CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200500128

Mechanistic Insights into the Reversible Formation of Iodosylarene–Iron Porphyrin Complexes in the Reactions of Oxoiron(IV) Porphyrin π-Cation Radicals and Iodoarenes: Equilibrium, Epoxidizing Intermediate, and Oxygen Exchange

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Abstract: We have shown previously that iodosylbenzene–iron(III) porphyrin intermediates (**2**) are generated in the reactions of oxoiron(IV) porphyrin π-cation radicals (**1**) and iodobenzene (PhI), that **1** and **2** are at equilibrium in the presence of PhI, and that the epoxidation of olefins by **2** affords high yields of epoxide products. In the present work, we report detailed mechanistic studies on the nature of the equilibrium between **1** and **2** in the presence of iodoarenes (ArI), the determination of reactive species responsible for olefin epoxidation when two intermediates (i.e., **1** and **2**) are present in a reaction solution, and the fast oxygen exchange between **1** and $H_2{}^{18}O$ in the presence of ArI. In the first part, we have provided strong evidence that **1** and **2** are indeed at equilibrium and that the equilibrium is controlled by factors such as the electronic nature of iron porphyrins, the electron richness of ArI, and the concentration of ArI. Secondly, we have demonstrated that **1** is the sole active oxidant in olefin epoxidation when **1** and **2** are present concurrently in a reaction solution. Finally, we have shown that the presence of ArI in a reaction solution containing **1** and $H_2{}^{18}O$ facilitates the oxygen exchange between the oxo group of **1** and $H_2{}^{18}O$ and that the oxygen exchange is markedly influenced by factors such as ArI incubation time, the amounts of ArI and $H_2{}^{18}O$ used, and the electronic nature of ArI. The latter results are rationalized by the formation of an undetectable amount of **2** from the reaction of **1** and ArI through equilibrium that leads to a fast oxygen exchange between **2** and $H_2{}^{18}O$.

Keywords: enzyme models · epoxidation · equilibrium · oxygen · reaction mechanisms

Introduction

Heme-containing enzymes such as cytochromes P450, peroxidases, and catalases utilize dioxygen and its partially reduced forms in a variety of enzymatic reactions such as the incorporation of oxygen atoms into organic substrates (cytochrome P450) and the oxidation of hydroperoxides (peroxidase and catalase).[1] A unique feature of the enzymes is to generate oxoiron(IV) porphyrin π-cation radicals, $[(\mathrm{Porp})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^+$ (**1**, Porp = porphyrin), as key intermediates in the catalytic oxidation reactions.[2,3] Extensive mechanistic studies with the enzymes and synthetic iron porphyrins have shown that **1** is generated through heterolytic O–O bond cleavage of iron(III)–hydroperoxide porphyrin intermediates [Eq. (1)].[1–4]

The reverse reaction of the O–O bond cleavage is the O–X bond formation between the oxo group of **1** and halides (X^-) [Eqs. (2) and (3)]. Among heme-containing enzymes, haloperoxidases catalyze the halogenation of activated C–H bonds, by generating putative $[(\mathrm{Porp})\mathrm{Fe}^{III}{-}\mathrm{OX}]$ species through O–X bond formation between **1** and X^-.[5] In met-

O-O bond cleavage

$$[(\mathrm{Porp})\mathrm{Fe}^{III}\text{-OOH}] \longrightarrow \underset{\mathbf{1}}{[(\mathrm{Porp})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^+} + \mathrm{OH}^- \qquad (1)$$

O-X bond formation

$$[(\mathrm{Porp})\mathrm{Mn}^{V}{=}\mathrm{O}]^+ + \mathrm{Br}^- \rightleftharpoons [(\mathrm{Porp})\mathrm{Mn}^{III}]^+ + \mathrm{BrO}^- \qquad (2)$$

$$[(\mathrm{Porp})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^+ + \mathrm{Cl}^- \longrightarrow [(\mathrm{Porp})\mathrm{Fe}^{III}\text{-O-Cl}] \qquad (3)$$

O-I bond formation

$$\underset{\mathbf{1}}{[(\mathrm{Porp})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^+} + \mathrm{PhI} \rightleftharpoons \underset{\mathbf{2}}{[(\mathrm{Porp})\mathrm{Fe}^{III}\text{-O-IPh}]^+} \qquad (4)$$

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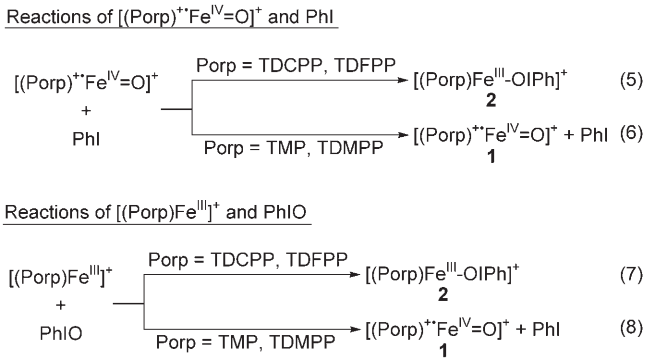
alloporphyrin models, there are two reported instances showing the O–X bond formation between high-valent metal–oxo porphyrin intermediates and halides.[6,7] Those are the reactions with oxo group transfer from $[(\mathrm{Porp})\mathrm{Mn}^{V}{=}\mathrm{O}]^{+}$ to Br^{-} to give $[(\mathrm{Porp})\mathrm{Mn}^{III}]^{+}$ and OBr^{-} [Eq. (2)][6] and the generation of $[(\mathrm{Porp})\mathrm{Fe}^{III}{-}\mathrm{OCl}]$ in the reaction of $[(\mathrm{Porp})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^{+}$ and Cl^{-} [Eq. (3)].[7] In the former case, it has been demonstrated unequivocally that the oxo transfer is a reversible process.[6]

