

## Intramolecular Arene Hydroxylation versus Intermolecular Olefin Epoxidation by $(\mu\text{-}\eta^2\text{:}\eta^2\text{-Peroxo})\text{dicopper(II)}$ Complex Supported by Dinucleating Ligand

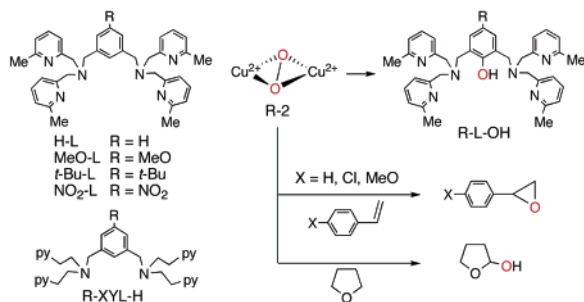
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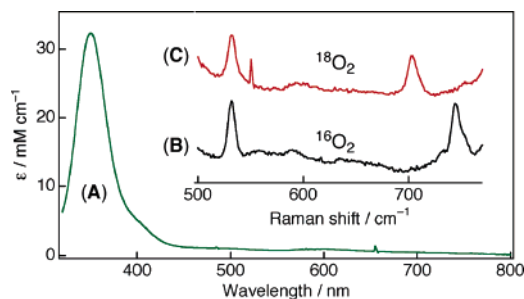
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Copper-mediated oxidation of organic substances have been attracting much attention due to their biological significance and industrial applicability.<sup>1</sup> Thus far, intramolecular aromatic and aliphatic ligand hydroxylation as well as intermolecular phenolate oxygenation, H-atom abstraction (including dehydrogenation), and sulfoxidation by the distinct copper-active oxygen species have been explored in detail.<sup>1</sup> Among those reactions, the  $\text{Cu}_2/\text{O}_2$ -mediated arene hydroxylation has been studied extensively in connection with the catalytic mechanism of tyrosinase, a unique example of dicopper monooxygenase.<sup>1–9</sup> The detailed mechanistic studies have indicated that both the aromatic ligand hydroxylation and the phenolate oxygenation reactions by the  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu(II)}_2$  species proceed via an electrophilic aromatic substitution mechanism,<sup>1–3,7,8</sup> similar to the enzymatic mechanism of phenolase activity of tyrosinase.<sup>10</sup> Recently, contribution of bis( $\mu\text{-oxo})\text{Cu(III)}_2$  species to the aromatic ligand hydroxylation and the phenolate oxygenation reactions has also been demonstrated to expand the scope of  $\text{Cu}_2/\text{O}_2$  chemistry, peroxo vs oxo, as in the case of heme chemistry.<sup>5,6</sup>

In this study, we have found novel reactivities of a discrete  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu(II)}_2$  complex,  $[\text{Cu}_2(\text{O}_2)(\text{H-L})]^{2+}$  (**H-2**), which is capable of performing not only intramolecular hydroxylation of the *m*-xylyl linker of the dinucleating ligand H-L but also intermolecular epoxidation of styrene and hydroxylation of THF. The results provide further insights into the reactivity of  $\text{Cu}_2/\text{O}_2$  complexes.



Reaction of  $[\text{Cu}_2(\text{H-L})]^{2+}$  (**H-1**)<sup>11</sup> with  $\text{O}_2$  in acetone at  $-80^\circ\text{C}$  gave a dark-green  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu(II)}_2$  species  $[\text{Cu}_2(\text{O}_2)(\text{H-L})]^{2+}$  (**H-2**), which was characterized by electronic and resonance Raman (rR) spectroscopies. The electronic spectrum showed an intense  $\pi_\sigma^*$  ( $\text{O}_2^{2-}$ )-to-Cu(II) LMCT band at 351 nm ( $\epsilon = 32000 \text{ M}^{-1} \text{ cm}^{-1}$ ), characteristic of those of the  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu(II)}_2$  complexes (Figure 1).<sup>1b</sup> The rR spectrum of an acetone solution of **H-2** ( $\sim 5$



