Synthesis and structure of tetranuclear zinc(II) and binuclear copper(II) complexes of a dithiolate compartmental macrocyclic ligand: a model for the binuclear Cu_A site in cytochrome c oxidase and N_2O reductase

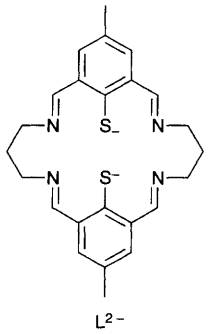
Neil D. J. Branscombe,[a] Alexander J. Blake,[a,b] Armando Marin-Becerra,[b,c] Wan-Sheung Li,[a] Simon Parsons,[b] Lena Ruiz-Ramirez[c] and Martin Schröder*[a,b]

[a] *Department of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD*
[b] *Department of Chemistry, The University of Edinburgh, West Main Road, Edinburgh, UK EH9 3JJ*
[c] *UNAM Facultad de Quimica, Departament di Quimica Inorganica, Ciudad Universitaria 04510, Mexico DF, Mexico*

The tetranuclear cluster $[Zn_2L(\mu\text{-}OH)]_2[ClO_4]_2\cdot 2H_2O$ (L = dianion of the condensation product of 1,3-diaminopropane and 2,6-diformyl-4-methylthiophenol) shows two unique dinuclear Zn^{II} units linked by two μ-hydroxy bridges; the structure of the Cu^{II} complex $[Cu_2L(HOMe)_2](NO_3)]PF_6$ shows square-pyramidal coordination at the Cu centres with two thiolate bridges and two terminal N-donors, with a Cu···Cu separation of 3.264(2) Å.

Thiolate bridges and binding at Ni, Cu and Zn centres have been implicated in a number of metalloproteins including hydrogenase from *Desulfovibrio gigas* (Ni/Fe),[1] cytochrome c oxidase from *Paracoccus denitrificans* (Cu/Cu)[2] and yeast alcohol dehydrogenase and zinc fingers (Zn).[3] Thiolate-bridged complexes of first-row transition-metal centres can be notoriously labile, and we reasoned that compartmental macrocyclic ligands incorporating endogeneous rather than exogeneous dithiolate donors represented a methodology for the stabilisation of polynuclear centres bridged by thiolate donors. Furthermore, such compartmental ligands may afford constrained metal environments akin to the influence of protein folds and pockets. We have reported[4] previously the template synthesis of the binuclear complex $[Ni_2L]^{2+}$ incorporating Ni^{II} centres bridged by two thiolate donors and terminal N-donors. Formally, the mixed Ni/Fe analogue would be a related structural model for the Ni/Fe site in hydrogenase. We were particularly interested in the binuclear Cu complexes of L^{2-} since this would be a direct structural model for the binuclear Cu_A site in cytochrome c oxidase. However, we found that template syntheses at Cu^{II} afforded very low yields of often intractable products. We report herein the synthesis and structures of a novel tetranuclear Zn^{II} complex of L^{2-} and its conversion to the binuclear Cu^{II} complex $[Cu_2L]^{2+}$, both complexes incorporating stable dithiolate bridges.

The reaction of equivalent amounts of $Zn(ClO_4)_2$,† 2,6-diformyl-4-methylthiophenol and 1,3-diaminopropane in MeOH gave a yellow product, which on recrystallisation from MeCN–Et_2O afforded yellow single crystals. The X-ray structure determination‡ revealed a tetranuclear complex $[Zn_2L(\mu\text{-}OH)]_2[ClO_4]_2\cdot 2H_2O$ (Fig. 1) with $(Zn_2L)^{2+}$ units bridged *via* two μ-OH bridges. The B subunit contains two equivalent Zn^{II} centres in square-pyramidal geometries, each equatorially bound to the N_2S_2 donor set of one macrocycle [Zn(B)–N 2.111(14), 2.144(14), 2.117(14), 2.12(2); Zn(B)–S 2.422(5), 2.486(6), 2.32(6), 2.457(5) Å] and axially bound to one μ-hydroxy moiety which bridges to form the dimeric links [Zn(B)–O 1.979(11), 1.976(11) Å] to subunit A. The macrocycle in subunit B adopts a folded conformation with an angle between the planes defined by the two thiophenolate moieties of 57.3° (see Graphical Abstract). This folding creates the necessary space required by the bulky bridging thiolates. However, the macrocycle in subunit A cannot fold in the same manner as in subunit B owing to the bent nature of the μ-OH bridges which would otherwise force the S(2A)···S(2B) distance to become prohibitively short. Thus, the macrocycle adopts an alternative orientation involving flipping of one thiophenolate head unit towards the B subunit, thereby disposing S(2A) in the opposite direction, away from S(2B). The angle between the planes defined by the two thiophenolate groups is 116.4° in subunit A with S(1A)···S(2A) 3.21(2) and S(1B)···S(2B) 3.43(2) Å. The coordination geometries at the Zn^{II} ions in subunit A



