Determination of Reactive Intermediates in Iron Porphyrin Complex-Catalyzed Oxygenations of Hydrocarbons Using Isotopically Labeled Water: Mechanistic Insights

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Received August 19, 1996[⊗]

Abstract: We have studied iron porphyrin complex-catalyzed oxygenations of hydrocarbons by several oxidants (i.e., hydrogen peroxide, *tert*-butyl hydroperoxide, and *m*-chloroperoxybenzoic acid (MCPBA)) in the presence of $H_2^{18}O$. In the olefin epoxidation and alkane hydroxylation reactions catalyzed by (*meso*-tetrakis(pentafluorophenyl)-porphinato)iron(III) chloride [Fe(F$_{20}$TPP)Cl], the percentages of ^{18}O incorporated into the oxygenated products were found to be the same in all of the reactions of hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA, leading us to conclude that a common high-valent iron oxo complex was the reactive intermediate responsible for oxygen atom transfer. When the epoxidation of cyclooctene by MCPBA and H_2O_2 was performed at low temperature in the presence of $H_2^{18}O$, it was found that there was no ^{18}O-incorporation from labeled water into cyclooctene oxide. We interpreted the lack of ^{18}O-incorporation in these reactions with that an electronegatively-substituted iron porphyrin complex forms a relatively stable (Porp)Fe^{III}−OOR species and this intermediate transfers its oxygen to olefin prior to the O−O bond cleavage at low temperature. As the reaction temperature raised from −78 °C to room temperature, the amount of ^{18}O incorporated into the oxide product gradually increased in the reactions of cyclooctene epoxidation. This was attributed to the fast conversion of Fe^{III}−OOR to the high-valent iron oxo complex *via* the O−O bond cleavage at higher temperature. We found, by studying the effects of the olefin and $H_2^{18}O$ concentrations on the amount of ^{18}O incorporated into the oxide product, that the rate of the oxygen exchange between high-valent iron oxo complex and labeled water was slower than that of the oxygen atom transfer from the intermediate to organic compounds in catalytic oxygenation reactions. Blocking an axial position of iron porphyrin complex with imidazole prevented the ^{18}O-incorporation from labeled water into the oxygenated products, explaining the phenomenon of no oxygen exchange in cytochrome P-450 systems.

Introduction

Elucidation of the structure of reactive intermediates responsible for oxygen atom transfer in catalytic oxygenation reactions by monooxygenase enzymes and metal complexes has been the major goal of bioinorganic and oxidation chemistry.[1] Since the intermediates are highly reactive and unstable in nature, characterization of the species has been difficult to obtain directly. Therefore, isotopically labeled water, $H_2^{18}O$, has been frequently used as indirect evidence for the intermediacy of high-valent metal oxo complexes in the catalytic oxygenation reactions of organic substrates by metal complexes.[2] When labeled ^{18}O is found to be incorporated from $H_2^{18}O$ into oxygenated products, it has been generally accepted that the oxygenating species is a high-valent metal oxo complex since the oxygen of high-valent metal oxo complexes is believed to exchange invariably fast with labeled water (Scheme 1).[2]

Although labeled water experiments have been useful to determine the involvement of high-valent metal oxo complexes in catalytic oxygenation reactions, a recent study showed that this method led to a false conclusion in iodosylbenzene

Scheme 1
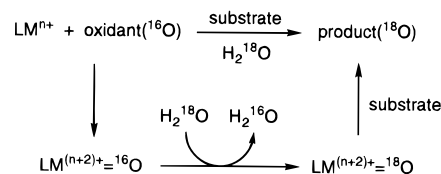
reactions, in which high-valent metal oxo complexes were always suggested as an oxygenating intermediate on the basis of the observation that the oxygen atom in products came from the labeled water.[2a] An alternative mechanism for the oxygen exchange in the iodosylbenzene reaction was proposed, in which iodosylbenzene exchanges its oxygen atom with labeled water prior to the formation of reactive intermediates. This study also proposed that high-valent metal oxo complexes might not rapidly exchange their oxygen atoms with labeled $H_2^{18}O$ in catalytic oxygenation reactions on the basis of the observation that the products yielded in metalloporphyrin-catalyzed oxygenations of hydrocarbons did not contain isotopically labeled oxygen. More recently, Meunier and co-workers observed that half of the oxygen atoms in epoxide product came from the solvent water in the olefin epoxidation by water-soluble manganese porphyrin complex.[3] A "redox tautomerism" was proposed to explain the mechanism of the oxygen exchange between high-valent manganese(V) oxo porphyrin and water in aqueous media.[3a]

In this paper, we describe our detailed studies of labeled water experiments in which organic compounds were oxygenated in

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

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Scheme 2
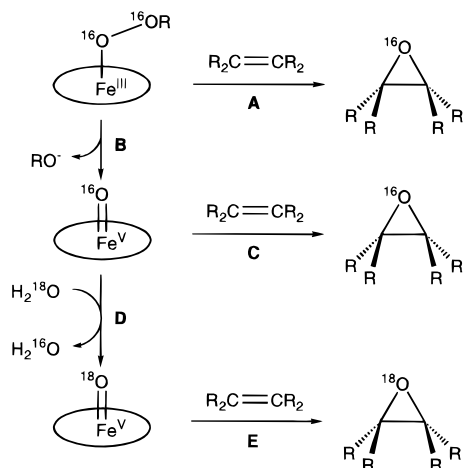
the reactions of iron porphyrin complexes with oxidants (i.e., hydrogen peroxide, *tert*-butyl hydroperoxide, and *m*-chloroperoxybenzoic acid (MCPBA) in the presence of $H_2^{18}O$ in organic solvent system. Reactive intermediates responsible for the oxygenation of hydrocarbons are proposed on the basis of the results obtained by measuring the extent of ^{18}O incorporated from labeled water into the products formed in the catalytic oxygenation reactions performed under various reaction conditions. Mechanistic aspects of the oxygen exchange between the reactive intermediates and labeled water are discussed as well.