**Figure 1.** Electronic spectrum of **H-2** (A) in acetone at  $-80^\circ\text{C}$ . (Inset) Resonance Raman spectra of **H-2** ( $\sim 5 \text{ mM}$ ) prepared from (B)  $^{16}\text{O}_2$  and (C)  $^{18}\text{O}_2$  in acetone at  $-90^\circ\text{C}$  (406.7 nm laser excitation).

mM) measured with a 406.7 nm laser excitation showed an isotope-sensitive band at  $744 \text{ cm}^{-1}$  ( $^{16-18}\Delta = 40$ ) typical of the  $\nu(\text{O-O})$  of the  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu(II)}_2$  species, and no symmetric stretch of the bis( $\mu\text{-oxo})\text{Cu(III)}_2$  core was observed as in the case of  $[\text{Cu}_2(\text{NO}_2\text{-XYL-H})(\text{O}_2)]^{2+}$ .<sup>3</sup> In addition, no intermolecular  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})$  species such as a dimer of dimer was detected at the concentrations below  $\sim 10 \text{ mM}$ .<sup>12</sup> Copper(I) complexes having various *p*-substituted *m*-xylyl groups,  $[\text{Cu}_2(\text{R-L})]^{2+}$  (**R-1: MeO-1, *t*-Bu-1, and NO<sub>2</sub>-1**) also gave the  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu(II)}_2$  species  $[\text{Cu}_2(\text{O}_2)(\text{R-L})]^{2+}$  (**R-2: MeO-2, *t*-Bu-2, and NO<sub>2</sub>-2**) which were also characterized by UV-vis and rR (Figures S2, S3, and S4).

Decomposition of **R-2** under the conditions ( $[\text{R-2}] = \sim 0.2 \text{ mM}$ ) in acetone at  $-60^\circ\text{C}$  gave the hydroxylated ligands, H-L-O<sup>-</sup>, *t*-Bu-L-O<sup>-</sup>, MeO-L-O<sup>-</sup>, and NO<sub>2</sub>-L-O<sup>-</sup> in fairly good yields (>98%, 90%, 75%, and 72%), where incorporation of the O-atom from  $\text{O}_2$  was confirmed by an isotope-labeling experiment using  $^{18}\text{O}_2$ . The crystal structure of the product  $[\text{Cu}_2(\text{H-L-O})(\text{OH})]^{2+}$  confirmed the aromatic ligand hydroxylation (Figure S5A). Decomposition of the **R-2** in acetone obeyed first-order kinetics ( $\nu = k_1[\text{R-2}]$ ).<sup>13</sup> The decay rates are significantly slower than those of  $[\text{Cu}_2(\text{O}_2)(\text{R-XYL-H})]^{2+}$  and  $[\text{Cu}_2(\text{O}_2)(m\text{-XYL}^{\text{Pr}4})]^{2+}$  (Table 1).<sup>2c,4</sup> The low reactivity is attributable to unfavorable enthalpy effect, although entropy effect is favorable. However, the origin of such high thermal stability of **R-2** is not known at present. As found for  $[\text{Cu}_2(\text{O}_2)(\text{R-XYL-H})]^{2+}$ , the hydroxylation rate increases as the electron-donating nature of the substituent R increases, and a Hammett plot gave  $\rho = -1.9$  at  $-50^\circ\text{C}$  (Figure S7B), which is almost the same as those of the arene hydroxylation by  $[\text{Cu}_2(\text{O}_2)(\text{R-XYL-H})]^{2+}$  ( $\rho = -2.1$  at  $-80^\circ\text{C}$ ),<sup>2c</sup>  $[\text{Cu}_2(\text{O}_2)(\text{Lpy}^{2\text{Bz}})_2]^{2+}$  ( $\rho = -1.8$ ),<sup>10</sup>  $[\text{Cu}_2(\text{O}_2)(\text{MeL66})]^{2+}$  ( $\rho = -1.84$  at  $-55^\circ\text{C}$ ),<sup>8</sup> and  $[\text{Cu}_2(p\text{-R-PhO})(\text{O}_2)(\text{DBED})_2]^{2+}$  ( $\rho = -2.2$  at  $-120^\circ\text{C}$ ).<sup>6</sup> These values are also similar to that found for tyrosinase ( $-2.4$  at  $25^\circ\text{C}$ ).<sup>10</sup> Thus, the aromatic hydroxylation in the present ligand system also proceeds via an electrophilic aromatic

