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Inorganic Chemistry Article

Modeling the Mononuclear, Dinuclear, and Trinuclear Copper(I) Reaction Centers of Copper Proteins Using Pyridylalkylamine Ligands Connected to 1,3,5-Triethylbenzene Spacer

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The structure and O_2-reactivity of copper(I) complexes supported by novel ligands, **Pye2** (1,3,5-triethyl-2,4-bis((*N*-benzyl-*N*-(2-(pyridin-2-yl)ethyl)-)aminomethyl)benzene), **Pye3** (1,3,5-triethyl-2,4,6-tris((*N*-benzyl-*N*-(2-(pyridin-2-yl)-ethyl))aminomethyl)benzene), **^{Me}Pym2** (1,3,5-triethyl-2,4-bis((*N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl))aminomethyl)-benzene), and **^{Me}Pym3** (1,3,5-triethyl-2,4,6-tris((*N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl))aminomethyl)benzene) have been examined. The ligands are designed to construct mono-, di-, and trinuclear copper(I) complexes by connecting two or three pyridylalkylamine metal-binding sites to a 1,3,5-triethylbenzene spacer. Thus, the reaction of the ligands with $[Cu^I(CH_3CN)_4]X$ ($X = PF_6$, CF_3SO_3) or Cu^ICl gave the expected mononuclear copper(I) complexes $[Cu^I($**Pye2**$)(CF_3SO_3)]$ (**1**) and $[Cu^I($**Pye3**$)](CF_3SO_3)$ (**2**), dinuclear copper(I) complex $[Cu^I_2($**^{Me}Pym2**$)(Cl)]Cu^ICl_2$ (**3**), and trinuclear copper(I) complex $[Cu^I_3($**^{Me}Pym3**$)(CH_3CN)_3](CF_3SO_3)_3$ (**4**), the structures of which were determined by X-ray crystallographic analysis. The mononuclear copper(I) complexes, **1** and **2**, exhibit a distorted three-coordinate T-shape structure and a trigonal planar structure, respectively, which are very close to the coordination geometry of the CuA site of PHM (peptidylglycine α-hydroxylating monooxygenase) and the CuB site of C*c*O (cytochrome *c* oxidase). Notably, **1** and **2** showed a significantly high oxidation potential (990 mV vs SCE), thus showing virtually no reactivity toward O_2. On the other hand, the metal centers of the dinuclear and trinuclear copper(I) complexes, **3** and **4**, exhibit a distorted trigonal planar geometry and a trigonal pyramidal geometry, respectively. In contrast to the mononuclear copper(I) complexes, these dinuclear and trinuclear copper(I) complexes reacted with O_2 to induce an aromatic ligand hydroxylation reaction involving an NIH-shift of one of the ethyl substituents on the benzene spacer. The NIH-shift of the alkyl substituent on the aromatic ring is strong evidence of the electrophilic aromatic substitution mechanism, although the active oxygen intermediate could not be directly detected during the course of the reaction. The biological relevance of the copper(I) complexes is also discussed on the basis of structure and O_2-reactivity.

Introduction

Copper proteins are ubiquitous in nature, for which a wide variety of physiological functions such as reversible dioxygen binding, electron transfer, oxidase and oxygenase activities, and superoxide dismutation are known.[1] These functions are accomplished at various types of copper reaction centers involving mono-, di-, and trinuclear structures.[1] To explore the structures, physicochemical properties, and functions of these copper active sites, a large number of model complexes have so far been developed during the last two decades, establishing biomimetic copper chemistry.[2−4]

For copper(I)/dioxygen chemistry, tridentate ligands such as hydrotris(1-pyrazolyl)borate ($HBpz_3$), 1,4,7-triazacyclononane (TACN), and bis[2-(2-pyridyl)ethyl]amine (PY2) derivatives as well as tetradentate ligands such as tris(2-pyridylmethyl)amine (TPA) and tris(aminoethyl)amine (tren) derivatives have been examined in detail.[2] Didentate ligands such as ethylene diamine (en), 2-(2-pyridyl)ethylamine

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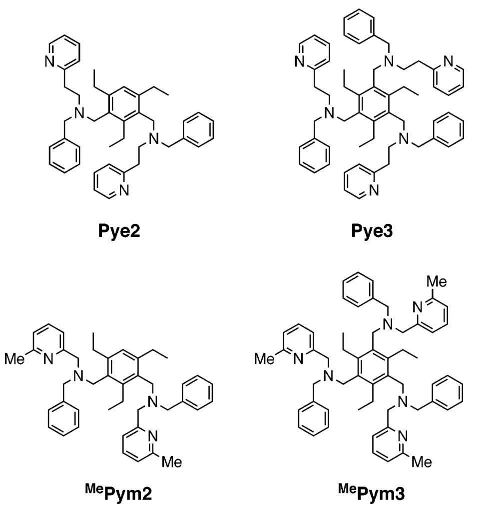
Chart 1



(PY1), and β-diketiminate derivatives have also been studied recently.[2] The copper(I) complexes supported by these capping ligands are usually very reactive toward O_2, producing a series of copper−dioxygen complexes such as mononuclear copper(II)−superoxo (both end-on and side-on), copper(III)−peroxo (side-on), dinuclear copper(II)−μ-peroxo (both end-on and side-on), bis(μ-oxo)dicopper(III), and bis-(μ_3-oxo)tricopper(II,II,III) complexes.[2] Characterization and reactivity studies of these copper−dioxygen complexes have provided significantly important insights into the dioxygen activation mechanisms at the mononuclear copper reaction centers of peptidylglycine α-hydroxylating monooxygenase (PHM) and dopamine β-monooxygenase (DβM) and the dinuclear type-3 copper active sites of hemocyanin (Hc), tyrosinase (Tyr), and catechol oxidase (CA).[2]

In this study, we have examined copper(I) coordination chemistry of **Pye2**, **Pye3**, **^{Me}Pym2**, and **^{Me}Pym3** (Chart 1) in order to model the mononuclear, dinuclear, and trinuclear copper(I) reaction centers in the biological systems. The 1,3,5-triethylbenzene derivatives have recently attracted much attention as an efficient building block for the development of receptors in molecular recognition chemistry and ligands in supramolecular, biomimetic, and coordination polymer chemistry.[5−11] The 1,3,5-triethylbenzene spacer plays an important role in controlling the steric configuration of the functional groups introduced into the 2,4,6-positions. Namely, the functional groups, the metal binding units in the present ligand system, attached to the 2,4,6-positions are enforced to positioning the same side of the benzene ring of the spacer, since the *ababab* configuration (*a* denotes ‘above’ and *b* denotes ‘below’) is the most stable conformation due to the steric repulsion between the neighboring substituents as

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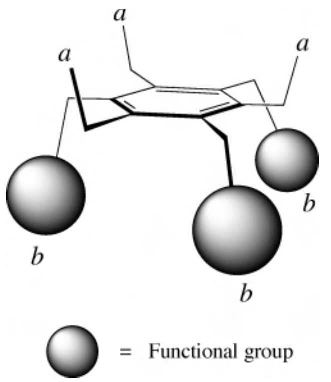

Figure 1. Schematic representation of the steric configuration of the substituents of 1,3,5-triethylbenzene derivatives.

illustrated in Figure 1. This geometric feature of the 1,3,5-triethylbenzene spacer may enable the molecules to adapt a favorable conformation for the formation of biomimetic copper(I) complexes and cause perturbation on the structure and reactivity of the resulting complexes as discussed below. So far, only a couple of examples of copper(I) complexes supported by the similar triethylbenzene ligands have been reported.[11d,e]

Experimental Section

General. All chemicals used in this study except the ligands and the copper(I) complexes were commercial products of the highest available purity and were further purified by the standard methods, if necessary.[12] FT-IR spectra were recorded with a Shimadzu FTIR-8200PC or JASCO FT-IR-4100. UV−vis spectra were obtained on a Hewlett-Packard 8453 photodiode array spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL FT-NMR Lambda 300WB, GX-400, or Bruker Advance 600 spectrometers. Mass spectra were obtained on a JEOL JMS-700T Tandem MS-station mass spectrometer. ESI-MS (electrospray ionization mass spectra) measurements were performed on a PE SCIEX API 150 EX. Elemental analysis was carried out on a Perkin-Elmer 240C or a Fisons instruments EA1108 elemental analyzer.

Electrochemical Measurement. The cyclic voltammetry (CV) was performed on an ALS-630A electrochemical analyzer in deaerated acetonitrile containing 0.1 M n-Bu_4NPF_6 as supporting electrolyte. The Pt electrodes was polished with BAS polishing alumina suspension and rinsed with H_2O before use. The counter electrode was a platinum wire. The measured potentials were recorded with respect to a Fc/Fc^+ (1.0×10^{-3} M) reference electrode. The E values (vs Fc/Fc^+) are converted to those versus SCE by adding 0.33 V (Mann, K.; Barnes, K. K. *Electrochemical Reactions in Non-aqueous Systems*; Marcel Dekker Inc.: New York, 1990). All electrochemical measurements were carried out at 25 °C under an atmospheric pressure of Ar in a glove box (Miwa Co. Ltd.).

