Self-Assembly of a Copper-Ligating Dendrimer that Provides a New Non-Heme Metalloprotein Mimic: "Dendrimer Effects" on Stability of the Bis(μ-oxo)dicopper(III) Core

Masashi Enomoto and Takuzo Aida*

Department of Chemistry and Biotechnology
Graduate School of Engineering, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Dendrimers are nanosized hyperbranched macromolecules with well-defined three-dimensional shapes, which are expected to serve as building blocks for the construction of organized functional materials.[1] Recently, self-assembly of dendrimers to generate well-defined nanoscale architectures have been investigated by utilization of van der Waals, hydrophobic, hydrogen-bonding, metal-ligating, and electrostatic interactions,[2,3] which play important roles in biological supramolecular assemblies. However, examples of self-asembled dendrimers which exhibit bio-related functions have been very limited to date. Herein we report the first example of a dendritic non-heme metalloprotein mimic by O_2-driven self-assembly of a copper-ligating dendrimer and wish to highlight a clear "dendrimer effect" on stability of the focal point bis(μ-oxo)dicopper species toward oxidative self-decomposition. Bis(μ-oxo)-bridged bimetallic complexes have attracted a great deal of attention as synthetic models of active sites of multinuclear metalloproteins such as methane monooxygenase and ribonucleotide reductase.[4] As an example, Tolman et al. have reported that Cu(I) complexes of *N*-substituted 1,4,7-triazacyclononanes such as [Bn₃TACNCu(MeCN)]PF₆ (**1b**; Bn = benzyl [Chart 1]) react with O_2 to form [(Bn₃TACNCu)₂(μ-O)₂]²⁺ (**1c**).[5] However, **1c** is thermally unstable with a half-life of only 7 s at −10 °C because of an oxidative self-decomposition at the *N*-Bn bonds.

A series of triamine-core aryl ether dendrimers (L*n*₃TACN, *n* [number of the aromatic layers of the dendron subunits] = 2 (**2a**), 3 (**3a**), and 4 (**4a**); Chart 1) was synthesized by alkaline-mediated coupling[6] of the corresponding dendron chlorides[7] with 1,4,7-triazacyclononane (TACN) and characterized by means of ¹H NMR, MALDI-TOF-MS, and elemental analysis.[8] The diamagnetic Cu(I) complexes ([L*n*₃TACNCu(MeCN)]PF₆, *n* = 2 (**2b**), 3 (**3b**), 4 (**4b**)) were prepared by the reaction of **2a**−**4a** (12 mM) with [Cu(MeCN)₄]PF₆ (12 mM) in CH₂Cl₂ under argon at 20 °C

Figure 1. Reaction of [L*n*₃TACNCu(MeCN)]PF₆ (**2b**−**4b**; 2.4 mM) with O_2 in CH₂Cl₂ at −78 °C; second-order rate constants (k_2) for the formation of [(L*n*₃TACNCu)₂(μ-O)₂](PF₆)₂ (**2c**−**4c**). Inset: UV−vis spectral change at −78 °C of a CH₂Cl₂ solution (2.4 mM, 1-mm path quartz cell) of **3b** after bubbling with dry O_2. Absorption of the dendron subunits at 280 nm is subtracted.

(Chart 1), in which the products displayed characteristic TACN signals in the ¹H and ¹³C NMR spectra,[8] in agreement with those reported for [Bn₃TACNCu(MeCN)]PF₆ (**1b**).[5a]

