

## Copper Mediated Hydroxylation of a Modified Monooxygenase Model System

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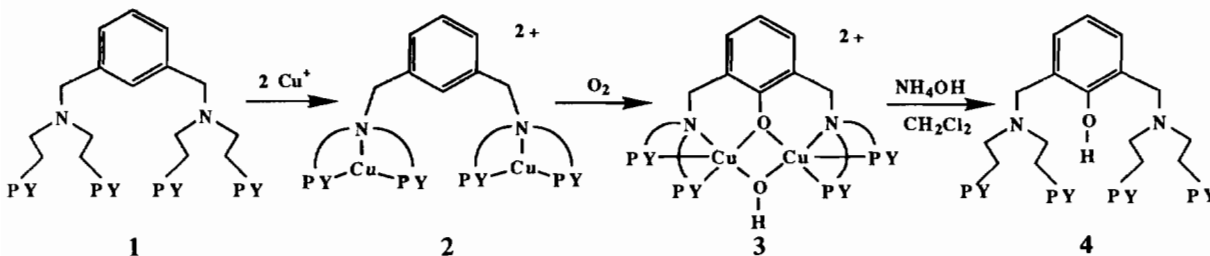
(Received March 23, 1988)

In this report, we describe a copper-ion mediated hydroxylation of an arene, in which a dinucleating ligand copper complex [1] has been modified in an attempt to not only mimic the cresolase reactivity observed in the monooxygenase copper protein tyrosinase (Tyr) [2–4] (*i.e.* hydroxylation, monophenol → *o*-diphenol), but to also duplicate the catecholase reaction (*o*-diphenol → *o*-quinone).

The chemical system previously investigated [1] involved the dinucleating ligand, *m*-XYL (1), in which two tridentate PY2 units (PY2 = bis[2-(2-pyridyl)ethyl]amine) are connected by a *m*-xylyl group. The three-coordinate dinuclear copper(I) complex, 2, reacts with dioxygen, resulting in the oxygenation of the ligand and concomitant formation of the phenoxo- and hydroxo-bridged dinuclear Cu(II) complex, 3. The hydroxylation reaction, 2 + O<sub>2</sub> → 3, is analogous to the reactions mediated by the copper monooxygenases such as Tyr and dopamine β-hydroxylase [3, 5]\*\* since labeling studies on the enzymes and this model system show that one atom of O<sub>2</sub> is incorporated into the organic substrate and the stoichiometry of the reaction is Cu:O<sub>2</sub> = 2:1. More recent studies have provided a number of mechanistic insights and it seems clear that the reaction of 2 with O<sub>2</sub> generates a copper–dioxygen intermediate (peroxo dicopper(II), Cu<sub>2</sub>–O<sub>2</sub>), which is capable of electrophilic attack of the suitably positioned arene substrate, with the resulting formation of 3 [7, 8].

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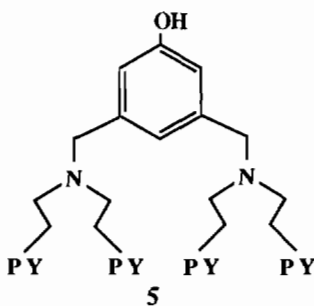
\*\*Recently, a pterin and copper ion dependent phenylalanine hydroxylase from *Chromobacterium violaceum* has been described [6].



PY = 2-pyridyl

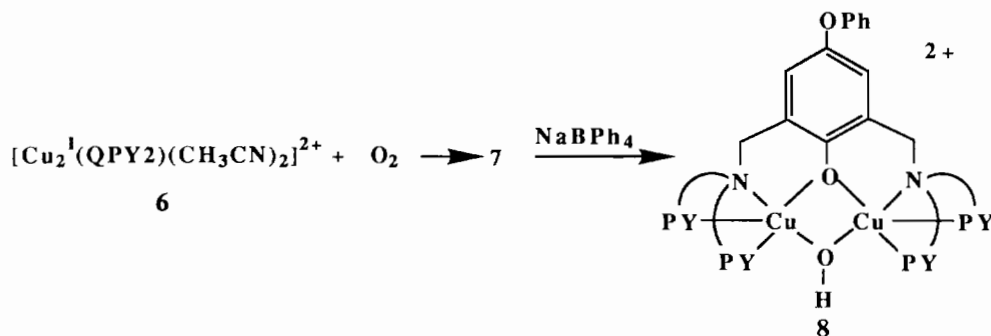
As part of ongoing investigations of copper(I)–dioxygen reactivity [9, 10], including reactions using modified *m*-XYL ligands, we synthesized a 5-hydroxy substituted ligand 5 (QPY2). The expectation was that a reaction analogous to that of 2 + O<sub>2</sub> → 3 would provide the 2,5-dihydroxo dicopper(II) product (or a phenoxo coordinated form of it) and that in a reaction similar to that occurring in Tyr, this would collapse by an intramolecular redox process to a *p*-quinone dicopper(I) species.

