A Tricopper(I) Complex Competent for O Atom Transfer, C–H Bond Activation, and Multiple O₂ Activation Steps

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ABSTRACT: Oxygenation of a tricopper(I) cyclophanate (1) affords reactive transients competent for C–H bond activation and O atom transfer to various substrates (including toluene, dihydroanthracene, and ethylmethylsulfide) based on 1H NMR, gas chromatography/mass spectrometry (MS), and electrospray ionization (ESI)/MS data. Low product yields (<1%) are determined for C–H activation substrates (e.g., toluene, ethylbenzene), which we attribute to competitive ligand oxidation. The combined stopped-flow UV/visible, electron paramagnetic resonance, ESI/MS, 1H NMR, and density functional theory (DFT) results for reaction of 1 with O₂ are consistent with transient peroxy- and di(oxo)-bridged intermediates. DFT calculations elucidate a concerted proton-coupled electron transfer from toluene to the di(μ-oxo) intermediate and subsequent radical rebound as the C–H activation mechanism. Our results support a multicopper oxidase-like mechanism for O₂ activation by 1, traversing species similar to the coplanar Cu₃O₂ unit in the peroxo and native intermediates.

INTRODUCTION

Dioxygen activation by multicopper oxidases (MCOs) couple dioxygen reduction to water with a number biochemical processes, including substrate oxidation and selective ion transport.1,2 The diverse reactivity of copper–dioxygen adducts arising from similar active-site structures has inspired ongoing work to replicate this reactivity in model compounds. In particular, the potential for copper complexes to function as catalysts for C–H bond functionalization and dioxygen reduction have applications in green synthesis and in fuel cells.3 The tricopper(I) state of MCOs is proposed to react with O₂ to arrest at a peroxide-bridged transient (PI) and requires a further one e⁻/H⁺ reduction to complete O₂ bond scission to yield the native intermediate (NI; Figure 1).1a,5 Contrastingly, no synthetic tricopper–dioxygen adduct arrests at the peroxide state, although stable peroxy–dicopper(II) species and those in equilibrium in the di(μ-oxo) congeners have precedent (Figure 1).7 These tricopper compounds are capable of H atom abstraction from substrates (e.g., phenols) or O atom transfer to phosphines. Density functional theory (DFT) studies on MCOs indicates that O₂ binds coplanar with the Cu₃ plane, whereas the O–O vector is orthogonal to the Cu₃ plane in model compounds.5b,6d,8 The consequence of O₂ orientation relative to the metal centers on bond activation remains poorly understood. Our hypothesis is that the orientation of the O₂ fragment relative to the tricopper plane is a key element differentiating the reactivity of reported model compounds from that of the enzymatic systems. With this consideration in mind, the steric constraints imposed by our cyclophane ligand can likely enforce the desired coplanar orientation of O₂ binding. To that end, we report the oxygenation of a Cu₃ cyclophanate, 1, in which the macrocycle enforces an MCO-like O₂ coordination to the metal ions.5a,7b,9 Oxygenated transients 1·O₂ are competent for C–H activation of C–H bonds of substrates such as 9,10-dihydroanthracene and toluene and O atom transfer to styrene and ethylmethyl sulfide. DFT calculations on this system point to a covalent [Cu₃(μ-μ-O)(μ-μ-O)]⁺ cluster as one likely reactive intermediate. These in silico studies point to a favorable H atom abstraction from PhMe followed by radical rebound to afford the alcohol product. In addition, the initial metal complex product of O atom transfer is identified as a μ₃-oxotricopper(II/II/II) complex, which can react with an additional equivalent of O₂. Our results highlight the importance of O₂ orientation as a key factor in dictating the reactivity of multimetallic species.

EXPERIMENTAL SECTION

General Considerations. All reactions were prepared under a dinitrogen atmosphere in an Innovative Technologies glovebox and then transferred to a Schlenk line. Unless otherwise explicitly stated, all...

