

O₂ Activation and Selective Phenolate *ortho* Hydroxylation by an Unsymmetric Dicopper $\mu\text{-}\eta^1\text{:}\eta^1\text{-Peroxido}$ Complex**

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Understanding the intimate details of O₂ activation at metal sites is of interest because of the relevance of such reactions in biological and technological processes.^[1] Of particular relevance is uncovering basic chemical principles and mechanisms for taming the high oxidizing potential of the O₂ molecule into highly selective oxidative transformations, especially those involving the selective hydroxylation of C–H bonds.

For the particular case of dicopper sites, three basic Cu₂O₂ core structures have been widely described as arising from the interaction of discrete Cu^I complexes and O₂ (Figure 1).^[2] Each specific Cu₂O₂ core determines particular spectroscopic and chemical properties:^[2b,c] whereas end-on *trans*-Cu^{II}₂($\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2$) species exhibit nucleophilic and basic behavior, side-on Cu^{II}₂($\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2$) and bis- μ -oxido dicopper(III)

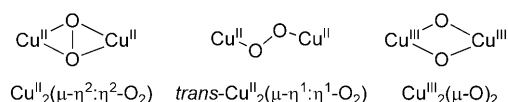


Figure 1.

(Cu^{III}₂($\mu\text{-O}$)₂) cores show electrophilic character, and can mediate tyrosinase-like phenolate *ortho*-hydroxylation reactions.^[3] The latter reactivity has never been observed for end-on Cu₂O₂ species; therefore its possible biological relevance has been ignored so far.

The rich and subtle chemistry exhibited by Cu₂O₂ cores makes unsymmetric options interesting. Actually, Cu₂O₂ species in systems containing distinct copper sites have been rarely observed.^[2b] Herein we describe a novel dicopper complex based on a heptadentate ligand that gives rise to an unsymmetric N₃Cu^{II}N₄Cu^{II}($\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2$) core, which hitherto exhibits reactivity patterns not observed for symmetric analogues. This nonsymmetric peroxide species shows an exquisite selectivity in its oxygen atom transfer reactivity. It performs the selective intermolecular *ortho* hydroxylation of a phenolate, but fails to oxidize many common oxophilic substrates.

Reaction of *m*-Xyl^{N₃N₄} with [Cu^I(CH₃CN)₄X] (X = CF₃SO₃, PF₆, ClO₄) in acetonitrile affords the unsymmetric dinuclear copper(I) complex [Cu^I₂(*m*-Xyl^{N₃N₄})](X)₂ (**1**-X; Figure 2). For comparative purposes, [Cu^I₂(*m*-Xyl^{N₄N₄})]-(ClO₄)₂ (**2**-ClO₄) was also prepared. Crystallographic characterization of **1**-CF₃SO₃ reveals that the copper ion bound to the tridentate arm adopts a highly distorted T-shape geometry, whereas the copper ion bound to the tetradentate arm has a distorted trigonal-pyramidal geometry, with structural parameters nearly superimposable with those of the two tetracoordinated copper ions in **2**-ClO₄.^[4]

Acetone solutions of **1**-X at –90 °C react with O₂ within seconds to form a red-brown species [Cu₂(O₂)(*m*-Xyl^{N₃N₄})]²⁺(**1**-O₂), characterized by a visible band at 478 nm (ϵ = 7800 M^{–1} cm^{–1}), and a broad shoulder between 575 and 700 nm (Figure 3). The visible spectrum of **1**-O₂ is intermediate between those of Itoh's proposed Cu^{II}₂($\mu\text{-}\eta^1\text{:}\eta^2\text{-O}_2$) species^[5] and reported Cu^{II}₂($\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2$) complexes.^[2b,6] UV/Vis monitoring of this reaction shows an isosbestic point at 414 nm indicating the clean transformation of **1**-CF₃SO₃ into **1**-O₂ without accumulation of any intermediate species. **1**-O₂ is stable for hours at –90 °C, but it decomposes within seconds when warmed to room temperature.