In addition to the biomimetic examples of haloperoxidases, we have shown very recently that the reaction of **1** and iodobenzene (PhI) generates an iodosylbenzene–iron(III) porphyrin complex, $[(\mathrm{Porp})\mathrm{Fe}^{III}{-}\mathrm{OIPh}]^{+}$ (**2**), by O–I bond formation between the oxo group of **1** and PhI [Eq. (4)].[8] In that study, we have demonstrated that the formation of **2** depends significantly on the electronic nature of the iron porphyrins and iodobenzene derivatives and that there is an equilibrium between **1** and **2** in the presence of PhI. In addition, we have shown that the epoxidation of olefins by **2** affords high yields of epoxide products, leading us to propose that **2** might be involved as an active oxidant in the olefin epoxidation. In this paper, we report detailed mechanistic studies on the nature of the equilibrium between **1** and **2** in the presence of iodoarenes (ArI), the determination of the nature of epoxidizing intermediate(s) when **1** and **2** are present concurrently through equilibrium in a reaction solution, and the fast oxygen exchange between the oxo group of **1** and $H_2{}^{18}O$ in the presence of ArI. Some aspects of this work have been published previously as a communication.[8]

Results and Discussion

Factors affecting the nature of equilibrium between 1 and 2: The electronic effect of iron porphyrin complexes on the reaction of **1** and PhI was investigated with **1** bearing electron-deficient and -rich porphyrin ligands (Supporting Information, Figure S1).[9] As we have shown previously,[8] addition of PhI to the solutions of **1** bearing an electron-deficient porphyrin ligand, such as $[(\mathrm{TDCPP})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^{+}$ (**1a**) and $[(\mathrm{TDFPP})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^{+}$ (**1b**),[9] generated iodosylbenzene–iron(III) porphyrin intermediates, $[(\mathrm{TDCPP})\mathrm{Fe}^{III}{-}\mathrm{OIPh}]^{+}$ (**2a**) and $[(\mathrm{TDFPP})\mathrm{Fe}^{III}{-}\mathrm{OIPh}]^{+}$ (**2b**), respectively [Eq. (5)] (Supporting Information, Figure S2). In contrast, addition of PhI to the solutions of **1** bearing an electron-rich porphyrin ligand, such as $[(\mathrm{TMP})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^{+}$ (**1c**) and $[(\mathrm{TDMPP})^{+\bullet}\mathrm{Fe}^{IV}{=}\mathrm{O}]^{+}$ (**1d**),[9] did not afford the formation of $[(\mathrm{TMP})\mathrm{Fe}^{III}{-}\mathrm{OIPh}]^{+}$ (**2c**) and $[(\mathrm{TDMPP})\mathrm{Fe}^{III}{-}\mathrm{OIPh}]^{+}$ (**2d**), respectively [Eq. (6)] (Supporting Information, Figure S2). In line with these results, we have observed the formation of different intermediates in the reactions of iron(III) porphyrin complexes and iodosylbenzene (PhIO), depending on the electronic nature of iron porphyrins. For example, the reactions of $[\mathrm{Fe}^{III}(\mathrm{TDCPP})]^{+}$ and $[\mathrm{Fe}^{III}(\mathrm{TDFPP})]^{+}$ with PhIO afforded **2a** and **2b**, respectively [Eq. (7)]. In contrast, **1c** and **1d** were formed in the reactions of $[\mathrm{Fe}^{III}(\mathrm{TMP})]^{+}$ and $[\mathrm{Fe}^{III}(\mathrm{TDMPP})]^{+}$ with PhIO [Eq. (8)] (Supporting Information, Figure S3). These results demonstrate that the formation of **2** from **1** and PhI and from iron(III) porphyrins and PhIO is significantly affected by the electronic nature of the iron porphyrins, in which electron-deficient iron porphyrins form **2** favorably, whereas **1** is a preferred intermediate in the case of electron-rich iron porphyrins.[10]



