were synthesized in several steps as shown in scheme 1. Formation of the complexes is illustrated in scheme 2.

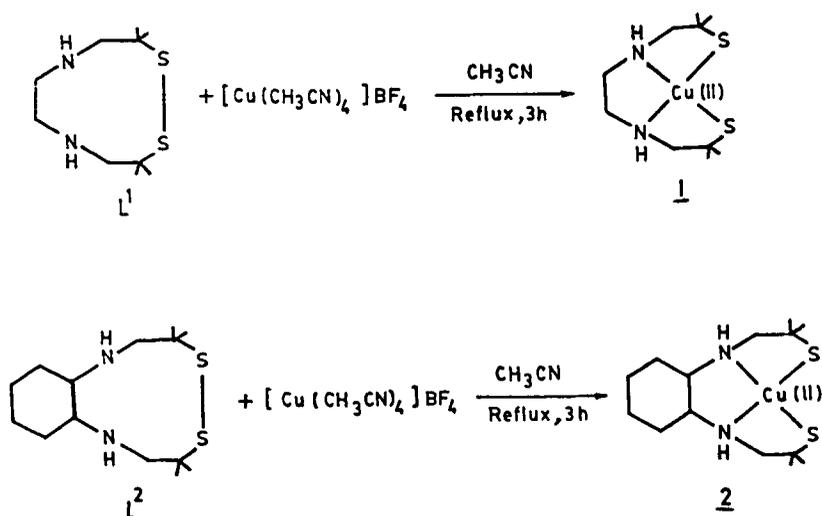
Di-isobutyraldehyde disulphide: It was prepared by homolytic cleavage of S-Cl bonds of sulphur monochloride with isobutyraldehyde by modifying a published procedure (D'Amico and Dahl 1975). Sulphur monochloride (20 g; 0.15 mol) mixed with 25 ml of dry CCl_4 was added dropwise to a warm (40°C) solution of freshly distilled isobutyraldehyde (21.4 g; 0.30 mol) in 40 ml of dry CCl_4 with stirring. As soon as sulphur monochloride came into contact with isobutyraldehyde, copious evolution of HCl gas



Scheme 1. Stepwise synthesis of the macrocycles.

took place which was driven out of the reaction vessel by occasional passage of N_2 gas through it. Total addition time was 2 h at the end of which the reaction mixture was maintained at 40°C for 48 h for completion of the reaction. After that period, CCl_4 was evaporated off completely, the pale yellow thick liquid washed several times with water and finally distilled under reduced pressure to obtain the dialdehyde as a pale yellow oily liquid (15 mm; $90\text{--}100^\circ\text{C}$) in 81% yield. $^1\text{H NMR}$ (80 MHz; solvent CDCl_3 ; standard SiMe_4) 1:1 (12H, s, 4 CH_3) and 9:0 (2H, s, 2CHO).

Synthesis of the Schiff base L^1 : Ethylenediamine (2 g; 0.03 mol) in 5 ml methyl alcohol was slowly added to di-isobutyraldehyde disulphide (7 g; 0.03 mol) in 20 ml of methyl alcohol at room temperature with constant stirring. The colourless solution was heated under reflux for 30 min, reduced to about 15 ml in a rotary evaporator and finally kept at



Scheme 2. Formation of the Cu(II)-thiolates.

