Synthesis, structure, and catalytic function of a disulfide-bridged dicopper(I) complex

Takehiro Ohta,[a] Takashi Tachiyama,[a] Kazunari Yoshizawa [a,*] and Tokio Yamabe [a,b]

[a]*Department of Molecular Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*
[b]*Institute for Fundamental Chemistry, 34-4 Takano-Nishihiraki-cho, Sakyo-ku, Kyoto 606-8103, Japan*

Abstract

A disulfide-bridged dicopper(I) complex $[Cu_2(Py_2SSPy_2)](ClO_4)_2$ (**1**), synthesized by the redox reaction of a Cu(II) salt with a thiol-containing N_3S-donor ligand, *N,N*-bis[2-(2-pyridyl)ethyl]-2-mercapto-2-methylpropylamine (Py_2SH), is demonstrated to catalyze epoxidation and hydroxylation with H_2O_2 as an oxidant. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: dicopper complexes; disulfides; X-ray crystal structures; epoxidation.

The activation of dioxygen and a C–H bond performed by copper-containing enzymes is attracting much current interest from chemical and biochemical points of view. Dopamine β-monooxygenase (DβM)[1] catalyzes the hydroxylation of dopamine at the benzylic positions to norepinephrine and peptidylglycine α-hydroxylating monooxygenase (PHM)[2] which mediates the stereospecific hydroxylation of the glycine α-carbon of peptidylglycine substrates, and is a new class of copper monooxygenase in that dioxygen binding and substrate hydroxylation are carried out on mononuclear copper sites, called Cu_B, of the dicopper active sites. A recent X-ray analysis[2] showed that the Cu_B site of PHM is coordinated by methionine (MetS), and a preparation and characterization of half-apo reduced DβM[3] demonstrated the coordination of an S-donor, presumably MetS, to the Cu_B center. Therefore, to elucidate the still unclear mechanism for the activation of dioxygen and a C–H bond performed by these copper enzymes, it is important to investigate oxidation reactions of a copper model complex that involves an S-donor ligand.[4,5]

In this paper we present that a combination of hydrogen peroxide (H_2O_2) with a new disulfide-bridged dicopper(I) complex (**1**), synthesized by the redox reaction of a Cu(II) salt with a thiol-containing N_3S-type ligand Py_2SH (Fig. 1), can mimic the biological C–H bond activation. The Py_2SH ligand was synthesized by the ring-opening reaction of isobutylene sulfide[6] with bis[2-(2-pyridyl)ethyl]amine[7] at

---

* Corresponding author. E-mail: kazunari@scl.kyoto-u.ac.jp (K. Yoshizawa)

60°C for 24 h.[†] Complex **1** was obtained by the redox reaction[8] of Py₂SH with Cu(ClO₄)₂·6H₂O in MeOH solution (82% yield based on Py₂SH).[‡] We carried out single-crystal structure analyses of **1** and found two independent structures (**1a,1b**), which mainly differ in the S–S bond distance and the C–S–S–C dihedral angle, as shown in Fig. 2.[§]
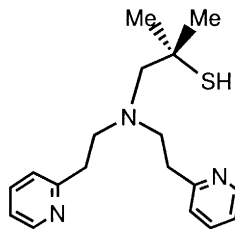

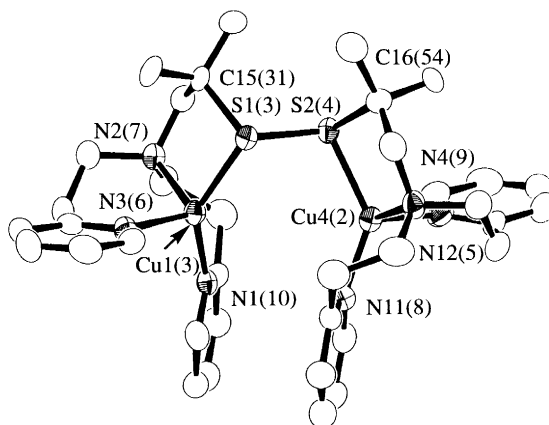Fig. 1. Schematic drawing of a thiol-containing N₃S-donor ligand Py₂SH

