Hydroxylation of an Aliphatic C−H Bond in an Imidazole-Ligated (μ-η^2:η^2-Peroxo)dicopper(II) Complex

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Dopamine β-monooxygenase (DβM) plays a vital role in the biosynthesis of norepinephrine by catalyzing the hydroxylation of a carbon−hydrogen bond at the benzylic position of dopamine. The observation of ^{18}O kinetic isotope effects in the DβM reaction has led to the proposal that an active-site tyrosine residue promotes cleavage of a copper hydroperoxide O−O bond prior to substrate activation, producing a reactive Cu(II)−O$^{\bullet}$ moiety, a tyrosinyl radical, and water.[1] Removal of H$^{\bullet}$ from dopamine is performed by the copper−oxo-radical complex, but the tyrosine oxygen atom is the ultimate acceptor of the hydrogen atom. Synthetic Cu_n/O_2 complexes which place two oxygen-centered radicals in proximity may therefore mimic the reactivity of DβM.

Copper(I) complexes that catalyze oxygen-atom insertion into an aliphatic C−H bond upon treatment with dioxygen have been prepared, but the identity of the oxidizing species in some of these systems is uncertain.[2] To our knowledge, there are only two groups that have reported aliphatic C−H bond activation by *well-defined* peroxocopper(II) complexes. Kitajima and coworkers established the oxidizing capability of $[Cu(Tp^{Me_2})]_2O_2$ toward a series of substrates,[3] and Tolman et al found that abstraction of hydrogen atoms from alkyl groups in complexes of the type $[LCu(O_2^{2-})CuL]^{2+}$ (L = 1,4,7-trialkyl-1,4,7-triazacyclononane) can occur, producing bis(hydroxo)-bridged dicopper(II) complexes and oxidized ligands.[4]

An earlier paper from our laboratory established that a bridging, side-on peroxide adduct $\{Cu[P(im^{iPr_2})_3]\}_2O_2^{2+}$ is generated by low-temperature oxygenation of a [tris(imidazolyl)phosphine]copper(I) complex.[5] This (μ-η^2:η^2-peroxo)dicopper(II) complex does not oxidize exogenous substrates, but we report here that intramolecular hydroxylation does occur at a formally benzylic position of the tris(imidazolyl)phosphine ligand.

Experimental Section[6]

{Tris[2-(1,4-diisopropylimidazolyl)]phosphine}(acetonitrile)copper(I) Trifluoromethanesulfonate, {Cu[P(im^{iPr_2})$_3$]CH$_3$CN}CF$_3$SO$_3$ (1). A solution of tris[2-(1,4-diisopropylimidazolyl)]phosphine (1.5 g, 3.1 mmol) in dichloromethane (8 mL) was treated with $[Cu(CH_3CN)_4]CF_3SO_3$ (1.1 g, 3.0 mmol), and the resulting light yellow solution was stirred for 30 min. Diethyl ether was added until the white solid product precipitated. The complex was collected by filtration, washed with ether, and dried under vacuum to afford 1.9 g (86%) of **1**. ^1H NMR ($CDCl_3$): δ 1.28 (18H, d, J = 7.0 Hz, 4-CH(CH_3)$_3$), 1.48 (18H, d, J = 6.6 Hz, 1-CH(CH_3)$_3$), 2.36 (3H, s, CH_3CN), 2.95 (3H, sept, J = 7.0 Hz, 4-CH(CH$_3$)$_3$), 4.95−5.20 (3H, m, 1-CH(CH$_3$)$_3$), 6.79 (3H, d, J = 4.1 Hz, imidazolyl C$_5H$). ^{31}P NMR (CD_2Cl_2, −78 °C): δ −118.0. Anal. Calcd for $C_{30}H_{48}N_7CuF_3O_3PS$: C, 48.80; H, 6.55; N, 13.28. Found: C, 49.11; H, 6.61; N, 13.01.

