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Copper(II)−Hydroperoxo Complex Induced Oxidative N-Dealkylation Chemistry

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In this report, we describe the generation of a new hydroperoxo−copper(II) mononuclear complex which effects oxidative N-dealkylation chemistry on a substrate which is juxtaposed to the reacting $Cu^{II}(^{-}OOH)$ moiety. The interest in such an investigation derives from copper bioinorganic chemistry: (a) There remain fundamental questions concerning the inherent coordination structures and reactivity of single-copper complexes bound to dioxygen and its reduced derivatives, such as superoxide (O_2^-), peroxide (O_2^{2-}), or hydroperoxide (^{-}OOH).[1−4] (b) Structurally similar peptidylglycine-α-hydroxylating monooxygenase (*PHM*) and dopamine *β*-monooxygenase (*DβM*)[5] effect related substrate hydroxylation reactions at a mononuclear copper center. A $Cu^{II}(^{-}OOH)$ moiety was previously implicated as the active species formed prior to *DβM* or *PHM* substrate H-atom abstraction.[5] More recent experimental and computational chemistries have, however, brought attention to a Cu^{I}/O_2-derived superoxo $Cu^{II}(O_2^-)$ moiety as the likely H-atom abstracting agent.[5−7] Still other theoretical treatments[8] prefer a prior (rather then subsequent) O−O cleavage from $Cu^{II}(^{-}OOH)$ leading to a high-valent $[Cu-O]^{2+}$ or $[Cu-O]^{+}$[9] moiety which effects H-atom transfer. As applied to *PHM*, the methylene H-atom abstraction from and subsequent rebound to the (peptide)C(O)-$NHCH_2COOH$ substrate would give hydroxylated (peptide)C(O)-NHCH(OH)−COOH; this subsequently transforms to amine (here carboxamide) (peptide)$C(O)NH_2$ and aldehyde HC(O)COOH products.[8c] Our results presented here suggest that a $Cu^{II}(^{-}OOH)$ species or a product derived from this merits further serious attention in discussions of enzyme mechanism or applications to practical chemistry.

Here, we employ the TMPA {≡ TPA ≡ tris(2-pyridylmethyl)-amine)} ligand framework; these derivatives or analogues have been extensively used to generate a variety of O_2-derived complexes[1−4] including binuclear $Cu^{II}_2(\mu\text{-}1,2\text{-}O_2^{2-})$ and $Cu^{III}_2(\mu\text{-}O^{2-})_2$ and mononuclear $Cu^{II}(O_2^-)$[10] or $Cu^{II}(^{-}OOH)$[1,11] species. Masuda and coworkers[11] have generated the latter wherein they placed H-bonding groups off of the pyridyl 6-position TMPA "arms", stabilizing the $Cu^{II}(^{-}OOH)$ moiety. Here, we instead place there a potentially oxidizable substrate and find that such a single pyridyl 6-dimethylamino group is indeed subjected to oxidation from copper−hydroperoxide-derived chemistry.

The copper(II) mononuclear complex $[(\mathbf{L}^{N(CH_3)_2})Cu^{II}(H_2O)]^{2+}$ (**1**) (as bis-perchlorate salt) was synthesized from $Cu^{II}(ClO_4)_2{\bullet}6H_2O$ plus ligand $L^{N(CH_3)_2}$ added together in acetone, precipitated with Et_2O, and recrystallized from acetone/Et_2O.[12] An X-ray structure (Figure 1) reveals a square-based pyramidal structure, with dipicolylamine (N1, N2, N3) and a water molecule in the basal plane; the pyridyl arm with a 6-dimethylamino group binds axially, Cu1−N4 = 2.3596 (17) Å.[12] The structure is likely maintained in solution, as a typical axial EPR spectrum (X-band, 77 K) for a mononuclear Cu(II) complex is observed, $g_{\|} = 2.253$, $g_{\perp} = 2.052$, $A_{\|} = 174$ G, $A_{\perp} = 31.5$ G. Following the method typically employed to generate hydroperoxo−Cu^{II} complexes,[13] addition of 2−3 equiv of H_2O_2/

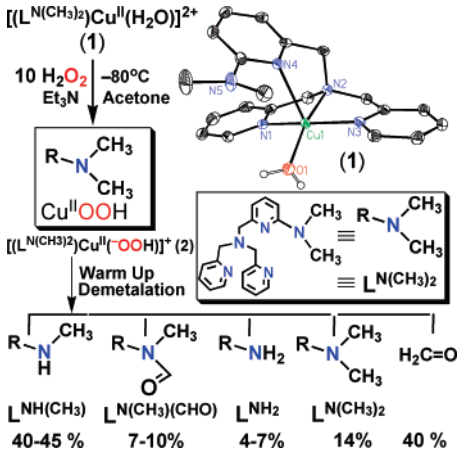

Figure 1. Formation and reactivity of a hydroperoxo−copper(II) complex effecting oxidative N-dealkylation of a ligand−substrate $-N(CH_3)_2$ group.

