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COMMUNICATION

Calcium-ion Binding Mediates the Reversible Interconversion of *Cis* and *Trans* Peroxido Dicopper Cores

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Abstract: Coupled dinuclear copper oxygen cores (Cu_2O_2) featured in type III copper proteins (e.g. hemocyanin, tyrosinase, catechol oxidase) are vital for O_2 transport and substrate oxidation in a range of organisms. μ-1,2-*cis* peroxido dicopper cores (**^{C}P**) have been proposed as key structures involved in the early stages of O_2 binding in these proteins, and their reversible isomerization to other Cu_2O_2 cores are directly relevant to enzyme function. Despite the relevance of such species to type III copper proteins and the broader interest in the properties and reactivity of bimetallic **^{C}P** cores in biological and synthetic systems, the properties and reactivity of **^{C}P** Cu_2O_2 species remain largely unexplored. Herein, we report our combined synthetic, spectroscopic, and theoretical studies which detail the first reversible interconversion of μ-1,2-*trans* peroxido (**^{T}P**) and **^{C}P** dicopper cores. Ca^{II} mediates this process through reversible binding at the Cu_2O_2 core, and highlights the unique capability for metal-ion binding events to stabilize novel reactive fragments and control O_2 activation in biomimetic systems.

Copper containing enzymes such as hemocyanin,[1] tyrosinase,[2] catechol oxidase,[3] and particulate methane monooxygenase[4] feature a variety of reactive oxygen species that range in function from O_2 transport, C–H oxidation/functionalization, and reduction of O_2 to water.[5] These enzymes have inspired numerous synthetic models[6] which have advanced our understanding of biological systems,[5c,6-7] alongside applications in catalysis,[8] materials science,[9] and renewable energy.[10] Amongst these copper oxygen species, dicopper oxygen (Cu_2O_2) cores are ubiquitous in both biological and synthetic systems, where Cu_2O_2 cores display dramatically different reactivity and properties depending on their binding mode (Figure 1a). While examples of μ-1,2-*trans* peroxido (end-on; **^{T}P**),[7c,11] η^2:η^2 peroxido (side-on; **^{S}P**),[7a,7b,12] bis(μ-oxido) (**O**),[7e,12g,13] structures are now well established, models of the μ-1,2-*cis* peroxido (**^{C}P**) or distorted **^{C}P** Cu_2O_2 core are exceedingly rare and have only recently been achieved using ancillary ligands specifically designed to constrain Cu–Cu distances to access this binding mode.[7j,14]

Solomon and coworkers proposed the **^{C}P** Cu_2O_2 core as a key structure in the early stages of reversible O_2 binding at type III multi-copper enzymes (Figure 1b).[15] Formation of **^{C}P** at type III active sites enables simultaneous electron transfer from the two Cu^{I} sites, and the reversible interconversion of the weakly coupled **^{C}P** species to strongly (antiferromagnetically) coupled **^{S}P** species is central to enzyme function. More broadly, **^{C}P** structures are relevant intermediates in the oxygenation chemistry of other first-row transition metal ions (e.g. Co and Fe),[16] including the bimetallic active sites of soluble methane monooxygenase and ribonucleotide reductase.[17] Despite the importance of such structures and their interconversion chemistry, **^{C}P** Cu_2O_2 cores remain largely unexplored.[7j,14]

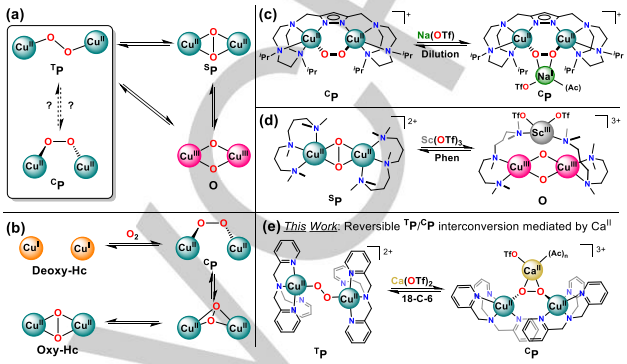

Figure 1. (a) Commonly observed O_2 binding modes found in Cu_2O_2 cores, and direct equilibria established in experimental systems. (b) Proposed species involved in O_2 binding at hemocyanin (Hc). (c) Reversible Na^{I} binding to a **^{C}P** Cu_2O_2 core.[7j] (d) $Sc(OTf)_3$ mediated reversible interconversion of **^{S}P**/**O**.[22b] (e) *This work*: Reversible interconversion of **^{T}P**/**^{C}P** (**1**/**2**) mediated by $Ca(OTf)_2$.