L^{2-}

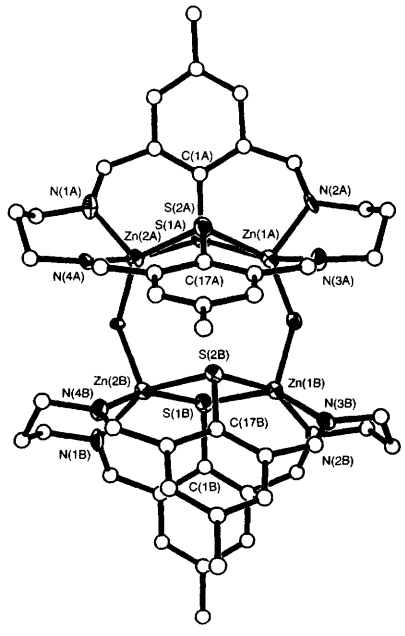


Fig. 1 View of the structure of $[Zn_2L(H_2O)_2][ClO_4]_2$ with numbering scheme adopted. Selected bond angles (°): N(2A)–Zn(1A)–N(3A) 92.9(5), N(2A)–Zn(1A)–S(2A) 114.1(4), N(3A)–Zn(1A)–S(2A) 85.4(4), N(2A)–Zn(1A)–S(1A) 87.1(4), N(3A)–Zn(1A)–S(1A) 164.2(4), S(2A)–Zn(1A)–S(1A) 80.2(2), N(1A)–Zn(2A)–N(4A) 94.0(6), N(1A)–Zn(2A)–S(2A) 118.1(4), N(4A)–Zn(2A)–S(2A) 88.9(4), N(1A)–Zn(2A)–S(1A) 86.0(4), N(4A)–Zn(2A)–S(1A) 167.4(4), S(2A)–Zn(2A)–S(1A) 80.0(2).

may be described as intermediate between square-pyramidal and trigonal-bipyramidal [Zn(A)–N 2.086(13), 2.164(6), 2.080(15), 2.134(15); Zn(A)–S 2.592(7), 2.384(6), 2.341(6), 2.637(5); Zn(A)–O 1.941(11), 1.956(10) Å]. The Zn···Zn distances and Zn–S–Zn angles within subunits A and B are 3.540(5)/3.497(5) Å, and 85.2(2)/97.0(2) and 90.1(2)/92.2(2)° respectively. Interestingly, hydroxy-bridged binuclear Zn^{II} centres have been shown to be the active sites of certain aminopeptidases.[5] Acidification of $\{[Zn_2L(\mu\text{-}OH)]_2^2\}^+$ affords $[Zn_2L(OH_2)]^{2+}$, while addition of $MeCO_2^-$ or reaction of $Zn(O_2CMe)_2$, 2,6-diformyl-4-methylthiophenol and 1,3-diaminopropane in MeOH affords $[Zn_2L(O_2CMe)]^+$.

Zn^{II} is redox inert and is thus a particularly efficient templating ion for thiolates which may potentially undergo oxidition to disulfides in the presence of Cu^{II}. Reaction of $[Zn_2L(O_2CMe)]PF_6$ with $Cu(NO_3)_2{\cdot}6H_2O$ in EtOH affords a very dark solution from which a black product can be isolated in high yield. Crystals of the product were grown from MeOH and the single-crystal structure‡ of $[Cu_2L(HOMe)_2(NO_3)]PF_6$ determined. The structure of the cation shows (Fig. 2) two Cu^{II} centres each bound to two imine N-donors [Cu–N 2.000(4), 2.011(4), 2.000(4), 2.005(4) Å] and two bridging benzenethiolate S-donors [Cu–S 2.290(2), 2.306(2), 2.294(2), 2.306(2) Å] of the compartmental macrocycle. Each metal centre is axially bound to one O-donor from MeOH to complete the distorted square-pyramidal coordination [Cu–O 2.359(4), 2.386(4) Å]. Also present within the cleft formed by the folded macrocycle is one NO_3^- counter ion, Cu···O(NO_3^-) 2.702(5) Å. The conformation of the macrocycle is very similar to that observed for the corresponding Ni^{II} complex,[4] with a Cu···Cu separation of 3.264(2) Å and S(1)···S(2) 3.098(5) Å.