Results and Discussion

Determination of Reactive Intermediate Responsible for Olefin Epoxidation and Alkane Hydroxylation. It has been proposed that a high-valent iron oxo species, which is generated by the heterolytic O–O bond cleavage of Fe^{III}–OOR, is the reactive intermediate for olefin epoxidation in the reactions of iron porphyrin complex with hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA.[4] In contrast, peroxyl radicals (i.e., ROO•) have also been proposed as an epoxidizing agent in the iron porphyrin-catalyzed epoxidation of olefins by alkyl hydroperoxides.[5] We therefore studied iron porphyrin complex-catalyzed epoxidation of cyclooctene by the oxidants (i.e., hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA) in the presence of $H_2^{18}O$ to determine whether a high-valent iron oxo species was involved in the olefin epoxidation reactions by analyzing the extent of ^{18}O incorporated from $H_2^{18}O$ into the products. If a common intermediate (i.e., high-valent iron oxo porphyrin complex) was generated in all of the reactions, the oxide product formed should contain the same number of ^{18}O percentage incorporated.

Since it is possible that the rate of oxygen exchange between the high-valent iron oxo species and labeled water (Scheme 2, pathway D) might be comparable to that of oxygen transfer from the high-valent iron oxo intermediate to substrate (Scheme 2, pathway C), we performed the reactions with only a small amount of olefin to give enough time for oxygen exchange

(4) (a) Traylor, T. G.; Kim, C.; Richards, J. L.; Xu, F.; Perrin, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 3468–3474. (b) Traylor, T. G.; Tsuchiya, S.; Byun, Y.-S.; Kim, C. *J. Am. Chem. Soc.* **1993**, *115*, 2775–2781. (c) Traylor, T. G.; Fann, W.-P.; Bandyopadhyay, D. *J. Am. Chem. Soc.* **1989**, *111*, 8009–8010. (d) Lee, K. A.; Nam, W. *Bull. Korean Chem. Soc.* **1996**, *17*, 669–671.

(5) (a) He, G.-X.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 2747–2753. (b) Labeque, R.; Marnett, L. J. *J. Am. Chem. Soc.* **1989**, *111*, 6621–6627. (c) Labeque, R. L.; Marnett, L. J. *Biochemistry* **1988**, *27*, 7060–7070.

Table 1. Percentages of ^{18}O-Incorporation from $H_2^{18}O$ into the Oxide Product in the Epoxidation of Cyclooctene by Various Oxidants Catalyzed by $Fe(F_{20}TPP)Cl$[a]

oxidants	^{18}O (%) in added water	^{18}O (%) in epoxide product[b]	yield (%) of epoxide product[c]
H_2O_2	94	48 ± 5	36
t-BuOOH	94	42 ± 5	18
MCPBA	95	44 ± 4	68

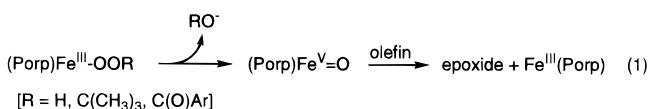[a] Reactions were run in a solution containing $Fe(F_{20}TPP)Cl$ (2.5×10^{-4} mmol), cyclooctene (0.01 mmol), and $H_2^{18}O$ (50 µL, 95% ^{18}O enrichment, 2.6 mmol of $H_2^{18}O$) in a mixture (0.5 mL) of CH_3OH/CH_2Cl_2 (3:1). Oxidant (0.01 mmol) was added to the reaction solution, and the solution was stirred for 0.5 h at room temperature. [b] A control reaction for the stability of cyclooctene oxide, performed by stirring cyclooctene oxide (0.01 mmol) in a solution containing $Fe(F_{20}TPP)Cl$ (2.5×10^{-4} mmol) and $H_2^{18}O$ (50 µL, 95% ^{18}O enrichment, 2.6 mmol of $H_2^{18}O$), showed that the oxygen of cyclooctene oxide did not exchange with labeled water under the reaction conditions. [c] Based on the amounts of oxidants added.

Table 2. Percentages of ^{18}O in Products Obtained in the Competitive Oxygenation of Cyclooctene and Cyclohexane by MCPBA[a]

products	^{18}O (%) in products	yield (%) of products[b]
cyclooctene oxide	50 ± 5	62
cyclohexanol	49 ± 5	6

[a] Reactions were run in a solution containing $Fe(F_{20}TPP)Cl$ (2.5×10^{-4} mmol), cyclooctene (0.01 mmol), cyclohexane (1 mmol), and $H_2^{18}O$ (50 µL, 95% ^{18}O enrichment, 2.6 mmol of $H_2^{18}O$) in a solvent mixture (0.5 mL) of CH_3OH/CH_2Cl_2 (3:1). Oxidant (0.01 mmol) was added to the reaction solution, and the solution was stirred for 0.5 h at room temperature. [b] Based on the amounts of oxidants added.

