# Oxidative Demethylation in Monooxygenase Model Systems. Competing Pathways for Binuclear and Helical Multinuclear Copper(I) Complexes

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**Abstract:** The ligand 2,6-bis[*N*-(2-pyridylethyl)formimidoyl]-1-methoxybenzene (2,6-BPB-1-$OCH_3$) (**4**) reacts with $Cu(CH_3CN)_4BF_4$ to form novel binuclear copper(I) complexes $[Cu_2(2,6\text{-BPB-1-}OCH_3)(BF_4)_2(CH_3CN)_4]$ (**11**) and $[Cu_2(2,6\text{-BPB-1-}OCH_3)(BF_4)_2(CH_2Cl_2)_{0.5}]$ (**14**), or the helical polynuclear copper(I) complex $[Cu(2,6\text{-BPB-1-}OCH_3)(BF_4)]_n$ (**16**). The complexes mimic certain monooxygenases as they rapidly take up $O_2$ followed by demethylation of the anisole moiety (up to 95% yield). $^{18}O$ experiments are provided that show competing aryl–oxygen (≥60%) and alkyl–oxygen (20%) bond cleavage pathways. Introduction of a *p*-methoxy substituent in the arene moiety of complex **11** decreases the oxygenation rate and led to an unprecedented $O_2$ induced arene–$OCH_3$–$OCD_3$ exchange at 20 °C in $CD_3OD$. A mechanistic rational is given.

Current interest in binuclear copper complexes as model compounds for copper proteins[1] focuses on the design and synthesis of active site mimics[2] and on the elucidation of the factors that govern the (reversible) binding[3] and reactivity[2,4-7] of molecular oxygen at the copper centers (i.e., monooxygenase mimics). With the aim of designing new catalysts for oxygenations with molecular oxygen we have been involved in studies on binuclear copper complexes and their (catalytic) properties in the presence of molecular oxygen. Previously[6] we described the synthesis and arene hydroxylation of a binuclear Cu(I) complex that contains a *m*-xylyl bridged ligand system. The unusual arene hydroxylation, which was first reported by Karlin and co-workers[2a] for a related case and which seems to depend critically on the ligands employed, may be considered as a mimic for a copper dependent monooxygenase reaction. In order to get more insight into the reactivity of the binuclear Cu(I) complexes and in particular in the dependency of the arene hydroxylation on the ligands employed different substituents were placed in the "bridging" arene 1-position.

The results presented here are of the unexpected oxidative demethylation of the anisole moiety, at ambient conditions with molecular oxygen, in binuclear Cu(I) complexes derived from methoxy-substituted ligand systems. Oxidative demethylation of aryl ethers is catalyzed by various enzymes such as P450 dependent monooxygenases,[8,9] ω-hydroxylases, and ligninase.[10] Although several pathways have been suggested, the general accepted mechanism for demethylations based on cytochrome P450 dependent monooxygenases involves α-hydroxylation to a hemiacetal followed by fragmentation to phenol and carbonyl compounds.[8,9]

The $O_2$-induced demethylation in the complexes described in the present study[11] proceeds (in part) via ipso hydroxylation of the anisole moiety. First the synthesis and reactivity toward dioxygen of novel binuclear (**11** and **14**) and helical polynuclear (**16**) copper(I) monooxygenase model systems are reported. By using $^{18}O_2$- and $^{18}O$-labeled complex **11** an investigation toward a possible mechanism of the $O_2$-induced demethylations, observed for these complexes, was executed. Finally a mechanistic interpretation is given.

## Experimental Section

All reactions and manipulations were performed (when necessary) under an inert atmosphere of dry, oxygen free nitrogen. Syntheses and manipulations of copper complexes were performed in Schlenck equipment with glassware from a hot oven (150 °C). All solvents were freshly distilled under nitrogen: tetrahydrofuran from Na/benzophenone, dichloromethane, acetonitrile, and diethyl ether from $P_2O_5$, and methanol from Mg. Melting points were recorded on a Mettler capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an Unicam II SP200 spectrophotometer; NMR spectra were obtained on a Varian VXR 300 spectrometer. Proton chemical shifts (at 300 MHz) are reported in parts per million (ppm) with TMS ($\delta$ = 0 ppm) as the reference. Carbon chemical shifts (obtained at 300 MHz) are reported in ppm relative to $CHCl_3$ (77.0 ppm). Elemental analyses were

(1) *Copper Proteins and Copper Enzymes*; Lontie, R., Ed.; CRC: Boca Raton, FL, 1984; Vol. 2. *Copper Coordination Chemistry: Biochemical & Inorganic Perspectieves*; Karlin, K. D., Zubieta, J., Eds.; Adenine: Guilderland, New York, 1983. Metal Ions in Biological Systems. In *Copper Proteins*; Sigel, H., Ed.; Marcel Dekker, New York, 1981; Vol. 13.

(2) (a) Karlin, K. D.; Gultneh, Y.; Hutchinson, J. P.; Zubieta, J. *J. Am. Chem. Soc.* **1982**, *104*, 5240. (b) Pate, J. E.; Cruse, R. W.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1987**, *109*, 2624. (c) Nelson, S. M.; Esho, F.; Lavery, A.; Drew, M. G. B. *J. Am. Chem. Soc.* **1983**, *105*, 5693. (d) Traylor, T. G.; Hill, K. W.; Tian, Z. Q.; Rheingold, A. L.; Peisach, J.; McCracken, J. *J. Am. Chem. Soc.* **1988**, *110*, 5571. (e) Nelson, S. M. *Inorg. Chim. Acta* **1982**, *62*, 39. (f) Sorrell, T. N.; Malachowski, M. R.; Jameson, D. L. *Inorg. Chem.* **1982**, *21*, 3250. (g) Tyeklar, Z.; Karlin, K. D. *Acc. Chem. Res.* **1989**, *22*, 241.

(3) (a) Bulkowski, J. E.; Burk, P. L.; Ludmann, M. F.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 498. (b) Simmons, M. G.; Merrill, C. L.; Wilson, L. J.; Bottomley, L. A.; Kadish, K. M. *J. Chem. Soc., Dalton Trans.* **1980**, 1827. (c) Karlin, K. D.; Cruse, R. W.; Gultneh, Y.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1984**, *106*, 3372.

(4) (a) Karlin, K. D.; Hayes, J. C.; Gultneh, Y.; Cruse, R. W.; McKown, J. W.; Hutchinson, J. P.; Zubieta, J. *J. Am. Chem. Soc.* **1984**, *106*, 2121. (b) Casella, L.; Rigoni, L. *J. Chem. Soc., Chem. Commun.* **1985**, 1668. (c) Burnett, M. G.; McKee, V.; Nelson, S. M. *J. Chem. Soc., Chem. Commun.* **1980**, 829. (d) Moore, K.; Vigee, G. S. *Inorg. Chim. Acta* **1982**, *66*, 125.

(5) (a) Cruse, R. W.; Kaderli, S.; Meyer, C. J.; Zuberbühler, A. D.; Karlin, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 5020. (b) Casella, L.; Gullotti, M.; Pallanza, G.; Rigoni, L. *J. Am. Chem. Soc.* **1988**, *110*, 4221.

(6) Gelling, O. J.; van Bolhuis, F.; Meetsma, A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1988**, 552.

