J|A|C|S
COMMUNICATIONS

Published on Web 03/02/2005

Dioxygen Activation and Catalytic Aerobic Oxidation by a Mononuclear Nonheme Iron(II) Complex

Sun Ok Kim, Chivukula V. Sastri, Mi Sook Seo, Jinheung Kim, and Wonwoo Nam*

Department of Chemistry and Center for Biomimetic Systems, Ewha Womans University, Seoul 120-750, Korea

Received November 17, 2004; E-mail: wwnam@ewha.ac.kr

Mononuclear nonheme iron enzymes comprise an important group of dioxygen-activating enzymes that are involved in many metabolically important oxidative transformations.[1] The mechanistic details of dioxygen activation and oxygen atom transfer reactions by the enzymes and their model compounds have been extensively studied over the past two decades, thereby proposing high-valent iron(IV)-oxo intermediates as the active oxidizing species.[1,2] Very recently, existence of such iron(IV)-oxo species has been evidenced in enzymatic and biomimetic reactions.[3−5] Notably, Münck, Nam, Que, and their co-workers have shown the generation, characterization, and substrate reactivity of mononuclear nonheme oxoiron(IV) complexes.[4]

Although the use of dioxygen as the primary oxidant is of fundamental importance in biomimetic oxidation reactions, there are many intrinsic problems that should be overcome to control dioxygen activation by metal complexes.[6] Very recently, Borovik and co-workers demonstrated that the activation of dioxygen by mononuclear nonheme iron(II) complexes afforded iron(III) species with a terminal oxo ligand.[7] More recently, Lippard and co-workers reported the aerobic oxidation of organic substrates by dinuclear nonheme iron(II) complexes.[8] Furthermore, it has been well documented that iron(II) porphyrins react with O_2 to yield oxoiron(IV) porphyrins that oxygenate PPh_3 to Ph_3PO.[9] With these precedents, we explored the chemistry of dioxygen activation by mononuclear nonheme iron(II) complexes. We now report that a mononuclear nonheme oxoiron(IV) complex, $[Fe(IV)(TMC)(O)]^{2+}$ (**2**) (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane), is generated in the reaction of its corresponding iron(II) complex, $[Fe(II)(TMC)(CF_3SO_3)_2]$ (**1**), and O_2. We also report the catalytic aerobic oxidation of substrates by **1** without the need to add an external reductant.

The iron(II) complex **1** was stable and did not show any spectral changes in O_2-saturated CH_3CN solution. Interestingly, when **1** was exposed to air in a solvent mixture (v/v = 1:1) of CH_3CN and ethanol, butyl ether, or THF at 25 °C,[10] the formation of a pale green intermediate **2** with λ_{max} at 825 nm (ϵ = 370 M^{-1} cm^{-1}) was observed (Supporting Information, Figure S1). The electrospray ionization mass spectrum (ESI MS) of **2** exhibited a prominent ion at a mass-to-charge ratio (m/z) of 477, whose mass and isotope distribution pattern correspond to $[Fe(IV)(O)(TMC)(CF_3SO_3)]^+$ (calculated m/z of 477) (Figure 1).[4a] The mass peak at m/z of 477 upshifted accordingly upon introduction of ^{18}O when ^{18}O-labeled dioxygen, $^{18}O_2$, was used instead of $^{16}O_2$ (Figure 1, inset B). Further, upon addition of a small amount of $H_2{}^{18}O$ (15 μL, 34 mM) to the solution of **2** prepared in the reaction of **1** and $^{16}O_2$, a mass peak corresponding to $[Fe(IV)(^{18}O)(TMC)(CF_3SO_3)]^+$ appeared immediately at m/z of 479 (Figure 1, inset C), indicating that **2** exchanges its oxygen with $H_2{}^{18}O$ at a fast rate under the conditions.[11] These results demonstrate that a mononuclear nonheme oxoiron(IV) intermediate was generated in the reaction of its corresponding iron(II) complex and O_2. It is of interest to note that other nonheme iron(II) complexes such as $[Fe(TPA)]^{2+}$ (TPA = tris(2-pyridylmethyl)amine),[4b] $[Fe(N4Py)]^{2+}$ (N4Py = *N*,*N*-bis(2-pyridylmethyl)-bis(2-pyridyl)methylamine),[4c] and $[Fe(BPMEN)]^{2+}$ (BPMEN = *N*,*N*′-bis(2-pyridylmethyl)-1,2-diaminoethane) did not afford oxoiron(IV) intermediates by reacting with O_2.

