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Mononuclear Copper Complex-Catalyzed Four-Electron Reduction of Oxygen

Shunichi Fukuzumi,*,†,‡ Hiroaki Kotani,† Heather R. Lucas,†,§ Kaoru Doi,† Tomoyoshi Suenobu,†
Ryan L. Peterson,‡,§ and Kenneth D. Karlin*,‡,§

Department of Material and Life Science, Graduate School of Engineering, Osaka University, and SORST, Japan Science and Technology Agency (JST), Suita, Osaka 565-0871, Japan, Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, and Department of Bioinspired Science, Ewha Womans University, Seoul 120-750, Korea

Received January 20, 2010; E-mail: fukuzumi@chem.eng.osaka-u.ac.jp; karlin@jhu.edu

Cytochrome *c* oxidases (C*c*Os), which have a bimetallic active site consisting of a heme *a* and Cu (Fe_{a3}/Cu_B), are the terminal enzymes of respiratory chains, catalyzing the reduction of molecular oxygen to water by the soluble electron carrier cytochrome *c*.[1,2] Synthetic Fe_{a3}/Cu_B analogues have attracted significant attention because the four-electron reduction of O_2 is of not only great biological interest[3,4] but also technological significance, such as in fuel cells.[5,6] Multicopper oxidases such as laccase also activate oxygen at a site containing a three-plus-one arrangement of four Cu atoms, exhibiting remarkable electroactivity for the four-electron reduction of oxygen at potentials approaching 1.2 V (vs RHE).[7] Such electrocatalytic reduction of O_2 has frequently been used to probe the catalytic reactivity of synthetic C*c*O model complexes,[3−5] and some copper (only) complexes have also been investigated.[8−10] However, there has been no report of copper-complex-catalyzed four-electron reduction of O_2 employing one-electron reductants in homogeneous solution; such situations would be amenable to systematic studies that would provide considerable mechanistic insights.[11]

We report herein that a copper complex, $[(\text{tmpa})\text{Cu}^{\text{II}}](\text{ClO}_4)_2$ [**1**; tmpa = tris(2-pyridylmethyl)amine],[12] efficiently catalyzes the four-electron reduction of O_2 by one-electron reductants such as ferrocene derivatives in the presence of $HClO_4$ in acetone. As described below, the catalytic mechanism is clarified on the basis of kinetic studies and detection of reactive intermediates.

The addition of a catalytic amount of **1** to an O_2-saturated acetone solution of decamethylferrocene (Fc*) and $HClO_4$ resulted in the efficient oxidation of Fc* by O_2 to afford ferrocenium cation (Fc^{*+}) (see the experimental section in the Supporting Information). Figure 1 shows the spectral changes obtained following stepwise addition of $HClO_4$ to this solution. For each time period, the concentration of Fc^{*+} ($\lambda_{\text{max}} = 380$ and 780 nm)[11] immediately formed was the same as the concentration of $HClO_4$ added. The reduced product of O_2 was confirmed to be H_2O on the basis of the detection of $H_2{}^{18}O$ in ^{18}O-labeled O_2 experiments (Figure S1). It was also confirmed via iodometric titration experiments that no H_2O_2 was produced (Figure S2).[13] When more than 4 equiv of Fc* relative to O_2 (i.e., limiting $[O_2]$) was employed, only 4 equiv of Fc^{*+} was formed in the presence of 4 equiv of $HClO_4$ (Figure S3).[14] Thus, the stoichiometry of the catalytic reduction of O_2 by Fc* is given by eq 1:[15]

$$4\text{Fc}^* + \text{O}_2 + 4\text{H}^+ \xrightarrow{[(\text{tmpa})\text{Cu}^{\text{II}}]^{2+}} 4\text{Fc}^{*+} + 2\text{H}_2\text{O} \qquad (1)$$

