

Electrostatic Contributions to the Stability of an End-on Cupric Superoxide

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ABSTRACT: We recently reported the presence of strong, local electrostatic fields in the secondary coordination sphere of a phosphinimine-decorated Cu^I complex, [(P₃tren)Cu^I]⁺ (**1**). Here, we show that the low-temperature oxygenation of **1** yields a long-lived, three-fold symmetric η¹-cupric superoxide complex, [(P₃tren)Cu^{II}(O₂)]⁺ (**2**). This latter complex was shown to abstract hydrogen atoms from 2,6-di-*tert*-butyl-4-methoxy phenol (KIE = 3.0 ± 0.3) and oxidize a cuprous tris(2-pyridylmethyl)amine complex to form a heteroleptic di(cupric)-μ-1,2-peroxide complex (**4**). The thermal stability of **2** was observed to be uncommonly high for sterically unprotected cupric superoxide complexes in this geometry (*t*_{1/2} = 10.4 h at -85 °C). Density functional theory (DFT) calculations implicate a unique electrostatic stabilization of the π*_v orbital of the O₂ unit, and the thermal stability of **2** is discussed in the context of the Cu^{I/II} redox potential of **1**, the steric bulk in the complex's secondary coordination sphere, and intramolecular electrostatic interactions.

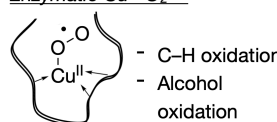
Copper ions bind and activate O₂ for a variety of applications in biological and synthetic chemistry, including oxygen transport and the use of oxygen as either a terminal oxidant or an oxygen-atom source. A commonly invoked intermediate in enzymatic copper oxidases¹⁻³ and oxygenases⁴⁻⁶ is the end-on (η¹) cupric superoxide (Cu^{II}-O₂^{*1-}), which activates substrates through initial hydrogen atom transfer (HAT) reactions. This broad biological basis of reactivity has inspired the synthesis of molecular Cu^{II}-O₂^{*1-} species,⁷⁻²¹ but the study and use of these complexes is complicated by their instabilities with respect to formation of di(cupric)-μ-1,2-peroxides (Figure 1). The development of strategies for improving the lifetimes of Cu^{II}-O₂^{*1-} complexes, while maintaining their oxidizing capacity, is expected to lead to the development of new catalysts based on the reactive superoxide moiety.

In the past two decades, an impressive range of work has made use of ligand design to yield substantial enhancements in the thermal stability of Cu^{II}-O₂^{*1-} complexes. In the earliest studies, short-lived Cu^{II}-O₂^{*1-} were detected by stopped-flow UV-vis spectroscopy under cryogenic conditions (-80 to -120 °C).^{8,9,21} Strategies developed since then for increasing the lifetimes of these complexes have focused on *i*) increasing the steric bulk in the secondary coordination spheres,^{12,13,15,16,18,20} *ii*) cathodically shifting the Cu^I/Cu^{II} redox potentials,⁹ and *iii*) incorporating intramolecular hydrogen bonding residues into the secondary coordination spheres (Figure 1).^{7,19}

Molecular-scale electrostatic effects are gaining attention for their ability to meaningfully impact the chemistry of organic, transition metal, and enzymatic systems.²²⁻³¹ We recently reported the synthesis of a Cu^I complex bound by the

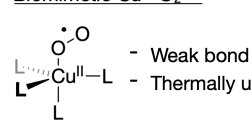
Biological and Biomimetic Cupric Superoxides

*Enzymatic Cu^{II}-O₂^{*1-}*



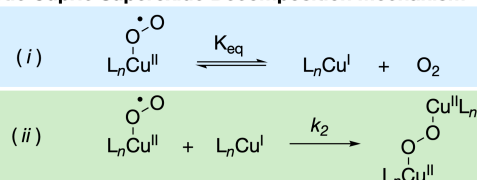
- C-H oxidation
- Alcohol oxidation

*Biomimetic Cu^{II}-O₂^{*1-}*



- Weak bond oxidation
- Thermally unstable

Biomimetic Cupric Superoxide Decomposition Mechanism



Strategies for Stabilizing Biomimetic Cupric Superoxides

- Cathodically shifting *E*_{1/2} of L_nCu^I
- H-bonding stabilization of L_nCu^{II}(O₂^{*1-})
- Steric prevention of (L_nCu^{II})₂(μ-O₂) formation

This work: Second Sphere Electrostatic Potential (ESP)

