Zitierweise: *Angew. Chem. Int. Ed.* **2021**, *60*, 19836–19842
Internationale Ausgabe: doi.org/10.1002/anie.202105421
Deutsche Ausgabe: doi.org/10.1002/ange.202105421

Bioinorganic Chemistry

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

Natasha P. Vargo, Jill B. Harland, Bradley W. Musselman, Nicolai Lehnert, Mehmed Z. Ertem* and Jerome R. Robinson**

Abstract: *Coupled dinuclear copper oxygen cores (Cu_2O_2) featured in type III copper proteins (hemocyanin, tyrosinase, catechol oxidase) are vital for O_2 transport and substrate oxidation in many organisms. μ-1,2-cis peroxido dicopper cores (^{C}**P**) have been proposed as key structures in the early stages of O_2 binding in these proteins; 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 the reversible interconversion of μ-1,2-trans peroxido (^{T}**P**) and ^{C}**P** dicopper cores. Ca^{II} mediates this process by reversible binding at the Cu_2O_2 core, highlighting the unique capability for metal-ion binding events to stabilize novel reactive fragments and control O_2 activation in biomimetic systems.*

Introduction

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; $^{\mathrm{T}}$**P**),[7c,11] η^2:η^2 peroxido (side-on; $^{\mathrm{S}}$**P**),[7a,b,12] bis(μ-oxido) (**O**),[7e,12g,13] structures are now well established, models of the μ-1,2-*cis* peroxido ($^{\mathrm{C}}$**P**) or distorted $^{\mathrm{C}}$**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]

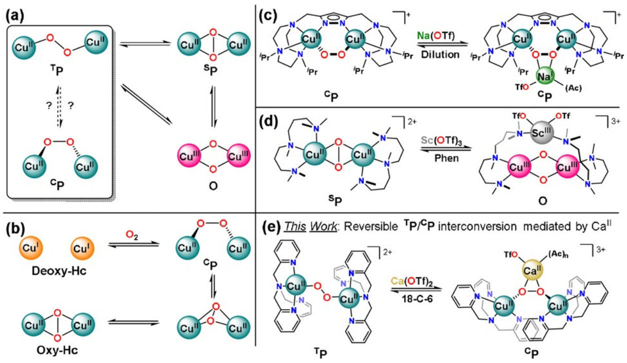

Figure 1. a) Commonly observed O_2 binding modes found in Cu_2O_2 cores, and direct equilibria established in experimental systems. b) Proposed species involved in O_2 binding at hemocyanin (Hc). c) Reversible Na^{I} binding to a $^{\mathrm{C}}$**P** Cu_2O_2 core.[7j] d) $Sc(OTf)_3$ mediated reversible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

Solomon and co-workers proposed the $^{\mathrm{C}}$**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 $^{\mathrm{C}}$**P** at type III active sites enables simultaneous electron transfer from the two Cu^{I} sites, and the reversible interconversion of the weakly coupled $^{\mathrm{C}}$**P** species to strongly (antiferromagnetically) coupled $^{\mathrm{S}}$**P** species is central to enzyme function. More broadly, $^{\mathrm{C}}$**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, $^{\mathrm{C}}$**P** Cu_2O_2 cores remain largely unexplored.[7j,14]

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-

---

[*] N. P. Vargo, Prof. J. R. Robinson
Department of Chemistry, Brown University
324 Brook Street, Providence, RI 02912 (USA)
E-Mail: jerome_robinson@brown.edu
J. B. Harland, B. W. Musselman, Prof. N. Lehnert
Department of Chemistry and Department of Biophysics
University of Michigan
930 North University Avenue, Ann Arbor, MI 41809-1055 (USA)
E-Mail: lehnertn@umich.edu
Dr. M. Z. Ertem
Chemistry Division, Energy & Photon Sciences
Brookhaven National Laboratory
PO Box 5000, Upton, NY 11973-5000 (USA)
E-Mail: mzertem@bnl.gov

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202105421.

derived fragments,[7j,20,21] yet few studies have centered on the reactivity of Cu_2O_2 cores.[7j,22] Meyer and co-workers reported the first synthetic Cu_2O_2 $^{\mathbf{C}}\mathbf{P}$ 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 co-workers reported that addition of $Sc(OTf)_3$ mediated the reversible interconversion of $\{[Cu^{II}(MeAN)]_2(\eta^2:\eta^2\text{-}O_2^{2-})\}^{2+}$ ($^{\mathbf{S}}\mathbf{P}$; 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 $^{\mathbf{T}}\mathbf{P}$ 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 ($\lambda_{max} = 394$ nm); however, its limited lifetime precluded further characterization.[22a]

Results and Discussion

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. 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 $^{\mathbf{T}}\mathbf{P}$, **1**, to a novel $^{\mathbf{C}}\mathbf{P}$ 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; $\lambda_{max} = 455$ nm, $\varepsilon = 4080\ M^{-1}cm^{-1}$) 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 [for example, NH_2,[23] NHAr;[11e] $\lambda_{max} \approx 450$ 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.

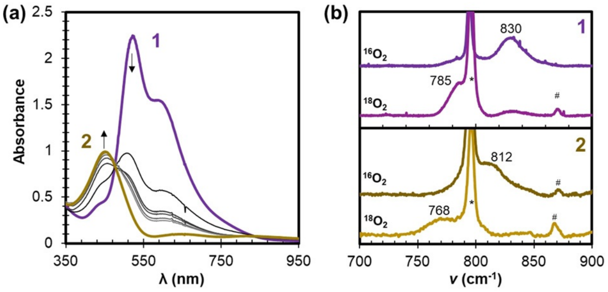

Figure 2. a) Selected electronic absorbance spectra following the addition of $Ca^{II}(OTf)_2$ (5 mM) to **1** (0.5 mM, purple trace) in acetone at −80 °C to form **2** (gold trace, time = 20 s). b) rRaman spectra ($\lambda_{ex} = 456.8$ nm) of **1** (purple) and **2** (gold) in acetone at 77 K (top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

