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Re-engineering Enzyme-Model Active Sites: Reversible Binding of Dioxygen at Ambient Conditions by a Bioinspired Copper Complex

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The rational design of enzyme-like active sites aimed at improving our understanding of parent enzymes and producing biologically inspired catalysts remains an important objective in chemistry. The interest in reversible O_2 binding by hemocyanin (Hc) has produced models exhibiting similar spectroscopic and functional properties.[1] Related copper enzymes promote oxygen insertion in C−H bonds of organic (e.g., methane), inorganic (ammonia) or biological (dopamine, peptidyl or tyrosine) substrates.[1] The colorless, deoxyHc binds O_2 at two imidazole-bound $\mathrm{Cu^I}$ centers[2] (Scheme 1) to give blue−purple oxyHc, which contains a side-on μ-η^2:η^2 peroxo group, as revealed by two structures[3] and resonance Raman (RR) experiments.[4]

The $\mathrm{Cu^{II}(O_2)Cu^{II}}$ chromophore exhibits characteristic 570 and 345 nm $\mathrm{O_2^{2-}}$−$\mathrm{Cu^{II}}$ ligand-to-metal charge-transfer bands (LMCT) and a low frequency (750 $\mathrm{cm^{-1}}$) $\nu_{\mathrm{O-O}}$ stretch (RR) and is ESR-silent at room temperature due to the strong antiferromagnetic coupling of the metals. Unlike Hc, model copper−peroxo complexes are stable only at low temperatures,[1e,5] or have limited stability at room temperature.[6]

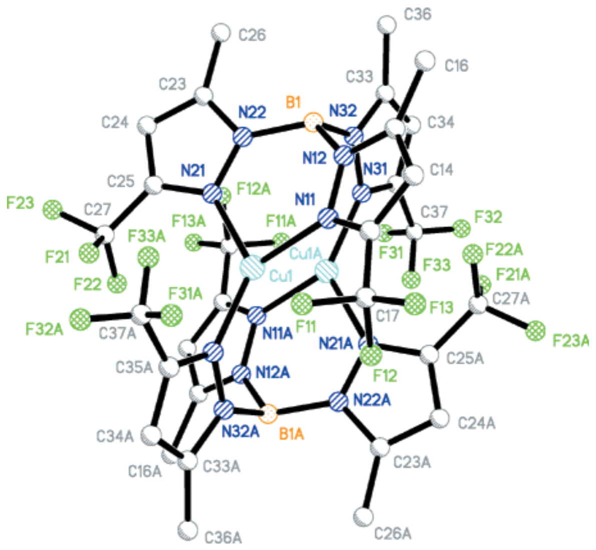
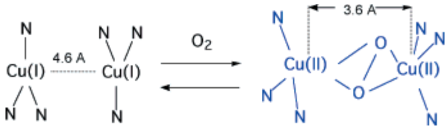


Figure 1. X-ray structure (hydrogens omitted) of **1**. Selected bond lengths [Å] and angles (deg): Cu(1A)−N(31) 1.942(4), Cu(1A)−N(11A) 1.988(4), Cu(1A)−N(21A) 1.994(4), N(31)−Cu(1A)−N(11A) 130.3(2), N(31)−Cu(1A)−N(21A) 128.5(2), N(11A)−Cu(1A)−N(21A) 97.7(2). Atoms labeled with "A" are related by an inversion center to their unlabeled counterparts.

Scheme 1. Schematic Representation of the Cu Coordination in DeoxyHc (left) and OxyHc (right)



We report here that replacing all C−H bonds by C−F bonds in the proximity of a copper center yields a Hc spectroscopic model which also binds O_2 under ambient conditions. The active site, located within a perfluorinated environment, is viewed as a "Teflon-coated" molecular reactor. The ligand, 3-trifluoromethyl-5-methyl-1-pyrazolyl borate,[7] $\mathrm{Tp^{CF_3,CH_3}}$, is a fluorinated analogue of 3, 5-dimethyl-1-pyrazolyl borate, $\mathrm{Tp^{CH_3,CH_3}}$. Its reaction with CuCl gives $\mathrm{Cu^I_2(Tp^{CF_3,CH_3})_2}$, **1** (Figure 1).[8]

In non-coordinating $\mathrm{CD_2Cl_2}$ **1** is partly dissociated, as shown by ^{1}H and ^{19}F NMR (Figure S1, Supporting Information). Addition of coordinating tetrahydrofuran (THF), acetone, or acetonitrile (ACN) shifts the equilibrium toward monomeric $\mathrm{[Cu^I(Tp^{CF_3,CH_3})(solvent)]}$ complexes, for example $\mathrm{[Cu^I(Tp^{CF_3,CH_3})(CH_3CN)]}$, **2**[9] (Figure S2).

