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Aryl Hydroxylation from a Mononuclear Copper-Hydroperoxo Species

Debabrata Maiti, Heather R. Lucas, Amy A. Narducci Sarjeant, and Kenneth D. Karlin*
Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218
Received March 11, 2007; E-mail: karlin@jhu.edu

Research advances concerning the active-site chemistry of dioxygen activating copper enzymes have shown that single copper center O_2-derived reactive Cu−oxygen species are implicated in a number of situations. This includes biological oxygenases such as peptidylglycine-α-hydroxylating monooxygenase (PHM) and dopamine-β monoxygenases (DβM).[1] While these possess two copper ions per active subunit which are ∼11 Å apart,[2a] the Cu_M (≡Cu_B) site is where substrate H-atom abstractions occur, resulting in overall O_2/ascorbate copper-mediated hydroxylation chemistry.[1a,b] Also, single-copper ion mediated amino-acid oxygenation or oxidative-coupling occurs in the biogenesis of active-site cofactors in 2,4,5-trihydroxyphenylalanine (TOPA) formation (copper amine oxidases) and Tyr−Cys coupling (galactose oxidase).[1c,2b,c]

In the last few decades, coordination chemistry efforts have generated considerable insights into ligand-Cu^I/O_2 chemistry, such as the generation of new types of copper−dioxygen adducts, their kinetics of formation, structures, associated spectroscopy, and reactivity.[3] Yet, the chemistry of mononuclear entities such as cupric-superoxides ($Cu^{II}-O_2^{\bullet-}$) and hydroperoxides ($Cu^{II}-{}^{-}OOH$) is not as well developed.[1a] For a long time, a $Cu^{II}-{}^{-}OOH$ species was considered to be the likely key intermediate in DβM and PHM reactivity, while more recent experimental and computational advances suggest an active-site $Cu^{II}-O_2^{\bullet-}$ entity most likely effects initial substrate H$^{\bullet}$-abstraction.[1b,4] However, other computational studies suggest that the O_2-derived O−O bond first cleaves to give a cupryl (e.g., $Cu^{III}{=}O \leftrightarrow Cu^{II}-O^{\bullet}$)[5] or higher oxidation state (e.g., $[CuO]^{2+}$)[6a] species and this effects the H-atom abstraction.[6] Synthetic chemistry investigations have thus far revealed only limited substrate reactivity with mononuclear $Cu^{II}-O_2^{\bullet-}$[7] or $Cu^{II}-{}^{-}$OOH complexes,[8,9] especially with C−H containing substrates. There are as yet no discrete examples or evidence for mononuclear high-valent copper-oxo species.[1a,10]

Two groups have recently achieved substrate C−H activation chemistries starting from well-characterized dinuclear μ-$^{-}$OOH−dicopper(II) complexes, oxidative *N*-dealkylation or $RCH_2C{\equiv}N$ oxidative cleavage (to $RCH{=}O$ + cyanide).[11] Suzuki has also observed a hydrocarbon attack from a $Cu^{II}_2({}^{-}OH)_2 + H_2O_2$ reaction, giving a $Cu^{II}-{}^{-}OOR_{ligand-substrate}$ product.[12] Here, we rather present the chemistry of a *mononuclear* $Cu^{II}-{}^{-}OOH$ complex which leads to the hydroxylation of an aryl substrate.

Complex **1**, with 6tBP ligand, is a derivative of the well-studied tris(2-pyridylmethyl)amine (TMPA) ligand, however it possesses a proximate aryl group (Figure 1).[13] The X-ray structure[13] of the Cu^{II} complex as perchlorate salt, $[(6tbp)Cu^{II}(acetone)]^{2+}$ (**1**) (Figure 1), reveals a square-based pyramidal coordination sphere with labile acetone ligand in an equatorial position; a longer axial ligand is provided by the pyridyl group with the 6-aryl substituent, Cu−N4 = 2.4454(13) Å. In the manner commonly used to generate hydroperoxo-Cu^{II} complexes,[8] we added ∼5 equiv H_2O_2/Et_3N using 50% $H_2O_{2(aq)}$ to a blue acetone solution of **1** at −80 °C. The green product solution is formulated as the hydroperoxide $[(6tbp)Cu^{II}({}^{-}OOH)]^{+}$ (**2**); λ_{max} = 380 nm (ϵ = 1500 M^{-1} cm^{-1}), assignable to a $^{-}OOH \rightarrow Cu^{II}$ LMCT band.[14] A typical Cu^{II} axial EPR

