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Hydroxylation of Aliphatic Hydrocarbons with *m*-Chloroperbenzoic Acid Catalyzed by Electron-Deficient Iron(III) Porphyrin Complexes

Mi Hee Lim, Yoon Jung Lee, Yeong Mee Goh, Wonwoo Nam,* and Cheal Kim,*,†

Department of Chemistry and Center for Cell Signaling Research, Ewha Womans University, Seoul 120-750, Korea

†Department of Fine Chemistry, Seoul National Polytechnic University, Seoul 139-743, Korea

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The catalytic hydroxylation of aliphatic hydrocarbons by *m*-chloroperbenzoic acid (MCPBA) has been studied in the presence of elecrtron-deficient iron(III) porphyrin complexes. High yields of alcohol products were obtained with small amounts of ketone formation under mild reaction conditions. The stereospecificity and regioselectivity of the iron porphyrin complexes have been investigated in hydroxylation reactions as well. The hydroxylation of alkanes has been performed in the presence of isotopically ^{18}O-labeled water, $H_2{}^{18}O$, in order to understand the effects of the electronic nature of iron porphyrin complexes, the concentration of $H_2{}^{18}O$, the C–H bond strength of alkanes, and the reaction temperature on the ^{18}O-incorporation from the labeled water into alcohols. We found that the amounts of ^{18}O incorporated into the alcohol products varied in the reactions; these results were interpreted with that the reaction of oxygen atom transfer from a high-valent iron oxoporphyrin complex to alkanes competes with that of oxygen atom exchange between the intermediate and labeled water that leads to ^{18}O-incorporation from $H_2{}^{18}O$ into the alcohol products. Deuterium kinetic isotope effects (KIEs) in the alkane hydroxylations by the iron porphyrin complexes and MCPBA have been studied with a mixture of cyclohexane and cyclohexane-d_{12}. The KIE values obtained in the reactions were found to depend significantly on the nature to the iron porphyrin complexes. The temperature dependence of k_H/k_D was also studied from −40 to 25 °C and the parameters of Arrhenius equation (i.e., the pre-exponential factor ratio, A_H/A_D, and the isotopic difference of C–H and C–D bond activation energies, $E_a(D)–E_a(H)$) were determined.

Cytochrome P-450 enzymes are capable of catalyzing a variety of oxidation reactions, including the most energetically difficult hydroxylation of unactivated C–H bonds of alkanes under mild reaction conditions.[1] Since the selective oxidation of the C–H bonds of alkanes is of importance in both synthetic chemistry and industrial processes, biomimetic hydroxylation reactions with synthetic iron(III) porphyrin complexes have attracted much attention for the last two decades.[2] Groves et al. were the first to report that a simple iron porphyrin complex, (*meso*-tetraphenylporphinato)iron(III) chloride [Fe(TPP)Cl], catalyzes the hydroxylation of alkanes by iodosylbenzene (PhIO).[3] Since then, much effort has been taken to improve the catalytic activity of the iron porphyrin complexes. An important finding for this was the introduction of electron-withdrawing substituents into the phenyl groups of the porphyrin ligand.[4] The reactivity of the electron-deficient iron porphyrins was greatly enhanced and the oxidative degradation of the porphyrin ligand was dramatically diminished. Even more effective iron porphyrin catalysts were achieved when the porphyrin ring was fully halogenated.[5] Therefore, the electronegatively-substituted iron porphyrins turned out to be remarkable catalysts with fast rates and high product yields in the oxidation reactions of hydrocarbons, even for the hydroxylation of poorly reactive alkanes, such as pentane and heptane.[6]