X-ray Structure Determination. The single crystal was mounted on a glass fiber. Diffraction data of complexes **1**, **3**, **4**, and **6** were collected by a RIGAKU RAXIS-RAPID imaging plate two-dimensional area detector using a graphite-monochromated Mo Kα radiation ($\lambda = 0.71075$ Å) to a $2\theta_{max}$ of 55.0°. Diffraction data of complex **2** were collected by a Rigaku AFC7/CCD Mercury area detector using a graphite-monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) to a $2\theta_{max}$ of 55.0°. All the crystallographic calculations were performed by using the Crystal Structure software package from the Molecular Structure Corporation [Crystal Structure: *Crystal Structure Analysis Package*, version 3.7.0; Molecular Structure Corp. and Rigaku Corp. (2000−2005)]. The crystal structures were solved by the direct method and refined by full-matrix least-squares using SIR92 for **1**, **2**, and **4** and SHELX97 for **3** and **6**. All non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. Summary of X-ray crystallographic data and selected bond lengths and angles are given in Tables 1 and 2, respectively. Atomic coordinates, thermal parameters, and intramolecular bond distances and angles are deposited in the Supporting Information (CIF file format).

Synthesis. 1,3,5-Triethyl-2,4-bis((*N*-benzyl-*N*-(2-(pyridin-2-yl)-ethyl))aminomethyl)benzene (Pye2). To a mixture of *N*-benzyl-*N*-(2-(pyridin-2-yl)ethyl)amine[13a] (4.0 g, 1.90 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) in dry CH_3CN (30 mL) was added a CH_3CN solution (40 mL) of 1,3-bis(bromomethyl)-2,4,6-triethylbenzene[14] (2.0 g, 5.7 mmol) under anaerobic conditions (Ar), and the mixture was stirred for 12 h at room temperature. The resulting precipitates were removed by filtration and washed with CH_2Cl_2. The combined organic layer was concentrated by evaporation to give a yellow residue, from which ligand **Pye2** was isolated by silica gel column chromatography (eluent; ethyl acetate/$CHCl_3$ = 1:1, $R_f = 0.41$) (1.7 g, 48%). IR (KBr, cm^{-1}): 3061, 3025 (aromatic C−H), 2961, 2929, 2869, 2793 (aliphatic C−H), 1591, 1569, 1474, 1453, 1435, 744, 699 (aromatic), 1125, 1115 (C−N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (3 H, t, $J = 7.6$ Hz, Ar−CH_2CH_3), 1.12 (6 H, t, $J = 7.6$ Hz, Ar−CH_2CH_3), 2.67 (4 H, q, $J = 7.6$ Hz, Ar−CH_2CH_3), 2.82−3.00 (8 H, m, Py−CH_2CH_2−), 3.01 (2 H, q, $J = 7.6$ Hz, Ar−CH_2-CH_3), 3.54 (4 H, s, −CH_2−), 3.67 (4 H, s, −CH_2−), 6.81 (2 H, d, $J = 7.7$ Hz, Py−3*H*), 6.84 (1 H, s, Ar−*H*), 7.01 (2 H, dd, $J = 7.0$ and 4.8 Hz, Py−5*H*), 7.17 (10 H, bs, Ar−*H*), 7.38 (2 H, td, $J = 7.7$ and 1.6 Hz, Py−4*H*), 8.41 (2 H, d, $J = 4.8$ Hz, Py−6*H*). HRMS (FAB, pos): m/z = 611.4107 calcd for ([M + H]$^+$, $C_{42}H_{51}N_4$ 611.4114).

1,3,5-Triethyl-2,4,6-tris((*N*-benzyl-*N*-(2-(pyridin-2-yl)ethyl))-aminomethyl)benzene (Pye3). This compound was synthesized

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Table 1. Summary of X-ray Crystallographic Data of Complexes **1**−**4** and **6**.

	1	**2**	**3**	**4**	**6**
formula	$C_{43}H_{50}CuF_3N_4O_3S$	$C_{58}H_{66}CuF_3N_6O_3S$	$C_{42}H_{50}Cl_3Cu_3N_4$	$C_{66}H_{75}Cu_3F_9N_9O_9S_3$	$C_{60}H_{78}Cu_{12}N_4O_4P_2$
fw	823.49	1047.80	907.88	1596.18	1336.32
cryst syst	monoclinic	monoclinic	triclinic	trigonal	triclinic
space group	$P2_1/a$ (No. 14)	$C2/c$ (No. 15)	$P\bar{1}$ (No. 2)	$P3$ (No. 143)	$P\bar{1}$ (No. 2)
a, Å	15.686(2)	21.6998(16)	9.4612(10)	24.4960(10)	11.318(4)
b, Å	15.410(4)	12.9667(10)	10.8782(10)	24.4960(10)	11.660(4)
c, Å	17.509(3)	39.095(3)	22.414(2)	10.4042(5)	12.129(4)
α, deg	90	90	89.649(4)	90	86.849(13)
β, deg	130.437(9)	90.454(4)	78.527(4)	90	78.394(15)
γ, deg	90	90	67.578(4)	120	87.442(14)
V, Å^3	4116.4(13)	11000.1(14)	2083.6(4)	5406.7(4)	1564.6(9)
Z	4	8	2	3	1
F(000)	1728.00	4416.00	936.00	2466.00	694.00
D_{calcd}, g/cm^{-3}	1.329	1.265	1.447	1.471	1.418
T, K	160	153	161	161	161
cryst size, mm^3	0.35 × 0.33 × 0.32	0.21 × 0.16 × 0.07	0.30 × 0.22 × 0.21	0.22 × 0.22 × 0.21	0.21 × 0.20 × 0.18
μ(Mo Kα), cm^{-1}	6.382	4.938	17.436	10.472	8.416
$2\theta_{max}$, deg	55.0	55.0	54.8	55.0	54.5
no. reflns measd	37895	40494	19192	50151	14625
no. reflns obsd	7347 ([$I > 1.00\sigma(I)$])	10628 ([$I > 1.00\sigma(I)$])	7843 ([$I > 1.00\sigma(I)$])	15964 ([$I > 0.00\sigma(I)$])	5927 ([$I > 1.00\sigma(I)$])
no. variables	546	715	522	968	422
R,^{a} R_W^{b}	0.0399, 0.0415	0.0764, 0.1570	0.0366, 0.0400	0.0435, 0.0479	0.0479, 0.0607
GOF	1.013	0.992	1.020	0.978	1.023

^{a} $R = \sum||F_o| - |F_c||/\sum|F_o|$. ^{b} $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o{}^2]^{1/2}$.

by following the same procedure as described above for **Pye2** by using 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene[14] instead of 1,3-di(bromomethyl)-2,4,6-triethylbenzene. Yellow powder precipitated from the final reaction mixture was collected by filtration to give **Pye3** (1.50 g, 26%). IR (KBr, cm^{-1}): 3060, 3026, 3007 (aromatic C−H), 2957, 2925, 2867, 2792 (aliphatic C−H), 1591, 1568, 1474, 1453, 1434, 743, 699 (aromatic), 1126, 1116 (C−N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93 (9 H, t, J = 7.6 Hz, Ar−CH$_2$CH_3), 2.79−2.91 (12 H, m, Py−CH_2CH_2−), 3.01 (6 H, t, J = 7.6 Hz, Ar−CH_2CH$_3$), 3.50 (6 H, s, −CH_2−), 3.66 (6 H, s, −CH_2−), 6.63 (3 H, d, J = 7.6 Hz, Py−3H), 6.91 (3 H, ddd, J = 7.6, 4.8, and 0.8 Hz, Py−5H), 7.09 (10 H, m, Ar−H), 7.15 (3 H, td, J = 7.6 and 1.6 Hz, Py−4H), 8.37 (3 H, d, J = 4.8 Hz, Py−6H). HRMS (FAB, pos): m/z = 835.5414 calcd for ([M + H]$^+$, $C_{57}H_{67}N_6$ 835.5427).

1,3,5-Triethyl-2,4-bis((*N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl))aminomethyl)benzene (^{Me}Pym2). To a mixture of *N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl)amine[13b] (4.0 g, 1.90 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) in dry CH_3CN (30 mL) was added a CH_3CN solution (40 mL) of 1,3-bis(bromomethyl)-2,4,6-triethylbenzene (2.0 g, 5.7 mmol) under anaerobic conditions (Ar), and the mixture was stirred for 2 days at room temperature. The resulting precipitates were removed by filtration and washed with CH_2Cl_2. The combined organic layer was concentrated by evaporation to give a yellow residue, from which ligand **^{Me}Pym2** was isolated by silica gel column chromatography (eluent; ethyl acetate/$CHCl_3$ = 1:9, R_f = 0.2) (0.58 g, 17%). IR (KBr, cm^{-1}): 3061, 3027 (aromatic C−H), 2961, 2926, 2870, 2822, 2793 (aliphatic C−H), 1592, 1577, 1455, 1370, 787, 743, 699 (aromatic), 1123, 1111 (C−N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.63 (3 H, t, J = 7.6 Hz, Ar−CH$_2$CH_3), 1.07 (6 H, t, J = 7.6 Hz, Ar−CH$_2$CH_3), 2.49 (6 H, s, −CH_3), 2.65 (4 H, q, J = 7.6 Hz, Ar−CH_2CH$_3$), 2.97 (2 H, q, J = 7.6 Hz, Ar−CH_2CH$_3$), 3.52 (4 H, s, −CH_2−), 3.57 (4 H, s, −CH_2−), 3.63 (4 H, s, −CH_2−), 6.80 (1 H, s, Ar−H), 6.92 (2 H, d, J = 7.6 Hz, Py−3H), 7.17 (2 H, d, J = 7.6 Hz, Py−5H), 7.20−7.31 (10 H, m, Ar−H), 7.43 (2 H, t, J = 7.6 Hz, Py−4H). HRMS (FAB, pos): m/z = 611.4108 calcd for ([M + H]$^+$, $C_{42}H_{51}N_4$ 611.4114).