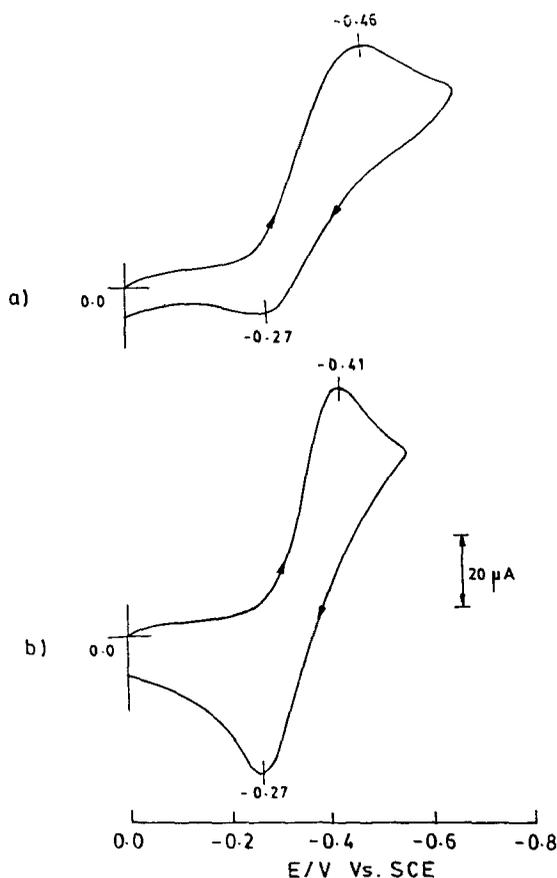


Figure 1. Cyclic voltammograms for 1 (a) and 2 (b).

5°C for 10 h. The desired product was collected as colourless plates by filtration and dried in air. Yield 80% m.pt. 170°C (uncorrected), $\text{IR}_{\text{max}}/\text{cm}^{-1}$ 1652 (C=N). $^1\text{H-NMR}$ (80 MHz, solvent CDCl_3 ; standard SiMe_4) 1.3(12H, *d*, CH_3); 3.2 and 4.1 (4H, AB type, $\text{NCH}_2\text{CH}_2\text{N}$) and 6.8 (2H, *s*, 2 imine). Formation of the macrocycle, L^1 was confirmed by X-ray crystallography (Clegg 1993).

The corresponding Schiff base, $\text{L}^{2'}$ could be prepared as colourless plates following the above procedure and using *trans*-1,2- diaminocyclohexane instead of ethylenediamine in 85% yield. m.p. 140°C (uncorrected) $\text{IR}_{\text{max}}/\text{cm}^{-1}$ 1653 (C=N). $^1\text{H-NMR}$ (80 MHz; solvent CDCl_3 ; standard SiMe_4) 1.3(12H, *d*, 4 CH_3); 1.8(8H, *m*, 4 CH_2); 2.8(2H, *d*, 2CH) and 6.8 (2H, *s*, 2 amine). Formation of the macrocycle, $\text{L}^{2'}$ was confirmed by X-ray crystallography (Bharadwaj *et al* 1991).

Synthesis of the ligand, L^1 : The ligand L^1 was synthesized by the reduction of the Schiff base, L^1 using NaBH_4 as the reductant following a published procedure (Joshua *et al* 1987). The ligand L^1 was isolated as its dihydrochloride salt. The free ligand was obtained as a colourless oily liquid by treating the dihydrochloride with aqueous KOH followed by extraction with CH_2Cl_2 and finally evaporating off all CH_2Cl_2 . Yield 32% $^1\text{H-NMR}$ (80 MHz; solvent CDCl_3 ; standard SiMe_4) 1.3(12H, *d*, 4 CH_3); 2.1(2H, *sbr*, 2NH) and 2.75(8H, *m*, 4 CH_2).

Synthesis of the ligand, L²: This ligand was synthesized using the same procedure as above. The pure compound was isolated in 56% yield as a colourless oily liquid. ¹H NMR (80 MHz; solvent CDCl₃; standard SiMe₄) 1.3(12H, *d*, 4CH₃) and 1.45–3.14(16H, *m*, all other protons).

Synthesis of the cuprous salts: Both [Cu(MeCN)₄]BF₄ and [Cu(MeCN)₄]ClO₄ were synthesized following a literature method (Hathaway *et al* 1961).

Reactivity of the cuprous salts towards L¹ and L²: The cuprous salts react readily with either macrocycles in boiling acetonitrile in an atmosphere of nitrogen forming the complexes, 1 and 2 respectively in high yields.

