guest substitution—must occur for either large or small guests. It seems likely that flaps[9] can open in the capsule to permit the exchange of small guests. The exchange of large guests may require the complete dissociation of the superstructure.

In summary, the encapsulation behavior of self-assembled capsule **1** derives from its considerable size and elongated shape. These features guarantee a selectivity for congruent molecules as guests. Even hydrogen-bonded systems—assemblies within assemblies—are temporarily frozen in space and time. The formation and dissipation of the systems ranges from seconds to days, and encapsulated species enjoy an environment insulated from the intrusions of the bulk solution where weakly bound complexes are forced to change of partners frequently. It should be possible to observe reactive intermediates whose lifetimes are on the appropriate timescales within these chambers.

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Is the Bis(*μ*-oxo)dicopper Core Capable of Hydroxylating an Arene?**

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A critical mechanistic issue in C–H bond activations by metal – dioxygen species in catalytic and biological systems concerns the sequence of the O–O and C–H bond-breaking events.[1] In the context of tyrosinase, a metalloenzyme that performs aromatic hydroxylations[2] with O_2 via a spectroscopically characterized (μ-η^2:η^2-peroxo)dicopper(II) intermediate,[3] a key question is whether this intermediate attacks the arene substrate directly (**A**), or whether the O–O bond first breaks to yield a bis(μ-oxo)dicopper unit that then performs the hydroxylation (**B**, Scheme 1). Studies of synthetic systems that model the protein active site often have used dinucleating ligands with *meta*-xylyl spacers that undergo hydroxylation upon oxygenation of their dicopper(I)

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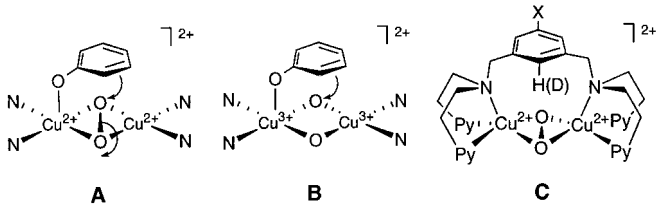
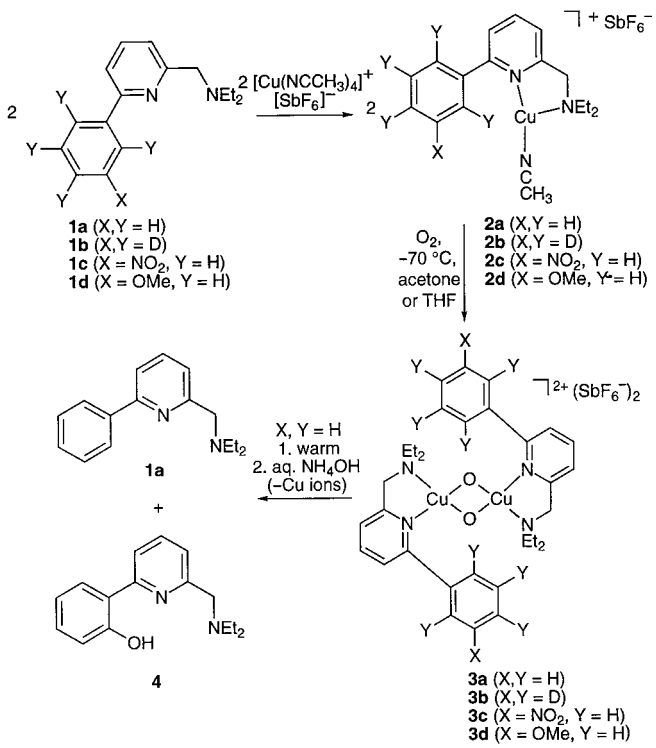


Scheme 1. Proposed intermediates in the hydroxylation of arenes. In **A** and **B** N represents nitrogen-containing ligands. Py = pyridyl.

complexes.[4, 5] In one such system well-studied by Karlin and co-workers, there is good evidence for a (μ-η^2:η^2-peroxo)dicopper(II) intermediate (**C**). Electron-withdrawing groups X on the *meta*-xylyl ring slow its hydroxylation rate, and there is a negligible H/D kinetic isotope effect.[5] Together, these results, as well as others on related systems,[4] imply that the hydroxylation involves attack of an electrophilic peroxide oxygen on the π system of the aromatic ring, which due to its bridging position is predisposed toward this intramolecular reaction.