The ligand 5 (QPY2) was synthesized by acetylation of 3,5-dimethylphenol and bromination (NBS) of the methyl groups, followed by reaction with PY2 and deprotection [11]. A dicopper(I) complex with QPY2, [Cu<sub>2</sub>(QPY2)(CH<sub>3</sub>CN)<sub>2</sub>](PF<sub>6</sub>)<sub>2</sub> (6), was synthesized by reaction of [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> with the ligand 5 under Ar in acetonitrile followed by precipitation using diethyl ether†. When 6 is reacted with O<sub>2</sub> in dichloromethane an intensely purple powder (7) precipitates whose analyses consistently provide that it can be formulated as [Cu<sub>2</sub>(QPY2 – H + O)Cl<sub>2</sub>](PF<sub>6</sub>)<sub>2</sub>‡. Thus, the reaction appears to be complex, since 7 apparently contains chlorine and its general insolubility suggests that it is polymeric. However, we were able to obtain a crystalline derivative via a metathesis reaction of 7 with excess NaBPh<sub>4</sub>



†Anal. for [Cu<sub>2</sub>(QPY2)(CH<sub>3</sub>CN)<sub>2</sub>](PF<sub>6</sub>)<sub>2</sub> (6). Calc. for C<sub>40</sub>H<sub>46</sub>Cu<sub>2</sub>F<sub>12</sub>N<sub>8</sub>O<sub>2</sub>P<sub>2</sub>: C, 44.77; H, 4.33; N, 10.45. Found: C, 44.99; H, 4.35; N, 10.64%. IR (Nujol): 3540 (OH), 2320 (CN), 2280 (CN) cm<sup>-1</sup>.

‡Anal. for [Cu<sub>2</sub>(QPY2 – H + O)Cl<sub>2</sub>](PF<sub>6</sub>)<sub>2</sub> (7). Calc. for C<sub>36</sub>H<sub>38</sub>Cl<sub>2</sub>Cu<sub>2</sub>F<sub>12</sub>N<sub>6</sub>O<sub>2</sub>P<sub>2</sub>: C, 40.22; H, 3.57; N, 7.82. Found: C, 40.22; H, 3.67; N, 7.58%. UV–Vis, λ<sub>max</sub> = 350 (sh), 502, and 680 nm.



dissolved in dimethylformamide, giving  $[\text{Cu}_2(\text{QP}Y2 - \text{H} + \text{O} + \text{Ph})(\text{OH})]^{2+}$  (8). This was recrystallized from acetone/diethyl ether to provide X-ray quality crystals of an acetone solvate<sup>‡</sup> and the structure analysis shows that the ligand 5 has, in fact, been hydroxylated while the 5-hydroxy group has also been arylated.

Complex  $8 \cdot (\text{BPh}_4)_2 \cdot \text{acetone}$  crystallizes in the triclinic space group  $P\bar{1}$  with  $a = 13.089$  (4),  $b = 15.146$  (3),  $c = 21.971$  (5) Å,  $\alpha = 101.13$  (2)°,  $\beta = 96.46$  (2)°,  $\gamma = 103.35$  (2)°,  $V = 4101.3$  (1.6) Å<sup>3</sup>, and  $Z = 2$ . A total of 5105 unique reflections have been refined to a  $R$  value of 0.0732 (Mo  $K\alpha$ ,  $\lambda = 0.71073$  Å). The structure of the dicationic dicopper(II) complex is shown in Fig. 1, and selected bond lengths and distances are given in the caption. It consists of a phenoxo and hydroxo-bridged dicopper(II) unit having a structure very close to that observed for 3. Each Cu(II) ion is found to be in a square-based pyramidal coordination environment with equatorial ligation from the amine nitrogen atoms (N1 or N4), one pyridine donor (N2 or N5) as well as the bridging phenoxo (O1) and hydroxo (O2) atoms. Longer axial pyridine (N3 or N6) coordination is also observed and there is a non-crystallographic pseudo two-fold axis which passes through O2, O1, C7 and C4 which relates the two Cu(II) ions. The  $\text{Cu} \cdots \text{Cu}$  separation is 3.108 Å. There is a 5-OPh group on the *m*-xylyl ligand, indicating that the hydroxo oxygen atom O3, derived from the ligand 5 precursor, has been arylated.

While the intense purple color of intermediate complex 7 suggests that it may possess a quinoid moiety, we have as yet been unable to prove this unambiguously, since the organic compound obtained by stripping the copper from 7 is thermally unstable [11]. Manometric dioxygen uptake experiments carried out on 6 indicate that  $\text{Cu}:\text{O}_2 = 4:1$  [11], a stoichiometry which is inconsistent with our initial supposition that the design of the 5-OH substi-