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} ($\nu_{O\text{-}O}$; $\Delta^{16}O_2\text{-}^{18}O_2 = -43\ cm^{-1}$) that was red-shifted by ≈18 cm^{-1} relative to **1** ($\nu_{O\text{-}O}(\mathbf{1})$: 830 cm^{-1}; $\Delta^{16}O_2\text{-}^{18}O_2 = -45\ cm^{-1}$). $\nu_{O\text{-}O}(\mathbf{2})$ falls within the characteristic range of $^{\mathbf{T}}\mathbf{P}$ and $^{\mathbf{C}}\mathbf{P}$ 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, $^{\mathbf{S}}\mathbf{P}$) peroxido dicopper ($\nu_{O\text{-}O}$: 715–730 cm^{-1}), and 1,1-hydroperoxido dicopper ($\nu_{O\text{-}O}$: 860–880 cm^{-1}).[6c,20b,24] Lewis acid binding at peroxido fragments have led to red-shifted $\nu_{O\text{-}O}$ (ca. 5–30 cm^{-1}), although the magnitude of this shift is sensitive to Lewis acid strength and complex geometry.[7j,21a,e,25] Taken together, we hypothesized the distinct spectroscopic changes going from **1** to **2** (blue-shifted LMCT λ_{max}, red-shifted $\nu_{O\text{-}O}$) 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 $[Cu^{II}_2(PzTACN^{Me})(\mu\text{-}1,2\text{-}O_2^{2-})Na(OTf)]^+$.[7j] Kinetic parameters obtained under flooding conditions (>10-fold excess $Ca(OTf)_2$; Figure 3b and Figure S13) revealed rapid association and dissociation of Ca^{II} at −80 °C, where the forward (k_+) and reverse (k_-) rate-constants were determined to be $2.71 \pm 0.25 \times 10^2\ M^{-1}s^{-1}$ and $0.22 \pm 0.02\ s^{-1}$, 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 chemically reversible (Figure 3c).

Complex **2** is EPR-silent at X-band frequencies (Figure S20) and ^1H NMR spectroscopy (Figure S26–28) provided

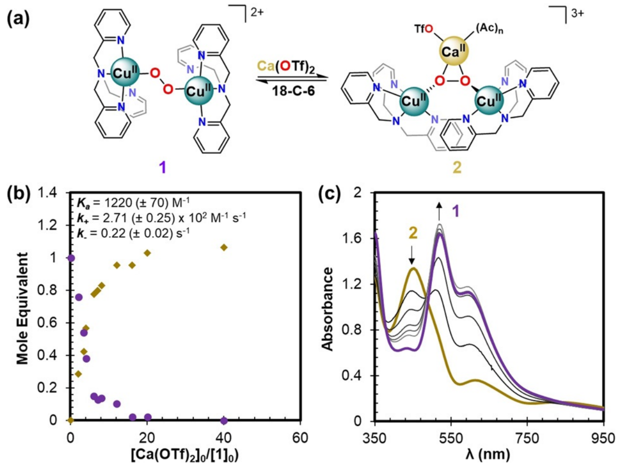

Figure 3. a) Proposed interconversion between **1** and **2** using Ca^{II}-$(OTf)_2$ and 18-C-6 chelate (0–10 s). Ac = acetone, $n=3$ or 4; b) Titration of Ca^{II} (guest) to **1** (host, purple; circles) to form **2** (gold; diamonds), inset: association constant ($K_{Ca^{II}}$), forward (k_+) and reverse (k_-) kinetic rate constants for Ca^{II} binding (see the Supporting Information 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.

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 ^1H NMR spectrum of **2** collected in $[D_6]$acetone at −80 °C displayed about 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 (see above).

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 ($\mu_{eff}\approx 2.83\,\mu_B$).[14,29] This is wholly inconsistent with a $^{\mathbf{T}}\mathbf{P}$ Cu_2O_2 core ($\phi_{Cu_2O_2}\approx 180°$), 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 $^{\mathbf{C}}\mathbf{P}$ Cu_2O_2 core ($\phi_{Cu_2O_2}\rightarrow 90°$). The two reported $^{\mathbf{C}}\mathbf{P}$ display paramagnetic NMR spectra and weak magnetic coupling for the Cu_2O_2 core (PzTACN^{Me}: $\phi_{Cu_2O_2}=62.5°$, $J=-77\,cm^{-1}$; PzTACN^{Et}: $\phi_{Cu_2O_2}=104.2°$, $J=+72\,cm^{-1}$; $H=-2J\mathbf{S_1S_2}$)[7j,14] due to interaction of the Cu^{II} $d_{x^2-y^2}$ orbitals with orthogonal $\pi^*(O_2)$ 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 ^1H 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.

