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Tripodal Bis(imidazole) Thioether Copper(I) Complexes: Mimics of the Cu(B) Site of Hydroxylase Enzymes

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Tripodal bis(imidazole) thioether ligands and the corresponding copper(I) complexes [(BIMT-OR)Cu(L)]PF_6 [L = CH_3CN (**2**), CO (**3**); R = H (**a**), CH_3 (**b**)] have been prepared as models for the Cu(B) site of copper hydroxylase enzymes. The IR ν(CO) values of **3a** and **3b** (L = CO) are comparable to those of the carbonylated enzymes. The reaction of **2a** with O_2 gives dinuclear complex **4** with bridging BIMT-O ligands and oxidized –SMe groups, whereas oxygenation of **2b** affords [(BIMT-OMe)$_2$$Cu_2O(H)_2$]($CF_3SO_3$)$_2$ (**5**) and Cu(BIMT-OMe)(DMF)$_2$](PF_6)$_2$ (**6**).

The copper hydroxylase enzymes, dopamine β-hydroxylase (DβH) and peptidylglycine α-hydroxylating monooxygenase (PHM), catalyze the regio- and enantioselective hydroxylation of mildly activated C−H bonds by O_2.[1] These enzymes appear to have very similar active-site structures, featuring two Cu centers separated by ca. 11 Å, with the Cu(A) site being ligated by three histidine-derived imidazoles and the Cu(B) site by two histidines and a methionine residue.[2] Spectroscopic and amino acid deletion studies suggest that upon reduction both O_2 and the substrate are activated at the Cu(B) site.[3] A recent X-ray structure of the O_2-bound PHM enzyme has revealed an unusual end-on coordination mode to the Cu(B) center,[4,5] contrasting with the more common side-on mononuclear and bridging bimetallic bonding modes found in most synthetic complexes and in the O_2-binding Cu−protein hemocyanin.[6]

Although many synthetic model complexes for these (and other) Cu enzymes have been prepared with a variety of polydentate amine and pyridine and pyrazolyl-based ligands,[6] remarkably few have incorporated the biologically most relevant imidazole donors.[7] Regarding the Cu(B) site of the hydroxylases, a few Cu^{II} complexes with mixed N_xS_y-polydentate imidazole thioether ligands have been characterized,[8] but only one Cu^{I} analogue has been reported.[9] Given the significantly different basicity[10] and donor−acceptor properties[11] of imidazole vis a vis the other common nitrogen ligands, the most accurate structural and functional mimics for histidine-rich metalloenzymes are likely to be provided by incorporating the actual biological donor set. Toward this goal, we report here the preparation of biomimetic tripodal bis(imidazole) thioether (BIMT) ligands, the corresponding Cu^{I} complexes, and their reactivity with CO and O_2.

To provide the desired bis(imidazole) thioether donor set of the Cu(B) center in a sterically encumbered environment that could limit the formation of bimetallic species, we targeted the phenylated tripodal ligands BIMT-OH (**1a**) and BIMT-OMe (**1b**), which are conveniently prepared from 4,5-diphenylimidazole (Scheme 1).[12] Compounds **1a** and **1b** react readily with [Cu(CH_3CN)$_4$]PF_6 (CH_2Cl_2, rt) to afford the somewhat air-sensitive [(BIMT-OR)Cu(CH_3CN)]PF_6 (**2a**,**b**); the former was characterized spectroscopically.

Complexes **2a** and **2b** are convenient precursors for investigating reactions with biorelevant substrates such as CO and O_2. Bubbling CO into a CH_2Cl_2 solution of **2a**,**b** (3 h, rt)

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(12) Preparative procedures and spectroscopic data for new compounds are provided in the Supporting Information.

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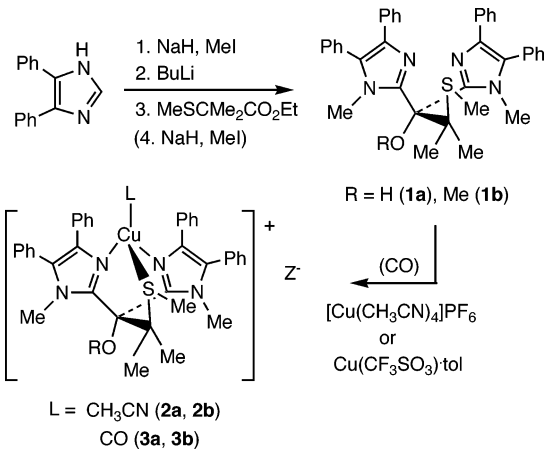
Scheme 1