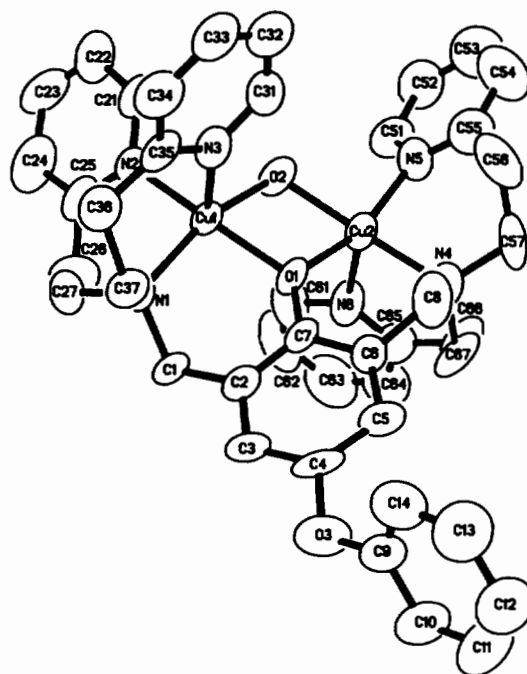


Fig. 1. ORTEP diagram of the dicationic portion of complex 8, showing the atom labeling scheme. Selected bond lengths (Å) and angles (°) are as follows:  $\text{Cu} \cdots \text{Cu}$  3.108;  $\text{Cu1}-\text{O1}$ , 1.984 (6);  $\text{Cu1}-\text{O2}$ , 1.960 (7);  $\text{Cu2}-\text{O1}$ , 1.953 (7);  $\text{Cu2}-\text{O2}$ , 1.958 (6);  $\text{Cu1}-\text{N1}$ , 2.061 (8);  $\text{Cu1}-\text{N2}$ , 2.007 (9);  $\text{Cu1}-\text{N3}$ , 2.225 (9);  $\text{Cu2}-\text{N4}$ , 2.047 (8);  $\text{Cu2}-\text{N5}$ , 1.987 (10);  $\text{Cu2}-\text{N6}$ , 2.219 (10);  $\text{O1}-\text{Cu1}-\text{O2}$ , 75.0 (3);  $\text{O1}-\text{Cu1}-\text{N1}$ , 93.6 (3);  $\text{O1}-\text{Cu1}-\text{N2}$ , 160.0 (3);  $\text{O1}-\text{Cu1}-\text{N3}$ , 99.1 (3);  $\text{O2}-\text{Cu1}-\text{N1}$ , 160.4 (3);  $\text{O2}-\text{Cu1}-\text{N2}$ , 91.0 (3);  $\text{O2}-\text{Cu1}-\text{N3}$ , 102.0 (3);  $\text{N1}-\text{Cu1}-\text{N2}$ , 95.5 (4);  $\text{N1}-\text{Cu1}-\text{N3}$ , 95.5 (4);  $\text{N2}-\text{Cu1}-\text{N3}$ , 97.7 (3);  $\text{O1}-\text{Cu2}-\text{O2}$ , 75.7 (3);  $\text{O1}-\text{Cu2}-\text{N4}$ , 93.5 (3);  $\text{O1}-\text{Cu2}-\text{N5}$ , 160.8 (3);  $\text{O1}-\text{Cu2}-\text{N6}$ , 96.4 (3);  $\text{O2}-\text{Cu2}-\text{N4}$ , 162.5 (3);  $\text{O2}-\text{Cu2}-\text{N5}$ , 90.8 (4);  $\text{O2}-\text{Cu2}-\text{N6}$ , 100.5 (3);  $\text{N4}-\text{Cu2}-\text{N5}$ , 96.1 (4);  $\text{N4}-\text{Cu2}-\text{N6}$ , 94.2 (4);  $\text{N5}-\text{Cu2}-\text{N6}$ , 99.5 (4);  $\text{Cu1}-\text{O1}-\text{Cu2}$ , 104.3 (3);  $\text{Cu1}-\text{O2}-\text{Cu2}$ , 105.0 (3).

tuted *m*-xylyl ligand would provide a copper mediated hydroxylation process (*i.e.*  $\text{Cu}:\text{O}_2 = 2:1$  [1]) followed by an internal redox reaction to give dicopper(I) plus quinone. The participation of dichloromethane in the reaction is also apparent. We suggest that arylation of 7 occurs in the reaction with  $\text{NaBPh}_4$ .

<sup>‡</sup>*Anal.* for  $8 \cdot (\text{BPh}_4)_2$  as an acetone solvate. Calc. for  $\text{C}_{93}\text{H}_{90}\text{B}_2\text{Cu}_2\text{N}_6\text{O}_4$ : C, 74.27; H, 5.99; N, 5.59. Found: C, 73.44; H, 5.95; N, 5.78%. UV-Vis,  $\lambda_{\text{max}} = 380, 470$ , and 635 nm. IR (Nujol): 3550 (OH), 1705 (acetone)  $\text{cm}^{-1}$ .

We have presently found that the reaction of  $\text{CH}_2\text{Cl}_2$  solutions of **6** with  $\text{O}_2$  to directly produce precipitate **7** can be useful in the quantitative analysis of dioxygen [10] since the product is an easily weighable solid formed in a reaction with a known  $\text{Cu}:\text{O}_2$  stoichiometry (*vide supra*). We are continuing studies aimed at the elucidation of the structure of the interesting organic moiety in complex **7**.

#### Acknowledgement

We thank the National Institutes of Health for their support of this research.

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