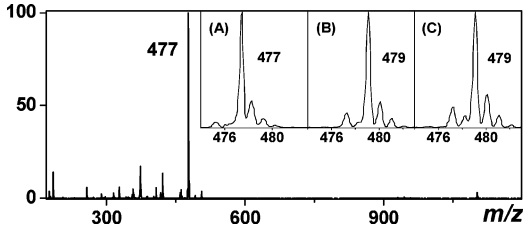


Figure 1. Electrospray ionization mass spectrum of **2** in a solvent mixture of CH_3CN and ethanol (v/v = 1:1). Insets show the observed isotope distribution patterns for **2** obtained in the reactions of (A) **1** and $^{16}O_2$, (B) **1** and $^{18}O_2$, and (C) **1** and $^{16}O_2$ followed by addition of $H_2{}^{18}O$. See detailed Experimental Conditions in Supporting Information.

The catalytic aerobic oxidation of organic substrates by **1** was then investigated in a solvent mixture of CH_3CN and butyl ether (v/v = 1:1) at 25 °C (Supporting Information, Experimental Conditions). Upon addition of 100 equiv of PPh_3 to a reaction solution containing **2** that was generated from **1** in the presence of O_2, **2** disappeared immediately. Analysis of the reaction mixture after 2 h incubation under O_2 atmosphere revealed that 8 equiv of PPh_3 were converted to Ph_3PO.[12] The catalytic aerobic oxidation of PPh_3 was also carried out in a reaction solution containing a small amount of $H_2{}^{18}O$ (15 μL) to understand whether the phosphine oxidation was mediated by **2** or a radical type of autoxidation process.[8b] Analysis of the reaction solution by LC-ESI MS revealed that 83% of the oxygen in the Ph_3PO product derived from $H_2{}^{18}O$, demonstrating that **2** formed in the reaction of **1** and O_2 exchanges its oxygen with $H_2{}^{18}O$ at a fast rate (vide supra) and that the phosphine oxidation was mediated by **2**, not by an autoxidation process. Other substrates such as thioanisole and benzyl alcohol were also aerobically oxidized to methyl phenyl sulfoxide (turnover number of 7) and benzaldehyde (turnover number of 6), respectively, under the catalytic conditions. Moreover, when PPh_3 oxidation by **1** and O_2 was carried out in a solvent mixture of CH_3CN and benzyl alcohol (v/v = 1:1), Ph_3PO and benzaldehyde were obtained with the turnover numbers of 7 and 8, respectively. Other iron(II) complexes (i.e., $[Fe(TPA)]^{2+}$, $[Fe(N4Py)]^{2+}$, and $[Fe(BPMEN)]^{2+}$) did not oxidize PPh_3 to Ph_3PO in the presence of O_2.

