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Differential Reactivity between Interconvertible Side-On Peroxo and Bis-μ-oxodicopper Isomers Using Peralkylated Diamine Ligands

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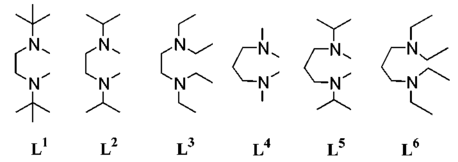
Interest in metal-mediated dioxygen (O_2) bond cleavage and formation has persisted over several decades due to its biological relevance and potential application in industrial redox processes. In biological systems, iron and copper sites play important roles in many O_2-activating enzymes that oxidize substrates.[1] Characterization of the oxidant structure is a first-line approach to understanding the reactivity of such enzymes. In the binuclear copper enzymes tyrosinase and catechol oxidase, the structurally and spectroscopically characterized μ-η^2:η^2-peroxodicopper(II) species is generally accepted to be the active oxidant.[1,2] Recent reports of a facile interconversion between the isoelectronic μ-η^2:η^2-peroxodicopper(II) species (**P**) and the bis-μ-oxodicopper(III) species (**O**) within a model system[3−5] offer an alternative oxidative mechanistic route: O−O bond cleavage preceding substrate hydroxylation, rather than the generally accepted electrophilic peroxide attack on the arene ring.[6,7] Additional findings that **O** is capable of ligand hydroxylation provide chemical plausibility for such hydroxylation reactivity.[8−10] Understanding the **P**:**O** equilibrium systems and determining the relative reactivity of each isomer with externally added substrates will provide keen insights into harnessing the oxidizing potential of these complexes. In this report, several new **P**:**O** equilibrium systems are described. In one particular case, the rate of isomer interconversion is significantly slower than the rate of the reaction with substrates, which allows the reactivity of each isomer, at parity of ligand, to be assessed. In all reactions examined, **P** is the more reactive species.

Ligand structure has proven critical in controlling not only the formation of small-molecule Cu/O_2 complexes but also their subsequent reactivity. Peralkylated diamine ligands (PDLs) provide sufficient Cu(I) ligation for O_2 activation while maintaining potential substrate access to the subsequently formed Cu/O_2 cores.[10,11] Selection of bidentate chelation follows from the structures of μ-η^2:η^2-peroxodicopper(II) complexes; each copper atom is ligated by a weak axial nitrogen ligand and two stronger equatorial nitrogen ligands.[12−14]

Scheme 1



The O_2 reaction of Cu(I)−PDL complexes has been generally thought to exclusively form **O** at low temperature in aprotic solvents using weakly coordinating counteranions.[3,10] Systematic structural variation has now allowed a limited subset of PDLs to be identified whose copper complexes are capable of stabilizing the μ-η^2:η^2-peroxodicopper(II) species. Mixtures of **P** and **O** are created. The existence of both species in solution has been verified using characteristic spectroscopic features in the UV−visible, resonance Raman (rR), and X-ray absorption (XAS) spectra.[15−18] In THF, acetone, and CH_2Cl_2 solutions, a facile equilibrium exists as evidenced by a rapid, reversible interconversion between **P** and **O** signaled by opposing changes in the intensity of characteristic optical bands upon temperature variation.[19]

The position of the **P**:**O** equilibrium is most sensitive to the ligand structure, and to a lesser extent on solvent,[20] counteranions, and temperature.[21] An increase in the equilibrium constant (K_{eq} = [**P**]/[**O**]; 193 K, CH_2Cl_2) coincides with increasing steric bulk of the ligand (Scheme 1).[3] Larger *N*-alkyl substituents, at parity of diamine backbone, bias the equilibrium toward **P**: $K_{\mathrm{eq}}(\mathrm{L}^3) \approx K_{\mathrm{eq}}(\mathrm{L}^2) < K_{\mathrm{eq}}(\mathrm{L}^1)$ for the 1,2-ethanediamine (**ED**) series, and $K_{\mathrm{eq}}(\mathrm{L}^4) < K_{\mathrm{eq}}(\mathrm{L}^5) < K_{\mathrm{eq}}(\mathrm{L}^6)$ for the 1,3-propanediamine (**PD**) series. A comparison of the **ED** and **PD** ligands, at parity of *N*-alkyl substituents, indicates that the **PD** ligands also bias the equilibrium toward **P** ($K_{\mathrm{eq}}(\mathrm{L}^6) > K_{\mathrm{eq}}(\mathrm{L}^3)$) and ($K_{\mathrm{eq}}(\mathrm{L}^5) > K_{\mathrm{eq}}(\mathrm{L}^2)$). These trends intimate interligand steric interactions as the major determinant in the position of the equilibrium; ligands that enhance such interactions bias the equilibrium away from **O** toward **P**. This interpretation assumes that the Cu_2O_2 core of **O** is intrinsically more stable than that of **P**, fully consistent with the simplest Cu(I)−PDL forming only measurable amounts of **O**.