(7) (a) Karlin, K. D.; Cruse, R. W.; Gultneh, Y.; Faroog, A.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1987**, *109*, 2668. (b) Jacobson, R, R.; Tyeklar, Z.; Faroog, A.; Karlin, K. D.; Liu, S.; Zubieta, J. *J. Am. Chem. Soc.* **1988**, *110*, 3690. (c) Karlin, K. D.; Haka, M. S.; Cruse, R. W.; Meyer, G. J.; Faroog, A.; Gultneh, Y.; Hayes, J. C.; Zubieta, J. *J. Am. Chem. Soc.* **1988**, *110*, 1196. (d) Merrill, C. L.; Wilson, L. J.; Thamann, T. J.; Loehr, T. M.; Ferris, N. S.; Woodruff, W. H. *J. Chem. Soc., Dalton Trans.* **1984**, 2207. (e) Thompson, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 4057, 8308. (f) Casella, L.; Silver, M. E.; Ibers, J. A. *Inorg. Chem.* **1984**, *23*, 1409 and references cited therein.

(8) Hamilton, G. A. In *Molecular Mechanisms of Oxygen Activation*; Hayaishi, O., Ed.; Academic Press: New York, 1974. Matsuura, T. *Tetrahedron* **1977**, *33*, 2869.

(9) Lindsay Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. II* **1983**, 621.

(10) (a) Miki, K.; Renganathan, V.; Gold, M. H. *FEBS Lett.* **1986**, *203*, 235. (b) Enoki, A.; Yajima, Y.; Gold, M. H. *Phytochemistry* **1981**, *20*, 1543. (c) Palmer, J. M.; Harvey, P. J.; Schoemaker, H. E. *Phil. Trans. R. Soc. Lond. A* **1987**, *321*, 495. (d) Schoemaker, H. E.; Harvey, P. J.; Bowen, R. M.; Palmer, J. M. *FEBS Lett.* **1985**, *183*, 7.

(11) Presented in part at the *6th* International Symposium on Homogeneous Catalysis, Vancouver, August 1988.

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obtained in the microanalytical department of the University of Groningen. Mass spectral analyses including high-resolution mass spectra and isotope analyses were carried out on an AEI-MS-902 spectrometer. $^{18}O_2$ oxygen gas (99.10% isotope content) was purchased from Rohstoff Einfuhr. The isotope content was analyzed at regular intervals by using high resolution mass spectrometry.

**2,6-Bis(dibromomethyl)-1-methoxybenzene (2).** To a stirred solution of 2,6-dimethyl-1-methoxybenzene (**1**) (13.6 g, 0.1 mol) in carbon tetrachloride (100 mL) was slowly added bromine (20.5 mL, 0.4 mol) at such a rate that the addition was completed in 3 h, while the solution was continuously irradiated by using an IR lamp (Philips 13372 E/06 * OK) and heated just at the reflux temperature. After the addition was completed, stirring and irradiation (under reflux) of the solution was continued for 12 h. The solvent was removed in vacuo, and the solid residue crystallized from hexane to furnish **2** as white needles (32.6 g, 72%): mp 100.4–102.3 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.90 (s, 3 H), 6.95 (s, 2 H), 7.08–7.47 (m, 1 H), 7.87 (d, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 32.98, 62.49, 126.16, 132.39, 135.32, 147.83 ppm. Anal. Calcd for $C_9H_8Br_4O$: C, 23.91; H, 1.77; Br, 70.77. Found: C, 23.87; H, 1.84; Br, 70.90.

**1-Methoxybenzene-2,6-dicarboxaldehyde (3).** A slurry of tetrabromide **2** (5.0 g, 11.0 mmol) in concentrated sulfuric acid (50 mL) was stirred for 36 h at room temperature. The resulting solution was poured onto crushed ice (100 g), and the aqueous mixture was extracted with ether (3 × 50 mL). Drying of the combined ether layers ($MgSO_4$) and concentration afforded a white solid which was crystallized from ether to give **3** as white needles (0.95 g, 53%): mp 99.2–100.1 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.07 (s, 3 H), 7.26–7.50 (m, 1 H), 8.06 (d, 2 H), 10.80 (s, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 66.38, 124.52, 129.61, 134.68, 165.01, 187.99 ppm; HRMS calcd for $C_9H_8O_3$ 164.047, found 164.048. Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.89. Found: C, 65.32; H, 4.88.

The $^{18}$O labeled ligand **3** was prepared by the analogous route, starting with a diazotation of 3.8 g of 2,6-dimethylaniline[9] in 10 mL of $H_2O$ (3% $^{18}$O enriched) to yield 1.3 g (33%) of 2,6-dimethylphenol. Mass analysis of **3** so obtained revealed an enrichment of 2.8(±0.3)% $^{18}$O in **3**.

**2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1-methoxybenzene (4).** To a stirred solution of dialdehyde **3** (164 mg, 1.0 mmol) in dichloromethane (20 mL) at 20 °C was added 2-(2-pyridyl)ethylamine (**9**) (244 mg, 2.0 mmol). After 60 min, $Na_2SO_4$ (1.0 g) was added, and stirring was continued for 30 min. The solids were removed by filtration, and the filtrate was concentrated to afford the pure bis-imine **4** (340 mg, 91%), yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 3.17 (t, 4 H), 3.54 (s, 3 H), 4.10 (t, 4 H), 6.80–7.67 (m, 7 H), 8.00 (d, 2 H), 8.50 (br s, 4 H); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.07 (t, 4 H), 3.52 (s, 3 H), 3.97 (t, 4 H), 7.12–7.28 (m, 3 H), 7.40–7.48 (m, 2 H), 7.89 (d, 2 H), 8.45 (s, 2 H), 8.48 (d, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 39.15, 61.11, 63.77, 120.85, 123.37, 124.25, 129.11, 129.54, 135.80, 148.92, 156.55, 159.34; $^{13}$C NMR (DMSO-$d_6$) $\delta$ 38.83, 60.51, 64.13, 121.28, 123.41, 124.42, 129.24, 129.33, 136.19, 148.94, 155.93, 159.29, 159.32; HRMS calcd for $C_{23}H_{24}N_4O$ 372.191, found 372.190.

**2,6-Bis(bromomethyl)-4-methoxyphenol (5).** This compound was prepared in two steps following the procedures described in ref 12, **5** (overall yield 60%), mp 112.1–113.6 °C (lit.[13] mp 113–114 °C).

**1-Hydroxy-4-methoxybenzene-2,6-dicarboxaldehyde (6).** A stirred mixture of 2,6-bis(bromomethyl)-4-methoxyphenol (**5**) (10.0 g, 32 mmol), aqueous acetic acid (50% HOAc, 150 mL), and hexamethylenetetraamine (15.0 g, 107 mmol) was heated at reflux for 2.5 h. After this period concentrated HCl (25 mL) was added, and reflux was continued for 15 min. The red aqueous acetic acid solution was cooled to room temperature and extracted with ether (3 × 100 mL). After separation, the organic layers were washed with water (3 × 25 mL), dried ($MgSO_4$), and concentrated. The yellow residue was crystallized from ethyl acetate to furnish dialdehyde **6** (1.99 g, 33%) as yellow needles: mp 121.5–123.4 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.85 (s, 3 H), 7.52 (s, 2 H), 10.20 (s, 2 H), 11.17 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 56.00, 122.23, 123.33, 152.42, 157.73, 191.58 ppm. Anal. Calcd for $C_9H_8O_4$: C, 60.05; H, 4.44. Found: C, 60.12; H, 4.54.