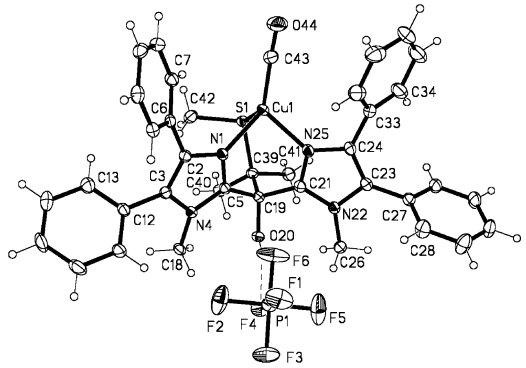
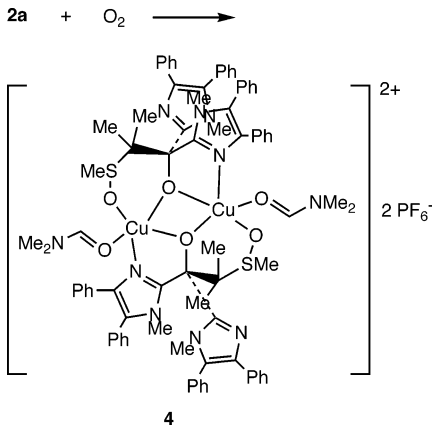


Figure 1. Crystal structure of **3a**. Selected bond lengths (Å) and angles (deg): Cu1−C43 1.811(2), Cu1−N25 2.0005(19), Cu1−N1 2.0259(17), Cu1−S1 2.4392(7), C43−O44 1.123(2); C43−Cu1−N25 122.90(9), C43−Cu1−N1 132.84(10), C43−Cu1−S1 118.81(9), N25−Cu1−N1 90.67(7), N25−Cu1−S1 93.37(6), N1−Cu1−S1 87.33(5), Cu1−C43−O44 177.4(2).

resulted in the appearance of a strong IR absorption near 2100 cm^{-1}. Addition of ether−petroleum ether induced crystallization of the colorless, air-sensitive carbonyl complexes [(BIMT-OR)Cu(CO)]PF_6 (**3a**,**b**; Scheme 1). The molecular structure of **3a** was established by X-ray diffraction (Figure 1)[13] and consists of a slightly distorted pyramidal arrangement about the Cu^I center formed by the tridentate BIMT and CO ligands. Notwithstanding the unique N_2S-(L)−Cu^I donor atom set and a bifurcated O−H−FPF_5 hydrogen bond, the observed bond lengths and angles are unexceptional relative to reported N_3Cu^I−CO structures.[14] A close electronic similarity of the Cu centers in the carbonyl complexes **3a** and **3b** with the Cu(B) site of the carbonylated copper hydroxylases is indicated by comparable CO vibrational frequencies: PHM (2093 cm^{-1}),[15] DβH (2089 cm^{-1}),[16] **3a** (2102 cm^{-1}), and **3b** (2095 cm^{-1}).

The reactions of the hydroxy and methoxy tripodal complexes **2a** and **2b** with O_2 produced remarkably different results. Slow recrystallization of **2a** from a dimethylformamide (DMF)−ether solution over a week's time afforded green crystals of a new complex **4**, whose electrospray ionization mass spectrum (ESI-MS) and X-ray structure (Scheme

Scheme 2



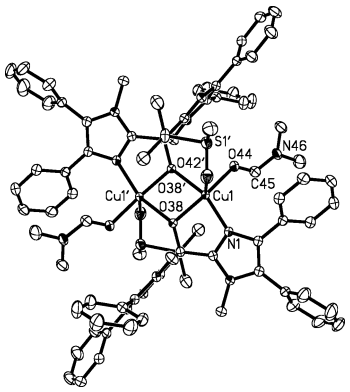


Figure 2. Crystal structure for the cation of **4**. Selected bond lengths (Å): Cu1−O42′ 1.909(9), Cu1−O44 1.9369(18), Cu1−O38 1.9436(16), Cu1−N1 1.958(2), Cu1−O38′ 1.9599(16), Cu1−Cu1A 3.0302(7).

