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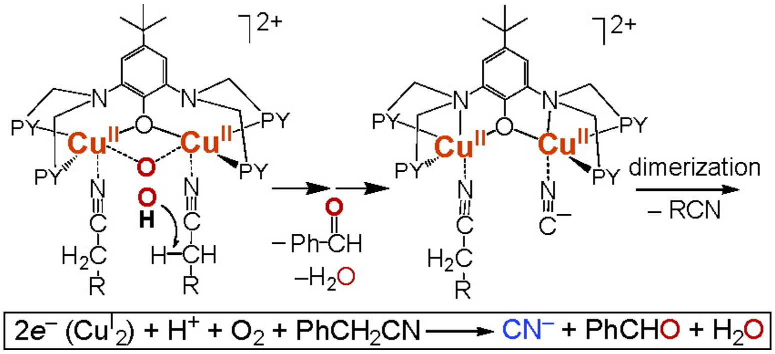

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Exogenous Nitrile Substrate Hydroxylation by a New Dicopper-Hydroperoxide Complex

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The copper-mediated activation of dioxygen is a subject of considerable current interest. Copper monooxygenases include Tyr (*o*-phenol hydroxylation)[1,2a] and *p*-MMO ($CH_4 \rightarrow CH_3OH$),[1,2b] as well as DβM and PHM;[1,2c,d] the latter effect aliphatic C−H bond substrate hydroxylations. In Tyr, a binuclear peroxodicopper(II) or bis-μ-oxo-dicopper(III) species is implicated in substrate oxygenation.[2e] For DβM and PHM, a Cu^{II}-($^-$OOH) (hydroperoxide) or Cu^{II}-(O_2^-) (superoxide) active species have been extensively discussed.[2c,d,f−h] Cu^I/O_2/substrate reactions are also important in synthetic methodologies and other applications.[2i,3]

Biomimetic studies have proved to be a powerful means to develop the fundamental chemistry of Cu^I/O_2 interactions, determine the nature of Cu_n-O_2 ($n = 1-3$) species, and elucidate mechanisms of substrate reactivity.[3] As Cu^I/O_2-derived entities, Cu_n-OOH species are less well studied than others, especially as concerns substrate reactivity.[4] Here, we report the chemistry of a new Cu^{II}_2-OOH complex that is able to effect the hydroxylation of exogenous nitrile substrates, releasing cyanide. This appears to be the first example of such a reaction induced by a Cu_n-O_2-derived species, which is of biological interest since DβM also effects a benzylcyanide to benzaldehyde plus cyanide conversion.[5,6]

The copper(I) complex $[Cu^I_2(PD'OH)(MeCN)_2]^{2+}$ (**1**) (Figure 1) is synthesized by reacting 2 equiv of $[Cu^I(MeCN)_4]^+$ with the binucleating PD′OH ligand.[7,8] X-ray analysis of a PPh_3 derivative, $[Cu^I_2(PD'OH)(PPh_3)_2](ClO_4)_2$ (Figure 1),[8] shows each copper(I) ion has a distorted tetrahedral geometry, but with weak Cu^I-$N_{alkylamino}$ interactions (Cu−N = 2.27 or 2.31 Å). As seen before,[9a−c] the phenol oxygen remains protonated and not coordinated (Cu···O > 3.0 Å), consistent with the dicationic complex formulation.

Addition of O_2 to **1** at −80 °C in EtCN generates a dark green species formulated as a μ-1,1-hydroperoxodicopper(II) complex, $[Cu^{II}_2(PD'O^-)(^-O_2H)]^{2+}$ (**2**) (Scheme 1), with LMCT absorption maxima at 407 ($\epsilon = 2700$ M^{-1} cm^{-1}) and 488 (sh, $\epsilon = 1600$) and a ligand field transition at 622 ($\epsilon = 600$) nm (Figure 2A). A resonance Raman spectrum reveals an O−O stretching vibration at 870 cm^{-1}, which downshifts by 50 cm^{-1} with ^{18}O-labeled O_2 (Figure 2B). These data compare closely with structurally related phenoxide- and hydroperoxide-bridged complexes $[Cu^{II}_2(XYL\text{-}O^-)(^-O_2H)]^{2+}$ (**3**) and $[Cu^{II}_2(UN\text{-}O^-)(^-O_2H)]^{2+}$ (**4**) ($\nu_{O-O} = 892$ cm^{-1} ($\Delta(^{18}O_2) = -52$ cm^{-1})),[9b−d] as well as with data from two recently reported μ-hydroxo-μ-hydroperoxodicopper(II) species from Suzuki and co-workers ($\nu_{O-O} = 868$ cm^{-1} (−45 cm^{-1}) (X-ray structure available) or 883 cm^{-1} (−50 cm^{-1})).[4,10] Thus, hydroperoxo complex **2** forms in a manner analogous to that known for **3** and **4**, via oxygenation of the phenol-dicopper(I) complex $[Cu^I_2(PD'OH)(MeCN)_2]^{2+}$ (**1**) (Scheme 1).[9b,c,11]

