A New Cu^{I} Complex that Mimics the Cresolase Reaction of Tyrosinase and the Crystal Structure of its Oxygenated Cu^{II} Complex

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A new dinuclear Cu^{II} complex with a unique structural arrangement and containing a doubly bridged macrocyclic ligand has been prepared from two different routes, one of which involves the reaction of oxygen and a Cu^{I} precursor, thus mimicking the cresolase activity of tyrosinase

Introduction

The synthesis, structural elucidation and characterization of the reactivity of copper-dioxygen compounds obtained from the interaction of molecular oxygen with Cu^{I} complexes is an important goal in the comprehension of the fundamental chemistry involved in oxidase and oxygenase reactions of synthetic and biological copper-containing catalysts.[1] Within this context, tyrosinase is a monooxygenase enzyme with a binuclear copper active-site and is responsible for the *ortho* hydroxylation of the existing hydroxyl group of substrates as shown in Equation (1).[2–5]

$$\text{R-Ph-OH} \xrightarrow[O_2]{\text{tyrosinase}} \text{R-Ph-(OH)}_2 \qquad (1)$$

A number of xylene-substituted ligands, including amines[6–11] and imines,[12,13] have been used to prepare binuclear Cu^{I} complexes that successfully mimic this reaction. The ligand influence in the modelling of such reactions is of great importance in order to elucidate the detailed pathways that can lead to the activation of the Cu complex towards the oxidation of C–H bonds, and therefore has implications in the understanding of metalloenzymes and other catalysts.[14,15]

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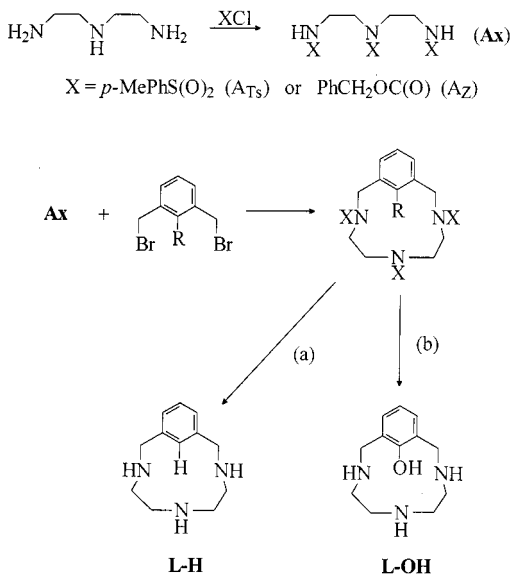
In this paper we present a new example of a Cu^{I} complex that is capable of producing an intramolecular hydroxylation reaction. We also report an alternative synthesis directly from the hydroxylated ligand and Cu^{II} that generates the same final complex. Furthermore, this oxygenated complex constitutes the first example of a macrocyclic ligand that does not contain pendant arms, and that doubly bridges the Cu metal[16–18] with an unusual geometry.[19]

Results and discussion

The synthetic strategy for the preparation of the new ligands L-H and L-OH is outlined in Scheme 1, and in both cases is based on the condensation of the protected triamine



(a) R = H, X = Z : H_2 (Pd/C); (b) R = OMe, X = Ts : Li/NH_3 (l)

Scheme 1. Synthetic strategy

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with 1,3-dibromoxylene or 1,3-dibromoanisole. The L-OH ligand was isolated after simultaneous deprotection of the amine and phenol groups with lithium in liquid ammonia.

The reaction of stoichiometric amounts of L-H and $[Cu^{I}(MeCN)_4](PF_6)$ in acetonitrile presumably produces a dinuclear complex $[Cu_2(L\text{-}H)_2]^{2+}$ in equilibrium with different conformers, as seen by variable temperature ^1H NMR and ESI spectroscopy. Molecular models clearly show that the monomeric species $[Cu(L\text{-}H)]^+$ contains two fused five-membered rings highly constrained due to the rigidity imposed by the *meta*-substituted phenyl group. On the other hand, the dimer contains only one five-membered ring per ligand and thus the steric strain is much lower. Solution equilibrium studies with Cu^{II} and the L-OH ligand, performed by potentiometric methods, are also in agreement with this behaviour.[20]