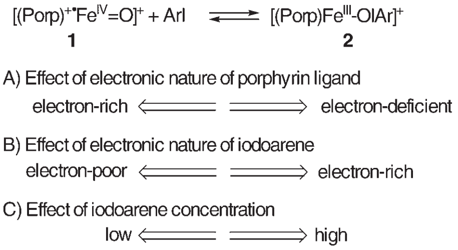
The electronic effect of iodobenzene on the formation of **2** from **1** and PhI was then investigated with various iodoarenes bearing electron-donating and -withdrawing substituents on the phenyl group of PhI. The conversion of **1** to **2** was not observed in the reactions of **1** bearing an electron-rich porphyrin ligand, irrespective of the electronic nature of ArI (see the columns of **1c** and **1d** in Table 1), however, the conversion of **1** to **2** was observed depending on the electronic nature of ArI in the reactions of **1** bearing an electron-deficient porphyrin ligand (see the columns of **1a** and **1b** in Table 1). In the latter cases, ArI containing electron-donating substituents afforded the formation of **2a** and **2b** (Table 1, entries 1–5), whereas a highly electron-poor ArI such as F_5C_6I did not form **2a** and **2b** (Table 1, entry 10). Interestingly, in the intermediate cases of ClC_6H_4I, FC_6H_4I, $F_2C_6H_3I$, and $CF_3C_6H_4I$ (Table 1, entries 6–9), both **1** and **2** were present concurrently in the reaction solutions. In line with these results, studies of *para*-substituted ArI revealed that the amounts of **2a** and **2b** formed in the reactions of **1a** and **1b**, respectively, increased with the increase of the electron-donating ability of *para*-substituents on ArI (Supporting Information, Figure S4). These results demonstrate that the electronic nature of ArI is another important factor in generating **2** from the reaction of **1** and ArI; that is, an electron-rich ArI favors the formation of **2**, the formation of **2** becomes less favorable as ArI becomes electron-poor, and a highly electron-poor ArI does not afford the formation of **2**.[11] In addition, the conversion of **1** to **2** was also affected by the amounts of ArI added to the reaction solutions; the amounts of **2a** formed in the reactions of **1a** and ArI increased proportionally with the amounts of ArI added (Supporting Information, Figure S5).[8]

As a conclusion, we have provided strong evidence that **1** and **2** are *indeed* at equilibrium in the presence of ArI (Scheme 1) and that the equilibrium is controlled by factors such as the electronic nature of the iron porphyrins, the electron richness of the iodoarenes, and the concentration of

Table 1. Intermediates observed in reaction solutions of $[(\mathrm{Porp})^{+\bullet}\mathrm{Fe}^{\mathrm{IV}}{=}\mathrm{O}]^{+}$ (**1**) and ArI.[a]

		For **1** =			
Entry	ArI	**1a**	**1b**	**1c**	**1d**
1	2,4,6-trimethyliodobenzene, $(CH_3)_3C_6H_2I$	**2a**	**2b**	**1c**	**1d**
2	5-iodo-*m*-xylene, $(CH_3)_2C_6H_3I$	**2a**	**2b**	**1c**	**1d**
3	4-iodoanisole, $CH_3OC_6H_4I$	**2a**	**2b**	**1c**	**1d**
4	4-iodotoluene, $CH_3C_6H_4I$	**2a**	**2b**	**1c**	**1d**
5	iodobenzene, C_6H_5I	**2a**	**2b**	**1c**	**1d**
6	1-chloro-4-iodobenzene, ClC_6H_4I	**1a**+**2a**	**1b**+**2b**	**1c**	**1d**
7	1-fluoro-4-iodobenzene, FC_6H_4I	**1a**+**2a**	**1b**+**2b**	**1c**	**1d**
8	1,2-difluoro-4-iodobenzene, $F_2C_6H_3I$	**1a**+**2a**	**1b**+**2b**	**1c**	**1d**
9	4-iodobenzotrifluoride, $CF_3C_6H_4I$	**1a**+**2a**	**1b**+**2b**	**1c**	**1d**
10	iodopentafluorobenzene, F_5C_6I	**1a**	**1b**	**1c**	**1d**

[a] Reactions were followed by monitoring UV/Vis spectral changes of reaction solutions. ArI (30 equiv) was added to the solutions of **1** (1 mM) in a solvent mixture (0.5 mL) of CH_3CN/CH_2Cl_2 (3:1) at −40 °C. See Experimental Section for detailed reaction conditions.

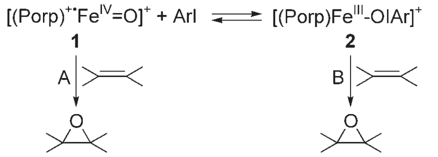


Scheme 1. The factors affecting the equilibrium between **1** and **2**.

the iodoarenes (Scheme 1). The electronic effect of porphyrin ligands and iodoarenes on the equilibrium is rationalized with the electrophilic character of the oxo group of **1**.[13] Thus, the O−I bond formation between the oxo group of **1** and ArI occurs readily when **1** is more electron-deficient (Scheme 1A) and the iodoarene is more electron-rich (Scheme 1B).[11] The concentration effect of ArI on the equilibrium is interpreted with Le Châtelier's principle,[14] in which the equilibrium shifts toward the formation of **2** with the increase of ArI concentration (Scheme 1C).

Determination of active oxidant in the epoxidation of olefins by 2: We have shown previously that the reactions of **2a** and **2b** with olefins gave high yields of epoxide products, and that the epoxidation of olefins by the intermediates, when performed in the presence of $H_2{}^{18}O$, resulted in a high ^{18}O incorporation from the labeled water into the epoxide products.[8] On the basis of the results, we have proposed that **2** might be involved as an active oxidant in the olefin epoxidation (Scheme 2, pathway B), although we did not exclude the possibility that a small amount of **1** present in the reaction solution through equilibrium might be responsible for the olefin epoxidation (Scheme 2, pathway A). As there is an intriguing, current controversy on the involvement of a second electrophilic oxidant (i.e., oxidant–iron(III) porphyrin adducts) in oxygen-atom transfer reactions by cytochromes P450 and iron porphyrin models,[15] we decided to determine the structure of active oxidant(s) responsible for oxygen-atom transfer when two different intermediates are present in a reaction solution (Scheme 2).