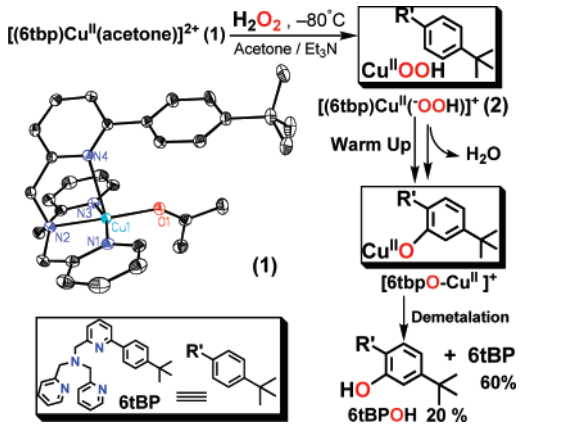

Figure 1. X-ray structure of **1**, as precursor to hydroperoxo-Cu^{II} complex **2**, leading to a phenolate-Cu^{II} entity which upon demetalation gives the *o*-hydroxylated phenol 6tBPOH. The oxygen atom(s) red-labeling tracks results from 18-O substitutions, see text.

spectrum for **2** is consistent with mononuclear formulation, $g_{||}$= 2.245, $g_{\perp}$ = 2.042, $A_{||}$ = 180 G.[13] Direct evidence comes from ESI-MS (−80 °C, acetone), showing a strong parent peak cluster with *m*/*z* 518.01 (and possessing the expected ^{63,65}Cu pattern) corresponding to $[(6tbp)Cu^{II}({}^{-}OOH)]^{+}$. When formation of **1** was instead carried out using $H_2{}^{18}O_2$, the positive ion peak shifts to 522.04, attributed to $[(6tbp)Cu^{II}(-{}^{18}O^{18}OH)]^{+}$; fitting of the parent peak pattern around *m*/*z* = 522 indicated >99% 18-O incorporation.[13]

While $[(6tbp)Cu^{II}({}^{-}OOH)]^{+}$ (**2**) is quite stable in solution at −80 °C, warming results in a change in color to brownish-green. TLC and ESI-MS data obtained from the product solution which was stripped of copper ion by addition of Na_2EDTA (aq) and extracted into CH_2Cl_2 revealed unreacted 6tBP ligand. However, a new product obtained in ∼20% yield (which decreases with less added H_2O_2) after chromatography exhibits *m*/*z* = 439.47, corresponding to a hydroxylated 6tBP moiety, $[6tBPOH + H]^{+}$ and *m*/*z* = 461.47 [6tBPOH + Na] (Figure 1). A parent anion peak at *m*/*z* = 437.20 ($6tBPO^{-}$) was obtained when mass spectra were recorded in negative ion mode.[13] This product is the *o*-phenol (Figure 1), as deduced by ^{1}H NMR and ^{13}C NMR data analyses. The 6tBPOH O-atom is derived from the $Cu^{II}-{}^{-}OOH$ moiety; an ion shift from 461.47 (6tBPOH + Na) to 463.63 ($6tBP^{18}OH$ + Na) was recorded for the $6tBP^{18}OH$ when $H_2{}^{18}O_2$ was used to generate **2**.[13]

Most interestingly, when the warmed reaction solution is subjected to ESI-MS analysis (prior to EDTA treatment), the predominant higher molecular weight species detected occurs at *m*/*z* = 500.52, corresponding to a likely reaction intermediate, a phenolate-Cu^{II} complex $[(6tbpO^{-})Cu^{II}]^{+}$ (Figure 1), confirmed again by the shift to *m*/*z* = 502.49 ($[(6tbp^{18}O^{-})Cu^{II}]^{+}$) when $H_2{}^{18}O_2$ is introduced to the reaction; a characteristic ArO^{-}-to-Cu(II) charge transfer absorption is also detected.[13,15] Taken together, the data suggest that hydroperoxo-Cu^{II} (**2**) derived chemistry effects the aryl hydroxylation of 6tBP, *a reaction that up to this point has only*

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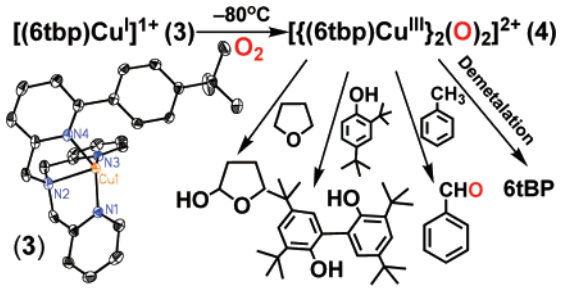
Scheme 1



been attributed to dinuclear complexes, either η^2:η^2-peroxodicopper(II) or bis-μ-oxo dicopper(III) species.[3b,16] We suggest a mechanism where the $Cu^{II}-{}^{-}OOH$ moiety undergoes O−O cleavage, leading to a high-valent copper-oxo species which attacks the aryl group.[17−20] This suggestion is compelling since for an iron complex with a nearly identical 6-PhTPA ligand {6-PhTPA is like 6tBP but with a 6-phenyl rather than 6-(4-*t*Buphenyl) group on one pyridyl arm}, Que and co-workers[21] established homolytic cleavage from an $Fe^{III}-{}^{-}OOR$ species to give an Fe^{IV}=O moiety which effects ligand aryl hydroxylation.[22]