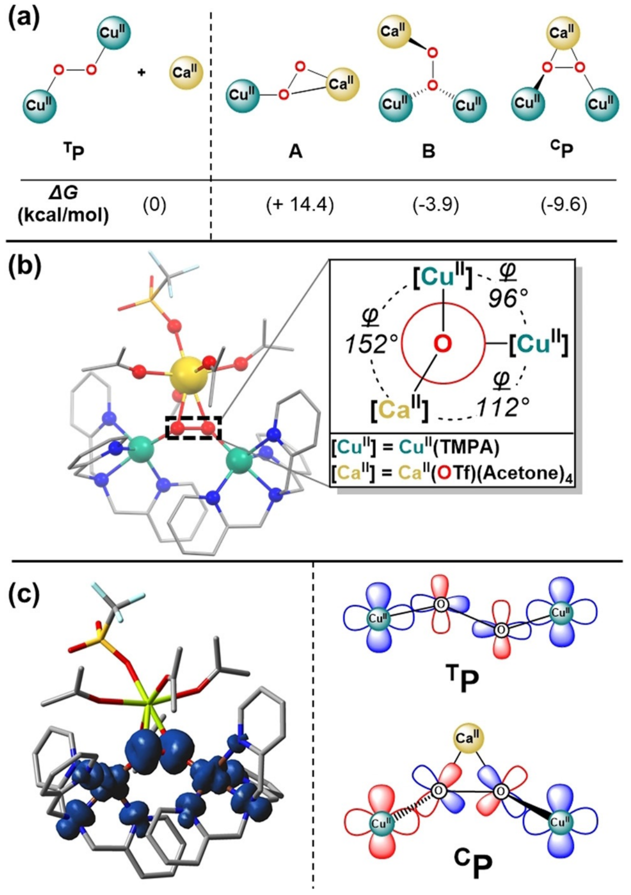

Figure 4. a) Possible heterobimetallic structures from the reaction of **1** with $Ca(OTf)_2(Ac)_4$ (Ac = Acetone); **A**: $\{[Cu^{II}(TMPA)](\mu\text{-}\eta_1{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)(Ac)_4]\}^+$, **B**: $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1{:}\eta_1{:}\eta_1\text{-}O_2^{2-})[Ca^{II}(OTf)(Ac)_4]\}^{3+}$,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

The reactivity of **1** with $Ca(OTf)_2$ was further substantiated by computational studies performed at the M06-L level of theory[31] (for the Computational Methods, see the 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 $\{[Cu^{II}(TMPA)](\mu\text{-}\eta_1{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)_x(Ac)_n]\}^{2-x+}$ 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^{-1} (Figures S32–S33, Scheme S3). Ca^{II} binding to the distal peroxido site of a 1,1-peroxido dicopper core, $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1{:}\eta_1{:}\eta_1\text{-}O_2^{2-})$ $[Ca^{II}(OTf)(Ac)_4]\}^{3+}$ (**B**) is slightly exergonic (−3.9 kcal mol^{-1}); however, this structure is a poor match with experimental data and literature expectations. Related 1,1-hydroperoxido dicopper cores display higher $\nu_{O\text{-}O}$ (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 $^{\mathbf{C}}\mathbf{P}$ is favored by 9.6 kcal mol^{-1}, and the calculated and experimental rRaman spectra are in excellent agreement with one another (Table S4). The optimized $^{\mathbf{C}}\mathbf{P}$ structure approaches the ideal $\phi_{Cu_2O_2}$ of 90°, which is expected to suppress strong antiferromagnetic coupling between the two Cu^{II} sites ($\phi_{Cu_2O_2}$($^{\mathbf{C}}\mathbf{P}$): 96°).[35] The $^{\mathbf{C}}\mathbf{P}$ 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 $^{\mathbf{C}}\mathbf{P}$ with a structural formula of $\{[Cu^{II}(TMPA)]_2(\mu\text{-}\eta_1{:}\eta_1{:}\eta_2\text{-}O_2^{2-})[Ca^{II}(OTf)_x(Ac)_{n-x}]\}^{3-x+}$ ($n=5$, $x=1$), although alternative speciation of the Ca-bound fragment may be possible (e.g. $n=5$, $x=0$, 2).

Conclusion

The reversible interconversion of $^{\mathbf{T}}\mathbf{P}$/$^{\mathbf{C}}\mathbf{P}$ 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,e,f,22,36] Reversible interconversion of $^{\mathbf{C}}\mathbf{P}$ cores have been proposed to occur in type III dicopper active sites such as hemocyanin, where a transient ferromagnetically coupled $^{\mathbf{C}}\mathbf{P}$ undergoes isomerization steps to reach the antiferromagnetically coupled $^{\mathbf{S}}\mathbf{P}$ resting state.[15] Our study establishes the first synthetic precedent for the reversible interconversion of a paramagnetic $^{\mathbf{C}}\mathbf{P}$ core, **2**, and the strongly antiferromagnetically coupled $^{\mathbf{T}}\mathbf{P}$ core, **1**. The reversible transformation is accessible under mild conditions through Ca^{II} ion binding, and provides a direct connection between the prototypical $^{\mathbf{T}}\mathbf{P}$ species, **1**, and the biologically relevant $^{\mathbf{C}}\mathbf{P}$ isomer, **2**. Notably, Sc(OTf)$_3$ binding at a diiron $^{\mathbf{C}}\mathbf{P}$ 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]

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,i,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 $^{\mathbf{C}}\mathbf{P}$ 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$_2$O$_2$ cores are currently underway.

Acknowledgements

The work at Brown University (J.R.R., N.P.V.) was financially supported by the National Science Foundation (CHE-1900248) and Brown University. The work at BNL (M.Z.E.) was supported by the U.S. Department of Energy (DOE), Office of Science, Office of Basic Energy Sciences, Division of Chemical Sciences, Geosciences & Biosciences, under Contract No. DE-SC0012704. The work at the University of Michigan was supported by the National Science Foundation (CHE-1900380 to N.L.). J.R.R. and N.P.V. thank Prof. Eunsuk Kim, Alex Brown, and Matthew Lueckheide for helpful discussions.

Conflict of Interest

The authors declare no conflict of interest.

Stichwörter: bioinorganic chemistry · calcium · copper · heterometallic complexes · peroxides

---

[1] K. A. Magnus, H. Ton-That, J. E. Carpenter, *Chem. Rev.* **1994**, *94*, 727 – 735.

[2] a) Y. Matoba, T. Kumagai, A. Yamamoto, H. Yoshitsu, M. Sugiyama, *J. Biol. Chem.* **2006**, *281*, 8981 – 8990; b) W. T. Ismaya, H. J. Rozeboom, A. Weijn, J. J. Mes, F. Fusetti, H. J. Wichers, B. W. Dijkstra, *Biochemistry* **2011**, *50*, 5477 – 5486.

[3] C. Gerdemann, C. Eicken, B. Krebs, *Acc. Chem. Res.* **2002**, *35*, 183 – 191.

[4] a) R. Balasubramanian, A. C. Rosenzweig, *Acc. Chem. Res.* **2007**, *40*, 573 – 580; b) S. I. Chan, S. S. F. Yu, *Acc. Chem. Res.* **2008**, *41*, 969 – 979; c) M. O. Ross, F. MacMillan, J. Wang, A. Nisthal, T. J. Lawton, B. D. Olafson, S. L. Mayo, A. C. Rosenzweig, B. M. Hoffman, *Science* **2019**, *364*, 566 – 570; d) C. W. Koo, A. C. Rosenzweig, *Chem. Soc. Rev.* **2021**, *50*, 3424 – 3436.

