Dioxygen Activation by Mononuclear Nonheme Iron(II) Complexes Generates Iron-Oxygen Intermediates in the Presence of an NADH Analogue and Proton

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Dioxygen Activation by Mononuclear Nonheme Iron(II) Complexes Generates Iron−Oxygen Intermediates in the Presence of an NADH Analogue and Proton

Seungwoo Hong,[†,‡] Yong-Min Lee,[†] Woonsup Shin,[*,‡] Shunichi Fukuzumi,[*,§] and Wonwoo Nam[*,†]

Department of Chemistry and Nano Science, Department of Bioinspired Science, Ewha Womans University, Seoul 120-750, Korea, Department of Chemistry and Interdisciplinary Program of Integrated Biotechnology, Sogang University, Seoul 121-742, Korea, and Department of Material and Life Science, Graduate School of Engineering, Osaka University, SORST, Osaka 565-0871, Japan

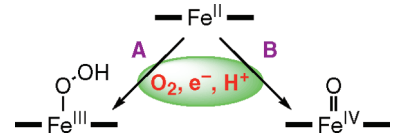
Received July 10, 2009; E-mail: shinws@sogang.ac.kr; fukuzumi@chem.eng.osaka-u.ac.jp; wwnam@ewha.ac.kr

One primary goal in biomimetic research is to understand mechanisms of dioxygen activation, structures of reactive intermediates, and reactivities of these intermediates in oxidation reactions by metalloenzymes such as heme and nonheme iron oxygenases.[1] Extensive mechanistic studies have been carried out on synthetic iron−oxygen adducts such as iron(III)-hydroperoxo and iron(IV)-oxo complexes, mostly formed using artificial oxidants such as iodosylarenes, peroxy acids, and H_2O_2.[1] However, enzymes instead use dioxygen and electrons plus protons or cofactors (e.g., a tetrahydropterin or an α-keto acid) in generating iron−oxygen intermediates.[2] Therefore, the use of O_2 as the primary oxidant and oxygen source in studies on synthetic iron complexes is of fundamental importance. However, there are many intrinsic problems in this approach, and only a few examples exist.[3−6]

Nam and co-workers and Banse, Que and co-workers have independently reported the generation of nonheme iron(IV)-oxo complexes by activating O_2.[5,6] The former group demonstrated the generation of $[(TMC)Fe^{IV}(O)]^{2+}$ in the reaction of $[Fe^{II}(TMC)]^{2+}$ and O_2 in solvent mixtures of CH_3CN/alcohols or CH_3CN/ethers,[5,7] whereas the latter group observed the formation of an iron(IV)-oxo complex in the reaction of $[Fe^{II}(TMC\text{-}py)]^{2+}$ and O_2 in the presence of an electron (BPh_4^-) and proton source ($HClO_4$).[6,7] In those reactions, however, the formation of iron(III)-hydroperoxo species, which are precursors to the iron(IV)-oxo intermediates, was not observed. In the present work, we report the generation of nonheme iron(III)-hydroperoxo and iron(IV)-oxo intermediates by activating O_2 in the presence of a biologically important electron donor, a dihydronicotinamide adenine dinucleotide (NADH) analogue, and an acid; the formation of iron(III)-hydroperoxo and iron(IV)-oxo complexes was found to depend on the supporting ligands (Scheme 1, pathway A with N4Py and Bn-TPEN and pathway B with TMC; see ligand structures in the Supporting Information (SI), Figure S1).[7]