between the high-valent iron oxo species, if such a species is indeed formed, and labeled water (Scheme 2, pathway D) by decreasing the rate of olefin epoxidation (Scheme 2, pathway C). As shown in Table 1, the percentages of ^{18}O found in the oxide product formed in the epoxidation of cyclooctene by hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA were the same within the experimental error, leading us to conclude that a common high-valent iron oxo porphyrin complex was indeed formed and was the reactive intermediate for the olefin epoxidation reactions (eq 1).
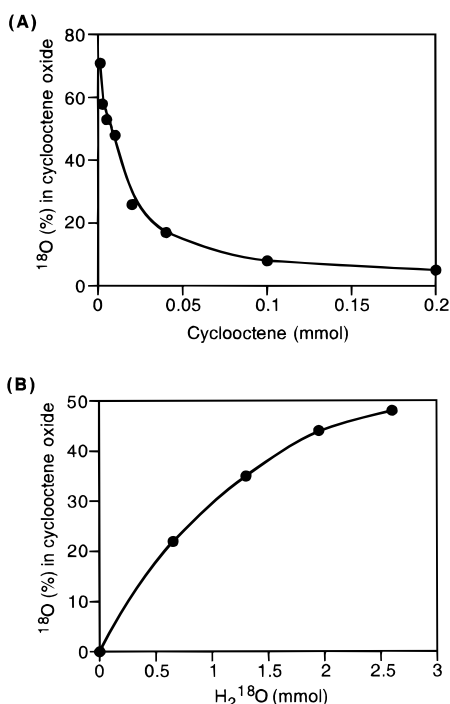
$$(Porp)Fe^{III}\text{-OOR} \xrightarrow{\quad RO^- \quad} (Porp)Fe^V{=}O \xrightarrow{\text{olefin}} \text{epoxide} + Fe^{III}(Porp) \quad (1)$$

$$[R = H, C(CH_3)_3, C(O)Ar]$$

We then studied a competitive oxygenation of cyclooctene and cyclohexane with MCPBA in the presence of $H_2^{18}O$ to understand the nature of the intermediate for alkane hydroxylation.[4d] Analysis of the cyclooctene oxide and cyclohexanol products formed in the competitive reaction showed that the amounts of ^{18}O incorporated from labeled water into the oxygenated products were identical (Table 2). Since high-valent iron oxo complex was unambiguously determined to be the reactive intermediate in the cyclooctene epoxidation by MCPBA, the result obtained in the competitive reaction clearly indicated that the same kind of high-valent iron oxo porphyrin complex must be responsible for the hydroxylation of cyclohexane.[6]

Effect of the Olefin and $H_2^{18}O$ Concentrations on the Percentage of ^{18}O Incorporated into the Product. Since the percentages of ^{18}O in the oxide product might be governed by

(6) (a) Groves, J. T.; McClusky, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 859–861. (b) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243–6248.

(A)

(B)

Figure 1. Effects of (A) olefin concentration and (B) the amount of labeled water on the incorporation of [18]O from labeled water into cyclooctene oxide product. Reaction conditions were the same as described in the Experimental Section except that H_2O_2 was used as the oxidant. Cyclooctene oxide was the predominant product, and the percent yield of the product formed in all the reactions was at least 10% based on the H_2O_2 used.

the relative rates of pathway C and D in Scheme 2 as discussed above, we performed the labeled water experiments by varying the amounts of cyclooctene and labeled water in the reaction solution to compare the rate of the oxygen exchange between high-valent iron oxo and labeled water to that of the oxygen transfer from the intermediate to the olefin. When either the amount of olefin in the reaction solution increased (Figure 1A) or the labeled water concentration decreased (Figure 1B), the amount of [18]O incorporated into the oxide product was found to be diminished in the iron porphyrin-catalyzed epoxidation of cyclooctene by hydrogen peroxide. These results clearly demonstrate that the reaction of high-valent iron oxo complex with substrates (Scheme 2, pathway C) was indeed competing with isotopically labeled water that led to oxygen exchange (Scheme 2, pathway D). Moreover, the percentage of [18]O found in the oxide product was 50% when the amounts of cyclooctene and labeled water in the reaction solution were 0.01 and 2.6 mmol (Table 1), respectively, demonstrating that the rate of oxygen transfer from the high-valent iron oxo complex to cyclooctene was faster than that of the oxygen exchange between the intermediate and labeled water under our reaction conditions. It was reported in the previous study[2a] that ^{18}O-incorporation from labeled water into oxygenated products did not occur in the metalloporphyrin-catalyzed oxygenations of organic compounds (i.e., olefin and alkane). The phenomenon of no ^{18}O-incorporation observed in the study can now be rationalized with our results that the oxygen transfer by a high-valent metal oxo complex was much faster than the oxygen exchange reaction when a large amount of substrates was present in the reaction solution. We therefore suggest the use of a small amount of substrate in conducting labeled water experiments, since the product formed in catalytic oxygenation reactions may not contain isotopically labeled oxygen when the reaction is
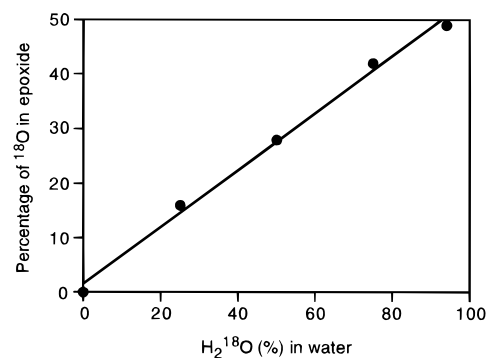
Figure 2. Correlation between the amount of [18]O found in the oxide product and the percentage of $H_2^{18}O$ in water. A slope of 0.52 was obtained with a good linear correlation of $R = 0.997$. See the Experimental Section for reaction procedures. H_2O_2 was used as oxidant. Cyclooctene oxide was the predominant product, and the percent yield of the product was above 35% based on the H_2O_2 used.