{2-[1-Isopropyl-4-(1-hydroxy-1-methylethyl)imidazolyl]bis[2-(1,4-diisopropylimidazolyl)]phosphine}hydroxocopper(II) Tetrafluoroborate, {Cu[P(im^{iPr_2})$_2$(im^{iPr,iPrOH})]OH}BF$_4$·1.625 CH$_2$Cl$_2$ (2a). Several crystals of this complex were obtained after tetrahydrofuran (THF) was carefully layered onto a concentrated methylene chloride solution of $\{Cu[P(im^{iPr_2})_3]_2\}(OH)_2\{BF_4\}_2$[5], and the mixture was allowed to stand for over 1 month. A crystal structure determination was carried out on a single crystal; details are given in the Supporting Information. Subsequent studies were carried out on the triflate salt, prepared according to the procedure below.

{2-[1-Isopropyl-4-(1-hydroxy-1-methylethyl)imidazolyl]bis[2-(1,4-diisopropylimidazolyl)]phosphine}(hydroxo)copper(II) Trifluoromethanesulfonate, {Cu[P(im^{iPr_2})$_2$(im^{iPr,iPrOH})]OH}CF$_3$SO$_3$·0.5 CH$_2$Cl$_2$ (2b). A solution of 200 mg (0.27 mmol) of **1** in 600 mL of dry CH_2Cl_2 was cooled in a dry ice−acetone bath and then stirred under 1 atm of dry O_2 for 4 h. The vessel was allowed to warm to ambient temperature, and the dichloromethane was evaporated under reduced pressure to leave a green residue. The solid was dissolved in ∼1 mL of CH_2Cl_2, and THF was carefully layered onto the solution. Several milligrams of long blue needles of analytically pure **2** formed over several days. FTIR (KBr): 3447 (OH), 2963, 2925, 2870, 2856, 1457, 1375, 1276, 1263, 1223 (CF_3SO_3), 1154 (CF_3SO_3), 1031 (CF_3SO_3), 638 (CF_3SO_3) cm^{-1}. UV−vis (CH_2Cl_2; λ, nm (ϵ, M^{-1} cm^{-1})): 343 (1100), 717 (75). Anal. Calcd for $C_{28}H_{46}N_6CuF_3O_5PS\cdot0.5CH_2Cl_2$: C, 44.30; H, 6.13; N, 10.88. Found: C, 44.45; H, 6.08; N, 10.94. Slightly larger crystals of **2** were obtained by recrystallization from CH$_3$CN−benzene. None of the cyrstals of this complex diffracted X-rays well enough to determine its structure.

2-[1-Isopropyl-4-(1-hydroxy-1-methylethyl)imidazolyl]bis[2-(1,4-diisopropylimidazolyl)]phosphine, P(im^{iPr_2})$_2$(im^{iPr,iPrOH}) (3). This compound was prepared by treating a $\sim 5 \times 10^{-4}$ M dichloromethane solution of **1** with dry O_2 for 4 h at −78 °C, warming to room temperature, evaporating the solvent, and partitioning the residue

