Isomerization of a Linear Pentamine, 1,4,7,10,13-Pentaazatridecane, to a Branched Form, 4-(Aminoethyl)-1,4,7,10-tetraazadecane, on a Schiff-base Copper Complex Relevant to Multi-copper Enzymes

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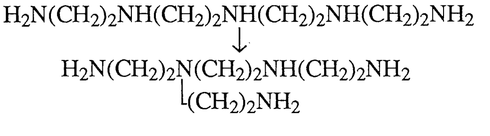
The 1:2 Schiff-base of 2,6-diformyl-4-methylphenol and 1,4,7,10,13-pentaazatridecane formed a tetranuclear assembly complex {Cu(II)-Cu_2(II,II)-Cu(II)} possessing a dinuclear Cu_2 core and two mononuclear Cu auxiliaries. The two-electron reduction of the complex and reoxidation in air resulted in the formation of a dinuclear Cu_2(II,II) complex of a macrocycle comprised of 2,6-diformyl-4-methylphenol and branched 4-(2-aminoethyl)-1,4,7,10-tetraazadecane (2:2) instead of the linear pentamine.

Multi-copper enzymes like laccase and ascorbate oxidase contain type 1, type 2 and type 3 coppers (four copper atoms altogether in each subunit) and catalyze the oxidation of substrates using molecular dioxygen.[1] Recent X-ray crystallographic studies for ascorbate oxidase[2] have proved a close proximity of the type 2 and type 3 coppers (ca. 4 Å). Type 1 copper is ~12 Å separated from type 3 copper but this is involved in the enzymatic function together with the type 2 and type 3 coppers. The first generation models for the trinuclear type 3 - type 2 constellation have appeared,[3,4] but no tetranuclear model system has been reported so far. In this context it is of great importance to provide tetranuclear assembly complexes, comprised of a dinuclear Cu_2 core and two mononuclear Cu auxiliaries, and examine their electrochemical properties and reactivity toward molecular dioxygen.

With the hope to provide such a model, we have prepared the tetranuclear assembly complex {Cu(II)-Cu_2(II,II)-Cu(II)} (Figure 1) using the 1:2 Schiff base of 2,6-diformyl-4-methylphenol and 1,4,7,10,13-pentaazatridecane. From electrochemical studies of this complex, it was found that a very rare isomerization of the linear pentamine to the branched form, 4-(2-aminoethyl)-1,4,7,10-tetraazadecane, occurs:



$$\begin{array}{c} H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2 \\ \downarrow \\ H_2N(CH_2)_2N(CH_2)_2NH(CH_2)_2NH_2 \\ \llcorner(CH_2)_2NH_2 \end{array}$$

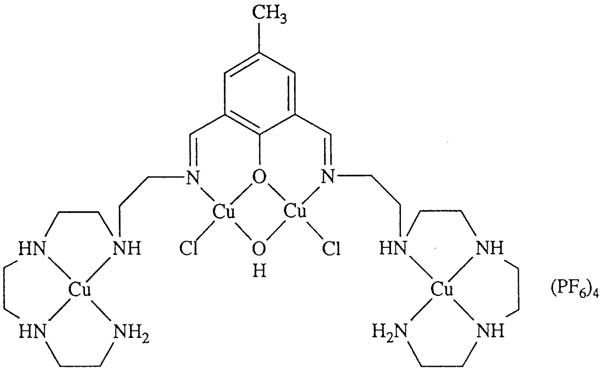


Figure 1. Chemical structure of the tetranuclear complex.

The tetranuclear assembly complex was prepared as green microcrystals[5] by the reaction of μ-chloro-μ-(2,6-diformyl-4-methylphenolato)dichlorodicopper(II)[6] and 1,4,7,10,13-pentaazatridecanecopper(II) hexafluorophosphate (in a 1:2 molar ratio) in acetonitrile at reflux temperature. The cyclic voltammogram of the assembly complex in acetonitrile showed pseudo-reversible couples at +0.47 and -0.65 (V vs. SCE), which are assigned to the oxidation of the dinuclear core (Cu_2(II,II)/Cu_2(II,III)) and the reduction of the two mononuclear auxiliaries (Cu(II)/Cu(I)), respectively, based on electrochemical studies of the reference complexes μ-hydroxo-μ-[2,6-di(N-alkyliminomethyl)-4-methylphenolato]dichlorodicopper(II) (Cu_2(II,II)/Cu_2(II,III): +0.4 ~ +0.6V) and triethylenetetraminecopper(II) hexafluorophosphate (Cu(II)/Cu(I): -0.44 V). Coulometry was done at -0.60 V with the aim to provide the {Cu(I)-Cu_2(II,II)-Cu(I)} complex, but the electrolyzed solution showed well resolved ESR signals (g_{ave}= 2.09 with $A_{ave}=62\times10^{-4}$ cm^{-1}) typical of monomeric Cu(II) at room temperature. It must be emphasized that the {Cu(I)-Cu_2(II,II)-Cu(I)} species is ESR-innocent because of the significantly antiferromagnetic spin-exchange in the dinuclear core.[6] Furthermore the reduced solution shows a d-d band at 619 nm (ε=320 $M^{-1}cm^{-1}$) which differs from that of μ-hydroxo-μ-[2,6-(N-alkyliminomethyl)-4-methylphenolato]dichlorodicopper(II) (~730 nm).[6] The results suggest an intramolecular electron transfer: {Cu(I)-Cu_2(II,II)-Cu(I)} → {Cu(II)-Cu_2(I,I)-Cu(II)}. Such an observed electron transfer is relevant to multi-copper enzymes.[7]