Supporting Information
solvants and reagents were purchased from Sigma-Aldrich. Solvents were dried using an Innovative Technologies solvent purification system and stored over activated 3 Å molecular sieves inside the dinitrogen-filled glovebox. Ultra High Purity (UHP) O2 was purchased from AirGas. Deuterated solvents were purchased from Cambridge Isotope Laboratories (CIL) and purified according to reported procedures for the proteo-solvents and then stored over activated 3 Å molecular sieves inside the glovebox. The tube was capped with a Tedlar valve, removed from the glovebox, and placed under N2O on a vacuum manifold. The solution was then degassed by three freeze−pump−thaw cycles, after which the tube was placed in CO2−/isopropanol bath. After the sample had thawed under vacuum, tube was refilled with O2 and then flash frozen after ~10 s using liquid nitrogen. The sample tube was then evacuated, flame-sealed, and stored at 7 K. Electron paramagnetic resonance (EPR) spectra were collected on a Bruker Elexsys E580 with a Bruker 4116DM resonator maintained at 5 K with a liquid helium-cooled cryostat. Data were collected in perpendicular mode from 50 to 7050 G with the following parameters: power = 2.00 mW; frequency = 9.407 GHz; modulation frequency = 100.00 kHz; modulation amplitude = 10.00 G; and modulation frequency = 100.00 kHz; modulation amplitude = 10.00 G; and gain = 60 dB. In parallel mode, from 50 to 7050 G with the following parameters: power = 0.633 mW; frequency = 9.410 GHz; modulation frequency = 100.00 kHz; modulation amplitude = 10.00 G; and gain = 60 dB.

**Synthesis of 2.** In a typical synthesis, 35.0 mg (0.0391 mmol) of CuOCL13 was dissolved in 10 mL of THF and added to a 50 mL round-bottom Schlenk flask with a Teflon screw-cap seal valve. This was attached to a Schlenk line and degassed with three consecutive freeze−pump−thaw cycles to remove dissolved gases. The flask was then backfilled with UHP O2 and allowed to thaw to room temperature. The reaction was allowed to stir vigorously for 30 min under static O2, which resulted in a color change from dark yellow to dark maroon. After this color change was complete, volatiles were removed from the reaction vessel under reduced pressure to yield the final product as a dark purple solid.14 H1 NMR (300 MHz, THF-d8, 298 K): δ (ppm), 129.0(br,12H), 18.4(s,18H), 30.9(s,3H). Other ligand-derived signals could not be reasonably assigned. Attenuated total reflectance (ATR) IR (cm−1): 2959(m), 2925(m), 2868(m), 1550(s), 1522(m), 1469(m), 1434(s), 1405(w), 1373(m), 1331(m), 1237(w), 1066(w), 1014(w), 730(m).

**H2O2 Quantification by Iodometric Titration.** Adapted from a previously reported procedure.15 Under N2, 15.8 mg (0.0174 mmol) of 1-N2 was dissolved in 50 mL of CH3H2 concentration (0.334 mM), and 9.0 mg (0.0101 mmol) of 2 was dissolved in 25 mL of CH3H2 (0.407 mM). These were then transferred to 20 mL scintillation vials were fitted with 14/20 rubber septa containing 5 mL of solution each. For 1-N2, a Schlenk line connected to UHP O2 was purged for 5 min to replace atmosphere. Under positive pressure of O2, each septum seal was pierced with a needle to allow O2 flow, which caused an immediate color change from pale orange to brown. After 5 s, 1.0 mL of 17.5 mM [H(DMF)]OTf in MeCN was used to quench, bringing the total volume to 6.0 mL, for a final analyte concentration of 0.291 mM (1-N2) and 0.336 mM (2). The final reaction mixture

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**Figure 1. Proposed mechanism for O2 reduction by multicopper oxidases traverses peroxy- and a (μ-hydroxo)(μ-oxo)tricopper transients abbreviated P1 and N1 (top).** The active site of laccase from Steccherinum maraschinskii (PDB ID: 5MIB) with Cu ions depicted as green spheres and the proteinaceous ligands as sticks (bottom, left). Crystallographically characterized d(μ-HO)(μ-CO)tricopper compounds synthesized by reaction of monocopper(1) complexes of the depicted ligands and dioxygen.6−8