The observation that the formation of **2** from **1** and O_2 was markedly dependent on solvents prompted us to investigate the solvent effect in various solvents (Table 1).[13] Among the tested solvents, the conversion of **1** to **2** was observed in ethers, THF, and alcohols, but not in CH_3CN, acetone, and CH_2Cl_2.[10] In addition, the formation of **2** was also dependent on the kinds of alcohols (see Table 1). Interestingly, a correlation was observed between the conversion of **1** to **2** and the $Fe^{III/II}$ redox potentials of **1** in solvents (Table 1 and Figure S2).[14] That is, **1** with a low $Fe^{III/II}$

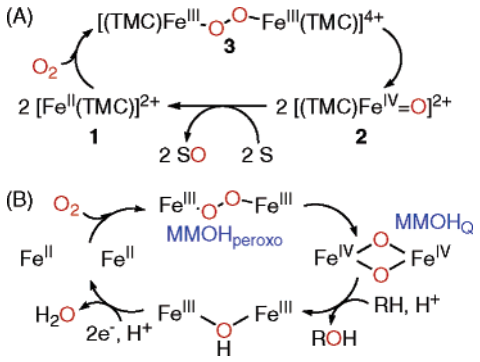
10.1021/ja043083i CCC: $30.25

Table 1. Solvent Effects on the Formation of **2** from **1** and O_2 and the Redox Potentials of **1** in a Solvent Mixture of CH_3CN and Cosolvent[a,b]

formation of **2** from **1** and O_2			
yes		no	
cosolvent	$E_{1/2}$ (V)[c,d]	cosolvent	$E_{1/2}$ (V)[c,d]
butyl ether	−0.28 (qr)	CH_3CN	0.01 (r)
propyl ether	−0.22 (qr)	acetone	0.08 (qr)
THF	−0.14 (qr)	CH_2Cl_2	0.02 (r)
CH_3OH	−0.08 (r)	$(CH_3)_3COH$	0.10 (qr)
CH_3CH_2OH	−0.15 (r)	CF_3CH_2OH	0.20 (r)
$(CH_3)_2CHOH$	−0.27 (qr)		
$C_6H_5CH_2OH$	−0.16 (r)	$C_6H_5C(CH_3)_2OH$	0.06 (qr)
$C_6H_5CH(CH_3)OH$	−0.23 (r)		

[a] Due to a low solubility of **1** in certain solvents, all reactions were carried out in solutions containing 50% CH_3CN in volume.[10] [b] See Experimental Conditions in Supporting Information. [c] $Fe^{III/II}$ redox potentials are vs Fc^+/Fc. [d] The r and qr in parentheses stand for reversible and quasi-reversible electrochemical processes, respectively, in the given solvent systems.

Scheme 1. Proposed Mechanisms for Dioxygen Activation by (A) **1** and (B) MMO



redox potential was converted to **2** (e.g., <-0.1 V). Moreover, other nonheme iron(II) complexes that did not show the formation of oxoiron(IV) species exhibited relatively high $Fe^{III/II}$ redox potentials (e.g., >0.2 V) (Supporting Information, Table S1). Since the $Fe^{III/II}$ redox potential is a measure of the electron richness and ease of oxidation of iron(II) complexes, the results presented above may suggest that the electron richness of iron(II) complexes is an important factor in activating O_2 to form oxoiron(IV) species.[15,16] However, other factors such as the change of spin states of iron ion in different solvents and steric effect of iron complexes may play an important role in the O_2 activation.[16] Thus, detailed investigations are needed to establish the solvent effect on the activation of O_2 by metal complexes.[13,16]

Finally, a mechanism for the O_2 activation by **1** is proposed on the basis of the analogy of O_2 activation by iron(II) porphyrins (Scheme 1A),[9,15b] in which two molecules of **1** react with O_2 to form a μ-peroxo-bridged diiron(III) species, $[(TMC)_2Fe^{III}_2(\mu\text{-}O_2)]^{4+}$ (**3**).[17] Subsequent O−O bond homolysis of **3** results in the generation of two molecules of **2** that are involved in oxygen atom transfer reactions. Although we failed to detect **3** with ESI mass spectrometry, the ratio of **1** to O_2 was determined to be ~2 for the complete conversion of **1** to **2** with dioxygen-uptake manometry (Supporting Information, Experimental Conditions). It is worth noting that the proposed mechanism may be relevant to the catalytic cycle of methane monooxygenases (MMO) (Scheme 1B),[18] in which a dinuclear nonheme iron(II) complex activates O_2 to form a di(μ-oxo)diiron(IV) intermediate ($MMOH_Q$) that effects the hydroxylation of organic substrates including CH_4.