Low-spin iron(II) complexes bearing N4Py and Bn-TPEN ligands, $[Fe^{II}(N4Py)]^{2+}$ and $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$, are air-stable in CH_3CN.[8,9] When we added 1-benzyl-1,4-dihydronicotinamide (BNAH; see structure in SI, Figure S1)[10] and $HClO_4$ to a CH_3CN solution of $[Fe^{II}(N4Py)]^{2+}$, no reaction took place. Interestingly, when we dissolved $[Fe^{II}(N4Py)]^{2+}$ in CH_3OH and added BNAH and $HClO_4$ to the solution in the presence of O_2, the color of the solution changed from yellow to purple within 3 min at 0 °C. By recording UV−vis and EPR spectra of the intermediate, we have confirmed the formation of $[(N4Py)Fe^{III}{-}OOH]^{2+}$ (**1**) (Figure 1; also see SI, Figure S2 for spectral data of **1** prepared in the reaction of $[Fe^{II}(N4Py)]^{2+}$ and H_2O_2 in CH_3OH).[8] The yield of **1** was determined to be ∼90% by comparing the intensity of the absorption band at 548 nm (Figure 1) with the known ϵ value of **1**.[8] In addition, the yield of **1** was found to be maximal when 5 equiv of BNAH and 1.4 equiv of $HClO_4$ were added to the reaction solution (SI, Figure S3). Under these conditions and in an O_2-saturated solution, the rate constant for this reaction, k_{obs}, was determined to be 8.3×10^{-3} s^{-1}.[11] Similarly, the formation of $[(Bn\text{-}TPEN)Fe^{III}{-}OOH]^{2+}$ (**2**) was not observed when $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$ reacted with O_2 in the presence of BNAH and $HClO_4$ in CH_3CN. However, a change of solvent from CH_3CN to CH_3OH led to the formation of **2** (SI, Figure S4 for UV−vis and EPR spectra; also see Figure S5 for spectral data of **2** prepared in the reaction of $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$ and H_2O_2 in CH_3OH).[9] In these reactions, both BNAH and $HClO_4$ were required to generate the iron(III)-hydroperoxo complexes.

Scheme 1



The activation of O_2 by $[Fe^{II}(TMC)]^{2+}$ was also investigated in the presence of BNAH and $HClO_4$ in CH_3CN. While $[Fe^{II}(TMC)]^{2+}$ was air-stable in CH_3CN,[5] it converted to $[(TMC)Fe^{IV}(O)]^{2+}$ (**3**)[12] in >90% yield with a k_{obs} value of 6.4×10^{-3} s^{-1} upon addition of 1 equiv each of BNAH and $HClO_4$ in CH_3CN at room temperature (Figure 2).[11] In this reaction, the generation of $[(TMC)Fe^{III}{-}OOH]^{2+}$ was not detected, probably due to this intermediate's instability. Indeed, it was shown previously that the reaction of $[Fe^{II}(TMC)]^{2+}$ and H_2O_2 afforded **3** rather than $[(TMC)Fe^{III}{-}OOH]^{2+}$ in CH_3CN.[12]

As shown above, solvent (i.e., alcohol) plays a key role in generating the iron(III)-hydroperoxo complexes in the reactions of

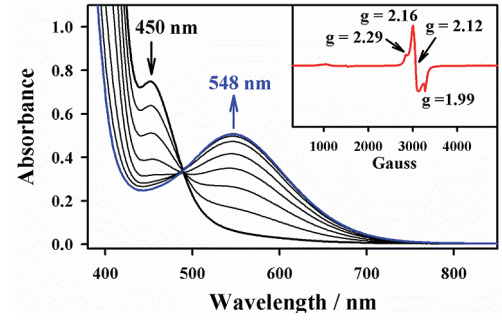


Figure 1. UV/vis spectral changes showing the formation of **1** (blue line) in the reaction of $[Fe^{II}(N4Py)](ClO_4)_2$ (0.5 mM) and O_2 in the presence of BNAH (0.7 mM) and $HClO_4$ (2.5 mM) in CH_3OH at 0 °C. Inset shows X-band EPR spectrum of **1** (1.0 mM) at 4 K.

[†] Ewha Womans University.
[‡] Sogang University.
[§] Osaka University.

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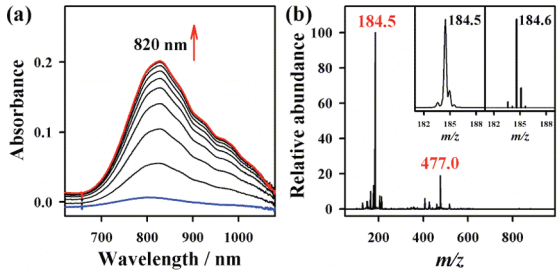
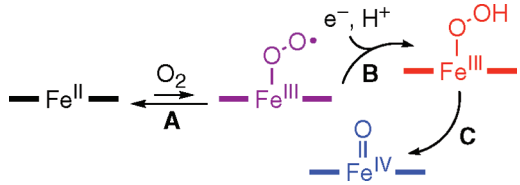


Figure 2. (a) UV/vis spectral changes showing the formation of **3** (red line) in the reaction of $[Fe^{II}(TMC)](CF_3SO_3)_2$ (0.5 mM) and O_2 in the presence of BNAH (0.5 mM) and $HClO_4$ (0.5 mM) in CH_3CN at 25 °C. (b) ESI MS spectrum of **3**. Peaks at *m/z* of 184.5 and 477.0 correspond to $[Fe^{IV}(TMC)(O)(CH_3CN)]^{2+}$ and $[Fe^{IV}(TMC)(O)(CF_3SO_3)]^{+}$, respectively. Insets show the observed (left panel) and calculated (right panel) isotope distribution patterns.

