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C–S Bond Formation Reaction between a Phenolate and Disulfide-Bridged Dicopper(I) Complexes

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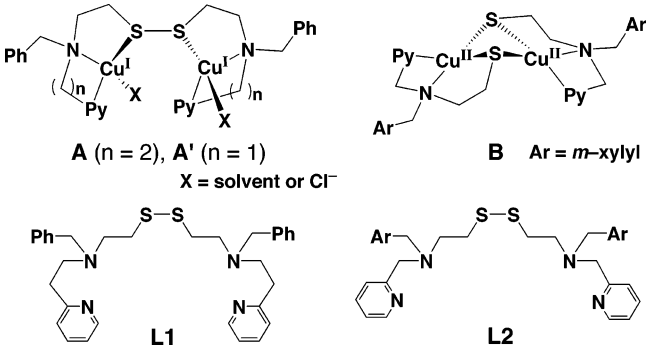
A novel C–S bond formation reaction took place, when a lithium phenolate derivative was treated with a disulfide-bridged dicopper(I) complex or a bis(μ-thiolato)dicopper(II) complex under very mild conditions. The reaction has been suggested to proceed via a disulfide-bridged (μ-phenoxo)dicopper(I) complex as the common reaction intermediate. Copper(II) complexes of the modified ligands containing a thioether group (products of the C–S bond formation reaction) have been isolated and structurally characterized by X-ray analysis as model compounds of the active site of galactose oxidase. Mechanism of the C–S bond formation reaction is also discussed in relation to the biosynthetic mechanism of the organic cofactor Tyr-Cys of galactose oxidase.

Copper−sulfur complexes have attracted considerable interest in connection with the structures and functions of copper reaction centers in biological electron-transfer systems.[1−3] Among the series of copper−sulfur complexes, dinuclear copper complexes bridged by sulfur atoms have been given much recent attention in relation to the bis(μ-thiolato)dicopper core, $Cu(RS)_2Cu$, of the Cu_A sites of cytochrome *c* oxidase (C*c*O) and nitrous oxide reductase (N_2OR).[4−7] To replicate such an interesting $Cu(RS)_2Cu$ core structure, Tolman's group and our group have developed the bis(μ-thiolato)dicopper complexes of both the $Cu^{1.5+}-Cu^{1.5+}$ (mix-valent) and $Cu^{2+}-Cu^{2+}$ oxidation states.[8−11] We have further demonstrated that a bis(μ-thiolato)dicopper(II) complex such as **B** can be reversibly converted to the corresponding disulfide-bridged dicopper(I) complex **A′** ($n = 1$; $X = Cl^-$) by treating the former with an external ligand such as Cl^- (see Chart 1).[11] Such a clean isomerization between the bis(μ-thiolato)dicopper(II) complex and the disulfide−dicopper(I) complex provides important insights into the mechanism of ubiquitous redox interconversion between thiolates and disulfides ($2RS^- \leftrightharpoons RS-SR + 2e^-$).

Chart 1



The isomerization between the bis(μ-thiolato)dicopper(II) complex and the disulfide−dicopper(I) complex is also worth investigating, since it is an isoelectronic process of the interconversion between a (μ-peroxo)dicopper(II) complex and a bis(μ-oxo)dicopper(III) complex, which has recently attracted a great deal of attention as a possible dioxygen activation mechanism by copper monooxygenases.[12−14] Thus, recent efforts in copper biomimetic chemistry have also been directed to the development of (μ-disulfido)dicopper(II) complexes with both the end-on (μ-η^1:η^1) and side-on (μ-η^2:η^2) binding modes as the sulfur versions of the corre-

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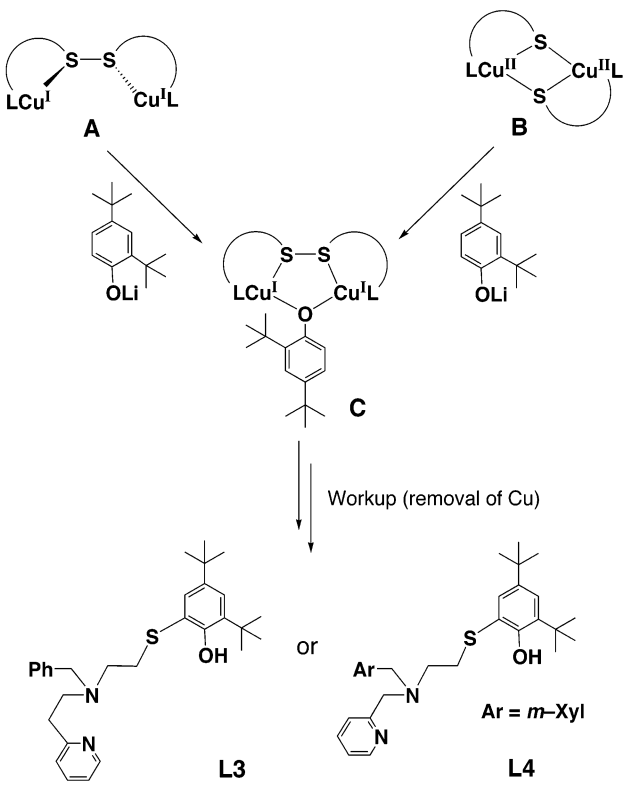
Scheme 1



