

Aryl Hydroxylation from a Mononuclear Copper-Hydroperoxo Species

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Research advances concerning the active-site chemistry of dioxygen activating copper enzymes have shown that single copper center O₂-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 monooxygenases (D β M).¹ While these possess two copper ions per active subunit which are ~ 11 Å apart,^{2a} the Cu_M (\equiv Cu_B) site is where substrate H-atom abstractions occur, resulting in overall O₂/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/O₂ 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}–O₂^{•−}) 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 D β M and PHM reactivity, while more recent experimental and computational advances suggest an active-site Cu^{II}–O₂^{•−} entity most likely effects initial substrate H-abstraction.^{1b,4} However, other computational studies suggest that the O₂-derived O–O bond first cleaves to give a cupryl (e.g., Cu^{III}=O \leftrightarrow Cu^{II}–O[•])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}–O₂^{•−} 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 RCH₂C \equiv N oxidative cleavage (to RCH=O + cyanide).¹¹ Suzuki has also observed a hydrocarbon attack from a Cu^{II}₂(–OH)₂ + H₂O₂ reaction, giving a Cu^{II}–OOH_{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 (TPMA) ligand, however it possesses a proximate aryl group (Figure 1).¹³ The X-ray structure¹³ 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 H₂O₂/Et₃N using 50% H₂O_{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 $^{\text{−}}\text{OOH} \rightarrow \text{Cu}^{\text{II}}$ LMCT band.¹⁴ A typical Cu^{II} axial EPR

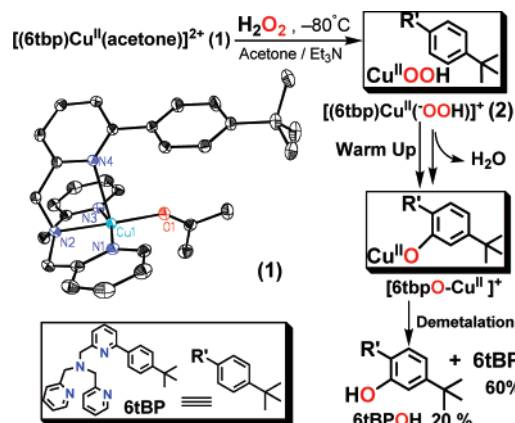


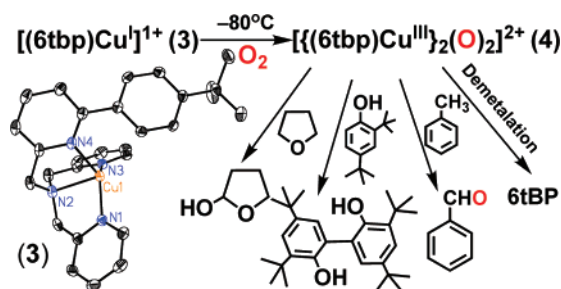
Figure 1. X-ray structure of **1**, as precursor to hydroperoxo–Cu^{II} complex **2**, leading to a phenolate–Cu^{II} entity which upon demetalation gives the *o*-hydroxylated phenol 6tBPOH. The oxygen atom(s) red-labeling tracks results from 18-O substitutions, see text.

spectrum for **2** is consistent with mononuclear formulation, g_{\parallel} = 2.245, g_{\perp} = 2.042, A_{\parallel} = 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 H₂¹⁸O₂, the positive ion peak shifts to 522.04, attributed to [(6tbp)Cu^{II}–(¹⁸O¹⁸OH)]⁺; 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 Na₂EDTA (aq) and extracted into CH₂Cl₂ revealed unreacted 6tBP ligand. However, a new product obtained in $\sim 20\%$ yield (which decreases with less added H₂O₂) 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 ¹H NMR and ¹³C 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 (6tBP¹⁸OH + Na) was recorded for the 6tBP¹⁸OH when H₂¹⁸O₂ 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 ([6tbp¹⁸O[−])Cu^{II}]⁺ when H₂¹⁸O₂ 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

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 $\text{Cu}^{\text{II}}-\text{OOH}$ 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-workers²¹ established homolytic cleavage from an $\text{Fe}^{\text{III}}-\text{OOR}$ species to give an $\text{Fe}^{\text{IV}}=\text{O}$ 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, $[(6\text{tbp})\text{Cu}^{\text{I}}]^+$ (**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 $[(6\text{tbp})\text{Cu}^{\text{III}}]_2(\text{O}_2)_2^{2+}$ (**4**, $\lambda_{\text{max}} = 383\text{ nm}$ ($\epsilon = 7000\text{ M}^{-1}\text{ cm}^{-1}$) (Scheme 1). The formulation is based on well-established spectral signatures^{3a} and the result is identical to that recently reported for a $[(6\text{-PhTPA})\text{Cu}^{\text{I}}]^+/\text{O}_2$ reaction [6-PhTPA described above], giving $[(6\text{-PhTPA})\text{Cu}^{\text{III}}]_2(\text{O}_2)_2^{2+}$ (**5**), $\nu_{\text{Cu}-\text{O}} = 599\text{ cm}^{-1}$.²³ Complex **4** in THF is unstable even at -80°C , decomposing within 15 min and affording oxidized solvent, 2-hydroxy-THF ($\sim 40\%$) 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 $^{18}\text{O}_2$ 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-*tert*-butyl-2,2'-biphenol (50%) after low-temperature reaction, warming, and workup (Scheme 1).

The reactivity of $[(6\text{tbp})\text{Cu}^{\text{III}}]_2(\text{O}_2)_2^{2+}$ (**4**) with substrates parallels the behavior known for $[\text{Cu}^{\text{III}}_2(\text{O}_2)_2]^{2+}$ species.³ Warming $[(6\text{-PhTPA})\text{Cu}^{\text{III}}]_2(\text{O}_2)_2^{2+}$ (**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 $\text{Cu}^{\text{II}}-\text{OOH}$ complex $[(6\text{tbp})\text{Cu}^{\text{II}}(-\text{OOH})]^+$ (**2**). The lack of aryl ring hydroxylation of 6tBP or 6-PhTPA by the $[\text{Cu}^{\text{III}}_2(\text{O}_2)_2]^{2+}$ 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 $[(6\text{-Me}_2\text{TPA})\text{Cu}^{\text{III}}]_2(\text{O}_2)_2^{2+}$ (**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 $[(6\text{-PhTPA})\text{Fe}^{\text{III}}(-\text{OOR})]^{2+}$, as mentioned above, in our complex $[(6\text{tbp})\text{Cu}^{\text{II}}(-\text{OOH})]^+$ (**2**) and for a $\text{Cu}^{\text{III}}_2(\text{O}_2)_2$ 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 $\text{Cu}^{\text{II}}-\text{hydroperoxo}$ complex or derived species. The reaction does not proceed from bis- μ -oxo-dicopper(III) chemistry. $[(6\text{tbp})\text{Cu}^{\text{II}}(-\text{OOH})]^+$ (**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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