Scheme 3
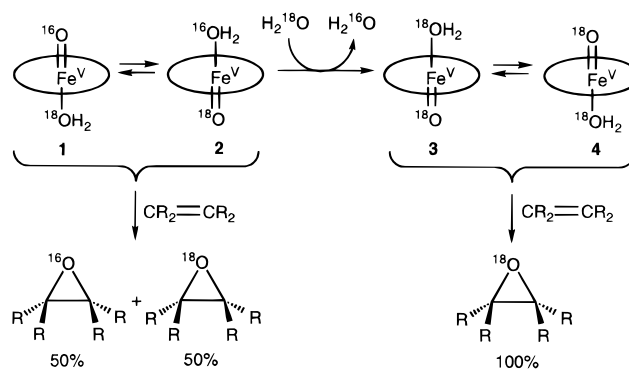
performed in the presence of a large amount of substrate, even though the oxygenating intermediate is a high-valent metal oxo species.

Meunier and co-workers observed that half of the oxygen atom in the oxide product came from the solvent water and half from the oxidant when the olefin epoxidation by water-soluble manganese porphyrin complex was performed in aqueous solution.[3] They proposed a redox tautomerism mechanism to explain a linear correlation with a slope of 0.47 for the percentage of [18]O oxide versus the percentage of $H_2^{18}O$. We also obtained a similar result: the percentage of [18]O in the oxide product linearly increased as the [18]O percentage in water added to the reaction solution increased (Figure 2). Nonetheless, the slope of 0.52 in Figure 2 does not imply that the maximum percentage of [18]O in the oxide product should be half of the labeled water. Since the percentage of [18]O found in the oxide product was above 70% when only a small amount of cyclooctene was used in the epoxidation reaction (Figure 1A), the slope of 0.5 in Figure 2 was accidentally obtained and the slope would be greater than 0.5 if smaller amount of olefin was used. We therefore propose a modified mechanism of the redox tautomerism to explain the high incorporation of [18]O (Scheme 3). If the olefin epoxidation takes place by the iron oxo complexes **1** and **2**, then the oxide product would be expected to contain 50% [18]O, as Meunier et al. suggested. In the case where only a small amount of olefin is present in the reaction medium, the ligated water molecule $H_2^{16}O$ in **2** exchanges with solvent $H_2^{18}O$ to give the iron complexes **3** and **4**. As a result, involvement of **3** and **4** in olefin epoxidation would result in higher ^{18}O-incorporation into the oxide product under our reaction conditions.

Low-Temperature Reactions with Iron Porphyrin Complexes Performed in the Presence of Labeled $H_2^{18}O$. Acyl-

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peroxo iron(III) porphyrin complexes have been proposed to be a potent oxidant for olefin epoxidation in the reactions of iron porphyrin complexes with peracids at low temperature.[7] If the acylperoxo iron complexes are the reactive oxidants for oxygenation reactions, then there will be no ^{18}O-incorporation into the oxide product in labeled water experiments (Scheme 2, pathway A). Therefore, we performed the cyclooctene epoxidation by MCPBA catalyzed by iron porphyrin complexes at −78 °C in the presence of $H_2^{18}O$ and analyzed the cyclooctene oxide product for the ^{18}O-incorporation. The iron complexes that we used were (*meso*-tetrakis(pentafluorophenyl)porphinato)-iron(III) chloride [Fe(F_{20}TPP)Cl], (*meso*-tetrakis(2,6-dichloro-phenyl)porphinato)iron(III) chloride [Fe(TDCPP)Cl], and (*meso*-tetramesitylporphinato)iron(III) chloride [Fe(TMP)Cl]. As shown in Table 3, the percentages of ^{18}O incorporated into the oxide product were found to depend on the nature of the porphyrin ligands bound to iron.[2a] The general trend appears to be that the presence of electron-donating groups on the porphyrin resulted in high ^{18}O-incorporation, whereas iron porphyrin complexes with electron-withdrawing substituents gave no or small amount of ^{18}O enrichment in the product. These results are interpreted as follows.

The observation of the ^{18}O-incorporation into the cyclooctene oxide product in the Fe(TMP)Cl reaction clearly demonstrate that (TMP$^{+\bullet}$)Fe^{IV}=O was formed as the epoxidizing agent at −78 °C.[2b,7a] With the result from Fe(F_{20}TPP)Cl, two possible explanations are considered: that acylperoxo iron(III) porphyrin complex transferred its oxygen to olefin prior to the O−O bond cleavage (Scheme 2, pathway A) or that the rate of oxygen exchange between high-valent iron oxo complex of electro-negatively-substituted porphyrin ligand and labeled water slowed at low temperature (Scheme 2, pathway D). In order to differentiate these two possibilities, we performed spectroscopic studies on the reaction of Fe(F_{20}TPP)Cl and MCPBA at −78 °C in the absence of olefin. When the reaction was monitored by EPR spectroscopy, a rhombic EPR signal ($g_1 = 2.20$, $g_2 = 2.15$, $g_3 = 1.96$) of a six-coordinated low-spin iron(III) complex appeared (Figure 3), indicating the formation of the Fe^{III}-MCPBA complex **5a**.[8] When the same reaction was performed

