

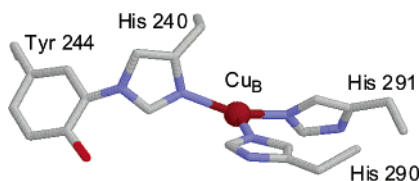
Copper(I) and Copper(II) Complexes Possessing Cross-Linked Imidazole-Phenol Ligands: Structures and Dioxygen Reactivity

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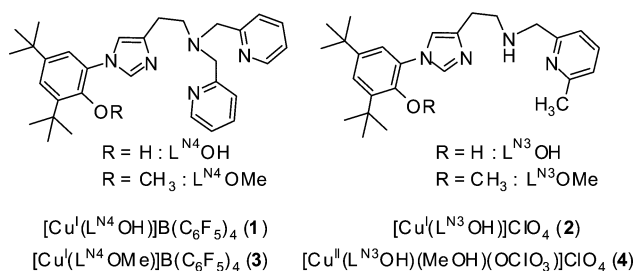
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Cytochrome *c* oxidase is the terminal respiratory enzyme that catalyzes the reduction of dioxygen to water and couples this redox reaction to the membrane translocation of protons for subsequent use in ATP synthesis.^{1,2} The O₂ binding/reduction site is comprised of a heme (heme a₃) and a copper (Cu_B) in close association (~4.5–5.0 Å). Recent X-ray crystallographic^{3–6} and biochemical⁷ studies reveal that one of the copper-bound histidines is covalently linked to a tyrosine through a posttranslationally modified cross-link between C6 of Tyr244 and the ϵ -nitrogen of His240. The His-Tyr



moiety is proposed to either function in a structural role^{8,9} or provide an electron and a proton during the O₂-reduction cycle.^{10–13} There are a few recent reports about syntheses and physicochemical investigations of organic models for the imidazole-phenol moiety;^{14–20} yet studies of copper complexes of the latter have not been described. Here, we report the first examples of Cu(I) and Cu(II) complexes possessing an imidazole-phenol cross-link, their X-ray structures, and initial chemical insights.



The ligands L^{N4}OR and L^{N3}OR were designed to have an imidazole-phenol (or anisole) cross-link with either a tetra- or a tridentate pyridylalkylamine-containing chelate, as shown, having the advantage that we have previously studied copper-dioxygen chemistry of close analogues.^{21–26} Syntheses of these ligands and various copper complexes have been achieved.²⁷ X-ray crystallographically determined structures of a Cu(I) complex, [Cu^I(L^{N4}-OH)]B(C₆F₅)₄ (**1**), and a Cu(II) complex, [Cu^{II}(L^{N3}OH)(MeOH)(OCIO₃)](ClO₄) (**4**), are shown in Figure 1. Both structures reveal mononuclear copper ion centers. In **1**, the Cu(I) geometry is

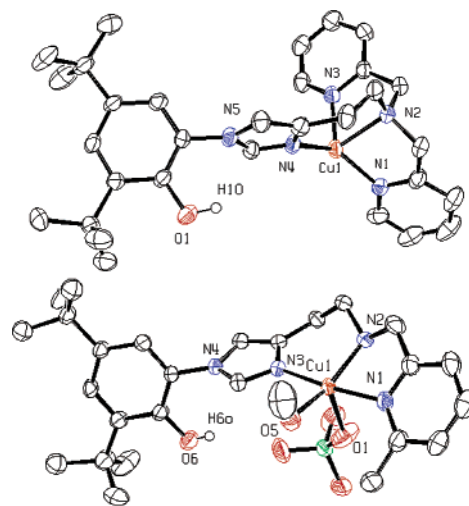


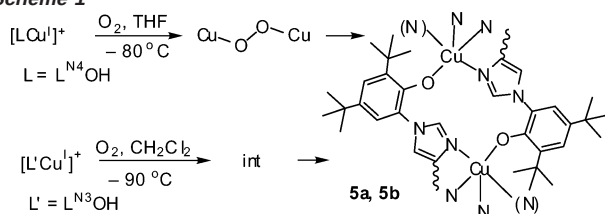
Figure 1. ORTEP diagrams (50% thermal ellipsoids) showing the cationic portions of [Cu^I(L^{N4}OH)]B(C₆F₅)₄ (**1**) (top) and [Cu^{II}(L^{N3}OH)(MeOH)(OCIO₃)](ClO₄) (**4**) (bottom). Selected bond distances (Å): **1**, Cu1–N1, 1.973(3); Cu1–N2, 2.191(3); Cu1–N3, 2.098(3); Cu1–N4, 1.944(2), **4**, Cu1–N1, 2.012(3); Cu1–N2, 2.001(3); Cu1–N3, 1.954(3), Cu1–O1, 2.323(3); Cu1–O5, 2.012(3). Interatomic distances (Å) between copper and phenol: **1**, Cu1...O1, 5.94; **4**, Cu1...O6, 5.66. Dihedral angles (deg) between the phenol and imidazole groups: **1**, 83.1; **4**, 73.0.