The most frequently-used oxidant in the hydroxylation of alkanes by iron porphyrin complexes was iodosylbenzenes.[2] Other primary oxidants used in the hydroxylation reactions were NaOCl, O_2, H_2O_2, alkyl hydroperoxides, O_3, and $KHSO_5$.[2] Although *m*-chloroperbenzoic acid (MCPBA) has long been employed as a useful oxidant in generating a reactive intermediate (i.e., a high-valent iron(IV) oxo porphyrin cation radical)[7] and in studying the mechanisms of O–O bond activation by iron porphyrin complexes,[8] this oxidant has been rarely used as terminal oxidant in the catalytic hydroxylation of alkanes. This is probably due to that MCPBA has been shown to be a less effective oxidant than PhIO in an electron-rich iron porphyrin-catalyzed oxidation reactions.[3b] However, we found in this study that the reactions of MCPBA with electron-deficient iron porphyrins hydroxylate aliphatic hydrocarbons to give the corresponding alcohols efficiently. We now report the results of the hydroxylations of aliphatic hydrocarbons by MCPBA catalyzed by electron-deficient iron(III) porphyrin complexes such as Fe(F_{20}TPP)Cl (**1**, F_{20}TPP = *meso*-tetrakis(pentafluorophenyl)porphyrin), Fe(TDFPP)Cl (**2**, TDFPP = *meso*-tetrakis(2,6-difluorophenyl)porphyrin), Fe(TDCPP)Cl (**3**, TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin), and Fe(TF_4TMAP)(CF_3SO_3)$_5$ (**4**, TF_4TMAP = *meso*-tetrakis(2,3,5,6-tetrafluoro-4-trimethylammonio)porphyrin) (see Chart 1 for structures). Other mechanistic studies such as ^{18}O-labeled water experiments and deuterium kinetic isotope effects in the hydroxylation of alkanes by MCPBA are presented as well.

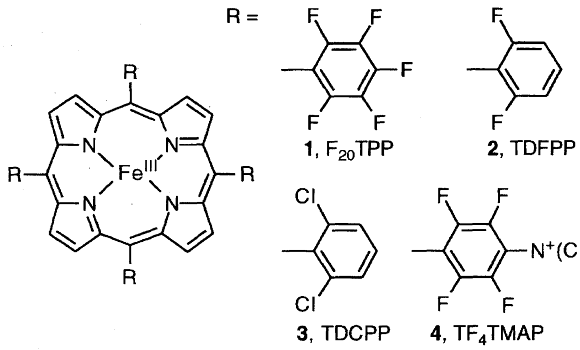


Chart 1. Structure of iron(III) porphyrin complexes used in this study.

Experimental

Materials. Acetonitrile (anhydrous) and dichloromethane (anhydrous) were obtained from Aldrich Chemical Co. and used without further purification. All chemicals obtained from Aldrich Chemical Co. were of the best available purity and used without further purification. $H_2{}^{18}O$ (95% ^{18}O enriched) and MCPBA (65% were purchased from Aldrich. Purity of MCPBA was determined by iodometric analysis.[9] $Fe(TF_4TMAP)(CF_3SO_3)_5$,[10] Fe(TDFPP)-Cl,[11] and Fe(TDCPP)Cl[7d] were obtained from Mid-Century Chemicals. $Fe(F_{20}TPP)Cl$[4g] was obtained from Aldrich. Fe(TDFPP)-(CF_3SO_3), $Fe(TDCPP)(CF_3FO_3)$, and $Fe(F_{20}TPP)(CF_3SO_3)$ were prepared by stirring the chloride iron(III) porphyrins with 1.2 molar amount of $Ag(CF_3SO_3)$ followed by filtering through a 0.45-μM filter. (1 M = 1 mol dm^{-3}) The resulting solution was used immediately for further studies.

Instrumentation. Product analyses were performed on either a Hewlett–Packard 5890 II Plus gas chromatograph interfaced with Hewlett–Packard Model 5989B mass spectrometer or a Donam Systems 6200 gas chromatograph equipped with a FID detector using 30-m capillary column (Hewlett–Packard, HP-1, HP-5, and Ultra 2). UV-vis spectra were recorded on a Hewlett–Packard 8453 spectrophotometer.

Electrochemical measurements were made with a BAS 50W (Bioanalytical Systems, USA) potentiostat. A conventional three-electrode system was employed with $Ag/AgNO_3$ (0.01 M) in CH_3CN reference, glassy carbon working, and Pt wire auxillary electrodes. The reported potentials are corrected to SCE by using an experimentally measured conversion factor +0.22 V.

Alkane Hydroxylations. Since the yields and product distributions formed in the hydroxylation reactions were not affected by the presence of molecular oxygen, all of the reactions were performed in air. MCPBA (2.5×10^{-2} mmol) was added to a solution containing an iron porphyrin complex (1.0×10^{-3} mmol) and substrate (2.0 mmol) in a solvent mixture (3.0 mL) of CH_3CN/CH_2Cl_2 (1 : 1) at room temperature. The reaction mixture was stirred for 60 min and then directly analyzed by GC of GC/MS with known authentic samples.

