Aromatic hydroxylation in a new tyrosinase model system and formation of a novel bis(μ-hydroxo)dicopper(II) complex due to an unprecedented ligand coupling reaction

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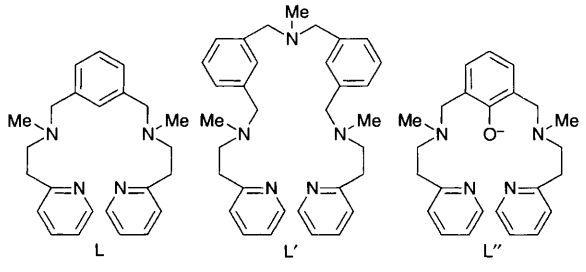
A new binucleating nitrogen-donor ligand exhibits tyrosinase-like activity by bringing about aromatic hydroxylation mediated by copper; the phenoxy- and hydroxy-bridged coppper(II) complex 1 and a novel dihydroxy-bridged copper(II) complex 2 are structurally characterized.

Notable progress has been made to mimic tyrosinase activity using tailor-made binucleating N-donor ligands having *m*-$CH_2C_6H_4CH_2$ spacers between the coordination units.[1–3] Karlin *et al.* reported the first model consisting of a ligand that provides two tridentate bis[2-(2-pyridylethyl)amine] donor units[4] to each copper ion. Interestingly, when 1-pyrazolyl or 2-imidazolyl donor groups fully or partially replace the 2-pyridyl ligands hydroxylation does not occur.[5a] However, when Schiff-base ligands providing three[6] or even only two[5b,7–9] nitrogen donors are used hydroxylation takes place. In order to complete the missing link between the Schiff-base and non-Schiff-base families, we herein report a new ligand system (L) providing only two nitrogen coordination sites at each copper centre and demonstrate hydroxylation of the arene ring. The X-ray structure of the hydroxylated product provides, within the non-Schiff-base family, the first example of a μ-phenolato and μ-hydroxo bridged copper(II) complex. Additionally, we present the first crystal structure of a $\{Cu_2(\mu\text{-}OH)_2\}^{2+}$ core with an unusual ligand assembly (L′).

Reaction of L† (0.4 g, 1.07 mmol) with $[Cu(MeCN)_4]ClO_4$[10] (0.7 g, 2.14 mmol) in dichloromethane (40 ml) under dinitrogen gave a yellow suspension of an extremely air-sensitive copper(I) complex, as noted for related systems.[4–9] When this was exposed to dioxygen (1 atm; room temp.) for 12 h, a deep green solution and a bluish grey precipitate (0.45 g) were obtained. Removal of this solid followed by solvent evaporation resulted in a deep green solid. Slow evaporation of an acetonitrile solution of this afforded at first only a few light blue crystals (**2**) and a bulk of microcrystalline green compound (**1**) while a deep blue solution (≈ 1 ml) still remained. Crystals of the green complex, $[Cu_2L''(OH)][ClO_4]_2$ **1** (0.32 g, 40%), suitable for X-ray analysis were obtained from acetonitrile–diethyl ether.

X-Ray analysis of **1**‡ revealed (Fig. 1) incorporation of two O atoms into the complex (presumably originating from molecular oxygen *via* peroxo–copper intermediates as documented by Karlin *et al.*[4c,d]): one into the aryl–hydrogen bond and the other into the hydroxy bridge. It is worth mentioning here that the present ligand L was so designed as to remove one of the ethylpyridine units in each arm of Karlin's ligand by a methyl group, to pinpoint the number of donor atoms necessary to bring about aromatic hydroxylation while keeping the basic ligand structure fixed.



The structure consists of a discrete dicationic complex. The two Cu^{II} ions are in almost identical square-planar coordination environments. The coordination about each copper is completed with one pyridyl donor and one tertiary aliphatic amine donor from the terminal arms of the binucleating ligand L, and the bridging phenolate and hydroxide donors. The Cu_2O_2 unit deviates from planarity with an O(2)–Cu(1)–O(1)–Cu(2) torsion angle of only 7.2(2)° compared to a value of 9.3(2)° for the corresponding Schiff-base analogue,[8] implying more flexibility in L. The other metric parameters are normal.[8,9]

The phenol ligand HL″ could be separated from complex **1** upon treatment with ammonia.[4b] The ^1H NMR spectrum of the product was similar to that of the ligand prepared separately by the reaction between 2,6-bis(chloromethyl)-4-methylphenol and 2-[(2-methylamino)ethyl]pyridine.[11]

Fig. 2 exhibits the X-ray structural characterization‡ of the light blue solid. It has a dicationic $Cu_2(OH)_2$ bridging unit supported by L′, $[Cu_2L'(OH)_2][ClO_4]_2$ **2**. The unprecendented ligand L′ (we are not aware of a similar ligand coupling reaction in related ligand synthetic methodologies) was formed during the synthesis of L under our experimental conditions.§ The two copper atoms are related by a crystallographically imposed mirror plane containing O(1) and O(2) of the hydroxy groups as well as N(3) and C(17) of the connecting NMe group between the two *m*-$CH_2C_6H_4CH_2$ fragments. The terminal coordination

