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Dioxygen Activation by a Non-Heme Iron(II) Complex: Formation of an Iron(IV)−Oxo Complex via C−H Activation by a Putative Iron(III)−Superoxo Species

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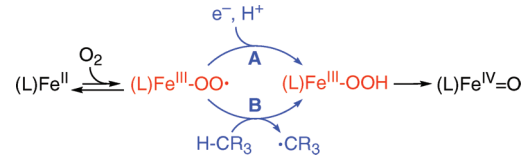
Abstract: Iron(III)−superoxo intermediates are believed to play key roles in oxygenation reactions by non-heme iron enzymes. We now report that a non-heme iron(II) complex activates O_2 and generates its corresponding iron(IV)−oxo complex in the presence of substrates with weak C−H bonds (e.g., olefins and alkylaromatic compounds). We propose that a putative iron(III)−superoxo intermediate initiates the O_2-activation chemistry by abstracting a H atom from the substrate, with subsequent generation of a high-valent iron(IV)−oxo intermediate from the resulting iron(III)−hydroperoxo species.

The nature of metal−oxygen intermediates involved in the catalytic cycles of dioxygen activation by oxygenase enzymes has been intensively investigated over the past several decades.[1] Among the metal−oxygen intermediates, such as metal−superoxo, −peroxo, −hydroperoxo, and −oxo, metal−superoxo species have attracted much attention recently, as iron(III)− and copper(II)−superoxo intermediates have been invoked as active oxidants in H-atom abstraction reactions by non-heme iron and copper enzymes, respectively.[2,3] In biomimetic models, synthetic Cu(II)−superoxo complexes have shown reactivities in the oxidation of ligand C−H bonds and weak O−H bonds of substrates,[4] but iron(III)−superoxo species have rarely been explored in H-atom abstraction reactions.[5]

In non-heme iron models, the formation of iron(III)−hydroperoxo and iron(IV)−oxo species has recently been demonstrated in the reactions of iron(II) complexes and O_2 in the presence of electron and proton donors (Scheme 1, pathway A).[6] In accord with the cytochrome P450 paradigm,[7] the electron and proton donors, respectively, were proposed to reduce an iron(III)−superoxo species to an iron(III)−peroxo intermediate and subsequently generate an iron(III)−hydroperoxo species by the protonation of the iron(III)−peroxo intermediate.[6] In another case, the reaction of $[Fe^{II}(TMC)]^{2+}$ (**1**) (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) with O_2 generated $[(TMC)Fe^{IV}(O)]^{2+}$ (**2**) in CH_3CN/alcohol or CH_3CN/ether solvent mixtures,[8] but the reaction mechanism was not well established. Herein, we report that **1** activates O_2 in the presence of olefins (i.e., as an H-atom donor), thereby generating **2** via H-atom abstraction by a putative iron(III)−superoxo species (Scheme 1, pathway B).

As reported previously,[6b,8] **1** is air-stable in CH_3CN at 25 °C (Scheme 2, pathway A). Interestingly, addition of olefins, such as