Fig. 2. Structure of a dication of **1a**(**1b**) (ORTEP plot) showing 30% probability ellipsoids. Numbers in the parentheses are atom numbering for **1b**; hydrogen atoms have been omitted for clarity. Bond distances are in Å and bond angles are in deg: for **1a**, Cu1···Cu4 4.035(3), Cu1–S1 2.228(6), Cu2–S4 2.242(6), S1–S2 2.088(7), and C15–S1–S2–C16 109.5(10); for **1b**, Cu2···Cu3 4.081(3), Cu2–S4 2.242(6), Cu3–S3 2.246(6), S3–S4 2.070(7), and C31–S4–S3–C54 103(1)

Although disulfide-dicopper(I) complexes are well-known, this is the first structurally characterized example obtained by the redox reaction[8] of a Cu(II) salt with a thiol-containing ligand. The two Cu(I) ions, which are separated by 4.035(3) Å for **1a** and 4.081(3) Å for **1b**, are bridged by the disulfide moiety of a resultant ligand, Py₂SSPy₂. The disulfide S–S distances of 2.088(7) Å for **1a** and 2.070(7) Å for **1b** are longer than the value of 2.04 Å which is frequently observed in aliphatic disulfides.[9] The C–S–S–C

[†] Py₂SH (*N,N*-bis[2-(2-pyridyl)ethyl]-2-mercapto-2-methylpropylamine): elemental analysis: calcd for C₁₈H₂₅N₃S: C, 68.53%; H, 7.99%; N, 13.32%; S, 10.16%. Found: C, 68.37%; H, 7.98%; N, 13.06%; S, 10.15%. ¹H NMR data: (δ/ppm vs TMS) in CDCl₃: 8.52 (d, *J*=4.9 Hz, 2H), 7.58 (t, *J*=6.8 Hz, 2H), 7.16 (d, *J*=7.8 Hz, 2H), 7.10 (d, *J*=6.3 Hz, 2H), 3.13–2.97 (m, 8H), 2.63 (s, 2H), 1.23 (s, 6H).

[‡] Caution: The perchlorate salt is potentially explosive and should be handled with care. Elemental analysis: calcd for Cu₂C₃₆H₄₈N₆S₂Cl₂O₈: C, 45.28%; H, 5.06%; N, 8.80%; Cl, 7.43%. Found: C, 45.08%; H, 5.07%; N, 9.30%; Cl, 7.34%. Mass(FAB) analysis: *m/z* calcd for Cu₂C₃₆H₄₈N₆S₂ClO₄: 855. Found: 855 (M⁺).

[§] X-Ray crystal data for **1**: intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated Mo–Kα radiation (λ=0.71069 Å) at 296 K, using the ω–2θ scan technique to a maximum 2θ value of 55°. C₇₂H₄₉Cl₄Cu₄N₁₂S₄O₁₆ (**1**)₂: triclinic space group P1̄ (No. 2), *a*=15.165 (3) Å, *b*=22.185 (4) Å, *c*=14.989 (3) Å, α=105.76°, β=90.82°, γ=75.23°, *V*=4684 (1) Å³, *Z*=2, *d*₍calcd₎=1.354 g/cm³, *R* [*I*>2σ(*I*)]=0.095 for 7373 independent reflections of the 21502 collected. *R* (all data)=0.125. The structure was solved by direct method (SHELX-86).

dihedral angles of 109.5°(10) for **1a** and 103°(1) for **1b** are different from those of aliphatic disulfides which are in most cases close to 90°.[9] These structural features of the elongated S–S bond, the short Cu–S bond and the C–S–S–C dihedral angle alteration from 90° would be a consequence of electron density delocalization from the Cu(I) ions to the sulfur 3d or 3p orbitals. Therefore, we can view complex **1** as an intermediate structure in the disulfide S–S bond formation by the catalytic oxidation of a thiol by a Cu(II) salt. Complex **1** in CH_3CN solution exhibits a UV–vis spectrum with an intense band at 300 nm ($\varepsilon=10810$ M^{-1} cm^{-1}), which would be ascribed to a charge transfer between the Cu(I) ions and the disulfide moiety or to a disulfide absorption that is significantly red-shifted due to complexation or the C–S–S–C dihedral angle alteration from 90°.[9]