**1,4-Dimethoxybenzene-2,6-dicarboxaldehyde (7).** A solution of phenol **6** (100 mg, 0.56 mmol), $Ba(OH)_2 \cdot H_2O$ (106 mg, 0.56 mmol), and methyl iodide (0.1 mL) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature for 16 h. The resulting mixture was poured into water (50 mL) and extracted with ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The solid residue was crystallized from ether to provide **7** (60 mg, 55%) as yellow-orange needles: mp 110.5–112.8 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.87 (s, 3 H), 4.03 (s, 3 H), 7.63 (s, 2 H), 10.50 (s, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.91, 66.93, 119.22, 130.72, 156.19, 159.40, 188.02 ppm; HRMS calcd for $C_{10}H_{10}O_4$ 194.04, found 194.05. Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.73; H, 5.15.

**2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1,4-dimethoxybenzene (8).** Dialdehyde **7** (124 mg, 0.64 mmol) was converted, following the same procedure as for **4**, into the pure bis-imine **8** (240 mg, 93%), yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 3.23 (t, 4 H), 3.55 (s, 3 H), 3.86 (s, 3 H), 4.10 (t, 4 H), 6.95–7.81 (m, 8 H), 7.60 (s, 2 H), 8.50 (s, 2 H), 8.63 (s, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 38.91, 55.18, 60.83, 63.88, 114.06, 120.71, 123.21, 129.62, 135.66, 148.67, 153.43, 155.44, 156.24, 159.07 ppm; HRMS calcd for $C_{24}H_{26}N_4O_2$ 402.206, found 402.204.

**(2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1-methoxybenzene)tetrakis(acetonitrile)dicopper(I) Bis(tetrafluoroborate), $Cu_2$(2,6-BPB-1-OC$H_3$)($CH_3CN$)$_4$($BF_4$)$_2$ (11).** A solution of **4** (240 mg, 0.65 mmol) in tetrahydrofuran (10 mL) was added to a suspension of $Cu(CH_3CN)_4BF_4$ (**10**) (410 mg, 1.3 mmol) in tetrahydrofuran (10 mL). The mixture was stirred vigorously for 16 h during which period an orange precipitate was formed. The product was isolated by filtration, washed with tetrahydrofuran, and dried in vacuo to afford bis Cu(I) complex **11** (480 mg, 90%), orange powder: $^1$H NMR (DMSO-$d_6$) $\delta$ 2.08 (s, 12 H), 3.20 (m, 4 H), 3.74 (s, 3 H), 4.14 (m, 4 H), 7.18–7.53 (m, 5 H), 7.85 (m, 2 H), 8.35 (s, 4 H), 8.75 (s, 2 H); IR (KBr, cm$^{-1}$) 2255 (w), 1600 (CH, str), 760. Anal. Calcd for $C_{31}H_{36}B_2Cu_2F_8N_8O$: C, 45.40; H, 4.58; Cu, 14.55; N, 12.83. Found: C, 44.63; H, 4.49; Cu, 14.52; N, 12.59. Several attempts to crystallize **11** from THF, $CH_3OH$, $CH_2Cl_2$, $CH_3CN$ and mixtures of these solvents failed to yield crystals of sufficient quality for an X-ray determination.

**(2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1-methoxybenzene)dicopper(I) Bis(tetrafluoroborate), $Cu_2$(2,6-BPB-1-$OCH_3$)($BF_4$)$_2$($CH_2Cl_2$)$_{0.50}$ (14).** To the orange precipitate of **11**, prepared from **4** (240 mg, 0.65 mmol) as described above, was added, after filtration and washing with tetrahydrofuran, dichloromethane (10 mL). The orange mixture was stirred and heated at reflux for 0.5 h. During dissolution of the orange material a white solid appeared, which was separated after cooling from the colorless solution by filtration. After washing with dichloromethane and methanol and drying in vacuo was obtained $Cu_2$(2,6-BPB-1-OC$H_3$)($BF_4$)$_2$ (**14**) (250 mg, 58%) as a white powder: $^1$H NMR (DMSO-$d_6$) $\delta$ 3.18 (br s, 4 H), 3.75 (s, 3 H), 4.12 (br s, 4 H), 7.30 (s, 2 H), 7.44 (d, 2 H), 7.50 (br s, 1 H), 7.82 (m, 2 H), 8.28 (br s, 4 H), 8.71 (br s, 2 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 36.30, 60.35, 64.47, 122.61, 122.67, 123.07, 124.56, 127.71, 130.33, 137.90, 148.80, 159.39, 159.81 ppm. Anal. Calcd for 0.5 dichloromethane solvate $C_{23.5}H_{25}B_2ClCu_2F_8N_4O$: C, 39.44; H, 3.52; Cl, 4.95; Cu, 17.76; F, 21.24; N, 7.83. Found: C, 38.78; H, 3.49; Cl, 4.79; Cu, 17.71; F, 21.28; N, 7.84.

When complex **14** (0.5 mmol) was dissolved in $CH_2Cl_2$ and 4 equiv of $CH_3CN$ were added, the orange color indicating the presence of **11** reappeared. Stirring for 2 h at room temperature was followed by concentration and workup as described for the preparation of **11**. After washing (THF) and drying in vacuo bis Cu(I) complex **11** (80–90%) was obtained, in all respects identical with **11** prepared as described above. The conversion of **11** to **14** and vice versa could be repeated several times with small (10–20%) loss of material.

When a solution of complex **14** in $CHCl_3/CH_3CN$ (10:1 ratio) was crystallized very slowly at room temperature, both orange and white crystalline material was obtained in 1:1 (±0.1) molar ratio. The white material was found to be $Cu(CH_3CN)_4BF_4$ (**10**). Crystals suitable for X-ray analysis were obtained from the orange material. This appeared to be a linear copper(I) coordination polymer **16**. Details of the synthesis and crystal and molecular structure determination will be published elsewhere.

**(2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1-hydroxybenzene)hydroxodicopper(II) Bis(tetrafluoroborate) Hydrate, $Cu_2$(2,6-BPB-1-O)(OH)(B$F_4$)$_2$·$H_2O$ (17).** Through a solution of 200 mg (0.23 mmol) of **11** in 10 mL of $CH_2Cl_2$ or a solution of **14** in MeOH at room temperature was bubbled oxygen. The color of the orange (or colorless) solution rapidly turned dark green. After 1 h the reaction was completed, and MeOH (10 mL) was added. The dark green solution was evaporated to dryness, and the solid residue was crystallized from $EtOH/H_2O$ (10:1) yielding dark blue-green crystals of **17** (150 mg, 95%), which were suitable for X-ray analysis. Anal. Calcd for $C_{22}H_{22}B_2Cu_2F_8N_4O_2 \cdot H_2O$: C, 38.12; H, 3.49; Cu, 18.34; F, 21.92; N, 8.08. Found: C, 38.13; H, 3.56; Cu, 18.17; F, 22.16; N, 8.03.

