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A three-coordinate copper(I)-phenoxide complex that models the reduced form of galactose oxidase

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A novel 3-coordinate Cu(I)-phenoxide complex with N-donor supporting ligation was structurally characterized and shown to be highly reactive towards dioxygen, similar to the reduced form of galactose oxidase.

Galactose oxidase (GAO) is a fungal enzyme that couples the 2-electron oxidation of primary alcohols to aldehydes with the reduction of O_2 to H_2O_2.[1] Structural and spectroscopic studies of this enzyme[1,2] and a related system, glyoxal oxidase,[3] have shown that they belong to an important class of metalloproteins that use metal centers and proximal organic radicals together to effect multielectron redox chemistry.[4] In GAO, 2-electron transformations are mediated by a single copper ion coordinated by a cysteine-modified tyrosinate ligand (Y_{272}). A mechanistic picture has emerged from biochemical studies that involves cycling of Cu(I)/Cu(II) and $Y_{272}/Y_{272}^{\bullet}$ redox states (Fig. 1).[1,2,5] The active form (**A**) contains a unique, antiferromagnetically coupled Cu(II)–$Y_{272}^{\bullet}$ pair. After binding of substrate to **A**, proton transfer to a second tyrosinate ligand (Y_{495}) is postulated to occur, followed by an internal 2-electron oxidation (here shown as sequential H atom and electron transfers) to yield the reduced form (**R**). Oxidation of **R** by O_2 yields the important enzyme product H_2O_2 and regenerates the catalytically competent form **A**. While extensive spectroscopic and physicochemical evidence supports the postulated structure of **A**, the proposed formulation for **R** is based solely on an analysis of X-ray absorption near edge and fine structure (XANES and EXAFS) spectroscopic data.[2g] These data show that **R** contains a Cu(I) ion coordinated to 3 or 4 N,O ligands, with the favored coordination number being 3 on the basis of the XANES edge and the average Cu–N,O bond distance from EXAFS of 1.99 Å.

Further understanding of the novel properties and reactivity of the GAO active site has come from synthetic studies, which, among other things, have succeeded in providing well-characterized mononuclear Cu(II)-phenoxyl radical species analogous to **A**.[6] Few examples of monomeric Cu(I)-phenolates that might model deprotonated **R** have been reported,[6g,7] although dicopper(I) complexes with bridging phenolate ligands are relatively common.[8] Of the two monomeric compounds that have been structurally defined by X-ray crystallography, one contains soft, abiological isocyanide coligands.[7a] Sorrell *et al.* published the X-ray structure of a monocopper(I)-phenoxide supported solely by N-donors, but it is 4-coordinate and no O_2 reactivity was reported.[7b] Herein we describe the synthesis and structural characterization of a novel mononuclear Cu(I)-phenoxide complex with a coordination number and coligand complement that closely mimic those proposed for form **R** of GAO. In addition, preliminary reactivity studies show that, like **R**,[5a] the complex is extremely sensitive to oxidation by O_2.

A new sterically hindered, potentially tridentate ligand with one phenolate and two amine donors, 1-(2-hydroxy-3,5-di-*tert*-butylbenzyl)-5-isopropyl-1,5-diazacyclooctane (HL), was prepared by treatment of 1-isopropyl-1,5-diazacyclooctane[9] with 3,5-di-*tert*-butyl-2-hydroxybenzyl bromide[10] and Na_2CO_3 in CH_3CN (Scheme 1).† Attempts to generate a Cu(I) complex by reacting NaL with CuCl or $[Cu(CH_3CN)_4]X$ (X = ClO_4^- or SbF_6^-) under an inert atmosphere in a variety of solvents only led to green mixtures indicative of disproportionation. However, treatment of HL with Cu_xMes_x (x = 2 and 5)[11] in THF under stringent anaerobic conditions followed by precipitation with pentane yielded LCu (**1**) as a white powder (Scheme 1). Combined ^1H and ^{13}C NMR, UV-vis, high resolution MS, and CHN analysis data corroborate the formulation of **1**, which was ultimately confirmed by an X-ray structure on a crystal grown from toluene–pentane (Fig. 2).‡ Only one of the two independent but chemically similar molecules (rotational twins) in the unit cell is shown. A planar T-shaped coordination geometry is adopted by the complex with divergent metal–ligand bond lengths.[12] Thus, one bond is quite long [Cu(1)–N(1) = 2.279(4) Å], one is more typical of Cu(I)–N bonds in 3-coordinate complexes [Cu(1)–N(2) = 1.979(4) Å],[13] and the Cu(I)–phenoxide distance is shorter than any reported previously for such a bond [Cu(1)–O(1) = 1.878(3) Å].[7] Interestingly, the