Because it has been shown previously that competitive oxygenation reactions are a useful mechanistic probe in proposing the nature of reactive species in metal-complex-catalyzed oxygenation reactions,[10c,16] we performed two sets of competitive olefin epoxidation reactions (i.e., *cis*-stilbene versus *trans*-stilbene and cyclooctene versus *trans*-stilbene) with in situ generated intermediates, **1b** and **2b**. If **2b** is involved as an active oxidant in the olefin epoxidation (Scheme 2, pathway B), then product ratios obtained in the competitive epoxidation by **2b** will be different from those obtained in the competitive epoxidation by **1b**. On the other hand, if **2b** is converted to **1b** at a fast rate by equilibrium and the olefin epoxidation takes place by **1b** (Scheme 2, pathway A), identical product ratios are expected to be observed in the competitive epoxidations performed with the two different intermediates, **1b** and **2b**. The results in Table 2 show clearly that the product ratios obtained in the competitive epoxidation reactions by **1b** and **2b** were identical within experimental error margins (Table 2, compare the data in entry 1 to those in entries 2–4). Moreover, the product ratios obtained with **2b** prepared with different iodoarenes (e.g., PhI, 4-CH_3PhI, and 2,4,6-$(CH_3)_3$PhI) were similar and not affected by the identity of iodoarenes bound to **2b** (Table 2, entries 2–4). In line with these results, when the competitive epoxidations were carried out with $[\mathrm{Fe^{III}}(\mathrm{TDFPP})]^+$ and iodosylarenes (e.g., PhIO, F_5PhIO, and 2,4,6-$(CH_3)_3$PhIO) under catalytic conditions, the product ratios were identical and not dependent on the kinds of iodosylarenes used (Supporting Information, Table S1). On the basis of the results of competitive olefin epoxidations carried out with in situ generated intermediates (**1b** and **2b**) and with different iodosylarenes under catalytic conditions, we propose that there is only one epoxidizing intermediate. Although **1b** was not detected in the solution of **2b**, the active oxidant responsible for the epoxidation of olefins by **2b** was **1b**, which was generated from **2b** by equilibrium (Scheme 2).[17]



Scheme 2. The possible olefin epoxidation routes (A and B) when two different intermediates are present in a reaction solution.

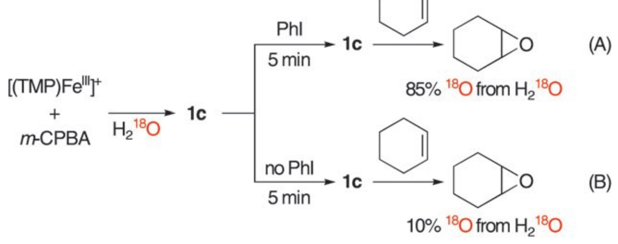
Table 2. Competitive olefin epoxidations carried out with in situ generated intermediates.[a,b]

Entry	Intermediate	*cis*-Stilbene versus *trans*-stilbene product yields [%][c]			Cyclooctene versus *trans*-stilbene product yields [%][c]		
		cis-oxide[d]	*trans*-oxide[d]	ratio of *cis*- to *trans*-oxide	co-oxide[d]	*trans*-oxide[d]	ratio of *cis*- to *trans*-oxide
1	**1b**	58	18	**3.2** ± 0.3	30	36	**0.8** ± 0.1
2	**2b** from **1b** + PhI[e]	60	19	**3.2** ± 0.3	24	32	**0.8** ± 0.1
3	**2b** from **1b** + CH_3PhI[e]	54	15	**3.6** ± 0.3	24	34	**0.7** ± 0.1
4	**2b** from **1b** + $(CH_3)_3PhI$[e]	56	15	**3.4** ± 0.3	25	29	**0.9** ± 0.1

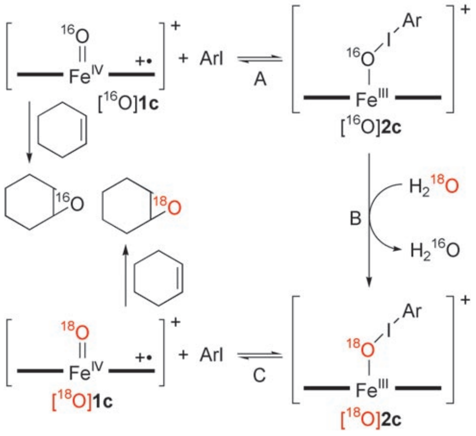
[a] Reactions were run at least three times, and the data represent an average of these reactions. [b] Control reactions performed with *cis*-stilbene and *trans*-stilbene individually demonstrated the formation of a trace amount of isomerized *trans*-stilbene oxide in the *cis*-stilbene epoxidation and no formation of *cis*-stilbene oxide in the *trans*-stilbene epoxidation.[16a] [c] Yields were calculated based on the amounts of intermediates generated. [d] *cis*-Oxide, *trans*-oxide, and co-oxide stand for *cis*-stilbene oxide, *trans*-stilbene oxide, and *cis*-cyclooctene oxide, respectively. [e] Compound **2b** was prepared by reacting **1b** with 30 equiv of iodoarene.