**$^{18}$O-Labeling Experiments.** Following the same procedure, but using a closed system, 100 mg (0.12 mmol) of **11** dissolved in 20 mL of $CH_2Cl_2$ was oxidized by using excess $^{18}O_2$ (99.1% enriched). After stirring for 24 h at room temperature the reaction mixture, a green slurry, was quenched with oxygen free aqueous ammonia (10 mL). The $CH_2Cl_2$ layer was separated and washed again with 10 mL of aqueous ammonia. After drying over $Na_2SO_4$ and evaporation to dryness a yellow oil (39 mg, 90%) was isolated. This compound was identical with **19** in all respects except for the mass spectral analysis. MS ($M^+$ at *m/e* 358, 360)

(12) Gelling, O. J.; Meetsma, A.; Feringa, B. L. *Inorg. Chem.* In press.
(13) Moran, W. J.; Schreiber, E. C.; Engel, E.; Behn, D. C.; Yamins, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 127.

revealed a 55–65 (±5)% $^{18}O$ incorporation in the ligand (triplicate experiments). $^{18}O$-Labeled complex **11** was prepared following exactly the procedures for unlabeled **11** from **3** (2.8(±0.3); $^{18}O$ enriched), **9**, and $Cu(CH_3CN)_4BF_4$. The oxidation of $^{18}O$-labeled **11** (0.1 mmol) was performed with $O_2$ under the same conditions as described above, and the resulting complex **17** was converted into **19** by using the ammonia extraction procedure (see above and experimental of **19**). The oil (90–95%) thus obtained was identical in all respects with **19** except for the MS spectrum. Mass spectral analysis ($M^+$ at *m/e* 358, 360) indicated 0.5(±0.2)% $^{18}O$ enrichment in the phenol **19** (duplicate experiments). When a solution of 100 mg (0.12 mmol) of **11** in 10 mL of highly purified $CH_2Cl_2$ was oxidized in a closed system for 1 h and the resulting solution was analyzed by GC with benzene as an internal standard, methanol up to 0.03 mmol could be detected. When however 60 mg of 2,6-dimethylphenol (0.5 mmol) was added after 1 h of oxidation and stirring was continued for an additional 5 min, up to 0.07 mmol (60%) of methanol was obtained (GCMS) (duplicate experiments). When **11**, prepared from $^{18}O$ enriched (2.8(±0.3)%) **3**, was used in the same procedure, GCMS analysis of the resulting solution showed an incorporation of 5(±1)% $^{18}O$ in the methanol. Finally when the oxidation of **11** with $^{18}O_2$ (99.1% enriched) was performed as described above and the liberated methanol was analyzed by GCMS, no incorporation of $^{18}O$ in the $CH_3OH$ could be detected (triplicate experiments).

**2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1-hydroxybenzene (19).** This compound was obtained from **17** by extraction with ammonia solution following the procedure described by Karlin.[4] Phenol **19** was prepared independently via condensation of **21** and 2-(2-pyridyl)ethylamine (**9**) as described for **4**. **19**: yellow oil; $^1H$ NMR ($CDCl_3$) δ 3.15 (t, 4 H), 4.00 (t, 4 H), 6.85 (t, 1 H), 7.04–7.20 (m, 4 H), 7.49–7.62 (m, 4 H), 8.43–8.56 (m, 4 H); $^{13}C$ NMR ($CDCl_3$) δ 38.49, 58.88, 117.14, 120.47, 122.62, 131.00, 135.40, 148.29, 158.34, 160.29, 160.58 ppm; HRMS calcd for $C_{22}H_{22}N_4O$ 358.179, found 358.177.

**1-Hydroxybenzene-2,6-dicarboxaldehyde (21).** This compound was obtained (together with 2 equiv of **9**) by treatment of **19** with diluted hydrochloric acid following the procedure described previously.[6,14] Dialdehyde **21** thus obtained was identical in all respects with a sample prepared independently from 2,6-dimethylphenol via reported procedures.[14]

**(2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1,4-dimethoxybenzene)dicopper(I) Bis(tetrafluoroborate), $Cu_2$(2,6-BPB-1,4-$OCH_3$)$(BF_4)_2$ (15).** Bis copper(I) complexes **12** and **15** were prepared from 2,6-bis[*N*-(2-pyridylethyl)formimidoyl]-1,4-dimethoxybenzene (**8**) following the same procedures as described for **11** and **14**. Thus starting with **8** (202 mg, 0.5 mmol) and $Cu(CH_3CN)_4BF_4$ (**10**, 314 mg, 1.0 mmol) the binuclear copper(I) complex **12** (350 mg, 80%) was obtained as an orange powder.

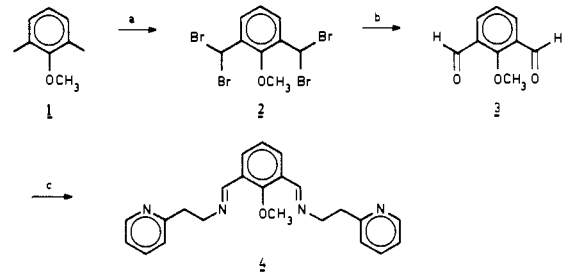
Elemental analysis gave a ratio Cu/N = 1/3.6 indicating a mixture of complexes with two and four $CH_3CN$ ligands coordinated. Unfortunately no satisfactory analysis for the tetraacetonitrile coordinated complex **12** was obtained.

Pure binuclear complex **15** (210 mg, 60%) was isolated as a white powder following the procedure of boiling of **12** (0.5 mmol) in $CH_2Cl_2$ (1 h), washing with $CH_3OH$, and drying in vacuo. Anal. Calcd for $C_{24}H_{26}Cu_2F_8N_4O_2$: C, 40.99; H, 3.73; Cu, 18.07; N, 7.96. Found: C, 40.93; H, 3.81; Cu, 18.11; N, 7.77. Acetonitrile complexation and decomplexation experiments with **15** and **12** were executed as described for **14** and **11**.

**Oxidation of 12 in $CH_2Cl_2/CD_3OD$ Mixtures: Typical Procedure.** Dry air (or $O_2$ gas) was bubbled through a solution of complex **12** (0.2 g, 0.26 mmol) in a mixture of $CH_2Cl_2/CD_3OD$ (40:1 ratio) at room temperature, while the solution was continuously stirred. A rapid color change from orange to dark green was observed. After 1 h the reaction mixture was poured into a cold aqueous 2 N HCl solution (10 mL). The dichloromethane layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (15 mL). After drying ($MgSO_4$) of the $CH_2Cl_2$ solution and evaporation of the solvent, a colorless solid material (45 mg, approximately 90%) was obtained. $^1H$ NMR analysis ($CDCl_3$) showed that this material consists of a mixture of **6** and **7** + **7a** (3:7 ratio). This mixture was dissolved in $CH_2Cl_2$ (30 mL), and the solution subsequently was washed with 1 N aqueous NaOH (2 × 10 mL). Drying of the organic solution ($MgSO_4$) and removal of the solvent in vacuo yielded 32 mg of a solid consisting of **7** and **7a** (1:1 (±0.06) ratio) based on $^1H$ NMR and GCMS analysis.

