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Reactivity of Hydroperoxide Bound to a Mononuclear Non-Heme Iron Site

Akira Wada,[†,‡] Seiji Ogo,[‡] Shigenori Nagatomo,[‡] Teizo Kitagawa,[‡] Yoshihito Watanabe,*[,‡] Koichiro Jitsukawa,[†] and Hideki Masuda*[,†,‡,§]

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan, and Institute for Molecular Science, Myodaiji, Okazaki 444-8585, Japan

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The first isolation and spectroscopic characterization of the mononuclear hydroperoxo–iron(III) complex $[Fe(H_2bppa)(OOH)]^{2+}$ (**2**) and the stoichiometric oxidation of substrates by the mononuclear iron–oxo intermediate generated by its decomposition have been described. The purple species **2** obtained from reaction of $[Fe(H_2bppa)(HCOO)](ClO_4)_2$ with H_2O_2 in acetone at –50 °C gave characteristic UV–vis ($\lambda_{max} = 568$ nm, $\epsilon = 1200$ M^{-1} cm^{-1}), ESR ($g = 7.54$, 5.78, and 4.25, $S = {}^5/_2$), and ESI mass spectra (*m*/*z* 288.5 corresponding to the ion, $[Fe(bppa)(OOH)]^{2+}$), which revealed that **2** is a high-spin mononuclear iron(III) complex with a hydroperoxide in an end-on fashion. The resonance Raman spectrum of **2** in d_6-acetone revealed two intense bands at 621 and 830 cm^{-1}, which shifted to 599 and 813 cm^{-1}, respectively, when reacted with ^{18}O-labeled H_2O_2. Reactions of the isolated $(bppa)Fe^{III}$–OOH (**2**) with various substrates (single turnover oxidations) exhibited that the iron–oxo intermediate generated by decomposition of **2** is a nucleophilic species formulated as $[(H_2bppa)Fe^{III}–O^{\bullet}]$.

Studies of hydroperoxo iron complexes[1] are extremely important in elucidation of the spectroscopic properties and reactivities of oxygen-activating heme and non-heme iron enzymes.[2a,3] In the past decade, iron/ROOH (R = H, alkyl) systems[1b−e,4] have been investigated in order to gain an understanding of the mechanisms of relevant biological oxidations and/or elucidate the relationships between electronic/steric structure and reactivity of iron−(per)oxo intermediates. Unfortunately, the oxidation reactions carried out using excess amounts of ROOH relative to iron catalyst typically yield large amounts of free radicals due to the rapid reaction of the iron intermediates with ROOH instead of the substrates,[1b−e,4] which tends to initiate radical chain autoxidations. This has hindered our ability to distinguish whether the reactions are metalloxo- or free-radical-based oxidations. Therefore, to confirm the electronic character and direct reactivity of the iron−oxo intermediate generated from O−O bond cleavage of an Fe−OOR precursor, investigations of the stoichiometric oxidation (single turnover) of substrate by an isolated peroxo iron species under ROOH-free conditions will be required. Herein, we describe the first isolation and recovery of the spectroscopically characterized hydroperoxo mononuclear iron(III) complex, $[Fe(H_2bppa)(OOH)]^{2+}$ using ligand H_2BPPA reported previously,[5] and discuss the stoichiometric oxidations of substrates by the non-heme iron−oxo intermediate resulting from O−O bond cleavage of the complex.

A reaction of $[Fe(H_2bppa)(HCOO)](ClO_4)_2$ (**1**, Figure 1S)[6,7] with a large excess of H_2O_2 in acetone at −50 °C produced a deep purple species (**2**) exhibiting spectroscopic characters: UV−vis ($\lambda_{max} = 568$ nm, $\epsilon = 1200$ M^{-1} cm^{-1}; Figure 2S), ESR ($g = 7.54$, 5.78, and 4.25, $S = {}^5/_2$; Figure 3S), and ESI mass spectra (*m*/*z* 288.5 corresponding to the

† Nagoya Institute of Technology.
‡ Institute for Molecular Science.
§ Address for correspondence: Professor Hideki Masuda, Department of Applied Chemistry, Faculty of Engineering, Nagoya Institute of Technology, Showa-ku, Nagoya 466-8555, Japan. Tel: +81-52-735-5228. Fax: +81-52-735-5228. E-mail: masuda@ach.nitech.ac.jp.