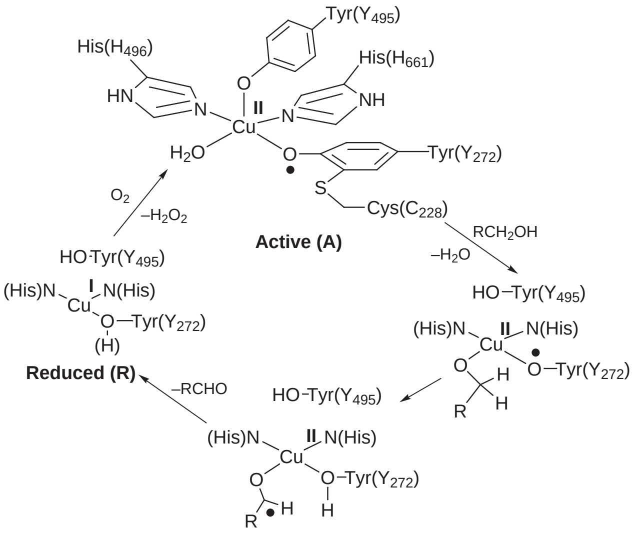
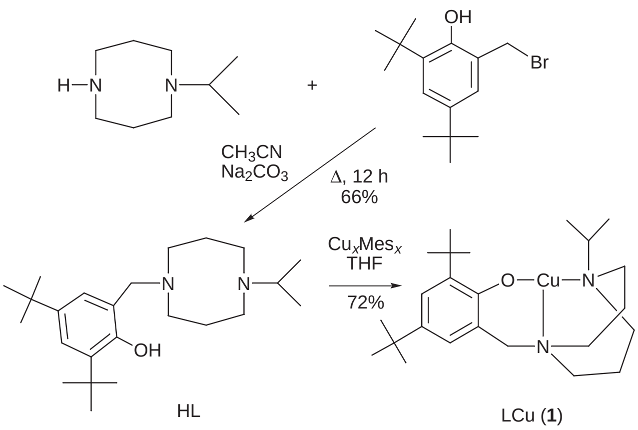


Fig. 1 Proposed mechanism for GAO (adapted from ref. 1).



Scheme 1

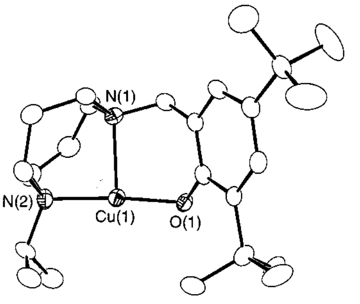


Fig. 2 Drawing of the X-ray crystal structure of LCu (**1**) (only one twin component shown). All ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (°): Cu(1)–O(1) 1.878(3), Cu(1)–N(1) 2.279(4), Cu(1)–N(2) 1.979(4), O(1)–Cu(1)–N(1) 96.3(2), O(1)–Cu(1)–N(2) 174.7(2).

average of these three disparate bond distances (2.05 Å) is more typical for 4- rather than 3-coordinate Cu(I) and is slightly greater than the average metal–ligand bond distance in **R** determined by EXAFS analysis (1.99 Å).[2g]