Reaction of [L*n*₃TACNCu(MeCN)]PF₆ (**b**) with O_2 was found to be highly dependent on the size of the dendron subunits. Upon bubbling of a CH₂Cl₂ solution of **3b** (2.4 mM) with O_2 at −78 °C, the color of the solution gradually turned from pale purple to deep orange-brown, and displayed growth of two intense absorption bands (302 and 411 nm) in the UV−vis spectrum (Figure 1, inset), characteristic of bis(μ-oxo)dicopper(III) species.[5] Resonance Raman spectroscopy of the reaction mixture at −78 °C[9] clearly showed an absorption band at 600 cm⁻¹ assignable to the [Cu₂(μ-O)₂]²⁺ core, which shifted to 569 cm⁻¹ when ¹⁸O_2 was used in place of ¹⁶O_2. Since the observed isotope shift of 31 cm⁻¹ agrees well with those reported for [Cu₂(μ-O)₂]²⁺ complexes,[10] the reaction product is unambiguously [(L*3*₃TACNCu)₂(μ-O)₂]-(PF₆)₂ (**3c**). In accord with the bimolecular reaction mechanism (Chart 1), the spectral change profile, thus observed in Figure 1 (inset), indicated that the oxygenation obeys a second-order kinetics for **3b** with a rate constant (k_2) of 1.3 × 10⁻² M⁻¹ s⁻¹ (Figure 1).[8] Likewise, the reaction of **2b** with O_2, under conditions identical to those of the above, also obeyed a second-order kinetics, where the observed rate constant (k_2 = 1.39 M⁻¹ s⁻¹) was two-orders of magnitude larger than that for **3b**. In sharp contrast, the largest **4b** showed virtually no spectral change throughout the observation for 16 h at −78 °C. Thus, the copper-ligating aryl ether dendrimers [L*n*₃TACNCu(MeCN)]PF₆, upon reaction with O_2, assemble to form [(L*n*₃TACNCu)₂(μ-O)₂](PF₆)₂,

(1) (a) Tomalia, D. A. *Adv. Mater.* **1994**, *6*, 529. (b) Fréchet, J. M. J. *Science* **1994**, *263*, 1710. (c) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Macromolecules: Concepts, Synthesis, Perspectives*; VCH: Weinheim, Germany, 1996.

(2) (a) Zimmerman, S. C.; Zeng, Reichert, D. E. C.; Lolotuchin, S. V. *Science* **1996**, *271*, 1095. (b) Balagurusamy, V. S. K.; Ungar, G.; Percec, V.; Johansson, G. *J. Am. Chem. Soc.* **1997**, *119*, 1539. (c) Hudson, S. D.; Jung, H.-T.; Percec, V.; Cho, W.-D.; Johansson, G.; Ungar, G.; Balagurusamy, V. S. K. *Science* **1997**, *278*, 449. (d) Huck, W. T. S.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1213. (e) Huck, W. T. S.; Hulst, R.; Timmerman, P.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1006. (f) Gitsov, I.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 3785. (g) Newkome, G. R.; Guther, R.; Moorefield, C. N.; Cardullo, F.; Echegoyen, L.; Perezcordero, E.; Luftmann, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2023. (h) Chow, H. F.; Chan, I. Y. K.; Chan, D. T. W.; Kwok, R. W. M. *Chem. Eur. J.* **1996**, *2*, 1085. (i) Tomioka, N.; Takasu, D.; Takahashi, T.; Aida, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1531.

(3) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681 and references therein.

(4) (a) Que, L., Jr.; Dong, Y. *Acc. Chem. Res.* **1996**, *29*, 190. (b) Wallar, B. J.; Lipscomb, J. D. *Chem. Rev.* **1996**, *96*, 2625 and references therein. (c) Kitajima, N.; Moro-oka, Y. *Chem. Rev.* **1994**, *94*, 735 and references therein.