Oxygen exchange between 1 and $H_2{}^{18}O$ in the presence of ArI: In this section, we report that the presence of ArI in a reaction solution containing **1** and $H_2{}^{18}O$ facilitates the oxygen exchange between the oxo group of **1** and $H_2{}^{18}O$. This phenomenon is rationalized with the generation of **2** from **1** and ArI through equilibrium, followed by a fast oxygen exchange between **2** and $H_2{}^{18}O$.[18]

Addition of PhI to a reaction solution of **1c**, prepared by treating [Fe(TMP)(CF_3SO_3)] with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of a small amount of $H_2{}^{18}O$ (3 µL), did not show any spectral changes, indicating that **2c** was not generated in the reaction of **1c** and PhI (see above). Upon addition of cyclohexene to the resulting solution, **1c** reverted back to the starting $[Fe(TMP)]^+$ complex, and product analysis of the reaction mixture revealed that cyclohexene oxide was yielded as a major product (60% yield based on the amount of **1c**). Interestingly, we found that most of the oxygen in the epoxide product was derived from $H_2{}^{18}O$ (Scheme 3, pathway A). For comparison, when we prepared **1c** in the presence of the same amount of $H_2{}^{18}O$ (3 µL) but without adding PhI, the epoxidation of cyclohexene by **1c** yielded cyclohexene oxide containing a relatively small amount of oxygen derived from $H_2{}^{18}O$ (Scheme 3, pathway B). These results imply that although **1c** was the sole species detected in the reaction solution of **1c** and PhI, another species that exchanges its oxygen with labeled water must be generated in the reaction solution. As we have shown above that **1** and **2** are at equilibrium in the presence of PhI and it has been reported previously that **2** exchanges its oxygen atom with labeled water at a fast rate,[18] such a high ^{18}O incorporation from $H_2{}^{18}O$ into the epoxide product implies that an undetectable amount of **2** was generated in the solution of **1** and PhI through equilibrium and that a fast oxygen exchange occurred between **2** and $H_2{}^{18}O$. We therefore propose a mechanism illustrating the phenomenon of a high ^{18}O incorporation from $H_2{}^{18}O$ into the epoxide product as follows: First, $[^{16}O]$**2c** is generated from $[^{16}O]$**1c** and ArI by equilibrium followed by a fast oxygen exchange between $[^{16}O]$**2c** and $H_2{}^{18}O$, resulting in the generation of $[^{18}O]$**2c** (Scheme 4, pathways A and B). Then, $[^{18}O]$**1c** is generated from $[^{18}O]$**2c** by equilibrium (Scheme 4, pathway C), and the epoxidation of cyclohexene by $[^{18}O]$**1c** produces cyclohexene $[^{18}O]$oxide. In order to prove this working hypothesis, we carried out isotopically labeled water experiments by changing reaction conditions such as PhI incubation time, the amounts of PhI and $H_2{}^{18}O$ in reaction solutions, and the electronic nature of iodoarenes, with an assumption that these variations will influence the degree of oxygen exchange between **1c** and $H_2{}^{18}O$ if the oxygen exchange occurs by the proposed mechanism.

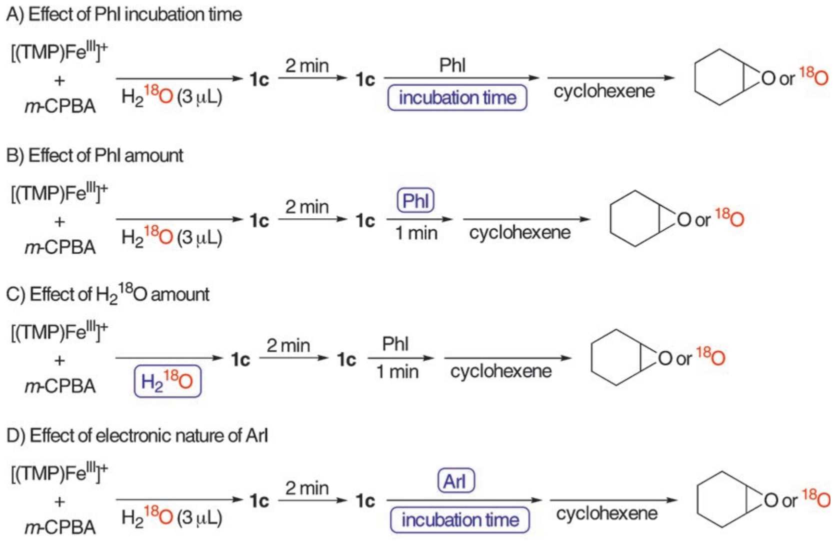


Scheme 3. The effect of PhI on the ^{18}O incorporation into the epoxide product.



Scheme 4. The proposed mechanism illustrating the phenomenon of a high ^{18}O incorporation from $H_2{}^{18}O$ into the epoxide product.