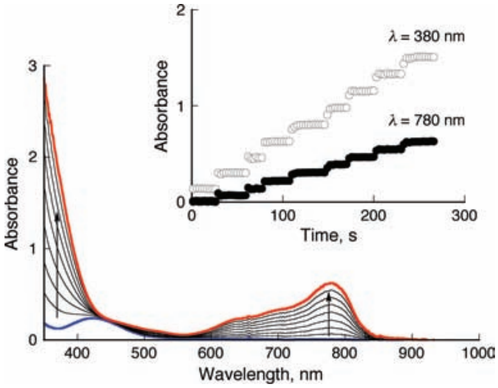

Figure 1. UV−vis spectral changes in four-electron reduction of O_2 by Fc* (1.5 mM) with **1** (9.0×10^{-5} M) in the presence of $HClO_4$ in acetone at 298 K. The inset shows the changes in absorbance at 380 and 780 nm due to Fc^{*+} produced by stepwise addition of $HClO_4$ (0.18−1.44 mM) to an O_2-saturated acetone solution ($[O_2] = 11$ mM) of Fc* and **1**.

The time profile of the four-electron reduction of O_2 with Fc* catalyzed by **1** in the presence of $HClO_4$ in acetone at 298 K was examined by stopped-flow measurements. Figure 2a shows the observed absorption spectral changes during the catalytic reaction. Under the conditions employed with the relative concentrations of reagents given in the Figure 2 caption, it was only after Fc^{*+} ($\lambda_{\text{max}} = 780$ nm) was completely formed that the peroxo species, $[(\text{tmpa})\text{Cu}^{\text{II}}(\text{O}_2)\text{Cu}^{\text{II}}(\text{tmpa})]^{2+}$ (**2**; $\lambda_{\text{max}} = 520$ nm),[16] started to be produced.[17] This is more clearly seen in Figure 2b, which compares the time profiles for the absorbance at 780 nm due to Fc^{*+} and the absorbance at 520 nm due to **2**. Because the concentration of $HClO_4$ was smaller than that of Fc*, $HClO_4$ had been consumed when the reaction was over. It is well-established that $[(\text{tmpa})\text{Cu}^{\text{I}}]^+$ reacts with O_2 to afford the superoxo species $[(\text{tmpa})\text{Cu}^{\text{II}}(\text{O}_2{}^{\bullet-})]^+$, which reacts rapidly with $[(\text{tmpa})\text{Cu}^{\text{I}}]^+$ to produce the peroxo species **2**.[16] Thus, electron-transfer reduction of **1** by Fc* with O_2 but without $HClO_4$ affords **2**. This is the reason why **2** started to appear only after all of the $HClO_4$ was consumed. The stoichiometry of the reaction of Fc* with **1** and O_2 is given by eq 2:

$$2\text{Fc}^* + 2[(\text{tmpa})\text{Cu}^{\text{II}}]^{2+} + \text{O}_2 \rightarrow 2\text{Fc}^{*+} + [(\text{tmpa})\text{Cu}^{\text{II}}(\text{O}_2)\text{Cu}^{\text{II}}(\text{tmpa})]^{2+} \qquad (2)$$

The rate of formation of Fc^{*+} in Figure 2b appears to be constant with respect to the concentration of Fc^{*+} when the concentration of Fc* is in large excess compared with that of $HClO_4$. The constant rate (M s^{-1}) increased linearly with increasing concentrations of **1** and Fc* (Figure S5a). The second-order rate constant (k_{obs}) was determined to be $(1.1 \pm 0.1) \times 10^5$ M^{-1} s^{-1} by dividing the slope of the plot in Figure S5a by the initial concentration of Fc* (1.0 mM).

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† Osaka University.
‡ Ewha Womans University
§ Johns Hopkins University.

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The rate of formation of Fc*$^+$, accompanied by formation of **2** via electron transfer from Fc* to **1** with O_2, was also determined without $HClO_4$ and found to obey pseudo-first-order kinetics when the concentration of Fc* was much larger than that of **1** (Figure S6). This rate constant increased linearly with concentration of Fc*. From the slope of the linear plot, the second-order rate constant (k'_{obs}) for formation of Fc*$^+$ without $HClO_4$ under single-turnover conditions was determined to be $(4.9 \pm 0.4) \times 10^4$ M^{-1} s^{-1} (Figure S6). This value is half that of the rate constant under catalytic conditions with $HClO_4$. This is quite consistent with the stoichiometries of the catalytic reaction (eq 1) and the single-turnover reaction (eq 2), because an additional equivalent of Fc*$^+$ is formed in the presence of $HClO_4$ under the catalytic conditions following formation of 1 equiv of Fc*$^+$ under the single-turnover reaction (see the Supporting Information for the kinetic analysis).

