Water as an Oxygen Source in the Generation of Mononuclear Nonheme Iron(IV) Oxo Complexes**

Yong-Min Lee, Sunder N. Dhuri, Sarvesh C. Sawant, Jaeheung Cho, Minoru Kubo, Takashi Ogura, Shunichii Fukuzumi,* and Wonwoo Nam*

High-valent iron(IV) oxo species have been implicated as the active oxidizing species in metabolically important oxidative transformations performed by mononuclear nonheme iron enzymes.1–3 Such nonheme iron(IV) oxo species were observed and characterized recently in enzymatic and biomimetic reactions.2,3 For example, intermediate high-spin iron(IV) oxo species were identified and proposed as active oxidants in the catalytic cycles of E. coli taurocysteine dioxygenase (TauD), prolyl-4-hydroxylase, and halogenase CytC3.2 In biomimetic studies, a number of mononuclear nonheme iron(IV) oxo complexes bearing tetradentate N4 and pentadentate N5 and N4S ligands were synthesized and characterized with various spectroscopic techniques.3 A notable example is the first crystal structure of a nonheme iron(IV) oxo complex, [Fe(IV)(O)(tmc)(NCCCH2)]2+ (tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane).4 The mononuclear iron(IV) oxo species were synthesized using artificial oxidants, such as iodosylbenzene, peroxyacids, oxone, N2O, XO−, ozone, H2O2, and alkyl hydroperoxides,4,5 and more recently using molecular oxidants in the catalytic cycles of E. coli photosystem II.5 At the OEC, manganese(IV) oxo species have been proposed to be formed by the oxidation of water in a proton-coupled electron transfer (PCET) mechanism.5–7 Thus, the oxygen atom in the MnV oxo species derives from water. In biomimetic studies, the formation of high-valent ruthenium oxo complexes has been well established for water oxidation in the presence of a strong oxidant, such as cerium(IV) or [Ru(bpy)3]3+.8–10 Since water is the most abundant, readily available oxygen source on earth, we attempted to generate mononuclear nonheme iron(IV) oxo complexes with water as an oxygen source.12 We now report for the first time the generation of mononuclear nonheme iron(IV) oxo complexes and the catalytic oxygenation of organic substrates using water as an oxygen source and cerium(IV) as a one-electron oxidant (Scheme 1).

Scheme 1.