distorted trigonal pyramidal with three aromatic nitrogens in the basal plane, while the Cu(II) ion in **4** is pentacoordinate, having ligation from the three nitrogens of the chelate plus methanol and perchlorate donors.²⁸ The imidazole-phenol moiety in both complexes, which includes imidazole-nitrogen copper-ligation, also yields a proximate phenol to the copper ion. The resulting Cu...O distances are in the range of 5–6 Å, analogous to those in the enzyme X-ray structures.^{3–6,29} Large dihedral angles (83.1° and 73.0°) are observed between the phenol and imidazole rings in **1** and **4**, suggesting minimal electronic interaction exists between the copper ion and the phenol in the solid state. For the proteins or the simple organic cofactor models studied thus far, these dihedral angles vary over a wide range, 36–66°.³⁰

The redox properties and O₂-reactivity of these complexes are of general interest, because such information may eventually provide insights into the O₂-reduction process occurring at the enzyme Cu_B site. We first note that the Cu(II)/Cu(I) redox potentials of [Cu^I(L^{N4}-OH)]B(C₆F₅)₄ (**1**), the anisole analogue [Cu^I(L^{N4}OMe)]B(C₆F₅)₄ (**3**), and [Cu^I(TPMA)(MeCN)]ClO₄ (TPMA = tris(2-pyridylmethyl)-amine)²¹ are nearly identical { $E_{1/2}(\mathbf{1}) \cong E_{1/2}(\mathbf{3}) \cong E_{1/2}([Cu^I(TPMA)(MeCN)]^+) = -0.42$ V versus FeCp₂/FeCp₂⁺ in MeCN}. Independent studies of a closely related imidazole complex (without a phenol moiety) [(L)Cu^I]⁺, L = [2-(1H-imidazol-4-yl)-ethyl]-bis-(2-pyridylmethyl)amine, also give $E_{1/2} = -0.42$ V. Thus, the

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Scheme 1



imidazole-phenol (or anisole) cross-links in **1** and **3** do not directly affect redox properties of copper, as expected from the large imidazole/phenol dihedral angle (vide supra).^{31,32}