The discovery that $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ and $[Cu_2(\mu\text{-}O)_2]^{2+}$ units can interconvert through a low-energy pathway in a model system has raised the possibility that the above synthetic and enzymatic arene hydroxylations could proceed through the intermediacy of a bis(μ-oxo)dicopper isomer like **B**.[6, 7] This possibility appears unlikely in the arene-bridged models, however, as indicated by the absence of spectroscopic features due to even small amounts of the *meta*-xylyl-bridged $[Cu_2(\mu\text{-}O)_2]^{2+}$ unit in oxygenated solutions.[4g, 8] Also, the dominant reaction pathway observed to date for bis(μ-oxo)dicopper complexes (heretofore capped solely by tertiary amine ligands that stabilize the formal Cu^{III} oxidation state) is intramolecular monooxygenation/N-dealkylation at aliphatic ligand C–H bonds α to the amine N-donor, even in the presence of arene appendages.[4g, 8, 9] Herein, on the other hand, we report the facile hydroxylation of aryl rings from spectroscopically observable bis(μ-oxo)dicopper complexes supported by bidentate ligands with mixed imine/amine ligation and a pendant phenyl group. In addition to enlarging the class of bis(μ-oxo)dicopper(III) complexes to include those supported by ligands with imine donors,[10] these results suggest that a $[Cu_2(\mu\text{-}O)_2]^{2+}$ unit could attack arene substrates in tyrosinase and model compounds.

Addition of 2-(diethylaminomethyl)-6-phenylpyridine (**1a**) to one equivalent of $[Cu(NCCH_3)_4][SbF_6]$ gave the 1:1 complex **2a** (Scheme 2), which was confirmed to have a three-coordinate T-shaped geometry by X-ray crystallography [Cu–N_{amine} 2.186(3); Cu–N_{imine} 1.974(3); Cu–$N_{nitrile}$ 1.867(4) Å].[11] Analogous copper(I) complexes were synthesized with $[D_5]$phenyl (**2b**), *m*-nitrophenyl (**2c**), and *m*-methoxyphenyl (**2d**) appendages. In acetone or THF at $-70\,^{\circ}C$, oxygenation of **2a**–**c** yielded EPR-silent yellow solutions with an optical feature ($\lambda_{max} = 404 \pm 2$ nm for **3a**–**c**; $\varepsilon = 13\,mM^{-1}cm^{-1}$ for **3c** in THF), which we attribute to a charge-transfer transition for transient bis(μ-oxo)dicopper species **3a**–**c** by analogy to previously reported data (Figure 1, Table 1).[6, 7, 12, 13] The absorption data are not consistent with a (μ-η^2:η^2-peroxo)dicopper complex ($\lambda_{max} = 340$–380 nm, $\varepsilon = 11$–$23\,mM^{-1}cm^{-1}$; $\lambda_{max} = 510$–580 nm, $\varepsilon \approx 1\,mM^{-1}$



Scheme 2. Synthesis and decomposition of complexes **3a**–**d**. Complex **3d** was not observed.

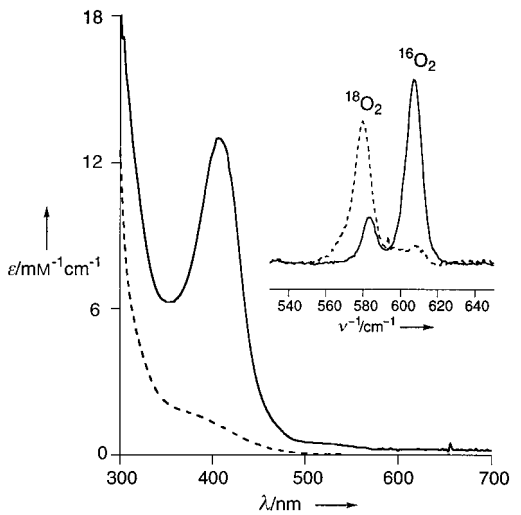


Figure 1. Absorption spectra of copper(I) complex **2c** (dashed line) and of the product of its oxygenation, **3c** (solid line), as acetone solutions at $-70\,^{\circ}C$. Inset: Resonance Raman spectra of **3c** (solid line) and its ^{18}O isotopomer (dashed line), as solutions in acetone at $-85\,^{\circ}C$ (λ_{ex} = 406.7 nm).