Addition of [Ce(IV)(NO3)6](NH4)2 (cerium(IV) ammonium nitrate, CAN; 4 mM) to a reaction solution containing nonheme iron(II) complex (1 mM) [Fe(II)(N4Py)(ClO4)2] or [Fe(II)(Bn-tpen)](OTf)2 (N4Py = N,N-bis(2-pyridylmethyl)-N′-bis(2-pyridylmethyl)ethane-1,2-diamine, OTf = CF3SO3−) affords the corresponding iron(IV) oxo complexes [Fe(IV)(O)(N4Py)]2+ (1) or [Fe(IV)(O)(Bn-tpen)]2+ (2)[*] in H2O, H2O/CH3CN, or buffered H2O/CH3CN at 25 °C (Figure 1a and Figure S2a in the Supporting Information).[*] The electrospray ionization mass spectra (ESI MS) of 1 and 2 exhibit prominent ion peaks at m/z 219.7 and 247.6, respectively (Figure 1b and Figure S2b in the Supporting Information), the mass and isotope distribution patterns of which correspond to [Fe(IV)(O)(N4Py)]2+ (calcd m/z 219.6) and [Fe(IV)(O)(Bn-tpen)]2+ (calcd m/z 247.6). When the reactions were carried out in isotopically labeled water (H218O), mass peaks corresponding to 1 and 2 appeared at m/z 220.7 and 248.6, respectively, thus indicating that the oxygen atom in the iron(IV) oxo com-
The stability of 1 and 2 generated in the present study ($t_{1/2} \approx 5$ and 1 day at 25°C for 1 and 2, respectively) was found to be greater than that of the compounds generated in the reaction with PhIO in CH$_2$CN ($t_{1/2} \approx 60$ and 6 h at 25°C for 1 and 2, respectively). We therefore attempted to generate other nonheme iron(IV) oxo complexes with water as an oxygen source and CAN as an oxidant at 25°C; these were synthesized only at low temperature (e.g. at $-40°C$) owing to their thermal instability. Such complexes include [Fe$^{IV}$(O)-(tma)]$^{3+}$ (3, tma = tris-(2-pyridylmethyl)amine), [Fe$^{IV}$(O)-(bpmen)]$^{3+}$ (4, bpmen = N,N'-dimethyl-N,N'-bis(2-pyridylmethyl)ethane-1,2-diamine) and [Fe$^{IV}$(O)(bqen)]$^{2+}$ (5, bqen = N,N'-dimethyl-N,N'-bis(8-quinoylimethyl)ethane-1,2-diamine) (see Figure S1 in the Supporting Information). Interestingly, we observed the formation of the iron(IV) oxo species in the reactions of the corresponding iron(II) complexes and CAN in the presence of H$_2$O and the slow decay of the intermediates at 25°C (Figure S3 in the Supporting Information), thus indicating that the intermediates generated by H$_2$O and CAN are stabilized under the present reaction conditions. As the enhanced stability of the iron oxo intermediates might be due to the high acidity of CAN, we compared the stability of 3 in the presence and absence of HClO$_4$ in H$_2$O/CH$_3$CN at 25°C (Figure S4 in the Supporting Information). The stability of 3 increased by a factor of approximately four when it was prepared with CH$_3$CO$_3$H in the presence of HClO$_4$, thus indicating that the high stability of nonheme iron(IV) oxo intermediates prepared with H$_2$O and cerium(IV) can be ascribed to the low pH value of the reaction solution. Furthermore, and in contrast to the reactions of H$_2$O and CAN (see above), the formation of 4 and 5 was not observed when [Fe$^{II}$(bpmen)]$^{2+}$ and [Fe$^{III}$(bqen)]$^{2+}$ were treated with CH$_3$CO$_3$H in the presence of HClO$_4$, which is also worth noting that other nonheme iron(IV) oxo complexes reported in the literature, including [Fe$^{IV}$(O)(tme)]$^{2+}$-[3,4] were easily prepared using water as an oxygen source and CAN as an oxidant.

In light of the observation that nonheme iron(IV) oxo complexes are formed using water as an oxygen source, we investigated the catalytic oxygenation of organic substrates by the nonheme iron(II) catalyst [Fe$^{II}$(Bn-tpen)](OTf)$_2$ and investigated the catalytic oxygenation of organic substrates by the nonheme iron(II) catalyst [Fe$^{II}$(Bn-tpen)](OTf)$_2$ and [Fe$^{IV}$(O)(tma)]$^{3+}$ (1) and [Fe$^{IV}$(O)(N4Py)]$^{4+}$ (2) in the hydroxylation of ethylbenzene by nonheme iron(IV) oxo complexes with water as an oxygen source and CAN as a one-electron oxidant. The hydroxylation of ethylbenzene (Table 1, entry 5) yielded acetophenone as the major product and the formation of sulfone was observed. Benzyl alcohol was oxidized to benzaldehyde with the formation of a small amount of benzoic acid (Table 1, entry 3). In the oxidation of cyclohexene (Table 1, entry 4), hexanedioic acid, which is the product of eight-electron oxidation, was formed, as reported in the ruthenium-catalyzed oxidation of cyclohexene by CAN[25] The hydroxylation of ethylbenzene (Table 1, entry 5) yielded acetophenone as the major product with the formation of a small amount of sec-phenethyl alcohol, as observed in the hydroxylation of ethylbenzene by 2[74]. The turnover number increased by reducing the catalyst amount (Table 1, entry 2). In the absence of the iron catalyst, only negligible amounts of products were formed by H$_2$O and CAN under the reaction conditions.