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ion $[Fe(H_2bppa)(OOH)]^{2+}$; Figure 4S).[6] These properties are quite similar to those of the corresponding high-spin η^1-alkylperoxo iron(III) complexes reported previously.[5b] The resonance Raman spectrum of **2** in d_6-acetone revealed two intense bands at 621 and 830 cm^{-1} (Figure 5S).[6] The former band shifted to 599 cm^{-1} upon reaction with ^{18}O-labeled H_2O_2. This agrees well with the theoretical value ($\Delta\nu$(Fe−O) = 22 cm^{-1}), allowing assignment of the feature as the Fe−O stretching mode. This stretching vibration was found at a much higher frequency compared to the ν(Fe−O) bands observed in other high-spin iron−peroxo complexes (415−503 cm^{-1}),[8] indicating the formation of a stronger Fe−O bond. The latter band, whose frequency is similar to the O−O vibration found in oxy-Hr with a η^1-hydroperoxide ion bound in an end-on fashion (844 cm^{-1}),[8a] showed only a small isotope shift to 813 ($\Delta\nu$ = 17 cm^{-1})[9] and 826 cm^{-1} ($\Delta\nu$ = 4 cm^{-1}) upon reaction with $H_2{}^{18}O_2$ and D_2O_2, respectively. However, the deuterium-dependent shift indicates the presence of a protonated peroxide moiety ligated to the iron(III) complex unlike the Fe^{III}(edta) complex bearing side-on peroxide.[10] These spectroscopic features are firmly consistent with the formulation of the mononuclear hydroperoxo high-spin iron(III) complex $[Fe(H_2bppa)(\eta^1\text{-}OOH)]^{2+}$.

Upon treatment of a solution containing **2** with Et_2O at −70 °C and subsequent removal of excess H_2O_2, the hydroperoxo iron complex **2** was isolated as a purple powder not suitable for X-ray crystal analysis.[6] In dissolving the dry powder into acetone, **2** was regenerated with a decomposition of not more than 10% as determined by UV−vis and ESR spectroscopies. The isolation and regeneration of the hydroperoxo iron species were first observed by the use of the ligand hexadentate H_2BPPA, which stands in contrast to activated bleomycin (BLM)[3a] and other hydroperoxo mononuclear iron(III) complexes with tetradentate ligand.[1]

In order to identify a non-heme iron−oxo intermediate generated by O−O bond cleavage and assess its reactivity, the reactions of the isolated (H_2bppa)Fe−OOH species (**2**) with various substrates were investigated in the absence of free H_2O_2. The regenerated complex **2** is relatively stable at −70 °C, which is distinct from (BLM)Fe−OOH,[3a] so that it was not capable of oxidizing substrates under such conditions. Fortunately, slow warming of the solutions to 20 °C proceeded gradual decomposition of **2** to accelerate the oxidation reactions. The below oxidation experiments for substrates were performed under such conditions. The product distributions determined by GC are listed in Table 1.

Table 1. Product Distributions for Stoichiometric Oxidations of Substrates by $[Fe(H_2bppa)(OOH)]^{2+}$ (**2**) under H_2O_2-free Conditions[a]

entry	substrate	products (%)	
1	cyclohexene	cyclohexenol, 53	cyclohexenone, trace
2[b]		cyclohexenol, 53	cyclohexenone, trace
3	cyclohexane	cyclohexanol, 7	cyclohexanone, nd[c]
4	Me_2S	Me_2SO, 10	
5	Me_2SO	dimethyl sulfone, 78	

[a] The reaction mixture containing substrates (1000 equiv of cyclohexene, 350 equiv of cyclohexane, 600 equiv of dimethyl sulfide = Me_2S, 350 equiv of dimethyl sulfoxide = Me_2SO) and **2** (4.5 mmol) in 3 mL of acetone was incubated at −70 °C under dry Ar atmosphere.[6] The reaction was initiated by the slow warming of the reaction mixture to 20 °C under a vigorous flow of Ar, and oxidation products were analyzed by GC. The yields are based on the average of at least three runs. [b] One hour after the reaction (entry 1). [c] Not detected.