cm^{-1}).[14] Likewise, resonance Raman (RR) spectra (λ_{ex} = 406.7 nm, $T = -85\,^{\circ}C$) of solutions of **3c** in acetone (Figure 1, inset) show an intense polarized ($I_{\perp}/I_{\parallel} = 0.35$) feature at 607 cm^{-1} which shifted to 580 cm^{-1} when $^{18}O_2$ was used.[15] Complexes with a bis(μ-oxo)dicopper core have such characteristic vibrations near 600 cm^{-1} ($\Delta(^{18}O) = 19$–$27\,cm^{-1}$) due to the symmetric breathing mode of the tetraatomic Cu_2O_2 unit,[16] while (μ-η^2:η^2-peroxo)dicopper complexes typically

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Table 1. Characterization and decomposition data for bis(μ-oxo)dicopper complexes in acetone.

Complex	λ_{max}[a] [nm]	$\tilde{\nu}(Cu_2O_2)$[b] [cm^{-1}]	k [c] [10^{-4} s^{-1}]	**1,4**[g] [%]	Yield[d] [%]
3a	406	606 (578)	6 ± 2	70, 30	60
3b	406	–[e]	6 ± 2	70, 30	60
3c	404	606 (579)	0.4 ± 0.1	80, 0	< 10
3d	–	–	–	60, 40	80
$[(L_{ME})_2Cu_2O_2]^{2+}$[f]	401	610 (587)	–	–	–

[a] Acetone solution, $-70\,^{\circ}$C for **3**; CH_2Cl_2 solution for $[(L_{ME})_2Cu_2O_2]^{2+}$.[7] [b] Values of the $^{18}O_2$ isotopomer in parentheses, $\lambda_{ex} = 406.7$ nm. [c] Acetone solution, $-70\,^{\circ}$C. [d] Yield of **4** [%] $\times$ 50% (theoretical yield of monooxygenase reaction). [e] Not measured. [f] $L_{ME} = (1R,2R)$-*N*,*N*′-diethyl-*N*,*N*′-dimethyldiaminocyclohexane.[7] [g] Recovered.

show O–O vibrations at 710–760 cm^{-1}.[14] No O–O vibrations were observed in RR spectra ($\lambda_{ex} = 514.5$ nm) of **3c**, showing that the amount of a potential peroxo complex must be small (less than about 10%).

When solutions of **3a–c** were allowed to stand at $-70\,^{\circ}$C or to warm, the absorption near 400 nm in the visible spectum gradually disappeared. Although it has not yet been possible to isolate clean copper(II) decomposition products in quantity, changes in the ligand were examined by removing copper with NH_4OH and examining the organic products by GC/MS and NMR spectroscopy. Treatment of **3a** in this way gave **1a** and **4** in an approximate 2:1 ratio (Scheme 2, Table 1). In a monooxygenation reaction, one ligand per bis(μ-oxo)dicopper complex would undergo hydroxylation; thus, the observed 2:1 product ratio corresponds to about 70% monooxygenase yield. This ratio was the same when **2a** was oxygenated at room temperature, and did not vary between acetone and THF solvents. We conclusively identified **4** on the basis of GC/MS and ^{1}H NMR spectroscopy; moreover, ^{18}O labeling of **3a** and deuterium labeling of the phenyl group confirmed that the oxygen atom in **4** derives from O_2 and is incorporated into the phenyl ring. Analogous organic products were obtained from the oxygenation of **2b** and **2d**, while the oxygenation of **2c** gave no phenol-containing products.

The decay of **3a–c** (monitored by the disappearance of the absorption at ca. 400 nm) was first-order in [**3**] in each case, yielding the first-order rate constants shown in Table 1. The decomposition clearly involves reaction with the aryl group because the aryl substituents significantly influence the decay rate. There is little, if any, kinetic isotope effect on replacing the aryl C–H bonds with C–D bonds, indicating that attack on the C–H bond is not rate-determining. A substantial electronic effect on the rate of decomposition is evident: an electron-withdrawing group causes a decrease in the decay rate constant and an electron-donating substituent makes the decomposition so fast that no intermediate could be observed. These observations are reminiscent of electrophilic aromatic substitution reactions[17] and of the electrophilic hydroxylation observed in **C**.[5] Complicating matters, however, are the negligible yield of hydroxylation from the slow decomposition of **3c** and the high yield from the rapid decay of the presumed intermediate **3d**. These data are consistent with the operation of a competitive pathway for degradation of the bis(μ-oxo)dicopper compounds that does not yield phenolic products and is less dependent on the substituents on the aryl group than the hydroxylation reaction. The nature of this second pathway is currently unclear, but appears not to involve attack on solvent on the basis of identical decomposition rates in acetone and [D_6]acetone (observed with **3a** and **3c**).