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**EPR Spectroscopy.** A solution of 1-N2 in toluene (1.5 mM, ~1 mL) was transferred to a quartz tube inside of a dinitrogen-filled glovebox. Ultra High Purity (UHP) O2 was purchased from AirGas. Deuterated solvents were purchased from Cambridge Isotope Laboratories (CIL) and purified according to reported procedures for the proteo-solvents and then stored over activated 3 Å molecular sieves inside the glovebox. The tube was capped with a Tedlar valve, removed from the glovebox, and placed under N2O on a vacuum manifold. The solution was then degassed by three freeze−pump−thaw cycles, after which the tube was placed in CO2−/isopropanol bath. After the sample had thawed under vacuum, tube was refilled with O2 and then flash frozen after ~10 s using liquid nitrogen. The sample tube was then evacuated, flame-sealed, and stored at 7 K. Electron paramagnetic resonance (EPR) spectra were collected on a Bruker Elexsys E580 with a Bruker 4116DM resonator maintained at 5 K with a liquid helium-cooled cryostat. Data were collected in perpendicular mode from 50 to 7050 G with the following parameters: power = 2.00 mW; frequency = 9.407 GHz; modulation frequency = 100.00 kHz; modulation amplitude = 10.00 G; and gain = 60 dB. In parallel mode, from 50 to 7050 G with the following parameters: power = 0.633 mW; frequency = 9.410 GHz; modulation frequency = 100.00 kHz; modulation amplitude = 10.00 G; and gain = 60 dB.

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was then freeze-pumped-thawed once more. The reaction mixture (0.2 mL) was added to a 1 cm quartz cuvette, and to this was added 1.8 mL of a 0.3 M NaI solution in MeCN, for a final concentration of 0.0291 mM Cu(N2)2L. Since 1-N2 has a ligand-based absorption that overlaps with $\Gamma_1 (\lambda_{max} = 361 \text{ nm}, f = 22,000 \text{ M}^{-1} \text{ cm}^{-1})$, a control of 1-N2 + O2 + [H(DMF)]OTf was used as a background (see Figures S42 and S43). From the five trials, a total of 94.5 ± 14.8% (1-N2) and 52.3 ± 9.5% (2) yield of H2O2.

**Oxidation of Hydrocarbons and Ether.** To a solid portion of 1-N2 (0.028 mmol, 25 mg) in a 20 mL vial was added an aliquot of a THF solution of either styrene (1.6 mL, 0.87 M), toluene (1.5 mL, 0.94 M), methylbenzene (1.7 mL, 0.82 M), ethylbenzene (1.4 mL, 0.95 M), hexanes (1.8 mL, 0.80 M), cyclohexane (1.5 mL, 0.94 M), or cyclohexene (28 μL, 0.055 M). This solution was then diluted with THF to give a final reaction volume of 3 mL with concentrations of 9.2 mM for 1-N2 and 460 mM for the given substrate. The vial was sealed with a septum and removed from the glovebox. UHP dioxygen was then introduced to the headspace of the vial for ~5 s. The reaction was then removed from the manifold and stirred overnight under a static atmosphere, after which the reaction was opened to air, filtered through diatomaceous earth, and the filtrate was used for GC/MS measurements. Oxidation reactions using 18O2 were prepared as described above. Reaction mixtures were injected splitless with either a 0.5 or 1 µL sample injection volume for UHP O2 or 18O2, respectively.

**Oxidation of Ethylmethylsulfide and 9,10-Dihydroanthracene.** A 50 mL pear-shaped Schlenk flask equipped with a poly(tetrafluoroethylene) (PTFE)-coated magnetic stir bar was charged with 1-N2 (25 mg, 0.028 mmol), and either ethylmethylsulfide (0.5 mL, 5.53 mmol)/0.5 mL of THF, 9,10-dihydroanthracene (DHA; 73 mg, 0.40 mmol)/1.0 mL of THF, or d4-DHA (31 mg, 0.017 mmol)/1.0 mL of THF. Naphthalene was included as a gas chromatography (GC) internal standard (14.1 mg, 0.11 mmol). The flask was then removed from the glovebox and placed under Ar on a vacuum manifold. The reaction mixture was degassed by repeated freeze–pump–thaw cycles and cooled to −78 °C (CO2/isopropanol). The flask was then filled with 1 atm of UHP oxygen gas or 18O2, and the vessel remained under a static atmosphere at −78 °C for 15 min. An aliquot was removed and then injected into the ESI/MS instrument. After the aliquot was removed and with the temperature maintained at −78 °C, all volatiles from the reaction flask were removed under reduced pressure, which required ~20 min. The solid residue was transferred to the glovebox, and 1H NMR spectra were recorded in either d-toluene or d-dichloromethane.