We first examined the effect of PhI incubation time on the degree of ^{18}O incorporation from $H_2{}^{18}O$ into the epoxide product in the epoxidation of cyclohexene by **1c**. A schematic diagram illustrating reaction conditions is depicted in Scheme 5A (see the blue rectangles for the change of PhI



Scheme 5. The experimental conditions for the reactions of PhI incubation time, PhI amount, $H_2{}^{18}O$ amount, and the electronic nature of iodoarenes to find the degree of ^{18}O incorporation from $H_2{}^{18}O$ into cyclohexene oxide in the epoxidation of cyclohexene by **1c**.

incubation time). The results in Figure 1a show that the amounts of ^{18}O found in cyclohexene oxide increased proportionally with the PhI incubation time. This phenomenon is explained by considering that through increasing the PhI incubation time, more [^{16}O]**1c** is converted to [^{16}O]**2c**, which exchanges its oxygen atom with $H_2{}^{18}O$ to give [^{18}O]**2c**. This results in the generation of [^{18}O]**1c** through equilibrium, and the epoxidation of cyclohexene by [^{18}O]**1c** yields cyclohexene oxide containing ^{18}O (Scheme 4). For comparison, when the isotopically labeled water experiment was carried out with **1c** in the absence of PhI, the amounts of ^{18}O incorporated into the epoxide product were small and did not change significantly depending on the increase of the **1c** incubation time in the presence of $H_2{}^{18}O$ only (Figure 1a, blue dotted line),[19] demonstrating that the increase of ^{18}O incorporation upon increasing the PhI incubation time results from the direct oxygen exchange between **1c** and $H_2{}^{18}O$.

Secondly, we have investigated the effects of the amounts of PhI and $H_2{}^{18}O$ on the ^{18}O incorporation from $H_2{}^{18}O$ into cyclohexene oxide, by carrying out cyclohexene epoxidation using **1c** with different amounts of PhI and $H_2{}^{18}O$ (see blue rectangles in Scheme 5B and C). Figure 1b and c show that the amounts of ^{18}O incorporated into cyclohexene oxide increased proportionally with the PhI and $H_2{}^{18}O$ amounts added to the reaction solutions. The increase of ^{18}O incorporation with the increase of PhI amount is rationalized with the shift of equilibrium toward the formation of [^{16}O]**2c** from [^{16}O]**1c** and PhI (Scheme 4, pathway A), resulting in a fast formation of [^{18}O]**2c** that leads to a high ^{18}O incorporation into the epoxide product. The fast increase of the ^{18}O incorporation upon increasing the $H_2{}^{18}O$ amounts in reaction solutions results from a fast oxygen exchange between [^{16}O]**2c** and $H_2{}^{18}O$ (Scheme 4, pathway B).

Finally, the electronic effect of iodoarenes was investigated with electron-rich and -deficient iodoarenes (see Scheme 5D for experimental conditions). As the results in Figure 1d show, the ^{18}O incorporation from $H_2{}^{18}O$ into cyclohexene oxide increased proportionally with ArI incubation time except in the case of F_5C_6I. In addition, the rates of ^{18}O incorporation were different depending on the electronic nature of iodoarenes, in which the ^{18}O incorporation increases at a fast rate as ArI becomes electron-rich. Such an electronic effect of iodoarenes on the ^{18}O incorporation results from the shift of equilibrium position depending on the electron richness of ArI. As we have discussed in Scheme 1B, the equilibrium position shifts toward the formation of [^{16}O]**2c** in the case of an electron-rich ArI (Scheme 4, pathway A), resulting in a fast oxygen exchange between [^{16}O]**2c** and $H_2{}^{18}O$. As ArI becomes electron-poor, the formation of [^{16}O]**2c** from [^{16}O]**1c** and ArI becomes less favorable (Scheme 4, pathway A). In the case of a highly electron-poor ArI such as F_5C_6I, the reaction of [^{16}O]**1c** and ArI does not form [^{16}O]**2c**.

In summary, we have shown that the oxygen exchange between **1** and $H_2{}^{18}O$ is facilitated by the presence of ArI and the oxygen exchange is markedly influenced by factors such as ArI incubation time, the amounts of ArI and $H_2{}^{18}O$, and the electron richness of ArI. These results are rationalized with the generation of an undetectable amount of **2** from the reaction of **1** and ArI through equilibrium and the occurrence of a fast oxygen exchange between **2** and $H_2{}^{18}O$. Moreover, all the results of isotope-labeling studies support the existence of equilibrium between **1** and **2** in the presence of ArI.[20]

Conclusion

Although the reactions of iron(III) complexes with iodosylarenes have been extensively studied over the past three decades to elucidate the chemistry of **1**, the so-called Compound I in heme-containing enzymes,[1,2,21] the reverse reaction, which is the O–I bond formation between **1** and ArI, has been unveiled very recently.[8] In the present work, we have thoroughly investigated mechanistic details on the formation of **2** in the reactions of **1** and ArI and demonstrated unambiguously that two different intermediates, **1** and **2**, can be present concurrently in a reaction solution through equilibrium and that the nature of equilibrium can be con-