To investigate the possibility that a dioxygen derived species may rather be effecting this aryl hydroxylation, we examined the product(s) of O_2 reaction with a copper(I) complex of 6tBP, [(6tbp)-Cu^I]$^+$ (**3**, X-ray, Scheme 1). Bubbling O_2 directly through a −80 °C THF solution of **3** results in a color change from light to bright brownish-yellow, giving an EPR silent bis-μ-oxo-dicopper(III) complex [{(6tbp)Cu^{III}}$_2$(O)$_2$]$^{2+}$ (**4**), λ_{max} = 383 nm (ϵ = 7000 M^{-1} cm^{-1}) (Scheme 1). The formulation is based on well-established spectral signatures[3a] and the result is identical to that recently reported for a [(6-PhTPA)Cu^I]$^+$/O_2 reaction [6-PhTPA described above], giving [{(6-PhTPA)Cu^{III}}$_2$(O)$_2$]$^{2+}$ (**5**), ν_{Cu-O} = 599 cm^{-1}.[23] Complex **4** in THF is unstable even at −80 °C, decomposing within 15 min and affording oxidized solvent, 2-hydroxy-THF (∼40%) and γ-butyrolactone (<5%).[13] When the formation of **4** was carried out in toluene at −80 °C, thermal decomposition produces PhCHO (35%) with 70% 18-O incorporation (giving PhCH^{18}O) when using $^{18}O_2$ labeled **4**. The reaction of **4** with 2,4-di-tert-butylphenol in diethyl ether produces the typical oxidative coupling product 4,4′,6,6′-tetra-*t*-butyl-2,2′-biphenol (50%) after low-temperature reaction, warming, and workup (Scheme 1).

The reactivity of [{(6tbp)Cu^{III}}$_2$(O)$_2$]$^{2+}$ (**4**) with substrates parallels the behavior known for [Cu^{III}_2(O)$_2$]$^{2+}$ species.[3] Warming [{(6-PhTPA)Cu^{III}}$_2$(O)$_2$]$^{2+}$ (**5**) gives a trace of oxidatively N-dealkylated ligand decomposition products.[23] *Thus, it appears that neither **4** nor **5** effect aryl hydroxylation chemistry, which does however derive from the $Cu^{II}-{}^{-}OOH$ complex [(6tbp)Cu^{II}($^{-}$OOH)]$^+$ (**2**).* The lack of aryl ring hydroxylation of 6tBP or 6-PhTPA by the [Cu^{III}_2(O)$_2$]$^{2+}$diamond core may be attributed to axial positioning of the arylpyridyl arm, precluding a geometry favorable for oxo-atom attack and transfer to the pendant aryl group.[23] Axial ligand elongation is observed for 6-substituted 2-pyridyl ligand arms in [{(6-Me_2TPA)Cu^{III}}$_2$(O)$_2$]$^{2+}$ (**5**) (X-ray).[24,25] However, the proximity of a reactive species and aryl substrate in the 6-position of a coordinating pyridyl ligand *does* lead to aryl hydroxylation for [(6-PhTPA)Fe^{III}($^{-}$OOR)]$^{2+}$, as mentioned above, in our complex [(6tbp)Cu^{II}($^{-}$OOH)]$^+$ (**2**) and for a Cu^{III}_2(O^{2-})$_2$ species supported by the bidentate 2-(diethylaminomethyl)-6-phenylpyridine ligand.[26]

In summary, the chemistry presented reveals that a significant aryl hydroxylation chemistry can be effected by a discrete mononuclear Cu^{II}−hydroperoxo complex or derived species. The reaction does not proceed from bis-μ-oxo-dicopper(III) chemistry. [(6tbp)Cu^{II}-($^{-}$OOH)]$^+$ (**2**) or complexes of similar design may now serve as important entities for further detailed mechanistic investigations which could lead to insights into copper promoted O−O cleavage and new high-valent copper-oxo chemistry of chemical and biochemical consequence.

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Supporting Information Available: Synthetic details, descriptions of reactions, 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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