sponding (μ-peroxo)dicopper(II) complexes.[15−17] In contrast to the extensive studies on the reactivity of dicopper−dioxygen complexes,[13] however, little is known about the reactivity of dicopper−disulfur complexes toward external substrates.

In this study, we have investigated the reaction of disulfide-bridged dicopper(I) complex **A** supported by ligand **L1** (n = 2; X = CH_3CN)[18] and bis(μ-thiolato)dicopper(II) complex **B** generated by using ligand **L2**[11] (see Chart 1) with a lithium phenolate derivative to find a novel C−S bond formation reaction as indicated in Scheme 1. The reaction is of particular interest, since the process is related to the biogenetic pathway of the novel organic cofactor Tyr-Cys of galactose oxidase (see Figure 1).[19] In addition, the reaction can be regarded as a sulfur version of the tyrosinase model reaction, the hydroxylation (C−O bond formation) of phenolates by the (μ-η^2:η^2-peroxo)dicopper(II) complex,[20] although the binding mode of bridging ligands and the oxidation state of copper are different between the peroxo and disulfide systems.

As stated already, the bis(μ-thiolato)dicopper(II) complex **B** can be easily converted to the corresponding disulfide-bridged dicopper(I) complex **A′** when it is treated with external ligand such as chloride ion in nonpolar solvent such as CH_2Cl_2.[11] Here we have also found that the equilibrium position between **B** and **A′** is largely affected by the solvent used as shown in Figure S1. Namely, the bis(μ-thiolato)-dicopper(II) complex **B** exists as a major component in CH_2-Cl_2, while replacement of the solvent to acetone significantly decreases the ratio of **B** (judging from the intensity of the LMCT band at 813 nm of **B**,[11] **B**/**A′** = 64:36 in acetone). Furthermore, **B** was completely converted into **A′**, when **B** was dissolved into CH_3CN (see Figure S1).[21] Thus, the stronger the coordination ability of solvent, the more favorable the disulfide-bridged dicopper(I) complex (**A′**) formation. Coordination of the solvent molecule may stabilize the tetrahedral geometry of copper to induce the formation of disulfide−dicopper(I) complex **A′**.[11]

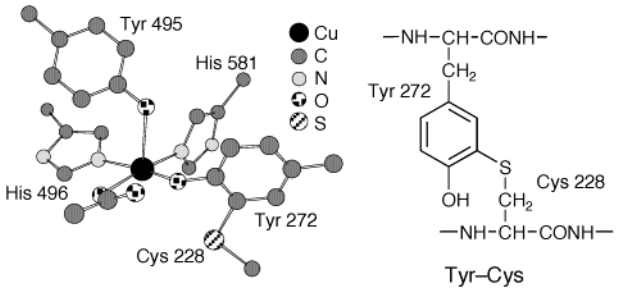


Figure 1. Active site structure (left) and the organic cofactor (right) of galactose oxidase.[19]

Then, the reactivity of complexes **A** and **B** toward an external substrate was examined. Addition of lithium 2,4-di-*tert*-butylphenolate to a CH_2Cl_2 solution of complex **B** also resulted in the disappearance of the LMCT band due to **B**, suggesting that the similar isomerization of **B** to a disulfide−dicopper(I) complex occurred. In this case, stoichiometry of the phenolate to **B** was 1:1 (phenolate/Cu = 1:2). Thus, the primary product of the phenolate titration may be a disulfide-bridged (μ-phenoxo)dicopper(I) complex **C** as indicated in Scheme 1. In this case, further reaction took place at a prolonged reaction time to induce the C−S bond formation reaction (Scheme 1). After the workup treatment of the reaction mixture in a preparative scale, ligand **L4** was isolated in a 68% yield based on the starting dicopper complex **B**.[22]

The same C−S bond formation reaction took place when the disulfide-bridged dicopper(I) complex **A** supported by

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(21) Titration of complex **B** with CH_3CN was performed in CH_2Cl_2 at 25 °C (Figure S2). The association constant of CH_3CN to **B** producing **A′**, defined by $K_{as} = (A - A_0)/(A \cdot [CH_3CN]^2)$, was determined as 24.6 M^{-2}. The thermodynamic parameters for the CH_3CN-binding were also determined as $\Delta H° = -73.8 \pm 7.9$ kJ mol^{-1} and $\Delta S° = -221 \pm 27$ J K^{-1} mol^{-1} from the temperature dependence of K_{as} according to the equation of $\ln K_{as} = -\Delta H°/RT + \Delta S°/R$ (Figure S3).