In summary, we have used O_2, not artificial oxidants such as peracids, iodosylarenes, and hydroperoxides,[4] in the generation of a mononuclear nonheme oxoiron(IV) complex and in the catalytic aerobic oxidation of organic substrates. We have demonstrated that the solvent system as well as the structure of nonheme iron complexes is an important factor that controls the formation of oxoiron(IV) intermediates by activating O_2. Future studies will focus on attempts to understand the solvent effect on the O_2 activation and to synthesize iron catalysts with greater oxidative reactivities that can be used in aerobic oxidation reactions.

Supporting Information Available: Text containing experimental details, Table S1, and Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., Jr. *Chem. Rev.* **2004**, *104*, 939−986.
(2) (a) He, C.; Mishina, Y. *Curr. Opin. Chem. Biol.* **2004**, *8*, 201−208. (b) Slep, L. D.; Neese, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2942−2945.
(3) (a) Price, J. C.; Barr, E. W.; Tirupati, B.; Bollinger, J. M., Jr.; Krebs, C. *Biochemistry* **2003**, *42*, 7497−7508. (b) Proshlyakov, D. A.; Henshaw, T. F.; Monterosso, G. R.; Ryle, M. J.; Hausinger, R. P. *J. Am. Chem. Soc.* **2004**, *126*, 1022−1023. (c) Riggs-Gelasco, P. J.; Price, J. C.; Guyer, R. B.; Brehm, J. H.; Barr, E. W.; Bollinger, J. M., Jr.; Krebs, C. *J. Am. Chem. Soc.* **2004**, *126*, 8108−8109.
(4) (a) Rohde, J.-U.; In, J.-H.; Lim, M. H.; Brennessel, W. W.; Bukowski, M. R.; Stubna, A.; Münck, E.; Nam, W.; Que, L., Jr. *Science* **2003**, *299*, 1037−1039. (b) Lim, M. H.; Rohde, J.-U.; Stubna, A.; Bukowski, M. R.; Costas, M.; Ho, R. Y. N.; Münck, E.; Nam, W.; Que, L., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3665−3670. (c) Kaizer, J.; Klinker, E. J.; Oh, N. Y.; Rohde, J.-U.; Song, W. J.; Stubna, A.; Kim, J.; Münck, E.; Nam, W.; Que, L., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 472−473.
(5) (a) Balland, V.; Charlot, M.-F.; Banse, F.; Girerd, J.-J.; Mattioli, T. A.; Bill, E.; Bartoli, J.-F.; Battioni, P.; Mansuy, D. *Eur. J. Inorg. Chem.* **2004**, 301−308. (b) Grapperhaus, C. A.; Mienert, B.; Bill, E.; Weyhermüller, T.; Wieghardt, K. *Inorg. Chem.* **2000**, *39*, 5306−5317.
(6) *Metal-Catalyzed Oxidations of Organic Compounds*; Sheldon, R. A., Kochi, J. K., Eds.; Academic Press: New York, 1981.
(7) (a) MacBeth, C. E.; Golombek, A. P.; Young, V. G., Jr.; Yang, C.; Kuczera, K.; Hendrich, M. P.; Borovik, A. S. *Science* **2000**, *289*, 938−941. (b) MacBeth, C. E.; Gupta, R.; Mitchell-Koch, K. R.; Young, V. G., Jr.; Lushington, G. H.; Thompson, W. H.; Hendrich, M. P.; Borovik, A. S. *J. Am. Chem. Soc.* **2004**, *126*, 2556−2567.
(8) (a) Carson, E. C.; Lippard, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 3412−3413. (b) Moreira, R. F.; Tshuva, E. Y.; Lippard, S. J. *Inorg. Chem.* **2004**, *43*, 4427−4434.