[5] a) H. Decker, T. Schweikardt, D. Nillius, U. Salzbrunn, E. Jaenicke, F. Tuczek, *Gene* **2007**, *398*, 183 – 191; b) J. W. Ginsbach, M. T. Kieber-Emmons, R. Nomoto, A. Noguchi, Y. Ohnishi, E. I. Solomon, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 10793 – 10797; c) E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659 – 3853.

[6] a) L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013 – 1046; b) E. A. Lewis, W. B. Tolman, *Chem. Rev.* **2004**, *104*, 1047 – 1076; c) C. E. Elwell, N. L. Gagnon, B. D. Neisen, D. Dhar, A. D. Spaeth, G. M. Yee, W. B. Tolman, *Chem. Rev.* **2017**, *117*, 2059 – 2107.

[7] a) N. Kitajima, K. Fujisawa, Y. Morooka, K. Toriumi, *J. Am. Chem. Soc.* **1989**, *111*, 8975 – 8976; b) N. Kitajima, K. Fujisawa, C. Fujimoto, Y. Morooka, S. Hashimoto, T. Kitagawa, K. Toriumi, K. Tatsumi, A. Nakamura, *J. Am. Chem. Soc.* **1992**, *114*, 1277 – 1291; c) R. R. Jacobson, Z. Tyeklar, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *J. Am. Chem. Soc.* **1988**, *110*, 3690 – 3692; d) K. D. Karlin, Z. Tyeklár, A. Farooq, R. R. Jacobson, E. Sinn, D. W. Lee, J. E. Bradshaw, L. J. Wilson, *Inorg. Chim. Acta* **1991**, *182*, 1 – 3; e) J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, L. Que, A. D. Zuberbuhler, W. B. Tolman, *Science* **1996**, *271*, 1397 – 1400; f) M. J. Henson, V. Mahadevan, T. D. P. Stack, E. I. Solomon, *Inorg. Chem.* **2001**, *40*, 5068 – 5069; g) B. A. Jazdzewski, A. M. Reynolds, P. L. Holland, V. G. Young, S. Kaderli, A. D. Zuberbühler, W. B. Tolman, *J. Biol. Inorg.*

Chem. **2003**, *8*, 381 – 393; h) L. M. Mirica, D. J. Rudd, M. A. Vance, E. I. Solomon, K. O. Hodgson, B. Hedman, T. D. P. Stack, *J. Am. Chem. Soc.* **2006**, *128*, 2654 – 2665; i) Z. Halime, M. T. Kieber-Emmons, M. F. Qayyum, B. Mondal, T. Gandhi, S. C. Puiu, E. E. ChufáN, A. A. N. Sarjeant, K. O. Hodgson, B. Hedman, E. I. Solomon, K. D. Karlin, *Inorg. Chem.* **2010**, *49*, 3629 – 3645; j) K. E. Dalle, T. Gruene, S. Dechert, S. Demeshko, F. Meyer, *J. Am. Chem. Soc.* **2014**, *136*, 7428 – 7434.

[8] a) L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333 – 340; b) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062 – 11087; c) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234 – 6458; d) L. Q. Hatcher, K. D. Karlin, *J. Biol. Inorg. Chem.* **2004**, *9*, 669 – 683; e) A. M. Kirillov, M. N. Kopylovich, M. V. Kirillova, M. Haukka, M. F. C. G. da Silva, A. J. L. Pombeiro, *Angew. Chem. Int. Ed.* **2005**, *44*, 4345 – 4349; f) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068 – 12073; g) M. Rolff, J. Schottenheim, G. Peters, F. Tuczek, *Angew. Chem. Int. Ed.* **2010**, *49*, 6438 – 6442; h) A. M. Kirillov, M. V. Kirillova, A. J. L. Pombeiro, In *Advances in Inorganic Chemistry*, *Advances in Inorganic Chemistry* Elsevier, Amsterdam, **2013**, pp. 1 – 31; i) A. Hoffmann, C. Citek, S. Binder, A. Goos, M. Rübhausen, O. Troeppner, I. Ivanović-Burmazović, E. C. Wasinger, T. D. P. Stack, S. Herres-Pawlis, *Angew. Chem. Int. Ed.* **2013**, *52*, 5398 – 5401; j) B. Xu, J.-P. Lumb, B. A. Arndtsen, *Angew. Chem. Int. Ed.* **2015**, *54*, 4208 – 4211; k) E. L. Presti, E. Monzani, L. Santagostini, L. Casella, *Inorg. Chim. Acta* **2018**, *481*, 47 – 55; l) L. Ciano, G. J. Davies, W. B. Tolman, P. H. Walton, *Nat. Catal.* **2018**, *1*, 571 – 577; m) S. C. Bete, C. Würtele, M. Otte, *Chem. Commun.* **2019**, *55*, 4427 – 4430.