^{18}O-Labeled $H_2{}^{18}O$ Experiments. MCPBA (1.0×10^{-2} mmol, diluted in a solvent mixture (20 μL) of CH_3CN/CH_2Cl_2 (4 : 1)) was added to a solution containing triflate iron(III) porphyrin complexes (1.0×10^{-3} mmol), cyclohexane (0.2 mmol), and $H_2{}^{18}O$ (3 μL, 0.16 mmol, 95% ^{18}O enriched) in a solvent mixture (1 mL) of CH_3CN/CH_2Cl_2 (4 : 1) at room temperature. The reaction mixture was stirred for 90 min and then directly analyzed by GC/MS. ^{16}O and ^{18}O compositions in cyclohexanol were determined by the relative abundances of mass peaks at $m/z = 57$ and 82 for ^{16}O and $m/z = 59$ and 84 for ^{18}O.

The reactions for the hydroxylation of various alkanes in the presence of $H_2{}^{18}O$ were performed as follows: MCPBA (2.4×10^{-3} mmol, diluted in CH_3CN (20 μL)) was added to a solution containing $Fe(TF_4TMAP)(CF_3SO_3)_5$ (2.0×10^{-3} mmol), substrate (0.2 mmol), and $H_2{}^{18}O$ (5 μL, 0.26 mmol, 95% ^{18}O enriched) in a solvent mixture (0.7 mL) of CH_3CN/CH_2Cl_2(6 : 1) at −40 and 25 °C. The reaction mixture was stirred for 10 min and then directly analyzed by GC/MS. ^{16}O and ^{18}O compositions in alcohol products were analyzed by the relative abundances of the following mass peaks: m/z = 71 (^{16}O) and 73 (^{18}O) and 85 (^{16}O) and 87 (^{18}O) for 1,*t*-2-dimethyl-*r*-1-cyclohexanol, m/z = 57 (^{16}O) and 59 (^{18}O) for cyclooctanol, $m/z = 57$ (^{16}O) and 59 (^{18}O) for cyclohexanol, m/z = 45 (^{16}O) and 47 (^{18}O) and 87 (^{16}O) and 89 (^{18}O) for 2-hexanol, m/z = 59 (^{16}O) and 61 (^{18}O) and 73 (^{16}O) and 75 (^{18}O) for 3-hexanol, m/z = 61 (^{16}O) and 63 (^{18}O) for cyclohexanol-d_{12}.

Kinetic Isotope Effects for the Hydroxylation of Cyclohexane by Iron Porphyrin Complexes with MCPBA at Various Temperatures. In order to improve the accuracy for measuring the amount of the deuterated cyclohexanol product, a 1 : 5 mixture of cyclohexane (0.08 mmol) and cyclohexane-d_{12} (0.4 mmol) was used. MCPBA (7.5×10^{-3} mmol, diluted in a solvent mixture (30 μL) of CH_3CN/CH_2Cl_2 (1 : 1)) was added to a solution containing an iron porphyrin complex (5.0×10^{-4} mmol) and substrates in a solvent mixture (1.0 mL) of CH_3CN/CH_2Cl_2 (1 : 1) at different temperatures. The reaction mixture was stirred for 40 min, and then PPh_3 (0.1 mmol, diluted in 0.2 mL of CH_2Cl_2) was added to quench the reaction. The reaction solution was analyzed by GC with known authentic samples.

Results and Discussion

Oxidation and Reduction Potentials of Iron(III) Porphyrins. The first oxidation and the first reduction potentials of the iron(III) porphyrins containing a variety of electron-withdrawing substituents on phenyl groups at the *meso*-position of the porphyrin ring were measured in a 1 : 1 mixture of CH_3CN and CH_2Cl_2 at 25 °C. The oxidation and the reduction of the iron(III) porphyrins exhibited quasi-reversible and reversible waves, respectively, and the redox potentials were taken as the midpoint of cathodic and anodic waves. As the data is shown in Table 1, the oxidation and reduction potentials of the iron porphyrin complexes were well correlated with the electronic nature of the iron porphyrins.[5b,7c,12] Both the oxidation and reduction potentials shifted to more positive values as the electron-withdrawing power of the substituents increased.[7c]