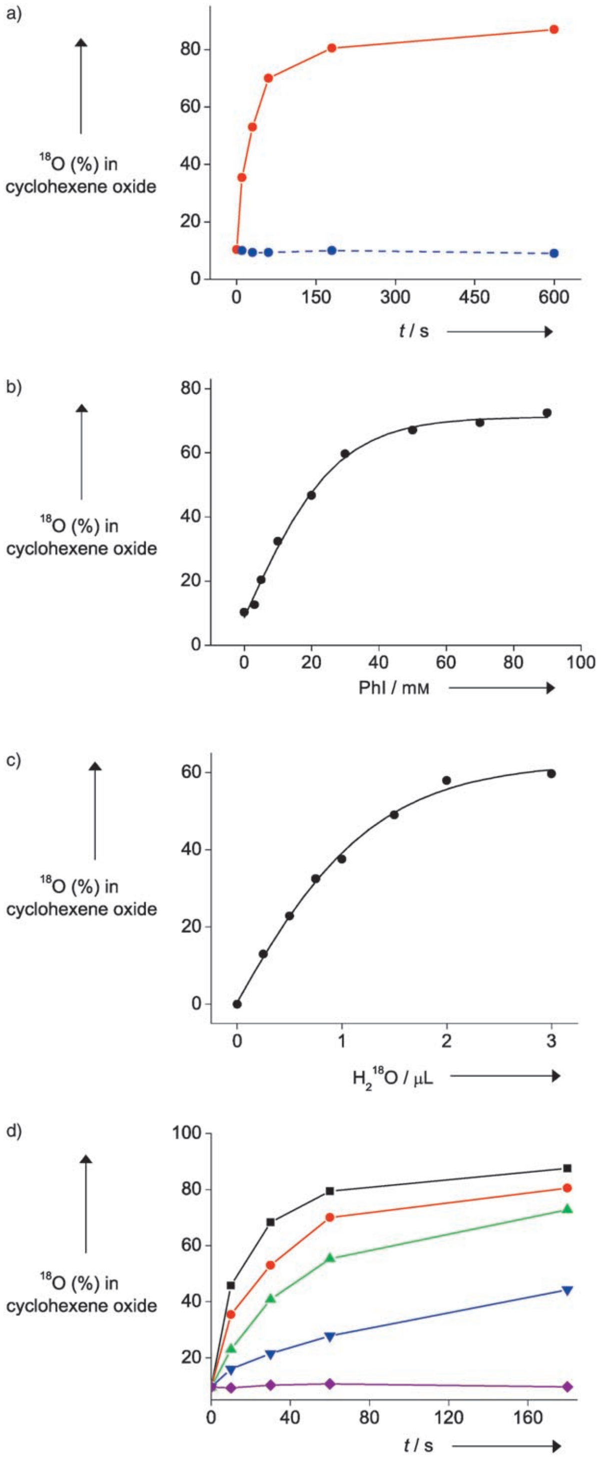


Figure 1. Plots showing the effects of a) PhI incubation time (red solid line; blue dotted line for the absence of PhI), b) PhI amount, c) $H_2{}^{18}O$ amount, and d) the electronic nature of ArI and ArI incubation time on the degree of ^{18}O incorporation from $H_2{}^{18}O$ into cyclohexene oxide in the epoxidation of cyclohexene by **1c**; $CH_3C_6H_4I$ (■), C_6H_5I (●), FC_6H_4I (▲), $F_2C_6H_3I$ (▼), F_5C_6I (◆). See the Experimental Section for detailed reaction procedures. All reactions were followed by monitoring UV/Vis spectral changes of reaction solutions. Cyclohexene oxide was produced with high yields in all of the reactions (>60% based on the intermediate **1c** formed). The product yields were calculated with an assumption that the intermediate **1c** was formed quantitatively in the reactions of [Fe(TMP)(CF_3SO_3)] (2 mM) and *m*-CPBA (1.5 equiv).

trolled by factors such as the electronic nature of iron porphyrins, the electron richness of ArI, and the concentration of ArI. Further evidence supporting the existence of equilibrium between **1** and **2** in the presence of ArI has been obtained by carrying out isotope-labeling experiments, in which the oxygen exchange between **1** and $H_2{}^{18}O$ is facilitated by the presence of ArI, and this phenomenon is rationalized with the formation of **2** from the reaction of **1** and ArI through equilibrium. We have also shown that the oxygen exchange is markedly affected by factors such as ArI incubation time, the amounts of ArI and $H_2{}^{18}O$, and the electronic nature of ArI. Finally, by carrying out competitive olefin epoxidations with in situ generated **1** and **2**, we have concluded that **1** is the sole active oxidant that effects olefin epoxidation when **1** and **2** are present concurrently in a reaction solution by equilibrium. Future studies will be focused on searching for a possibility that hydroperoxide–iron(III) porphyrin complexes, [(Porp)Fe^{III}–OOR], are formed by O–O bond formation between oxoiron(IV) porphyrin π-cation radicals and hydroxides (RO^-).[22]

Experimental Section

Materials: Dichloromethane (anhydrous) and acetonitrile (anhydrous) were obtained from Aldrich Chemical Co. and purified by distillation over CaH_2 prior to use. All reagents purchased from Aldrich were the best available purity and used without further purification unless otherwise indicated. *m*-CPBA was purified by washing with phosphate buffer (pH 7.4) followed by water and was then dried under reduced pressure. Iodosylarenes were prepared by following a method in the literature.[23] The purities of the oxidants were determined by using iodometric titration.[24] $H_2{}^{18}O$ (95% ^{18}O enriched) was purchased from ICON Services Inc. (Summit, NJ, USA). [Fe(TMP)Cl], [Fe(TDCPP)Cl], and [Fe(TDFPP)Cl] were obtained from Mid-Century Chemicals (Posen, IL, USA). [Fe(TDMPP)Cl] was synthesized by following a literature method.[25] [(Porp)Fe(CF_3SO_3)] was prepared by stirring equimolar amounts of [(Porp)FeCl] and [Ag(CF_3SO_3)] followed by filtering through a 0.45 µM filter. The resulting solution was used immediately for further studies.

