Synthesis and Structure of a Semi-rigid Dinucleating Macrocycle containing the 2,6-Bis(thiomethyl)pyridine Unit and Reactions of its Copper(II) Complex

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A new dinucleating macrocyclic ligand (**5**), possessing two 'soft' pyridyldithio chelating units held rigidly apart by a *m*-xylyl group, is readily synthesized; its crystal structure has been determined, and its dinuclear copper(II) complex shows moderate activity as a catalyst for alkene oxidation and phosphate hydrolysis.

Pyridine containing macrocycles have received considerable attention owing to their metal ion complexing properties.[1] Those capable of dinuclear complexation are of particular interest as catalysts and as models of certain metalloenzymes. A number of dinucleating macrocyclic ligands are known which incorporate two or more sulphur atoms into each metal co-ordination site.[2,3] However, most of the dinucleating mono-macrocyclic ligands recently studied are composed of two metal binding sites linked by flexible polymethylene chains. We sought dinucleating macrocycles in which the separation and orientation of the two metal chelating units were more clearly defined by a rigid spacer.

The bis-(pyridyldithio)-containing macrocycle (**5**) possesses two 'soft' co-ordination sites separated by *m*-xylylene bridges. Molecular mechanics calculations suggested that a low energy conformation of the macrocycle [Figure 1(b)] might exist if lone pair repulsions between heteroatoms were overcome through metal ion co-ordination. In such a conformation, the metal ions would lie approximately 5 Å apart and might share a bridging ligand, L [Figure 1(a), (**5**)·M_2L]. Separation of the metal binding sites by rigid groups also protects against collapse of the ligand around a single metal.

Macrocycle (**5**) was prepared as shown in Scheme 1 by the reaction first of 1,3-bis(mercaptomethyl)benzene with 2-(bromomethyl)-6-(hydroxymethyl)pyridine[4] (2 equiv.), using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2 equiv.) in tetrahydrofuran (THF), (reflux, 48 h) to yield diol (**3**) in 41% yield after column chromatography (silica, 5% MeOH in $CHCl_3$). Conversion to the reactive bismethanesulphonate (**4**) [$MeSO_2Cl$ (4 equiv.), NEt_3 (2.5 equiv.), 12 h] proceeded in 90% yield. High dilution techniques were employed for the macrocyclization. Compounds (**1**) and (**4**) in dimethylformamide (DMF) were added separately using a syringe pump to a suspension at 50 °C Cs_2CO_3 (4 equiv.) in DMF during 3 h and then allowed to further react overnight. After aqueous work-up and filtration through silica gel, the macrocycle was obtained in 65% crude yield. Colourless crystals† were precipitated from $CHCl_3$–MeOH.

An *X*-ray crystal structure determination‡ indicated that the macrocycle is only partially pre-organized for dinuclear complexation, as shown in Figure 2. The macrocycle is centred about an inversion centre, and each Py–S_2 group has one sulphur atom rotated outwards to avoid lone pair repulsion. Addition of copper bistrifluoromethanesulphonate to a solution of (**5**) in $CHCl_3$ gave a green solution of the dinuclear copper(II) complex with absorbances at 390 and 690 (weak) nm in the visible spectrum. The stoicheiometry of complexation could be monitored spectroscopically at 390 nm and clearly indicated formation of a 1 : 2 ligand–Cu complex. The i.r. spectrum indicates the presence of small amounts of water, which suggests that H_2O may occupy vacant co-ordination sites in the dinuclear complex.

Dinuclear copper complexes are currently under investigation as models for copper-containing enzymes.[5] As an initial step toward determining the efficacy of the (**5**)·$2Cu^{2+}$ complex

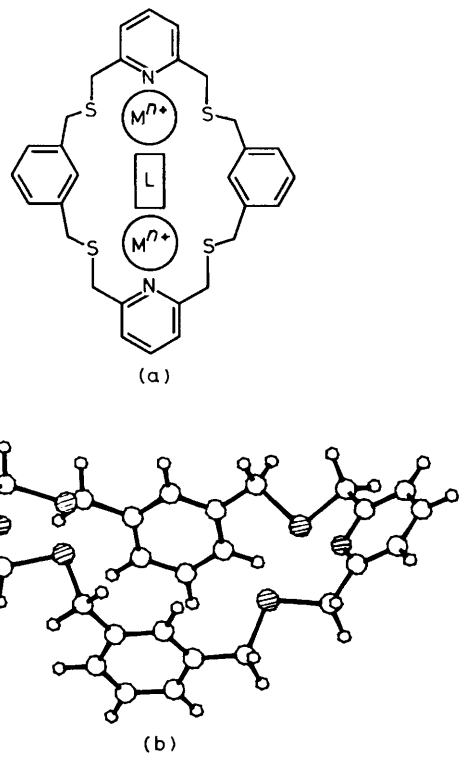
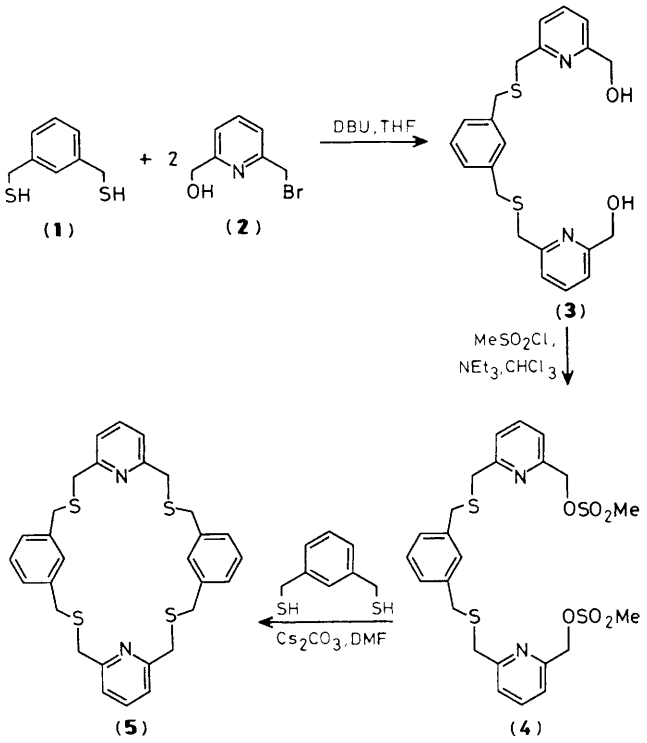


Figure 1. (a) Possible structure of a dinuclear complex of (**5**); (b) structure of (**5**) based on molecular mechanics calculations.