The formation constant value of this dinuclear complex [Equation (2)] is $\log K = 38.47$, more than twice that of the mononuclear species ($\log K = 17.53$), indicating that the association process of two mononuclear species is highly favoured.

$$2\,Cu^{2+} + 2\,L\text{-}OH \longrightarrow [Cu_2(L\text{-}O)_2]^{2+} \quad (2)$$

Bubbling oxygen through an acetonitrile solution of the colourless complex $[Cu^{I}_2(L\text{-}H)_2]^{2+}$ at low temperatures (−40 °C) generates a blue intermediate, whose nature is currently under investigation, which upon warming to room temperature turns green [Equation (3)]. Addition of ether to this solution and cooling to 5 °C overnight produces green crystals of the binuclear Cu^{II} bisphenolate complex $[Cu^{II}_2(L\text{-}O)_2]^{2+}$ in 22% isolated yield.

$$[Cu_2(L\text{-}H)_2]^{2+} + O_2 \rightleftharpoons [Cu_2(L\text{-}O)_2]^{2+} + 2\,H^+ + 2\,e^- \quad (3)$$

Exactly the same dicationic complex can be obtained in quantitative yield by the direct reaction of the L-OH ligand and $CuCl_2$ or $Cu(ClO_4)_2$.

The crystal structure of $[Cu_2(L\text{-}O)_2](PF_6)_2$ was determined by X-ray crystallography and its ORTEP diagram is shown in Figure 1.

The molecule sits on a centre of symmetry that transforms one macrocyclic ligand into the other. The Cu_2O_2 core atoms lie in a plane forming a rhomboidal arrangement. Each copper atom has a slightly distorted square-pyramidal geometry (with a τ factor of 0.21).[21] The base of the pyramid is occupied by two N atoms from one of the macrocyclic ligands together with a third N atom and a phenoxo O atom from the other macrocyclic ligand. The apical position is occupied by a phenoxo O atom from the former macrocyclic ligand and therefore the copper centres become doubly bridged by each macrocyclic ligand. The oxygen atoms of the phenoxo groups bridge the copper centres so that the apical oxygen atom from one pyramid is also the base of the other pyramid. As a result, the geometry of the complex consists of two square pyramids sharing a base-to-apex edge with the bases nearly parallel to one another. The constraint imposed by the macrocyclic ligand in this bis(μ-phenoxo)dicopper complex gives rise to long Cu−O [1.927(2) Å, 2.201(2) Å], Cu−Cu [2.864(1) Å] and O−O [2.988(1) Å] distances relative to unconstrained systems.[14]

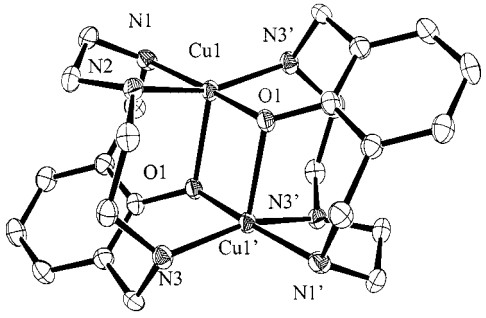

Figure 1. ORTEP view of the molecular structure of complex $[Cu_2(L\text{-}O)_2]^{2+}$ (ellipsoids at 50% probability); H atoms are omitted for clarity; selected bond lengths (Å) and angles (°): Cu1−N1 2.026(3), Cu1−N2 20142(3), Cu1−N3′ 2.044(3), Cu1−O1′ 1.927(2), Cu1−O1 2.201(2), Cu1−Cu1′ 2.864(1), O1−O1′ 2.988(1); Cu1−O1′−Cu1′ 92.44(9), O1−Cu1−O1′ 87.56(9), N1−Cu1−N2 85.13(11), N1−Cu1−N3′ 99.53(11), N2−Cu1−O1′ 86.41(10), O1−Cu1−N3′ 87.97(10), N2−Cu1−N3′158.78(11), N1−Cu1−O1′ 171.48(10), N1−Cu1−O1 89.51(10), N2−Cu1−O1 96.17(11), N3′−Cu1−O1 104.51(11)