1,3,5-Triethyl-2,4,6-tris((*N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl))aminomethyl)benzene (^{Me}Pym3). This compound was prepared by following the same procedure as described above for **^{Me}Pym2** using 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene instead of 1,3-di(bromomethyl)-2,4,6-triethylbenzene. The eluent of silica gel column chromatography was ethyl acetate (R_f = 0.2) (3.60 g, 95%). IR (KBr, cm^{-1}): 3060, 3026 (aromatic C−H), 2955, 2925, 2867, 2820, 2787 (aliphatic C−H), 1592, 1577, 1455, 1368, 796, 743, 700 (aromatic), 1125, 1114 (C−N). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.64 (9 H, t, J = 7.6 Hz, Ar−CH$_2$CH_3), 2.47 (9 H, s, −CH_3), 2.91 (6 H, q, J = 7.6 Hz, Ar−CH_2CH$_3$), 3.51 (6 H, s, −CH_2−), 3.55 (6 H, s, −CH_2−), 3.62 (6 H, s, −CH_2−), 6.82 (3 H, d, J = 7.6 Hz, Py−3H), 7.01 (3 H, d, J = 7.6 Hz, Py-5H), 7.15−7.28 (18 H, m, Ar−H, Py−4H). HRMS (FAB, pos): m/z = 835.5413 calcd for ([M + H]$^+$, $C_{57}H_{67}N_6$ 835.5427).

[Cu^I(Pye2)(CF_3SO_3)] (1). An acetone solution (3.0 mL) of **Pye2** (101.2 mg, 0.166 mmol) was added slowly to an acetone solution (0.5 mL) of [Cu^I(CH_3CN)$_4$]CF_3SO_3[15] (62.4 mg, 0.166 mmol) under anaerobic conditions (in a glove box, [O_2] < 1 ppm, [H_2O] < 1 ppm). The suspension was turned to a yellow solution. After the mixture was stirred for 12 h, insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. Addition of Et_2O (15 mL) to the residue provided pale yellow precipitates, which were isolated by decantation as pale yellow powder (96.3 mg, 70%). Single crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from acetone/CH_2Cl_2/hexane. IR (KBr, cm^{-1}): 638, 1031, 1157, 1224, 1254, 1284 ($CF_3SO_3^-$). HRMS (FAB, pos): m/z = 673.3333 calcd for ([M + Cu^I]$^+$, $C_{42}H_{50}CuN_4$ 673.3332). Anal. Calcd for [Cu^I(Pye2)(CF$_3$SO$_3$)], $C_{43}H_{50}CuF_3N_4O_3S$: C, 62.72; H, 6.12; N, 6.80. Found: C, 62.85;H, 6.15; N, 6.86.

[Cu^I(Pye3)](CF_3SO_3) (2). A methanol solution (4.5 mL) of **Pye3** (79.2 mg, 0.10 mmol) was added slowly to a methanol solution (0.5 mL) of [Cu^I(CH_3CN)$_4$](CF_3SO_3) (35.9 mg, 0.10 mmol) in a glove box ([O_2] < 1 ppm, [H_2O] < 1 ppm). The mixture turned into pale yellow. After the mixture was stirred for 24 h, insoluble materials were removed by filtration. The filtrate was then concentrated under reduced pressure. Addition of Et_2O (10 mL) to the resulting residue gave pale yellow powder (78.4 mg, 79%). Single crystals suitable for X-ray analysis were obtained by recrystallization from acetone/hexane. IR (KBr, cm^{-1}): 637, 1031, 1149, 1275 ($CF_3SO_3^-$). HRMS (FAB, pos): m/z = 897.4644 calcd

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Table 2. Selected Bond Lengths (Å) and Angles (deg) of Complexes **1**−**5**[a]

1			
Cu(1)−N(1)	1.8974(18)	Cu(1)−N(3)	1.900(2)
Cu(1)−O(3)	2.5972(19)		
N(1)−Cu(1)−N(3)	165.73(8)	N(1)−Cu(1)−O(1)	105.90(7)
N(3)−Cu(1)−O(1)	87.26(7)		
2			
Cu(1)−N(1)	2.008(5)	Cu(1)−N(3)	2.022(4)
Cu(1)−N(5)	2.019(4)		
N(1)−Cu(1)−N(3)	118.28(19)	N(1)−Cu(1)−N(5)	124.6(2)
N(3)−Cu(1)−N(5)	114.88(19)		
3			
Cu(1)−Cl(1)	2.1765(7)	Cu(2)−Cl(1)	2.1824(9)
Cu(1)−N(1)	2.040(2)	Cu(2)−N(3)	2.065(2)
Cu(1)−N(2)	2.008(2)	Cu(2)−N(4)	2.095(2)
Cu(1)−Cu(2)	3.1858(3)		
Cl(1)−Cu(1)−N(1)	129.98(7)	Cl(1)−Cu(2)−N(3)	128.58(6)
Cl(1)−Cu(1)−N(2)	145.91(5)	Cl(1)−Cu(2)−N(4)	148.23(5)
N(1)−Cu(1)−N(2)	83.34(8)	N(3)−Cu(2)−N(4)	83.11(8)
Cu(1)−Cl(1)−Cu(2)	93.92(3)		
4			
molecule 1		molecule 2	
Cu(1)−N(1)	2.021(3)	Cu(2)−N(4)	2.008(3)
Cu(1)−N(2)	2.163(2)	Cu(2)−N(5)	2.178(2)
Cu(1)−N(3)	1.883(3)	Cu(2)−N(6)	1.879(2)
Cu(1)−O(1)	2.459(3)	Cu(2)−O(1)	2.367(3)
Cu(1)−Cu(1)*	6.2338(8)	Cu(2)−Cu(2)*	5.9235(8)
N(1)−Cu(1)−N(2)	82.23(11)	N(4)−Cu(2)−N(5)	82.00(12)
N(1)−Cu(1)−N(3)	137.62(15)	N(4)−Cu(2)−N(6)	138.62(16)
N(2)−Cu(1)−N(3)	133.19(14)	N(5)−Cu(2)−N(6)	133.23(14)
molecular 3			
Cu(3)−N(7)	2.028(4)		
Cu(3)−N(8)	2.158(4)		
Cu(3)N(9)	1.885(5)		
Cu(3)−O(3)	2.371(2)		
Cu(3)−Cu(3)*	5.8844(5)		
N(7)−Cu(3)−N(8)	82.32(15)		
N(7)−Cu(3)−N(9)	131.74(17)		
N(8)−Cu(3)−N(9)	136.72(15)		
6			
Cu(1)−N(1)	1.971(2)	Cu(1)−N(2)	1.998(2)
Cu(1)−O(1)	1.9246(18)	Cu(1)−O(1)*	1.9623(19)
Cu(1)−Cu(1)*	3.0040(4)	O(1)−O(1)*	2.467(2)
N(1)−Cu(1)−N(2)	85.32(10)	N(1)−Cu(1)−O(1)*	105.17(9)
N(2)−Cu(1)−O(1)	93.45(9)	O(1)−Cu(1)−O(1)*	78.78(8)
Cu(1)−O(1)−Cu(1)*	101.22(9)		

[a] Estimated standard deviations are given in parentheses. Symmetry code: for complex **4**; Cu(1)* = (1 − *x*, 1 + *x* − *y*, *z*), Cu(2)* = (1 − *y*, 2 + *x* − *y*, *z*), Cu(3)* = (2 − *y*, 2 + *x* − *y*, *z*), for complex **6**; X* = (− *x*, 1 − *y*, 1 − *z*).

for ([L + Cu^I]$^+$, $C_{57}H_{66}N_6Cu^I_1$ 897.4645). Anal. Calcd for [Cu^I(Pye3)](CF_3SO_3), $C_{58}H_{66}Cu_1F_3N_6O_3S_1$: C, 66.48; H, 6.35; N, 8.02. Found: C, 66.25; H, 6.33; N, 7.81.

[Cu^I_2(^{Me}Pym2)(Cl)]$CuCl_2$ (3). An acetone solution (3.0 mL) of **^{Me}Pym2** (181.7 mg, 0.297 mmol) was added slowly to a suspension of Cu^ICl (58.9 mg, 0.595 mmol) in acetone (0.5 mL) under anaerobic conditions (in a glove box, [O_2] < 1 ppm, [H_2O] < 1 ppm). The suspension turned into a yellow solution. After the mixture was stirred for 18 h, insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure. Addition of Et_2O (15 mL) to the residue gave pale yellow precipitates, which were isolated by decantation as pale yellow powder (175.0 mg, 65%). Single crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from acetone/hexane. HRMS (FAB, pos): m/z = 771.2313 calcd for ([2Cu^I + M + Cl]$^+$, $C_{42}H_{50}ClCu_2N_4$ 771.2316). Anal. Calcd for [Cu^I_2(^{Me}Pym2)Cl]$CuCl_2$, $C_{42}H_{50}Cl_3Cu_3N_4$: C, 55.56; H, 5.55; N, 6.17. Found: C, 55.63; H, 5.56; N, 6.10.