$$\text{[Fe}^{III}\text{Cl(O)}\text{]}^{2+} + \text{Fe}^{II}\text{(tma)NO}_3^{+} \rightarrow \text{[Fe}^{IV}\text{O(tma)}\text{]}^{3+} + \text{Fe}^{II}\text{(tma)Cl}^{+}$$
Table 1: Catalytic oxidation reactions using [FeII(Bn-tpen)]2+ as a catalyst, water as an oxygen source, and CAN as an oxidant.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Products</th>
<th>TON[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>thioanisole</td>
<td>methyl phenyl sulfoxide</td>
<td>10:±1</td>
</tr>
<tr>
<td>2[a]</td>
<td>thioanisole</td>
<td>methyl phenyl sulfoxide</td>
<td>95:±5</td>
</tr>
<tr>
<td>3</td>
<td>benzyl alcohol</td>
<td>benzaldehyde</td>
<td>10:±1</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexene</td>
<td>hexanedioc acid</td>
<td>5.6:±0.5</td>
</tr>
<tr>
<td>5</td>
<td>ethylbenzene</td>
<td>sec-phenethyl alcohol</td>
<td>1:±0.2</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: CAN (10 mm), 50 equiv relative to iron catalyst was added to a reaction solution containing [FeII(Bn-tpen)][OTf]2 (0.2 mm) and substrate (40 mm) in H2O/CH3CN (1:3) at 25 °C. After 30 min stirring, the reaction solution was analyzed by HPLC for the reactions of thioanisole, benzyl alcohol, and ethylbenzene and by 1H NMR spectroscopy for the reaction of cyclohexene.[18] [b] Turnover number was calculated by dividing product yields by the amount of catalyst used. [c] [FeII(Bn-tpen)][OTf]2 (0.02 mm) and CAN (10 mm, 500 equiv relative to iron catalyst) were used.

The catalytic oxidation of thioanisole was also carried out in H2O/CH3CN (1:3) to confirm the source of oxygen in the oxygenated products. The methyl phenyl sulfoxide produced contained 93 % 18O derived from 95 % 18O-enriched H2O. The 18O percentage in the sulfoxide product was sensitive to the ratio of H2 to be expanded to a system in which nonheme iron complexes contained 93%18O derived from 95% 18O-enriched H2O in the oxygenated products was assigned nonheme iron(IV) oxo complexes and the catalytic oxygenation reaction mechanisms.

Keywords: bioinorganic chemistry · enzyme models · iron · oxidation · reaction mechanisms


[12] Electrochemical generation of a nonheme iron(IV) oxo complex in aqueous CH3CN and CH2Cl2 has been reported: M. J. Collins, K. Ray, L. Que Jr., Inorg. Chem. 2006, 45, 8009–8011.

[13] The generation and stability of iron(IV) oxo intermediates do not depend on solvent systems (e.g. organic vs aqueous solutions).

[14] The rate of oxygen exchange between nonheme iron(IV) oxo complexes and labeled water is slow: M. S. Seo, J.-H. In, S. O. Kim, N. Y. Oh, J. Hong, J. Kim, L. Que Jr., W. Nam, Angew. Chem.
Thus, the full $^{18}$O incorporation from $^2$H$^{18}$O into the iron oxo complex is strong evidence that water is the oxygen source.

Very recently, Solomon and co-workers reported the Fe–O stretching vibration of $^1$ to be 820 cm$^{-1}$ (788 cm$^{-1}$ with $^{18}$O) by nuclear resonance vibrational spectroscopy (NRVS; see Ref. [16]). We find that $^1$ prepared with PhIO in CH$_3$CN exhibits a vibration at 840 cm$^{-1}$ that shifts to 807 cm$^{-1}$ upon introduction of $^{18}$O. The latter result indicates that the Fe–O stretching vibration of $^1$ does not change depending on solution conditions (e.g. aqueous vs. CH$_3$CN).


The $^{16}$O and $^{18}$O compositions in methyl phenyl sulfoxide were determined by the relative abundances of $m/z = 141$ for $^{18}$O and $m/z = 143$ for $^{16}$O in LC-ESI MS analysis of the reaction solution. See the Experimental Section in the Supporting Information for detailed reaction procedures.