**Computational Methods.** Density functional theory (DFT) calculations were performed in Gaussian09 Version D.01.15 A model of the dinitrogen complex 1 was built from crystallographic coordinates and optimized as the neutral singlet with the BP86 functional. Ahrlich’s triple-ζ basis set with polarization (tzvp)16 was used on Cu, O, and N atoms, and split valence with polarization (svp)17 was used on C and H atoms. The oxygenated products and reaction trajectory were computed analogously. Analytical frequency calculations were performed on all complexes to ensure stationary points on the potential energy surface had been reached, and no imaginary frequencies were found. Single-point energy calculations were performed with the b3lyp functional18 within the unrestricted formalism with an ultrafine integration grid as implemented in Gaussian09. These single-point calculations included solvation using Gaussian09. These single-point calculations included solvation using S43). From the five trials, a total of 94.5 ± 14.8% (1-N2) and 52.3 ± 9.5% (2) yield of H2O2.

**RESULTS AND DISCUSSION**

Monitoring reaction of 1-N2 with O2 in THF at −78 °C by stopped-flow (SF) UV/visible spectroscopy, we observe an initial rapid decay at $\lambda_{max} = 505 \text{ nm} (<100 \text{ ms})$ followed by absorption increases at $\lambda_{max} = 490$ and 630 nm (Figures S1 and S2). $\Delta_{A_{505}}$ may arise from N2 dissociation, and those at 490 and 630 nm are consistent with reported CuO3 species.14,21 $\Delta_{A_{505}}$ and $\Delta_{A_{630}}$ kinetic traces were complex, and we were unable to simulate the data with two- or three-sequential elementary step mechanisms. We then re-examined this reaction using 1 synthesized under Ar (1’), which lacks the 505 nm band of 1-N2, to better resolve $\Delta_{A_{505}}$ and $\Delta_{A_{630}}$ (Figures S3, S5, and S7). 1’ can be quantitatively converted to 1-N2 upon exposure to N2, supporting 1’ as Cu-L (Figures S3 and S4). Reaction of 1’ with O2 in n-hexane at −80 °C results in similar increases in $A_{505}$ and $A_{630}$ as with 1-N2 (Figure 2). $A_{505}$ and $A_{630}$ data are best modeled using an $A \rightarrow B \rightarrow C \rightarrow D$ scheme (Figure 2 inset and Figures S7–S12). The employed model is consistent with the profiles of $A_{630}$ versus $A_{505}$ (specifically, the initial maximization time for $A_{630}$ differs from that for $A_{505}$). As a caveat, however, the initial 0.28 absorption change within the instrument dead time, and the gradual persistent absorption

![Figure 2](image-url)
increases out to long reaction times (>40 min) required truncation of the data sets (4 ms–1.0 s). Our absorption maxima are comparable to ligand-to-metal charge-transfer bands at 480 nm reported for PI and Chan’s tricopper–dioxxygen intermediate(s).\textsuperscript{21a,b,23} Thus, we tentatively assign B, and a paramagnetic product (Figure S36).