5   a: R = C(O)Ar
    b: R = H
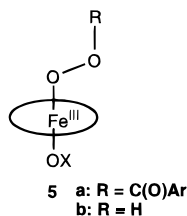
in the presence of cyclooctene, the EPR signal corresponding to **5a** was not detected and the formation of the cyclooctene oxide product was observed, suggesting that **5a** was the epoxidizing agent. We therefore conclude that the lack of oxygen incorporation from labeled water into the oxide product at low temperature was due to the direct oxygen atom transfer by the (F_{20}TPP)Fe^{III}−MCPBA complex (Scheme 2, pathway A). From the reaction of Fe(TDCPP)Cl, the data in Table 3 indicates that a small but significant amount of (TDCPP$^{+\bullet}$)-Fe^{IV}=O was generated in the catalytic epoxidation by MCPBA

Table 3. Epoxidation of Cyclooctene by MCPBA and Iron Porphyrin Complexes Performed in the Presence of $H_2^{18}O$ at −78 °C and at 20 °C[a]

iron porphyrins	percentage of ^{18}O in epoxide product[b]	
	−78 °C	20 °C
Fe(F_{20}TPP)Cl	0 ± 0 (59)	44 ± 4 (68)
Fe(TDCPP)Cl	8 ± 1 (65)	33 ± 3 (62)
Fe(TMP)Cl	16 ± 2 (13)	28 ± 3 (15)

[a] Reactions were run in a solution containing iron porphyrin complex (2.5×10^{-4} mmol), cyclooctene (0.01 mmol), and $H_2^{18}O$ (50 µL, 95% ^{18}O enrichment, 2.6 mmol of $H_2^{18}O$) in a mixture (0.5 mL) of CH_3OH/CH_2Cl_2 (3:1). MCPBA (0.01 mmol) diluted in CH_3OH was added to the reaction solution, and the solution was stirred for 2 h at −78 °C and for 0.5 h at 20 °C. For the low temperature reaction, saturated aqueous $Na_2S_2O_3$ was added to prevent possible oxidation reactions at higher temperature. The resulting solution was directly analyzed by GC/MS. [b] Numbers in parentheses are the percent yield of cyclooctene oxide based on the amount of MCPBA added.
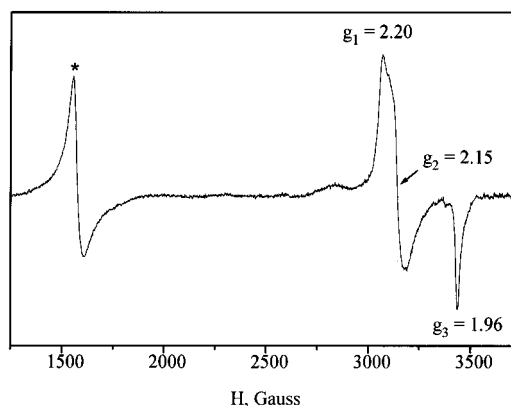
Figure 3. The X-band EPR spectrum obtained in the reaction of Fe(F_{20}TPP)Cl and MCPBA at −78 °C. The signal with the asterisk (g = 4.3) arose from decomposed porphyrin compound. See the Experimental Section for detailed reaction conditions. Instrumental parameters: temperature, 77 K; microwaves, 9.44 GHz at 5 mW; modulation amplitude, 10 G.

at −78 °C under our reaction conditions.[9,10] We conclude from these results that an iron complex with electron-withdrawing substituents on porphyrin ligand forms a relatively stable acylperoxo iron(III) complex at low temperature and that this intermediate transfers an oxygen atom to olefin prior to the formation of high-valent iron oxo complex.[7a] In contrast, the introduction of electron-donating groups on the phenyl groups facilitates the O−O bond cleavage of the acylperoxo group via the "push-effect",[7a,11] resulting in the formation of high-valent iron oxo porphyrin complex readily even at low temperature. Therefore, the involvement of Fe^{III}−OOR species in the epoxidation reaction depends on the relative rates of the direct oxygen atom transfer (k_1) and the O−O bond cleavage (k_2) as shown in Scheme 4.

We were able to conclude unambiguously by carrying out labeled water experiments that the intermediate generated in the reaction of an electronegatively-substituted iron porphyrin complex (Fe(F_{20}TPP)Cl) with MCPBA at low temperature was **5a**. We then studied the epoxidation of cyclooctene by H_2O_2 at low temperature in the presence of $H_2^{18}O$, in order to

(7) (a) Machii, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1995**, *117*, 6691−6697. (b) Watanabe, Y.; Yamaguchi, K.; Morishima, I.; Takehira, K.; Shimizu, M.; Hayakawa, T.; Orita, H. *Inorg. Chem.* **1991**, *30*, 2581−2582.
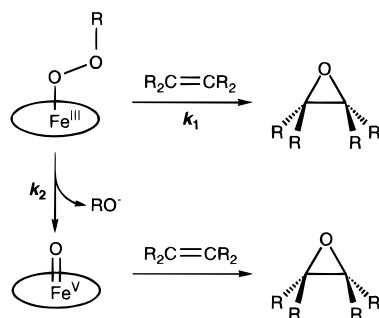
(8) (a) Tajima, K.; Jinno, J.; Ishizu, K.; Sakurai, H.; Ohya-Nishiguchi, H. *Inorg. Chem.* **1989**, *28*, 709−715. (b) Tajima, K. *Inorg. Chim. Acta* **1990**, *169*, 211−219. (c) Sam, J. W.; Peisach, J. *Biochemistry* **1993**, *32*, 1488−1491.