(22) Analytical data for **L4**. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 1.26 (s, 9 H, ^{t}Bu), 1.39 (s, 9 H, ^{t}Bu), 2.33 (s, 3 H, Xyl-CH_3), 2.70 (t, J = 6.3 Hz, 2 H, −N−CH_2−CH_2−S−), 2.88 (t, J = 6.3 Hz, 2 H, −N−CH_2−CH_2−S−), 3.64 (s, 2 H, −N−CH_2−Xyl), 3.76 (s, 2 H, −N−CH_2−Py), 7.06 (d, J = 6.4 Hz, 1 H, Xyl_{H-2}), 7.14−7.21 (m, 4 H, $Xyl_{H-4,5,6}$ and Py_{H-5}), 7.29 (d, J = 2.4 Hz, 1 H, ArO_{H-5}), 7.33 (d, J = 2.4 Hz, 1 H, ArO_{H-3}), 7.45 (d, J = 8 Hz, 1 H, Py_{H-3}), 7.64 (td, J = 8 Hz, 2 Hz, 1 H, Py_{H-4}), 8.16 (br, 1 H, −O*H*), 8.49 (d, J = 4.8 Hz, 1 H, Py_{H-6}). HRMS (FAB$^+$): m/z = 477.2938, calcd for $C_{30}H_{41}N_2OS$ = 477.2939.

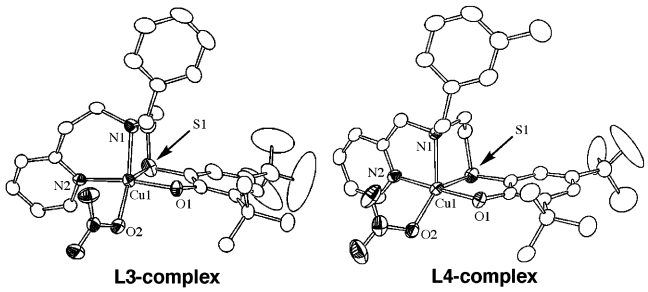
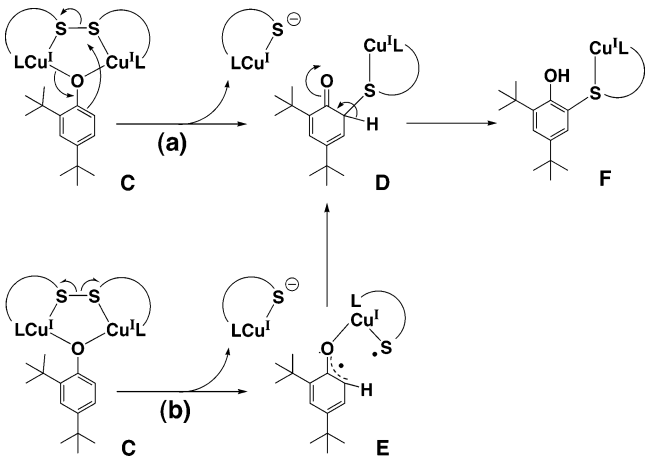


Figure 2. ORTEP drawings of the **L3**- and the **L4**-complexes showing 50% probability thermal-ellipsoid. The hydrogen atoms are omitted for clarity.

L1 was treated with the lithium phenolate under the same experimental conditions to give the modified ligand **L3** in a 74% yield.[23] These results clearly suggest that the C−S bond formation proceeds through a disulfide-bridged (μ-phenoxo)-dicopper(I) complex **C** as the common reaction intermediate. In fact, the yields of **L3** and **L4** increased to 90% and 84%, respectively, when the reactions were carried out in CH_3-CN, that is, the solvent favoring the disulfide complex formation as described. On the other hand, no reaction took place, when the ligand itself (without copper) was treated with lithium phenolate under the same experimental conditions.

Although the structures of modified ligands **L3** and **L4** were well supported by the ^{1}H NMR and MS analyses,[22,23] the C−S bond formation was definitely confirmed by the X-ray crystallographic analysis of the copper(II) complexes prepared by treating $Cu(NO_3)_2 \cdot 3H_2O$ and the isolated **L3** and **L4** ligands, respectively.[24,25] As clearly shown in Figure 2, there exists a thioether bond between the sulfur atom of the ligand and the α-position of the phenolate. Each cupric ion exhibits a significantly distorted five-coordinate trigonal bipyramidal geometry ($\tau = 0.52$ for the **L3**-complex and $\tau = 0.64$ for the **L4**-complex), where the basal plane consists of sulfur atom S(1), tertiary amine nitrogen N(1), and one of the oxygen atoms of the nitrate anion O(2), and the axial positions are occupied by pyridine nitrogen N(2) and phenolate oxygen O(1).