Cyclic voltammetry of **1** in THF with 0.2 M tetrabutylammonium hexafluorophosphate revealed a quasireversible wave with $E_{1/2} = -0.10$ V *vs*. SCE (scan rate = 100 mV s^{-1}; $\Delta E_p = 183$ mV; $i_{pa} \approx i_{pc}$) and a further irreversible oxidation at +0.32 V.[14] We have been unable to discern whether the quasireversible wave is a 1- or 2-electron process through coulometric measurements due to rapid decomposition of the product of oxidation of **1**. Consistent with a high thermodynamic driving force for oxidation reflected by the negative potential, **1** is extremely air sensitive; room temperature exposure instantly yields a light green solution [λ_{max}/nm (ε/$M^{-1}cm^{-1}$ per copper) 324 (15000), 394 (sh, 800), 656 (250)] of Cu(II) species that we presume is(are) multinuclear on the basis of its(their) EPR silence. By oxygenating a solution of **1** in THF at −72 °C a dark green intermediate was observed [λ_{max}/nm (ε/$M^{-1}cm^{-1}$ per copper) 390 (3800), 418 (3900), 670 (1900); EPR (X-band, 77 K) silent]. This intermediate is short-lived, decaying by a first order process to the aforementioned light green solution at −72 °C with $k = 3.9(1) \times 10^{-3}$ s^{-1} (UV-vis monitoring). Its spectroscopic properties are consistent with a copper-dioxygen adduct [Cu(II)-superoxo or $Cu(II)_2$-peroxo][15] or a Cu(II)-phenoxyl radical species (like **A**),[6a,b,d,e,g,i] all of which would be expected to give rise to low energy CT absorption bands and EPR silence (due to magnetic coupling) and to decay rapidly. Efforts to discern among these possibilities by further characterizing this highly reactive intermediate are ongoing.

In summary, we have prepared and structurally characterized a unique example of a three-coordinate Cu(I)-phenoxide complex supported by N-donors. Its coordination environment and high reactivity with O_2 bear striking similarities to the proposed GAO intermediate **R**. With the aim of gaining insights into the detailed role of **R** in the GAO mechanism, aspects of the reactivity of **1** will be the subject of future studies.[16]

Notes and references

† Characterized by ^1H and ^{13}C NMR, high resolution EI-MS, and CHN analysis.

‡ *Crystal data for* **1**: $C_{24}H_{41}CuN_2O$, $M = 437.15$, monoclinic, space group $P2_1$, $a = 13.3193(2)$, $b = 10.9789(2)$, $c = 16.0969(1)$ Å, $\beta = 92.349(1)°$, $V = 2351.89(6)$ $Å^3$, $Z = 4$, $T = 173$ K, $\mu = 0.944$ mm^{-1}. The crystal used for collection was determined to be twinned (twin law −1.0, 0.0, −0.067; 0.0, −1.0, 0.0; 0.0, 0.0, 1.0; Sparks Twinning Programs, Sparks, R. A., Madison, WI, 1977). The rotational twin was modeled by converting the reflection data to the SHELXTL HKLF 5 format using the twin law, the reciprocal metric tensor, and ascending partial-overlap groupings by 0.005 $Å^{-1}$ (7 altogether), by use of the UNTWIN program (V. G. Young, Jr., 1997). Side-by-side comparison of the two twin components (0.49 : 0.21) shows only minor differences in the diazacyclooctane ring conformation, and both molecules appear to be the same enantiomer. The final cycle of full-matrix least-squares refinement (on F^2), based on 7455 reflections ($2.54 < 2\theta < 50.64°$) and 527 variable parameters, with 1 restraint, converged with $R1 = 0.0482$ and $wR2 = 0.1121$. A total of 5515 of the 7455 reflections were either exactly or partially overlapped, and 1950 reflections were considered normal data. Data were collected on a Siemens SMART system and calculations were performed using the SHELXTL-Plus V5.0 suite of programs. CCDC 182/1055.

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