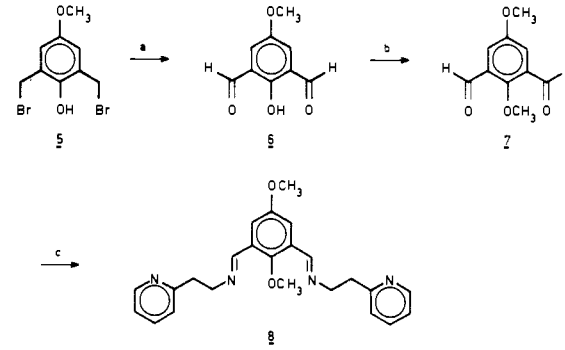
Compounds **6** and **7** were in all respects identical with independently prepared samples (see above) [**7a**: $^1H$ NMR ($CDCl_3$) δ 3.82 (s, 3 H), 7.54 (s, 2 H), 10.32 (s, 2 H), MS *m/e* at $M^+$ = 197; for the **7,7a** mixture: MS *m/e* at $M^+$ = 194, 197 (1:1 ratio)]. The oxidation experiment was repeated several times with different solvent ratios and reaction times. The ratio **6** to **7** + **7a** increased with prolonged reaction times, the ratio **7**/**7a** was 1:1 within the limits of detection in all cases. Various control experiments were performed under the conditions described above, for instance by using either ligand **8** and 2 equiv of copper(II) salts or **12** under oxygen free conditions. No trace of **23** or **7a** was obtained however.

**Scheme I**[a]



[a] (a) 4 equiv of $Br_2$, $CCl_4$, *hν*, 72%; (b) $H_2SO_4$, $H_2O$, 52%; (c) 2 equiv of 2-(2-pyridyl)ethylamine (**9**), $CH_2Cl_2$, 91%.

**Scheme II**[a]



[a] (a) $(CH_2)_6N_4$, 50% $CH_3CO_2H$, $H_2O$, 33%; (b) $CH_3I$, $Ba(OH)_2$, DMF, 55%; (c) 2 equiv of **9**, $CH_2Cl_2$, 93%.

**(2,6-Bis[*N*-2-pyridylethyl)formimidoyl]-1-hydroxy-4-methoxybenzene)hydroxodicopper(II) Bis(tetrafluoroborate) Methanol, $Cu_2$(2,6-BPB-4-$OCH_3$-2-O)(OH)$(BF_4)_2$·$CH_3OH$ (18).** This compound was prepared in ≥95% yield (oxidation time 6 h) from **12**, dissolved in $CH_2Cl_2/CH_3OH$ mixtures, following the procedure described for **17** and the typical procedure given above. Complex **18**, as its bisperchlorate salt, was prepared independently from **20** by using the same procedure as described for **17** from **19** and was isolated as a dark green crystalline methanol adduct. Anal. Calcd for $C_{23}H_{24}Cl_2Cu_2N_4O_{11}$·$CH_3OH$: C, 37.79; H, 3.67; Cu, 16.67; N, 7.34. Found: C, 37.60; H, 3.80; Cu, 16.74; N, 7.84.

**2,6-Bis[*N*-(2-pyridylethyl)formimidoyl]-1-hydroxy-4-methoxybenzene (20).** Following the same procedure as for **19** compound **20** was isolated as a yellow oil: $^1H$ NMR ($CDCl_3$) δ 3.17 (m, 4 H), 3.82 (s, 3 H), 4.05 (m, 4 H), 6.75–7.82 (m, 10 H), 8.45–8.69 (m, 4 H); HRMS calcd for $C_{23}H_{24}N_4O_2$ 388.190, found 388.191.

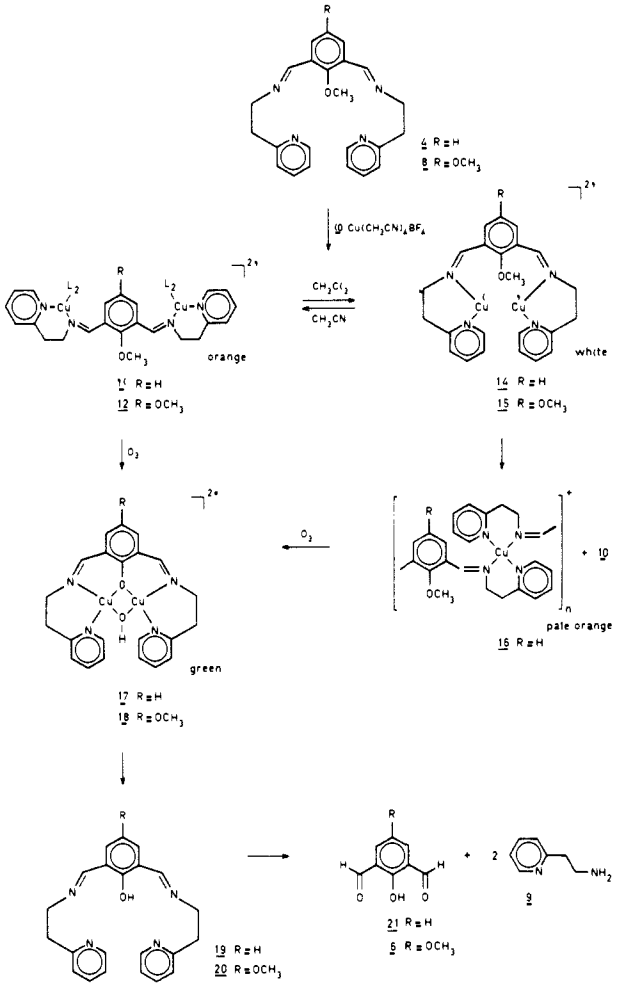
Phenol **20** was identical with an independently prepared sample via condensation of dialdehyde **6** and diamine **9**. Hydrolysis of **20** in hydrochloric acid as described for **19** yielded phenol **6** (90%).

## Results

**Synthesis of the Complexes.** The ligand 2,6-bis[*N*-(2-pyridylethyl)formimidoyl]-1-methoxybenzene, (2,6-BPB-1-$OCH_3$) (**4**), was prepared from 2,6-dimethyl-1-methoxybenzene (**1**) (Scheme I). Tetrabromination of **1** in 72% yield was achieved by using carefully controlled conditions. Hydrolysis of **2** and condensation of 1-methoxybenzene-2,6-dicarboxaldehyde (**3**) with 2-(2-pyridyl)ethylamine (**9**) provided **4**. Scheme II shows the preparation of 2,6-bis[*N*-(2-pyridylethyl)formimidoyl]-1,4-dimethoxybenzene (2,6-BPB-1,4-di-$OCH_3$) (**8**). A Sommelet reaction of 2,6-bis(bromomethyl)-4-methoxyphenol (**5**)[13] followed by methylation using $Ba(OH)_2$ as the base and condensation of the resulting dialdehyde **7** with **9** afforded ligand **8** in 17% overall yield.

The ligand 2,6-BPB-1-$OCH_3$ (**4**) reacts with 2 equiv of $Cu(CH_3CN)_4BF_4$ (**10**) in THF under a nitrogen atmosphere to produce an orange dicopper(I) complex **11** (Scheme III). Although we have been unable to obtain crystalline material of sufficient quality for an X-ray analysis of **11**, we presume that

**Scheme III**[a]



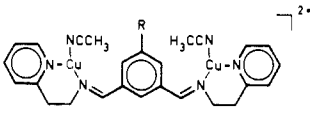
[a] L = $CH_3CN$.

