Notes

Generation of a Nonheme Oxoiron(IV) Intermediate and Its Reactivities in Oxidation Reactions

Mi Sook Seo, Ho G. Jang,[†,*] Jinheung Kim,[*] and Wonwoo Nam[*]

*Department of Chemistry, Division of Nano Sciences, and Center for Biomimetic Systems, Ewha Womans University, Seoul 120-750, Korea. *E-mail: wwnam@ewha.ac.kr; jinheung@ewha.ac.kr
†Department of Chemistry and Molecular Engineering, Korea University, Seoul 136-701, Korea. *E-mail: hgjang@korea.ac.kr*
*Received February 22, 2005*

Key Words : Enzyme model, High-valent iron-oxo species, Nonheme iron enzyme

High-valent iron(IV)-oxo species have been invoked as the key reactive intermediates in the catalytic cycles of nonheme iron enzymes involved in dioxygen metabolism.[1] Direct experimental evidence for such intermediates has been obtained in the chemistry of methane monooxygenase[2] and taurine-2-oxoglutarate dioxygenase.[3] To gain insight into this interesting chemistry, we have made much effort in the design and synthesis of functional models for such systems. Recently, it has been reported that synthetic mononuclear oxoiron(IV) complexes were generated using tetradentate N4 ligands such as macrocyclic TMC and tripodal TPA ligands and pentadentate N5 ligands such as N4Py and Bn-tpen.[4-6] While the TMC oxoiron(IV) intermediate can effect oxygen-atom transfer to PPh3 and the TPA complex is able to epoxidize cyclooctene, the N4Py and Bn-tpen complexes are capable of activating C-H bonds of alkanes. As the TMC ligand provides relatively weak reactivity to oxoiron(IV) species, we have tried to modify cyclam (cyclam = 1,4,8,11-tetraazacyclotetradecane) with

other substituents on nitrogens of the ligand, in order to understand the effect of ligand environment by cyclam derivatives on the spectroscopic properties and reactivities of oxoiron(IV) species. We now report the synthesis and characterization of an Fe(IV)-oxo complex bearing a tetradentate macrocyclic TBC (TBC = 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclotetradecane) which has benzyl groups instead of methyl on TMC. This new $Fe^{IV}=O$ species exhibits an ability to oxidize a variety of organic substrates such as triphenylphosphine, thioanisole, N,N-dimethylaniline, and triphenylmethane.

The tetradentate TBC ligand (**1**) was prepared from cyclam by alkylation with benzyl bromide (Scheme 1). After purification by column chromatography, the TBC ligand was obtained in 60% yield. Reaction of **1** with Fe(OTf)₂ afforded white powder of [Fe(TBC)(CH₃CN)₂](OTf)₂ (**2**). Complex **2** collected by recrystallization was subjected to comprehensive spectroscopic analysis.