Dioxygen reactivities of the Cu^I complexes were followed by UV–vis spectroscopy. In THF at $-78\text{ }^{\circ}\text{C}$, $[\text{Cu}^{\text{I}}(\text{L}^{\text{N4}}\text{OME})]\text{B}(\text{C}_6\text{F}_5)_4$ (**3**) binds O_2 reversibly to yield a stable deep purple solution ($\lambda_{\text{max}} = 537\text{ nm}$ ($\epsilon = 9500\text{ M}^{-1}\text{ cm}^{-1}$), 610 nm ($\epsilon = 7500\text{ M}^{-1}\text{ cm}^{-1}$)) with spectral features indicative of a *trans*- μ -1,2-peroxodicopper(II) complex.^{21,27} Under the same conditions, introduction of O_2 to a solution of phenol complex $[\text{Cu}^{\text{I}}(\text{L}^{\text{N4}}\text{OH})]\text{B}(\text{C}_6\text{F}_5)_4$ (**1**) gives a spectrally similar intermediate ($\lambda_{\text{max}} = 537, 610\text{ nm}$),²⁷ but it is not stable and converts in minutes to a reddish-purple dimeric copper(II) complex $[\{\text{Cu}(\text{L}^{\text{N4}}\text{O}^-)\}_2](\text{B}(\text{C}_6\text{F}_5)_4)_2$ (**5a**) ($\lambda_{\text{max}} = 510\text{ nm}$, $\epsilon = 3000\text{ M}^{-1}\text{ cm}^{-1}$) in a nearly quantitative yield (Scheme 1). The structure of the latter phenoxide-bridged dimer has been confirmed by X-ray crystallography, exhibiting the Cu $\cdots$ Cu distance at $5.78\text{ \AA}$.²⁷ A similar dimer complex (X-ray structure determined)^{27,33} is also obtained from the oxygenation of the tridentate Cu^I complex $[\text{Cu}(\text{L}^{\text{N3}}\text{OH})]\text{ClO}_4$ (**2**) (Scheme 1). UV–vis monitored stopped-flow kinetics of the reaction of **2** with O_2 in CH_2Cl_2 indicates a steady formation of the purple dimer product $[\{\text{Cu}(\text{L}^{\text{N3}}\text{O}^-)\}_2](\text{ClO}_4)_2$ (**5b**) ($\lambda_{\text{max}} = 510\text{ nm}$, $\epsilon = 1300\text{ M}^{-1}\text{ cm}^{-1}$), which can be readily analyzed in the temperature range from -40 to $+20\text{ }^{\circ}\text{C}$, $\Delta H^\ddagger = -9.6(6)\text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -168(2)\text{ J mol}^{-1}\text{ K}^{-1}$ ($k_{-40\text{ }^{\circ}\text{C}} = 1.05(4) \times 10^6$ and $k_{+20\text{ }^{\circ}\text{C}} = 4.6(2) \times 10^5\text{ M}^{-2}\text{ s}^{-1}$). At the lowest temperatures ($-90\text{ }^{\circ}\text{C}$), there is evidence for an intermediate, whose UV–vis spectrum ($\lambda_{\text{max}} = \sim 360\text{--}380\text{ nm}$) points to the presence of a μ - η^2 : η^2 side-on peroxo dicopper(II) species.²³ Further kinetic and mechanistic analyses and investigations are needed, but we suggest that for both **1** and **2**, reactions of O_2 give peroxo-dicopper(II) Cu–O $_2$ –Cu intermediates, preorganized for subsequent deprotonation of the ligand phenol ($\text{L}^{\text{N4}}\text{OH}$ or $\text{L}^{\text{N3}}\text{OH}$) and following formation of dimer products **5a** or **5b**.³⁴

In summary, we have prepared novel copper complexes with imidazole-phenol cross-links as initial models for the Cu_B site in cytochrome c oxidase. We have begun systematic studies on redox properties, dioxygen reactivity, and other aspects which may be relevant to the enzyme chemistry.³² Heme-containing models with appended copper chelates having imidazole-phenol groups are also being synthesized for investigation.

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Supporting Information Available: Synthetic details, UV–vis spectra, Eyring kinetic plot, ORTEP diagrams of **5a** and **5b** (PDF),