Attempts to probe the O–O bond order spectroscopically for 1·O₂ species were unsuccessful. Absorptions assignable to O–O stretching modes for a peroxide transient were unobservable by stopped-flow infrared (SF-IR) or in Raman spectra on frozen samples using ¹⁶O₂ or ¹⁸O₂. We note that vibrational data on PI have not been reported, albeit due to protein absorption and fluorescence.\textsuperscript{24} X-band EPR spectra recorded on 1·O₂ revealed absorptions at 3244 G and ~1570 G in perpendicular and parallel mode (Figure S36). These spectra are comparable to those for triplet di(μ-oxo)tricopper(II/II/III) clusters.\textsuperscript{6d,a,25} However, the intensity ratio of the half-maxima are comparable to ligand-to-metal charge-transfer transients. GC data on oxygenated mixtures of 1·N₂ and styrene or toluene using ¹⁸O₂ were shifted by 2 mass units, confirming that the incorporated O atom is O₂-derived (Figures S18–S21). Scrambling of the ¹⁸O label is observed in the products, but similar results are reported for other copper and related systems.\textsuperscript{28} Oxidation products were not observed with cyclohexane, hexane, pentane, or diethyl ether as the substrates.

Thus, we estimate the oxidizing power of 1·O₂ intermediates as 88.5 kcal/mol (bond dissociation energy (BDE) of PhC=O), although the expected competitive ligand oxidation complicates this analysis.\textsuperscript{27} For DHA oxidation, the predominant ion envelopes in ESI/MS data are well-simulated to a mixture of [Cu₃O₂L+H⁺] and [Cu₃O₂L+2H⁺] (Figure S32), and anthracene was observed by ¹H NMR (Figure S31). If d₆-DHA is used, resonances for d₆-anthracene and a parent ion consistent with [Cu₃O₂L+D]⁺, which suggests H atom abstraction (HAA), are observed in the product mixtures by ¹H NMR and ESI/MS, respectively (Figures S35 and S34). This result, however, is not unambiguous, as the mass is within 5 ppm of that for [Cu₃O₂L+2H⁺]. For EtSMe oxidation, ions corresponding to [Cu₃O₂L⁢H⁺], [Cu₃O₂L+H⁺], [Cu₃O₂L⁺], [Cu₃O₂L⁢H⁺], and [EtS(O)Me+M⁺] (M = Li⁺, Na⁺, K⁺) were observed in ESI/MS data (Figures 3 and S26). An ion envelope consistent with a dicopper species is also assignable; however, similar envelopes are also present in MS data for other purified tricopper complexes,\textsuperscript{9a,35} suggesting potential demetallation under analysis conditions. Using ¹⁸O₂ for EtSMe oxidation affords ions with m/z values consistent with [Cu₃¹⁸O₂L⁺] and [Cu₃¹⁸O₂L⁢H⁺], and [Cu₃¹⁸O₂L⁺] and [Cu₃¹⁸O₂L⁢H⁺]. Similar to our GC/MS results, incorpor-

Table 1. Yields of Oxidation Products

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<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>-</td>
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<tr>
<td>Me = 0.46⁷</td>
<td></td>
<td></td>
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<tr>
<td>R = H, Me</td>
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<tr>
<td>Me = 0.46⁷</td>
<td>H = 0.46⁷</td>
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<td>0.50⁷</td>
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<td>1.6⁷</td>
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\(^{9}\text{On the basis of [1·N₂].}^{10}\text{Determined by GC.}^{11}\text{Determined by ¹H NMR.}\)

Figure 3. High-resolution ESI/MS(+) data from the oxygenation reaction of 1·N₂ in the presence of EtSMe. Each isotopic pattern is best simulated as a combination of [M⁺] and [M + H⁺] with m/z = 895.3047 assigned to [Cu₃OL]⁺ and [Cu₃OL+H⁺], m/z = 910.2942 as [Cu₃O₂L]⁺ and [Cu₃O₂L+H⁺], and m/z = 928.3004 as [Cu₃O₂L+2H⁺] and [Cu₃O₂L+H₂O]⁺.
A reaction of the O atom label is also not nearly quantitative for the copper products; the cause of this scrambling remains under investigation. Resonances corresponding to Cu3OL are also evident in 1H NMR spectra of EtSMe and DHA oxidation reactions (Figures S24, S25, and S31). We conclude then that 1 exhibits mono-oxygenase-like reactivity leading to C–H bond activation and OAT as potential reaction pathways.