Although thiolate complexes of Cu^{I}[6] and Cu^{II}[7] are well known, $[Cu_2L(HOMe)_2(NO_3)]PF_6$ represents a rare example of a stable, dithiolate-bridged dinuclear Cu^{II} complex, and is therefore an important structural model for the Cu_A site in cytochrome c oxidase. However, most importantly, $[Cu_2L]^{2+}$ is stable in MeCN, and shows two reversible one-electron (by coulometry) reductions in MeCN (0.1 M $NBu^n_4PF_6$, Pt electrodes, 293 K) at $E_{\frac{1}{2}}$ = −0.605 and −0.805 V *vs.* Fc–Fc$^+$ assigned to the formation of $[Cu^{II}Cu^{I}]$ and $[Cu^{I}Cu^{I}]$ respectively. In addition, a quasi-reversible oxidation is observed at $E_{\frac{1}{2}}$ = +0.585 V *vs.* Fc–Fc$^+$. This oxidative chemistry may reflect oxidation at the metal centres or of the thiolate donors to form disulfide ($2RS^- \rightarrow RSSR$), now implicated in several biological systems including [Ni–Fe] hydrogenase.[1] In comparison, $[Ni_2L]^{2+}$ shows two reversible reductions at $E_{\frac{1}{2}}$ = −1.10, −1.58 V and one reversible and one quasi-reversible oxidation at $E_{\frac{1}{2}}$ = +0.55 and +0.96 V *vs.* Fc–Fc$^+$ respectively. Magnetochemical measurements (μ_{eff} = 1.8 μ_B, Weiss constant $\theta = -1.0 \pm 0.017$ cm^{-1}) and EPR spectroscopy (g_{av} = 2.07, broad signal) confirm that the Cu^{II} centres in $[Cu_2L(HOMe)_2(NO_3)]PF_6$ are essentially non-interacting.

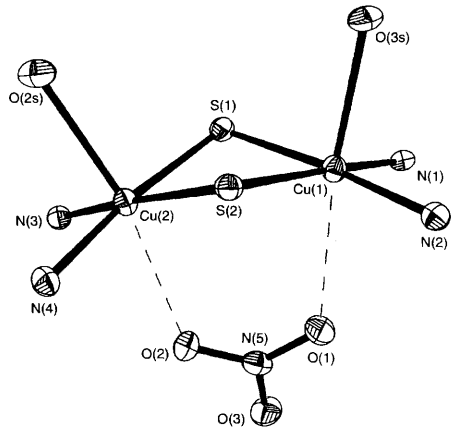


Fig. 2 View of the structure of $[Cu_2L(HOMe)_2(NO_3)]PF_6$ with numbering scheme adopted. Selected bond angles (°): N(2)–Cu(1)–N(1) 95.0(2), N(2)–Cu(1)–S(1) 174.00(12), N(1)–Cu(1)–S(1) 89.64(12), N(2)–Cu(1)–S(2) 90.27(12), N(1)–Cu(1)–S(2) 172.80(12), S(1)–Cu(1)–S(2) 84.77(6), N(4)–Cu(2)–N(3) 94.8(2), N(4)–Cu(2)–S(2) 89.49(13), N(3)–Cu(2)–S(2) 172.71(12), N(4)–Cu(2)–S(1) 172.29(12), N(3)–Cu(2)–S(1) 90.46(12), S(2)–Cu(2)–S(1) 84.68(6).

Tolman and coworkers have reported recently elegant syntheses of separate $[Cu^{II}Cu^{II}]$[8] and $[Cu^{II}Cu^{I}]$[9] complexes incorporating aza headgroups with exogeneous thiolate arms as models for cytochrome c oxidase and N_2O reductase. The complex $[Cu_2L(HOMe)_2](NO_3)]PF_6$ not only models the dithiolate bridge and the two terminal N-donors, but it is also stable in polar solvents including MeCN and unlike the Tolman systems shows fully reversible redox activity suggesting that all three oxidation states $[Cu^{II}Cu^{II}]$, $[Cu^{II}Cu^{I}]$ and $[Cu^{I}Cu^{I}]$ can be stabilised within the same coordination framework. Current work is aimed at characterising the mixed-valence species $[Cu_2L]^+$ to ascertain whether it is a spin-delocalised $[Cu^{1.5}Cu^{1.5}]$ or spin-trapped $[Cu^{II}Cu^{I}]$ species.