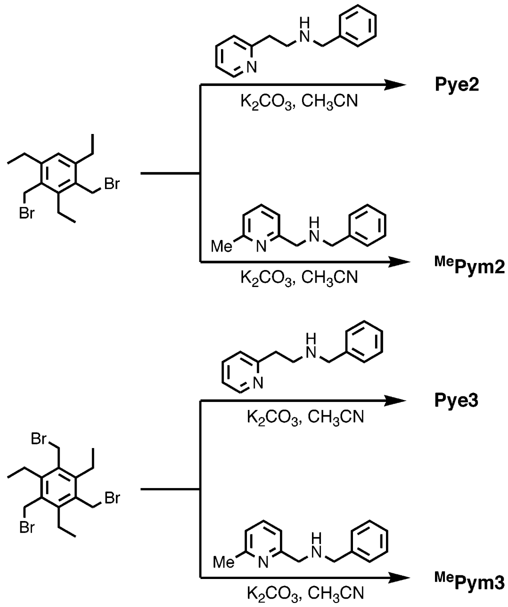
[Cu^I_3(^{Me}Pym3)(CF_3SO_3)(CH_3CN)$_3$](CF_3SO_3)$_2$ (4). An acetone solution (3.0 mL) of **^{Me}Pym3** (219.4 mg, 0.263 mmol) was added slowly to an acetone solution (0.5 mL) of [Cu^I(CH_3CN)$_4$]CF_3SO_3 (297.0 mg, 0.788 mmol) under anaerobic conditions (in a glove box, [O_2] < 1 ppm, [H_2O] < 1 ppm). The suspension turned into a yellow solution. After the mixture was stirred for 30 h, insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure. Addition of Et_2O (15 mL) to the resulting residue gave pale yellow precipitates, which were isolated by decantation as pale yellow powder (388.0 mg, 92%). Single crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from acetone/CH_2Cl_2 (v:v = 1:1)/hexane. IR (KBr, cm^{-1}): 2097 (C≡N), 638, 1031, 1150, 1224, 1271 ($CF_3SO_3^-$). HRMS (FAB, pos): m/z = 1321.2266 calcd for ([M + 3Cu^I + 2CF_3SO_3]$^+$, $C_{59}H_{66}Cu_3F_6N_6O_6S_2$ 1321.2278). Anal. Calcd for [Cu^I_3(^{Me}Pym3)(CH_3CN)$_3$](CF_3SO_3)$_3$, $C_{67}H_{76}Cu_3F_9N_9O_9S_3$: C, 49.66; H, 4.74; N, 7.90. Found: C, 49.57; H, 4.74; N, 7.85.

Product Analysis. Oxygenation of 3 and Isolation of the Modified Ligand ^{Me}Pym1-OH. Complex **3** (200.5 mg, 0.221 mmol) was dissolved in 5.0 mL of acetone under Ar. The solution was then exposed to $^{16}O_2$ for 24 h at −40 °C using an acetonitrile/dry ice bath. After removal of the solvent by evaporation, the resulting materials were dissolved into 20 mL NH_3 aq (7%), extracted with CH_2Cl_2 (10 mL × 3), and dried over K_2CO_3. By removing CH_2Cl_2 by evaporation, a crude oily material was obtained. The modified ligand **^{Me}Pym1-OH** was isolated from the crude oily material by silica gel column chromatography (eluent; ethyl acetate, R_f = 0.19) (74.7 mg, 84%). IR (KBr, cm^{-1}): 3205 (O−H), 3063, 3030 (aromatic C−H), 2963, 2930, 2872 (aliphatic C−H), 1593, 1577, 1506, 1456, 783, 743, 698 (aromatic), 1109, 1061 (C−N). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.14 (3 H, t, J = 7.6 Hz, −CH_2CH_3), 1.17 (3 H, t, J = 7.5 Hz, −CH_2CH_3), 1.19 (3 H, t, J = 7.5 Hz, −CH_2CH_3), 2.55 (3 H, s, Ar−CH_3), 2.56 (2 H, q, J = 7.6 Hz, −CH_2CH_3), 2.58 (2 H, q, J = 7.5 Hz, −CH_2CH_3), 2.68 (2 H, q, J = 7.5 Hz, Ar−CH_2CH_3), 3.66 (2 H, s, Ar−CH_2−), 3.74 (2 H, s, Py−CH_2−), 3.81 (2 H, s, Ar−CH_2−), 6.48 (1 H, s, Ar−H), 7.01 (1 H, d, J = 7.7 Hz, Py−5H), 7.15 (1 H, d, J = 7.7 Hz, Py−3H), 7.24 (1 H, t, J = 7.3 Hz Ar−H), 7.31 (2 H, t, J = 7.3 Hz, Ar−H), 7.34 (2 H, d, J = 7.3 Hz, Ar−H), 7.53 (1 H, t, J = 7.7 Hz, Py−4H), 11.21 (1 H, s, O−H). HRMS (FAB, pos): m/z = 403.2744 calcd for ([M + H]$^+$, $C_{57}H_{67}N_6$ 403.2749). Formation of another product, *N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl)amine, was confirmed by ^{1}H NMR and mass spectroscopy. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (1 H, bs, N−H), 2.54 (3 H, s, −CH_3), 3.86 (2 H, s, Ar−CH_2), 3.90 (2 H, s, Py−CH_2), 7.02 (1 H, d, J = 7.7 Hz, Py−3H), 7.12 (1 H, d, J = 7.7 Hz, Py−5H), 7.21−7.38 (5 H, m, Ar−H), 7.52 (1 H, t, J = 7.7 Hz, Py−4H). HRMS (FAB, pos): m/z = 213.1396 calcd for ([M + H]$^+$, $C_{14}H_{17}N_2$ 213.1392).

^{18}O-Labeling. The reaction of **3** (1.0 × 10^{-4} M, 3.0 mL) and $^{18}O_2$ (introduced by gentle bubbling from 5.0 mL gastight syringe) was carried out in anhydrous acetone at −40 °C. After 3 h, the resulting brown solution was reduced in volume by evaporation. Then, the residue was dissolved into 2 mL NH_3 aq (14%), extracted with CH_2Cl_2 (3.0 mL × 3), and dried over K_2CO_3. After removal of K_2CO_3 by filtration, the solvent was removed by evaporation. Formation of the ^{18}O-labeled product, **^{Me}Pym1-^{18}OH**, was confirmed by ESI-MS (see Figure S3).

Oxygenation of 4. Complex **4** (91.4 mg, 5.7 × 10^{-5} mmol) was dissolved in deaerated acetone (10 mL), and the solution was cooled to −40 °C using an acetonitrile/dry ice bath. Then, dry O_2 gas was introduced into the solution at this temperature. The resulting

Scheme 1



solution was stirred for several hours at −40 °C. After the reaction, evaporation of the solvent gave a crude product, which was dissolved into 20 mL NH_3 aq (7%), extracted with CH_2Cl_2 (10 mL × 3), and dried over K_2CO_3. Identification and quantification of the oxygenated product were carried out by ^{1}H NMR (internal reference; 1,1,2,2-tetrachloroethane) and mass spectroscopy. Yield of the oxygenated product, **^{Me}Pym2-OH**, was 72% based on the starting copper(I) complex. IR (KBr, cm^{-1}): 3361 (O−H), 3055, 3001 (aromatic C−H), 2959, 2869, 2826 (aliphatic C−H), 1590, 1569, 1473,1438, 779, 757, 697 (aromatic), 1284, 1245, 1185, 1104 (C−N). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.86 (3 H, t, J = 7.5 Hz, −CH_2CH_3), 0.93 (3 H, t, J = 7.4 Hz, −CH_2CH_3), 1.13 (3 H, t, J = 7.4 Hz, −CH_2CH_3), 2.48 (3 H, s, −CH_3), 2.53 (3 H, s, −CH_3), 2.64 (2 H, q, J = 7.4 Hz, −CH_2CH_3), 2.75 (4 H, br q, −CH_2CH_3), 3.54 (2 H, s, Ar−CH_2−), 3.55 (2 H, s, Ar−CH_2−), 3.61 (2 H, s, Ar−CH_2−), 3.67 (2 H, s, Py−CH_2−), 3.70 (2 H, s, Py−CH_2−), 3.80 (2 H, s, Ar−CH_2−), 6.91 (1 H, d, J = 7.7 Hz, Py−5H), 6.99 (1 H, d, J = 7.7 Hz, Py−5H), 7.14 (1 H, d, J = 7.7 Hz, Py−3H), 7.18−7.34 (10 H, m, Ar−H), 7.22 (1 H, d, J = 7.7 Hz, Py−3H), 7.47 (1 H, t, J = 7.7 Hz, Py−4H), 7.51 (1 H, t, J = 7.7 Hz, Py−4H), 11.3 (1 H, bs, O−H). HRMS (FAB, pos): m/z = 626.3962 calcd for ([M]$^+$, $C_{57}H_{67}N_6$ 626.3985). Another product, *N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl)amine, was confirmed by ^{1}H NMR and mass spectroscopy as described above.