Redox-inactive metal ions serve critical roles as natural[18] and synthetic[19] co-factors for the activation or production of oxygen at transition-metal complexes. Lewis acid binding events can stabilize and modulate the reactivity of novel O_2-derived fragments,[20],[7j,20c,21] yet few studies have centered on the reactivity of Cu_2O_2 cores.[7j,22] Meyer and coworkers reported the first synthetic Cu_2O_2 **^{C}P** core, $[Cu^{II}_2(PzTACN^{Me})(\mu\text{-}1,2\text{-}O_2^{2-})]^+$ (Figure 1c).[7j] Na^{I} reversibly binds at the peroxido fragment; however, minimal structural changes were observed due to the rigidity of the binucleating chelate (Figure 1c). Karlin and coworkers reported that addition of $Sc(OTf)_3$ mediated the reversible interconversion of $\{[Cu^{II}(MeAN)]_2(\eta^2\text{:}\eta^2\text{-}O_2^{2-})\}^{2+}$ (**^{S}P**; MeAN: *N*-methyl-*N*,*N*-bis[3-(dimethylamino)propyl]amine) to $[Cu^{III}_2(MeAN)_2(\mu\text{-}O)_2]^{2+}$ (**O**) by promoting dissociation of the axially-bound tertiary amine donor (Figure 1d).[22b] Karlin and Fukuzumi observed that the prototypical **^{T}P** species, $\{[Cu^{II}(TMPA)]_2(\mu\text{-}1,2\text{-}O_2^{2-})\}^{2+}$ (TMPA = tris(2-pyridylmethyl)amine) (**1**), reacts with $Sc(OTf)_3$ in acetone at –80 °C to generate a transient intermediate believed to be responsible for the catalytic peroxide-selective reduction of oxygen (λ_{max} = 394 nm); however, its limited lifetime precluded further characterization.[22a]

We were especially intrigued by the rapid reactivity of **1** with $Sc(OTf)_3$, as this implies that the Cu_2O_2 core is flexible enough to reorganize and interact with a redox-inactive metal ion.

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Recognizing the importance of matching Lewis acid strength and size to support reactive transition-metal fragments, we hypothesized that weaker Lewis acids could stabilize otherwise transient heterobimetallic species through direct binding at the peroxido fragment while reducing the driving force for complete dissociation. Herein, we report our combined synthetic, spectroscopic, and theoretical studies which detail the first reversible interconversion of the prototypical ^{T}**P**, **1**, to a novel ^{C}**P** species, **2** (Figure 1e). This process is mediated through *reversible* Ca^{II} ion binding to the Cu_2O_2 core, and our observed reactivity contrasts with that of **1** with stronger Lewis acids (e.g. $Sc(OTf)_3$) or Brønsted acids (e.g. TFA, $HClO_4$). These results highlight the unique capability for metal-ion binding events to stabilize novel reactive fragments and control O_2 activation in biomimetic systems.

At –80 °C, freshly prepared acetone solutions of dark purple **1** (0.25 mM; $t_{1/2}$ = 150 s) react with excess $Ca(OTf)_2$ (5 mM) within seconds to form a bright yellow species, **2** (Figure 2a; $t_{1/2}$ = 285 s; λ_{max} = 455 nm, ε = 4080 M^{-1} cm^{-1}) without accumulation of observable intermediates and displays a clean isosbestic point at 490 nm. The charge transfer band position and molar absorptivity of **2** are comparable to those found for *μ*-1,2- peroxido dicopper cores supported by TMPA frameworks with hydrogen bond donors in the 6-position [e.g. NH_2,[23] NHAr;[11e] λ_{max} ~ 450 nm (ε = 2,400 – 4,620 M^{-1} cm^{-1})]. Similar reactivity and spectroscopic signatures were observed upon addition of $Ca(ClO_4)_2$ to **1** in place of $Ca(OTf)_2$, albeit with incomplete conversion and lower product thermal stability (Figure S14). In contrast, addition of excess free triflate to **1** ([NBu_4][OTf], 20 equiv; Figure S10) caused negligible changes in its electronic absorbance spectrum, and further confirmed that formation of **2** was the result of Ca^{II} binding. While thermally-sensitive, concentrated acetone solutions of **2** (≥ 2 mM) are stable at –80 °C for weeks in the absence of excessive moisture, which facilitated further spectroscopic characterization.