The complex $[Cu_2(L\text{-}O)_2]^{2+}$ constitutes the first example of a complex bearing a macrocyclic ligand that does not contain pendant arms, and that doubly bridges the Cu centres. In the structure the Cu pyramids have an unusual parallel bases type of relative arrangement due to the constraints imposed by the macrocyclic ligand. The driving force for the doubly bridged disposition of $L\text{-}O^-$ is due to both the tendency of phenoxo groups to act as bridging ligands and to the release of steric strain that would otherwise exist if the $L\text{-}O^-$ ligand had all three N atoms coordinating to the same Cu metal centre. Molecular models clearly show that the corresponding oxygenated dinuclear Cu^{I} complex has the adequate geometry, thanks to the specific coordination of the macrocyclic ligand, to undergo oxygen insertion into the aromatic C−H bond, as indeed occurs in our case. This reaction is of importance since it results in a low molecular weight complex capable of mimicking the reactivity exhibited by tyrosinase in its cresolase activity.

Experimental Section

Materials and Instruments: All reagents used in the present work were obtained from Aldrich Chemical Co. and were used without further purification. Reagent-grade organic solvents were obtained from SDS. IR spectra were recorded with a Mattson Satellite FT-IR spectrometer on KBr pellets. UV/Vis spectroscopy was performed with a Cary 50 Scan (Varian) UV/Vis spectrophotometer with 1-cm quartz cells. The ^1H-NMR spectroscopy was performed with a Bruker DPX 200 MHz or a Bruker 400 MHz. Samples were

run in $CDCl_3$, CD_2Cl_2 or deuterium oxide with internal references (residual protons and/or tetramethylsilane). Elemental analyses were performed using a CHNS-O Elemental Analyzer EA-1108 from Fisons. FAB-MS experiments were run with a Fisons VG-Quattro and the ESI-MS experiments with a Navigator LC/MS chromatography from ThermoQuest. X-ray analyses were carried out using a Siemens Smart CCD diffractometer.

Ligand L-H: The protected linear amine A_z (1.75 g, 3.46 mmol), Cs_2CO_3 (2.82 g, 8.66 mmol) and α,α′-dibromo-*m*-xylene (0,.914 g, 3.46 mmol) were heated to reflux in CH_3CN (180 mL) under a N_2 atmosphere for 14 h. After cooling to room temperature, the mixture was filtered and the solvent removed under reduced pressure. The protected triazamacrocycle was then purified by column chromatography using silica as the chromatographic support and CH_2Cl_2/EtOAc (98:2) as the eluting agent to give the protected amine (0.469 g, 0.73 mmol, 22.3% isolated yield). Deprotection was achieved by hydrogenation with H_2/Pd(C) in methanol at 0 °C. The product was then purified by column chromatography using silica as the chromatographic support and CH_2Cl_2/MeOH/NH_4OH (75:25:7) as the eluting agent to obtain ligand L-H in 62.3% yield. ^1H NMR (200 MHz, $CDCl_3$, 298 K, TMS): δ = 2.01 (s, 3 H), 2.08 (m, 4 H), 2.71 (t, *J* = 3.0 Hz, 4 H), 3.90 (s, 4 H), 6.99−7.26 (m, 3 H), 8.26 (s, 1 H). MS (FAB): *m*/*z* = 206 [M + H^+]. $C_{12}H_{19}N_3$ (205.3): C 70.2, H 9.3, N 20.3; found C 69.9, H 9.4, N 20.1.

Ligand L-OH·3HCl: This ligand was prepared according to a published synthetic procedure.[22] ^1H NMR (200 MHz, D_2O, pH 3, 298 K, HOD): δ = 3.22 (t, *J* = 12.4 Hz, 4 H), 3.32 (t, *J* = 12.4, 4 H), 4.44 (s, 4 H), 7.04 (t, *J* = 7.3, 1 H), 7.53 (d, *J* = 7.3, 2 H). MS (FAB): *m*/*z* = 222 [M + H^+]. $C_{12}H_{22}Cl_3N_3O$ (330.7): C 43.6, H 6.7, N 12.7; found C 43.5, H 6.7, N 12.6.