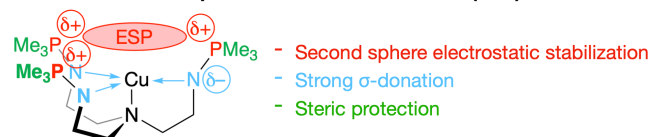
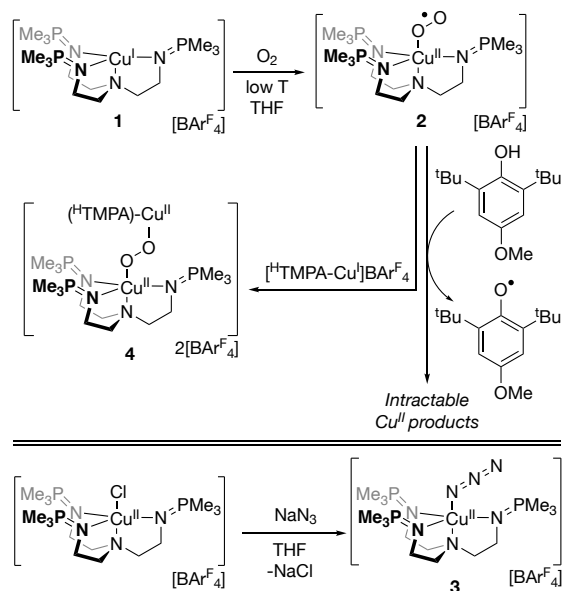


Figure 1. Overview of biomimetic η¹ cupric superoxide complexes.

novel *tris*[2-(trimethylphosphinimino)ethyl]amine (Me₃P₃tren) ligand (**1**, Scheme 1).³² The phosphinimine moieties in the secondary coordination sphere of **1** are best described by a zwitterionic resonance picture that results in the development of significant cationic electrostatic potential in

the small molecule binding pocket of **1** (Figure 1, bottom). The following report details the low-temperature oxygenation of **1**, along with spectroscopic, reactivity, and computational analyses of the resulting cupric superoxide product. This study suggests that electrostatic effects, along with more traditional ligand field and steric effects (Figure 1), work both to tune the valence electronic structure associated with the Cu–O₂ interaction and to improve the thermal stability of the Cu^{II}–O₂^{•1-} complex with respect to decomposition through a peroxide intermediate.

Scheme 1. Syntheses of **2**, **3**, and **4**; HAT reactivity of **2**.



Treatment of a colorless THF solution of **1** with an excess of dioxygen gas at -100 °C resulted in the rapid (< 10 s) formation of a vivid green solution of **2**, the color of which persisted at low temperatures (Scheme 1, top). An electronic absorption spectrum of the product (-100 °C) displayed an intense feature at 413 nm (24,200 cm⁻¹, ε = ~3,500 M⁻¹cm⁻¹) and lower intensity bands at 700 nm (14,300 cm⁻¹, ε = ~800 M⁻¹cm⁻¹) and 950 nm (10,500 cm⁻¹, ε = ~100 M⁻¹cm⁻¹) (Figure 2), characteristic of the formation of an η¹ cupric superoxide complex.^{7,9,12,14–16,20,21,33} The DFT-optimized structure of **2** predicts a *pseudo*-C_{3v}-symmetric primary coordination sphere about the Cu^{II} center, with Cu–O (2.040 Å) and O–O (1.284 Å) distances that are consistent with a Cu^{II}–O₂^{•1-} formulation. The TD-DFT calculated spectrum closely reproduces the experimental features (Figure 2, see *Supporting Information* (SI) for details), which bleach upon warming to room temperature. A more detailed analysis of the thermal stability of **2** will be described below, but its kinetic profile is consistent with reversible O₂ dissociation followed by irreversible decomposition through a process that is bimolecular in Cu, presumably via a dicupric μ-peroxide (Figure 1, middle).^{8,9,21}