(9) (a) Mandon, D.; Weiss, R.; Jayaraj, K.; Gold, A.; Terner, J.; Bill, E.; Trautwein, A. X. *Inorg. Chem.* **1992**, *31*, 4404−4409. (b) Sugimoto, H.; Tung, H.-C.; Sawyer, D. T. *J. Am. Chem. Soc.* **1988**, *110*, 2465−2470.

(10) It has been reported that the (TDCPP)Fe^{III}−MCPBA adduct is stable for more than 2 h in dichloromethane solution at −78 °C and is the sole oxidant for olefin epoxidation. See ref 7a.
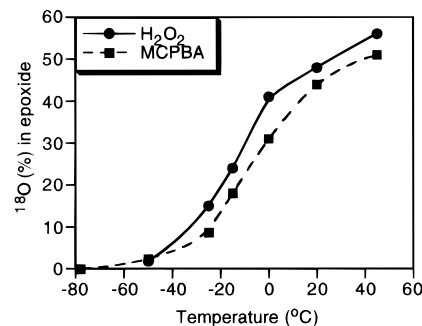
(11) (a) Yamaguchi, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1993**, *115*, 4058−4065. (b) Fujii, H. *J. Am. Chem. Soc.* **1993**, *115*, 4641−4648.

Scheme 4

Figure 4. Temperature effect on the [18]O percentage incorporated from labeled water into product. See the Experimental Section for reaction conditions. Cyclooctene oxide was the predominant product, and the percent yield of the product was at least 30% based on the H_2O_2 used.

understand whether an iron(III) porphyrin hydroperoxide complex (**5b**) is able to transfer an oxygen atom to olefins prior to the formation of high-valent iron oxo species. As shown in Figure 4, less than 2% of oxygen in the oxide product was found to come from labeled water at −50 °C, suggesting that **5b** is a plausible intermediate for olefin epoxidation at low temperature as well.[12] The direct participation of (Porp)Fe[III]−OOH species in oxidation mechanisms has been reported in recent years.[15] In non-heme iron systems, iron(III) hydroperoxide complexes of non-porphyrin ligands[16] and "activated bleomycin"[17] have been suggested to be the intermediates for oxidation reactions. We suggest, on the basis of the result obtained in the ^{18}O-labeled water experiment, that it is highly possible that an iron porphyrin complex with highly electron-withdrawing substituents on the porphyrin ligand is capable of directly transferring an oxygen atom from Fe[III]−OOH to easily oxdizable organic substrates, (e.g., olefins).

Temperature Effect on the Extent of ^{18}O-Incorporation into the Product. We established that high-valent iron oxo and Fe[III]−OOR porphyrin complexes were the epoxidizing agents at room temperature and at −78 °C, respectively. We then studied the dependence of the relative rates for the high-valent iron oxo formation (k_2 in Scheme 4) and the oxygen atom transfer (k_1 in Scheme 4) by the Fe[III]−OOR complexes on reaction temperature by measuring the percentage of [18]O in the

oxide product formed in the catalytic epoxidation of cyclooctene by MCPBA and H_2O_2 in the presence of Fe(F$_{20}$TPP)Cl at various temperatures. As shown in Figure 4, the [18]O enrichment in the oxide product gradually increased as the reaction temperature raised from −78 to 45 °C in both the MCPBA and H_2O_2 reactions. This result indicates that as the reaction temperature became high, the rate of the O−O bond cleavage was enhanced (k_2 in Scheme 4), resulting in the fast formation of high-valent iron oxo porphyrin complex. As a result, the amount of [18]O incorporated into the oxide product increased. The temperature dependence study also suggests that both the high-valent iron oxo and Fe[III]−OOR [R = H, C(O)Ar] porphyrin complexes participated in the olefin epoxidation even at high temperature.[18]

Imidazole Effect on the ^{18}O-Incorporation into the Product. The source of the oxygen in oxygenated products formed in monooxygenase enzyme-catalyzed reactions is dioxygen not solvent water.[19] This implies that there is no oxygen exchange between oxygenating intermediates and water in the enzyme systems. In cytochrome P-450, the high-valent iron oxo species is believed to be the intermediate, suggesting that the oxygen of the high-valent iron oxo intermediate does not exchange with water. The lack of oxygen exchange might be attributed to the structure of the cytochrome P-450, in which a cysteinato ligand bound to an axial position prevents water from coordinating to iron. In order to investigate this hypothesis, we examined the effect of blocking an axial position of iron porphyrin complex with an imidazole ligand on the extent of ^{18}O-incorporation from labeled water into the product. Since imidazole binds to iron to form both five- and six-coordinated iron porphyrin complexes,[20] titration of the iron porphyrin complex with 5-chloro-1-methylimidazole was monitored by following the spectral changes with UV−vis spectrophotometer. Addition of 5-chloro-1-methylimidazole to the solution of Fe(F$_{20}$TPP)$^+$ in a solvent mixture of methanol and dichloromethane resulted in the appearance of a new Soret band at 390 nm (Figure 5A). Upon subsequent additions of the imidazole to the resulting solution, the Soret band at 390 nm disappeared and the appearance of