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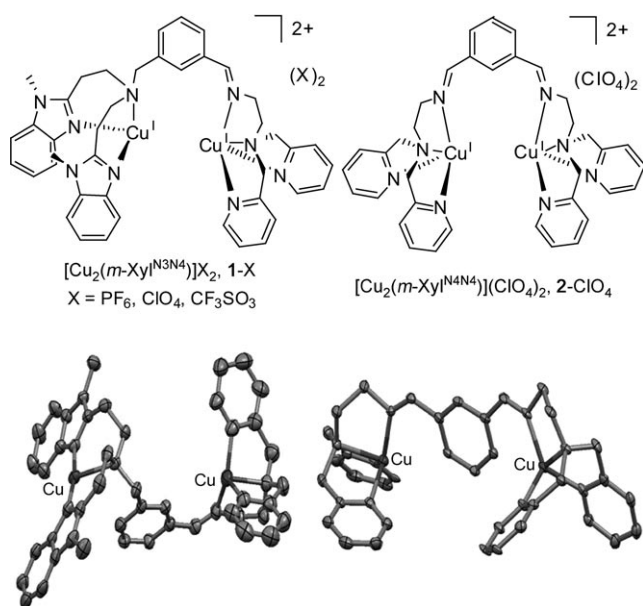


Figure 2. Top: Chemical diagram of **1-X** (left) and **2-ClO₄** (right). Bottom: Ellipsoid diagrams (30% probability) of the cationic parts of **1-CF₃SO₃** (left) and **2-ClO₄** (right). H atoms were omitted for clarity.

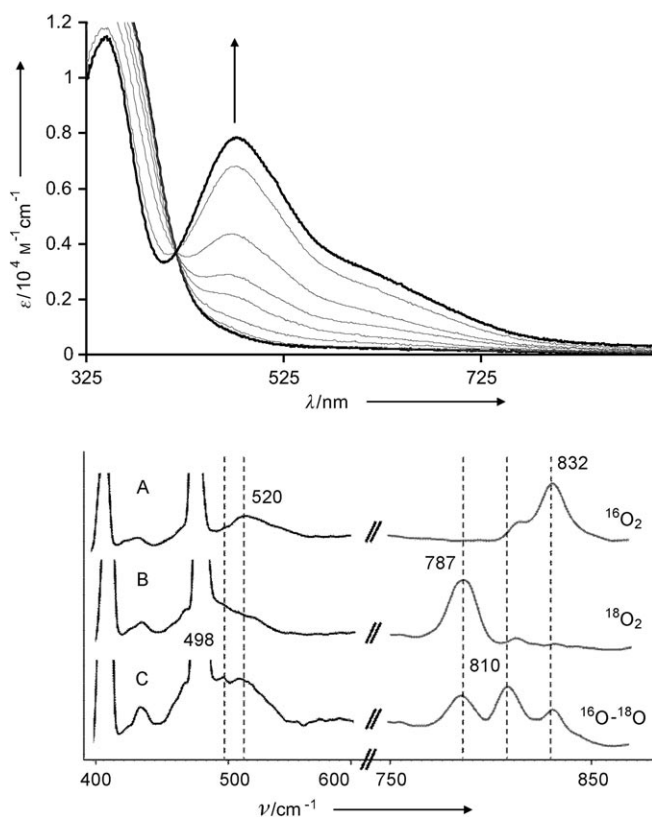


Figure 3. Top: UV/Vis spectra for the reaction of **1-CF₃SO₃** with O_2 in acetone at -90°C to form **1-O₂**. Bottom: Resonance Raman spectra ($\lambda_{\text{ex}} = 488 \text{ nm}$) of frozen acetone solutions of **1-O₂** from $^{16}\text{O}_2$ (A), $^{18}\text{O}_2$ (B), and $^{16}\text{O}-^{18}\text{O}$ (C).

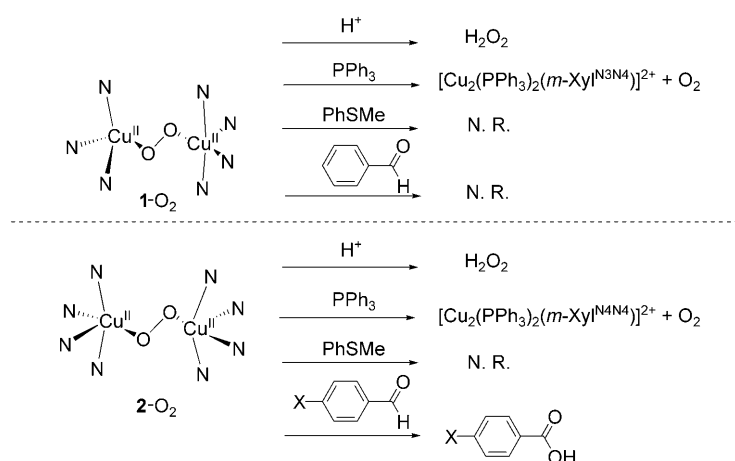
To gain insight into the peroxido binding mode of **1-O₂**, resonance Raman spectra of frozen samples of **1-O₂** were obtained. Laser excitation at 488 nm (Figure 3 bottom, insets A and B) gives rise to two resonance-enhanced peaks at 832