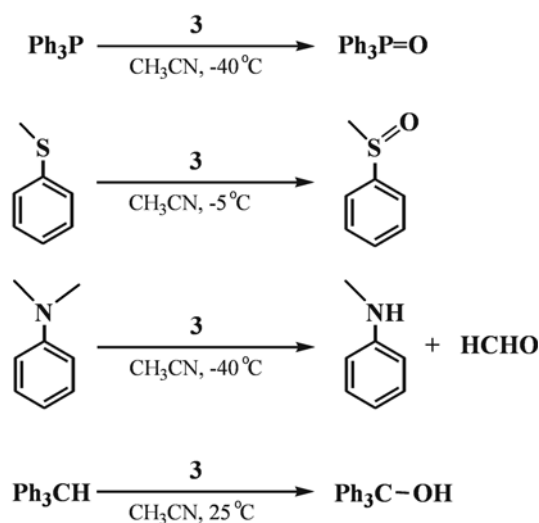We then tried to test the generation of oxoiron(IV) species
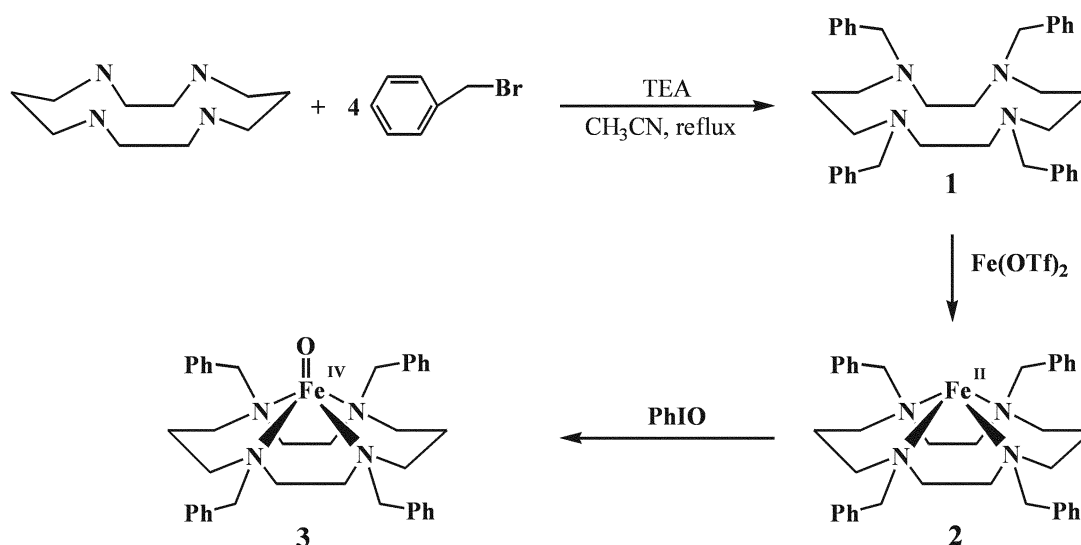
Scheme 1
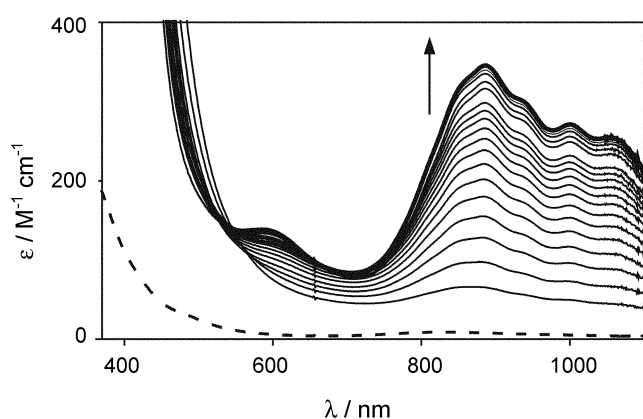
Figure 1. UV-visible spectral changes observed in the formation of $[Fe^{IV}(O)(TBC)]^{2+}$ from $[Fe(TBC)(CH_3CN)_2]^{2+}$ by addition of 3 equiv PhIO in CH_3CN at 25 °C.

by reacting **2** with various oxidants. Treatment of **2** with 3 equiv PhIO in CH_3CN at 25 °C afforded a green intermediate **3** that persists for several hours ($t_{1/2} \sim 100$ min). The green color is associated with a band at 880 nm (ε 350 $M^{-1}cm^{-1}$) with shoulders near 920 and 1000 nm (Figure 1). This new species can be assigned to an $[Fe^{IV}(TBC)(O)]^{2+}$ species on the basis of its characteristic near IR absorption band and low extinction coefficient (vide infra). The fact that TBC gives rise to a lower energy transition relative to TMC (λ_{max} at 820 nm) supports the idea that this band is ligand
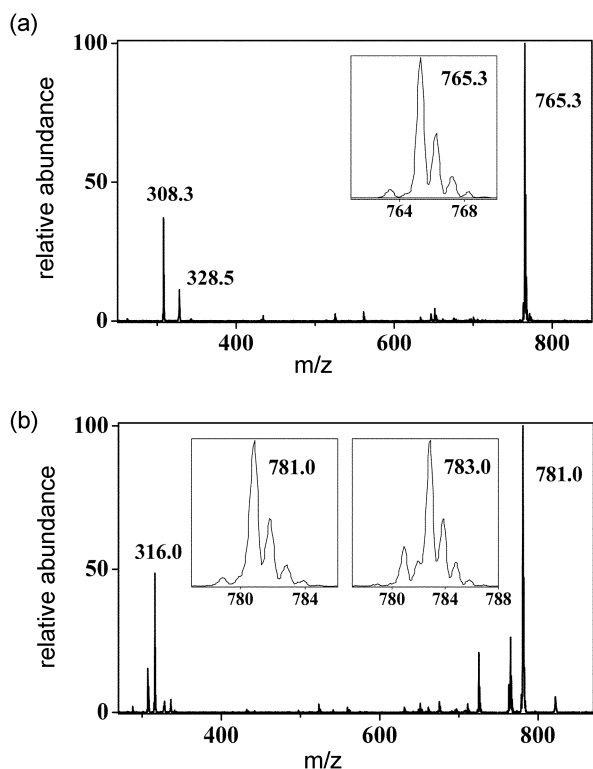