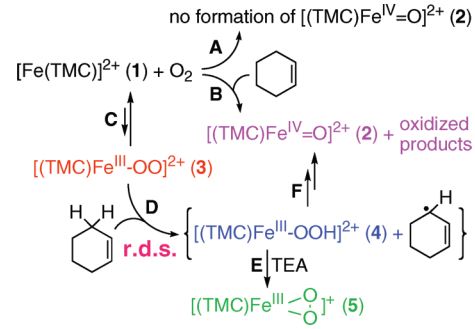
Scheme 1



cyclohexene, cycloheptene, and cyclooctene, to the solution of **1** gave a green intermediate within 1 min (Scheme 2, pathway B).[9] By UV−vis and ESI-MS analysis of the green intermediate (left panel of Figure 1a for UV−vis spectral changes; Figure S1 in the Supporting Information for ESI-MS), we confirmed the formation of **2** with a yield of >90% as determined from the absorbance at 820 nm (ε = 400 M^{-1} cm^{-1}).[10] In this reaction, the formation of **2** was observed because of the low reactivity of **2** toward olefins at 25 °C. Pseudo-first-order fitting of the kinetic data allowed us to determine k_{obs} values (Figure 1a, right panel), and the first-order rate constants increased proportionally with the concentration of substrate (see the k_2 values in the Figure 1b caption).[11] The second-order rate constants were correlated with the C−H bond dissociation energies (BDEs) of the olefins;[12] the formation of **2** was faster with olefins having lower BDEs (Figure 1c).[13] In addition, through the use of deuterated cyclohexene as a substrate, a kinetic isotope effect (KIE) value of 6.3(3) in the formation of **2** was obtained [Figure 1b; compare the plots for cyclohexene (black line) and cyclohexene-d_{10} (red line)].[14,15] *The large KIE value, with the dependence of the rate constants on the allylic C−H BDE of the olefin, indicates that C−H bond activation of the olefin is the rate-determining step for the formation of* ***2*** (see below).

Product analysis of the reaction solutions was carried out using ^{1}H NMR spectroscopy, GC, and GC−MS after the complete formation of **2**. In the reaction of **1** and O_2 in the presence of

Scheme 2



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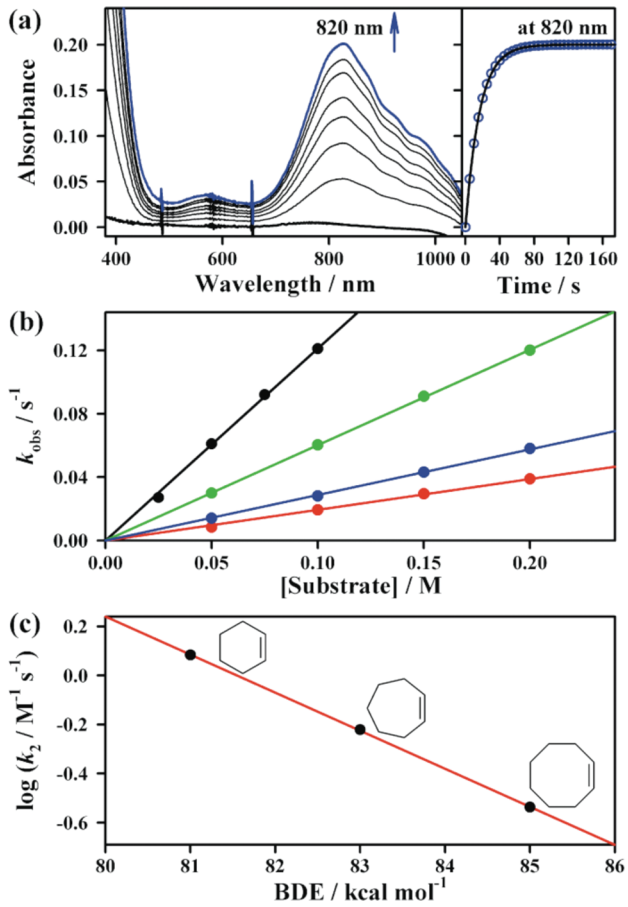

Figure 1. (a) UV−vis spectral changes (left panel) and time course (right panel) for the formation of **2** (blue line) in the reaction of **1** (0.5 mM) and O_2 in the presence of cyclohexene (50 mM) in CH_3CN at 25 °C. (b) Plots of k_{obs} against substrate concentration to determine second-order rate constants for the formation of **2** with cyclohexene (black, $k_2 = 1.2$ M^{-1} s^{-1}), cycloheptene (green, $k_2 = 6.0 \times 10^{-1}$ M^{-1} s^{-1}), cyclooctene (blue, $k_2 = 2.9 \times 10^{-1}$ M^{-1} s^{-1}), and cyclohexene-d_{10} (red, $k_2 = 1.9 \times 10^{-1}$ M^{-1} s^{-1}). (c) Plot of log k_2 against olefin C−H BDE (cyclohexene, 81 kcal mol^{-1}; cycloheptene, 83 kcal mol^{-1}; cyclooctene, 85 kcal mol^{-1}).[12]