and X-ray crystallographic data files (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Ferguson-Miller, S.; Babcock, G. T. *Chem. Rev.* **1996**, *96*, 2889–2907.
- Michel, H.; Behr, J.; Harrenga, A.; Kannt, A. *Annu. Rev. Biophys. Biomol. Struct.* **1998**, *27*, 329–356.
- Yoshikawa, S.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yamashita, E.; Inoue, N.; Yao, M.; Jei-Fei, M.; Libeu, C. P.; Mizushima, T.; Yamaguchi, H.; Tomizaki, T.; Tsukihara, T. *Science* **1998**, *280*, 1723–1729.
- Ostermeier, C.; Harrenga, A.; Ermler, U.; Michel, H. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 10547–10553.
- Soulimane, T.; Buse, G.; Bourenkov, G. P.; Bartunik, H. D.; Huber, R.; Than, M. E. *EMBO J.* **2000**, *19*, 1766–1776.
- Svensson-Ek, M.; Abramson, J.; Larsson, G.; Tornroth, S.; Brzezinski, P.; Iwata, S. *J. Mol. Biol.* **2002**, *321*, 329–339.
- Buse, G.; Soulimane, T.; Dewor, M.; Meyer, H. E.; Blüggel, M. *Protein Sci.* **1999**, *8*, 985–990.
- Das, T. K.; Pecoraro, C.; Tomson, F. L.; Gennis, R. B.; Rousseau, D. L. *Biochemistry* **1998**, *37*, 14471–14476.
- Pinakoulaki, E.; Pfizner, U.; Ludwig, B.; Varotsis, C. *J. Biol. Chem.* **2002**, *277*, 13563–13568.
- Gennis, R. B. *Biochim. Biophys. Acta* **1998**, *1365*, 241–248.
- Proshlyakov, D. A.; Pressler, M. A.; DeMaso, C.; Leykam, J. F.; DeWitt, D. L.; Babcock, G. T. *Science* **2000**, *290*, 1588–1591.
- MacMillan, F.; Kannt, A.; Behr, J.; Prisner, T.; Michel, H. *Biochemistry* **1999**, *38*, 9179–9184.
- Blomberg, M. R. A.; Siegbahn, P. E. M.; Babcock, G. T.; Wikström, M. *J. Am. Chem. Soc.* **2000**, *122*, 12848–12858.
- McCauley, K. M.; Vrtis, J. M.; Dupont, J.; Van der Donk, W. A. *J. Am. Chem. Soc.* **2000**, *122*, 2403–2404.
- Cappuccio, J. A.; Ayala, I.; Elliott, G. I.; Szundi, I.; Lewis, J.; Konopelski, J. P.; Barry, B. A.; Einarsdottir, O. *J. Am. Chem. Soc.* **2002**, *124*, 1750–1760.
- Aki, M.; Ogura, T.; Naruta, Y.; Le, T. H.; Sato, T.; Kitagawa, T. *J. Phys. Chem. A* **2002**, *106*, 3436–3444.
- Collman, J. P.; Wang, Z.; Zhong, M.; Zeng, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1217–1222.
- Elliott, G. I.; Konopelski, J. P. *Org. Lett.* **2000**, *2*, 3055–3057.
- Naruta, Y.; Tachi, Y.; Chishiro, T.; Shimazaki, Y.; Tani, F. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2001**, *E57*, o550–o552.
- Tomson, F.; Bailey, J. A.; Gennis, R. B.; Unkefer, C. J.; Li, Z.; Silks, L. A.; Martinez, R. A.; Donohoe, R. J.; Dyer, R. B.; Woodruff, W. H. *Biochemistry* **2002**, *41*, 14383–14390.
- Tyeklár, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubietta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 2677–2689.
- Wei, N.; Murthy, N. N.; Tyeklár, Z.; Karlin, K. D. *Inorg. Chem.* **1994**, *33*, 1177–1183.
- Karlin, K. D.; Kaderli, S.; Zuberbühler, A. D. *Acc. Chem. Res.* **1997**, *30*, 139–147.
- Zhang, C. X.; Liang, H.-C.; Kim, E.-i.; Shearer, J.; Helton, M. E.; Kim, E.; Kaderli, S.; Incarvito, C. D.; Zuberbühler, A. D.; Rheingold, A. L.; Karlin, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 634–635.
- Liang, H.-C.; Zhang, C. X.; Henson, M. J.; Sommer, R. D.; Hatwell, K. R.; Kaderli, S.; Zuberbühler, A. D.; Rheingold, A. L.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 4170–4171.
- Liang, H.-C.; Karlin, K. D.; Dyson, R.; Kaderli, S.; Jung, B.; Zuberbühler, A. D. *Inorg. Chem.* **2000**, *39*, 5884–5894.
- See Supporting Information.
- X-band EPR spectrum of **4** (MeOH, 19 K): $g_{\perp} = 2.06$, $g_{\parallel} = 2.26$, $A_{\parallel} = 173\text{ G}$.
- Cu $\cdots$ O(Tyr) distances are $5.70\text{--}5.94$,³ 5.02 ,⁴ 5.66 ,⁵ and 5.78 ⁶ Å.
- His-Tyr dihedral angles (deg) from enzyme X-ray structures: 44 ,³ 66 ,⁴ and 57 .⁵ Dihedral angles (deg) from the organic model compounds: 36 ,³¹ and 42 .¹⁹
- Only irreversible electrochemical behavior is observed for the tridentate copper complex **2**. $E_{\text{pa}} = -0.42\text{ V}$ and $E_{\text{pc}} = -0.74\text{ V}$ versus $\text{FcP}^+/\text{FcP}^0$ in DMF, $i_{\text{a}}/i_{\text{p}} = 1.1$.
- Generation, characterization, and electronic interaction of a Cu(II)-phenoxyl radical species are currently under investigation.
- X-ray quality crystals of **5b** were obtained from MeCN/Et $_2$ O, giving a complex with ligated acetonitrile, $[\{\text{Cu}(\text{L}^{\text{N3}}\text{O}^-)(\text{MeCN})\}_2](\text{ClO}_4)_2$.
- Tests for hydrogen peroxide as expected products were negative, but we separately observe that **5a** and **5b** effect the decomposition of H_2O_2 .

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