(9) (a) Chin, D.-H.; La Mar, G. N.; Balch, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 5945−5947. (b) Balch, A. L.; Chan, Y.-W.; Cheng, R.-J.; La Mar, G. N.; Latos-Grazynski, L.; Renner, M. W. *J. Am. Chem. Soc.* **1984**, *106*, 7779−7785. (c) Ghiladi, R. A.; Kretzer, R. M.; Guzei, I.; Rheingold, A. L.; Neuhold, Y.-M.; Hatwell, K. R.; Zuberbühler, A. D.; Karlin, K. D. *Inorg. Chem.* **2001**, *40*, 5754−5767.
(10) In general, a solvent mixture of CH_3CN and cosolvent (v/v = 1:1) was used to make the reaction solution homogeneous due to the insolubility of **1** in certain solvents such as ethers. However, the formation of **2** was not affected by the presence and absence of CH_3CN. That is, **2** was formed in pure solvents such as THF, CH_3OH, CH_3CH_2OH, etc.
(11) Seo, M. S.; In, J.-H.; Kim, S. O.; Oh, N. Y.; Hong, J.; Kim, J.; Que, L., Jr.; Nam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2417−2420.
(12) **1** became inactive when the color of the reaction solution turned to yellow, and the characterization of the dead catalyst is under investigation.
(13) Mahammed, A.; Gray, H. B.; Meier-Callahan, A. E.; Gross, Z. *J. Am. Chem. Soc.* **2003**, *125*, 1162−1163.
(14) The formation rate of **2** was also dependent on the $Fe^{III/II}$ redox potentials of **1** in solvents, in which **2** was formed at a fast rate when the $Fe^{III/II}$ redox potential of **1** was low. For example, the rates for the full formation of **2** in alcohol solvents were in the order of $(CH_3)_2CHOH$ ($t \approx$ <30 s) > CH_3CH_2OH ($t \approx$ 5 min) > CH_3OH ($t \approx$ 1 h).
(15) The electronic effect of metal complexes on O_2 reactions has been well demonstrated in O_2 carriers and O_2-activating catalysts: (a) Zhang, C. X.; Kaderli, S.; Costas, M.; Kim, E.-i.; Neuhold, Y.-M.; Karlin, K. D.; Zuberbuhler, A. D. *Inorg. Chem.* **2003**, *42*, 1807−1824. (b) Traylor, T. G.; Traylor, P. S. In *Active Oxygen in Biochemistry*; Valentine, J. S., Foote, C. S., Greenberg, A., Liebman, J. F., Eds.; Blackie Academic and Professional: London, 1995; pp 84−187.
(16) Kryatov, S. V.; Taktak, S.; Korendovych, I. V.; Rybak-Akimova, E. V.; Kaizer, J.; Torelli, S.; Shan, X.; Mandal, S.; MacMurdo, V. L.; Payeras, A. M.; Que, L., Jr. *Inorg. Chem.* **2005**, *43*, 85−99.
(17) Riordan and co-workers reported that $[Ni^I(TMC)]^+$ activates O_2 to afford $[(TMC)Ni-O_2-Ni(TMC)]^{2+}$, which then decomposes to $[Ni(TMC)(OH)]^+$: Kieber-Emmons, M. T.; Schenker, R.; Yap, G. P. A.; Brunold, T. C.; Riordan, C. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6716−6718.
(18) (a) Lee, D.; Lippard, S. J. In *Comprehensive Coordination Chemistry II: From Biology to Nanotechnology*; Que, L., Jr., Tolman, W. B., Eds.; Elsevier: Oxford, 2004; Vol. 8, pp 309−342. (b) Tshuva, E. Y.; Lippard, S. J. *Chem. Rev.* **2004**, *104*, 987−1012.

JA043083I