Table 1. Half-Wave First Oxidation and Reduction Potentials of Iron(III) Porphyrins[a]

Iron porphyrins	First oxidation	First reduction
1-Cl	1.47	−0.09
2-Cl	1.30	−0.23
3-Cl	1.29	−0.25
4-$(CF_3SO_3)_5$	1.54	0.27

a) Potentials were taken as the midpoint of reversible anodic and cathodic waves in a solvent mixture of CH_3CN and CH_2Cl_2 (1 : 1), referenced to SCE, tetra-*n*-butylammonium tetrafluoroborate ($TBABF_4$) 0.1 M, and iron porphyrin 0.002 M.

Hydroxylation of Alkanes by MCPBA Catalyzed by

Iron(III) Porphyrin Complexes. The catalytic hydroxylation of alkanes with MCPBA was carried out in the presence of electron-deficient iron(III) porphyrin complexes in a solvent mixture of CH_3CN and CH_2Cl_2 at room temperature. As the results are shown in Table 2, high yields of alcohol products were obtained with the small amounts of ketone formation under mild reaction conditions, indicating that MCPBA is a competent oxidant for the alkane hydroxylations by the iron porphyrin complexes. This result is different from the previous report that MCPBA is a much less effective oxidant than PhIO in the hydroxylation of cyclohexane by Fe(TPP)Cl.[3b] In this reaction, only a small amount of cyclohexanol was yielded with the complete destruction of the iron porphyrin complex. We also found, by taking UV-vis spectra of the reaction solutions during the hydroxylation of cyclohexane, that the iron porphyrins such as **1**, **2**, and **3** were stable in the MCPBA reactions. The Soret band of **1** was not changed after the oxidation reaction, indicating that no porphyrin destruction occurred, whereas about a 25 and 30% loss of the Soret band for **2** and **3** was observed, respectively. However, **4** was completely destroyed in the catalytic reactions.

The stereospecificity for the alkane hydroxylation reactions by the iron porphyrin complexes has been investigated with *cis*-and *trans*-1,2-dimethylcyclohexane and norbornane. The hydroxylations of *cis*- and *trans*-1,2-dimethylcyclohexane afforded the corresponding tertiary alcohol products with high stereoretention, indicating that the hydroxylation reactions by the iron porphyrins and MCPBA are highly stereospecific.[13] In the case of *trans*-1,2-dimethylcyclohexane, alcohols derived from the secondary C–H bonds (i.e., 2,3- and 3,4-dimethyl-1-cyclohexanols) were the major products. This is probably due to the steric effect of the tertiary carbon center of *trans*-1,2-dimethylcyclohexane.[3b] The hydroxylation of norbornane by the iron porphyrin complexes yielded *exo*-norborneol as a major product with a small amount of *endo*-norbornanol formation.[14] However, the amount of the latter product formed was significant enough to imply the involvement of the loss of stereochemistry. This result is in sharp contrast to the results of the *cis*- and *trans*-1,2-dimethylcyclohexane, in which almost complete stereoretention was observed with these substrates. One possible explanation for the relatively high amount of the rearranged product formation with the norbornane substrate is that rotation of 2-norbornyl radical may be faster than that of 1,2-dimethylcyclohexyl radical when the radicals are formed by hydrogen atom abstraction of the C–H bonds by high-valent iron oxo intermediates.[14,15]

The regioselectivity of the hydroxylation of *n*-hexane has been studied with the iron porphyrin complexes as well. The products formed in the reactions were 2- and 3-hexanols and the formation of 1-hexanol was not detected. Worth noting is the ratios of the 2- and 3-hexanol products, since the ratios have been used as a measure of the shape selectivity of a particular iron porphyrin derivative.[18] The iron porphyrins with fluoro substituents at the ortho positions (i.e., **1**, **2**, and **4**) yielded equal amounts of 2- and 3-hexanols, indicating that there is no steric effect with the fluoro substituents. In contrast, the iron porphyrin complex with chloro substituents at *ortho* positions (i.e., **3**) showed a significant preference for the 2-position over 3-position of hexane; this is attributed to the steric effect of the bulky chloro substituent on site selection.