Resonance Raman (rRaman) spectroscopy (77 K; λ_{ex} = 457 nm; Figure 2b) was performed on frozen acetone glasses of **1** and **2** prepared with $^{16}O_2$ and $^{18}O_2$. The rRaman spectrum of **2** revealed a single isotopically-sensitive vibration at 812 cm^{-1} (ν_{O-O}; $\Delta^{16}O_2$–$^{18}O_2$ = –43 cm^{-1}) that was red-shifted by ~18 cm^{-1} relative to **1** (ν_{O-O}(**1**): 830 cm^{-1}; $\Delta^{16}O_2$–$^{18}O_2$ = –45 cm^{-1}). ν_{O-O}(**2**) falls within the characteristic range of ^{T}**P** and ^{C}**P** dicopper species (800–850 cm^{-1}), but well outside the range of mononuclear superoxido or peroxido (η^1 or η^2: 960–1150 cm^{-1}), μ-η^2:η^2 (side-on, ^{S}**P**) peroxido dicopper (ν_{O-O}: 715–730 cm^{-1}), and 1,1-hydroperoxido dicopper (ν_{O-O}: 860–880 cm^{-1}).[6c,20b,24] Lewis acid binding at peroxido fragments have led to red-shifted ν_{O-O} (~5–30 cm^{-1}), although the magnitude of this shift is sensitive to Lewis acid strength and complex geometry.[7j,21a,21e,25] Taken together, we hypothesized the distinct spectroscopic changes going from **1** to **2** (blue-shifted LMCT λ_{max}, red-shifted ν_{O-O}) was due to Ca^{II} binding to the peroxido fragment of **1**, and prompted further structural investigation.

A reversible 1:1 binding stoichiometry for [**1**]:[$Ca(OTf)_2$] (Figure 3a) was established from nonlinear regression of multiple independent titrations with **1** performed at –80 °C across a range of [**1**]:[Ca] ratios (1:1–1:20; Figure 3b, S11; see Section 3.4 for further details).[26] The association constant for the 1:1 binding of $Ca(OTf)_2$ to **1**, K_{Ca}^{II}, was determined to be 1,220 ± 70 M^{-1} and is comparable K_{Na}^{I} (1,770 M^{-1}) observed for $[Cu^{II}_2(PzTACN^{Me})(\mu\text{-}1,2\text{-}O_2^{2-})Na(OTf)]^{+}$.[7i] Kinetic parameters obtained under flooding conditions (> 10-fold excess $Ca(OTf)_2$; Figure 3b and Figure S13)

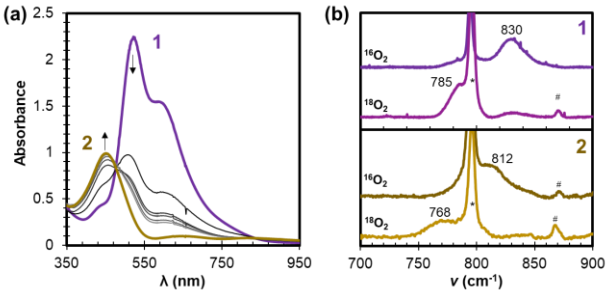

Figure 2. (a) Selected electronic absorbance spectra following the addition of $Ca^{II}(OTf)_2$ (5 mM) to **1** (0.5 mM, purple trace) in acetone at –80 °C to form **2** (gold trace, time = 20 s). (b) rRaman spectra (λ_{ex} = 456.8 nm) of **1** (purple) and **2** (gold) in acetone at 77 K (top = $^{16}O_2$, bottom = $^{18}O_2$). * = ν_{CF3} (OTf); 796 cm^{-1} and # = ν_{C-C} (Acetone); 870 cm^{-1}.

revealed rapid association and dissociation of Ca^{II} at –80 °C, where the forward (k_+) and reverse (k_-) rate-constants were determined to be 2.71 ± 0.25 x 10^2 $M^{-1}s^{-1}$ and 0.22 ± 0.02 s^{-1}, respectively. Addition of 18-crown-6 (18-C-6) to **2** ([Ca]:[18-C-6] = 1:2) cleanly regenerates **1** within ~10 seconds at –80 °C, clearly demonstrating that interconversion of **1** and **2** is both rapid and