We thank the EPSRC, the Wolfson Foundation, the University of Nottingham, and the British Council and UNAM-DGAPA and IN10089 (to A. M.-B.) for support. We thank Dr A. Harrison and Dr G. Whittaker (University of Edinburgh) for magnetochemical measurements and the Manchester University EPSRC National Service for EPR spectra. We also thank referees for helpful comments.

Footnotes

† **CAUTION**: Perchlorates are potentially explosive.

‡ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/268.

References

1 A. Volbeda, M.-H. Charon, C. Piras, E. C. Hatchikian, M. Frey and J. C. Fontecilla-Camps, *Nature*, 1995, **373**, 580.

2 S. Iwata, C. Ostermeier, B. Ludwig and H. Michel, *Nature*, 1995, **376**, 660; T. Tsukihara, H. Aoyama, E. Yamashita, T. Tomizaki, H. Yamaguchi, K. Shinzawa-Itoh, R. Nakashima, R. Yaono and S. Yoshikawa, *Science*, 1995, **269**, 1069.

3 T. Viland and B. Krebs, *Abstracts of Papers of the American Chemical Society*, 1995, **210**, Part 1, 508 (INORG); B. A. Krizek, D. L. Merkle and J. M. Berg, *Inorg. Chem.*, 1993, **32**, 937; J. P. Crow, J. S. Beckman and J. M. McCord, *Biochemistry*, 1995, **34**, 3544.

4 A. J. Atkins, A. J. Blake and M. Schröder, *J. Chem. Soc., Chem. Commun.*, 1993, 1662; A. J Atkins, A. J. Blake, D. Black, A. Marin-Becerra, S. Parsons, L. Ruiz-Ramirez and M. Schröder, *Chem. Commun.*, 1996, 457.

5 S. K. Burley, P. R. David, R. M. Sweet, A. Taylor and W. N. Lipscomb, *J. Mol. Biol.*, 1992, **224**, 113; N. Sträter and W. N. Lipscomb, *Biochemistry*, 1995, **34**, 14792; B. Chevrier, C. Shalk, H. D'Orchymont, J.-M. Rondeau, D. Moras and C. Tarnus, *Structure*, 1994, **2**, 283.

6 I. G. Dance and J. C. Calabrese, *Inorg. Chim. Acta*, 1976, **19**, L41; I. G. Dance, L. J. Fitzpatrick and M. L. Scudder, *J. Chem. Soc., Chem Commun.*, 1983, 546; G. A. Bowmaker, G. R. Clark, J. K. Seadon and I. G. Dance, *Polyhedron*, 1984, **3**, 535; C. P. Rao, J. R. Dorfman and R. H. Holm, *Inorg. Chem.*, 1986, **25**, 428; D. M. Knotter, A. L. Spek, D. M. Grove and G. van Koten, *Organometallics*, 1992, **11**, 4083; D. M. Knotter, D. M. Grove, W. J. J. Smeets, A. L. Spek and G. van Koten, *J. Am. Chem. Soc.*, 1992, **114**, 3400.

7 N. Aoi, Y. Takano, H. Ogino, G.-E. Matsubayashi and T. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1985, 703; N. Aoi, G.-E. Matsubayashi and T. Tanaka, *J. Chem. Soc., Dalton Trans.*, 1987, 241; P. K. Bharadwaj, E. John, C.-L. Xie, D. Zhang, D. N. Hendrickson, J. A. Potenza and N. J. Suger, *Inorg. Chem.*, 1986, **25**, 4541.

8 R. P. Houser, J. A. Halfen, V. G. Young Jr., N. J. Blackburn and W. B. Tolman, *J. Am. Chem. Soc.*, 1995, **117**, 10745 and references therein. See also: R. P. Houser and W. B. Tolman, *Inorg. Chem.*, 1995, **34**, 1632. See also H. Bertagnolli and W. Kaim, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 771.

9 R. P. Houser, V. G. Young Jr and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **118**, 2101.

Received, 12th August 1996; Com. 6/05615F