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(6) Tris[2-(1,4-diisopropylimidazolyl)]phosphine,[5] {tris[2-(1,4-diisopropylimidazolyl)]phosphine}(acetonitrile)copper(I) tetrafluoroborate,[5] {tris[2-(1-ethyl-4-isopropylimidazolyl)]phosphine}(acetonitrile)copper(I) tetrafluoroborate,[7] and 1,4-diisopropylimidazole[8] were prepared according to the literature procedures. Tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate was synthesized from Cu(0) powder and Cu(CF$_3$SO$_3$)$_2$ in a manner similar to one previously reported.[9] Syntheses and manipulations of copper(I) complexes were performed in a Vacuum Atmospheres drybox operating at <5 ppm O_2, using anhydrous solvents that were degassed by purging with N_2 for 20 min. All other solvents and reagents were obtained from commercial sources and used without further purification. Proton and ^{31}P NMR spectra were recorded on Bruker AC200 or AMX300 instruments. Chemical shifts (δ) of protons are reported in parts per million relative to an internal standard of tetramethylsilane, and phosphorus shifts are reported in parts per million relative to an external standard of 85% H_3PO_4. Analtech precoated silica gel plates (0.25 mm) were used for thin layer chromatography. Flash column chromatography was carried out according to the method of Still et al.[10] Infrared spectra were obtained using a Bio-Rad FTS-7 spectrophotometer. Electronic absorption spectra were recorded on a Perkin−Elmer Lambda 6 instrument; ϵ values have units of M^{-1} cm^{-1}. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.
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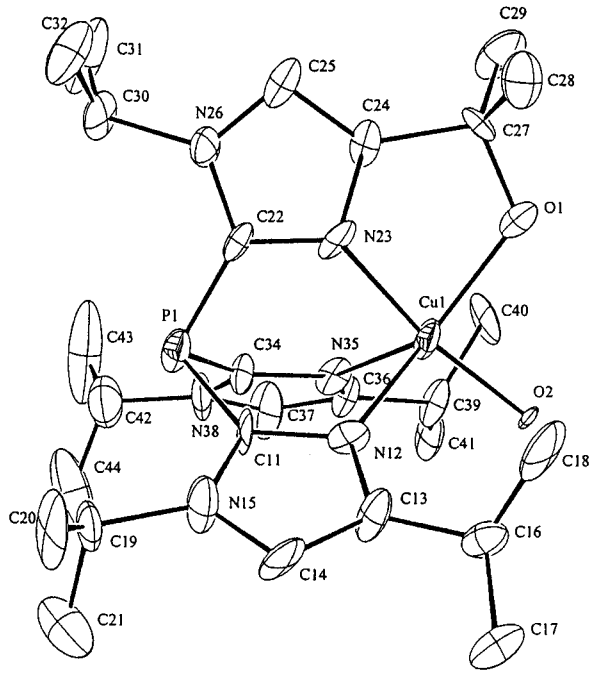


Figure 1. ORTEP drawing of the cation portion of $\{Cu[P(im^{iPr_2})_2(im^{iPr,iPrOH})]OH\}BF_4 \cdot 1.625CH_2Cl_2$. Thermal ellipsoids are scaled to the 30% probability level. Selected bond lengths (Å): Cu1−O1, 2.095(11); Cu1−O2, 1.854(9); Cu1−N12, 2.123(12); Cu1−N23, 1.889(13); Cu1−N35, 2.170(13). Selected bond angles (deg): O1−Cu1−O2, 92.8(4); N12−Cu1−N23, 88.6(5); O1−Cu1−N12, 132.9(5); N12−Cu1−N35, 89.8(5); O1−Cu1−N23, 77.4(5); N23−Cu1−N35, 88.0(6); O1−Cu1−N35, 133.4(5); O2−Cu1−N12, 98.7(4); O2−Cu1−N23, 170.1(5); O2−Cu1−N35, 98.6(4).

between diethyl ether and concentrated NH_4OH (2:1). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to afford a white solid. Flash chromatography using ethyl acetate separated **3** from unmodified $P(im^{iPr_2})_3$. Typical yields were 35−45% of white solid. TLC: R_f (EtOAc) = 0.35. ^{1}H NMR ($CDCl_3$): δ 1.04−1.33 (30H, m, 1- and 4-CH(CH_3)$_2$), 1.51 (6H, s, COH(CH_3)$_2$), 2.88 (2H, sept, J = 7.0 Hz, 4-C*H*(CH_3)$_2$), 3.36 (1H, br s, O*H*), 4.59−4.86 (3H, m, 1-C*H*(CH_3)$_2$), 6.84 (2H, s, imidazolyl C_5H), 6.96 (1H, s, imidazolyl C_5H). FTIR (KBr): 3457 (^{16}OH), 3446 (^{18}OH) cm^{-1}. Anal. Calcd for $C_{27}H_{45}N_6OP$: C, 64.77; H, 9.06; N, 16.79. Found: C, 64.50; H, 9.02; N, 16.53.