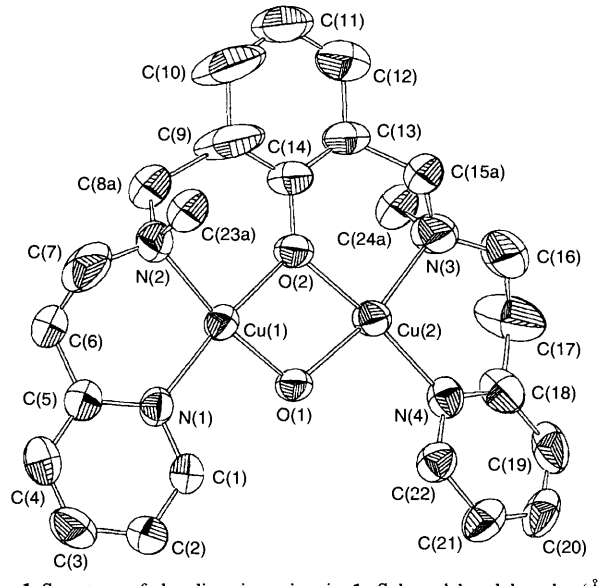


Fig. 1 Structure of the dimeric cation in **1**. Selected bond lengths (Å): Cu(1)–O(1), 1.901(5), Cu(1)–O(2) 1.964(5), Cu(1)–N(1) 2.008(6), Cu(1)–N(2) 2.016(7), Cu(2)–O(1) 1.924(5), Cu(2)–O(2) 1.958(5), Cu(2)–N(3) 2.017(8), Cu(2)–N(4) 1.997(6), Cu(1)···Cu(2) 2.999(1). Selected angles (°): O(1)–Cu(1)–O(2) 78.2(2), N(1)–Cu(1)–N(2) 96.6(3), O(1)–Cu(2)–O(2) 77.8(2), N(3)–Cu(2)–N(4) 96.6(3), N(1)–Cu(1)–O(2) 171.7(2), O(1)–Cu(1)–N(2) 169.2(3), O(1)–Cu(2)–N(3) 166.7(3), O(2)–Cu(2)–N(4) 171.5(2), O(1)–Cu(1)–N(1) 93.6(2), O(2)–Cu(1)–N(2) 91.5(2), O(1)–Cu(2)–N(4) 94.8(2), O(2)–Cu(2)–N(3) 91.3(3).

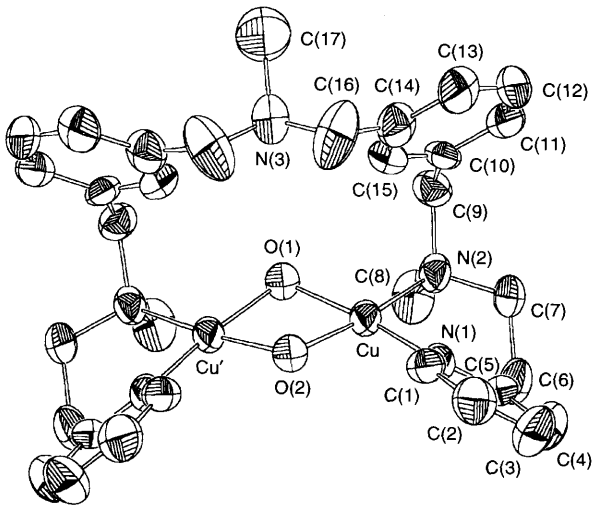


Fig. 2 Structure of the dimeric cation in **2**. Selected bond lengths (Å): Cu–O(1) 1.927(5), Cu–O(2) 1.922(5), Cu–N(1) 1.997(8), Cu–N(2) 2.045(8), Cu···Cu′ 3.004(2). Selected angles (°): O(1)–Cu–O(2) 76.5(3), N(1)–Cu–N(2) 95.0(3), O(1)–Cu–N(1) 92.7(3), O(2)–Cu–N(2) 95.8(3), N(1)–Cu–O(2) 169.0(3), N(2)–Cu–O(1) 172.2(3), Cu–O(1)–Cu′ 102.2(4), Cu–O(2)–Cu′ 102.5(4).

at each copper ion is the same as that of **1** and the stereochemistry at each copper centre is again square planar. The other metric parameters are normal.[12–14] In order to adopt the doubly bridged binuclear structure the Cu_2O_2 core in **2** is bent with a dihedral angle of ≈12°. Note that proper placement of the *m*-$CH_2C_6H_4CH_2$ group is a prerequisite for aromatic ring hydroxylation and this is the reason why L′ has a dihydroxy bridged structure with no ring hydroxylation being observed.