[9] a) M. H. Groothaert, P. J. Smeets, B. F. Sels, P. A. Jacobs, R. A. Schoonheydt, *J. Am. Chem. Soc.* **2005**, *127*, 1394 – 1395; b) P. Vanelderen, R. G. Hadt, P. J. Smeets, E. I. Solomon, R. A. Schoonheydt, B. F. Sels, *J. Catal.* **2011**, *284*, 157 – 164; c) S. Grundner, M. A. C. Markovits, G. Li, M. Tromp, E. A. Pidko, E. J. M. Hensen, A. Jentys, M. Sanchez-Sanchez, J. A. Lercher, *Nat. Commun.* **2015**, *6*, 7546; d) N. A. Carmo Dos Santos, F. Lorandi, E. Badetti, K. Wurst, A. A. Isse, A. Gennaro, G. Licini, C. Zonta, *Polymer* **2017**, *128*, 169 – 176; e) J. Baek, B. Rungtaweevoranit, X. Pei, M. Park, S. C. Fakra, Y.-S. Liu, R. Matheu, S. A. Alshmimri, S. Alshehri, C. A. Trickett, G. A. Somorjai, O. M. Yaghi, *J. Am. Chem. Soc.* **2018**, *140*, 18208 – 18216; f) S. Thanneeru, N. Milazzo, A. Lopes, Z. Wei, A. M. Angeles-Boza, J. He, *J. Am. Chem. Soc.* **2019**, *141*, 4252 – 4256; g) J. Zheng, J. Ye, M. A. Ortuño, J. L. Fulton, O. Y. Gutiérrez, D. M. Camaioni, R. K. Motkuri, Z. Li, T. E. Webber, B. L. Mehdi, N. D. Browning, R. L. Penn, O. K. Farha, J. T. Hupp, D. G. Truhlar, C. J. Cramer, J. A. Lercher, *J. Am. Chem. Soc.* **2019**, *141*, 9292 – 9304; h) F. De Bon, C. M. R. Abreu, A. C. Serra, A. Gennaro, J. F. J. Coelho, A. A. Isse, *Macromol. Rapid Commun.* **2020**, 2000532; i) X. Feng, Y. Song, J. S. Chen, Z. Xu, S. J. Dunn, W. Lin, *J. Am. Chem. Soc.* **2021**, *143*, 1107 – 1118.

[10] a) M. L. Pegis, C. F. Wise, D. J. Martin, J. M. Mayer, *Chem. Rev.* **2018**, *118*, 2340 – 2391; b) M. S. Thorum, J. Yadav, A. A. Gewirth, *Angew. Chem. Int. Ed.* **2009**, *48*, 165 – 167; c) M. A. Thorseth, C. S. Letko, T. B. Rauchfuss, A. A. Gewirth, *Inorg. Chem.* **2011**, *50*, 6158 – 6162; d) C. C. L. McCrory, A. Devadoss, X. Ottenwaelder, R. D. Lowe, T. D. P. Stack, C. E. D. Chidsey, *J. Am. Chem. Soc.* **2011**, *133*, 3696 – 3699; e) S. M. Barnett, K. I. Goldberg, J. M. Mayer, *Nat. Chem.* **2012**, *4*, 498 – 502; f) S. Fukuzumi, L. Tahsini, Y.-M. Lee, K. Ohkubo, W. Nam, K. D. Karlin, *J. Am. Chem. Soc.* **2012**, *134*, 7025 – 7035; g) M. A. Thorseth, C. E. Tornow, E. C. M. Tse, A. A. Gewirth, *Coord. Chem. Rev.* **2013**, *257*, 130 – 139; h) M. A. Thorseth, C. S. Letko, E. C. M. Tse, T. B. Rauchfuss, A. A. Gewirth, *Inorg. Chem.* **2013**, *52*, 628 – 634; i) D. Das, Y.-M. Lee, K. Ohkubo, W. Nam, K. D. Karlin, S. Fukuzumi, *J. Am. Chem. Soc.* **2013**, *135*, 2825 – 2834; j) D. Das, Y.-M. Lee, K. Ohkubo, W. Nam, K. D. Karlin, S. Fukuzumi, *J. Am. Chem. Soc.* **2013**, *135*, 4018 – 4026; k) M. Asahi, S.-i. Yamazaki, S. Itoh, T. Ioroi, *Dalton Trans.* **2014**, *43*, 10705 – 10709; l) K. Ray, F. Heims, M. Schwalbe, W. Nam, *Curr. Opin. Chem. Biol.* **2015**, *25*, 159 – 171; m) X.-J. Su, M. Gao, L. Jiao, R.-Z. Liao, P. E. M. Siegbahn, J.-P. Cheng, M.-T. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4909 – 4914; n) R.-J. Xiang, H.-Y. Wang, Z.-J. Xin, C.-B. Li, Y.-X. Lu, X.-W. Gao, H.-M. Sun, R. Cao, *Chem. Eur. J.* **2016**, *22*, 1602 – 1607; o) M. Asahi, S.-i. Yamazaki, S. Itoh, T. Ioroi, *Electrochim. Acta* **2016**, *211*, 193 – 198; p) M. Langerman, D. G. H. Hetterscheid, *Angew. Chem. Int. Ed.* **2019**, *58*, 12974 – 12978; q) N. W. G. Smits, B. van Dijk, I. de Bruin, S. L. T. Groeneveld, M. A. Siegler, D. G. H. Hetterscheid, *Inorg. Chem.* **2020**, *59*, 16398 – 16409.

[11] a) Z. Tyeklar, R. R. Jacobson, N. Wei, N. N. Murthy, J. Zubieta, K. D. Karlin, *J. Am. Chem. Soc.* **1993**, *115*, 2677 – 2689; b) K. Komiyama, H. Furutachi, S. Nagatomo, A. Hashimoto, H. Hayashi, S. Fujinami, M. Suzuki, T. Kitagawa, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 59 – 72; c) C. Würtele, O. Sander, V. Lutz, T. Waitz, F. Tuczek, S. Schindler, *J. Am. Chem. Soc.* **2009**, *131*, 7544 – 7545; d) T. Hoppe, S. Schaub, J. Becker, C. Würtele, S. Schindler, *Angew. Chem. Int. Ed.* **2013**, *52*, 870 – 873; e) E. W. Dahl, H. T. Dong, N. K. Szymczak, *Chem. Commun.* **2018**, *54*, 892 – 895.