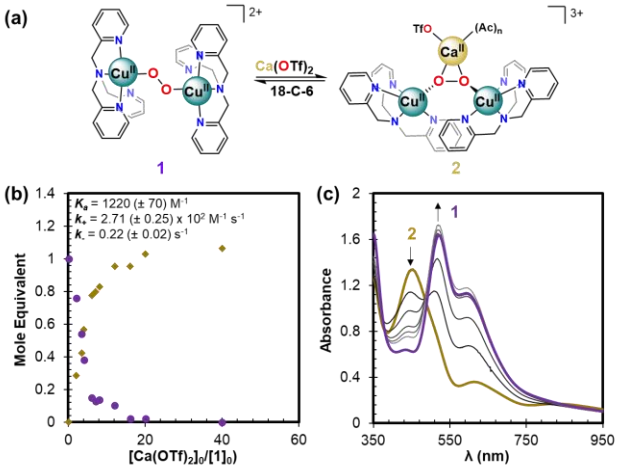

Figure 3. (a) Proposed interconversion between **1** and **2** using $Ca^{II}(OTf)_2$ and 18-C-6 chelate (0 - 10 s). Ac = acetone, n = 3 or 4; (b) Titration of Ca^{II} (guest) to **1** (host, purple; circles) to form **2** (gold; diamonds), inset: association constant (K_{Ca}^{II}), forward (k_+) and reverse (k_-) kinetic rate constants for Ca^{II} binding (see SI for details). (c) Spectral changes upon 18-C-6 addition (10 mM) to **2** (0.5 mM; 5 mM $Ca(OTf)_2$) in acetone at –80 °C.

chemically reversible (Figure 3c).

Complex **2** is EPR-silent at X-band frequencies (Figure S20) and ^{1}H-NMR spectroscopy (Figure S26-28) provided clear evidence for **2** being paramagnetic. The EPR silence of **2** is inconsistent with the formation of any mono-copper peroxido species (including hydro or alkylperoxido), as these would display strong and distinct signals at X-band frequencies.[27] The ^{1}H-NMR spectrum of **2** collected in d_6-acetone at –80 °C displayed ~15 paramagnetically shifted resonances (–4 to +120 ppm; Figure S28), and reflected the loss of 3-fold symmetry of the TMPA ligand. Desymmetrization would be expected for a dicopper peroxido with hindered rotation about the Cu–O bond, and was consistent with the tight Ca^{II} binding determined from our spectrophotometric titrations (*vide supra*).

Complex **2** has an effective magnetic moment (μ_{eff}) of 2.44 μ_B as determined by Evans' method (d_6-acetone, –80 °C; Table S3).[28] The μ_{eff} of **2** is significantly greater than **1** or $[Cu^{II}(TMPA)]^{2+}$ (Figure S31), but lower than that expected for two strongly

ferromagnetically coupled Cu^{II} ions (μ_{eff} ~ 2.83 μ_B).[14,29] This is wholly inconsistent with a ^{T}**P** Cu_2O_2 core (φ_{Cu2O2} ~180°), which are EPR silent and display effectively diamagnetic NMR spectra due to strong antiferromagnetic coupling mediated through the peroxido bridge ($J \leq -600$ cm^{-1}; Figure 4c, right).[11a] In contrast, the EPR silence and non-zero μ_{eff} of **2** is consistent with a ^{C}**P** Cu_2O_2 core ($\varphi_{Cu2O2} \rightarrow 90°$). The two reported ^{C}**P** display paramagnetic NMR spectra and weak magnetic coupling for the Cu_2O_2 core (PzTACN^{Me}: φ_{Cu2O2} = 62.5°, J = –77 cm^{-1}; PzTACN^{Et}: φ_{Cu2O2} = 104.2°, J = +72 cm^{-1}; $H = -2J\mathbf{S_1S_2}$)[7j,14] due to interaction of the Cu^{II} $d_{x^2-y^2}$ orbitals with orthogonal π*(O_2) orbitals (Figure 4c, right). Unfortunately, the thermal sensitivity of **2** has prevented our experimental determination of J through solid-state magnetometry or fitting of variable temperature ^{1}H-NMR spectra like other recent bimetallic peroxides,[7j,14,30] but a more detailed investigation of the electronic structure of **2** is warranted for future studies.