**11** contains two four-coordinated Cu(I) centers. This is based on a copper–nitrogen ratio of 1:4 (combustion analysis). In addition **11** has been characterized by IR and $^1H$ NMR (singlet at 2.08 ppm for four $CH_3CN$ molecules) indicating four identical $CH_3CN$ molecules per molecule of binuclear complex. The spectral data indicate coordinated acetonitrile but do not exclude noncoordinated acetonitrile. Presumably each Cu(I) ion is four-coordinated with one bidentate and two monodentate ($CH_3CN$) ligands in accordance with a related four-coordinated binuclear Cu(I) complex ($CH_3CN$ included) described by Karlin.[7c]

Attempts to crystallize **11** from $CH_2Cl_2$ led to dicopper(I) complex **14** [$Cu_2$(2,6-BPB-1-$OCH_3$)$(BF_4)_2 \cdot 0.5CH_2Cl_2$)] (80% yield). Two coordination of each Cu(I) center in **14** is likely [4b,15] considering a number of two-coordinated Cu(I) complexes reported,[15] for instance, a related histamine derived binuclear Cu(I) complex with proposed two coordination has been described.[5b] It cannot be excluded that a three-coordinated structure is present due to methoxy bridging or the occurrence of Cu(I)–Cu(I) bonding.[15] $^1H$ and $^{13}C$ NMR of **14** show symmetric coordination of the ligand with a downfield shift (0.23 ppm in DMSO-$d_6$) for the methoxy protons upon Cu(I) binding.[16]

It cannot be excluded that the copper ions expand their coordination number through intermolecular interactions. Addition of 4 equiv of $CH_3CN$ to **14** in $CH_2Cl_2$ produces **11** indicating reversible $CH_3CN$ binding.[17] Karlin and co-workers[7c] have reported a related case where reversible $CH_3CN$ binding takes place. The $CH_3CN$ induced cycle, **14** → **11** and vice versa, can be repeated several times.[18] However the addition of excess $CH_3CN$ to **11** or **14** in $CHCl_3$ leads to equimolar amounts of **10** and pale orange Cu(2,6-BPB-1-$OCH_3$)$BF_4$ (**16**). X-ray analysis of **16** revealed a helical coordination polymer with each pyridylethylimine bidentate unit bound to a different Cu(I) ion with tetragonal coordination spheres.[19] The Cu–Cu distance in **16** is 7.65 Å compared to 4.95 Å in **13**,[6] and one left-handed and one right-handed single helix are found in the infinite unit cell.

**Oxygenations.** Complexes **11** or **14** in $CH_2Cl_2$ or **16** + **10** (1:1 ratio) dissolved in $CH_2Cl_2/CH_3OH$ mixtures react with molecular oxygen (25 °C, 1 h) leading to the blue-green phenoxyhydroxy bridged dinuclear Cu(II) complex **17** previously reported by us.[6] Starting from **11** complex **17** was obtained in 95% yield with a stoichiometry of $O_2$ uptake: Cu:$O_2$ = 2:1 (manometric determination). Within the limits of detection similar results were obtained in $CH_3CN$ or $CH_2Cl_2$/DMF mixtures. X-ray analysis of [$Cu_2$(2,6-BPB-1-O)$(BF_4)_2$] (**17**) revealed a structure almost identical with the dinuclear Cu(II) complex obtained via arene hydroxylation upon addition of $O_2$ to **13**.[6] Oxygen-induced demethylation of the anisole moiety in **11**, **14**, and **16** has taken place,



**13** (R = H)
**25** (R = $NO_2$)

In the absence of $O_2$ under an inert atmosphere ($N_2$) complexes **11**, **14**, and **16** are stable, and no trace of demethylation has been observed.

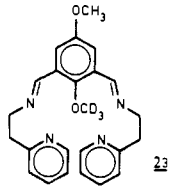
In order to obtain more insight into the mechanism of this unusual oxidative demethylation and to understand the copper mediated oxygen activation, we executed various $^{18}O$ labeling experiments. Oxidation of **11** or **14** with $^{18}O_2$ (99.1% enriched) under the conditions described above showed ≥60% $^{18}O$-incorporation in the phenol group of **19** liberated from **17** by using Karlin's method.[4a] Phenol **19** was in all respects identical with an independently prepared sample. Subsequently similar experiments were conducted with complexes **11** and **14** prepared from $^{18}O$-enriched ligand **4**, which was synthesized in five steps from 2,6-dimethylaniline and $H_2{}^{18}O$ (3% enriched, see Experimental Section). The oxidations carried out with $O_2$ and **11** and **14** which were 2.8(±0.3)% $^{18}O$ enriched in the anisole group (based on HRMS analysis of 4) resulted in the formation of **19** 0.5(±0.2)% $^{18}O$ enriched in the phenol moiety. Next the lost methyl or methoxy substituent was looked for. On the basis of numerous experiments using various techniques, the liberation of formaldehyde was qualitatively proven, but a quantitative analysis turned out to be extremely difficult in the present system. In most cases traces of formaldehyde were detected by using the method described by Nash.[20] Methanol was liberated in ≥60% yield based on **11** or **14** during the oxidation, as was readily detected by GC-MS techniques. Furthermore by using **11**, 2.8(±0.3)% $^{18}O$ enriched in the methoxy substituent, 5(±1)% $^{18}O$ incorporation in the liberated $CH_3OH$ was observed based on HRMS analysis (duplicate experiments, see Experimental Section). These data

(14) Snell, J. M.; Weissberger, A. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 788.
(15) Hendriks, H. M. J.; Birker, P. J. M. W. L.; van Rijn, J.; Verschoor, G. C.; Reedijk, J. *J. Am. Chem. Soc.* **1982**, *104*, 3607. Sorrell, T. N.; Jameson, D. L. *J. Am. Chem. Soc.* **1983**, *105*, 6013. Pasquali, M.; Floriani, C.; Gaetani-Manfredotti, A.; Guastini, C. *J. Am. Chem. Soc.* **1981**, *103*, 185. Mehrotra, P. K.; Hoffmann, R. *Inorg. Chem.* **1978**, *17*, 2187.
(16) Although solvent coordination is less plausible, $CH_2Cl_2$ coordination has set a recent precedent except not for copper: Newbound, T. D.; Colsman, M. R.; Miller, M. M.; Wulfsberg, G. P.; Anderson, D. P.; Strauss, S. H. *J. Am. Chem. Soc.* **1989**, *111*, 3762.
(17) Unfortunately structural characterization of **11** and **14** by X-ray analysis failed so far.
(18) Complex **11** (and **12**) presumably are in equilibrium with their three coordinated counterparts, containing one acetonitrile ligand per copper(I) (depending upon the amount of $CH_3CN$ present), as was indicated by $^1H$ NMR studies and elemental analyses. The structure of the desmethoxy analogue **13** of **11** containing one $CH_3CN$ per Cu(I) center has been determined by X-ray.[6]
(19) Details of the synthesis and structural characterization will be described separately.

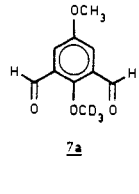
support dual pathways with at least 60% aryl–oxygen and approximately 20% alkyl–oxygen bond cleavage. Both oxidative pathways lead to the same phenoxy bridged binuclear Cu(II) complex **17**. In the first route an oxidative demethoxylation takes place, and $CH_3OH$ is liberated as was detected quantitatively (≥60% yield, in accordance with the maximum yield based on labeling experiments). In the second and minor route oxidative demethylation occurs with ultimate oxidation of the anisole methyl group to formaldehyde; however, the formation of other products besides formaldehyde cannot be excluded at present.