[12] a) M. Kodera, K. Katayama, Y. Tachi, K. Kano, S. Hirota, S. Fujinami, M. Suzuki, *J. Am. Chem. Soc.* **1999**, *121*, 11006 – 11007; b) B. M. T. Lam, J. A. Halfen, V. G. Young, J. R. Hagadorn, P. L. Holland, A. Lledós, L. Cucurull-Sánchez, J. J. Novoa, S. Alvarez, W. B. Tolman, *Inorg. Chem.* **2000**, *39*, 4059 – 4072; c) Z. Hu, G. N. George, S. M. Gorun, *Inorg. Chem.* **2001**, *40*, 4812 – 4813; d) M. Kodera, Y. Kajita, Y. Tachi, K. Katayama, K. Kano, S. Hirota, S. Fujinami, M. Suzuki, *Angew. Chem. Int. Ed.* **2004**, *43*, 334 – 337; e) G. J. Karahalis, A. Thangavel, B. Chica, J. Bacsa, R. B. Dyer, C. C. Scarborough, *Inorg. Chem.* **2016**, *55*, 1102 – 1107; f) S. Zhang, H. Fallah, E. J. Gardner, S. Kundu, J. A. Bertke, T. R. Cundari, T. H. Warren, *Angew. Chem. Int. Ed.* **2016**, *55*, 9927 – 9931; g) V. E. Goswami, A. Walli, M. Förster, S. Dechert, S. Demeshko, M. C. Holthausen, F. Meyer, *Chem. Sci.* **2017**, *8*, 3031 – 3037.

[13] a) S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Young, C. J. Cramer, L. Que, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11555 – 11574; b) S. Mahapatra, V. G. Young, S. Kaderli, A. D. Zuberbühler, W. B. Tolman, *Angew. Chem. Int. Ed.* **1997**, *36*, 130 – 133; c) V. Mahadevan, Z. Hou, A. P. Cole, D. E. Root, T. K. Lal, E. I. Solomon, T. D. P. Stack, *J. Am. Chem. Soc.* **1997**, *119*, 11996 – 11997; d) H. Hayashi, S. Fujinami, S. Nagatomo, S. Ogo, M. Suzuki, A. Uehara, Y. Watanabe, T. Kitagawa, *J. Am. Chem. Soc.* **2000**, *122*, 2124 – 2125; e) B. F. Straub, F. Rominger, P. Hofmann, *Chem. Commun.* **2000**, 1611 – 1612; f) N. W. Aboelella, E. A. Lewis, A. M. Reynolds, W. W. Brennessel, C. J. Cramer, W. B. Tolman, *J. Am. Chem. Soc.* **2002**, *124*, 10660 – 10661; g) A. P. Cole, V. Mahadevan, L. M. Mirica, X. Ottenwaelder, T. D. P. Stack, *Inorg. Chem.* **2005**, *44*, 7345 – 7364; h) L. Zhou, D. Powell, K. M. Nicholas, *Inorg. Chem.* **2006**, *45*, 3840 – 3842; i) R. M. Ramadan, S. M. Shohayeb, R. G. Mohamed, *Inorg. Nano-Met. Chem.* **2013**, *43*, 609 – 616; j) A. Walli, S. Dechert, M. Bauer, S. Demeshko, F. Meyer, *Eur. J. Inorg. Chem.* **2014**, 4660 – 4676.

[14] N. Kindermann, E. Bill, S. Dechert, S. Demeshko, E. J. Reijerse, F. Meyer, *Angew. Chem. Int. Ed.* **2015**, *54*, 1738 – 1743.

[15] a) E. I. Solomon, P. Chen, M. Metz, S.-K. Lee, A. E. Palmer, *Angew. Chem. Int. Ed.* **2001**, *40*, 4570 – 4590; b) M. Metz, E. I. Solomon, *J. Am. Chem. Soc.* **2001**, *123*, 4938 – 4950.

[16] a) R. D. Jones, D. A. Summerville, F. Basolo, *Chem. Rev.* **1979**, *79*, 139 – 179; b) E. C. Niederhoffer, J. H. Timmons, A. E. Martell, *Chem. Rev.* **1984**, *84*, 137 – 203; c) E. I. Solomon, F. Tuczek, D. E. Root, C. A. Brown, *Chem. Rev.* **1994**, *94*, 827 – 856;

d) M. Calligaris, G. Nardin, L. Randaccio, A. Ripamonti, *J. Chem. Soc. A* **1970**, 1069–1074; e) A. L. Gavrilova, C. J. Qin, R. D. Sommer, A. L. Rheingold, B. Bosnich, *J. Am. Chem. Soc.* **2002**, *124*, 1714–1722; f) G. Givaja, M. Volpe, M. A. Edwards, A. J. Blake, C. Wilson, M. Schröder, J. B. Love, *Angew. Chem. Int. Ed.* **2007**, *46*, 584–586; g) P. D. Southon, D. J. Price, P. K. Nielsen, C. J. McKenzie, C. J. Kepert, *J. Am. Chem. Soc.* **2011**, *133*, 10885–10891; h) S. Fukuzumi, S. Mandal, K. Mase, K. Ohkubo, H. Park, J. Benet-Buchholz, W. Nam, A. Llobet, *J. Am. Chem. Soc.* **2012**, *134*, 9906–9909; i) M. L. Rigsby, S. Mandal, W. Nam, L. C. Spencer, A. Llobet, S. S. Stahl, *Chem. Sci.* **2012**, *3*, 3058–3062; j) Y. Dong, S. Yan, V. G. Young, Jr., L. Que, Jr., *Angew. Chem. Int. Ed.* **1996**, *35*, 618–620; k) T. Ookubo, H. Sugimoto, T. Nagayama, H. Masuda, T. Sato, K. Tanaka, Y. Maeda, H. Ōkawa, Y. Hayashi, A. Uehara, M. Suzuki, *J. Am. Chem. Soc.* **1996**, *118*, 701–702; l) K. Kim, S. J. Lippard, *J. Am. Chem. Soc.* **1996**, *118*, 4914–4915; m) X. Zhang, H. Furutachi, S. Fujinami, S. Nagatomo, Y. Maeda, Y. Watanabe, T. Kitagawa, M. Suzuki, *J. Am. Chem. Soc.* **2005**, *127*, 826–827; n) M. Sekino, H. Furutachi, R. Tojo, A. Hishi, H. Kajikawa, T. Suzuki, K. Suzuki, S. Fujinami, S. Akine, Y. Sakata, T. Ohta, S. Hayami, M. Suzuki, *Chem. Commun.* **2017**, *53*, 8838–8841.