$[Cu_2(L\text{-}H)_2(MeCN)_2](PF_6)_2$: L-H (21.6 mg, 0.105 mmol) and [Cu(MeCN)$_4$](PF_6) (39.2 mg, 0.105 mmol) were placed in a Schlenk tube under an argon atmosphere, 2 mL of CH_2Cl_2 were added and the solution stirred for 5 min. Addition of Et_2O (approx. 5 mL) to the resulting light yellow solution produced a white solid which was filtered, and dried under vacuum (38.3 mg, 80.0%). ^1H NMR (200 MHz, CD_2Cl_2, 300 K): δ = 1.50 (br. s, 2 H), 2.22 (br. s, 2 H), 2.49 (br. s, 2 H), 2.76 (br. s, 2 H), 3.50 (br. s, 2 H), 4.25 (br. s, 2 H), 7.1−7.3 (m, 3 H), 8.78 (s, 1 H). The resonances in the aromatic region were sharp with a clear hyperfine structure whereas the other resonances were broad. Upon lowering the temperature all resonances progressively broadened but no splitting was observed even at 210 K. FT-IR (KBr): $\tilde{\nu}$ = 2253cm^{-1} (C≡N), 846 (PF_6^-), 559 (PF_6^-).

Complex $[Cu_2(L\text{-}O)_2](PF_6)_2$: The ligand L-H (0.02 g, 0.097 mmol) and $[Cu^I(CH_3CN)_4]PF_6$ (0.036 g, 0.097 mmol) were dissolved in 1 mL of degassed, anhydrous CH_3CN under an argon atmosphere. The resulting colorless solution was cooled to −20 °C and O_2 was bubbled through at this temperature for 10min, during which time the solution turned blue. The mixture was then warmed to room temp. whilst stirring overnight. Slow diffusion of diethyl ether into the resulting solution allowed the formation of green crystals of the final product in 20% yield (0.0084 g, 0.010 mmol). FT-IR (KBr): $\tilde{\nu}$ = 3337 cm^{-1} (NH), 3291 (NH), 1595 (Ph-O), 1455 (C=C), 1297 (O-Ph), 843 (PF_6^-), 559 (PF_6^-). UV/Vis (CH_3CN): λ_{max} (ε) = 406 nm (542), 578 (323). ESI-MS (CH_3CN): *m*/*z* = 711 $[Cu_2(L\text{-}O)_2(PF_6)]^+$, 283 $[(L\text{-}O)Cu^{II}]^+$. $C_{24}H_{36}Cu_2F_{12}N_6O_2P_2$ (857.6): C 33.6, H 4.2, N 9.8; found C 34.0, H 4.5, N 9.7.

Crystal Data for $[Cu_2(L\text{-}O)_2](PF_6)_2$: $C_{24}H_{36}Cu_2F_{12}N_6O_2P_2$, *M* = 857.61, green crystals, triclinic, space group $P\bar{1}$ (no. 2), *a* = 8.818(4), *b* = 9.696(3), *c* = 10.801(6) Å, *Z* = 1, α = 113.89(5)°, β = 113.20(2)°, γ = 90.28(3)°, *V* = 761.0(6) Å^3, D_c = 1.871 g cm^{-3}, *T* = 173(2) K, Mo-K_α radiation (λ = 0.71073 Å), 4306 reflections measured, 3653 unique (R_{int} = 0.0212) which were used in all calculations. *R* = 0.0429, *Rw* = 0.0954.

CCDC-137239 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[20] Stability constants of the Cu^{II} complex with **L-OH** (0.15 mol dm^{-3} NMe_4Cl aqueous solution, 298.1 K): $2Cu^{2+} + 2\ L\text{-}O^- = [Cu_2(L\text{-}O)_2]^{2+}$, log K = 38.47(2); $Cu^{2+} + L\text{-}O^- = [Cu(L\text{-}O)]^+$, log K = 17.47(2); $Cu^{2+} + L\text{-}OH = [Cu(L\text{-}OH)]^{2+}$, log K = 12.70(2); $Cu^{2+} + HL\text{-}OH^+ = [Cu(HL\text{-}OH)]^{3+}$, log K = 4.70(3). The values in parenthesis are the standard deviation in the last significant figure. Ligand and metal concentration: 0.5 $\times 10^{-3}$ M. Potentiometric measurements were carried out in the pH range 2−7 due to the precipitation of the dinuclear species at higher pH.

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