Synthesis of the complex, 1: To a solution of the ligand L¹ (0.47 g; 2 mmol) in 30 ml of acetonitrile, solid Cu(I)-salt (0.63 g; 2 mmol) was added and the mixture was heated under reflux. Colour of the solution slowly changed to dark red-brown. After 3 h of reflux, the solution was filtered using Schlenk techniques and the filtrate was reduced to about 10 ml in a stream of nitrogen gas. The red-brown solid that deposited was collected by filtration and dried in a stream of nitrogen. Yield 32% (based on the ligand). (Found: C, 41.03; H, 7.21; N, 9.70; S, 21.62. C₁₀H₂₂N₂S₂Cu requires C, 40.33; H, 7.39; N, 9.41; S, 21.51%).

Synthesis of the complex, 2: A similar procedure afforded the Cu(II) complex with ligand L² in 34% yield (based on the ligand). (Found: C, 48.17; H, 8.10; N, 7.75; S, 18.61. C₁₄H₂₈N₂S₂Cu requires C, 47.79; H, 7.96; N, 7.96; S, 18.20%).

The complexes could be synthesized in 29% and 27% yields respectively by reacting [Cu(MeCN)₄]ClO₄ instead of [Cu(MeCN)₄]BF₄ with the macrocycles.

Caution – Care must be taken when reacting with a perchlorate salt as it may form explosive mixtures with organic compounds.

4. Results and discussion

The complexes are air-stable in the solid state. In solvents like acetonitrile, DMF and DMSO, they are air-stable for at least two days. Both the complexes behave as nonelectrolytes in solvents like dichloromethane, methanol and acetonitrile. The infrared spectra of the complexes rule out the presence of BF₄⁻ or ClO₄⁻ groups (Nakamoto 1986).

Electronic absorption bands observed for 1 and 2 at 300 K in acetonitrile are listed in table 1 along with assignments. The band positions are not shifted to any significant extent when the electronic spectra are recorded in the non-coordinating solvent, dichloromethane in case of either complexes, signifying minimum solvent interactions with the chromophore. For four-coordinate Cu(II) complexes, the *d-d* bands may occur in the range 500–850 depending upon the stereochemistry and nature of the donor atoms as well (Hathaway 1972). Cu(II) complexes with N₂S₂ donor set (Becher *et al* 1982; Bharadwaj *et al* 1986; Casella *et al* 1990) and having square planar or slightly distorted square planar coordination geometry, the ligand field transitions occur in the region, 550–600 nm. The broad band that occurs at 570 nm in 1 is, therefore, assigned as the ligand field transition. The corresponding transition in 2 occurs at 590 nm. High intensities of these bands are due to intensity stealing from nearby charge transfer bands (Miskowski *et al* 1976; Bharadwaj *et al* 1986). The σ(N) → Cu(II) LMCT transition, for parent [Cu(en)₂]²⁺ (en = ethylenediamine) complex, appears at 240 nm; alkylation of the amine lowers its ionization potential (Robin 1974) and results in a systematic red-shift of this absorption (Yokoi and Isobe 1969; Kennedy and Lever 1973). The strong bands at 285 and 280 nm for 1 and 2 respectively are thus assignable to σ(N) → Cu(II) LMCT transitions. The near-UV bands at 370 (for 1) and 390 nm (for 2) are too low in energy to be charge transfer

Table 1. Cyclic voltammetric and electronic spectral data for the complexes in acetonitrile at 298 K.

Complex	Cu(II)/Cu(I) couple ^a		λ_{\max} (nm) (ϵ_{\max} (dm ³ mol ⁻¹ cm ⁻¹))	Assignment
	E_f (V)	ΔE_p (mV)		
<u>1</u>	-0.37	185	570(375) 370(1250) 270(5100)	<i>d-d</i> σ (thiolate) \rightarrow Cu(II) σ (N) \rightarrow Cu(II) + ligand absorption
<u>2</u>	-0.34	140	585(665) 475(1560) 390(1675) 280(5220)	<i>d-d</i> π (thiolate) \rightarrow Cu(II) σ (thiolate) \rightarrow Cu(II) σ (N) \rightarrow Cu(II) + ligand absorption