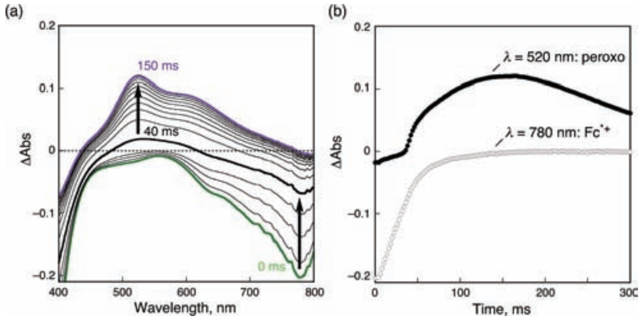
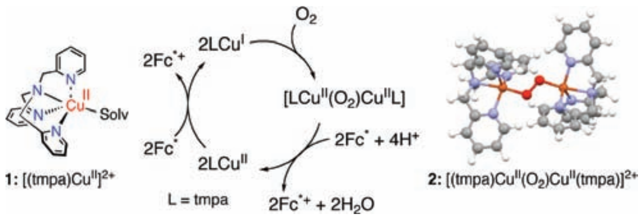


Figure 2. (a) Visible absorption spectral changes for formation of peroxo species **2** ($\lambda_{max} = 520$ nm) by electron transfer from Fc* (1.0 mM) to **1** (0.12 mM) in the presence of $HClO_4$ (0.35 mM) in aerated acetone at 298 K. (b) Time profile of the absorbances at 520 nm (●) and 780 nm (○) due to **2** and Fc*$^+$, respectively.

No further reduction of the peroxo species **2** occurs without an acid. However, the addition of $HClO_4$ facilitates electron transfer and the further two-electron reduction of **2** to produce 2 equiv of Fc*$^+$, accompanied by regeneration of **1**. This was confirmed by low-temperature measurements (Figure S7). Thus, the overall catalytic cycle is given in Scheme 1. Initial electron transfer from Fc* to **1** followed by reaction with O_2 affords the two-electron reduction of oxygen to produce the peroxo species, which can be further reduced in the presence of $HClO_4$ to facilitate the four-electron reduction of O_2 to H_2O by Fc* (Scheme 1).[18]

Scheme 1



In summary, a copper complex, **1**, acts as an effective catalyst for the four-electron reduction of O_2 by one-electron reductants such as Fc* in the presence of an acid. The present study opens a new approach and the use of copper ion to develop efficient catalysts for the four-electron reduction of O_2, because the catalytic activity and stability of intermediates can certainly be controlled and tuned by variation of ligands for copper ion.