Scheme 2



The copper(II) complexes of the modified ligands can be regarded as model compounds of the active site of galactose oxidase, since **L3** and **L4** involve the 2-alkylthiophenol skeleton existed in the organic cofactor Tyr-Cys of the enzyme (Figure 1).

Although mechanistic details of the C−S bond formation reaction have yet to be clarified, there may be two possible reaction pathways from intermediate **C** (Scheme 2). Path a is an ionic mechanism where heterolytic cleavage of the S−S bond occurs to induce an electrophilic attack of the generated cationic sulfur to the α-position of phenolate to give intermediate **D**, which may readily rearrange to product **F** (aromatization). This mechanism is analogous to the electrophilic aromatic substitution mechanism of the tyrosinase reaction, where aromatic hydroxylation (C−O bond formation) of phenolates occurs in the reaction with the (μ-η^2:η^2-peroxo)dicopper(II) complex.[20] Another possibility is a homolytic cleavage of the S−S bond in **C** [path b]. In this case, electron-transfer from the bound phenolate to one of the generated thiyl radicals may occur to give phenoxyl-thiyl diradical intermediate **E**, from which radical coupling between the α-carbon and the thiyl radical centers occurs to give intermediate **D**. This mechanism resembles the proposed mechanism of post-translational modification of galactose oxidase.[26] Detailed mechanistic studies as well as further characterization of the **L3**- and **L4**-complexes are being undertaken in order to shed light on the enzymatic functions.

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Supporting Information Available: UV−vis spectra of complex **B** in different solvents (CH_2Cl_2, acetone, and CH_3CN) (Figure S1), the spectral change for the titration of complex **B** with CH_3-CN (Figure S2), and its van't Hoff plot (Figure S3). X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Analytical data for **L3**. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 1.27 (s, 9 H, ^{t}Bu), 1.39 (s, 9 H, ^{t}Bu), 2.68 (t, $J = 6.1$ Hz, 2 H, −N−CH_2−CH_2−S−), 2.82−2.95 (m, 6 H, −N−CH_2−CH_2−S− and −N−CH_2−CH_2−Py), 3.72 (s, 2 H, −N−CH_2−Ph), 7.03−7.09 (m, 2 H, $Py_{H-3,5}$) 7.23−7.32 (m, 5 H, Ph), 7.35 (br, 1 H, ArO_{H-5}), 7.37 (d, $J = 2.2$ Hz, ArO_{H-3}), 7.54 (t, $J = 5.8$ Hz, Py_{H-4}), 8.44 (d, $J = 4.6$ Hz, Py_{H-6}), 8.67 (br, 1 H, −O*H*). HRMS (FAB$^+$): $m/z = 477.2943$, calcd for $C_{30}H_{41}N_2OS = 477.2939$.

(24) Analytical data for **L3**-complex. FT-IR (KBr): 1279 and 1475 cm^{-1} (NO_3^-). FAB-MS: $m/z = 538.2$ ([M − NO_3]$^+$). Anal. Calcd for $C_{30}H_{40}N_3SCuO_{4.5}$: C, 59.04; H, 6.61; N, 6.89. Found: C, 59.20; H, 6.47; N, 6.98. Crystal data of **L3**-complex: $C_{30}H_{39}N_3O_4SCu$, FW = 601.26, monoclinic, space group $P2_1/a$, $a = 11.72(1)$ Å, $b = 13.80(1)$ Å, $c = 19.45(2)$ Å, $\beta = 103.95(3)°$, $V = 3055(4)$ Å^3, $D_c = 1.307$ g/cm^{-3}, and μ(Mo Kα) = 8.21 cm^{-1}. Final R and R_w values were 0.048 and 0.056, respectively.

(25) Analytical data for **L4**-complex. FT-IR (KBr): 1279 and 1475 cm^{-1} (NO_3^-). FAB-MS: $m/z = 538.2$ ([M − NO_3]$^+$); Anal. Calcd for $C_{30}H_{40}N_3SCuO_{4.5}$: C, 59.04; H, 6.61; N, 6.89. Found: C, 59.17; H, 6.47; N, 6.94. Crystal data of **L4**-complex: $C_{30}H_{39}N_3O_4SCu$, FW = 601.26, monoclinic, space group $P2_1/a$, $a = 11.227(2)$ Å, $b = 13.716(2)$ Å, $c = 19.488(2)$ Å, $\beta = 101.568(9)°$, $V = 2940.1(8)$ Å^3, $D_c = 1.358$ g/cm^{-3}, and μ(Mo Kα) = 8.53 cm^{-1}. Final R and R_w values were 0.036 and 0.037, respectively.

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