^{18}O-Labeled Water Experiments. High-valent iron(IV) oxo porphyrin cation radical complexes have been generally proposed as oxygenating intermediates in the catalytic cycle of cytochrome P-450 enzymes and iron porphyrin complexes. Since it has been difficult to obtain direct evidence that such species are reactive intermediates responsible for the oxygenation of organic substrates, isotopically labeled water, $H_2{}^{18}O$, has been frequently used to obtain indirect evidence for the intermediacy of the high-valent metal oxo complexes

Table 2. Hydroxylation of Alkanes with MCPBA Catalyzed by Iron(III) Porphyrin Complexes[a]

		Yield (%)[b]			
Substrate	Products	**1**	**2**	**3**	**4**
Cyclohexane	Cyclohexanol	89	62	40	56
	Cyclohexanone	2	4	8	5
cis-1,2-Dimethylcyclohexane	1,*t*-2-Dimethyl-*r*-1-cyclohexanol	74	52	33	66
	1,*c*-2-Dimethyl-*r*-1-cyclohexanol	0	0.4	0.6	0.2
	2,3-and 3,4-Dimethyl-1-cyclohexanol[c]	19	21	20	17
trans-1,2-Dimethylcyclohexane	1,*t*-2-Dimethyl-*r*-1-cyclohexanol	0.3	0	0.3	0.5
	1,*c*-2-Dimethyl-*r*-1-cyclohexanol	21	13	5	15
	2,3-and 3,4-Dimethyl-1-cyclohexanol[c]	50	53	35	38
Norbornane	*exo*-Norborneol	55	48	29	37
	endo-Norborneol	5	3	1	2
	Norcamphor	0	0	1	1
Hexane	1-Hexanol	0	0	0	0
	2-Hexanol	21	20	13	11
	3-Hexanol	22	20	6.6	11

a) See Experimental for detailed reaction procedures. b) Based on the amount of MCPBA used. c) The yield of 3,4-dimethyl-1-cyclohexanol was determined with commercially available 2,3-dimethyl-1-cyclohexanol, with an assumption that the response factors for these alcohols are identical.

in the catalytic oxygenation reactions of organic substrates by metal complexes.[19] When labeled ^{18}O is found to be incorporated from $H_2{}^{18}O$ into oxygenated products, a high-valent metal oxo complex is proposed as an oxygenating species, since the intermediate exchanges its oxygen atom with labeled water prior to the oxygen atom transfer to organic substrates.[7a,19] Recently, we and Groves et al. have shown that the rate of oxygen exchange between a high-valent iron oxo porphyrin complex and $H_2{}^{18}O$ is slower than that of oxygen transfer from the intermediate to olefin substrates in the catalytic epoxidation of olefins[20] and that the ^{18}O-incorporation from the labeled water into the oxide product depends significantly on the electronic nature of the porphyrin ligands bound to iron.[21] Here we report that the results of $H_2{}^{18}O$ experiments studied in the catalytic hydroxylation of alkanes by the iron porphyrin complexes and MCPBA.

When the hydroxylation of cyclohexane by triflate iron(III) porphyrin complexes and MCPBA was performed in the presence of $H_2{}^{18}O$, we observed ^{18}O-incorporation from the labeled $H_2{}^{18}O$ into the cyclohexanol product (Table 3), suggesting that high-valent iron oxo porphyrin intermediates were generated as reactive species in the reactions of the iron porphyrins and MCPBA. The amounts of ^{18}O incorporated into the cyclohexanol product were found to depend on the nature of the iron porphyrin complexes. We also performed labeled water experiments by varying the amounts of labeled water in the hydroxylation of cyclohexane by **4** and MCPBA and found that the amounts of ^{18}O incorporated into cyclohexanol increased as the concentration of labeled water in the reaction mixture increased (Fig. 1). The extent of ^{18}O-incorporation from $H_2{}^{18}O$ into the alcohol products formed in the hydroxylation of various alkanes by **4** and MCPBA was also investigated at 25 and −40 °C. We observed that the amounts of ^{18}O found in the alcohol products depended on the C–H bond strength of the alkanes and the reaction temperatures (Table 4). As the C–H bond strength of alkanes increases,[20] the amount of ^{18}O incorporated into the alcohol product increases. Also, the extent of ^{18}O-incorporation was greater at −40 °C than at 25 °C. All the results observed in the $H_2{}^{18}O$ experiments can be interpreted with the relative rates of oxygen exchange and oxygen atom transfer by high-valent iron oxo intermediates (see Scheme 1).