Results and Discussion

Ligand Synthesis. The bis(didentate) ligands, **Pye2** and **^{Me}Pym2** (Chart 1), were prepared by the S_N2 reaction between 1,3-bis(bromomethyl)-2,4,6-triethylbenzene[14] and *N*-benzyl-*N*-(2-(pyridin-2-yl)ethyl)amine[13a] or *N*-benzyl-*N*-(6-methylpyridin-2-ylmethyl)amine,[13b] respectively, in the presence of potassium carbonate as a base in dry acetonitrile (Scheme 1). The tris(didentate) ligands, **Pye3** and **^{Me}Pym3** (Chart 1), were synthesized in a similar manner using 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene[14] instead of 1,3-bis-(bromomethyl)-2,4,6-triethylbenzene. Treatment of the respective ligands with $[Cu^I(CH_3CN)_4]X$ (X = CF_3SO_3 or PF_6) or Cu^ICl under anaerobic conditions (Ar) gave the corresponding copper(I) complexes **1**−**4** as follows.

Mononuclear Copper(I) Complexes. The ligand carrying two 2-(pyridin-2-yl)ethylamine metal binding sites, **Pye2**, afforded mononuclear copper(I) complex **1** in the reaction with $[Cu^I(CH_3CN)_4](CF_3SO_3)$ as shown in Figure 2. The crystallographic data and the selected bond lengths and angles are summarized in Tables 1 and 2, respectively. The copper-(I) complex exhibits a two-coordinate almost linear structure with two pyridine nitrogen atoms of the ligand [angle N(1)−Cu(1)−N(2) = 165.7°]. Thus, the alkylamine nitrogen atoms are free from coordination. On the other hand, one of the oxygen atoms of $CF_3SO_3^-$ weakly interacts with the cuprous ion ($d_{Cu(1)-O(1)}$ = 2.598 Å). Thus, the coordination geometry of **1** can also be regarded as a distorted T-shape structure (the deviation of Cu(1) from the trigonal plane consisted of N(1), N(2), and O(3) is 0.084 Å). The aromatic ring of the triethylbenzene spacer is placed just above the copper(I) ion, although there is no direct interaction between them; the distance between Cu(1) and one of the nearest carbon atom of the aromatic ring is 3.694 Å. All the ethyl groups on the benzene spacer point to the opposite face against the metal-binding site (Figure 2). It should be noted that complex **1** exhibited a high oxidation potential at 990 mV versus SCE (Figure S1). Thus, this complex showed virtually no reactivity toward O_2 in contrast to ordinary copper(I) complexes supported by the didentate ligands.[2]

Another mononuclear copper(I) complex, **2**, was obtained when **Pye3** carrying three 2-(pyridin-2-yl)ethylamine metal binding groups was treated with $[Cu^I(CH_3CN)_4](CF_3SO_3)$. The crystal structure of **2** is shown in Figure 3, and the crystallographic data and the selected bond lengths and angles are also listed in Tables 1 and 2, respectively. The whole molecule of **2** exhibits a slightly distorted C_3-like symmetry, and the copper(I) center exhibits a three-coordinate trigonal planar structure supported by the three pyridine donor groups of **Pye3**. The deviation of Cu(1) from the trigonal plane consisting of N(1), N(3), and N(5) is only 0.176 Å. In this case as well, the alkylamine nitrogen atoms are free from coordination, and all the methyl groups of the ethyl substituents are located on the opposite side of the copper coordination site with respect to the central benzene plane. Notably, complex **2** also exhibits a high oxidation potential at 990 mV versus SCE (Figure S2), thus exhibiting virtually no reactivity toward O_2 as in the case of **1**. The copper(I) coordination geometry of **2** and its less O_2-reactivity are similar to those of Riordan's complex.[11e]

Biological Relevance of Mononuclear Copper(I) Complexes 1 and 2. It is interesting to note that the trigonal planar structure of **2** closely resembles the structure of the CuA site of the reduced form of peptidylglycine α-hydroxylating monooxygenase (PHM) shown in Figure 4, where the copper(I) ion is ligated by three histidine imidazoles forming a distorted trigonal planar geometry (deviation of CuA from the trigonal plane consisting of three histidine imidazole nitrogen atoms is 0.264 Å).[16]

The copper(I) ion at the CuB site in the fully reduced form of cytochrome *c* oxidase (C*c*O) is also ligated by three

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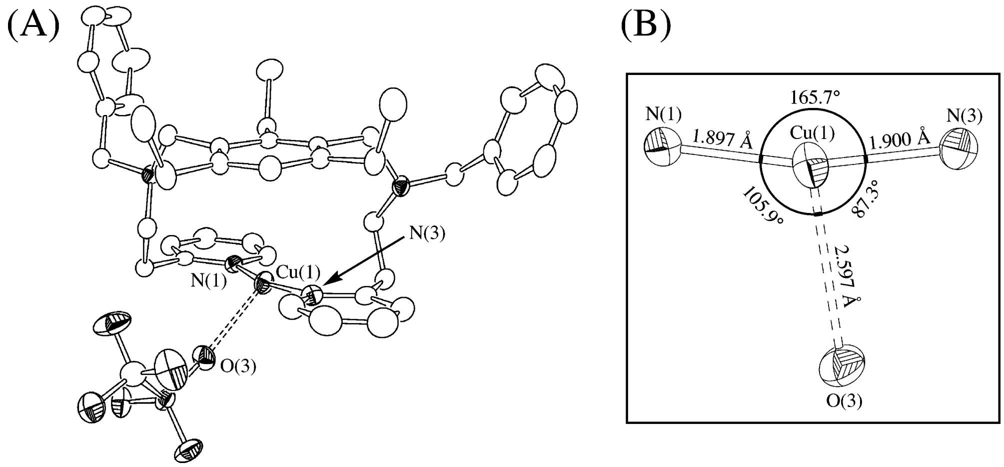

Figure 2. (A) ORTEP drawing of [Cu^{I}(**Pye2**)(CF$_3$SO$_3$)] (**1**) showing 50% probability thermal ellipsoids. The hydrogen atoms are omitted for clarity. (B) Expanded view of the copper(I) center of **1**.

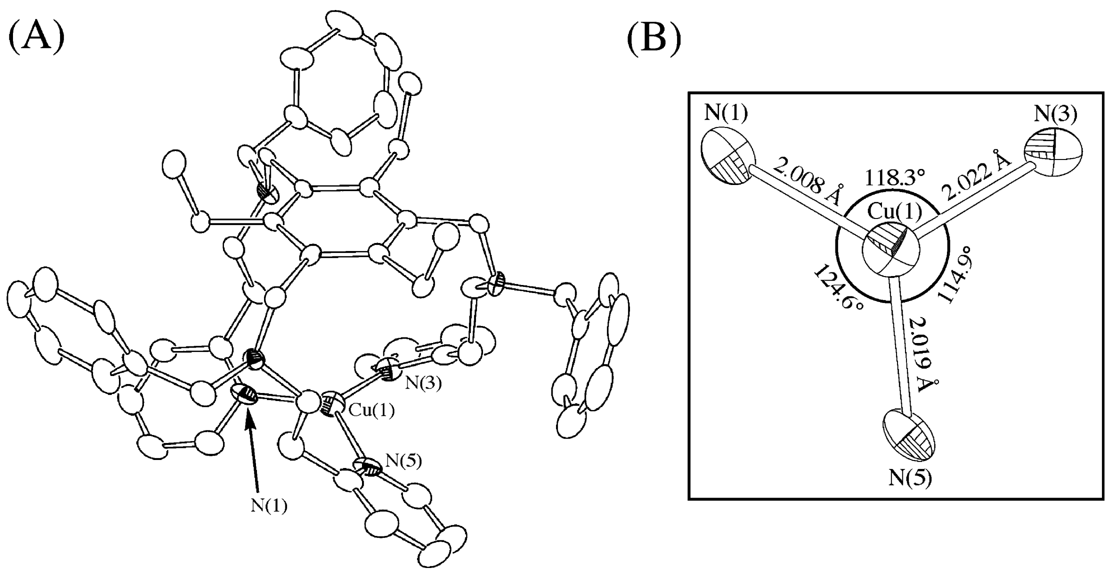

Figure 3. (A) ORTEP drawing of [Cu^{I}(**Pye3**)](CF$_3$SO$_3$) (**2**) showing 50% probability thermal ellipsoids. The counteranion and the hydrogen atoms are omitted for clarity. (B) Expanded view of the copper(I) center of **2**.

histidine imidazoles. In this case, the coordination geometry is more like a distorted T-shape like complex **1** (deviation of CuB from the trigonal plane consisted of three histidine imidazole nitrogen atoms is 0.177 Å) (Figure 5).[17]

In the case of PHM, it is believed that one electron stored at CuA is transferred to CuB where O_2 is bound and activated for the substrate oxygenation. One of the most important but still unresolved mechanistic issues is the timing of electron transfer from CuA to CuB. If the electron at reduced CuA is transferred to the O_2-bound CuB before the substrate oxygenation, a copper(II)−hydroperoxo (Cu$_B$−OOH) intermediate may be the reactive species.[18] However, the recent enzymatic and theoretical studies have suggested that the electron transfer occurs after the C−H bond activation of the substrate.[19] In this case, a copper(II)−superoxo (Cu$_B$−OO$^{\bullet}$) intermediate could be the real active species rather than Cu$_B$−OOH. Judging from the high oxidation potential of complex **2**, we would suggest that the electron transfer from CuA to O_2-bound CuB might not take place so easily. Thus, the recent mechanism involving Cu$_B$−OO$^{\bullet}$ would be more plausible as compared to the previous mechanism involving Cu$_B$−OOH.