cyclohexene, allylic oxidation products (i.e., 2-cyclohexen-1-ol and 2-cyclohexen-1-one) together with dehydrogenation products (i.e., 1,3-cyclohexadiene and benzene) were obtained, and the product yields were 26(4)% for 2-cyclohexen-1-ol, 21(3)% for 2-cyclohexen-1-one, 9(2)% for 1,3-cyclohexadiene, and 5(2)% for benzene (Figure S4).[16] In addition, the source of oxygen in the allylic oxidation products was determined to be dioxygen on the basis of an ^{18}O-labeling experiment with $^{18}O_2$ (Figures S1b and S5 for ESI-MS of [^{18}O]**2** and product analysis, respectively). Although further studies are needed to elucidate the detailed mechanism of the product formation, what we can propose at this moment is that all of the oxidized products, such as allylic oxidation and dehydrogenation products, might be derived from a cyclohexenyl radical that was the initial product formed by H-atom abstraction of cyclohexene by an iron(III)−superoxo species (Scheme 2, pathways D and F).

One of the most important mechanistic points that deserve discussion here is the nature of an active oxidant that activates allylic C−H bonds of olefins. As the proposed mechanism is depicted in Scheme 2, the reaction is initiated by binding of O_2 by **1**, which leads to the generation of an iron(III)−superoxo species (**3**) (pathway C).[17] Subsequently, **3** abstracts a H atom from the allylic C−H bond of the olefin, giving an iron(III)−hydroperoxo intermediate (**4**) and an alkenyl radical (pathway D).[18] Although **4** was not detected in the reaction solution,[19] we observed an iron(III)−peroxo species (**5**) when the reaction was carried out in the presence of base [e.g., triethylamine (TEA)] (pathway E) (Figures S6 and S7 for UV−vis and EPR spectra).[20] This result is indirect but compelling evidence that **4** was indeed generated in the reaction but could not be detected under the conditions.[19] In addition, the rate of the formation of **5** was dependent on the substrate, with the order of xanthene > cyclohexene > cyclohexene-d_{10}; this order indicates that the formation of **4** from the C−H bond activation of the substrate by **3** is the rate-determining step (pathway D).[21] In the final step of the proposed mechanism, which is the formation of **2** and oxidized products from **4** and an alkenyl radical (pathway F), allylic oxidation products might be formed from the rebound between **4** and the alkenyl radical or from the reaction of the alkenyl radical and O_2.[22] In addition, the mechanism for the formation of dehydrogenation products is not clear at this moment, although such dehydrogenations have been observed in enzymatic reactions[23] as well as in non-heme iron models.[16]

In conclusion, we have shown that a non-heme iron(II) complex activates O_2 in the presence of substrates with weak C−H bonds, thereby generating an iron(IV)−oxo complex. We have proposed that an iron(III)−superoxo intermediate is the active oxidant that abstracts a H atom from the substrate. The present results are probably relevant to the chemistry of mononuclear non-heme iron enzymes such as isopenicillin *N* synthase and 1-aminocyclopropane-1-carboxylic acid oxidase that initiate oxidation of their substrates by putative iron(III)−superoxo species (i.e., H-atom abstraction) and then generate iron(IV)−oxo species for further oxidation reactions.[2] Future studies, including theoretical calculations, will focus on elucidating the chemical properties of metal−superoxo species in oxidation reactions.

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

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(15) The reaction rates were also dependent on the reaction temperature; linear Eyring plots between 20 and 35 °C were obtained, from which the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated (see Figures S2 and S3).

(16) Que and co-workers reported the dehydrogenation of cyclohexene in the reaction of an iron(II) complex and O_2, affording cycloxadiene as a major product. An iron(IV)−oxo complex was proposed as an active oxidant for the dehydrogenation reaction. See: Mukherjee, A.; Martinho, M.; Bominaar, E. L.; Münck, E.; Que, L., Jr. *Angew. Chem., Int. Ed.* **2009**, *48*, 1780–1783.

(17) We failed to detect **3** in a solution containing **1** under an O_2 atmosphere using various spectroscopic methods, including EPR spectroscopy.

(18) We have recently shown that an isolated $(TMC)Cr^{III}$−superoxo complex is capable of abstracting a H atom from alkylaromatic compounds. See: Cho, J.; Woo, J.; Nam, W. *J. Am. Chem. Soc.* **2010**, *132*, 5958–5959.

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