(12) We monitored the reaction of Fe(F$_{20}$TPP)Cl with H_2O_2 at −50 °C with EPR spectroscopy. The EPR spectrum taken at −50 °C did not show the rhombic EPR signal of low-spin iron(III) complex, as obtained in the MCPBA reaction, but exhibited a characteristic absorption of high-spin iron(III) at $g = 5.5$. Since it has been reported in some cases that the alkylperoxo complex of non-porphyrin iron(III)[13] and acylperoxo iron(III) porphyrin complexes[11a,14] show the characteristic EPR spectra of a high-spin iron(III) complex, the high-spin iron(III) complex may be an iron(III) porphyrin hydroperoxide complex, (F$_{20}$TPP)Fe[III]-OOH.

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(18) The involvement of acylperoxo Fe(III) porphyrin complex in the epoxidation of olefins at high temperatures was achieved by taking EPR spectra in the reactions of Fe(F$_{20}$TPP)Cl and MCPBA. We obtained the same type of a rhombic EPR signal as shown in Figure 3 until the reaction temperature reached −10 °C, indicating that a significant amount of acylperoxo Fe(III) porphyrin complex was still responsible for the cyclooctene epoxidation at high temperature.

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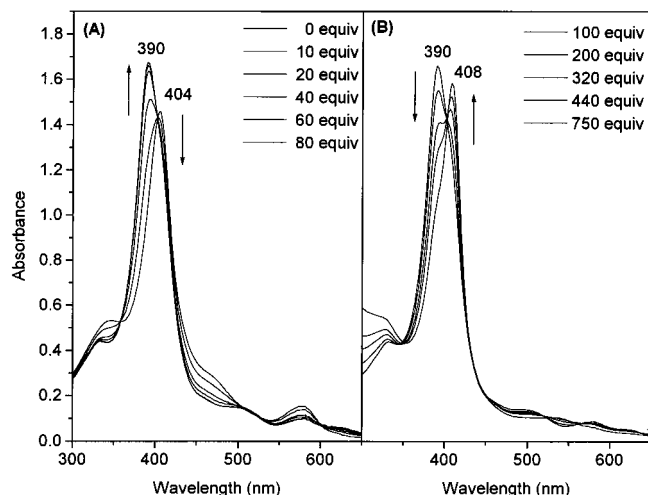
Figure 5. UV-vis spectral changes obtained during the incremental addition of 5-chloro-1-methylimidazole to the solution of Fe(F$_{20}$TPP)-Cl in a solvent mixture of CH$_3$OH/CH$_2$Cl$_2$ (3:1).
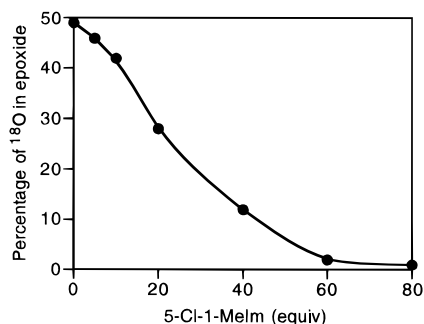
Figure 6. Imidazole effect on the amount of ^{18}O incorporated from H$_2$^{18}O into the cyclooctene oxide product yielded in the catalytic epoxidation of cyclooctene by Fe(F$_{20}$TPP)Cl and H$_2$O$_2$. See the Experimental Section for reaction conditions. The yield of the cyclo-octene oxide product was not significantly affected by the imidazole added to the reaction solution.

another Soret band at 408 nm was observed (Figure 5B). We therefore postulate the following reaction scheme (eq 2). The
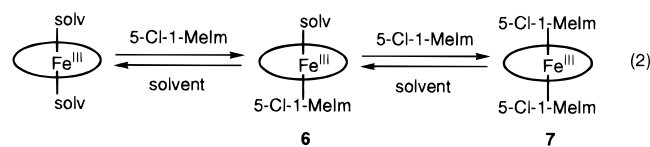
iron complex with the Soret band at 390 nm is **6** and the iron complex with the Soret band at 408 nm is **7**. In aprotic solvent systems, iron porphyrin complexes are known to favor the formation of bisimidazole complexes. In our reaction conditions, such as the presence of protic solvent, a large excess of imidazole is required for the formation of **7**.

On the basis of the UV-vis spectral studies, we measured the percentages of ^{18}O in the oxide product obtained in olefin epoxidation reactions in which various amounts of 5-chloro-1-methylimidazole were added until the iron porphyrin complex was completely converted to **6**. The amount of ^{18}O incorporated into the product was found to diminish as the amount of 5-chloro-1-methylimidazole added to the reaction solution increased (Figure 6). We conclude from these data that when the axial position opposite to the oxo group of the high-valent iron oxo porphyrin is blocked by a ligand, the high-valent iron oxo porphyrin complex cannot exchange its oxygen with water, giving the result that the oxygen of the product was not from the labeled water but from the oxidant (Scheme 5). It has been

Scheme 5
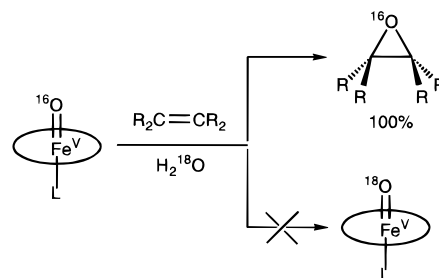
shown in manganese porphyrin systems that the addition of pyridine prevented the oxygen exchange with high-valent manganese(V) oxo complex.[21] Thus, one can conclude that high-valent metal oxo intermediates do not show any oxygen exchanges for the complexes that do not have an appropriate binding site for water.[22-24]