Fluorination has a dramatic effect upon oxygen chemistry. While the protio analogue of **1**, $\mathrm{Cu^I_2(Tp^{CH_3,CH_3})_2}$, **1a**, has a similar Cu−ligand topology,[10] it forms peroxo complexes stable only at low temperature. Extraction of Cl from $\mathrm{CH_2Cl_2}$ resulting in the

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(9) The structure of **2** has been reported after ours was independently completed but not submitted: Schneider, J. L.; Carrier, S. M.; Ruggiero, C. E.; Young, V. G., Jr.; Tolman, W. B. *J. Am. Chem. Soc.* **1998**, *120*, 11408.

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10.1021/ja992017r CCC: $19.00

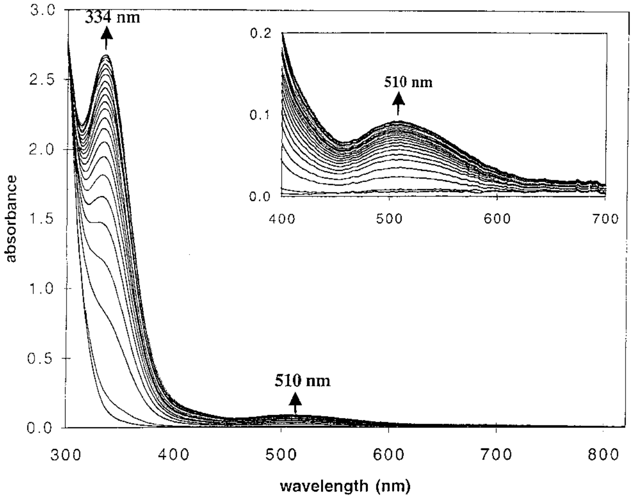

Figure 2. UV–vis monitored dioxygen uptake at 25 °C by a CH_2Cl_2 solution of **1**.

formation of CuCl bonds has also been noted.[11] In contrast, exposure of a CH_2Cl_2 solution of **1** to air results in the rapid formation at 25 °C of a purple color (Figure 2 and S4), that reverses completely (to colorless **2**) upon addition of acetone or ACN.

The reduction with ACN is irreversible, but O_2 can displace the acetone at low temperatures. Thus, O_2 is displaced by a coordinating solvent to form $[Cu^I(Tp^{CF_3,CH_3})(solvent)]$, without any noticeable (by NMR) ligand decomposition or rearrangement.

The purple solution, stable for days when diluted, exhibits oxyHc-like Cu^{II}–peroxo absorptions at 334 and 510 nm. When concentrated, it deposits **3** as a purple solid,[12a] stable indefinitely at 25 °C, whose diffusion reflectance spectrum corresponds to the solution one.

A peroxo-binding mode for O_2 has been established via RR using ^{16}O- and ^{18}O-labeled **3** (Figure 3).[12b]

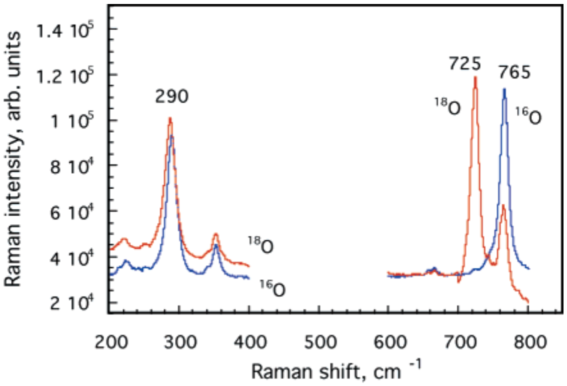

Figure 3. RR spectra of **3** prepared using ^{16}O- and ^{18}O-enriched dioxygen. A residual $^{16}O-^{16}O$ stretch is visible at 765 cm^{-1} in the ^{18}O spectrum. No $^{16}O-^{18}O$ isotope scrambling is detected.