The UV-vis spectrum of the cupric azide complex [(P₃tren)Cu(N₃)] [BARF₄] (**3**)³⁴ adds support for the assignment of **2** as an end-on Cu^{II}–O₂^{•1-} complex (Scheme 1, bottom; SI, Figure S10). An intense feature at 380 nm (2500 M⁻¹cm⁻¹) and lower intensity d→d transitions at ca. 720 and 980 nm (SI) are

consistent with previous reports of isostructural η¹ cupric superoxide and azide complexes.^{7,35–39} The solid-state structure of **3**³⁴ confirmed that the geometry about copper closely matches the DFT-optimized structure of **2** (SI). Considering the demonstrated importance of H-bonding to cupric superoxide stability,^{7,19,40} we evaluated the potential for H-bonding in the secondary coordination spheres of **2** and **3**. The shortest N_{azide}–C_{PMe₃} distance was found to be 3.300(2) Å, with an N_{azide}–H–C_{PMe₃} angle of 137.7°. This is comparable to the DFT-optimized structure of **2**, which found a closest contact between a potential H-bond donor and the superoxide acceptor as O_{proximal}–C_{PMe₃} of 3.25 Å, with an O_{prox}–H–C_{PMe₃} angle of 136.1°. These data, and the other interactions in the secondary coordination sphere, are a poor match for traditional H-bonding interactions,⁴¹ though it should be noted that the distances between the azide/superoxide ion and 6 methyl group carbons for each complex fall within the range traditionally associated with weak, electrostatic H-bonds (3.3–3.9 Å) (Figure 3).

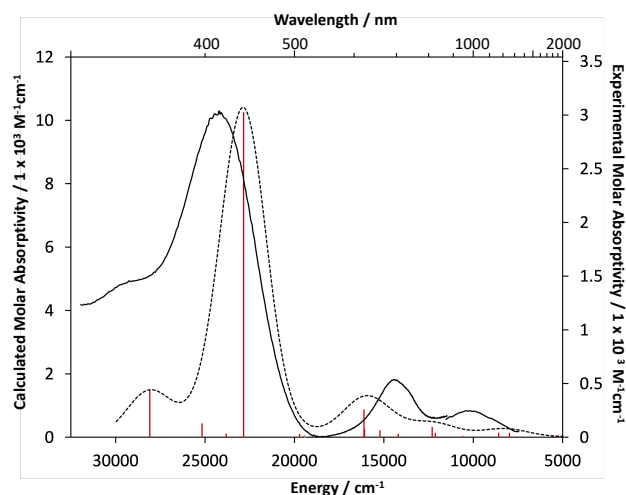


Figure 2. Experimental (solid) and calculated (dashed) UV-vis-NIR spectra for **2**. Calculated electronic transitions are depicted as vertical maroon bars.

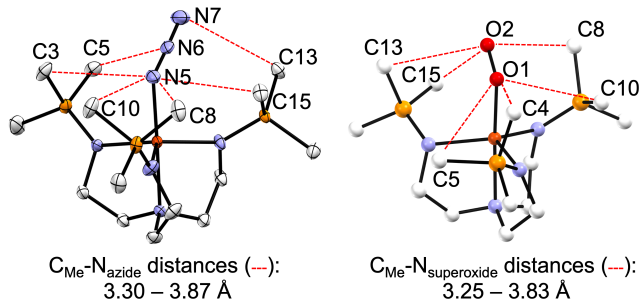


Figure 3. Structures of the cationic portions of **3** (XRD, left) and **2** (DFT, right), highlighting the closest C_{Me}–X distances with dashed red lines. Hydrogen atoms have been removed for clarity.

Features in the UV-vis spectrum associated with **2** are remarkably long-lived. The simplest *pseudo*-C_{3v}-symmetric¹¹ cupric superoxide complexes typically exhibit half-lives (t_{1/2}) at -80 to -120 °C on second - minute timescales.^{7,9,19} Sterically protected cupric superoxides prevent decomposition by

precluding the formation of di(cupric)- μ -peroxides (decreasing k_2 in Figure 1), which has allowed for their observation at higher temperatures but not necessarily with higher binding affinities.^{12,13,15,16,18,20} Alternatively, several studies have successfully imparted increased binding affinity of O₂ (K_{eq} in Figure 1). Derivatized TMPA ligands containing H-bonding moieties in the secondary coordination spheres were able to support cupric superoxides that were found to be persistent at -135 °C ($t_{1/2} > 30$ h).⁷ Quantitative data on the relative thermal stabilities of these compounds are not always available due to inequivalent conditions, but the longest-lived analogs in this class appear to be those supported by the electron-donating *tris*(4-dimethylamino)-substituted TMPA ligand ($[(^{NMe_2}TMPA)CuO_2]^+$, $t_{1/2} = \sim 4$ h in THF at -85 °C) and the *tris*(4-methoxy)-substituted TMPA ligand ($[(^{OMe}TMPA)CuO_2]^+$, $t_{1/2} = \sim 3$ h in 2-MeTHF at -90 °C).⁹ For comparison, the half-life of **2** in THF was found to be >30 h at -100 °C and 10.4 h at -85 °C, placing it in the upper echelon of stabilized η^1 cupric superoxides.