† All new compounds yielded satisfactory spectral and microanalytical data.

‡ *Crystal data for* (**5**): $C_{30}H_{30}N_2S_4$, monoclinic, space group $P2_1/c$, a = 11.651(2), b = 9.415(2), c = 12.292(3) Å, β = 98.75(2)°, Z = 2, D_c = 1.36 g/cm³, U = 1332.6(5) Å³. All intensity measurements were made at room temperature with graphite-monochromated Cu-K_α radiation using an ω-scan technique (3° ≤ 2θ ≤ 114°) on a Nicolet R3m diffractometer. 1679 of 1800 unique reflections ($|F_o|>3\sigma|F_o|$) were used in the refinement. The structure was solved by direct methods using SHELXTL. Following refinement of the non-hydrogen atoms using anisotropic thermal parameters, the hydrogen atoms were entered at idealized positions (C–H 0.96 Å, ∠CCH 109 or 120°) and were varied using a riding model. Refinement converged at R = 0.067, R_w = 0.073. The four largest peaks in a final difference map (e⁻/Å³ = 0.60—0.73) were in the vicinity of the sulphur atoms. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 1. Synthesis of macrocyclic ligand (**5**).

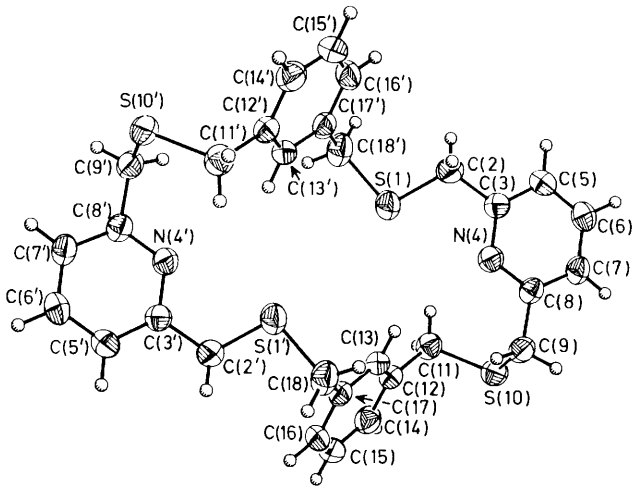


Figure 2. ORTEP view of macrocycle (**5**). Relevant dimensions (Å or °) are: S(1)–C(2) 1.799(3), C(9)–S(10) 1.822(4), C(18)–S(1′) 1.825(4), S(10)–C(11) 1.825(3); C(2)–S(1)–C(18′) 101.1(2), S(1)–C(2)–C(3) 109.9(2), C(8)–C(9)–S(10) 112.8(2), C(9)–S(10)–C(11) 101.0(1), S(10)–C(11)–C(12) 113.9(2), C(17)–C(18)–S(1′) 114.2(2).

in redox reactions, we studied catalysis of alkene oxidation by iodosylbenzene. Both $Cu(OSO_2CF_3)_2$ and dinuclear copper complexes have been reported to catalyse alkene epoxidation.[6] Using similar reaction conditions,§ we found that (**5**)·$2Cu^{2+}$ reacted rapidly with PhIO and caused its complete dissolution within a few hours, while a $Cu(OSO_2CF_3)_2$ solution showed PhIO remaining even after 24 h. The oxidations of styrene and *trans*-stilbene were monitored by gas chromatography. Both styrene oxide and benzaldehyde were detected as products of styrene oxidation (7 and 4%, respectively, based on initial alkene concentration); however, PhCHO (9%) was the only product of *trans*-stilbene oxidation in the presence of the macrocyclic complex. The reactions containing $Cu(OSO_2CF_3)_2$ produced only trace quantities of oxidation products under these reaction conditions. Although yields are still rather low, it seems that the dinuclear complex is more effective than a simple copper salt as an oxidation catalyst. Re-isolation of the macrocycle after removal of copper indicated partial decomposition of the ligand during the oxidations.

Copper salts have also been reported to facilitate ester and amide hydrolysis.[7] When one equivalent of the dinuclear copper trifluoromethanesulphonate complex of (**5**) was added to a solution of 2,4-dinitrophenyl phosphate,¶ the half-life for appearance of 2,4-dinitrophenolate decreased from 278 to 179 min, representing a nearly twofold increase in the rate of hydrolysis in the presence of the complex. From this result and those of the oxidation studies above, it appears that the dinuclear copper complexes of semi-rigid macrocyclic ligands such as (**5**) are of interest in promoting *both* hydrolytic and oxidative processes. Related macrocycles in which the distance between metal ions and relative orientation of the chelating groups are carefully controlled may show enhanced activity as catalysts.

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§ Alkene (0.1 mmol), PhIO (0.2 mmol), and copper complex (0.01 mmol) in MeCN at 20 °C for 6 h.

¶ 5×10^{-5} M in EtOH–H_2O (1 : 1) buffered to pH 7.4.

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