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Supporting Information Available: Experimental section, kinetic analysis, and Figures S1−S7. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Ferguson-Miller, S.; Babcock, G. T. *Chem. Rev.* **1996**, *96*, 2889. (b) Pereira, M. M.; Santana, M.; Teixeira, M. *Biochim. Biophys. Acta* **2001**, *1505*, 185.
(2) (a) Tsukihara, T.; Aoyama, H.; Yamashita, E.; Tomizaki, T.; Yamaguchi, H.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yoshikawa, S. *Science* **1995**, *269*, 1069. (b) Yoshikawa, S.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yamashita, E.; Inoue, N.; Yao, M.; Fei, M. J.; Libeu, C. P.; Mizushima, T.; Yamaguchi, H.; Tomizaki, T.; Tsukihara, T. *Science* **1998**, *280*, 1723.
(3) (a) Kim, E.; Chufán, E. E.; Kamaraj, K.; Karlin, K. D. *Chem. Rev.* **2004**, *104*, 1077. (b) Chufán, E. E.; Puiu, S. C.; Karlin, K. D. *Acc. Chem. Res.* **2007**, *40*, 563.
(4) (a) Collman, J. P.; Boulatov, R.; Sunderland, C. J.; Fu, L. *Chem. Rev.* **2004**, *104*, 561. (b) Collman, J. P.; Boulatov, R.; Sunderland, C. J. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2003; Vol. 11, pp 1−49.
(5) (a) Cracknell, J. A.; Vincent, K. A.; Armstrong, F. A. *Chem. Rev.* **2008**, *108*, 2439. (b) Willner, I.; Yan, Y.-M.; Willner, B.; Tel-Vered, R. *Fuel Cells* **2009**, *9*, 7.
(6) (a) Anson, F. C.; Shi, C.; Steiger, B. *Acc. Chem. Res.* **1997**, *30*, 437. (b) Shin, H.; Lee, D.-H.; Kang, C.; Karlin, K. D. *Electrochim. Acta* **2003**, *48*, 4077.
(7) (a) Blanford, C. F.; Heath, R. S.; Armstrong, F. A. *Chem. Commun.* **2007**, 1710. (b) Mano, N.; Soukharev, V.; Heller, A. *J. Phys. Chem. B* **2006**, *110*, 11180.
(8) (a) Zhang, J.; Anson, F. C. *J. Electroanal. Chem.* **1993**, *348*, 81. (b) Watanabe, H.; Yamazaki, H.; Wang, X.; Uchiyama, S. *Electrochim. Acta* **2009**, *54*, 1362.
(9) Thorum, M. S.; Yadav, J.; Grewirth, A. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 165.
(10) Weng, Y. C.; Fan, F.-R. F.; Bard, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 17576.
(11) For the catalytic reduction of O_2 by chemical reductants with cobalt porphyrins and cobalt corroles, see: (a) Fukuzumi, S.; Okamoto, K.; Gros, C. P.; Guilard, R. *J. Am. Chem. Soc.* **2004**, *126*, 10441. (b) Kadish, K. M.; Frémond, L.; Shen, J.; Chen, P.; Ohkubo, K.; Fukuzumi, S.; Ojaimi, M. E.; Gros, C. P.; Barbe, J.-M.; Guilard, R. *Inorg. Chem.* **2009**, *48*, 2571.
(12) Karlin, K. D.; Kaderli, S.; Zuberbühler, A. D. *Acc. Chem. Res.* **1997**, *30*, 139.
(13) (a) Mair, R. D.; Graupner, A. J. *Anal. Chem.* **1964**, *36*, 194. (b) Fukuzumi, S.; Kuroda, S.; Tanaka, T. *J. Am. Chem. Soc.* **1985**, *107*, 3020.
(14) The O_2 concentration in an O_2-saturated acetone solution (11 mM) was determined by a spectroscopic titration for the photooxidation of 10-methyl-9,10-dihydroacridine by O_2, see: (a) Fukuzumi, S.; Imahori, H.; Yamada, H.; El-Khouly, M. E.; Fujitsuka, M.; Ito, O.; Guldi, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 2571. (b) Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1037.
(15) The turnover number (TON = 7) based on **1** was determined under the catalytic conditions as shown in Figure S3.
(16) (a) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.-i.; Neuhold, Y.-M.; Karlin, K. D.; Zuberbuhler, A. D. *Inorg. Chem.* **2003**, *42*, 1807. (b) Fry, H. C.; Scaltrito, D. V.; Karlin, K. D.; Meyer, G. J. *J. Am. Chem. Soc.* **2003**, *125*, 11866.
(17) It should be noted that the recorded spectra were taken as difference spectra obtained by subtracting final from original spectra; recovery of bleaching absorption at 780 nm corresponds to the formation of Fc*$^+$ (see Figure S4).
(18) The value of the turnover frequency (TOF = 17 s^{-1}) was obtained in the catalytic four-electron reduction of O_2 by Fc* (1.0 mM) with **1** (5.0×10^{-6} M) in the presence of $HClO_4$ (0.1 mM) in acetone at 298 K at 300 ms (TON = 5), as shown in Figure S5b.

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