^aCyclic voltammetric data presented here were recorded at 20 mV s⁻¹

transitions involving aliphatic amines and Cu(II) (Miskowski *et al* 1976). It is known, however, that for tetragonal thiolato complexes, the σ (thiolate) \rightarrow Cu(II) LMCT transition occurs (Bharadwaj *et al* 1986) around 350 nm. Therefore, the 370 nm band in 1 and the 390 nm band in 2 are similarly assigned. A thiolate coordinated to Cu(II) can exhibit two π -symmetry LMCT transitions one on either side of the σ -transition (Penfield *et al* 1985; Mandal and Bharadwaj 1992). In 2 a band appears at 475 nm which is of right energy to be the lower energy π -transition. This band is not observable in 1. Also, in neither case is the higher energy π (thiolate) \rightarrow Cu(II) transition seen.

Effective magnetic moments at 300 K for 1 and 2 are found to be 2.01 and 1.98 BM respectively. The values are typical of discrete mononuclear Cu(II) complexes (Cotton and Wilkinson 1988). Each of the complexes show only a broad EPR signal in the solid state at room temperature ($g_{\text{iso}} = 2.046$ and 2.076 for 1 and 2 respectively). The spectral shape does not change upon cooling to liquid nitrogen temperature (77 K). In acetonitrile solution ($\approx 1 \times 10^{-3}$ M) a four-line signal typical of Cu(II) in solution is observed for each complex. The isotropic parameters are: $g_{\text{iso}} = 2.113$ and $A_{\text{iso}}^{\text{Cu}} = 76 \times 10^{-4}$ cm⁻¹ for 1; $g_{\text{iso}} = 2.057$ and $A_{\text{iso}}^{\text{Cu}} = 82 \times 10^{-4}$ cm⁻¹ for 2. These values resemble closely with those obtained with an almost planar CuN₂S₂ complex (Bharadwaj *et al* 1986). Upon cooling to 77 K, the solution spectra of 1 and 2 change to broad solid-state like spectra ($g_{\text{iso}} = 2.052$ and 2.081 for 1 and 2 respectively) which are not indicative of their structures.

The electron transfer properties of the complexes are probed by cyclic voltammetry. The data at 20 mV s⁻¹ are shown in table 1. The following observations are made: Complex 1 exhibits a quasi-reversible one electron cyclic response ($E_p = 185$ mV) with E_f at -0.37 V at the scan rate of 20 mV s⁻¹, with tenfold increase in the scan rate, E_p increases by 70 mV; the ratio, i_{pa}/i_{pc} is 0.95 for all the scan rates; complex 2 also exhibits a quasi-reversible ($\Delta E_p = 140$ mV) one electron response with E_f at -0.34 V at 20 mV s⁻¹; with tenfold increase in the scan rate, ΔE_p increases by 50 mV; the ratio, i_{pa}/i_{pc} is 1.1 for all the scan rates. The peaks are assignable to the following redox reactions,



For complex **1**, on scanning further in the negative side, one more cathodic peak is observed at -1.26 V although on scan reversal, the corresponding anodic peak is not observed which is due to instantaneous decomposition of the reduced product (Nicholson and Shain 1964). However, a broad and intense anodic peak is observed at about -0.27 V. The peak at -1.26 V corresponds to reduction of Cu(I) to formally Cu(0) state when it undergoes chemical decomposition and the metallic copper gets deposited at the electrode surface. The peak at -0.27 V is then due to oxidation of deposited copper (Pilo *et al* 1991). In case of **2**, the corresponding peaks appear at -0.82 and -0.25 V. No peak is seen on scanning in the positive side for either complex.

5. Conclusion

This study shows for the first time that Cu(I) can cleave disulphide bonds in suitably designed macrocycles to form Cu(II)-thiolates. A few other macrocycles containing disulphides are being probed in order to establish the generality of this method of synthesis of Cu(II)-thiolates.

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