and 520 cm^{-1} [$\Delta^{18}\text{O}_2-^{16}\text{O}_2 = 45$ and 22 cm^{-1} , respectively], characteristic of O–O and Cu–O stretching vibrations of an end-on $\text{Cu}^{\text{II}}(\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2)$ species.^[2b] Excitation profiles indicate that the two vibrations are in resonance with the lower energy band, and no features resulting from a $\text{Cu}_2^{\text{II}}(\mu\text{-}\eta^2\text{:}\eta^2\text{-O}_2)$ species were observed. Experiments with mixed labeled O_2 (Figure 3 bottom, inset C) showed a $\nu(\text{O}-\text{O})$ region with three isotopomeric peaks at frequencies that suggest insensitivity of the bound O_2 to the unsymmetrical nature of the ligand.^[7]

In contrast, symmetric complex **2-ClO₄** reacts at -90°C in acetone to form a different metastable purple species, **2-O₂**, which is characterized by two intense UV/Vis bands at $\lambda_{\text{max}} = 500 \text{ nm}$ ($\epsilon = 5000 \text{ M}^{-1} \text{ cm}^{-1}$) and 635 nm ($\epsilon = 3300 \text{ M}^{-1} \text{ cm}^{-1}$), typical of an end-on *trans*- $\text{Cu}^{\text{II}}_2(\mu\text{-}\eta^1\text{:}\eta^1\text{:O}_2)$ species.^[2b] The O_2 -binding mode was confirmed by the resonance Raman spectra of a frozen **2-O₂** solution, collected with laser excitation at 488 nm (see the Supporting Information), which shows a characteristic resonance-enhanced $\nu(\text{O}-\text{O})$ band at 826 cm^{-1} [$\Delta^{18}\text{O}_2-^{16}\text{O}_2 = 44 \text{ cm}^{-1}$]. The fact that both **1-O₂** and **2-O₂** give rise to $\nu(\text{O}-\text{O})$ features of nearly the same frequency strongly suggests that the dioxygen moiety is bound in the same fashion in the two complexes. Because of the high energy of the $\nu(\text{O}-\text{O})$ stretching frequency,^[2b] and because a $\mu\text{-}\eta^1\text{:}\eta^2\text{-O}_2$ binding mode is unlikely for **2-O₂**,^[8] we favor a $\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2$ mode for both O_2 adducts.

The reactivities of **1-O₂** and **2-O₂** with different substrates were explored (Schemes 1 and 2). **1-O₂** and **2-O₂** rapidly and quantitatively react with $\text{CF}_3\text{CO}_2\text{H}$ releasing H_2O_2 (99% yield, see the Supporting Information). Titration experiments reveal that both reactions are complete with 1 equivalent of H^+ (per Cu), and no other intermediate species are detected when substoichiometric amounts of H^+ are added. **1-O₂** and **2-O₂** react neither with thioanisole, styrene, triphenylmethane, nor with electron donors such as ferrocene. Thermal decomposition of **1-O₂**, by warming up acetone solutions to room temperature, in the presence of large excess of toluene (1000 equiv), did not cause toluene oxidation.^[9] The addition of PPh_3 (10 equiv) to **1-O₂** and **2-O₂** at -90°C induces fast O_2 release ($t_{1/2} \approx 5 \text{ min}$) without formation of OPPh_3 .^[10] In sum, all the above observations suggest that **1-O₂** and **2-O₂** are not electrophilic oxidants, and typically react like other end-on *trans*- $\text{Cu}^{\text{II}}_2(\mu\text{-}\eta^1\text{:}\eta^1\text{-O}_2)$ complexes.^[11]