Results of catalytic oxidation of hydrocarbons by the **1**/H_2O_2 combination are listed in Table 1. Due to self-oxidation of the complex the yield is not so high. Interestingly, the selective oxidation of cyclohexane to cyclohexanol with an alcohol/ketone ratio of 2 was achieved. A combination of a metal complex with a peroxide is often considered to generate a hydroxyl or an alkoxyl radical that can initiate radical chain autoxidation reactions,[10] and in this reaction alkane is oxidized with an alcohol/ketone ratio of about 1. We thus think that a metal-based oxidant may be formed by the **1**/H_2O_2 combination. On the other hand, the **1**/^{t}BuOOH combination oxidized cyclohexane to cyclohexanol (12% yield) and to cyclohexanone (14% yield) with an alcohol/ketone ratio of 1. The formation of a metal-based oxidant in **1**/H_2O_2 is further supported by the results of the oxidation of cyclohexene to its epoxide, while the **1**/^{t}BuOOH combination was unable to catalyze the epoxidation. The observed oxidation selectivity for the epoxidation (E) versus the allylic oxidation (A) with an E/A ratio of 0.18 is much higher than 0.03 of E/A shown by Kitajima's μ-peroxo dicopper(II) complex.[11] DβM also catalyzes olefin epoxidations,[1b] and thus the oxidation reaction of **1**/H_2O_2 may be analogous to the oxygenation by DβM.

Table 1
Oxygenation of substrates by the **1**/H_2O_2 system[a]

Substrate	Product[b]	Yield[c] (%)
cyclohexane	cyclohexanol	41(41)[d]
	cyclohexanone	18(27)[d]
cyclohexene	cyclohexene oxide	9
	2-cyclohexene-1-ol	24
	2-cyclohexene-1-one	24
2,6-di-*tert*-butylphenol	3,3',5,5'-tetra-*tert*-butyl-4,4'-diphenoquinone	3

[a] Reaction conditions: 0.05 mL of 30% aqueous H_2O_2 was slowly added to a stirred 5 mL CH_3CN solution containing **1** (50 μmol) and 1 mmol of substrate. The reaction mixture was stirred for 30 min at 25°C under Ar. [b] The products listed were analyzed and quantified by GC using PhCl as an internal standard. [c] Moles of product/moles of **1**. [d] Yield in parentheses was obtained under O_2 conditions.

Preliminary UV–vis, EPR, and resonance Raman (RR) studies have shown that a transient dark-green species is formed in the early stage of the reaction of **1** with H_2O_2. Intermediate **2** is fairly stable below 0°C, and shows absorption maxima at 295 nm ($\varepsilon=7700$ M^{-1} cm^{-1}) and 325 nm (sh) ($\varepsilon=6414$ M^{-1} cm^{-1}) and a very weak, broad d–d transition band at 670 nm ($\varepsilon=30$ M^{-1} cm^{-1}) (Fig. 3). This change in the absorption spectrum is indicative of a coordination of an anionic donor such as a deprotonated hydrogen

peroxide anion to a copper center.[12,13] An EPR spectrum of a CH$_3$CN solution of **2** at 77 K exhibits axial signals at $g_{||}$=2.21 ($A_{||}$=170 G) and $g_{\perp}$=2.01 and isotropic weak broad signals at g=1.66, 2.94, and 5.55. The signal of g=5.55 (Fig. 3 inset) indicates that a half-field transition of ΔM_s=±2 occurs within the dipolar interacting Cu(II) ions of the dimer site.[14] After the decomposition of **2**, the half-field transition faded away and only the g=2 signals were observed. Therefore a dinuclear copper(II) structure should be involved in **2**. Similar observations of the co-existence of dinuclear and mononuclear copper(II) species in the formation of dicopper–dioxygen complexes were reported.[7,14] We obtained elemental analysis data of the crystal of the decomposed complex,[15] which indicate the occurrence of ligand sulfoxidation, as observed by Champloy and co-workers.[5] The elemental composition suggests that a cuprous center should be included in the decomposed complex, which is innocent of the g=2 signal.
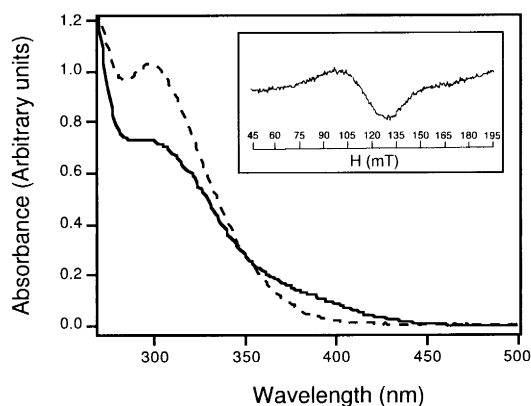