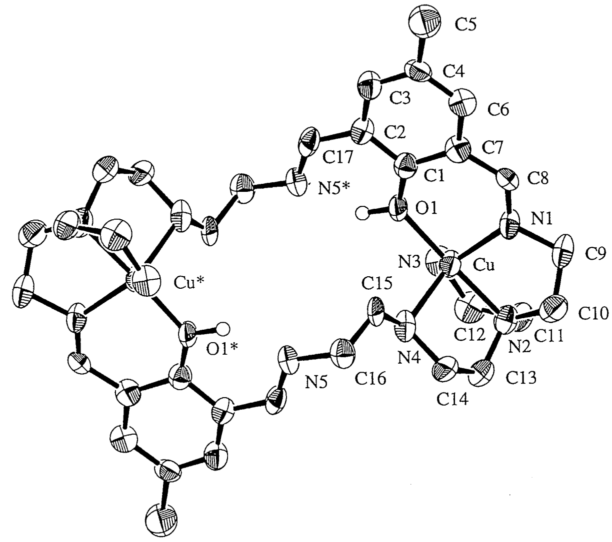
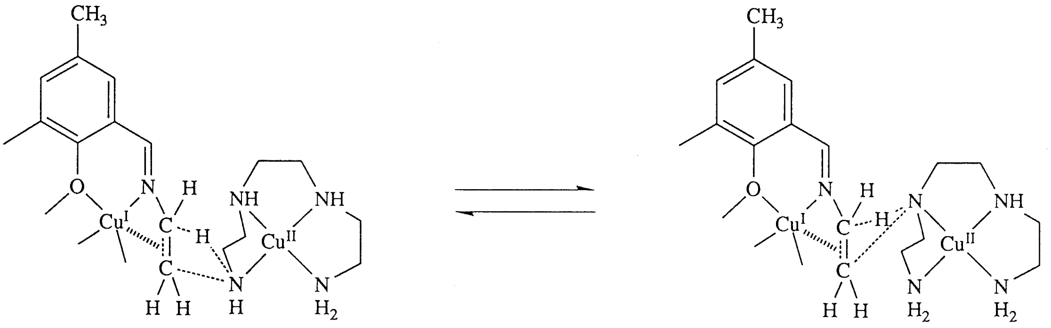


Figure 2. ORTEP view of macrocyclic dinuclear copper(II) complex.



Scheme 1. A proposed mechanism for the isomerization of a linear pentamine to the branched form.

From the reoxidized solution, after prelonged standing in air, green prismatic crystals suitable for X-ray crystallographic study were obtained.[8] An ORTEP view of the essential part of the new complex is shown in Figure 2, together with the numbering scheme.

The complex molecule consists of the centrosymmetric dinuclear copper(II) cation $\{Cu_2(H_2L)\}^{2+}$, four perchlorate ions, and two water molecules. The dinuclear cation contains a macrocycle in the neutral form (H_2L) which may be derived by the 2:2 condensation of 2,6-diformyl-4-methylphenol and branched 4-(2-aminoethyl)-1,4,7,10-tetraazadecane instead of the linear 1,4,7,10,13-pentaazatridecane incorporated into the assembly complex. The geometry around each Cu(II) is best depicted as a distorted trigonal-bipyramid with the imino nitrogen N1, the primary amino nitrogen N3 and the secondary amino nitrogen N4 at the basal plane and with the phenolic oxygen O1 and the tertiary amino nitrogen N2 at the apical sites. The Cu-O and Cu-N bond distances fall in the range of 1.94-2.14 Å. One of the imine nitrogens (N5) is free from coordination and is hydrogen-bonded to O1*. The Cu and Cu' in the macrocycle are separated by 8.15 Å from each other.