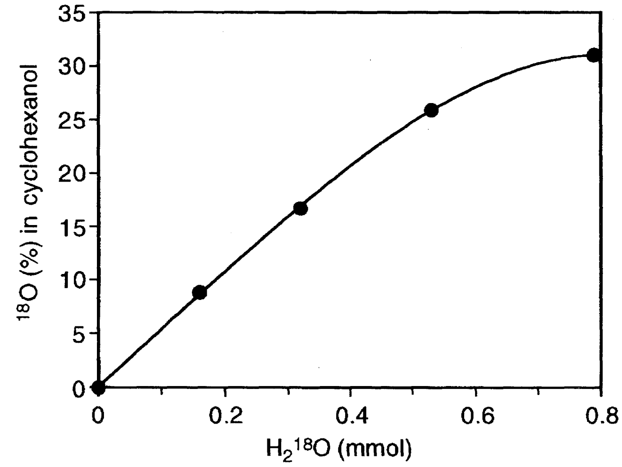


Fig. 1. Correlation between the amount of $H_2{}^{18}O$ in the reaction mixture and the amount of ^{18}O found in cyclohexanol product. Reaction conditions were the same as described in the Experimental except that the amounts of $H_2{}^{18}O$ present in the reaction mixture were varied.

Table 3. Percentages of ^{18}O-Incorporation from $H_2{}^{18}O$ into the Alcohol Product Formed in the Hydroxylation of Cyclohexane by Various Iron(III) Porphyrin Complexes[a,b]

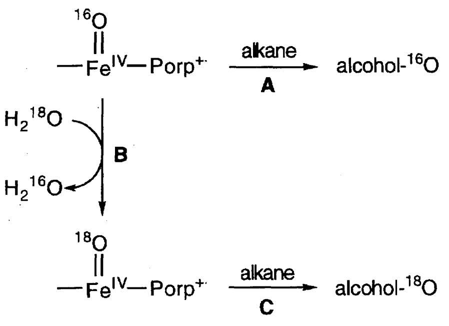
Iron porphyrins	^{18}O (%) in cyclohexanol	Yield (%) of cyclohexanol[c]
1	10±2	44
2	23±3	23
3	14±2	10
4	9±2	49

a) See Experimental for detailed reaction procedures. b) All reactions were run at least in duplicate, and the data reported represent the average of these reactions. c) Based on the amount of MCPBA added.

Table 4. Percentages of ^{18}O Incorporated from $H_2{}^{18}O$ into Alcohol Products in the Hydroxylation of Various Alkanes by **4** and MCPBA[a,b]

		^{18}O (%) found in alcohols	
Substrate	Product	25 °C	−40 °C
cis-1,2-Dimethylcyclohexane	1,*t*-2-Dimethyl-*r*-1-cyclohexanol	21±2	47±4
Cyclooctane	Cyclooctanol	19±2	50±5
Cyclohexane	Cyclohexanol	34±3	62±6
Hexane	2-Hexanol	51±4	68±6
	3-Hexanol	50±4	71±6
Cyclohexane-d_{12}	Cyclohexanol-d_{12}	47±4	78±6

a) See Experimental for detailed reaction procedures. b) All reactions were run at least in duplicate, and the data reported represent the average of these reactions.



Scheme 1.