However, substantial differences arise when the reactions of **1-O₂** and **2-O₂** with benzaldehydes are studied. **2-O₂** reacts with benzaldehydes to generate the corresponding benzoic acids in quantitative yields. Kinetic analyses of the reactions were performed by using UV/Vis methods to monitor the decay of the spectral features of **2-O₂**. The **2-O₂** decay rate can be fitted to single exponential processes, and the measured k_{obs} values are linearly dependent on substrate concentration (see the Supporting Information). Reaction of **2-O₂** against a series of *para*-substituted benzaldehydes was studied and the corresponding decay rate constants were extracted by using UV/Vis methods to monitor the reactions. Plotting the decay rate of **2-O₂** against the corresponding Hammett substituent constants (σ^+) affords a linear correlation which gives a ρ value of 1.4 ($R^2 = 0.98$, see the Supporting Information), consistent with a nucleophilic oxidizing species that attacks

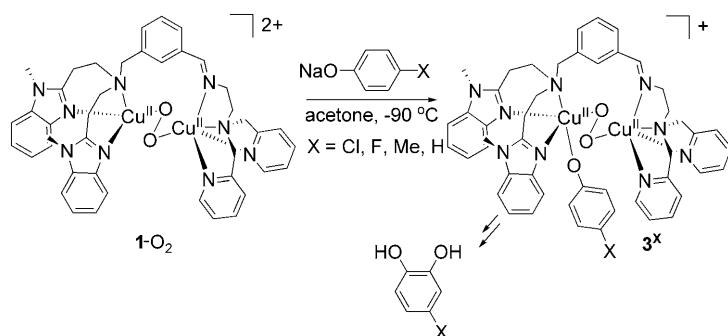


Scheme 1. Schematic representation of selected reactivity exhibited by **1-O₂** and **2-O₂**. (N.R. = no reaction).

the carbonyl moiety. In contrast, **1-O₂** fails to react with benzaldehyde. Thus we conclude that **1-O₂** is unreactive in oxygen atom transfer reactions to common substrates which are either electrophilic or nucleophilic in nature.

Strikingly, addition of *p*-Cl-C₆H₄ONa (3 equiv, Scheme 2) to a solution of **1-O₂** at −90 °C causes rapid conversion into a short-lived (*t*_{1/2} ≈ 1 min) yellow-brown species **3^{Cl}** (λ_{max} = 470 nm, ε > 6000 M^{−1} cm^{−1}, see the Supporting Information). The resemblance in the UV/Vis spectral features of **1-O₂** and **3^{Cl}** strongly suggests that the Cu^{II}₂(μ-η¹:η¹-O₂) core is retained, but the instability of **3^{Cl}** has thus far precluded its Raman characterization. Surprisingly, after complete decomposition of the **3^{Cl}** species, acidic work-up and subsequent HPLC/MS analyses show the formation of *p*-chlorocatechol in 39 % yield with respect to **1-O₂**. Similar addition of *p*-chlorophenolate to **2-O₂** causes fast bleaching of its spectral features, without accumulation of any intermediate species, and without any sign of phenolate *ortho* hydroxylation.

Kinetic analysis indicates that the decay of **3^{Cl}** is a first-order process. The analogous species **3^X** (X = F, Me, H, and OMe) were generated by the addition of 3 equivalents of *p*-X-C₆H₄ONa to **1-O₂** at −90 °C in acetone, and their corresponding UV/Vis decay rates were fitted to a single exponential function by nonlinear regression methods. Product analysis after **3^X** (X = F, Me, H, and OMe) decomposition reveals that the corresponding catechol is formed in 34 %, 34 %, 36 %, and 14 % yields, respectively. A Hammett plot (log (*k*_{obs}) for **3^X** versus σ⁺) affords a linear correlation which gives a ρ value of



Scheme 2. Reaction of **1-O₂** with the sodium salt of *para*-substituted phenolate.

−0.6 (*R*² = 0.98, see the Supporting Information), consistent with an electrophilic oxidizing species that attacks the aromatic ring in the rate-determining step of the reactions. In line with this reactivity, no catechol product was formed when electron-poor phenolates (X = CN, NO₂, and CO₂Me) were used as substrates. In contrast, substrate hydroxylation does not appear to be only determined by the electron-releasing nature of the substrate because the electron-rich, sterically more demanding 2,4-di-*tert*-butylcatechol was neither hydroxylated nor oxidized to the corresponding diphenol coupled product. We conclude that hydroxylation occurs exclusively for non-electron-poor, sterically unhindered phenolate substrates. Furthermore **1-O₂** differs from any other Cu^{II}₂(μ-η¹:η¹-O₂) intermediate in its capacity to carry out electrophilic arene hydroxylation.^[2c] We propose that the difference in the reactivity of **1-O₂** and any

previously reported end-on Cu^{II}₂(μ-η¹:η¹-O₂) species (including **2-O₂**) stems from the possibility that phenolate can initially bind at the N₃Cu site, as proposed in a symmetric *m*-xylyl-bridged bis-tridentate Cu^{II}₂(μ-η²:η²-O₂) system.^[3b] Indeed, in the present example, the substrate binding event can be understood as playing a selective peroxide-activation role, since **1-O₂** by itself lacks oxygen atom transfer reactivity.