The yield of the macrocyclic complex is greater than 35% (based on 2,6-diformyl-4-methylphenolate). Thus, it is evident that the very rare isomerization of linear 1,4,7,10,13-pentaazatridecane to branched 4-(2-aminoethyl)-1,4,7,10-tetraazadecane occurs along with the reconstruction of the tetranuclear assembly complex to the macrocyclic dinuclear complex. It must be emphasized that the electrolyzed complex $\{Cu(II)\text{-}Cu_2(I,I)\text{-}Cu(II)\}$ is fairly stable against oxidation from atmospheric dioxygen; the reoxidation was barely completed after a couple of days as judged from the time-couse of the visible spectra. It is also noted that the visible spectrum of the reoxidized solution (λ_{max} at 610 nm with ε=320 $M^{-1}cm^{-1}$) differs from that of the original tetranuclear assembly complex (λ_{max}=655 nm with ε=540 $M^{-1}cm^{-1}$).

It is presumed that the reduced form of the assembly complex, $\{Cu(II)\text{-}Cu_2(I,I)\text{-}Cu(II)\}$, is stabilized for some reason and the isomerization of the linear pentamine occurs in the stabilized stage. The observed isomerization of the pentamine suggests that the ethylene group of the pentamine, adjacent to the imino nitrogen of the Schiff base, is labilized. Together with the fact that alkenes can form Cu(I)-alkene complexes,[9] we postulate a mechanism via the vinylene-containing intermediate complex (see Scheme 1) where the vinylene group contributes to the stabilization of the $Cu_2(I,I)$ core through the back-donation from Cu(I) to the antibonding orbital of the C=C group. This illustrates a probable pathway for the isomerization mechanism of the linear pentamine to the branched form. The reconstruction of the tetranuclear assembly complex to form the macrocyclic dinuclear complex may result from the preference of this type of macrocycles formed by the 2:2 condensation of 2,6-diformyl-4-methylphenol and tetramines.[10,11]

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References and Notes

1 A. Messerschmidt and R. Huber, *Eur. J. Biochem.*, **187**, 341 (1990).

2 A. Messerschmidt, A. Rossi, R. Ladenstein, R. Huber, M. Bolognesi, G. Gatti, A. Marchesini, R. Petruzzeli, and A. Finazzi-Agro, *J. Mol. Biol.*, **206**, 513 (1989).

3 H. Adams, N. A. Bailey, M. J. S. Dwyer, D. E. Fenton, P. C. Hellier, and P. D. Hempstead, *J. Chem. Soc., Chem. Commun.*, **1991**, 1297.

4 P. Hubberstey and C. E. Russell, *J. Chem. Soc., Chem. Commun.*, **1995**, 959.

5 Yield: 46%. Anal. Found: C, 24.35; H, 3.98; N, 9.46; Cu, 16.25%. Calcd for $C_{31}H_{62}Cl_2Cu_4F_{24}N_{10}O_4P_4$: C, 24.12; H, 4.05; N, 9.07; Cu, 16.45%.

6 H. Ōkawa, *Bull. Chem. Soc. Jpn.*, **43**, 3091 (1970).

7 T. E. Meyer, A. Marchesini, M. A. Cusanovich, and G. Tollin, *Biochem.*, **30**, 4619 (1991).

8 Crystal data: $C_{34}H_{58}Cl_4Cu_2N_{10}O_{20}$, F.W.=1195.79, monoclinic, space group $P2_1/n$ (No.14), a =10.328(5), b = 3.806(2), c=18.761(3) Å, β=99.82(3) deg, V=2636(1) $Å^3$, Z=2, D_c=1.51 g cm^{-3}, D_m=1.55 g cm^{-3}, μ(MoKα)=10.88 cm^{-1}. Intensity data were collected on a Rigaku AFC-7R diffractiometer with graphite monochromated MoKα radiation (λ=0.71069) at 293 K. The structure was solved, expanded and refined using the teXsan crystallographic software package from Molecular Structure Corporation. Non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement based on 1846 observed reflections ($I \geq 3\sigma(I)$) converged with R =0.074 and R_w =0.084.

9 J. S. Thompson and J. F. Whitney, *Inorg. Chem.*, **23**, 2813 (1984).

10 H. Sakiyama, K. Motoda, H. Ōkawa, and S. Kida, *Chem. Lett.*, **1991**, 1133.

11 H. Sakiyama, K. Tokuyama, J. Nishio, N. Matsumoto, and H. Ōkawa, *Chem. Lett.*, **1992**, 1021.