Scheme 2

Figure 2. Positive ion electrospray ionization mass spectra of (a) **2** and (b) **3**. Insets in (b) show the isotopic distributions of molecular ion $[Fe(O)(TBC)(OTf)]^+$ (left panel) and $[Fe(^{18}O)(TBC)(OTf)]^+$ (right panel).

field in character as interpreted previously in other reports.[5] Similar near IR bands have also been reported for $[Fe^{IV}(TPA)(O)]^{2+}$ (λ_{max} at 720 nm), $[Fe^{IV}(N4Py)(O)]^{2+}$ (λ_{max} at 695 nm), and $[Fe^{IV}(Bn-tpen)(O)]^{2+}$ (λ_{max} at 739 nm).[5]

The nature of **2** and **3** can be established by high-resolution electrospray mass spectrometry (ESI-MS). Thus, ESI-MS reveals a respective molecular ion at *m/z* 765.3 for **2**, mass value consistent with its formulation as $\{[Fe^{II}(TBC)](O_3SCF_3)\}^+$ ion (*m/z* calculated 765.3) (Figure 2a), and a molecular ion at *m/z* 781.0 for **3**, mass value consistent with its formulation as $\{[Fe^{IV}(O)(TBC)](O_3SCF_3)\}^+$ (*m/z* calculated 781.0) ion (Figure 2b). Taken together, the accumulated information allows us to assign the formation of the TBC oxoiron(IV) intermediate. The oxygen atom of **3** was exchangeable with solvent water, as the mass shift from *m/z* 781.0 to 783.0 is observed when $H_2^{18}O$ is added before the addition of PhIO to **2** (Figure 2b, inset).