Et_3N using 50% $H_2O_{2(aq)}$ to a greenish blue acetone solution of **1** at −80 °C gives a green product solution with complex formulated as the hydroperoxide $[(\mathbf{L}^{N(CH_3)_2})Cu^{II}(^{-}OOH)]^{+}$ (**2**); a charge-transfer absorption maximum often seen for such species in the 350−400 nm region[11] is not clearly present,[14] but direct evidence for **2** comes from electrospray ionization mass spectrometry (ESI-MS). Injection of −80 °C acetone solutions of **2** gives a dominant parent peak cluster with $m/z = 429.02$ and an expected $^{63,65}Cu$ pattern. When formation of **2** was instead carried out using $H_2{}^{18}O_2$, the positive ion peak shifts to 433.15, that is, $[(\mathbf{L}^{N(CH_3)_2})Cu^{II}(^{-18}O^{18}OH)]^{+}$; fitting of the parent peak pattern around $m/z = 433$ indicates >99% ^{18}O incorporation. The EPR spectrum of **2** is also axial, consistent with a single species that is different from **1**.[12]

$[(\mathbf{L}^{N(CH_3)_2})Cu^{II}(^{-}OOH)]^{+}$ (**2**) is stable in solution at −80 °C, but warming results in a change to a darker green color. Analysis of the reaction mixture obtained by addition of $Na_2EDTA_{(aq)}$, extraction into CH_2Cl_2 to remove the Cu ion, and chromatographic separation/isolation reveals that only ∼14% yield of the original $\mathbf{L}^{N(CH_3)_2}$ ligand remains.[12] The major (40−45%) new organic product is the oxidatively N-dealkylated compound $\mathbf{L}^{NH(CH_3)}$; complementing this is the formation of formaldehyde (∼40%) as determined from the Nash test (Figure 1).[12] Confirmation comes from X-ray analysis of a Cu^{II}−chloride derivative formed from isolated $\mathbf{L}^{NH(CH_3)}$, $[(\mathbf{L}^{NH(CH_3)})Cu^{II}(Cl)]^{+}$ (**3**).[12] The chemistry leading to $\mathbf{L}^{NH(CH_3)}$ plus $CH_2{=}O$ thus mimics the monooxygenase activity occurring in *PHM* (vide supra), where **2** or a product derived from it reacts with the $-N(CH_3)_2$ substrate placed in close proximity to the $Cu^{II}(^{-}OOH)$ moiety. We also observe an intermediate suggested in *PHM* mechanistic discussions, a product-based alkoxide, here $[(\mathbf{L}^{N(CH_3)(CH_2O^{-})})Cu^{II}]^{+}$ (**4**; diagram below). This complex with $m/z = 411.12$ is detected upon mass spectrometric analysis of reaction mixtures prior to removal of the Cu ion (vide supra); use of $H_2{}^{18}O_2$

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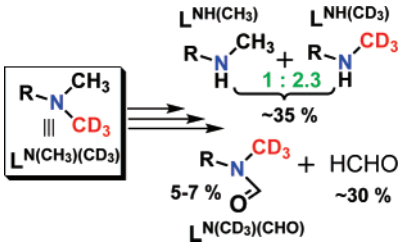
Scheme 1



in the reaction confirms the formulation (*m*/*z* 413.20).[12] The release of Cu from **4** would directly produce the major products $\mathbf{L^{NH(CH_3)}}$ and $CH_2{=}O$.

Small but significant amounts of doubly oxidized (formally four-electron oxidation products) aldehyde $\mathbf{L^{N(CH_3)(CHO)}}$ and amine $\mathbf{L^{NH_2}}$ are also formed (Figure 1), likely due to the fact that the chemistry described here occurs when **2** is formed from reaction of **1** with 10 equiv of H_2O_2/Et_3N. The over-oxidized products likely derive from further reaction with hydrogen peroxide. When only 1 equiv of H_2O_2/Et_3N is used to generate $[(\mathbf{L^{N(CH_3)_2}})Cu^{II}(^{-}OOH)]^{+}$ (**2**), warming and workup leads to considerably more (~60%) unreacted $\mathbf{L^{N(CH_3)_2}}$, the yield of primary mono-N-demethylated ligand substrate $\mathbf{L^{NH(CH_3)}}$ drops to 15−20%, only 3−4% $\mathbf{L^{N(CH_3)(CHO)}}$ is obtained and no $\mathbf{L^{NH_2}}$ is observed.[12] Thus, the major reaction product, the biomimetic oxidatively N-dealkylated ligand, $\mathbf{L^{NH(CH_3)}}$, is formed in a "dose"-dependent manner.