The results presented here demonstrate the synthesis of the first *m*-$CH_2C_6H_4CH_2$ hydroxylation ligand system L, within the non-Schiff-base family, providing only two nitrogen coordination centres at each copper centre—a finding of considerable interest in the context of biomimetic studies aimed at the functional properties of tyrosinase. The structural analysis of **2** has shed light on the nature of the impurity L′ and a bonus is the characterization of a novel dihydroxy bridged copper(II) complex. The characterization of the bluish grey solid is under investigation.

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Footnotes

† The ligand L, α,α′-bis[(*N*-methyl-2-pyridyl)ethylamino]-*m*-xylene, was prepared by condensation of α,α′-*m*-dibromoxylene (3.75 mmol) and 2-(2-methylaminoethyl)pyridine (7.5 mmol) in the presence of Na_2CO_3 (3.75 mmol) in refluxing acetonitrile (80 ml) for 4 days. To the resulting brown solution addition of water and subsequent extraction into dichloromethane and usual work-up yielded a brown oil (yield 90%). ^{1}H NMR (60 MHz; $CDCl_3$): δ 2.3 (s, NMe), 2.93 (s, NCH_2CH_2C), 3.56 (s, $PhCH_2N$), 7.0–7.9 (m, aromatic protons). Some minor peaks closely associated with the peaks for the methylene and methyl protons due to some other product(s) were also observed. All our ligand preparations gave similar results. FAB mass spectrum: *m*/*z* 375 (major, HL^+) and minor (508, HL'^+). All our attempts to purify this ligand have thus far failed. In the complexation reaction an unpurified solution of the ligand L was reacted with $[Cu(MeCN)_4]ClO_4$.

‡ *Crystal data*: for **1**; $C_{24}H_{30}Cl_2Cu_2N_4O_{10}$, M = 732, dark green crystal, 0.3 × 0.2 × 0.1 mm, monoclinic, space group $P2_1/c$ (no. 14), a = 9.316(4), b = 30.748(6), c = 9.958(3) Å, β = 92.94(3)°, U = 2852.45(4) Å^3, D_c = 1.708 g cm^{-3}, Z = 4, F(000) = 1495.7, μ(Mo-Kα) = 1.74 mm^{-1}; 4244 reflections collected with 2 < 2θ < 45°; of these 3693 were unique and the 2654 in which $I > 3\sigma(I)$ were used in structural analysis; refinements converged to R = 0.049, R_w = 0.052 for 375 variables. For **2**; $C_{33}H_{43}Cl_2Cu_2N_5O_{10}$: M = 867, light blue crystal, 0.50 × 0.15 × 0.10 mm, orthorhombic, space group *Pnma* (no. 62), a = 13.137(10), b = 13.489(3), c = 21.516(4) Å, U = 3812.74(3.1) Å^3, D_c = 1.512 g cm^{-3}, Z = 8, F(000) = 1791.6, μ(Mo-Kα) = 1.32 mm^{-1}; 7544 reflections collected with 2 < 2θ < 50°; of these 3509 were unique and the 1560 in which $I > 2\sigma(I)$ were used in structural analysis; refinements converged to R = 0.070, R_w = 0.052 for 239 variables. The highest peak in the final difference map was 1.25 e Å^{-3} near Cl(2) of a disordered perchlorate ion. All measurements were made at 293 K on a Enraf-Nonius CAD4 Mach four-circle diffractometer using Mo-Kα (λ = 0.71093 Å) radiation. For both structures extinction, Lorentz, polarization and analytical absorption corrections were applied. Anomalous dispersion was applied for all non-hydrogen atoms. Crystallographic calculations were carried out with the XTAL3.2 package (S. R. Hall, H. D. Flack and J. M. Stewart, University of Western Australia, Geneva and Maryland, 1992) on a PC-486 computer. The structures were solved by direct methods and were refined by full-matrix least-square analysis. The hydrogen atoms were added in fixed, calculated positions and included in the refinements with fixed isotropic thermal parameters. For **1**, disorders in the *m*-$CH_2C_6H_4CH_2$ and >N*Me* groups were successfully modelled over two sites with occupancy factors of ½, and owing to the large thermal parameters for the ring C atoms the phenyl group was treated as a rigid body. The remaining atoms were refined anisotropically. For **2**, severe disorder of the perchlorate groups was found, and site occupancies of O atoms were properly fixed to model this. The pyridyl and phenyl groups were fixed to refine as rigid hexagons. The hydrogen atoms of the hydroxy bridges were located from the difference map. All non-hydrogen atoms except O atoms were refined anisotropically. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ We are currently engaged in rationalizing the formation of L′ during the synthesis of L. Attempts to obtain more than a few crystals of **2** have thus far failed, implying that the amount of this contaminant is very low. The directed synthesis of L′ is in progress.

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