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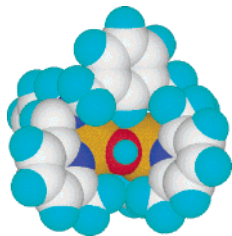
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**Table 1.** Kinetic Parameters for Arene Hydroxylation by  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu}(\text{II})_2$ 

ligand	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$	$k_1/\text{s}^{-1\text{a}}$	ref
<b>NO<sub>2</sub>-2</b>	65 ± 1	−26 ± 3	1.43 × 10 <sup>−4</sup>	this work
<b>H-2</b>	63 ± 1	−11 ± 3	2.12 × 10 <sup>−3</sup>	this work
<b><i>t</i>-Bu-2</b>	62 ± 1	1 ± 4	1.79 × 10 <sup>−2</sup>	this work
<b>MeO-2</b>	59 ± 1	8 ± 4	1.35 × 10 <sup>−1</sup>	this work
H-XYL-H	50 ± 1	−35 ± 2	1.49 × 10 <sup>−1</sup>	2c
<i>m</i> -XYL <sup>Pr4</sup>	50.1 ± 0.2	−50.4 ± 0.9	1.99 × 10 <sup>−2</sup>	4
MeL66	29.1 ± 3.0	−115 ± 15		8

<sup>a</sup> At −50 °C. The  $k_1$  values for **NO<sub>2</sub>-2** and **MeO-2** are estimated by extrapolation using the kinetic parameters ( $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ).



**Figure 2.** Space-filling model of  $[\text{Cu}_2(\text{OH})_2(\text{H-L})]^{2+}$  generated by Chem3D. Hydrogen atoms were placed at the calculated positions (C-H = 1.10 Å). Yellow: copper, red: oxygen, dark blue: nitrogen, gray: carbon, and light blue: hydrogen.

substitution mechanism, which is consistent with the lack of a kinetic isotope effect by deuterium-substitution at the hydroxylated position ( $k_1(\text{H}) = 2.12 \times 10^{-3} \text{ s}^{-1}$  and  $k_1(\text{D}) = 2.24 \times 10^{-3} \text{ s}^{-1}$  at −50 °C).