We have shown that the formation of bis(μ-oxo)dicopper species is not limited to complexes capped solely by amine donor ligands; thus, the identification of compounds **3** with softer imine donors makes the biological histidine imidazolyl ligand set a plausible scaffold for the $[Cu_2(\mu\text{-}O)_2]^{2+}$ core.[10] Complexes **3** decompose through electrophilic attack on aromatic rings, suggesting that the bis(μ-oxo)dicopper core is capable of hydroxylating an arene directly and making the possibility of stepwise O–O bond breaking followed by C–H bond activation in tyrosinase appear more feasible. Thus, aromatic hydroxylation has now been observed to arise from both isomeric $[L_2Cu_2O_2]^{2+}$ cores: those like **C** in which the O–O bond is intact and those like **3** in which the O–O bond has already been cleaved. In each case, however, the experimental data do not allow one to rule out unambiguously rapid preequilibration of the observed (major) complex with a small amount of the other (unseen) isomer that may be more reactive. As a result, it is possible that either core is solely responsible for the observed reactivity, or that each is capable of direct attack on a properly positioned arene ring. Further experiments are necessary to resolve this dilemma.

Experimental Section

The methods used here were described previously.[16a] Resonance Raman spectra were collected using CCD detectors interfaced with Winspec software; those with $\lambda_{ex} = 457.9$ and 514.5 nm were recorded for frozen samples at 77 K, and samples with $\lambda_{ex} = 406.7$ nm for liquid acetone samples at $-85\,^{\circ}$C. Raman shifts were referenced externally through a quadratic fit to the known spectrum of indene at room temperature.[18] 2-(Chloromethyl)-6-phenylpyridine[19] was isolated as the free base and purified by Kugelrohr distillation (90 °C, 0.05 Torr), and phenyl-substituted analogues were synthesized by analogous procedures.

1a: Powdered KOH (1.0 g, 56 mmol), 2-(chloromethyl)-6-phenylpyridine (0.41 g, 2.0 mmol), and $HNEt_2$ (3 mL) were refluxed under N_2 for 14 h, and then all volatile materials were removed in vacuo. Water (5 mL) and brine (5 mL) were added to the brown residue, and the solution was extracted with diethyl ether (2×20 mL). The organic fractions were dried over Na_2SO_4, dried in vacuo, and purified by Kugelrohr distillation (100 °C, 0.05 Torr), giving **1a** (469 mg, 98%) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$): $\delta = 7.98$ (dd, 2H, $J = 2$, 8 Hz), 7.69 (t, 1H, $J = 8$ Hz), 7.56 (d, 1H, $J = 8$ Hz), 7.44 (m, 3H), 7.38 (tt, 1H, $J = 8$, 1 Hz), 3.82 (s, 2H), 2.62 (q, 4H, $J = 7$ Hz), 1.08 (t, 6H, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 160.6$, 156.3, 139.6, 136.8, 128.6, 128.5, 126.8, 120.9, 118.2, 59.4, 47.3, 12.0; correct C,H,N analysis. Ligands **1b–d** were synthesized and characterized in a similar fashion.

2a: Under N_2 atmosphere, a solution of **1a** (91.1 mg, 0.379 mmol) in anhydrous THF (1 mL) was added to $[Cu(NCMe)_4][SbF_6]$ (175.6 mg, 0.379 mmol), causing a color change to yellow. Anhydrous diethyl ether (10 mL) was used to precipitate the product as a yellow oil, which turned into a pale yellow solid upon exposure to vacuum (198 mg, 90%). ^{1}H NMR ([D_6]acetone): $\delta = 8.15$ (t, 1H, $J = 6$ Hz), 7.92 (ddd, 2H, $J = 1$, 2, 7 Hz), 7.85 (ddd, 1H, $J = 1$, 2, 7 Hz), 7.6 (m, 4H), 4.15 (s, 2H), 2.91 (q, 4H, $J = 7$ Hz), 2.36 (s, 3H), 1.27 (t, 6H, $J = 7$ Hz); ^{13}C NMR ([D_6]acetone): $\delta = 159.9$, 159.5, 141.1, 140.7, 130.7, 129.5, 129.3, 124.4, 123.3, 118.9, 60.8, 50.3, 12.3, 2.2; Correct C,H,N analysis. Complexes **2b–d** were synthesized and characterized in a similar fashion.