Dramatic alterations in the equilibrium position can be achieved by addition of various weakly coordinating counteranions to mixtures of **P** and **O**. Isosbestic shifts of the equilibrium position is observed optically upon addition of tetra-*n*-butylammonium perchlorate to a mixture of $[(\mathrm{L}^1)_2Cu_2O_2](OTf)_2$ in CH_2Cl_2 [**P** → **O**]

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(18) The absorbance spectrum exhibits intense bands characteristic of both **O** (∼300 nm, ∼400 nm) and **P** (∼360 nm). Resonance Raman experiments identified an $^{18}O_2$ isotope sensitive rR band at ∼600 cm^{-1} ($\Delta\nu = -24$ cm^{-1}; 406.7 nm excitation) characteristic of **O** and an isotope insensitive band at 294 cm^{-1} (363.8 and 406.7 nm excitation) in THF, indicating the presence of **P**. This mixture has further been identified in solution by XAS.

(19) See Supporting Information.

(20) As different solvents generate various **P**:**O** ratios, interconversion between **P** and **O** can be conveniently achieved by 10-fold dilution of the mixture in THF with acetone (**P** to **O**) and vice-versa (**O** to **P**) when the mixture in acetone is diluted 10-fold with THF.

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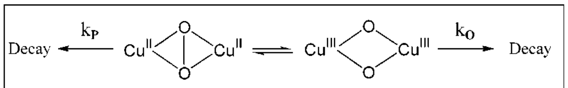
Table 1



k_P	Decay at 233K	k_O
$5(1) \times 10^{-4}$ s^{-1}	**Acetone**	$5(1) \times 10^{-4}$ s^{-1}
$7(2) \times 10^{-4}$ s^{-1}	**2-MeTHF**	$6(2) \times 10^{-5}$ s^{-1}

and upon addition of tetra-*n*-butylammonium triflate to a mixture of $[(L^1)_2Cu_2O_2](SbF_6)_2$ in acetone [**P** ← **O**].[19] Similar shifts have also been confirmed by rR spectroscopy. Variable temperature studies of the optical features associated with several **P**:**O** mixtures at equilibrium consistently show that **O** is enthalpically, but not entropically, favored relative to **P**.[22] It is the combination of the small magnitude and opposing nature of the enthalpic and entropic contributions that allows significant quantities of each isomer to form at low temperatures with specific ligands.[21]

In general, the rates of formation for **P** and **O** are equal, as are their rates of thermal decomposition. Such behavior is consistent with an equilibrium in which isomer interconversion is faster than the rate-determining step (RDS) of both formation and decomposition.[5,24] In contrast, the isomer interconversion rate between **O** and **P** for $[(L^1)_2Cu_2O_2]^{2+}$ in 2-MeTHF is significantly slower.[23] The decay of the optical features associated with **P**, while comparable to rates determined in other solvents, is an order of magnitude faster than the decomposition rate for **O** (Table 1).[19] Deuteration of the methyl substituents of L^1, d_6-L^1, allows the role of methyl C−H bond cleavage in the RDS of the decomposition pathway of each isomer to be assessed. Only the decomposition of **O** is significantly impacted with a kinetic isotope effect of 4.5[8−10,19,25] at 233 K, suggesting independent decomposition pathways for **P** and **O**. However, the observed differential decay indicates that **P** is the more reactive of the two isomers at parity of ligand.[26]