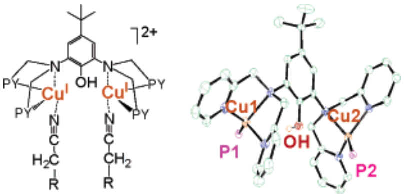
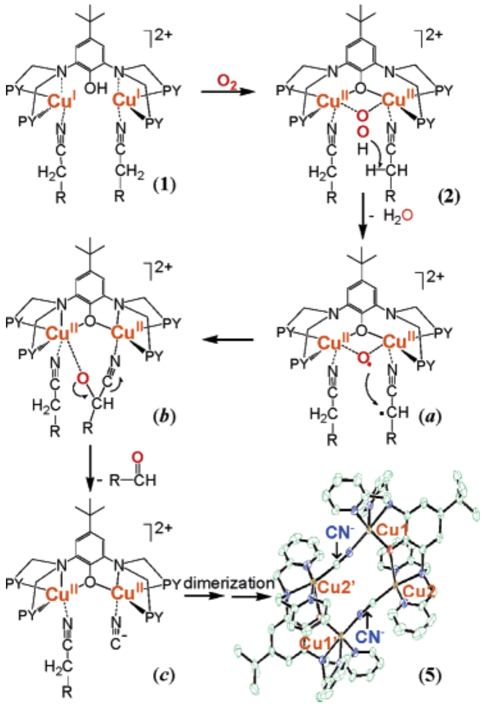


Figure 1. $[Cu^I_2(PD'OH)(MeCN)_2]^{2+}$ (**1**) and representation of the X-ray structure of the derivative, $[Cu^I_2(PD'OH)(PPh_3)_2]^{2+}$; the PPh_3 phenyl groups are omitted for clarity. Cu−N_{py} = 2.04 to 2.11 Å; Cu−P = 2.17 and 2.19 Å; Cu···O = 3.09 to 3.23 Å; and Cu···Cu = 6.25 and 6.38 Å.[8]

Scheme 1



The structures of these hydroperoxide-dicopper(II) complexes are presumed to all be the same as Suzuki's[4] and an acylperoxo complex with the XYL-O$^-$ (vide supra) ligand,[9e] with one μ-oxygen bridging ligand (hydroxide in Suzuki's complexes or phenoxide in the others) plus the μ-1,1-OOH donor (Scheme 1). The Cu···Cu distances for $Cu^{II}_2(\mu\text{-OR})(\mu\text{-OR}')$[12] complexes fall in the relatively small range of 2.93 to 3.10 Å.[4,9a−c] However, within the PD′O$^-$ ligand framework, copper(II) coordination to all three nitrogens of the bis(2-pyridylmethylamine) chelate plus the phenolate oxygen

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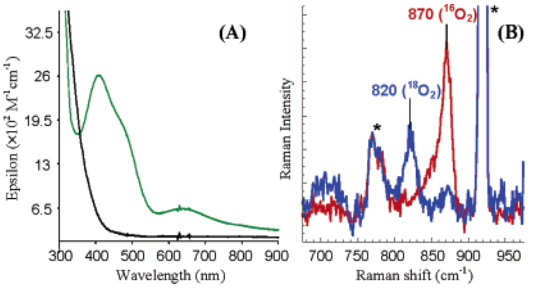

Figure 2. (A) UV−vis absorption of **1** (black) and $[Cu^{II}_2(PD'O^-)(^-O_2H)]^{2+}$ (**2**) (green) at −80 °C in EtCN. (B) rRaman spectrum of **2** (ClO_4^- as counterion) with $^{16}O_2$ and $^{18}O_2$ isotopic substitution. The samples were run at 77 K in MeCN with 407 nm excitation. Solvent peaks denoted by *. **2** ($B(C_6F_5)_4^-$ as counterion) has ν_{O-O} at 855 cm^{-1} ($\Delta(^{18}O_2) = \sim 45-50$ cm^{-1}).[8] No ν_{Cu-O} stretch is observed above signal-to-noise in this photosensitive compound.

atom should lead to a complex with a Cu···Cu distance > 3.7 Å[13,14] (also see the structure of **5**), far too long to maintain a μ-1,1-hydroperoxide coordination mode. Thus, we propose that $[Cu^{II}_2(PD'O^-)(^-O_2H)]^{2+}$ (**2**) possesses a coordination where the alkylamino N atoms are not metal-bound, and solvent nitrile groups instead coordinate (Scheme 1). Supporting this supposition are the following: (i) The metal−metal distance in related binucleating ligand frameworks can decrease dramatically through weakening or loss of the bridgehead $N_{alkylamino}$ coordination.[15] (ii) Cu^{II}-nitrile coordination is precedented in a complex closely related to **2**.[9a] (iii) Further, formation of **2** occurs only in nitrile solvents, unlike other systems,[9a−c] suggesting RCN involvement in the chemistry. Thus, when **1** reacts with O_2, each Cu ion releases the weakly coordinated $N_{alkylamino}$ atom and the hydroperoxide formed (i.e., **2**) is a nitrile solvent coordinated (and stabilized) species (Scheme 1).