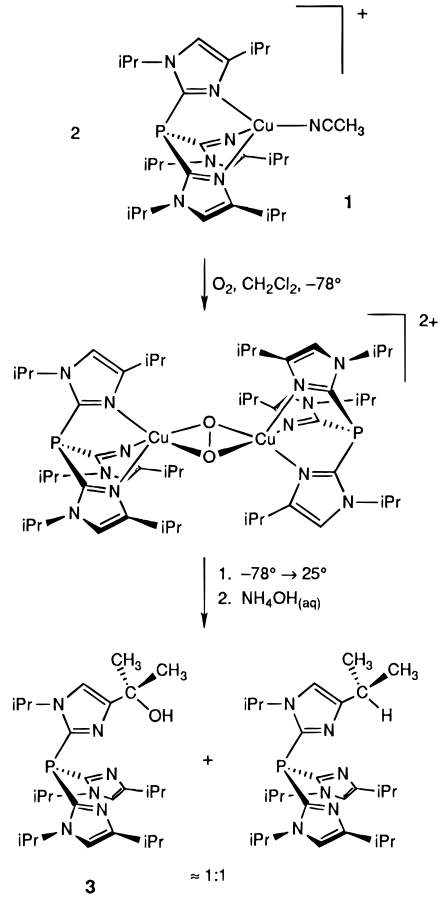
Results and Discussion

As reported previously, thermal decomposition of a methanolic solution of $\{Cu[P(im^{iPr_2})_3]\}_2O_2(BF_4)_2$ yields a hydroxo- or carbonato-bridged dinuclear complex.[5] Variable-temperature magnetic susceptibility measurements revealed that the strongly-coupled carbonate complex is contaminated by a small percentage of a monomeric, paramagnetic impurity,[11] and a side product was subsequently isolated in very low yield as blue crystals during the attempted crystallization of $\{Cu[P(im^{iPr_2})_3]_2\}(OH)_2\{BF_4\}_2$, formed by allowing $\{Cu[P(im^{iPr_2})_3]\}_2O_2(BF_4)_2$ to warm to room temperature in air.[5] Figure 1 shows the molecular structure of the cationic portion of this material, formulated as

$$\{Cu[P(im^{iPr_2})_2(im^{iPr,iPrOH})]OH\}BF_4 \cdot 1.625CH_2Cl_2,\ \mathbf{2a}$$

Despite the marginal quality of the X-ray data used to obtain the structure of **2a**,[12] it was clear to us that an oxygen atom had been inserted into the tertiary C−H bond of one of the isopropyl groups of the $P(im^{iPr_2})_3$ ligand and was coordinated in an equatorial position of an axially-compressed trigonal-bipyramidal Cu(II) ion. Because there is only a single BF_4 counterion per copper ion, the ligands bonded to copper must carry an overall charge of −1, which in turn dictates that the oxygen atom donors comprise either a deprotonated alkoxide ligand and bound water molecule or an alcohol ligand and coordinated hydroxide ion. The higher pK_a value for a tertiary alcohol vs water favors the alcohol/OH^- formulation, as does the longer bond distance for Cu−O1 and the smaller thermal ellipsoids for O2.[13]

Scheme 1



Because **2a** (as well as its triflate analog **2b**) is difficult to obtain in reasonable yields,[13] we explored the efficacy of this apparent hydroxylation reaction by isolating the modified ligand $P(im^{iPr_2})_2(im^{iPr,iPrOH})$, **3**, according to Scheme 1. We found that higher yields of **3** are obtained when CH_2Cl_2 is used in place of CH_3OH as the solvent and when triflate is employed as the counterion in the starting material. Thus, a dilute ($<10^{-3}$ M) dichloromethane solution of $\{Cu[P(im^{iPr_2})_3]CH_3CN\}CF_3SO_3$ (**1**), when treated with dioxygen at −78 °C, acquires a deep, purple

(11) O'Connor, C. J.; Sorrell, T. N.; Allen, W. E. Unpublished results.