Given the complexity of our reaction kinetics, we challenged our assumption that Cu3OL is a terminal product of O2 activation by 1. Cu3OL does not effect OAT (e.g., Me3P) and is unreactive toward O atom donors (e.g., PhIO). Exposure of a d8-THF solution of Cu3OL to O2 at −78 °C results in complete consumption of Cu3OL to yield a paramagnetic species, 2 ($\lambda_{\text{max}}$ = 488 nm, Figure S39). 2 is unstable under an O2 atmosphere, precipitating a brown solid after ~2 h (Figure S40), but it can be isolated if the reaction is degassed. Oxidation products are identifiable in 1H NMR spectra of reactions of isolated 2 with DHA (Figure S45) but are undetected for reactions with toluene, ethylbenzene, or styrene. Assuming quantitative conversion of Cu3OL to 2, the H2O2 yield of S2(10)% by iodometric titration on samples of 2 (Figure S43) hints at a peroxo-bridged bis[Cu3OL] species analogous to our bis(triiron) compound. Another possible formula assignment for 2 is superoxo-adduct of Cu3OL, which cannot be excluded by our data. Taken together, 1 can react with multiple equivalents of O2 in the presence of substrates. To our knowledge, the ability of the product cluster of a mono-oxo reaction to react with dioxygen in the absence of additional reducing equivalents is unprecedented.

Geometry optimization of a dinitrogen-for-dioxygen substituted 1-N2 affords two stationary points: a peroxotricopper-(I/II/II) species (3) at −18.1 kcal/mol and a ($\mu$-oxo)/($\mu$-oxo)/tricopper(II/III/III) intermediate (4) at −22.9 kcal/mol (Figure 4). Notably, the Cu3O2 is planar in both 3 and 4, as implying that geometric and electronic structures are reliable, whereas the relative thermodynamics between species should be used with caution.

The relatively short O–O distance of 1.45 Å in 3 reflects minimal back-bonding from the unique Cu(II) ion into the O2 $\sigma^*$ orbital as is typically observed in side-on adducts to Cu. Consequently, this orbital, which would be the acceptor orbital for potential H atom abstraction, is unactivated, as the O2 $\sigma^*$ orbital is high in energy. Analysis of the unoccupied orbitals of 4—the lower energy isomer of 4—revealed a highly covalent [Cu3O2]$^{3+}$ core (Table S3), with three copper-based orbitals (241a, 240β, and 241β) and an unoccupied O orbital on the $\mu_2$-O donor (62.0% O, Figure 5). This unoccupied predominant O-centered orbital has out-of-plane p character, indicative of a highly electrophilic O atom. One could, therefore, describe the [Cu3O2]$^{3+}$ core of 4 as a ($\mu$-oxyl)/($\mu$-oxo)/tricopper(II) species.

To evaluate the mechanism of C–H activation, a toluene molecule was docked into the structure of 3 near the $\mu_2$-O atom to afford the stationary point (Figure S51, 4-Tol). Using the maximum along a linear transit for H-abstraction from CH3 to the $\mu_2$-O of 3 as an initial guess of the transition state (TS), we obtained an optimized TS with C–O and H–O distances of 2.56 and 1.27 Å, respectively. This evolves to a ($\mu$-hydroxo)/($\mu$-oxo)/tricopper(II) species and a benzyl radical (5·R; Figure S50). Whereas the $\mu_2$-O bears radical character resides in an orbital of out-of-plane p-character, the H atom acceptor orbital is of in-plane O p + Cu d$_{z^2}$ character and equivalent to orbital 241β in 4 (Figure S55 and Table S3). Inspection of the molecular orbitals of the TS reveals that electron and proton transfer are simultaneous, consistent with a concerted proton–electron transfer. Subsequent radical rebound is favorable (−33.6 kcal/mol versus 5·R), yielding PhCH2OH and Cu3OL (Figure S51). From analysis of the two-dimensional (2D) potential energy surface of C–O bond making versus O–Cu bond breaking for this rebound, the step is essentially barrierless (Figure S50), suggesting that accumulation of 5 and benzyl radical dimerization are disfavored.