$[Cu^{II}_2(PD'O^-)(^-O_2H)]^{2+}$ (**2**) is stable at −80 °C in EtCN but less so with $PhCH_2CN$ present. Warming to RT and workup leads to the isolation of a blue crystalline solid (≥15% yield);[8,16] an X-ray analysis reveals it to be a cyanide-bridged tetranuclear copper(II) complex, $[\{Cu^{II}_2(PD'O^-)(CN^-)\}_2](ClO_4)_4$ (**5**) (Cu···Cu = $3.91_{(intra)}$ and $5.02_{(inter)}$ Å; $\nu_{C\equiv N} = 2160$ cm^{-1}) (Scheme 1). The source of the CN$^-$ is the nitrile solvent, which has been attacked by the hydroperoxo group in **2**. This conclusion is reached from the following observations: (i) A 1:4 mixture of $PhCH_2CN/CH_2Cl_2$ was employed as the solvent for the oxygenation of **1** at −80 °C. After warming to RT and workup, GC-MS analysis showed that benzaldehyde was formed (18% yield, based on **2**; paralleling the yield of **5**).[16,17] (ii) Furthermore, a reaction carried out using $^{18}O_2$ revealed a 60% ^{18}O incorporation into the PhC(O)H product.[8]

As a proposed mechanism for RCN oxidation (Scheme 1), we suggest initial Cu_2-OOH α-hydrogen atom abstraction from a EtCN- or $PhCH_2CN$-coordinated substrate (**2** → ***a***);[18] under the experimental conditions employed where **2** is warmed with the substrate, product analysis for a reaction run in $C_6H_5CH_2CN/C_6D_5CD_2CN$ (1:1) gives an apparent (based on aldehyde product yields) $k_H/k_D = 2.9 \pm 0.2$.[8] Elimination of water and oxygen rebound would lead to a coordinated (and deprotonated) α-hydroxynitrile (***b***). This could de-ligate from copper (via protonation)[4,17] or directly eliminate to give the aldehyde, leaving a cyanide complex (***c***), which dimerizes to the observed tetranuclear product **5**.

Villafranca et al. reported that *p*-hydroxybenzylcyanide is a suicide substrate for DβM. The enzyme hydroxylates 4-OH-$C_6H_4CH_2CN$, giving 4-hydroxymandelonitrile, which decays to 4-hydroxybenzaldehyde and cyanide.[6] Our system closely mimics this enzymatic reaction. As mentioned, Suzuki et al. have shown their Cu^{II}_2-OOH species to effect *intra*molecular-coordinated ligand Ar-CH_2NR_2 methylene hydroxylation and subsequent N-dealkylation.[4] Although recent experiments and calculations suggest that a Cu-superoxide may be the preferred active species in DβM and PHM,[2f−h] both Suzuki's[4] and the present study argue that a Cu^I_n/O_2-derived Cu^{II}_2-OOH moiety could initiate useful substrate hydroxylation reactions in biological or chemical systems. Further studies to delineate Cu^{II}-O_2^- vs Cu^{II}-OOH reactivity are in progress.

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Supporting Information Available: Copper complex synthesis, rRaman, GC/MS product analyses (PDF), and X-ray data files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The LMCT bands in **2** are of lower intensity than those of similar systems, indicating less covalent overlap of the $^-$OOH orbitals with the Cu LUMO likely due to geometric constraints and the lack of hydrogen bonding for this ligand system.
(11) As previously described, the hydroperoxo hydrogen derives from the ligand phenol OH. Complex $[Cu^{II}_2(XYL-O^-)(^-O_2H)]^{2+}$ (**3**) forms either from oxygenation of the phenol complex $[Cu^I_2(XYL-OH)]^{2+}$ or by direct protonation of the peroxo complex $[Cu^{II}_2(XYL-O^-)(O_2^{2-})]^+$.[9b]
(12) R or R′ can be H, Ar, OH (the hydroperoxide)[4,9a−c] or OAr (an acylperoxide).[9e]
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(16) Material balance is overall excellent: When **2** is warmed from −80 °C, a ligand arm oxidative dehydrogenation (∼60% yield) and autoxidation occur, the latter giving a hydroxo-bridged tetranuclear cluster (≤25% yield). These results will be described elsewhere.
(17) Under the GC conditions, mandelonitrile could not be detected; it elutes beneath the $PhCH_2CN$ solvent peak. Thus, if mandelonitrile is simultaneously produced in the nitrile oxidation reaction, our estimate for the overall yield of the process is low.
(18) Note, **2** does not react well with added PPh_3 or 9,10-dihydroanthracene, consistent with favored coordination of RCN solvent molecules; they facilitate stabilization of **2** but this then undergos two types of oxidation reactions[16] due to their favorable proximity.

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