In the C*c*O system as well, the timing of electron-transfer from reduced CuB to the O_2-bound heme a$_3$ is a mechanistic issue in the multielectron reduction process of O_2.[4,17] In the model systems, the reaction of Fe^{II}(Por)−Cu^{I}(L) model compounds and dioxygen mostly provided peroxo-bridged Fe^{III}(Por)−O_2−Cu^{II}(L) species. In those systems, TPA or PY2 type capping ligands are employed to mimic the Cu-binding site (CuB). Such ligands have been well demonstrated to produce copper(I) complexes exhibiting high reactivity toward O_2.[2] On the other hand, it has been reported

(17) Tsukihara, T.; Shimokata, K.; Katayama, Y.; Shimada, H.; Muramoto, K.; Aoyama, H.; Mochizuki, M.; Shinzawa-Itoh, K.; Yamashita, E.; Yao, M.; Ishimura, Y.; Yoshikawa, S. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 15304−15309.
(18) Klinman, J. P. *Chem. Rev.* **1996**, *96*, 2541−2561.
(19) (a) Chen, P.; Solomon, E. I. *J. Am. Chem. Soc.* **2004**, *126*, 4991−5000. (b) Francisco, W. A.; Wille, G.; Smith, A. J.; Merkler, D. J.; Klinman, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13168−13169. (c) Bauman, A. T.; Yukl, E. T.; Alkevich, K.; Ashley, L. McCormack, A. L.; Blackburn, N. J. *J. Biol. Chem.* **2006**, *281*, 4190−4198.

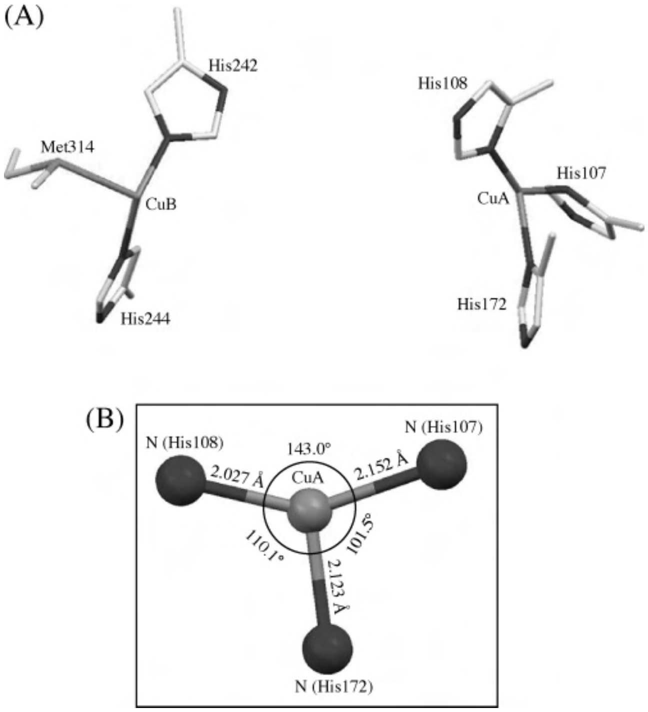

Figure 4. (A) Active site structure of the reduced form of PHM (PDB ID code 3PHM) and (B) expanded view of the reduced CuA center.

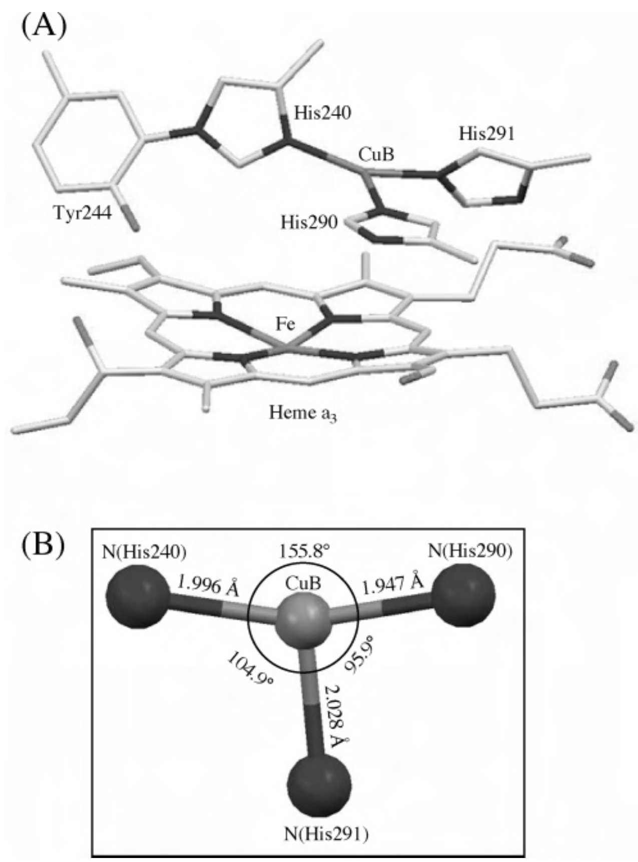

Figure 5. (A) Active site structure of the fully reduced CcO (PDB ID code 1V55) and (B) expanded view of the reduced CuB center.

that CuB in the native enzyme is kept as a copper(I) reduced state during the catalytic cycle, while the electrons are supplied to heme a_3 site through Tyr244 covalently bound

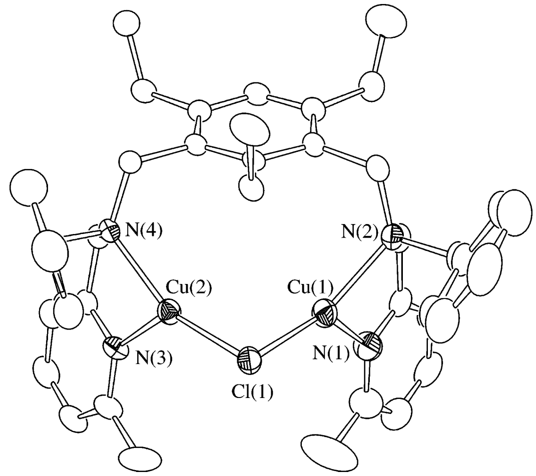

Figure 6. ORTEP drawing of $[Cu^I_2(^{Me}\mathbf{Pym2})(Cl)]Cu^ICl_2$ (**3**) showing 50% probability thermal ellipsoid. The counteranion ($CuCl_2^-$) and the hydrogen atoms are omitted for clarity.

to His240, one of the ligands of CuB.[20] Judging from the geometric similarity between CuB of C*c*O and our model complex **1** having the high oxidation potential (990 mV vs SCE), the participation of CuB for the direct reduction of O_2 might be unlikely as suggested by the enzymatic studies.[17,20]

Dinuclear Copper(I) Complex. In contrast to the case of **Pye2** that gave mononuclear copper(I) complex **1** (Figure 2), bis(didentate) ligand **^{Me}Pym2** provided dinuclear copper-(I) complex $[Cu^I_2(^{Me}\mathbf{Pym2})(Cl)]CuCl_2$ (**3**) in the reaction with Cu^ICl.[21] The crystal structure of **3** is shown in Figure 6, and the crystallographic data and the selected bond lengths and angles are summarized in Tables 1 and 2, respectively. The copper(I) ions are bridged by chloride ion and exhibit largely distorted trigonal planar structure with the N_2Cl donor set (deviation of Cu(1) and Cu(2) from the N_2Cl trigonal plane are 0.098 and 0.032 Å, respectively). The angle of Cu−Cl−Cu is 93.9°, and the Cu−Cu distance is 3.186 Å.

So far, X-ray structures of the deoxy dicopper(I) forms of type-3 copper proteins have been reported for *Limulus polyphemus* hemocyanin (Hc),[22] sweet potato catechol oxidase (CO),[23] and bacterial tyrosinase (Tyr).[24] In all cases, each copper(I) ion is ligated by three histidine imidazoles, and the Cu^I−Cu^I distances are much longer (4.6, 4.4, and 4.1 Å, respectively).[22−24] Thus, dinuclear copper(I) complex **3** could not be a precise structure model for those reduced type-3 copper proteins. Nonetheless, complex **3** exhibited a notable reactivity toward O_2, providing a functional model system of tyrosinase (vide infra).