[17] A. J. Jasniewski, L. Que, *Chem. Rev.* **2018**, *118*, 2554–2592.

[18] a) I. Bertini, H. B. Gray, E. I. Stiefel, J. S. Valentine, *Biological Inorganic Chemistry: Structure and Reactivity*, University Science Books, Sausalito, CA, **2007**; b) J. Yano, V. Yachandra, *Chem. Rev.* **2014**, *114*, 4175–4205; c) M. Suga, F. Akita, K. Hirata, G. Ueno, H. Murakami, Y. Nakajima, T. Shimizu, K. Yamashita, M. Yamamoto, H. Ago, J.-R. Shen, *Nature* **2015**, *517*, 99–103.

[19] a) S. Fukuzumi, K. Ohkubo, Y.-M. Lee, W. Nam, *Chem. Eur. J.* **2015**, *21*, 17548–17559; b) T. Devi, Y.-M. Lee, W. Nam, S. Fukuzumi, *Coord. Chem. Rev.* **2020**, *410*, 213219; c) B. Gerey, E. Gouré, J. Fortage, J. Pécaut, M.-N. Collomb, *Coord. Chem. Rev.* **2016**, *319*, 1–24; d) J. S. Kanady, E. Y. Tsui, M. W. Day, T. Agapie, *Science* **2011**, *333*, 733–736; e) E. Y. Tsui, R. Tran, J. Yano, T. Agapie, *Nat. Chem.* **2013**, *5*, 293–299; f) H. Ohtsu, Y. Shimazaki, A. Odani, O. Yamauchi, W. Mori, S. Itoh, S. Fukuzumi, *J. Am. Chem. Soc.* **2000**, *122*, 5733–5741; g) S. Fukuzumi, *Roles of Metal Ions in Controlling Bioinspired Electron-Transfer Systems. Metal Ion-Coupled Electron Transfer.* In *Progress in Inorganic Chemistry*, John Wiley & Sons, Ltd: **2009**, pp 49–154.

[20] a) S. Fukuzumi, K. Ohkubo, *Chem. Eur. J.* **2000**, *6*, 4532–4535; b) M. Mizuno, K. Honda, J. Cho, H. Furutachi, T. Tosha, T. Matsumoto, S. Fujinami, T. Kitagawa, M. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 6911–6914; *Angew. Chem.* **2006**, *118*, 7065–7068; c) S. Yao, Y. Xiong, M. Vogt, H. Grützmacher, C. Herwig, C. Limberg, M. Driess, *Angew. Chem. Int. Ed.* **2009**, *48*, 8107–8110; d) Y. J. Park, J. W. Ziller, A. S. Borovik, *J. Am. Chem. Soc.* **2011**, *133*, 9258–9261; e) Y. J. Park, S. A. Cook, N. S. Sickerman, Y. Sano, J. W. Ziller, A. S. Borovik, *Chem. Sci.* **2013**, *4*, 717–726; f) J. T. Henthorn, T. Agapie, *Angew. Chem. Int. Ed.* **2014**, *53*, 12893–12896; g) F. Schax, S. Suhr, E. Bill, B. Braun, C. Herwig, C. Limberg, *Angew. Chem. Int. Ed.* **2015**, *54*, 1352–1356; h) S. Hong, Y.-M. Lee, M. Sankaralingam, A. K. Vardhaman, Y. J. Park, K.-B. Cho, T. Ogura, R. Sarangi, S. Fukuzumi, W. Nam, *J. Am. Chem. Soc.* **2016**, *138*, 8523–8532; i) T. Devi, Y.-M. Lee, W. Nam, S. Fukuzumi, *J. Am. Chem. Soc.* **2019**, *142*, 365–372; j) M.-L. Wind, S. Hoof, C. Herwig, B. Braun-Cula, C. Limberg, *Chem. Eur. J.* **2019**, *25*, 5743–5750; k) M.-L. Wind, S. Hoof, B. Braun-Cula, C. Herwig, C. Limberg, *Inorg. Chem.* **2020**, *59*, 6866–6875.

[21] a) Y.-M. Lee, S. Bang, Y. M. Kim, J. Cho, S. Hong, T. Nomura, T. Ogura, O. Troeppner, I. Ivanović-Burmazović, R. Sarangi, S. Fukuzumi, W. Nam, *Chem. Sci.* **2013**, *4*, 3917; b) S. Bang, Y.-M. Lee, S. Hong, K.-B. Cho, Y. Nishida, M. S. Seo, R. Sarangi, S. Fukuzumi, W. Nam, *Nat. Chem.* **2014**, *6*, 934–940; c) S. H. Bae, Y.-M. Lee, S. Fukuzumi, W. Nam, *Angew. Chem. Int. Ed.* **2017**, *56*, 801–805; d) M.-L. Wind, S. Hoof, B. Braun-Cula, C. Herwig, C. Limberg, *J. Am. Chem. Soc.* **2019**, *141*, 14068–14072; e) F. Li, K. M. Van Heuvelen, K. K. Meier, E. Münck, L. Que, *J. Am. Chem. Soc.* **2013**, *135*, 10198–10201; f) S. Banerjee, A. Draksharapu, P. M. Crossland, R. Fan, Y. Guo, M. Swart, L. Que, *J. Am. Chem. Soc.* **2020**, *142*, 4285–4297.

[22] a) S. Kakuda, C. J. Rolle, K. Ohkubo, M. A. Siegler, K. D. Karlin, S. Fukuzumi, *J. Am. Chem. Soc.* **2015**, *137*, 3330–3337; b) I. Garcia-Bosch, R. E. Cowley, D. E. Díaz, R. L. Peterson, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2017**, *139*, 3186–3195.

[23] S. Yamaguchi, A. Wada, Y. Funahashi, S. Nagatomo, T. Kitagawa, K. Jitsukawa, H. Masuda, *Eur. J. Inorg. Chem.* **2003**, 4378–4386.

[24] B. Kim, S. Kim, T. Ohta, J. Cho, *Inorg. Chem.* **2020**, *59*, 9938–9943.