The slow equilibration between **O** and **P** for $[(L^1)_2Cu_2O_2]^{2+}$ in 2-MeTHF also allows the examination of each isomer's reactivity with externally added substrates such as PPh_3 and 2,4-di-*tert*-butylphenol. Addition of PPh_3 at 193 K results in preferential decay of the optical features of **P**, at a rate equaling the formation rate of PPh_3O; ∼50% yields of PPh_3O were found upon workup.[19] This contrasts with the low yield (5%) of PPh_3O obtained using $[(L^2)_2Cu_2O_2]^{2+}$, the most closely related complex, except that only measurable quantities of **O** are formed. One might conclude that **O** is ineffective at oxygen-atom transfer were it not for the result that the complex with the least bulky ligand in this study, $[(L^4)_2Cu_2O_2]^{2+}$, which also only forms measurable amounts of **O**, nearly quantitatively converts PPh_3 to PPh_3O (>95%). A possible explanation for the observed reactivity involves the structures of **P** and **O**. Since **O** is significantly more compact than **P** at parity of ligand (**O**: Cu−Cu, 2.75−2.83 Å; **P**: Cu−Cu, 3.5−3.6 Å), a reaction requiring access to the Cu_2O_2 core would likely proceed at a slower rate with **O**. Combined, these results implicate that accessibility of substrate to the Cu_2O_2 core is as important as the electronic composition of the isomers in determining oxygen-atom transfer reactivity.

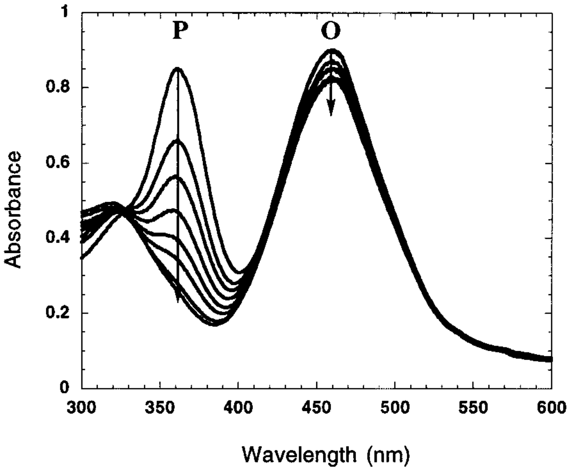


Figure 1. Reaction of $[(L^1)_2Cu_2O_2](OTf)_2$ (0.05 mM Cu, ∼50:50 mixture of **P**:**O**) in 2-MeTHF with 2,4-di-*tert*-butylphenol (20 equiv) at 193 K. Preferential decay of **P** is observed.

2,4-Di-*tert*-butylphenol also reacts preferentially with **P** at 193 K (Figure 1), yet the decay of **P** does not track with the rate of formation of the product 3,3′,5,5′-tetra-*tert*-butyl 2,2′-biphenol. A possible **P** decay pathway is peroxide displacement by the phenol resulting in a phenoxide-bound Cu(II) complex.[27] The oxidative coupling of the phenol closely tracks the decay of **O**,[19] and the yield (40%) closely matches the initial estimate of **O** in the mixture. Thus, at parity of ligands, **P** appears to be a better oxygen-atom transfer reagent[28] while **O** is a better hydrogen-atom acceptor,[29] consistent with theoretical studies.[15]

Various PDLs that generate a mixture of isomeric Cu/O$_2$ binuclear complexes, **P** and **O**, have been identified. While less bulky PDLs preferentially form the bis-*μ*-oxodicopper(III) complex, increasing the steric demands of the N-substituents favors **P**. Isomers **P** and **O** can be interconverted by temperature, solvents and counteranions. In contrast to a previously reported system with rapid equilibrium between **P** and **O**, differential reactivity for **P** and **O** with $[(L^1)_2Cu_2O_2]^{2+}$ in 2-MeTHF can be observed due to slow interconversion. Slow equilibration is observed during thermal decomposition of **P** and **O** as well as during reactions with PPh_3 and phenols. Under all reported conditions **P** reacts faster, a result that may have potential mechanistic relevance for enzymes such as tyrosinase and catechol oxidase and for the design of organic oxidants.

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Supporting Information Available: Synthetic details, optical spectrum of $[(L^1)_2Cu_2O_2](OTf)_2$, experimental details for kinetic, ligand product analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) $\Delta H° = \sim 0.6$ kcal/mol; $\Delta S° = \sim 2$ cal/mol in CH_2Cl_2 for $[(L^1)_2Cu_2O_2](OTf)_2$. The enthalpic difference is similar for the TACN based **P**:**O** equilibrium (ref 21).

(23) The slow interconversion rate is independent of the anion used ($CF_3SO_3^-$, ClO_4^-).

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(25) The KIE was calculated from rate constants based on a **P** → C; **O** → C model. k_O (Table 1) is the largest contributor to the KIE (∼4.5).

(26) Mono-demethylated ligand is the only significant ligand decay product of this reaction, but the yields of this oxidized ligand account for only ∼10% of the required reducing equivalents to give Cu(II) products. The exact chemical nature of the decay process thus remains unclear.

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(29) **O** likely reacts by abstracting a hydrogen atom from the phenol.