Although the structural information of **H-2** is not available, a closely related bis( $\mu\text{-OH}$ )Cu(II)<sub>2</sub> complex,  $[\text{Cu}_2(\text{OH})_2(\text{H-L})]^{2+}$  (Figure 2), provides important structural information for the reaction with exogenous substrates such as styrene and THF. Inspection of the crystal structure suggests that there is enough space around the side-on peroxide to allow the substrate to approach the peroxide moiety. In fact, the reaction of **H-2** (2.9 mM) and styrene (2.9 M) in acetone at −70 °C gave ~90% of styrene oxide, in which incorporation of O-atom from dioxygen was confirmed by using <sup>18</sup>O<sub>2</sub>. Kinetic study in acetone yielded the rate equation  $v = (k_1 + k_2[\text{styrene}])[\text{H-2}]$  ( $k_{\text{obs}} = (k_1 + k_2[\text{styrene}])$ ), where  $k_1$  and  $k_2$  are the rate constants for the ligand hydroxylation of **H-2** and epoxidation of styrene, respectively. Plot of  $k_{\text{obs}}$  vs concentrations of styrene gave a linear line with an intercept corresponding to  $k_1$  ( $4.64 \times 10^{-4} \text{ s}^{-1}$ ) and yielded  $k_2$  ( $4.50 \times 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ ) at −60 °C (Figure S8B), the former of which is in agreement with that obtained for the decay of **H-2** ( $4.10 \times 10^{-4} \text{ s}^{-1}$ , see Table S1).<sup>14</sup> It is noteworthy that the epoxidation rate constant  $k_2$  increases as the electron-donating power of the *p*-substituent of styrene ( $X = \text{MeO}$ , H, and Cl) increases. A Hammett plot gave  $\rho = -1.9$  at −60 °C, which is almost the same as that for the aromatic ligand hydroxylation. Thus, both reactions seem to involve a rate-limiting electrophilic attack of the peroxo ligand to the sp<sup>2</sup> carbon of the substrate. Such  $\rho$  values have also been reported for the epoxidation of *p*-X-styrenes mediated by the high-valent M=O(porphyrin) (M = Mn and Fe) (−2.1 to −0.93).<sup>15</sup>

In addition, it is noteworthy that **H-2** also oxidizes THF to 2-hydroxytetrahydrofuran (yield = ~62%). In the case of *d*<sub>8</sub>-THF, a large kinetic isotope effect (KIE = 50 at −80 °C) was observed, which is significantly larger than that reported for the  $[\{\text{Cu}(\text{MePY2})\}_2(\text{O}_2)]^{2+}$  system (KIE = 3.2).<sup>16</sup> Such a large KIE value clearly indicates that the hydroxylation of THF by **H-2** involves a rate-limiting H-atom abstraction process from the substrate.

In summary, the  $\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxide}$  of **H-2** is capable of performing not only hydroxylation of the *m*-xylyl linker of the ligand but also the epoxidation of styrenes via an electrophilic addition of the peroxide to the C=C bond and hydroxylation of THF by H-atom abstraction. To the best of our knowledge, this is the first example of the epoxidation of styrene and hydroxylation of THF mediated by a discrete  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu}(\text{II})_2$  species. Although no detectable bis( $\mu\text{-oxo}$ )dicopper(III) exists in the present reaction system, a small amount of bis( $\mu\text{-oxo}$ )dicopper(III) species present in a rapid preequilibrium may not be excluded as a reactive intermediate.

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**Supporting Information Available:** Synthesis, characterization, kinetics, ligand recovery experiment, and intermolecular oxidation reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (11) Synthesis and characterization of the complexes are given in Supporting Information.
- (12) Resonance Raman spectrum of **H-2** (~30 mM) measured in acetone at −90 °C with a 514.5 nm laser excitation showed two bands at 714 and 743 cm<sup>−1</sup> as shown in Figure S2. The former can be assigned as the  $\nu(\text{O-O})$  of an intermolecular  $(\mu\text{-}\eta^2\text{:}\eta^2\text{-peroxo})\text{Cu}(\text{II})_2$  species, since this band disappeared under the concentrations below ~10 mM.
- (13) For **H-2**, deviation of Eyring plot was observed below at −70 °C, which seems to be due to photochemical decomposition as found for  $[\text{Cu}_2(\text{H-XYL-H})(\text{O}_2)]^{2+}$ .
- (14) The yield of styrene oxide (~90%) at −70 °C is in good agreement with that estimated from the kinetic study; the  $k_1$  and  $k_2[\text{styrene}]$  values under the conditions ([styrene] = 2.91 M, at −70 °C) are  $6.90 \times 10^{-5} \text{ s}^{-1}$  and  $4.62 \times 10^{-4} \text{ s}^{-1}$ , respectively, where  $k_1$  is estimated by extrapolation using the kinetic parameters ( $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ) for the decay of **H-2**, since  $k_1$  was not directly measured as mentioned above ref 13. These values gave 87% yield of epoxidation.
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