(5) (a) Mahapatra, S.; Halfen, J. A.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11575. (b) Halfen, J. A.; Mahapatra, S.; Wilkinson, E. C.; Kaderli, S.; Young, V. G., Jr.; Que, L., Jr.; Zuberbühler, A. D.; Tolman, W. B. *Science* **1996**, *271*, 1397.
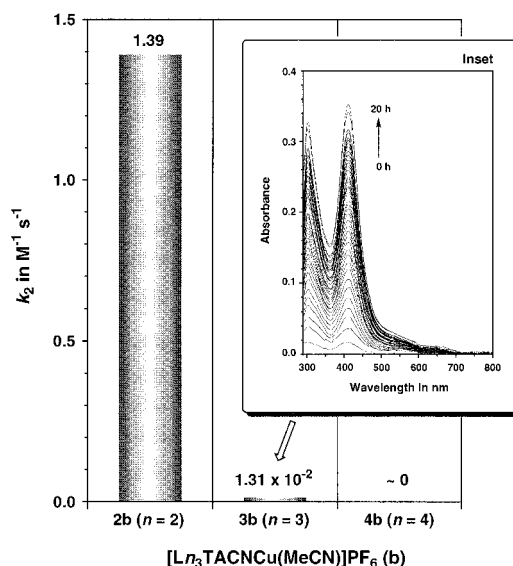
(6) Beissel, T.; Della Vedova, B. S. P. C.; Wieghardt, K.; Boese, R. *Inorg. Chem.* **1990**, *29*, 1736.
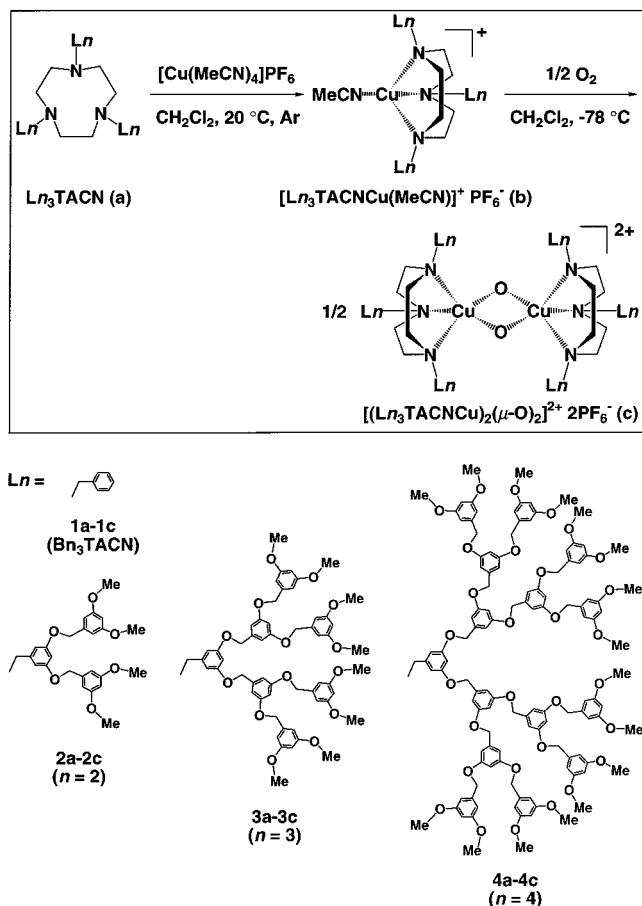
(7) (a) Balagurusamy, V. S. K.; Ungar, G.; Percec, V.; Johansson, G. *J. Am. Chem. Soc.* **1997**, *119*, 1539. (b) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

(8) See Supporting Information.

(9) Excitation wavelength = 488 nm.

(10) (a) Mahapatra, S.; Halfen, J. A.; Wilkinson, E. C.; Pan, G.; Wang, X.; Young, V. G., Jr.; Cramer, C. J.; Que, L., Jr.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 11555. (b) Mahadevan, V.; Hou, Z.; Cole, A. P.; Root, D. E.; Lal, T. K.; Solomon, E. I.; Stack, T. D. P. *J. Am. Chem. Soc.* **1997**, *119*, 11996.

Chart 1. Schematic Representations of the Structures of Triamine-Core Dendrimers (Ln_3TACN, **1a−4a**) and Self-Assembly of Their Cu(I) Complexes by the Reaction with O$_2$

Figure 2. Oxidative decomposition of [(Ln_3TACNCu)$_2$(μ-O)$_2$](PF$_6$)$_2$ (**1c−3c**) in CH$_2$Cl$_2$: (A) Half-lives at −10 °C (2.4 mM) and (B) kinetic parameters. The half-life of [(Bn$_3$TACNCu)$_2$(μ-O)$_2$]$^{2+}$ (**1c**) is taken from ref 5a.

where the dendron subunits obviously affects the accessibility of the two copper cores to form the di-μ-oxo bridge.