2) showed it to be a product of adventitious oxidation. The centrosymmetric dinuclear structure of **4** (Figure 2)[17] consists of two five-coordinate Cu^{II} centers, each terminally coordinated to one imidazole N, a DMF O, and a sulfoxide O, with the Cu centers bridged by two alkoxo O atoms from the deprotonated tripodal ligands. Thus, both the Cu and S atoms are oxidized during the conversion of **2a** to **4**. This facile S oxidation can be compared to known Cu-mediated oxidations of thioethers[18] and of the methionine residue of the amyloid β-peptide (Aβ)[19] but contrasted with the apparent oxidative inertness of the Cu(B) active-site methionine in DβH and PHM. Related tris(imidazole) carbinol ligands have also been found to form polynuclear, alkoxo-bridged Cu^{II} complexes.[20]

In contrast, room-temperature oxygenation of the BIMT-OMe complexes **2b** or **3b** (1 atm of O_2, CH_2Cl_2, 12 h), for which alkoxide formation is blocked, followed by crystallization from CH_2Cl_2−Et_2O produced an amber compound

(13) X-ray crystal data for **3a**: $(C_{38}H_{36}CuN_4O_2S)(PF_6)$, fw = 821.28, $P2_1/n$ (No. 14), a = 13.066(2) Å, b = 14.065(2) Å, c = 20.789(3) Å, β = 100.227(5)°, V = 3759.8(10) Å^3, Z = 4, T = −173 °C, D_{calcd} = 1.451 g cm^{-3}, λ = 0.710 73 Å, μ = 7.48 cm^{-1}, $R1_{obsd}$ = 0.0360, $wR2_{all}(F^2)$ = 0.0930.

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(17) X-ray crystal data for **4**: $(C_{80}H_{84}Cu_2N_{10}O_6S_2)(PF_6)_2(C_3H_7NO)_2$-$(C_4H_{10}O)$, fw = 1983.02, $P\bar{1}$ (No. 2), a = 9.7020(12) Å, b = 15.521(2) Å, c = 15.775(2) Å, α = 83.976(5)°, β = 79.171(5)°, γ = 81.070(5)°, V = 2297.9(5) Å^3, Z = 1, T = −173 °C, D_{calcd} = 1.433 g cm^{-3}, λ = 0.710 73 Å, μ = 6.31 cm^{-1}, $R1_{obsd}$ = 0.0457, $wR2_{all}(F^2)$ = 0.1298.

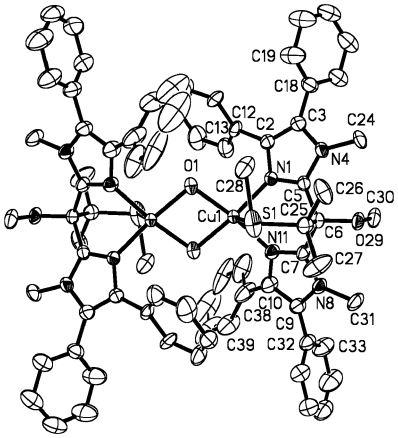
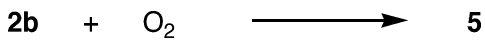


Figure 3. Crystal structure of the cation of **5**. Selected bond lengths (Å): Cu(1)−O(1)′ 1.917(3), Cu(1)−O(1) 1.931(3), Cu(1)−Cu(1)′ 3.0206(9), Cu(1)−S(1) 2.868(3), O(1)−O(1) 2.383(3).

5, whose ESI-MS was indicative of a dinuclear complex that had incorporated two oxygens.

The X-ray structure of **5** (Scheme 3 and Figure 3)[21] revealed it to be a dinuclear complex having a Cu_2O_2 core with each copper coordinated to a BIMT-OMe ligand and forming a square pyramid at Cu. The Cu−O, O−O, and Cu−Cu distances in **5** are indicative of either a μ-oxocopper(III) or μ-hydroxocopper(II) formulation, which cannot be distinguished definitively with the available spectroscopic data.[22] Thus, by capping the hydroxyl group, as in the BIMT-OMe complexes, Cu-centered oxygenation proceeds to give **5**, avoiding not only the alkoxo-bridging tripod (as in **4**) but also S oxidation as well. The relatively unhindered S center of the BIMT-OMe ligand apparently is insufficient (at least at room temperature), however, to prevent the formation of an O_2-bridged dinuclear complex.