As we have shown previously in olefin epoxidation reactions,[20] the reaction of oxygen atom transfer from a high-valent iron oxo porphyrin complex to alkanes (Scheme 1, pathway A) is competing with that of oxygen atom exchange between the intermediate and labeled water (Scheme 1, pathway B). When the intermediates formed in the reactions of the iron porphyrin complexes with MCPBA have a high reactivity toward alkane hydroxylation, then small amounts of ^{18}O would be incorporated into alcohol products since the intermediates transfer their oxygen to alkanes with a fast rate. It has been known that iron porphyrins with electron-withdrawing substituents are powerful oxidizing agents;[7c,21] therefore, the oxygen atom transfer by the high-valent iron oxo intermediates containing electron-withdrawing substituents should occur with a fast rate. As a result, small amounts of ^{18}O-incorporation into the cyclohexanol product were observed in the hydroxylation of cyclohexane by the iron porphyrins such as **1** and **4**.[22] The dependence of ^{18}O-incorporation on the concentration of labeled water can also be explained with the relative rates of oxygen atom transfer and oxygen exchange. As the amount of labeled water increases in the reaction solution, the rate of oxygen exchange between the intermediate and $H_2{}^{18}O$ should increase (Scheme 1, pathway B). This is the result of the concentration effect of labeled water on the extent of ^{18}O-incorporation into the cyclohexanol product (Fig. 1). The data for the substrate and temperature effects, shown in Table 4, can also be interpreted similarly. An alkane having a strong C–H bond gives more time for the high-valent iron oxo porphyrin complex to exchange its oxygen with labeled water, resulted in a high ^{18}O-incorporation into the alcohol product. Also, the dependence of ^{18}O-incorporation on the reaction temperatures can be ascribed to the fact that the rate of alkane hydroxylation by a high-valent iron oxo porphyrin intermediate becomes slow at low temperature. Therefore, the high-valent iron oxo porphyrin complex has more time to exchange its oxygen with labeled water at low temperature,[23] resulted in a higher ^{18}O-incorporation at −40 °C than at 25 °C.

Deuterium Kinetic Isotope Effect. The kinetic isotope effects (KIEs) have been often studied in both enzymatic and biomimetic hydroxylation reactions,[24—26] and large KIEs observed in the reactions provided strong evidence that a hydrogen atom abstraction in the "oxygen rebound" mechanism[16] is the rate-determining step for the C–H bond activation of alkanes. The KIE values obtained with cytochrome P-450 models were found to depend on the nature of porphyrin ligands and the kind of metal ions in metalloporphyrins, the oxidant used, the solvent systems, and the reaction temperatures.[25,26] We report here the results of the deuterium isotope effects studied in the alkane hydroxylations by the electron-deficient iron porphyrin complexes and MCPBA with a mixture of cyclohexane and cyclohexane-d_{12} at various temperatures (Table 5). The KIE values given in Table 5 indicate that the rate-determining step for the hydroxylation is the C–H bond cleavage by high-valent iron oxo intermediates. Also, it was found that the KIE values were significantly dependent on the electronic nature of the iron porphyrin complexes.[26] The iron porphyrins with less electron-withdrawing substituents such as **2** and **3** gave relatively high k_H/k_D ratios, and the highly electron-deficient iron porphyrins such as **1** and **4** gave low k_H/k_D ratios. This result is explained with the fact that intermediates with electron-deficient porphyrin ligands are highly reactive toward oxygen atom transfer reactions;[21] therefore, the electron-deficient iron porphyrins are less selective in the competitive hydroxylations of cyclohexane and cyclohexane-d_{12}, giving relatively low k_H/k_D values. Although we tried to include the reactivity of (*meso*-tetramesitylporphinato)iron(III) chloride [Fe(TMP)Cl], which is an electron-rich iron porphyrin complex and has been used in other studies,[25—27] in this study, it was not successful because this complex yielded only a small amount of cyclohexanol product (< 3% based on MCPBA used) and was completely destroyed during the catalytic hydroxylation reaction under our reaction conditions.

The temperature dependence of KIEs could be investigated in the cyclohexane hydroxylations by the iron porphyrin complexes and MCPBA between −40 and 25 °C, since the yields of cyclohexanol product formed in the reactions were high even at low temperatures. As the results are shown in Table 5, the KIE values increased as the reaction temperature was lowered. Since the temperature dependence of k_H/k_D is based on the Arrhenius equation (Eq. 1),[25,26]

$$\frac{k_H}{k_D} = \frac{A_H}{A_D}\exp\{[E_a(D) - E_a(H)]/RT\} \qquad (1)$$

the pre-exponential factor ratio, A_H/A_D, and the difference

Table 5. KIE Values Obtained in the Hydroxylation of Cyclohexane by Iron Porphyrin Complexes and MCPBA at Various Temperatures[a,b]

Temperature °C	k_H/k_D 1	2	3	4
25	5.2	7.0	7.6	3.9
0	6.6	8.2	9.7	4.9
−20	8.0	11	12	5.4
−40	9.7	13	14	6.4
A_H/A_D	0.57	0.85	0.81	0.72
$E_a(D) - E_a(H)$[c]	1.3	1.3	1.3	1.0

a) See Experimental for detailed reaction procedures. b) All reactions were run at least in triplicate, and the data reported represent the average of these reactions. c) In units of kcal mol^{-1}.