It initially appeared as though the unusually cathodic Cu^{I/II} redox couple for **1** ($E_{1/2} = -780$ mV vs. Fc^{0/+})³² would be largely responsible for the thermal stability of **2** by increasing the binding affinity of O₂, thereby slowing the irreversible formation of a dicupric μ -peroxide (Figure 1). The next most reducing Cu^I complex that has been reported as a synthon for a cupric superoxide is, in fact, $[(^{NMe_2}TMPA)Cu]^+$, for which $E_{1/2}(Cu^{I/II}) = -700$ mV vs. Fc^{0/+}. However, **1** is unique in that it undergoes a Jahn-Teller distortion on oxidation that shifts the measured $E_{1/2}(Cu^{I/II})$ to more cathodic potentials.³² The retention of a local C_{3v} geometry on formation of **2** suggests that the *effective* $E_{1/2}$ for the conversion of **1** to **2** is more anodic (computationally estimated to be -630 ± 120 mV), suggesting that other factors play a role in the enhanced thermal stability of **2**.

We next sought to identify markers of an electrostatic effect on the bound O₂ ligand. The DFT computational results for **2** were compared to those from analogous calculations on $[(^H)TMPA)CuO_2]^+$ and $[(^{NMe_2}TMPA)CuO_2]^+$, all of which presented β -spin molecular orbitals (Figure 4) in qualitative agreement with those calculated previously for the cupric superoxide complex bound by TMG₃tren.⁴² In all cases, bonding between the superoxide anion and the cupric center involves a σ interaction between the O₂-based π^*_σ and Cu d_z^2 , while the O₂-based π^*_ν mixes with a small amount of Cu d_{xz} through a polar π -interaction. The most notable difference between the valence manifolds of $[(^H)TMPA)CuO_2]^+$ and $[(^{NMe_2}TMPA)CuO_2]^+$ is found in the energies of $d_{x^2-y^2}$ and d_{xy} , which are more destabilized in $[(^{NMe_2}TMPA)CuO_2]^+$ due to the enhanced electron-donating properties of the ^{NMe₂}TMPA ligand. This trend continues when comparing the TMPA derivatives to **2**. The $d_{x^2-y^2}/d_{xy}$ set is shifted higher in energy for **2**, which is in agreement with the relative donor strength of the P₃tren ligand.³²

More surprising was the stabilization of the d_z^2 and π^*_ν in **2** compared to $[(^H)TMPA)CuO_2]^+$ and $[(^{NMe_2}TMPA)CuO_2]^+$ (Figure 4). The change in ^HTMPA ligand has a negligible effect on the energies of this set (*ca.* 2 kcal/mol), but the ^{Me₃}P₃tren ligand causes a more substantial decrease in the energy of each: *ca.* -6 kcal/mol for d_z^2 and -5 kcal/mol for π^*_ν . These

stabilizations are reminiscent of the effect on d_z^2 in the Cu^I complex bound by P₃tren and are consistent with an electrostatic interaction between the superoxide anion and the phosphonium residues.³² Importantly, even when constraining the Cu–O and Cu–N bond distances for a variety of cupric superoxide analogs to equal those calculated for **2**, the stabilization of these orbitals in **2** is maintained (SI, Figures S12 and S13).

Based on these findings, it would be expected that the electrostatic stabilization of the d_z^2 -based molecular orbital would produce low-energy electronic transitions into d_z^2 , particularly from the $d_{x^2-y^2}/d_{xy}$ set, which is destabilized via strong σ -donation in the *xy*-plane. Indeed, the broad feature centered at 950 nm in the NIR spectrum of **2** is uniquely low in energy compared to analogous transitions for other *pseudo*-C_{3v}-symmetric cupric superoxide complexes.^{9,33,42} Further, while the five lowest energy electronic transitions calculated for **2** and $[(^H)TMPA)CuO_2]^+$ correspond in both cases to HOMO(-1/-2)→LUMO(+1) transitions, the energy range for these transitions is substantially lower for **2** (3900 – 8600 cm⁻¹) than for $[(^H)TMPA)CuO_2]^+$ (8900 – 13200 cm⁻¹).