Upon reaction with cyclohexene (Table 1, entry 1), a specific oxidation at the allylic position yielded cyclohexenol as the main product with a trace amount of cyclohexenone. No evidence for epoxidation was obtained. The product yields did not increase with additional reaction time, and radical−radical coupling products were not detected (entry 2). When cyclohexane (CyH) was employed as substrate, only cyclohexanol was given as an oxidation product (entry 3). This result is in contrast to the product distribution observed in stoichiometric oxidation of CyH by the isolated $[Co(PyPz_2P)(t\text{-}BuOO)]^{2+}$ where the ratio of cyclohexanol/cyclohexenone is almost 1.[11] Interestingly, the observed high selectivity for hydroxylation over ketonization is similar to that found in heme iron-based oxidations[2] and is distinguished from those shown in Harber−Weiss[12a] and Russell termination[12b] reactions. Therefore, these findings unequivocally reveal that molecular oxygen and free radicals, which can initiate nonselective radical chain autoxidations,[12c,d] do not participate in the oxidations. Furthermore, in comparative oxidation experiments for Me_2S and Me_2SO[13] to assess the electronic character of the active species (entries 4, 5), a higher efficiency was observed in oxidation of Me_2SO than in the case of Me_2S. This result strongly demonstrates that the active species not only acts as a two-electron oxidant but also displays nucleophilicity.

Since the higher selectivities were observed for hydroxylation of hydrocarbons and oxygenation of organosulfurs, the O−O bond cleavage in the Fe^{III}−OOH species **2** seems to have proceeded heterolytically to generate the two-electron oxidant formulated as Fe^{V}=O. However, epoxidation of olefins (e.g., cyclohexene), in which oxo ferryl porphyrin π-cation radical has been supposed to participate as an electrophilic oxidant,[2] was not observed here. These may

(7) Physicochemical properties for complex **1** are as follows. Crystal data: $C_{46}H_{55}C_{12}FeN_6O_{13}$, MW = 683, monoclinic, $P2_1/c$, a = 13.047(2) Å, b = 18.552(2) Å, c = 18.651(2) Å, β = 94.59(1)°, V = 4500.0(9) $Å^3$, Z = 4, D_c = 1.421 g·cm^{-3}, μ = 5.26 cm^{-1}, $F(000)$ = 2020.0, R = 0.074, R_w = 0.113 for 7802 unique reflections. ESR data: g = 8.05, 5.31, and 4.25 (assignable to $S = {}^5/_2$) in acetone at 4 K. Electrochemical data: $E_{1/2}$ = 0.7 V vs NHE (corresponding to the Fe^{III}/Fe^{II} couple).

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(9) The exact understanding of small isotope shifts in the Raman spectra would require further study, and the minor feature observed at 832 cm^{-1} upon the use of $H_2{}^{18}O_2$ indicates that another hydroperoxo iron species might be present.

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indicate that a high valent iron−oxo species Fe^{V}═O is not responsible for the oxidations.

The fact that allylic oxidation of alkene instead of epoxidation proceeded might imply that the reaction is a radical type reaction. However, the predominant hydroxylation of the C−H bond and efficient oxidation of Me_2SO rather than Me_2S are characteristic of metal-based reactions by nucleophilic oxidant. Furthermore, as presumed from the resonance Raman data, the Fe−O bond in complex **2** is strengthened in such a way as to induce the O−O bond cleavage.[15] The neutral ligand H_2BPPA would afford more electronegative iron−oxo species, in contrast to the corresponding species generated by porphyrin ligands with double negative charges.[2] Thus, we judged that complex **2** could undergo homolysis of the O−O bond in the Fe^{III}−OOH unit to generate the active species formulated as Fe^{IV}═O rather than Fe^{V}═O. Moreover, the detection of the iron(II) complex $[Fe^{II}(Hbppa^{-})]^{+}$ by ESI mass spectroscopy after the oxidations, the Fe^{IV}═O species could perform the following two-step processes by use of reduction from the Fe^{IV} center to the Fe^{II} species; i.e., the hydrogen abstraction and oxygen rebound for C−H bonds, and the one-electron oxidation and oxygen rebound for sulfoxide or sulfide. Such redox behavior between Fe^{IV} and Fe^{II} in the two-electron oxidation may be unique to non-heme iron complex with the electron-deficient ligand H_2BPPA. The observed nucleophilic property and lower reactivity of the active species will successfully be explained by this proposal rather than that in cytochrome P450 which involves reduction of Fe^{V} to Fe^{III} species.[2]