The ability of **3** to mediate its oxygen transfer to phosphine and sulfides was examined using triphenylphosphine and thioanisole as model substrates. When triphenylphosphine or thioanisole was added to a reaction solution containing **3**, the intermediate **3** reverted back to the iron(II) TBC precursor. Product analysis of the reaction mixture revealed that triphenylphosphine oxide or methylphenylsulfoxide was yielded quantitatively, demonstrating that **3** is capable of oxygenating the phosphine and sulfide to the corresponding oxide products (Scheme 2). The pseudo-first-order decay of the intermediate as monitored by UV-vis spectrophotometer was observed by its reverting back to the starting iron complex (Figure 3a), and the rate constants increased proportionally with the thioanisole concentrations leading to a second-order rate constant of 3.48×10^{-1} $M^{-1}s^{-1}$ (Figure 3b). Intermediate **3** also reacts with *tertiary*-methylarylamines at −40 °C. The addition of 20 equiv of *N,N*-dimethylaniline results in a rapid decay of **3**, concomitant with the nearly quantitative appearance of its iron(II) precursor (Figure 4a): *N*-methylaniline is obtained in a high yield (> 60% based on the intermediate generated), demon-
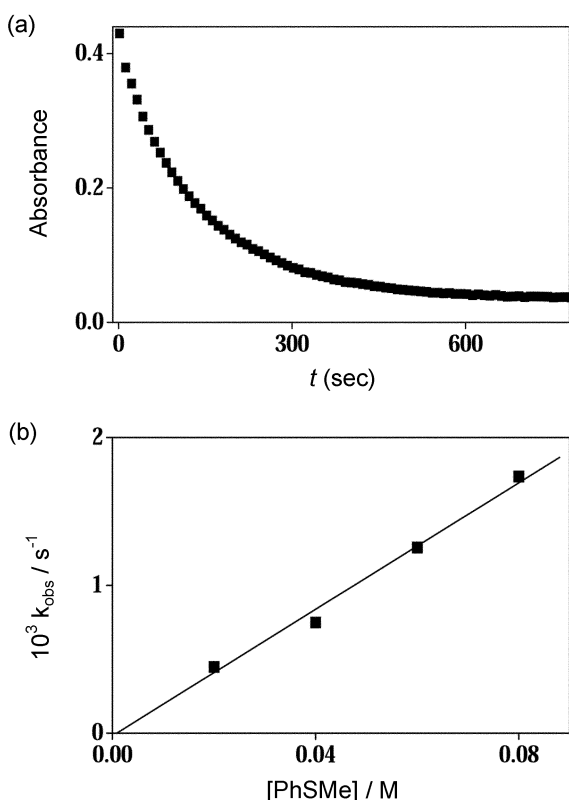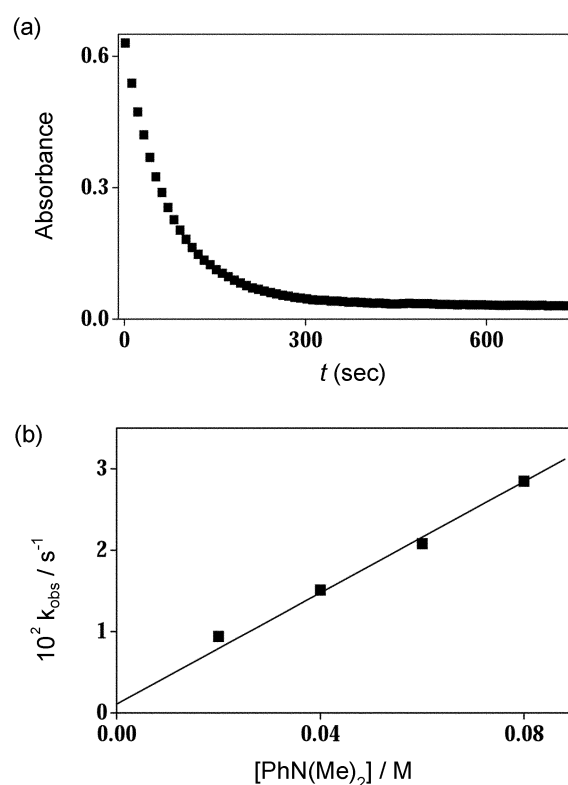
Figure 3. (a) A kinetic trace at 880 nm that corresponds to a pseudo-first-order decay of **3** (2 mM) in CH_3CN upon addition of 20 equiv thioanisole at −40 °C. (b) Plot of the observed pseudo-first-order rate constant, $k_{(obs)}$, *vs* thioanisole concentration for the sulfoxidation reaction by **3** in CH_3CN at −10 °C.

Figure 4. (a) Time course of absorbance change at 880 nm in the first-order process of the reaction between **3** (2 mM) and 20 equiv DMA in CH_3CN at −40 °C. (b) Plot of $k_{(obs)}$ against DMA concentration for the N-demethylation reaction by **3** in CH_3CN at −40 °C.

strating that **3** is capable of demethylating *N,N*-dimethyl-aniline. Reduction of **3** by substrate results primarily in a simple exponential relaxation to Fe(II) precursor. Typical reaction timecourse is displayed in Figure 4a for the reaction with 20 equiv DMA in CH_3CN. The observed rate constants for decay of **3** are plotted as a function of the concentration of substrate. This plot appears second order and the calculated second-order rate constants are 3.42×10^{-1} $M^{-1}s^{-1}$ for *N*-methylation (Figure 4b). Further, **3** shows an ability of activating C-H bond of triphenylmethane, yielding tri-phenylmethanol (Scheme 2), and demonstrating that **3** is stronger oxidant than the TMC oxoiron(IV) species.[5b] Finally, when the oxidation of triphenylphosphine by **3**, generated with PhIO and $H_2^{18}O$,[7] is carried out, the oxygen of $H_2^{18}O$ is incorporated into the triphenylphosphine oxide product. This result demonstrates unambiguously that the oxo ligand of **3** is transferred to the oxidized product.