Further insights come from using $[(\mathbf{L^{N(CH_3)(CD_3)}})Cu^{II}(^{-}OOH)]^{+}$ (**2-CD$_3$**), setting up an intramolecular substrate competition, $N(CH_3)$ versus $-N(CD_3)$ oxidation (Scheme 1). On the basis of the relative product yields after warming −80 °C solutions and workup, an apparent deuterium isotope effect of ~2.3 is deduced (Scheme 1).[15] The k_H/k_D observed in *PHM* is ~11,[5] while k_H/k_D values vary greatly (1−25) for a variety of chemical systems studied, primarily bis-μ-oxo-dicopper(III) complexes.[3] Our low value is similar to that observed for oxidative N-dealkylations mediated by cytochrome P450 monooxygenase, heme synthetic analogues,[16] as well as non-heme $Fe^{IV}{=}O$.[16a] Thus, in our system, a reactive copper-based intermediate (vide infra) may initiate the oxidative process by $N(CH_3)_2$ methyl group H-atom abstraction; such a N−Cα H-atom abstraction or another route involving initial rate-limiting electron-transfer oxidation to give an amine radical cation and follow-up are the two mechanisms extensively discussed for enzyme/chemical iron or copper oxidative N-dealkylations.[16,17] We note that **2-CD$_3$** chemistry also leads to some aldehyde $\mathbf{L^{N(CD_3)(CHO)}}$ (Scheme 1), but only reaction on the CH_3 group occurs as no $\mathbf{L^{N(CH_3)(CDO)}}$ product is detected. Formation of $\mathbf{L^{NH_2}}$ is also not observed.

While we and others have observed and studied oxidative N-dealkylation chemistry using well characterized dicopper complexes possessing bis-μ-oxo-dicopper(III) $Cu^{III}_2(\mu\text{-}O^{2-})_2$ or hydroperoxo $Cu^{II}_2(\mu\text{-}^{-}OOH)$ cores,[3,17b,c] this is the first detailed report with mechanistic insights on a discrete mononuclear copper(II)−hydroperoxide complex **2** which mediates an effective oxidative N-dealkylation reaction similar to that occurring in *PHM*.[18−20] While a superoxo−Cu^{II} moiety may be effective as a H-atom abstracting agent,[10,11a] the further consideration of a $Cu^{II}(^{-}OOH)$ entity in *PHM* or *DβM* mechanism is warranted. We cannot say whether the $Cu^{II}(^{-}OOH)$ moiety or a subsequently formed high-valent Cu-oxo species is the actual initial oxidant in our system; further studies including attention to O−O cleavage and proton inventories are in progress.

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Supporting Information Available: Synthetic and reactivity details, product analyses/characterization, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Increased absorption does occur in this region; at λ = 380 nm, an absorptivity of 1200 M^{-1} cm^{-1} is observed.
(15) The k_H/k_D of 2.4 is based on ^{1}H NMR spectroscopy of product solutions (Scheme 1); ESI-MS data give k_H/k_D = 2.2, thus the average = 2.3. These calculations do not include any consideration of $\mathbf{L^{N(CD_3)(CHO)}}$ formation, which could transform to additional $\mathbf{L^{NH(CD_3)}}$ product; if this occurred, k_H/k_D would even be larger, as pointed out by reviewers. Note that comparisons of our k_H/k_D with literature values are difficult to interpret since we cannot yet ascribe a specific temperature to our k_H/k_D.
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(18) $Cu^{II}(O_2^{-})$ or $Cu^{III}_2(\mu\text{-}O^{2-})_2$ complexes are unlikely to be involved in the present system. A −80 °C O_2 reaction of a copper(I) complex of $L^{N(CH_3)_2}$, $[(L^{N(CH_3)_2})Cu^{I}]^{+}$ (**5**) leads to a species with $Cu^{III}_2(\mu\text{-}O^{2-})_2$ spectroscopic signatures;[12] warming to rt and workup affords only 7% N-dealkylated product $L^{NH(CH_3)}$ and 3% $L^{N(CH_3)(CHO)}$. Dipicolylamine is also detected, indicating a completely different position of attack and oxidative chemistry by the $Cu^{III}_2(\mu\text{-}O^{2-})_2$ core. A copper(I) reaction with O_2 would necessarily proceed through a $Cu^{II}(O_2^{-})$ initial species, suggesting this is not important in the oxidative chemistry observed.
(19) There are literature examples where oxidative C−N cleavage occurs from reactions with O_2, H_2O_2, or other oxidants, where copper complex characterization is unavailable.[20a−c] Also, amine oxidation can occur by initial electron transfer from high redox potential Cu complexes.[20d,e]
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