Conclusion

We reported the following significant findings by studying the iron porphyrin complex-catalyzed oxygenations of organic compounds in the presence of labeled water. (1) The reactive intermediate generated in the reactions of Fe(F$_{20}$TPP)Cl and oxidants (i.e., hydrogen peroxide, *tert*-butyl hydroperoxide, and MCPBA) is the common high-valent iron oxo porphyrin complex at room temperature. (2) Electronegatively-substituted iron porphyrin complexes form relatively stable (Porp)Fe^{III}−OOR [R = H, C(O)Ar] species at low temperature, and these intermediates are capable of epoxidizing olefins prior to the O−O bond cleavage. (3) The oxygen exchange between high-valent iron oxo complex and labeled water is slow in rate compared to that of the oxygen transfer from the intermediate to olefin. (4) When the axial position of high-valent iron oxo intermediates is coordinated by a ligand, oxygen exchange cannot occur at a fast rate. (5) Finally, for observed ^{18}O-incorporation from H$_2$^{18}O into products in catalytic oxygenation reactions, high-valent metal oxo complexes can be proposed as a reactive intermediate for oxygen atom transfer. However, care should be taken in determining the intermediacy of high-valent iron oxo complexes based on the results obtained in the labeled water experiments since the extent of ^{18}O incorporated into products depends on the reaction conditions and/or the structure of the catalysts.

Experimental Section

Materials. Methanol and dichloromethane were refluxed over CaH$_2$ and distilled under argon. All chemicals obtained from Aldrich Chemical Co. were of the best available purity and used without further purification. Fe(F$_{20}$TPP)Cl, H$_2$^{18}O (95% ^{18}O enrichment), and MCPBA (65%) were purchased from Aldrich. The purity of MCPBA was

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(23) The observation of no oxygen exchange between the oxo Cr(V) complex of heteropolytungstate and labeled water might be due to the fact that the water molecule cannot bind to the axial position of the chromium oxo complex. Khenkin, A. M.; Hill, C. L. *J. Am. Chem. Soc.* **1993**, *115*, 8178−8186.

(24) The oxygen atom of the Fe^{IV}=O group in compound II of horseradish peroxidase has been reported to exchange rapidly with H$_2$^{18}O, although the axial position of horseradish peroxidase is coordinated by a histidine residue. The authors suggested that the oxygen exchange takes place at the same site of the oxo group. (a) Hashimoto, S.; Tatsuno, Y.; Kitagawa, T. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 2417−2421. (b) Hashimoto, S.; Teraoka, J.; Inubushi, T.; Yonetani, T.; Kitagawa, T. *J. Biol. Chem.* **1986**, *261*, 11110−11118.

determined by iodometric analysis.[25] H_2O_2 (30%) and *tert*-butyl hydroperoxide (70%) were purchased from Fluka and Sigma, respectively. Fe(TDCPP)Cl and Fe(TMP)Cl were obtained from Mid-Century Chemicals.

Instrumentation. Product analyses were performed on a Hewlett-Packard 5890 II gas chromatograph interfaced with Hewlett-Packard Model 5988 mass spectrometer. ESR spectra were obtained on Bruker ESP-300 spectrometer. UV-vis spectra were recorded on a Hewlett-Packard 5890 spectrophotometer.

Reaction Conditions. Reactions were performed at ambient temperatures under argon unless otherwise indicated. All reactions were run at least in duplicate, and the data reported represent the average of these reactions.

In general, the iron porphyrin complex (2.5×10^{-4} mmol) was dissolved in a solvent mixture (0.5 mL) of CH_3OH/CH_2Cl_2 (3:1) containing cyclooctene (0.01 mmol) and $H_2^{18}O$ (50 μL, 95% ^{18}O enrichment). After oxidants (0.01 mmol dissolved in CH_3OH) were added to the reaction mixture, the resulting solution was directly analyzed by GC/MS. The ^{16}O and ^{18}O compositions in cyclooctene oxide were determined by the relative abundances of mass peaks at $m/z = 111$ for ^{16}O and $m/z = 113$ for ^{18}O. For the competitive reaction,

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the ^{16}O and ^{18}O compositions in cyclohexanol were determined by the relative abundances of mass peaks at $m/z = 57$ for ^{16}O and $m/z = 59$ for ^{18}O.

EPR Measurement. A solvent mixture of CH_3OH/CH_2Cl_2 (3:1) containing Fe($F_{20}TPP$)Cl (5 mM) in an EPR tube was cooled to −78 °C. After 50 equiv of MCPBA (50 μL, 2 M in methanol) was added, the reaction solution was immediately frozen by liquid nitrogen for EPR measurement. An identical reaction was performed at −78 °C in the presence of cyclooctene (0.25 M).

UV-vis Measurements. To a solution of Fe($F_{20}TPP$)Cl (0.017 mM), prepared in a solvent mixture of CH_3OH/CH_2Cl_2 (3:1) were incrementally added appropriate amounts of 5-chloro-1-methylimidazole diluted in a methanol solution. Spectral changes were directly monitored by stirring the resulting solution with a magnetic bar in a UV cuvette (1 cm pathlength).