In our proposed mechanism for O2 activation and substrate oxidation by 1, coplanar coordination of O2 to the Cu3 centers...
results in peroxo-and di(μ-oxo)-tricopper transients, with the former being analogous to PI in MCOs (Scheme 1). The perpendicular alignment of the O···O vector with respect to the μ diketiminate differs from reported di(μ-oxo)tricopper compounds and decreases metal-O₂ backboning, which we attribute to the observed reactivity differences. Although we cannot exclude HAA or hydride abstraction by Et₂O oxidation is not observed despite its lower heterolytic HAA is rare for peroxo-bridged dicopper complexes and that activation by a tricopper system to our knowledge. We do and co-workers in the reactivity of the transient being competent for HAA from DHA, whereas that attribute to the observed reactivity dičpecies.6d,8 Although we references.6d,8 Although we cannot exclude HAA or hydride abstraction by 3, we note that HAA is rare for peroxo-bridged dicopper complexes and that Et₂O oxidation is not observed despite its lower heterolytic BDE versus PhMe. Importantly, our results parallel O₂ reduction by MCOs, as the μ₂-oxide is the favored site of formal H atom transfer in both systems, hinting at similar electronic structure in both.32 Whereas NI is protected from reaction with adventitious substrates within the enzyme active site, our NI-like species undergoes a rebound reaction with a previously generated substrate radical.33

Although dioxygen–copper transients are well-known for HAA, intermolecular O atom transfer coupled to C–H activation remain uncommon. Tricopper complexes facilitate OAT to triphenylphosphine, mediate phenol oxidation, and ligand oxidation.7a,b,21a,b Maji et al. reported oxygenated Cu₃ transients competent for acetonitrile hydroxylation and catalytic oxidation of methane, which is the only example of C–H activation by a tricopper system to our knowledge.6d,22 We do not observe activation of C–H bonds stronger than that of toluene, suggesting that oxidation of these substrates is not accessible kinetically (e.g., rate of ligand oxidation is competitive). OAT to substrates in both systems is proposed to arise from a di(μ-oxo) tricopper transient, with the μ₂-O bearing oxyl or oxene character and being the H atom acceptor from substrates. Our system here diverges from that of Chan and co-workers in the reactivity of the μ₃-O tricopper species. Cu₃OL is reactive toward O₂ with the downstream oxygenated transient being competent for HAA from DHA, whereas that reported by Chan and co-workers is a terminal unreactive species. This deviation likely originates from the difference in ligand donor strength; the anionic β-diketiminate arms of our cyclophane afford a more electron-rich tricopper cluster as compared to the neutral donors in Chan’s ligand.

Regarding our low yields for OAT to hydrocarbon substrates, we surmise that intramolecular ligand oxidation is competitive with exogenous substrate bond activation. As noted above, the ligand presents four benzylic C–H bonds in the locale for substrate approach. The 2 orders of magnitude increase in product yield with EtSMe as the substrate as compared to toluene or DHA is consistent with our assertion. More pointedly, this increase in yield of the oxidized products leads to a concomitant increase in the formation of Cu₃OL and thereby supports our proposed mechanism; that is, 1-O₂ₚ which could be either a peroxo or di(μ-oxo) transient, is indeed the initial active oxidant and not a low-yield minor component in the reaction mixture.

## CONCLUSION

In conclusion, we report that 1-O₂ₚ transients are competent for OAT to hydrocarbon C–H bonds through an HAA mechanism. Our kinetic, spectroscopic, and DFT analyses are consistent with transient peroxo- and/or di(μ-oxo) species as the likely identity of these reactive species. In addition, the product cluster of OAT, Cu₃OLₚ, is itself reactive toward dioxygen, presenting a unique instance in which the product of a mono-oxygenase reaction retains reactivity toward O₂. Future studies aim to trap reactive species and enhance ligand stability toward oxidation.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.8b00921.

Data from experiments including diode array absorbance changes, ¹H NMR spectra, A₄₀⁰ versus time plots, gas chromatograms, mass spectra, ESI/MS spectra, ATR-IR spectra, calculated (TD-DFT) UV–visible spectra, optimized Cartesian coordinates (PDF)

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#### Author Contributions

These authors contributed equally.

#### Notes

The authors declare no competing financial interest.

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