Scheme 2



$[Fe^{II}(N4Py)]^{2+}$ and $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$. This observation is in line with previous reports that only in alcohol or acetone are iron(III)-hydroperoxo complexes generated in the reactions of iron(II) complexes with H_2O_2.[8,9] Also, the spin states of the iron(II) complexes were shown to be different depending on solvents; a low-spin iron(II) complex formed in CH_3CN, whereas, in acetone, a high-spin iron(II) complex formed.[8b] We have also confirmed in the present study that $[Fe^{II}(N4Py)]^{2+}$ and $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$ are low-spin complexes in CH_3CN while they are high-spin in CH_3OH (SI, Figure S6 for ^1H NMR spectra). Further, cyclic voltammetric measurements indicate that the $Fe^{III/II}$ redox potentials of high-spin iron(II) complexes are significantly lower than those of the corresponding low-spin iron(II) complexes. For example, the high-spin iron(II) complexes in CH_3OH show irreversible redox behavior at lower potentials (E_{pc} = 0.29 V and E_{pa} = 0.63 V vs SCE for $[Fe^{II}(N4Py)]^{2+}$ and E_{pc} = 0.29 V and E_{pa} = 0.75 V for $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$), whereas the low-spin iron(II) complexes in CH_3CN show reversible behavior at higher potentials ($E^{0\prime}$ = 1.00 V for $[Fe^{II}(N4Py)]^{2+}$ and $E^{0\prime}$ = 0.95 V for $[Fe^{II}(Bn\text{-}TPEN)]^{2+}$) (SI, Figure S7 for cyclic voltammograms). In the case of $[Fe^{II}(TMC)]^{2+}$, it is in a high-spin Fe(II) state in CH_3CN (0.38 V vs SCE).[5] Thus, the present results demonstrate that high-spin iron(II) complexes with a low $Fe^{III/II}$ redox potential are able to bind and activate O_2 to form iron−oxygen adducts in the presence of an NADH analogue and an acid. It is worth noting that it is high-spin Fe(II) species which bind and activate O_2 in heme and nonheme iron enzymes and in bleomycin.[2,13]

A proposed mechanism for O_2-activation in the complexes described here is depicted in Scheme 2. The reaction is initiated by O_2-binding by a high-spin iron(II) complex that leads to the generation of an iron(III)-superoxo intermediate (pathway A); consecutive electron- and proton-transfer steps result in conversion to a low-spin iron(III)-hydroperoxo intermediate (pathway B). While iron(III)-hydroperoxo intermediates were formed as the final product in the reaction of iron complexes bearing pentadentate N4Py and Bn-TPEN ligands, the iron complex bearing a tetradentate TMC ligand afforded the iron(IV)-oxo complex via O−O bond cleavage in an unidentified $[(TMC)Fe^{III}-OOH]^{2+}$ intermediate (pathway C).[14]

In conclusion, we have reported the first example showing the generation of nonheme iron(III)-hydroperoxo and iron(IV)-oxo complexes by activating O_2 with a biologically important electron donor, an NADH analogue, and an acid. The formation of the iron(III)-hydroperoxo and iron(IV)-oxo complexes was found to depend on the supporting ligands. We have also demonstrated that it is high-spin nonheme iron(II) complexes with low $Fe^{III/II}$ redox potentials which are able to bind and activate O_2 to generate iron−oxygen intermediates.

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Supporting Information Available: Experimental details and spectroscopic and cyclic voltammetric data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Abbreviations: TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraaza-cyclotetradecane, TMC-Py = 1-(2′-pyridylmethyl)-4,8,11-trimethyl-1,4,8,11-tetraaza-cyclotetradecane, N4Py = *N*,*N*-bis(2-pyridylmethyl)-bis(2-pyridyl)methylamine, Bn-TPEN = *N*-benzyl-*N*,*N*′,*N*′-tris(2-pyridylmethyl)-1,2-diaminoethane.
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(14) We have previously proposed that the formation of $[(TMC)Fe^{IV}(O)]^{2+}$ (**3**) from the reaction of $[Fe^{II}(TMC)]^{2+}$ and O_2 in solvent mixtures of CH_3CN/alcohols or CH_3CN/ethers occurs via O−O bond cleavage of a (μ-1,2-peroxo)diiron(III) intermediate: see ref 5.

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