Fig. 3. Electronic absorption spectra of **1** (dashed line) and **2** (solid line) in CH$_3$CN at 0°C. Inset: EPR spectrum of **2** in the half-field transition region; 77 K, microwave frequency 9.09 GHz, modulation 0.63 mT, microwave power 0.4 mW

The preliminary RR studies[16] of **2** in a CH$_3$CN solution measured at −25°C (laser excitation wavelength 325 nm) revealed resonance-enhanced Raman features in the region of 800–850 cm^{-1} which were fitted by two Gaussian functions, revealing the two peaks at 822 and 836 cm^{-1}. The two peaks shift to the lower frequencies upon introduction of H$_2{}^{18}$O$_2$ with peak features at 781 and 791 cm^{-1}. These vibrational features are in the range characteristic for the ν(O–O) band of peroxide species. The electrospray ionization (ESI) mass spectroscopy is a powerful tool for characterizing such an intermediate, so that we will apply the method to **2** in future work in order to gain more accurate information about the structure of the peroxide species. Further studies on the vibrational and reaction aspects of **2** are now in progress and will be reported in due course.[16]

References

1. (a) Tian, G.; Berry J. A.; Klinman, J. P. *Biochemistry* **1994**, *33*, 226–234; (b) Padgette, S. R.; Wimalasena, K.; Herman, H. H.; Sirimanne, S. R.; May, S. W. *Biochemistry* **1985**, *24*, 5826–5839.

2. Prigge, S. T.; Kolhekar, A. S.; Eipper, B. A.; Mains, R. E.; Amzel, L. M. *Science* **1997**, *278*, 1300–1305.

3. Reedy, B. J.; Blackburn, N. J. *J. Am. Chem. Soc.* **1994**, *116*, 1924–1931.

4. Casella, L.; Gullotti, M.; Bartosek, M.; Pallanza, G.; Laurenti, E. *J. Chem. Soc., Chem. Commun.* **1991**, 1235–1236.

5. Champloy, F.; Benali-Chérif, N.; Bruno, P.; Blain, I.; Pierrot, M.; Rélier, M.; Michalowicz, A. *Inorg. Chem.* **1998**, *37*, 3910–3918.

6. Sanders, M. *Chem. Rev.* **1966**, *66*, 297–339 and references cited therein.

7. Sanyal, I.; Mahroof-Tahir, M.; Nasir, M. S.; Gosh, P.; Cohen, B. I.; Gultneh, Y.; Cruse, R. W.; Farooq, A.; Karlin, K. D.; Liu, S.; Zubieta, J. *Inorg. Chem.* **1992**, *31*, 4322–4332.

8. Reaction of a Cu(II) salt with a thiol is known to lead to the redox decomposition [Cu(II)+RSH→Cu(I)+RSSR].

9. Ottersen, T.; Warner, L. G.; Seff, K. *Inorg. Chem.* **1974**, *13*, 1904–1911 and references cited therein.

10. (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981; (b) Kim, J.; Harrison, R. G.; Kim, C.; Que Jr., L. *J. Am. Chem. Soc.* **1996**, *118*, 4373–4379.

11. Kitajima, N.; Koda, T.; Iwata, Y.; Moro-oka, Y. *J. Am. Chem. Soc.* **1990**, *112*, 8833–8839.

12. Wada, A.; Harata, M.; Hasegawa, K.; Jitsukawa, K.; Masuda, H.; Mukai, M.; Kitagawa, T.; Einaga, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 798–799.

13. Sobkowiak, A.; Quin, A.; Liu, X.; Llobet, A.; Sawyer, D. T. *J. Am. Chem. Soc.* **1993**, *115*, 609–614.

14. Wilcox, D. E.; Long, J. R.; Solomon, E. I. *J. Am. Chem. Soc.* **1984**, *106*, 2186–2194.

15. The decomposed complex obtained by the reaction of $[Cu_2(Py_2SSPy_2)](SbF_6)_2$ (**1′**) with H_2O_2 gave a pale yellow crystal (**3**): Elemental analysis: C, 34.52%; H, 3.84%; N, 6.54%. This elemental analysis is best fitted by the formula as $Cu_1C_{18}H_{24}N_3S_1O_1Sb_1F_6$ (C, 34.33%; H, 3.84%; N, 6.67%), indicating that an O atom should be attached to the oxidizable S atom of the disulfide unit.

16. Ohta, T.; Tachiyama, T.; Yoshizawa, K.; Yamabe, T.; Uchida, T.; Kitagawa, T., manuscript in preparation.