Substantial evidence has been provided by Karlin and coworkers[2b,7b,21] for the initial formation of peroxodicopper complexes upon $O_2$ binding in dinuclear Cu(I) systems. Subsequent attack of an electrophilic copper–oxy species has been proposed in related arene hydroxylations.[4a,5,6,22]

In order to investigate the role of an electrophilic species in the O-demethylation and demethoxylation described here the 4-methoxy analogue 4-$CH_3O$-2,6-BPB-1-$OCH_3$ (**8**) was studied. Dinuclear Cu(I) complex **12** was obtained from **8** and 2 equiv of $Cu(CH_3CN)_4BF_4$, and it produced a white binuclear complex of proposed structure **15** upon treatment with $CH_2Cl_2$. Addition of 4 equiv of $CH_3CN$ to **15** reconverted this complex to **12** completely in agreement with the reversible $CH_3CN$ binding observed with **11** and **14**. Surprisingly slow cleavage of the 1-methoxy substituent takes place when **12** was allowed to react with $O_2$ in $CH_2Cl_2$ or a $CH_2Cl_2/CD_3OD$ (40:1 ratio) mixture. Only 10–30% of **18** was obtained after 1 h at 25 °C, the extent of hydroxyl formation was further proven by conversion into **20** and **6** by methodology described for **17**. These products were identical with independently prepared samples of **20** and **6**. However $^1H$ NMR and HRMS analyses of **8** recovered in ≥70% yield from the copper complex **12** after 1 of treatment with $O_2$ in the $CH_2Cl_2/CD_3OD$ solvent mixture showed that it consists of 4-$CH_3O$-2,6-BPB-1-$OCH_3$ (**8**) and 4-$CH_3O$-2,6-BPB-1-$OCD_3$ (**23**) (1:1 ratio). This means that 50(±2)% $OCH_3$, $OCD_3$ exchange has taken place exclusively at the 1-position. Control experiments proved that the exchange process *only* occurs in the binuclear Cu(I) complex **12** in the presence of $O_2$ to form complex **22** (the 1-$OCD_3$ isomer of **12**). The significance of the experimental conditions is emphasized as




23



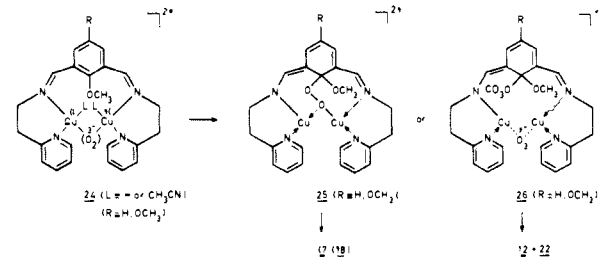

7a

generally Lewis acids are able to demethylate methoxy substituents in aryl compounds. To ensure that the exchange reaction observed here is not a simple Lewis acid reaction involving Cu(II) ions, produced from Cu(I) and $O_2$, the experiments were run with ligand **8** in $CD_3OD$ in the presence of various Cu(II) salts under otherwise identical conditions. No exchange process was observed however within the limits of detection (<2% by $^1H$ NMR).

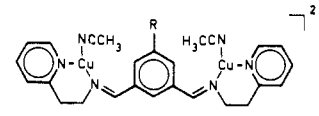
## Discussion

Although we have at present no evidence for the intermediates in the oxidative demethylations described here, several mechanistic features might relate to those proposed for $O_2$ binding and arene hydroxylation.[2-7] It is conceivable that in the first instance the reaction of **11** and **12** (and **14** and **15**) with $O_2$ produces an intermediate dioxygen copper adduct with proposed structure **24** (a peroxo dicopper(II) complex). The copper ions might coordinate a $CH_3CN$ ligand or employ the $OCH_3$ moiety as a bridging ligand. The reversible binding of $O_2$ in binuclear copper complexes

**Scheme IV**

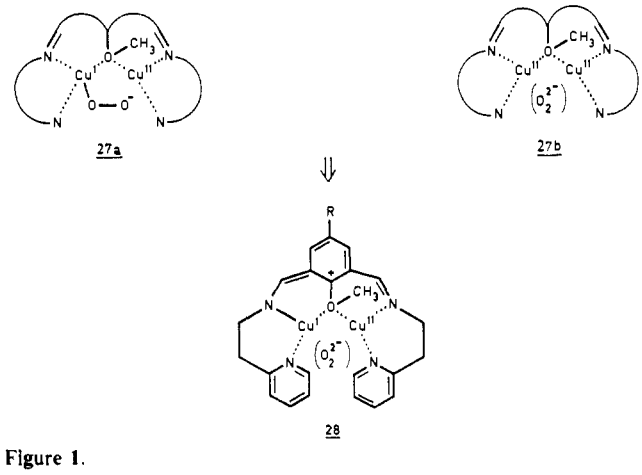


with tetracoordinated copper ions is now well precedented mainly based on the results from Karlin's group.[2,3] Furthermore the structure of a pentacoordinated ($\mu$-1,2-peroxo)dicopper(II) complex with distorted trigonal-bipyramidal geometry has been obtained.[7b] Additional support for $O_2$ binding to the copper complexes described here comes from the recent observation of reversible $O_2$ binding to a structurally closely related system, i.e., the nitroaryl substituted binuclear Cu(I) complex **29**.[23] As arene–oxygen bond cleavage and methoxide elimination is the



13 (R = H)
29 (R = $NO_2$)

preferred pathway in the demethylation of the anisole group of **4** and **8**, our data do not seem to support the attack of an electrophilic peroxodicopper(II) species to generate, in the first step, an intermediate with an arene–peroxide bond. Karlin and coworkers described related arene hydroxylations as electrophilic in the sense that the arene is attacking the peroxodicopper(II) generating a cationic arene peroxide intermediate. The introduction of the *p*-$OCH_3$ substituent (as in **12**) decreases the rate of the ipso oxygenation reaction. Although alternative mechanisms for the demethoxylation and $OCH_3$–$OCD_3$ exchange might be proposed, the following scheme (Scheme IV) accounts for the experimental observations. The increased Lewis acidity upon $O_2$ binding by the binuclear copper centers as present in the peroxodicopper(II) complex **24** could result in decreased electron density at the 2,6-bis-imine substituted aryl moiety making it more vulnerable for nucleophilic attack. The effect of the *p*-$OCH_3$ substituent on the oxygenation (slower oxidation) is consistent with this scheme. Detailed knowledge about what step in this process is actually slower awaits full kinetic analysis; preliminary[23] kinetic studies indicate however that the binding of $O_2$ to form the peroxodicopper(II) species is only slightly influenced by the introduction of a *p*-methoxy substituent (i.e., complexes **11** vs **12**). For **24** (R = $OCH_3$) ipso attack of either the copper(II) peroxy species or deuteriomethanol leads to the formation of **25** and **26**,



27a 27b

28

Figure 1.

(20) Nash, T. *Biochem. J.* **1953**, *55*, 416.
(21) Blackburn, N. J.; Strange, R. W.; Cruse, R. W; Karlin, K. D. *J. Am. Chem. Soc.* **1987**, *109*, 1235.
(22) Karlin, K. D.; Cohen, B. I.; Jacobson, R. R.; Zubieta, J. *J. Am. Chem. Soc.* **1987**, *109*, 6194.
(23) Gelling, O. J.; Alkema, J.; Feringa, B. L. Manuscript in preparation.

respectively. In the absence of $CD_3OD$ (or $CH_3OH$) only **25** will be formed as is the case in the demethoxylations in $CH_2Cl_2$ and $CHCl_3$.