of C–H and C–D bond activation energies, $E_a(D)-E_a(H)$, were determined by plotting ln (k_H/k_D) vs. $1/T$. The correlation was good as shown in Fig. 2, and the values of the pre-exponential factor ratios and the activation energy differences determined were listed in Table 5. With the date of k_H/k_D, A_H/A_D, and $E_a(D)-E_a(H)$, a possibility of tunneling contribution to the hydroxylation of alkanes by electron-deficient iron porphyrins was examined, since it has been shown previously that the tunneling contribution to the C–H bond-cleavage step exists in alkane hydroxylations catalyzed by electron-rich iron porphyrins such as Fe(TMP)Cl.[25,26] Evidence for the occurrence of tunneling is (1) a large KIE value at room temperature (k_H/k_D) $\gg 7$), (2) the value of $E_a(D)-E_a(H)$ larger than the difference in C–H and C–D bond zero-point energies (≥ 1.3 kcal mol^{-1}), and (3) an unusually low pre-exponential ratio of A_H/A_D (<0.6).[28] Since the results shown in Table 5 do not meet these criteria, we conclude that the tunneling contribution is not involved in the alkane hydroxylations by the electron-deficient iron porphyrin complexes used in this study.

Conclusion

We have shown in this study that the reactions of electron-deficient iron(III) porphyrin complexes with MCPBA in the presence of alkanes efficiently yielded the corresponding alcohols as a major product with high alcohol to ketone ratios. The alkane hydroxylations were found to be highly stereospecific, since the hydroxylations of *cis*- and *trans*-1,2-dimethylcyclohexane afforded tertiary alcohol products with almost complete stereoretention. When the hydroxylation reactions were performed in the presence of $H_2{}^{18}O$, ^{18}O-incorporation from the labeled water into alcohol products was observed. The extent of the ^{18}O-incorporation into the products were found to depend on the electronic nature of iron porphyrins, the concentration of $H_2{}^{18}O$, the C–H bond strength of alkanes, and the reaction temperature. These phenomena were interpreted with that the reaction of oxygen atom transfer from a high-valent iron oxo porphyrin intermediate to alkanes competes with that of oxygen atom exchange between the intermediate and labeled water. Deuterium kinetic isotope effects have also been studied in the hydroxylation of cyclohexane by the iron porphyrin complexes, and the KIE values obtained in the reactions indicated that the rate-determining step is the C–H bond cleavage by high-valent iron oxo porphyrin intermediates. The KIE values were found to depend on the nature of iron porphyrin complexes, indicating that the reactivity of iron porphyrins is significantly affected by the electronic nature of iron porphyrins. By studying the temperature dependence of KIEs between −40 and 25 °C, we concluded that tunneling contribution to the C–H bond cleavage does not exist in the alkane hydroxylations by electron-deficient iron porphyrin complexes.

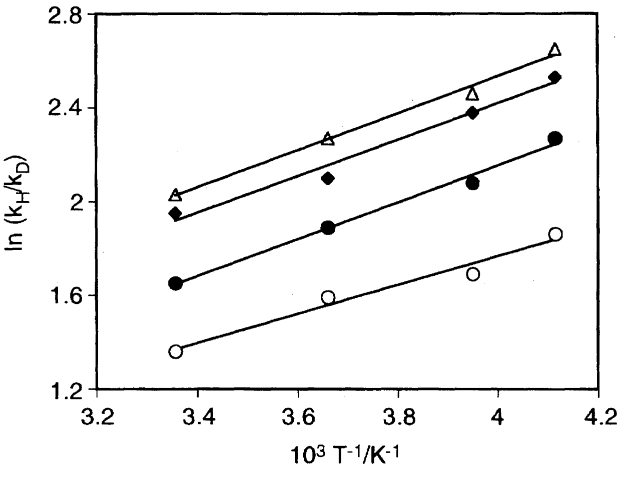


Fig. 2. Plot of ln (k_H/k_D) vs. $1/T$. for the temperature dependence of KIE values in the hydroxylation of cyclohexane by MCPBA catalyzed by **1** (●), **2** (◆), **3** (△), and **4** (○).

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