More interestingly, the dendron subunits also have a great influence on the apparent stability of the resulting complexes toward oxidative decomposition. On warming a CH$_2$Cl$_2$ solution of **3c** from −78 to −10 °C, the characteristic UV−vis absorption bands started to decay with time[8] and completely disappeared in 24 000 sec, indicating the occurrence of an oxidative decomposition of the [Cu$_2$(μ-O)$_2$]$^{2+}$ core. MALDI-TOF-MS and ^{1}H NMR analyses of the reaction mixture, after treatment with aqueous NH$_3$, showed that the decomposition is accompanied by an oxidative cleavage of the *N*-C (dendron) bonds to give partially dealkylated TACNs and a formyl-ended L*3*-dendron.[8] From the absorption spectral change profile, the decomposition was found to obey a first-order kinetics,[8] indicating that **3c** decomposes in an intra-complex fashion. Here, it is also interesting to note that the half-life of **3c** at −10 °C was evaluated to be 3075 s (Figure 2A), which is considerably longer than the reported half-life of 7 s for nondendritic [(Bn$_3$TACNCu)$_2$(μ-O)$_2$]$^{2+}$ (**1c**) under similar conditions.[5] Even at higher temperatures such as 0 and 20 °C, the half-lives were as long as 925 and 77 s, respectively. Compared with **3c**, one-generation smaller **2c** decomposed much faster at −10 °C, where the half-life was only 24 s. Thus, a discrete gap in stability is present between **2c** and **3c**. The temperature dependence of the rate constant of decomposition gave kinetic parameters,[8,11] which are compared with those observed for the oxidative decomposition of nondendritic **1c**[12] (Figure 2B): The enthalpies of activation ($\Delta H^\ddagger$, kcal mol^{-1}) of **2c** (14.3) and **3c** (14.8) are not much different from that of
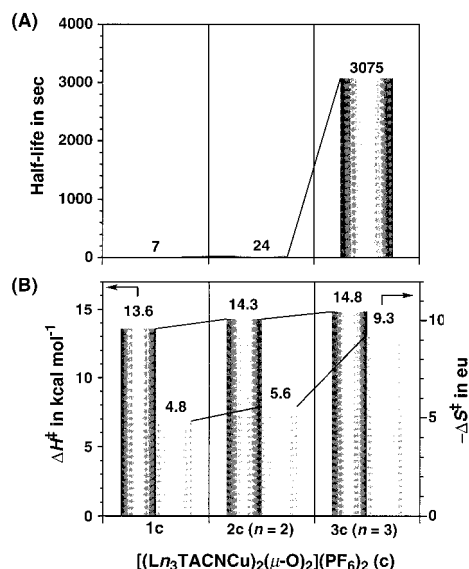
nondendritic **1c** (13.6), indicating that the active centers of these three bis(μ-oxo)dicopper complexes are almost comparable to one another. On the other hand, quite interestingly, the entropies of activation ($\Delta S^\ddagger$, eu) are highly dependent on the size of the dendron subunits: **3c** in the decomposition showed the most negative $\Delta S^\ddagger$ (−9.3) among the three complexes, while the $\Delta S^\ddagger$ for **2c** (−5.6) was only a little more negative than that for **1c** (−4.8).[12] Therefore, the apparent stability of **3c** toward oxidative decomposition is given by the large entropy loss required for the reaction. Namely, the intra-complex oxidative decomposition requires access of the *N*-benzyl moieties at the dendron focal points to the bis(μ-oxo)dicopper active center. In the case of **3c**, it is likely that the large six dendron subunits are so densely packed that the focal point TACN ligands may be conformationally frozen in such a way that the *N*-C (dendron) bonds are pointing away from the active center. On the other hand, the dendron subunits in **2c** are not large enough to affect the conformational motion of the TACN ligands. Thus, this is the first example of highly robust non-heme metalloprotein mimic by supramolecular interaction.

Much effort has been made to design bis(μ-oxo)-bridged bimetallic complexes which are thermally robust but exhibit relevant reactivities for oxygenation.[4] The present study with dendritic ligands provides a new synthetic approach to non-heme metalloproteins, where the susceptibility to the oxidative self-decomposition is considerably reduced by the steric interaction among the self-assembled dendrimer subunits that surround the active site. Utilization of other oxophilic transition metals for this reaction is one of the subjects worthy of further investigation.

Supporting Information Available: Details for synthetic procedures and spectroscopic data for Ln_3TACN (**1a−4a**), [Ln_3TACNCu(MeCN)]-PF$_6$ (**1b−4b**), and [(Ln_3TACNCu)$_2$(μ-O)$_2$](PF$_6$)$_2$ (**1c−3c**), kinetic measurements for formation and decomposition of **1c−3c**, product analyses for decomposition of **2c** and **3c**, resonance Raman spectra of **3c** (^{16}O$_2$, ^{18}O$_2$) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Calculated on the basis of the rate constants of decomposition observed at 242−263 K for **2c** and 263−293 K for **3c**.

(12) The kinetic parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) for **1c** were obtained on the basis of the rate constants of decomposition at 212−243 K, which are in excellent agreement with those reported in ref 5a.