The reactivity of **1** with $Ca(OTf)_2$ was further substantiated by computational studies performed at the M06-L level of theory[31] (*Computational Methods*; see Supporting Information). Given the expected speciation of $Ca(OTf)_2$ in acetone based on conductivity measurements (Figure S32),[32] 1:1 Ca^{II} binding to mononuclear and dinuclear copper peroxido species were explored from $[Ca(OTf)_2(Ac)_4]$ and $[Ca(OTf)(Ac)_5]^+$ with an exhaustive search of possible conformers (Scheme S3 and S4). Consistent with our spectroscopic data (i.e. NMR, UV-Vis), the generation of a heterobimetallic $\{[Cu^{II}(TMPA)](\mu\text{-}\eta_1\text{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)_x(Ac)_n]\}^{2-x+}$ core (**A**) and an equivalent of $[Cu^{II}(TMPA)]^{2+}$ is unlikely, where the reaction is predicted to be endergonic by 14.4 kcal/mol (Figures S32-S33, Scheme S3). Ca^{II} binding to the distal peroxido site of a 1,1-peroxido dicopper core, $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1\text{:}\eta_1\text{-}\eta_1\text{-}O_2^{2-})[Ca^{II}(OTf)(Ac)_4]\}^{3+}$ (**B**) is slightly exergonic (–3.9 kcal/mol); however, this structure is a poor match with experimental data and literature expectations. Related 1,1-hydroperoxido dicopper cores display higher ν_{O-O} (860-880 cm^{-1})[33] and strong antiferromagnetic coupling,[33e,34] both of which are reflected in the calculated properties of **B** and its conformers (Figure S33, S34, Table S4). Alternatively, formation of ^{C}**P** is favored by 9.6 kcal/mol, and the calculated and experimental rRaman spectra are in excellent agreement with one another (Table S4). The optimized ^{C}**P** structure approaches the ideal φ_{Cu2O2} of 90°, which is expected to suppress strong antiferromagnetic coupling between the two Cu^{II} sites (φ_{Cu2O2}(^{C}**P**): 96°).[35] The ^{C}**P** structure displays significant spin-density at Cu^{II} and orthogonal peroxido orbitals (Figure 4c, J = +83 cm^{-1}), and is consistent with the μ_{eff} of **2** and its EPR silence at X-band frequencies. Taken together, our experimental and computational studies support the formulation of **2** as a ^{C}**P** with a structural formula of $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1\text{:}\eta_1\text{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)_x(Ac)_{n-x}]\}^{3-x+}$ (n = 5, x = 1), although alternative speciation of the Ca-bound fragment may be possible (e.g. n = 5, x = 0, 2).

In sum, the reversible interconversion of ^{T}**P**/^{C}**P** isomers mediated by Ca^{II} binding at the bridging peroxido ligand marks an important first in Cu/O_2 chemistry, and is distinct from the reactivity of redox-inactive metal ions with other transition-metal peroxides.[7j,21a-c,21e,21f,22,36] Reversible interconversion of ^{C}**P** cores have been proposed to occur in type III dicopper active sites such as hemocyanin, where a transient ferromagnetically coupled ^{C}**P** undergoes isomerization steps to reach the antiferromagnetically coupled ^{S}**P** resting state.[15] Our study establishes the first synthetic precedent for the reversible interconversion of a paramagnetic ^{C}**P** core, **2**, and the strongly antiferromagnetically coupled ^{T}**P** core, **1**. The reversible transformation is accessible under mild conditions through Ca^{II} ion binding, and provides a direct connection between the prototypical ^{T}**P** species, **1**, and the biologically relevant ^{C}**P** isomer, **2**. Notably, $Sc(OTf)_3$ binding at a diiron ^{C}**P** fragment was essential in establishing the first synthetic precedent for converting a model of soluble methane monooxygenase intermediate P, sMMO-P ($[Fe^{III}]_2(\mu\text{-}1,2\text{-}O_2^{2-})(\mu\text{-}O^{2-})$), to the reactive high-valent intermediate, sMMO-Q ($[Fe^{IV}]_2(\mu\text{-}O^{2-})_2$), and suggests that access to such interactions may be broadly important in uncovering novel structure and function of biomimetic cores.[21f]