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Ligand recovery: In a typical experiment, **2a** (14.4 mg, 24.8 μmol) was dissolved in acetone (2 mL) in a vial under nitrogen, oxygen was bubbled through the solution at room temperature for 0.5 h, and then volatile materials were removed from the brown solution in vacuo. The residue was dissolved in concentrated NH_4OH (2 mL), and the blue mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic fractions were dried over $MgSO_4$ and filtered, and volatile materials were removed in vacuo to leave a yellow oil (5.0 mg). ^{1}H NMR spectroscopy with an internal standard (1,1,2,2-tetrachloroethane) was used to verify the yield as $>90\%$ and to determine the ratio of **1a** and **4** (7:3). GC/MS (30 m $\times$ 0.25 mm HP-5 5% crosslinked PhMe-silicone column, 1 mL min^{-1} He flow, initial solvent delay 2 min at 50 °C, ramp rate 20 °C min^{-1} to 250 °C): $t_R = 11.78$ (*m/z* 239, **1a**), 13.12 min (*m/z* 255, **4**); ^{1}H NMR of **4** ($CDCl_3$): $\delta = 14.7$ (br s, OH, exchangeable with D_2O), 7.02 (dd, $J = 8.1$, 1.3 Hz, *ortho* to OH), 6.90 (ddd, $J = 8.1$, 6.9, 1.3 Hz, *para* to OH), 3.77 (s, CH_2) (other resonances were hidden below those of **1a**). These shifts and coupling constants compare favorably to the known spectrum of 2-(2-hydroxyphenyl)pyridine.[20]

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[10] While this paper was undergoing review, a bis(μ-oxo)dicopper complex supported by bis[2-(2-pyridyl)ethyl](methyl)amine was reported: H. V. Obias, Y. Lin, N. N. Murthy, E. Pidcock, E. I. Solomon, M. Ralle, N. J. Blackburn, Y.-M. Neuhold, A. D. Zuberbühler, K. D. Karlin, *J. Am. Chem. Soc.* **1998**, *120*, 12960 – 12961.

[11] Crystallographic data for **2a** ($C_{18}H_{23}N_3F_6CuSb$, $M_r = 580.68$): monoclinic, space group $P2_1/c$, $a = 14.498(3)$, $b = 8.329(2)$, $c = 19.254(4)$ Å, $\beta = 110.06(3)°$, $V = 2183.9(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.766$ g cm^{-3}, $\mu = 22.7$ cm^{-1}, $2\theta_{max} = 50°$. Data were collected using a Siemens SMART system, with $2\theta_{max} = 50°$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and $T = 173$ K, and were solved by direct methods. Non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were treated as riding atoms in idealized positions. Rotational disorder in the SbF_6 fragment was modeled by using two conformations in an 85:15 ratio. Full-matrix least-squares refinement on F^2 using SHELXTL V5.0 converged with $R1 = 0.0338$, $wR^2 = 0.0742$, and GOF = 1.039 for 3038 independent reflections with $I > 2\sigma(I)$, 278 parameters, and 45 restraints. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-105596. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[12] The extinction coefficient (in THF solution) was determined with **3c**, because its stability was greater than that of **3a.** Intense pyridine-to-metal charge-transfer bands obscured the presumed bis(μ-oxo)dicopper band at about 300 nm.

[13] *Syn* and *anti* isomers of **3** that differ with respect to the relative position of the imine and amine donors of the two ligands are possible, but we favor the *anti* form drawn in Scheme 1 because molecular models suggest that steric clashes between arene rings prohibit adoption of a *syn* geometry. Consistent with this idea, a preliminary crystal structure of a bis(μ-hydroxo)dicopper(II) complex ligated to **2a** has the *anti* conformation (P. L. Holland, W. B. Tolman, unpublished results).

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[15] A smaller resonance Raman peak is present at 584 cm^{-1} ($\Delta(^{18}O) = 14$ cm^{-1}). Preliminary experiments indicate that this band has the same depolarization ratio, excitation profile, and decomposition rate constant as the larger band. Theoretical calculations suggest that this band is a second A_g core vibrational mode (C. J. Cramer, P. L. Holland, W. B. Tolman, unpublished results).

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