Trinuclear Copper(I) Complex. Trinuclear copper(I) complex $[Cu^I_3(^{Me}\mathbf{Pym3})(CF_3SO_3)(CH_3CN)_3](CF_3SO_3)_2$ (**4**) was obtained when tris(didentate) ligand **^{Me}Pym3** was

(20) Kitagawa, T.; Ogura, T. *Prog. Inorg. Chem.* **1997**, *45*, 431−479.
(21) The reaction of **^{Me}Pym2** and $[Cu^I(CH_3CN)_4]PF_6$ also gave a similar dicopper(I) complex $[Cu^I_2(^{Me}\mathbf{Pym2})(CH_3CN)_2](PF_6)_2\cdot 1/2CH_2Cl_2$.
(22) Hazes, B.; Magnus, K. A.; Bonaventura, C.; Bonaventura, J.; Dauter, Z.; Kalk, K. H.; Hol, W. G. J. *Protein Sci.* **1993**, *2*, 597−619.
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(24) Matoba, Y.; Kumagai, T.; Yamamoto, A.; Yoshitsu, H.; Sugiyama, M. *J. Biol. Chem.* **2006**, *281*, 8981−8990.

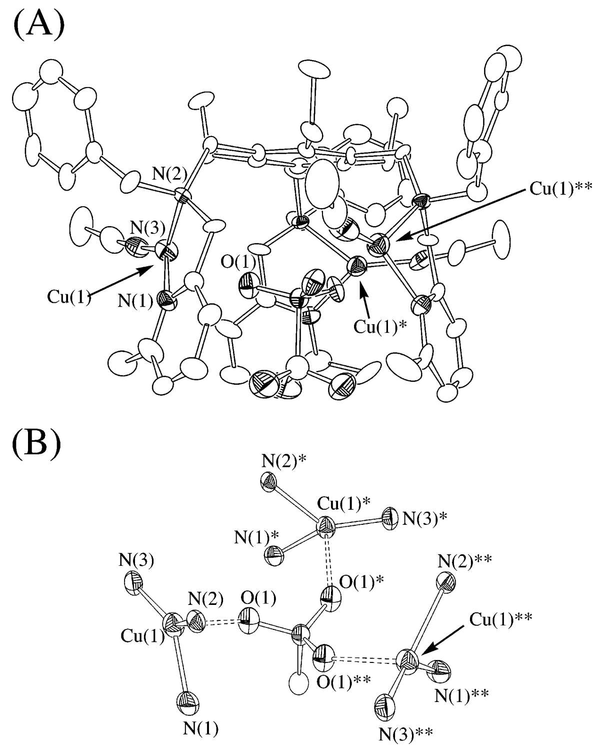


Figure 7. ORTEP drawings of (A) $[Cu^I_3(^{Me}\mathbf{Pym3})(CF_3SO_3)(CH_3CN)_3](CF_3SO_3)_2$ (**4**) (molecule 1) and (B) its closed view of the trinuclear copper(I) site showing 50% probability thermal ellipsoids. The noncoordinated counteranions and hydrogen atoms are omitted for clarity.

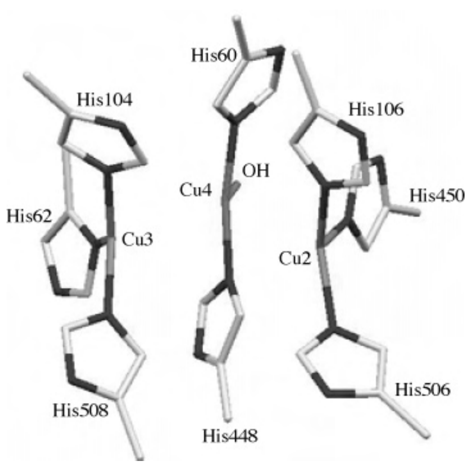


Figure 8. Active site structure of the fully reduced form of ascorbate oxidase (PDB ID code 1ASO).

employed. The crystal structure of **4** is presented in Figure 7, and the crystallographic data and the selected bond lengths and angles are listed in Tables 1 and 2, respectively. The molecule has C_3 symmetry, and one of the counteranions, $CF_3SO_3^-$, is encapsulated in the molecular cavity constructed by the three $Cu^I(^{Me}\mathbf{Pym})(CH_3CN)$ units.[25] Each copper(I) ion exhibits a trigonal pyramidal structure with two nitrogen atoms N(1) and N(2) of the ligand and one nitrogen atom N(3) of the coordinated acetonitrile molecule occupying the trigonal basal plane and one of the oxygen atoms O(1) of the encapsulated $CF_3SO_3^-$at the axial position ($d_{Cu(1)-O(1)} =$

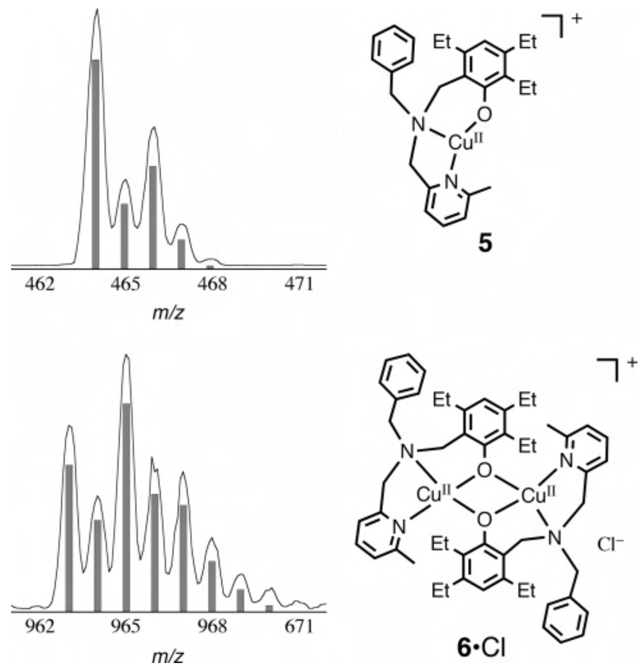


Figure 9. Experimental and calculated peak envelopes in the positive-ion electrospray mass spectra of of the monomeric copper(II) compound **5** (m/z = 464) and the dimeric copper(II) compound **6**·Cl (m/z = 965).

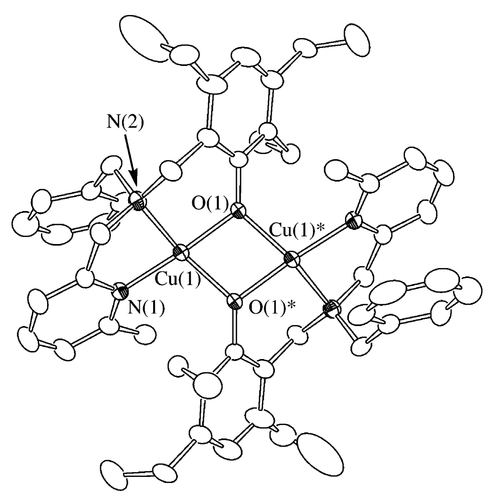


Figure 10. ORTEP drawing of $[Cu^{II}_2(^{Me}\mathbf{Pym1\text{-}O})_2](PF_6)_2$ (**6**) showing 50% probability thermal ellipsoids. The counteranions and the hydrogen atoms are omitted for clarity.

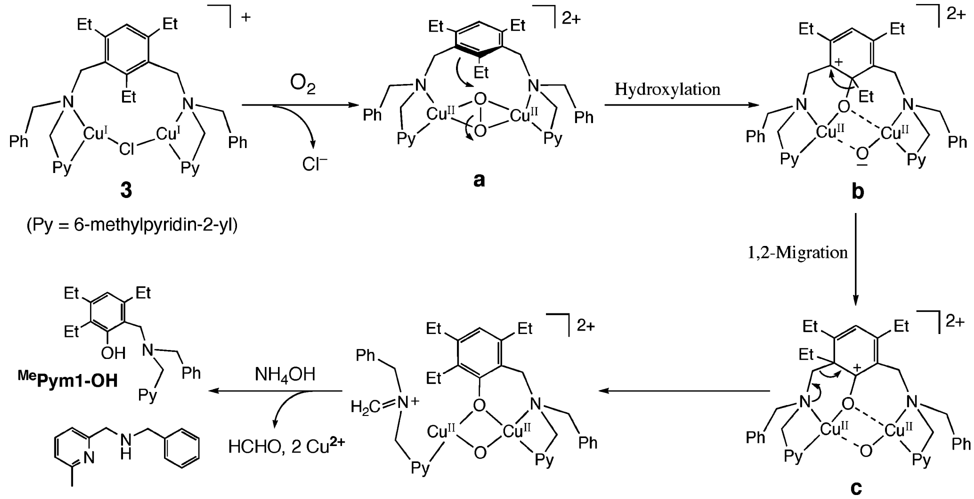
~2.4 Å). The trigonal arrangement of three copper(I) ions in **4** resembles that of the trinuclear copper reaction center of the fully reduced form of ascorbate oxidase (Figure 8), even though the Cu−Cu distance of ~6.0 Å in **4** (averaged value of the three crystallographically independent molecules 1−3, see Table 2) is relatively longer than that in the enzyme (Cu2−Cu3, 5.087 Å; Cu2−Cu4, 4.461 Å; Cu3−Cu4, 4.031 Å) (Figure 8).[26] This complex showed a similar reactivity toward O_2 as discussed below.