The selective oxygen atom transfer reactivity exhibited by **1-O₂** was additionally substantiated by DFT computational methods.^[12] The computed structure of **1-O₂** (see the Supporting Information) reveals a Cu^{II}₂(μ-η¹:η¹-O₂) complex with a Cu⋯Cu distance of 4.31 Å and structural parameters in good agreement with a crystallographically characterized example.^[13] We have also found that the Cu^{III}₂(μ-O₂) isomer is 36.8 kcal mol^{−1} higher in energy.^[12] In addition, attempts to perform geometry optimizations on side-on Cu^{II}₂(μ-η²:η²-O₂) isomeric cores proved unsuccessful.^[14] Therefore, consistent with the experimental observations, the end-on Cu^{II}₂(μ-η¹:η¹-O₂) is the most stable species.^[14–16] Phenolate binding to **1-O₂** retains the Cu^{II}₂(μ-η¹:η¹-O₂) core as the most stable isomer (in agreement with our formulation of **3^X** based on its UV/Vis spectrum), and causes an elongation of the Cu⋯Cu distance up to 4.50 Å. Interestingly, the phenolate π system is adjacent to the peroxide oxygen atom bound to the other Cu in **3^{Me}** (Figure 4), offering a plausible pathway for a σ* electrophilic attack of the peroxide moiety on the aromatic ring.^[17] Most remarkably, the computed activation barrier for this reaction is only 14.7 kcal mol^{−1}, and no intermediates regarding the isomerization to side-on Cu^{II}₂(μ-η²:η²-O₂) or Cu^{III}₂(μ-O₂) cores are found along this attack, thereby strongly suggesting that the *trans* end-on peroxido core is a competent species for executing the aromatic C–H hydroxylation event.^[12]

In conclusion, our study of O₂ activation at a novel asymmetric dicopper complex **1-O₂** has hitherto uncovered reactivity patterns thus far not observed for symmetric analogues. **1-O₂** is basically unreactive in oxygen atom transfer reactions. However, it has an available coordination site that selectively binds phenolate and mediates its *ortho* hydroxylation, therefore functionally mimicking tyrosinase through

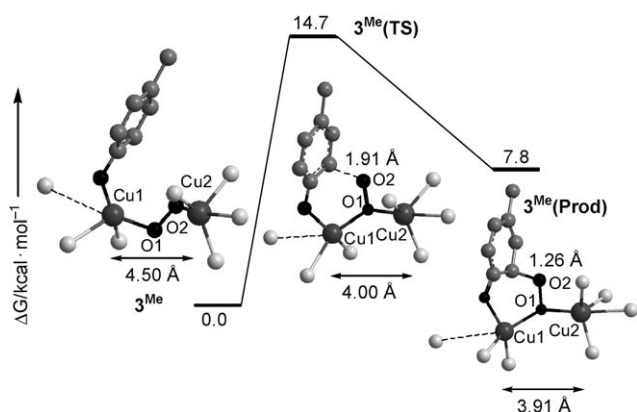


Figure 4. Stationary points along the reaction pathway of the *ortho* hydroxylation of *para*-methyl phenolate into 4-methyl catechol from **3^{Me}**.

a unique pathway. Furthermore, coordination of the phenolate substrate turns on the unprecedented electrophilic reactivity of the asymmetric end-on *trans*-peroxido core. The combined experimental and computational evidence indicate that the *ortho* hydroxylation of a phenolate by a Cu₂O₂ species can occur by adjacent binding of phenolate and O₂ at a common N₃Cu site without requiring the peroxido to be side-on bound, thus offering a conceptually new understanding of O₂ activation at dicopper sites.

Experimental Section

See the Supporting Information for the full experimental details for the synthesis, spectroscopic, and crystallographic characterization of **1-X** (X = CF₃SO₃, PF₆, ClO₄) and **2-ClO₄**, the experimental procedures for the generation, characterization, and reactivity studies of **1-O₂** and **2-O₂**, and the computational details on the DFT calculations.

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