Scheme 3



Lability of the Cu_2O_2 linkage of **5** was suggested during its recrystallization from DMF−ether when blue crystals of a new compound **6** were also obtained. The ESI-MS of **6** suggested a $[(\text{BIMT-OMe})Cu^{II}(DMF)_n]^{2+}$ formulation. Indeed, the X-ray structure of **6** (Figure 4)[22] revealed a cationic mononuclear Cu^{II} complex of square-pyramidal geometry with its basal plane defined by the two imidazole N atoms and two DMF O atoms with an apical −SMe group. It is

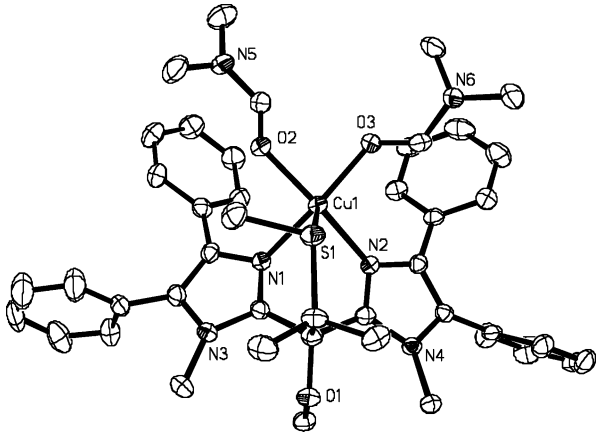


Figure 4. Crystal structure of the dication of **6**. Selected bond lengths (Å) and angles (deg): Cu1−O3 1.9474(18), Cu1−N2 1.952(2), Cu1−O2 1.9527(17), Cu1−N1 1.968(2), Cu1−S1 2.6892(8); O3−Cu1−N2 98.75(8), O3−Cu1−O2 84.85(7), N2−Cu1−N1 84.70(9), O2−Cu1−N1, 91.45(8).

noteworthy that **6** retains the N_2S coordination mode of the oxidized Cu(B) site of the hydroxylase enzymes.[2,3] Furthermore, the Cu^{II}−S distance of **6** (2.69 Å) is considerably longer than the Cu^{I}−S length of **3a** (2.44 Å), suggestive of tighter binding of the S ligand to the reduced Cu center. The same effect has been seen with the oxidized (2.68 Å) and reduced (2.27 Å) forms of PHM.[25]

In conclusion, the biomimetic (BIMT-OR)Cu complexes reported herein exhibit several close parallels with the Cu(B) site of the copper hydroxylases, including the formation of electronically similar carbonyl adducts and their Cu-centered oxidation and oxygenation (when R = Me). Our ongoing-efforts are focused on identifying oxygenation reaction intermediates, potentially including $Cu-O_2$ adducts, and exploring the stoichiometric and catalytic oxidation reactions promoted by these and related poly(imidazole) complexes.

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Supporting Information Available: Listings of preparative and characterizational data for compounds **1**−**6**, including X-ray crystallographic data for **3a**, **4**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) X-ray crystal data for **5**: $(C_{76}H_{76}Cu_2N_8O_4S_2)(PF_6)_2(CH_2Cl_2)_2(C_4H_{10}O)$, fw = 1890.56, *Pc* (No. 7), a = 14.446(2) Å, b = 18.150(3) Å, c = 18.005(3) Å, β = 113.351(5)°, V = 4334.2(12) Å^3, Z = 2, T = −173(2) °C, D_{calcd} = 1.449 g cm^{-3}, λ = 0.710 73 Å, μ = 7.80 cm^{-1}. The metal complex suffers from "whole-molecule" disorder. Apparently, good quality intensity data from four crystals has led to essentially this same model.

(22) Average reported distances for μ-peroxo, -oxo (refs 6a−d), and -hydroxo (ref 23) complexes, respectively: Cu−Cu, 3.51, 2.80, 3.00 Å; O−O, 1.42, 2.33, 2.40 Å; Cu−O, 1.92, 1.84, 1.93 Å.

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(24) X-ray crystal data for **6**: $(C_{44}H_{52}CuN_6O_3S)(PF_6)_2(C_4H_{10}O)$, fw = 1172.58, $P2_1/c$ (No. 14), a = 12.448(2) Å, b = 28.000(5) Å, c = 16.848(3) Å, β = 100.739(5)°, V = 5769.4(17) Å^3, Z = 4, T = −173(2) °C, D_{calcd} = 1.350 g cm^{-3}, λ = 0.710 73 Å, μ = 5.54 cm^{-1}, $R1_{obsd}$ = 0.0476, $wR2_{all}(F^2)$ = 0.1193.

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