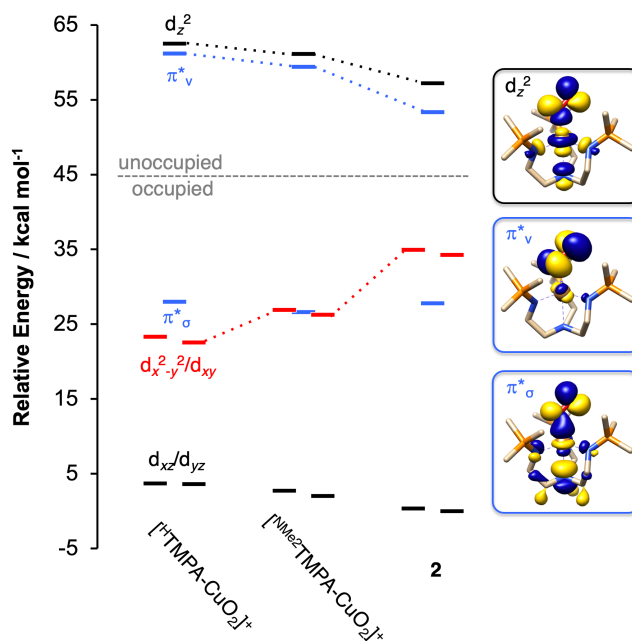


Figure 4. Quantitative comparison of the β orbitals across cupric superoxide complexes, with select orbitals of **2** shown to the right.

Complex **2** was shown to undergo reactivity that is characteristic of a Cu^{II}-O₂^{•1-} moiety. Enzymatic η^1 cupric superoxides are known to perform HAT reactivity,¹⁻⁶ and several synthetic complexes have modeled this reactivity.^{7,14,15,19,43-46} HAT to **2** from 2,6-di-*tert*-butyl-4-methoxyphenol (O–H BDE = 78.31 ± 0.13 kcal/mol)⁴⁷ was monitored by UV-vis spectroscopy (Scheme 1, top). Upon addition of the phenol to a deoxygenated THF solution of **2** at -100 °C, features associated with the superoxide were observed to decay, concomitant with the growth of sharp features at *ca.* 400 nm that correspond to the 2,6-di-*tert*-butyl-4-methoxyphenoxy radical (SI, Figure S2).⁴⁸ The reaction was found to display second order kinetics, and a kinetic isotope

effect ($k_{2(H)}/k_{2(D)}$, KIE) of 3.0 ± 0.3 was measured upon use of the deuterio (OD) analogue of the phenol (SI, Figure S3). This primary KIE is consistent with the HAT reactivity reported for other η^1 cupric superoxides.^{7,14,15,19,43–46}

The formulation of **2** as a $\text{Cu}^{\text{II}}\text{-O}_2^{\bullet-}$ complex was also supported by using **2** for the rational formation of a μ -1,2-peroxide complex. Such complexes display characteristic UV-vis spectral features as intense bands between 500–650 nm. The homoleptic P_3tren -based peroxide was not observed, so we targeted the formation of a heteroleptic dicupric-1,2- μ -peroxide complex from **2**.¹⁰ Upon treatment of a deoxygenated solution of **2** with 1 equiv of $[(^{\text{H}}\text{TMPA})\text{Cu}][\text{BAR}^{\text{F}}_4]$ at -100°C , features associated with **2** immediately bleached, concomitant with the growth of bands at 520 nm ($19,200\text{ cm}^{-1}$, $\epsilon \sim 860\text{ M}^{-1}\text{cm}^{-1}$) and 610 nm ($16,400\text{ cm}^{-1}$, $\epsilon \sim 570\text{ M}^{-1}\text{cm}^{-1}$) (Scheme 1; SI, Figure S8). We assign these to the heteroleptic peroxide complex $[(\text{P}_3\text{tren})\text{Cu}(\mu\text{-O}_2)\text{Cu}(\text{HTMPA})]^{2+}$ (**4**). These data confirm, at the very least, that an intact O_2 unit is imbedded in the structure of **2**.

The results presented above suggest that secondary coordination sphere electrostatic effects can be used to impact the valence manifold of an η^1 $\text{Cu}^{\text{II}}\text{-O}_2^{\bullet-}$ complex. The scope of the current report prevents us from delineating the extent to which electrostatic effects, the Cu^{II} redox potential, and steric effects individually contribute to the improved thermal stability of the cupric superoxide, but the inclusion of through-space electrostatic effects in the mix suggests that this approach may be useful for a range of small molecule activation applications. Studies to disentangle the individual contributions of these design principles to the thermal stability of **2** and its analogs are underway.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare

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