(12) The high residual values are presumably caused by large thermal motion of the isopropyl groups and partial loss of solvate molecules, giving rise to crystals of marginal quality. Other structurally characterized copper(II) complexes of highly alkylated tripodal ligands sometimes have $R > 0.1$ because of low crystallinity. See: (a) Kitajima, N.; Fujisawa, K.; Fujimoto, C.; Moro-oka, Y.; Hashimoto, S.; Kitagawa, T.; Toriumi, K.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1992**, *114*, 1277. (b) Fujisawa, K.; Tanaka, M.; Moro-oka, Y.; Kitajima, N. *J. Am. Chem. Soc.* **1994**, *116*, 12079.

(13) Another possibility is that the hydroxide ion ligand is actually a fluoride ion, derived from the BF_4^- counterion, a phenomenon that has been documented by: Holm; et al. *Inorg. Chem.* **1993**, *32*, 4745. Refining the structure with a fluoride ion as the nonchelating axial ligand did not improve the quality of the structure significantly. Furthermore, the triflate complex does not suffer from this bothersome side reaction, and the characterization of **2b** is consistent with its formulation as $Cu[L^{OH}](OH)^+$. The ambiguity about the composition of **2a** and **2b** is another reason why we focused on isolating the hydroxylated ligand instead of the complex.

color.[14] After the solution is warmed to room temperature and the copper ion is removed by stirring with aqueous ammonium hydroxide, pure **3** can be isolated in up to 45% yield after column chromatography. Under optimum conditions, unmodified $P(im^{iPr_2})_3$ is recovered in 45−50% yield.[15] When $^{18}O_2$ is used during oxygenation, the ligand O−H stretching frequency is observed to be appropriately shifted by the isotopic substitution [$\Delta\nu(^{16}OH-^{18}OH) = 11$ cm^{-1}], confirming that the new oxygen atom derives from O_2.

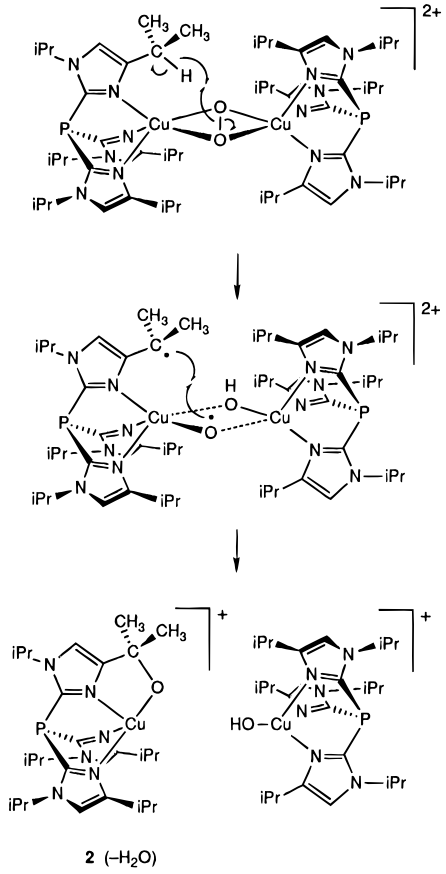
We next looked at reactions of the copper(I) complexes of related ligands to see how general this reaction is. Oxygenation at low temperature of the *N*-ethyl-4-isopropyl derivative $\{Cu[P(im^{Et,iPr})_3]CH_3CN\}BF_4$,[7] followed by the standard workup, affords a 24% yield of $P(im^{Et,iPr})_2(im^{Et,iPrOH})$, **4**.[16] In contrast, oxygenation at low temperature of $\{Cu[P(im^{iPr,Ph})_3]CH_3CN\}CF_3SO_3$, **6**,[16] in which phenyl groups have replaced the isopropyl groups at the 4-position of the imidazole rings, and $\{Cu[P(Ph)(im^{iPr_2})_2]CH_3CN\}CF_3SO_3$, **8**,[16] which bears a phenyl ring near the metal ion instead of one of the imidazole groups, produce uncharacterized green complexes instead of the corresponding violet-colored peroxide adducts. Removing the Cu(II) ion from these oxidized complexes with NH_4OH yielded ligands in which neither the isopropyl groups nor the phenyl substituents have been modified. These experiments, taken together, provide evidence that intermediacy of a peroxo complex is required for hydroxylation to proceed.