The $^{16}O-^{16}O$ stretch is observed at a low, 765 cm^{-1} frequency and shifts to 725 cm^{-1} upon ^{18}O substitution. Both the 765 cm^{-1} value and its 40 cm^{-1} isotopic shift are indicative of the side-on, μ-η^2:η^2 peroxo binding mode of oxyHc and similar peroxo complexes.[5,6] Unlike them, complexes with end-on peroxo groups[6c,13] exhibit $^{16}O-^{16}O$ stretches above 800 cm^{-1}, while the same stretch for a copper superoxo complex[14] occurs above 1000 cm^{-1}. A strong band at 290 cm^{-1}, which shifts only 2 cm^{-1} upon ^{18}O substitution, is either assigned to a Cu–O core vibration, a mode which primarily involves Cu motion,[5a,g] or is primarily Cu–N (pyrazol) stretching in character.[15] The solid **3** is ESR-silent at room temperature, thus establishing (within the Heisenberg–Dirac–Van Vleck formalism) that the triplet state of the antiferromagnetically coupled copper(II) pair lies at least 600 cm^{-1} above the ground state. While O_2 oxidizes many Cu^I–ACN complexes to Cu^{II} peroxo species, the latter are unstable, even when macrocyclic ligands entropically enhance their room-temperature stability.[6] In contrast, the stability of **2** and its formation from **3** argues for a solvent (ACN)-induced reduction, favored electronically and, perhaps, sterically by fluorine. These observations suggest the following Cu(I) binding order at 25 °C: ACN ≥ acetone > O_2 > CH_2Cl_2. This ranking prompted us to devise a cyclic, reversible O_2 binding procedure: acetone reduces **3** to a Cu^I complex by displacing O_2. Removal of acetone followed by addition of CH_2Cl_2 (to give **1**) and binding of O_2 regenerates **3** (see Scheme S1). This is a self-contained process for reversible O_2 binding, both solvents being recycled.

In conclusion, the use of robust, electron-withdrawing C–F groups allowed us to demonstrate that reversible O_2 binding at a dinuclear copper center at ambient conditions can be achieved outside a protein environment. Other biomimetic or bioinspired metal centers aimed at catalytic oxygen activation (or other harsh chemistry) might be designed following the same principles, similar to chemistry performed in real Teflon (or glass)-coated reactors.

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Note Added in Proof. While this work was reviewed, two relevant articles have been published. A copper–peroxo complex of a dinucleating ligand decays with $t_{1/2}$ of about one day at 25 °C (Kodera, M. et al. *J. Am. Chem. Soc.* **1999**, *121*, 11006). A low-temperature Cu(I)/bis(μ-oxo)Cu(III) equilibrium using a non-dinucleating ligand is postulated to occur via a peroxo intermediate (Suzuki, M. et al. *J. Am. Chem. Soc.* **2000**, *122*, 2124).

Supporting Information Available: Preparation details, crystallographic and NMR data for **1** and **2**, O_2 uptake plots, and reversible binding scheme (PDF). This material is available free of charge at http://pub.acs.org.

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[12] (a) **3** was prepared by passing O_2 through a solution of 90 mgs of **1** in 100 mL CH_2Cl_2 until no more color change occurred. A purple solid was collected upon solvent removal and washing with CH_2Cl_2 (over 90% yield). Anal. Calcd for $C_{30}H_{26}B_2N_{12}F_{18}O_2Cu_2$: C, 33.45; H, 2.43; N, 15.60. Found: C, 33.14; H, 2.53; N, 15.35. (b) Labeled **3** was prepared similarly by using ^{18}O-enriched gas. RR spectra of solid **3** were obtained using Ar^+ laser excitation at 514 nm, and calibrated against DMF. The RR spectra of a sample of **3** kept in a desiccator did not change in over 12 months indicating the retention of the peroxo group. The IR and solid-state UV–vis spectra did not change either, suggesting ligand and overall complex stability, respectively. See figure S5 for the UV–vis spectrum.

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