Instrumentation: UV/Vis spectra were recorded on a Hewlett–Packard 8453 spectrophotometer equipped with an Optistat DN variable-temperature liquid-nitrogen cryostat (Oxford Instruments). Product analyses for the epoxidation of *cis*- and *trans*-stilbenes were performed by HPLC analysis using a Dionex Summit P580 equipped with a variable-wavelength UV-200 detector. Products were separated on a Waters Symmetry C18 reverse-phase column (4.6×250 mm), eluted first with 50% methanol in water for 15 min and then with 85% methanol in water for 10 min at a flow rate of 1 mL min^{-1}. Detection was made at $\lambda = 215$ and 254 nm. Product analyses for the epoxidation of cyclohexene and cyclooctene were performed on a Hewlett–Packard 5890 II Plus gas chromatograph equipped with a flame ionization detector and a Hewlett–Packard 5890 II Plus gas chromatograph interfaced with a Hewlett–Packard model 5989B mass spectrometer.

Reactions of 1 with ArI: Compound **1** was prepared by adding *m*-CPBA (1.5 equiv, 1.5 mM, diluted in CH_3CN (50 µL)) into a 0.1 cm UV cuvette containing a reaction solution of a triflate iron(III) porphyrin complex (1 mM) in a solvent mixture of CH_3CN/CH_2Cl_2 (3:1, 0.5 mL) at −40 °C. Then, appropriate amounts of iodoarenes (diluted in CH_3CN (50 µL)) were added into the UV cuvette, and spectral changes of **1** were monitored by using a UV/Vis spectrophotometer.

Competitive olefin epoxidations: All reactions were run at least three times and the data reported are the average of these reactions. The competitive epoxidations of *cis*- and *trans*-stilbenes and of cyclooctene and *trans*-stilbene were carried out as follows: **1b** was prepared by reacting [Fe(TDFPP)(CF_3SO_3)] (2 mM) with *m*-CPBA (1.5 equiv, 3 mM) in a solvent mixture of CH_3CN/CH_2Cl_2 (3:1, 1 mL) at −40 °C. **2b** was prepared by adding ArI (30 equiv, 60 mM, diluted in CH_3CN (50 μL)) to the reaction solution of **1b** at −40 °C. Then, olefins (equal amounts of competing olefins, 40 mM each, diluted in CH_2Cl_2 (0.2 mL)) were added to the reaction solutions. After the intermediates reverted back to the starting [Fe(TDFPP)]$^+$ complex, the reaction solutions were directly analyzed by HPLC or GC/GC–MS. Product yields were determined by comparison against standard curves prepared with known authentic samples.

Isotopic-labeling studies: All reactions were run at least three times and the data reported are the average of these reactions and calculated on the basis of the ^{18}O enrichment of $H_2{}^{18}O$ (95 % ^{18}O enriched). Scheme 5 shows experimental conditions for the reactions of PhI incubation time (Scheme 5A), PhI amount (Scheme 5B), $H_2{}^{18}O$ amount (Scheme 5C), and the electronic nature of iodoarenes (Scheme 5D). In general, **1c** was prepared by treating [Fe(TMP)(CF_3SO_3)] (2 mM) with *m*-CPBA (1.5 equiv) in the presence of $H_2{}^{18}O$ (3 μL) in a solvent mixture of CH_3CN/CH_2Cl_2 (3:1, 0.5 mL) at −40 °C. After ArI (30 equiv, 60 mM, diluted in CH_3CN (50 μL)) was added to the solution of **1c**, cyclohexene (0.2 mmol, diluted in CH_2Cl_2 (50 μL)) was added to the reaction mixture. After **1c** reverted back to the starting [Fe(TMP)]$^+$ complex, the resulting solution was directly analyzed by using GC and GC–MS. Product yields were determined by comparison against standard curves prepared with cyclohexene oxide and decane as an internal standard. The ^{16}O and ^{18}O compositions in cyclohexene oxide were determined by the relative abundances of the mass peaks at *m*/*z* 83 and 97 for ^{16}O and *m*/*z* 85 and 99 for ^{18}O.

Acknowledgements

This research was supported by the Ministry of Science and Technology of Korea through the Creative Research Initiative Program. We are grateful to Professor Lawrence Que, Jr. at the University of Minnesota for insightful discussions. We also thank the Korea Science and Engineering Foundation (KOSEF) and the National Science Foundation (NSF) for stimulating this international cooperative research effort.

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Received: February 4, 2005
Revised: July 30, 2005