Copper(I)−O_2 Reactivity of Dinuclear and Trinuclear Copper(I) Complexes 3 and 4. As noted in the above section, mononuclear copper(I) complexes **1** and **2** showed no reactivity toward O_2 due to their high oxidation potential

(25) Recently, Anslyn and coworkers developed a shape selective anion binding using a similar type of receptor consisted of the trietylbenzene spacer.[5,6c,e,8b]

(26) Messerschmidt, A.; Luecke, H.; Huber, R. *J. Mol. Biol.* **1993**, *230*, 997−1014.

Scheme 2

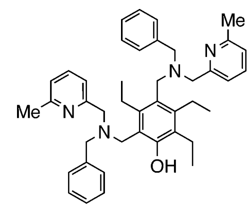


(990 mV vs SCE). On the other hand, dinuclear copper(I) complex **3** and trinuclear copper(I) complex **4** reacted with O_2 at −40 °C in acetone to induce an aromatic ligand hydroxylation reaction as follows. In the reaction of **3**, for example, the ESI-MS of the final reaction mixture gave new peaks at m/z = 464 and 965, the peak positions and isotope distribution patterns of which are consistent with the chemical formulations of the mononuclear and dinuclear copper(II) complexes of the hydroxylated ligand **^{Me}Pym1-O**$^-$, [Cu^{II}(**^{Me}Pym1-O**)]$^+$ (**5**), and {[Cu$^{II}_2$(**^{Me}Pym1-O**)$_2$]Cl}$^+$ (**6**·Cl), respectively (Figure 9). From the final reaction mixture, the hydroxylated ligand **^{Me}Pym1-OH** was isolated in 84% yield by the workup treatment with aqueous ammonia (for detailed MS and NMR analyses, see Experimental Section).

In addition, an isotope labeling experiment using $^{18}O_2$ instead of $^{16}O_2$ has clearly demonstrated that the oxygen atom introduced into the hydroxylated ligand originated from molecular oxygen as indicated in Figure S3. Furthermore, single crystals of the dimeric copper(II) complex **6**·$(PF_6)_2$ suitable for the X-ray analysis have been isolated from the final reaction mixture by allowing it to stand for a couple of days. The crystal structure of **6**·$(PF_6)_2$ is shown in Figure 10 together with the selected bond lengths and angles presented in Tables 1 and 2, respectively.

Complex **6** is a dimeric copper(II) complex of the modified ligand **^{Me}Pym1-OH**, where the deprotonated phenolate oxygen atom introduced into the ligand by the oxygenation reaction acts as a bridging ligand to form a rhombic Cu_2O_2 core structure. The compound has a center of symmetry in the Cu_2O_2 core, and the cupric ion has a largely distorted four-coordinate square planar structure with the N_2O_2 donor set. It should be noted that, as the ^{1}H NMR suggested, one of the ethyl groups of the trietylbenzene spacer migrated from its original position to the neighboring carbon atom and the hydroxylation occurred just on the carbon where the ethyl group was originally attached. It is also obvious that one of the **^{Me}Pym** metal binding groups is detached from the benzene spacer. Thus, the NIH-type alkyl rearrangement occurred during the aromatic ligand hydroxylation reaction. Thus, the overall chemistry of the present system is essentially the same as that of Karlin's aromatic ligand

Chart 2



hydroxylation reaction in the dinuclear copper(I)−xylyl complex by molecular oxygen,[27] where electrophilic aromatic substitution reaction by a (μ-η^2:η^2-peroxo)dicopper(II) intermediate has been proposed.[28] Although we have not yet succeeded in detecting the active oxygen intermediate, the reaction mechanism could be the same as that proposed for Karlin's aromatic ligand hydroxylation reaction as illustrated in Scheme 2. Namely, oxygenation of **3** may give an active oxygen intermediate such as the (μ-η^2:η^2-peroxo)dicopper(II) complex **a**, from which electrophilic attack of the peroxo group by the aromatic ring of the spacer occurs intramolecularly to give cationic intermediate **b**. The 1,2-migration of the ethyl group proceeds to give rearranged intermediate **c**, from which one of the **^{Me}Pym** metal-binding moieties is released by the electron flow during the rearrangement shown in Scheme 2. The NIH-shift of the ethyl group is the strong evidence for the formation of the cationic intermediate **b** as suggested in Karlin's reaction.[28]

A similar reaction (aromatic ligand hydroxylation accompanied by an NIH-shift of ethyl substituent) occurred, when the reaction of the trinuclear copper(I) complex **4** and O_2 was carried out under the same experimental conditions. Thus, the hydroxylated ligand **^{Me}Pym2-OH** (Chart 2) was obtained from the final reaction mixture by the ordinary

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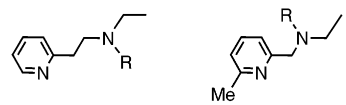
(28) (a) Cruse, R. W.; Kaderli, S.; Karlin, K. D.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6882−6883. (b) Karlin, K. D.; Nasir, M. S.; Cohen, B. I.; Cruse, R. W.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1994**, *116*, 1324−1336. (c) Mahapatra, S.; Kaderli, S.; Llobet, A.; Neuhold, Y.-M.; Palanché, T.; Halfen, J. A.; Young, V. G. Jr.; Kaden, T. A.; Que, L. Jr.; Zuberbühler, A. D.; Tolman, W. B. *Inorg. Chem.* **1997**, *36*, 6343−6356.

Chart 3



Pye^R **^MePym^R**

workup treatment with NH_4OH, in which one of the ^MePym metal binding groups of **^MePym3** was removed and one of the ethyl groups migrated to the next carbon where ^MePym group was originally attached before the ligand modification (for detailed product analysis, see Experimental Section).

Conclusion

In this study, we have developed a series of pyridylalkylamine ligands containing a 1,3,5-triethylbenzene spacer, **Pye2, Pye3, ^MePym2,** and **^MePym3** (Chart 1). The ligands consisting of the 2-(pyridin-2-yl)ethylamine didentate metal-binding moiety **Pye2** and **Pye3** gave mononuclear copper(I) complexes **1** and **2**, exhibiting distorted three-coordinate T-shape structure and trigonal planar structure, respectively. These coordination geometries resemble those of CuA site of PHM (peptidylglycine α-hydroxylating monooxygenase) and CuB site of C*c*O (cytochrome *c* oxidase), providing good structural models for those enzymes. Notably, copper(I) complexes **1** and **2** showed high oxidation potential at 990 mV versus SCE, thus exhibiting virtually no reactivity toward O_2. These results suggest that the mononuclear copper site in PHM and C*c*O may not be a good electron donor for the multielectron reduction process of O_2.

On the other hand, the ligands carrying the (6-methylpyridin-2-yl)methylamine didentate metal binding sites such as **^MePym2** and **^MePym3** provided the dinuclear and trinuclear copper(I) complexes with a distorted trigonal planar geometry and a trigonal pyramidal geometry, respectively. These complexes showed moderate reactivity toward O_2 to induce an aromatic ligand hydroxylation reaction involving an NIH-shift of one of the ethyl substituents on the aromatic spacer. The NIH-shift is strong evidence of the electrophilic aromatic substitution mechanism shown in Scheme 2. If so, the most plausible active oxygen intermediate is (μ-η^2:η^2-peroxo)-dicopper(II) complex **a** (Scheme 2) as demonstrated in Karlin's aromatic ligand hydroxylation reaction.[28] However, a bis(μ-oxo)dicopper(III) complex could also be a possible reactive intermediate as recently demonstrated by Stack et al.[29] Unfortunately, we could not detect such active oxygen intermediates during the course of the reaction.

It should be emphasized that the 1,3,5-triethylbenzene spacer induces significantly large effects on the structure and O_2-reactivity of the copper(I) complexes. For example, we have already demonstrated that the didentate ligands **Pye^R** (Chart 3) provided mononuclear copper(I) complexes, exhibiting significantly high reactivity toward O_2.[30] In this case, the oxygenated product was a bis(μ-oxo)dicopper(III) complex, in which aliphatic hydroxylation occurred effectively on the ligand sidearm.[31] On the other hand, **Pye2** and **Pye3** containing 1,3,5-triethylbenzene spacer (Chart 1) afforded the mononuclear copper(I) complexes with virtually no reactivity toward O_2. Moreover, the copper(I) complexes supported by **^MePym^R** (Chart 3) also gave a bis(μ-oxo)-dicopper(III) complex as the oxygenation product,[32] while **^MePym2** and **^MePym3** involving the triethylbenzene spacer produced an active oxygen intermediate which exhibits a peroxo-like reactivity (aromatic ligand hydroxylation, see Scheme 2). The importance of the ethyl substituents on the benzene spacer is also evident, since the PY2 type ligand connected to the 1,3,5-positions of simple benzene spacer (without the ethyl substituents) produced a complicated hexanuclear copper(II) complex in the oxygenation reaction of the copper(I) complex.[33]

Acknowledgment. This work was financially supported in part by Grants-in-Aid for Scientific Research (No. 17350086, 18037062, and 18033045) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Crystallographic data in CIF format, cyclic voltammograms, and ESI-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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