Subsequent fragmentation of **25** and **26** results in the formation of **17** (**18**) and **12** (1-$OCH_3$) and **22** (1-$OCD_3$ isomer), respectively.

It should be emphasized that data obtained by Solomon and Karlin and co-workers[2] on a phenoxo-bridged dinuclear peroxocopper(II) complex indicate either a nonsymmetrical $\mu$-1,2-bridged peroxo ligand or a peroxo group bound to a single Cu(II) ion. It is not too far fetched to suggest that similar binding modes, shown schematically in Figure 1 (**27A** and **27B**), exist in complex **24** ($CH_3CN$ omitted). Considering the next complex **28**, which is a *resonance structure* of **27A** and which can be formed from **27B** by copper–oxygen bond fission, it is conceivable that ipso attack of the peroxy group or deuteriomethanol can be a favorable pathway leading to **25** and **26**, respectively. Furthermore protonation of either **27A** or **27B** by methanol to form copper bound hydroperoxide and methoxide ion adjacent to the arene ring might contribute to the formation of **26**.[24] If **28** has an important contribution to the overall mechanism, it should be noted that this *formally* means an electron transfer from the arene ring to the peroxodicopper moiety.[25] Due to the presence of the imine bonds this does not likely lead to long-living arene-centered radicals, which is consistent with the high selectivity that is observed, although a one-electron oxidation by the peroxodicopper(II) group followed by highly selective radical type conversion cannot be excluded in the specific ligand system present here.

In conclusion the conversions of **4** and **8** represent, as far as we know, the first examples of an ipso hydroxylation induced demethoxylation of aryl ethers using copper ions and $O_2$.[26] Furthermore we provided evidence for competing pathways in aryl ether bond fissions and arene hydroxylations[5,6] by using copper monooxygenase model systems. Our data indicate that electrophilic attack[4a,5,22] on arenes, with formation of an arene peroxide bond in the first step, might not be an exclusive pathway for these model compounds. Further studies to support the proposed mechanisms are in progress.

**Acknowledgment**. We are grateful to Dr. H. E. Schoemaker for stimulating discussions and Mr. A. Kiewiet for mass spectral analyses.

(24) We acknowledge this suggestion made by one referee.
(25) Walling, C.; El-Taliawi, G. M.; Amarnath, K. *J. Am. Chem. Soc.* **1984**, *106*, 7573. Kersten, P. J.; Tien, M.; Kalyanaraman, B.; Kirk, T. N. *J. Biol. Chem.* **1985**, *260*, 2609. Nozaki, M. *Top. Curr. Chem.* **1979**, *78*, 145.
(26) See, also: Ito, S.; Kunai, A.; Okada, H.; Sasaki, K. *J. Org. Chem.* **1988**, *53*, 296.

# Electron-Exchange Reactions between Heteropoly Anions: Comparison of Experimental Rate Constants with Theoretically Predicted Values†

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*Contribution from the Department of Chemistry, Georgetown University, Washington, D.C. 20057.* *Received May 15, 1989*

**Abstract:** This paper presents the first variable ionic strength study of the rates of intercomplex electron transfers between species wherein the electron to be exchanged is delocalized over numerous equivalent metal atoms. The complexes used were heteropoly tungstophosphates and their isomorphous heteropoly blue reduction products, the latter being class II mixed-valence species wherein the added "blue" electrons are delocalized over a dozen or more $WO_6$ units. Heteropoly complexes characteristically have extremely low interactions with solvent. Electron-exchange rates in solution were evaluated from $^{31}P$ NMR data. In the case of the nearly spherical $\alpha$-$[PW_{12}O_{40}]^{3-}$ exchanging with its heteropoly blue 1e reduction product, the experimental rates coincide very closely with those calculated from current theory of electron transfer in solution. These results lead to the general conclusion that extensive electron delocalization (over all 12 $WO_6$ octahedra) does not significantly contribute to activation energy for intercomplex electron exchange. In the case of the paramagnetic 1e blue reduction product $\alpha$-$[PW_{12}O_{40}]^{4-}$ exchanging with its diamagnetic 2e-reduced isomorph, there is intrusion of an energy consideration for unpairing the delocalized electron to be exchanged. This significantly lowers the electron-exchange rate. Other cases, wherein geometric factors are expected to lower the rates, gave deviations in the expected direction and in the expected order. The exchanging pairs considered are as follows: (1) $\alpha$-$[PW_{12}O_{40}]^{3-}$ and its 1e heteropoly blue reduction product, (2) $\alpha$-$[PW_{12}O_{40}]^{4-}$ and the corresponding 2e reduction product $\alpha$-$[PW_{12}O_{40}]^{5-}$, (3) $\alpha$-$[P_2W_{18}O_{62}]^{6-}$ and its 1e blue reduction product, and (4) $\alpha$-$[PMo_3W_{15}O_{62}]^{6-}$ and its 1e blue reduction product.

## Background

Reduced heteropoly anions constitute a large, distinct, and potentially important, group of mixed-valence complexes commonly known as "heteropoly blues".[1-3] Recently we reported the first NMR spectra of *paramagnetic* 1e-reduced heteropoly blues.[4] In 1e-reduced Mo-substituted derivatives of Wells–Dawson tungstophosphate anions,[5] $\alpha_1$- and $\alpha_2$-$[P_2MoW_{17}O_{62}]^{7-}$ (see Figure 1), the added electron is localized on the Mo,[3a,4] and the $^{31}P$ NMR signals of the phosphorus located nearer the reduced Mo atom are very broad ($\Delta\nu_{1/2}$'s of 900 and 400 Hz for the $\alpha_1$ and $\alpha_2$ isomers, respectively), as expected on the basis of their electronic ground states. On the other hand, in the complexes where the added electron is delocalized over part or all of a complex's

† Presented in part at the Third American Congress of the North American Continent, Toronto, June 1988, Inorganic Paper No. 204.
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(1) Pope, M. T. *Heteropoly and Isopoly Oxometalates*; Springer-Verlag: Berlin, 1983; Chapter 6.
(2) Buckley, R. I.; Clark, R. J. H. *Coord. Chem. Rev.* **1985**, *65*, 167.
(3) (a) Kozik, M.; Hammer, C. F.; Baker, L. C. W. *J. Am. Chem. Soc.* **1986**, *108*, 2748. (b) Kozik, M.; Casañ-Pastor, N.; Hammer, C. F.; Baker, L. C. W. *Ibid.* **1988**, *110*, 7697. (c) Kozik, M.; Baker, L. C. W. *Ibid.* **1987**, *109*, 3159.
(4) Kozik, M.; Hammer, C. F.; Baker, L. C. W. *J. Am. Chem. Soc.* **1986**, *108*, 7627.
(5) (a) Wells, A. F. *Structural Inorganic Chemistry*, 1st ed.; Oxford University Press: Oxford, UK, 1945; p 344. (b) Dawson, B. *Acta Crystallogr.* **1953**, *6*, 113. (c) D'Amour, H. *Acta Crystallogr.* **1976**, *B32*, 729.

0002-7863/90/1512-7604$02.50/0 