In keeping with the experimental observation that only half of the original $P(im^{iPr_2})_3$ is hydroxylated, Scheme 2 illustrates one possible pathway for the formation of the hydroxylated ligand product. Alternatively, cleavage of the peroxide O−O bond may yield a bis(μ-oxo) species, $[L_2Cu_2(\mu\text{-}O)_2]^{2+}$, which has been documented for complexes of *N*,*N*′,*N*″-trialkylated 1,4,7-triazacyclononane ligands.[4]

We cannot exclude the possibility that the hydroxylated ligand product is formed by a mechanism akin to the one observed by Kitajima in the oxidation of cyclohexene by $[Cu(Tp^{Me_2})]O_2$, which produces 2-cyclohexen-1-ol and 2-cyclohexen-1-one.[3] There, isotopic labeling experiments revealed that the new oxygen atoms in the products were derived from reaction with exogenous O_2 and not from the bound peroxide moiety. A mechanism proposed to account for those results suggests that the O−O bond of the peroxide complex undergoes homolysis to generate LCu−O$^\bullet$ species. These fragments abstract H$^\bullet$ from cyclohexene, which subsequently reacts with molecular oxygen to generate the observed products.

For the complexes reported here, homolysis could also generate LCu−O$^\bullet$ species. Abstraction of a hydrogen atom from the isopropyl group of the ligand followed by reaction with O_2 in solution would also produce the hydroxylated product. Complex **1** reversibly binds dioxygen, so we cannot ensure that exogenous O_2 is absent from the reaction mixture.[17]

Scheme 2



Hydrogen atom abstraction from sp^3 centers is emerging as a common reaction pathway for μ-η^2:η^2-peroxo and bis(μ-oxo) complexes, regardless of the identity of the ligand or metal ion.[3,4,18−20] While the $Cu(O_2^{2-})Cu$ moiety is capable of acting as an oxidant, changes in the steric properties of the tris(imidazolyl)phosphine ligands described here will be necessary to produce a Cu/O_2 system that is suited for use in catalytic hydroxylations of exogenous substrates.

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Supporting Information Available: Text describing experimental details for the synthesis and reactions of compounds **4**−**8** and X-ray crystallographic data collection for **2a** (10 pages). Ordering information is given on any current masthead page.

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(14) The yield of **3** is greatly reduced if the oxygenation is carried out on solutions of **1** that are $>10^{-3}$ M, presumably because the higher concentrations favor intermolecular reduction of the peroxide group by unreacted Cu(I) complex instead of hydroxylation. Low-temperature ^{31}P NMR spectra reveal that initial dioxygen binding by **1** in CD_2Cl_2 is not quantitative at these higher concentrations needed to obtain the NMR spectra, a phenomenon we observed previously; see ref 5.

(15) The hydroxylation proceeds in 25−35% yield if the purple solution is first subjected to vacuum to remove unbound O_2 before it is allowed to warm. Under no set of conditions, however, have we found the yield of **3** to exceed 50%, which is the theoretical maximum for this type of reaction; see ref 2c. A small amount (<5%) of the phosphine oxide derivative of the ligand is sometimes observed, too; however, the ligand slowly oxidizes under dioxygen even when no metal ion is present.

(16) The experimental details for the syntheses and reactions of compounds **4**−**8** are included in the Supporting Information.

(17) In fact, free radicals apparently can form during the decomposition of $\{Cu[P(im^{iPr_2})_3]\}_2O_2(CF_3SO_3)_2$ because this complex also promotes coupling in 33% yield of 2,4-di-*tert*-butylphenol to 3,3′-5,5′-tetra-*tert*-butyl-2,2′-dihydroxybiphenyl (cf.: Paul, P. P.; Tyeklár, Z.; Jacobson, R. R.; Karlin, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 5322).

(18) Reinaud, O. M.; Theopold, K. H. *J. Am. Chem. Soc.* **1994**, *116*, 6979.
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(20) Wallar, B. J.; Lipscomb, J. D. *Chem. Rev.* **1996**, *96*, 2625, and references cited therein.