[25] F. Li, K. K. Meier, M. A. Cranswick, M. Chakrabarti, K. M. Van Heuvelen, E. Münck, L. Que, *J. Am. Chem. Soc.* **2011**, *133*, 7256–7259.

[26] P. Thordarson, *Chem. Soc. Rev.* **2011**, *40*, 1305–1323.

[27] a) S. Kakuda, R. L. Peterson, K. Ohkubo, K. D. Karlin, S. Fukuzumi, *J. Am. Chem. Soc.* **2013**, *135*, 6513–6522; b) T. Fujii, A. Naito, S. Yamaguchi, A. Wada, Y. Funahashi, K. Jitsukawa, S. Nagatomo, T. Kitagawa, H. Masuda, *Chem. Commun.* **2003**, 2700–2701; c) S. Yamaguchi, A. Wada, S. Nagatomo, T. Kitagawa, K. Jitsukawa, H. Masuda, *Chem. Lett.* **2004**, *33*, 1556–1557.

[28] a) D. F. Evans, *J. Chem. Soc.* **1959**, 2003–2005; b) E. M. Schubert, *J. Chem. Educ.* **1992**, *69*, 62; c) C. Piguet, *J. Chem. Educ.* **1997**, *74*, 815.

[29] J. M. Brink, R. A. Rose, R. C. Holz, *Inorg. Chem.* **1996**, *35*, 2878–2885.

[30] N. Zhao, A. S. Filatov, J. Xie, E. A. Hill, A. Y. Rogachev, J. S. Anderson, *J. Am. Chem. Soc.* **2020**, *142*, 21634–21639.

[31] Y. Zhao, D. G. Truhlar, *J. Chem. Phys.* **2006**, *125*, 194101.

[32] a) W. J. Geary, *Coord. Chem. Rev.* **1971**, *7*, 81–122; b) P. V. Rysselberghe, R. M. Fristrom, *J. Am. Chem. Soc.* **1945**, *67*, 680–682.

[33] a) L. Li, A. A. Narducci Sarjeant, M. A. Vance, L. N. Zakharov, A. L. Rheingold, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2005**, *127*, 15360–15361; b) S. Teramae, T. Osako, S. Nagatomo, T. Kitagawa, S. Fukuzumi, S. Itoh, *J. Inorg. Biochem.* **2004**, *98*, 746–757; c) K. Itoh, H. Hayashi, H. Furutachi, T. Matsumoto, S. Nagatomo, T. Tosha, S. Terada, S. Fujinami, M. Suzuki, T. Kitagawa, *J. Am. Chem. Soc.* **2005**, *127*, 5212–5223; d) G. Battaini, E. Monzani, A. Perotti, C. Para, L. Casella, L. Santagostini, M. Gullotti, R. Dillinger, C. Näther, F. Tuczek, *J. Am. Chem. Soc.* **2003**, *125*, 4185–4198; e) N. Kindermann, S. Dechert, S. Demeshko, F. Meyer, *J. Am. Chem. Soc.* **2015**, *137*, 8002–8005.

[34] a) K. D. Karlin, R. W. Cruse, Y. Gultneh, *Chem. Commun.* **1987**, 599–600; b) K. D. Karlin, P. Ghosh, R. W. Cruse, A. Farooq, Y. Gultneh, R. R. Jacobson, N. J. Blackburn, R. W. Strange, J. Zubieta, *J. Am. Chem. Soc.* **1988**, *110*, 6769–6780; c) L. Li, A. A. N. Sarjeant, K. D. Karlin, *Inorg. Chem.* **2006**, *45*, 7160–7172.

[35] Several low-energy conformers are also present, including Conf. 1 ($\phi_{Cu_2O_2}$: 118°), which is predicted to display weak antiferromagnetic coupling. See the Supporting Information for details.

[36] Y.-M. Lee, S. Bang, H. Yoon, S. H. Bae, S. Hong, K.-B. Cho, R. Sarangi, S. Fukuzumi, W. Nam, *Chem. Eur. J.* **2015**, *21*, 10676–10680.

[37] a) S. Hong, F. F. Pfaff, E. Kwon, Y. Wang, M.-S. Seo, E. Bill, K. Ray, W. Nam, *Angew. Chem. Int. Ed.* **2014**, *53*, 10403–10407; *Angew. Chem.* **2014**, *126*, 10571–10575; b) M. Sankaralingam, Y.-M. Lee, Y. Pineda-Galvan, D. G. Karmalkar, M. S. Seo, S. H.

Jeon, Y. Pushkar, S. Fukuzumi, W. Nam, *J. Am. Chem. Soc.* **2019**, *141*, 1324–1336.

[38] a) J. Suh, *Acc. Chem. Res.* **1992**, *25*, 273–279; b) D. E. Wilcox, *Chem. Rev.* **1996**, *96*, 2435–2458; c) E. L. Hegg, J. N. Burstyn, *Coord. Chem. Rev.* **1998**, *173*, 133–165; d) S. Lim, S. J. Franklin, *Cell. Mol. Life Sci.* **2004**, *61*, 2184–2188; e) M. Leopoldini, N. Russo, M. Toscano, *Chem. Eur. J.* **2007**, *13*, 2109–2117; f) J. A. Bogart, A. J. Lewis, E. J. Schelter, *Chem. Eur. J.* **2015**, *21*, 1743–1748; g) H. Lumpe, A. Pol, H. J. M. Op den Camp, L. J. Daumann, *Dalton Trans.* **2018**, *47*, 10463–10472; h) J. A. Cotruvo, E. R. Featherston, J. A. Mattocks, J. V. Ho, T. N. Laremore, *J. Am. Chem. Soc.* **2018**, *140*, 15056–15061; i) M. Prejanò, N. Russo, T. Marino, *Chem. Eur. J.* **2020**, *26*, 11334–11339.

Manuskript erhalten: 21. April 2021
Veränderte Fassung erhalten: 7. Juni 2021
Akzeptierte Fassung online: 8. Juni 2021
Endgültige Fassung online: 29. Juli 2021