In C−H bond activations of hydrocarbons, if the electronegative Fe^{IV}═O species, as compared with Fe^{V}═O one, can carry out the hydrogen abstraction but not subsequent oxygen rebound, an alternative mechanism should be proposed for the observed highly selective hydroxylations. Judging from the spectroscopic data, the active species responsible for the oxidations is not the Fe−OOH intermediate itself because complex **2** is relatively stable at −70 °C even in the presence of substrates. On the other hand, the experimental procedure utilizing gradual decomposition of Fe−OOH species in the absence of excess H_2O_2 could compulsorily prevent from increase of free $HO^{\bullet}$ through the oxidations.[15] Even if the alkyl and hydroxyl radicals diffuse freely in the solutions, their lifetimes will be too much short to achieve the radical-based oxidations because their free radicals are very quickly quenched by acetone solvent that plays as a radical trapping reagent.[16] Indeed, the coupling products arising from alkyl radicals,[12d] which would be generated from hydrogen abstraction of substrates, were not detected. On the basis of the above results, we can repropose the following mechanism as a reasonable explanation for the selective hydroxylations under such a condition: By the homolytic O−O bond cleavage of Fe^{III}−OOH species, Fe^{IV}═O (↔ Fe^{III}−$O^{\bullet}$) and $HO^{\bullet}$ are generated and then both of them simultaneously attack a substrate in nearly concerted fashion. Namely, after the hydrogen abstraction of C−H bond by either of the oxygen radicals, the oxygen atom of another radical species immediately binds to the alkyl radical remaining near the metal center, which will cause to yield hydroxylated product predominantly. Furthermore, as generally considered, it is very difficult for these active species, which easily give rise to self-decomposition before the reaction, to associate with substrate under such restricted conditions, so that the yields of oxidation products would be lower than the expected ones (Table 1). As additional evidence for the mechanism, we have observed formation of the two species $[Fe^{III}(Hbppa^{-})]^{2+}$ and $[Fe^{III}(H_2bppa)(OH)]^{2+}$ after the oxidation experiments, as measured by ESI mass and ESR spectroscopies. The detection of the former could suggest that the oxygen atom of the iron−oxo species, generated via O−O bond cleavage of **2**, has been transferred to substrates. On the other hand, the presence of the latter would indicate that iron−oxo species has played a part in the hydrogen abstraction. Thus, we concluded that Fe^{IV}═O (↔ Fe^{III}−$O^{\bullet}$) and $HO^{\bullet}$ [17]species are generated as the active species after the homolytic O−O bond cleavage, and they cooperatively perform a C−H bond cleavage step with a subsequent C−O bond formation step in the hydroxylation which must exhibit not only the nucleophilic character but also lower oxidative ability as compared with heme iron−oxo compounds.[2]

In summary, this paper describes the first success of the isolation and recovery of the mononuclear iron(III) complex with hydroperoxide in the end-on mode, $[Fe(H_2bppa)(OOH)]^{2+}$. It is interesting that the stoichiometric oxidations of substrates with the isolated Fe−OOH species in the absence of free H_2O_2 afforded the reasonable understandings for the reactivity and electronic property of non-heme metal−oxo species. The implication of the non-heme iron−oxo radical species with nucleophilic property confirmed here stands in sharp contrast to the typical heme iron−oxo compounds[2] and thus may represent an intrinsic difference in oxidations catalyzed by natural heme and non-heme iron enzymes.

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Supporting Information Available: Experimental synthetic procedure and physical measurements, X-ray structure (Figure 1S), and UV−vis (Figure 2S), ESR (Figure 3S), ESI mass (Figure 4S), and resonance Raman spectra (Figure 5S). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) If $HO^{\bullet}$ would proceed oxygen transfer reaction of substrates completely, the two equimolar amounts of $HO^{\bullet}$ for one substrate should be required because such oxygen transfer reactions are generally supposed to proceed by two-electron oxidation processes as mentioned in the text. In our experiments, oxidation products with more than 50% yields (Table 1, entries 1, 5) based on the Fe−OOH complex are observed, so that the results cannot theoretically be explained by the $HO^{\bullet}$-based reaction mechanism.