In summary, we have demonstrated that the TBC oxo-iron(IV) intermediate, derived from the corresponding (TBC)Fe(II) complex and PhIO, was characterized and showed its ability to oxidize phosphine, sulfide, *tertiary*-methylamine, and triphenylmethane. This insight may allow for the rational design of new biologically-relevant iron complexes for high-valent oxoiron(IV) species with more interesting properties and reactivities.[8]

Experimental Section

In the synthesis of TBC, 1,4,8,11-tetraazacyclopentadecane (0.5 g, 2.5 mmol), benzyl bromide (1.94 mL, 12.5 mmol), and triethylamine (1.81 mL, 13.0 mmol) were combined in CH_3CN and refluxed overnight. After the solvent was rotary-evaporated, the solution was turned to basic (pH ~12) by titrating with conc. KOH solution, then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated to afford white powder. Yield (60%). ^1H-NMR ($CDCl_3$): δ (ppm) = 1.74 (m, -CH_2-), 2.52 (m, N-CH_2-), 2.60 (t, N-CH_2-), 3.44 (s, Bz-CH_2-), 7.22 (m, Ph-) (see Supporting Information, Figure S1).

Supporting Information: NMR data for TBC is available *via* the Internet at http:/www.kcsnet.or.kr/bkcs.

References

1. (a) Borovik, A. S. *Acc. Chem. Res.* **2005**, *38*, 54. (b) Que, L. Jr. *J.*

Biol. Inog. Chem. **2004**, *9*, 643. (c) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L. Jr. *Chem. Rev.* **2004**, *104*, 939. (d) He, C.; Mishima, Y. *Curr. Opin. Chem. Biol.* **2004**, *8*, 201. (e) Slep, L. D.; Neese, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 2942. (f) Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J. *Chem. Rev.* **2000**, *100*, 235.

2. (a) Lee, S.-K.; Nesheim, J. C.; Lipscomb, J. D. *J. Biol. Chem.* **1993**, *268*, 21569. (b) Lee, S.-K.; Fox, B. G.; Froland, W. A.; Lipscomb, J. D.; Munch, E. *J. Am. Chem. Soc.* **1993**, *115*, 6450. (c) Liu, K. E.; Valentine, A. M.; Wang, D.; Hyunh, B. H.; Edmondson, D. E.; Salifoglou, A.; Lippard, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 10174.

3. Ryle, M.; Liu, A.; Muthukumaran, R. B.; Ho, R. Y. N.; Koehntop, K. D.; McCracken, J.; Que, L. Jr.; Hausinger, R. P. *Biochemistry* **2003**, *42*, 1854.

4. Ligand abbreviations used: TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane, N4Py = *N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine, TPA = tris(2-pyridylmethyl), Bn-tpen = *N*-benzyl-*N,N',N''*-tris(2-pyridylmethyl)-1,2-diaminoethane.

5. (a) Kim, S. O.; Sastri, C. V.; Seo, M. S.; Kim, J.; Nam, W. *J. Am. Chem. Soc.* **2005**, *127*, 4178. (b) 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. (c) Rohde, J. U.; In, J. H.; Lim, M. H.; Brennessel, W. W.; Bukowski, M. R.; Stubna, A.; Münck, E.; Nam, W.; Que, L. *Science* **2003**, *299*, 1037. (d) 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. USA* **2003**, *100*, 3665-3670.

6. (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. (b) Grapperhaus, C. A.; Mienert, B.; Bill, E.; Weyhermüller, T.; Wieghardt, K. *Inorg. Chem.* **2000**, *39*, 5306.

7. The formation of $[Fe^{IV}(TBC)(^{18}O)]^{2+}$ species from the reaction of **2** with PhIO and $H_2^{18}O$ in CH_3CN was confirmed by ESI-MS.

8. J. Y. Ryu, S. O. Kim, W. Nam, S. Heo, J. Kim, *Bull. Korean Chem. Soc.* **2003**, *24*, 1835.