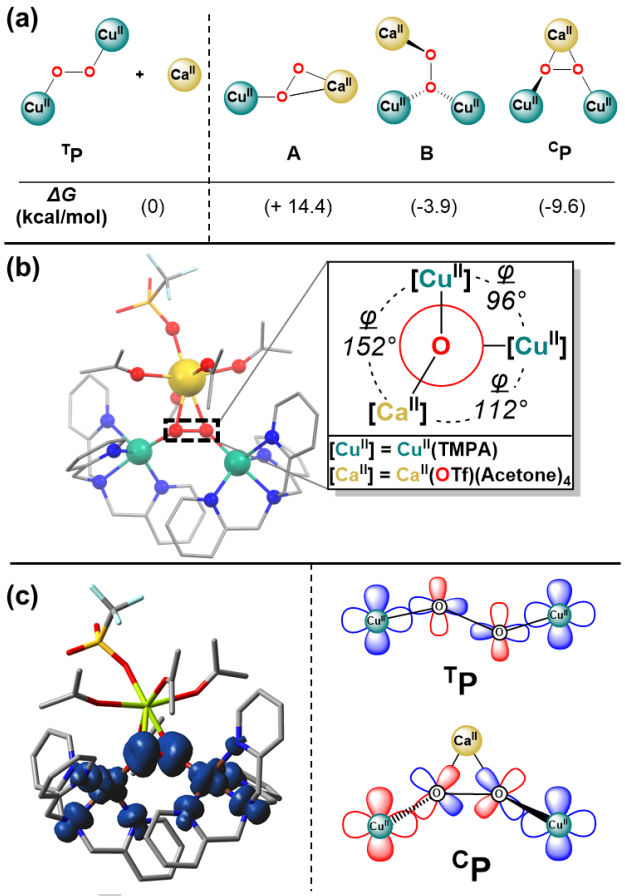

Figure 4. (a) Possible heterobimetallic structures from the reaction of **1** with $Ca(OTf)_2(Ac)_4$ (Ac = Acetone); **A**: $\{[Cu^{II}(TMPA)](\mu\text{-}\eta_1\text{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)(Ac)_4]\}^{+}$, **B**: $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1\text{:}\eta_1\text{:}\eta_1\text{-}O_2^{2-})[Ca^{II}(OTf)(Ac)_4]\}^{3+}$, ^{C}**P**: $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1\text{:}\eta_1\text{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)(Ac)_4]\}^{3+}$. (b) Optimized structure of ^{C}**P** and Newmann projection down the O–O bond and corresponding dihedral angles. $Cu\text{–}O_{avg}$ = 1.949 Å, $Ca\text{–}O_{avg}$ = 2.342 Å, O–O = 1.422 Å. (c) *Left*, Spin-density plot of ^{C}**P**; *right*, simplified orbital depictions giving rise to antiferromagnetic coupling of ^{T}**P** and weak coupling of ^{C}**P**.

Lewis acid identity plays a key role in the observed reactivity in this study, and continues to be a broadly recurring theme for synthetic[20d,20i,21b,37] and biological[38] systems alike. While addition of the strong Lewis acid, $Sc(OTf)_3$, to **1** at low temperatures ultimately generates $[Cu^{II}(TMPA)]^{2+}$ (2 equivalents) and "$[Sc^{III}(O_2^{2-})]^{+}$",[22a] we have discovered that a weaker Lewis acid, $Ca(OTf)_2$, can stabilize the isomerized heterobimetallic ^{C}**P** species, **2**. We have demonstrated that appropriately selected redox-inactive metal-ions can stabilize rare multimetallic species, and anticipate this can be applied to stabilize otherwise transient intermediates of direct relevance to bioinorganic systems. Future studies focused on establishing the relevance and broader reactivity of Lewis acids with Cu_2O_2 cores are currently underway.

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Keywords: Bioinorganic chemistry • Peroxides • Copper • Calcium • Heterometallic complexes

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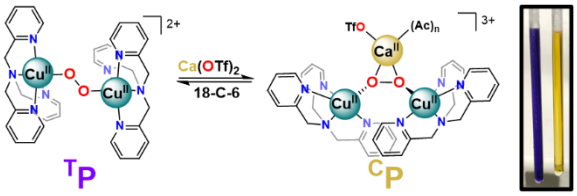

(Ca)tch and release. Calcium-ion binding mediates the reversible interconversion of the prototypical *trans*-peroxido Cu_2O_2 core (^{T}**P**) to the rare and biologically relevant *cis*-peroxido Cu_2O_2 core (^{C}**P**). This provides new opportunities to stabilize novel reactive fragments and control O_2 activation in biomimetic systems.

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