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On the Mechanism of Oxygenation of Olefins by Tetraphenylporphinatoiron(III)–Peroxide Systems¹⁾

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The mode of oxygenation by *meso*-tetraphenylporphinatoiron(III)chloride (Fe(III)TPPCL)–peroxide systems was characterized by using *cis*-stilbene (**1**) and cholesteryl acetate (**3**) as substrates. The stereoselectivity of epoxidation of **1** by the Fe(III)TPPCL–*tert*-butyl hydroperoxide ('BuOOH) system depended on the concentration of Fe(III)TPPCL; the reaction was nonstereoselective at 0.1 mM Fe(III)TPPCL but stereoselective at 10 mM Fe(III)TPPCL. In the reaction of **3** with the same system, both allylic oxidation and epoxidation proceeded. However, the epoxidation was β -selective independently of the concentration of Fe(III)TPPCL. Thus, 'BuOOH is assumed to decompose by a radical chain reaction mechanism to give *tert*-butylperoxyl radical ('BuOO·) and *tert*-butoxyl radical ('BuO·) at 0.1 mM Fe(III)TPPCL. At 10 mM Fe(III)TPPCL, on the other hand, the O–O bond in the Fe(III)TPPCL–'BuOOH complex may cleave in both a homolytic manner (quasi-Fenton mechanism) and a heterolytic one (ferryl ion mechanism). The former leads to 'BuO· as the active oxygen species responsible for the allylic oxidation of **3** and the latter to ferryl ion (Fe=O·) as that responsible for the stereoselective epoxidation of **1** and β -epoxidation of **3**.

In the reaction with the Fe(III)TPPCL–*m*-chloroperbenzoic acid (MCPBA) system at –30 °C in the presence of γ -collidine, β -selective epoxidation of **3** proceeded predominantly while **1** was epoxidized stereoselectively. The stereoselectivities of these epoxidations closely resemble those with the Fe(III)TPPCL–iodosylbenzene system, which is known to give the ferryl ion. These results suggest that the O–O bond in the Fe(III)TPPCL–MCPBA complex cleaves mainly in the heterolytic manner (ferryl ion mechanism).

Keywords—epoxidation stereoselectivity; cholesteryl acetate; *cis*-stilbene; *meso*-tetraphenylporphinatoiron(III)chloride; *tert*-butyl hydroperoxide; *m*-chloroperbenzoic acid, quasi-Fenton mechanism; oxyradical; ferryl ion

Cytochrome P-450 catalyzes oxygenations of a wide variety of organic compounds. The proposed mechanisms for the oxygenation involve the uptake of two electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH), the reduction of one atom of molecular oxygen to water and the insertion of the other into the substrate.²⁾ The enzyme can also catalyze the hydroxylation of organic compounds without any electron donor or molecular oxygen if certain hydroperoxides (ROOH) are present (hydroperoxide-dependent hydroxylation).²⁾ This hydroxylation has been assumed to proceed by the quasi-Fenton mechanism.²⁾ Recently, several chemical models for the enzymatic hydroxylation have been studied by using ROOH and a metalloporphyrin such as *meso*-tetraphenylporphinatoiron(III)chloride (Fe(III)TPPCL).^{3,4)} Groves *et al.* showed that the Fe(III)TPPCL–ROOH system oxidized cyclohexene by a free radical chain reaction mechanism.^{3a)} On the other hand, several investigators have proposed that the quasi-Fenton mechanism operates in such reactions.^{3d,4)}

The mode of oxygenation has often been investigated with *cis*-stilbene (**1**) as a typical substrate. The epoxidation of **1** by a nonradical reagent such as *m*-chloroperbenzoic acid

(MCPBA) is stereoselective, retaining the original geometry.^{1b)} In contrast, **1** is epoxidized nonstereoselectively by a free radical reagent such as peroxy radical to give a mixture of *cis*- (**2a**) and *trans*- (**2b**) epoxides, since free rotation of the C–C bond is allowed in the formation of the radical intermediate.^{1b)} However, the epoxidation of **1** by the ferryl ion (Fe–O·), which has a radical character and is generated in the reaction of Fe(III)TPPCL and iodosylbenzene (PhIO), has recently been shown to be stereoselective owing to the participation of a solvent cage.⁵⁾ Thus, **1** cannot be used as a substrate for discrimination between oxygenations by a nonradical reagent and by the ferryl ion.

Our previous paper has demonstrated that the stereoselectivity in the epoxidation of cholesteryl acetate (**3**) also depends on the mode of oxygenation; nonradical reagents show α -selectivity, and radical ones including ferryl ions lead to β -selectivity, regardless of the participation of a solvent cage. Thus, by using both **1** and **3** as substrates, it would be possible to differentiate between oxygenations by nonradical reagents, free radical ones and the ferryl ion.^{1b)} In this paper, the mode of oxygenation by Fe(III)TPPCL–peroxide systems was characterized by examining the stereoselectivities in the epoxidations of **1** and **3**.

Results and Discussion

Epoxidations of *cis*-Stilbene (**1**) and Cholesteryl Acetate (**3**) by the Fe(III)TPPCL–*tert*-Butyl Hydroperoxide (*t*-BuOOH) System

The oxygenation of **1** and **3** by the Fe(III)TPPCL–*t*-BuOOH system was carried out in chlorobenzene at 25 °C for 1 h under an argon atmosphere. The oxygenations did not proceed in the absence of Fe(III)TPPCL. In the presence of catalytic amounts of Fe(III)TPPCL (0.1 mM), however, **1** was epoxidized nonstereoselectively by *t*-BuOOH (200 mM) to give a mixture of **2a** and **2b** in a ratio of 2:98 (Table I). Under the same conditions, β -selective epoxidation and allylic oxidation took place in the oxygenation of **3** (Table II). These results are similar to those obtained in the oxygenations of **1** and **3** by the tris(acetylacetonato)iron(III) (Fe(acac)₃)–*t*-BuOOH system (Tables I and II). The Fe(acac)₃–*t*-BuOOH system has been shown to give *tert*-butyl peroxy radical (*t*-BuOO·) and *tert*-butoxy radical (*t*-BuO·) through the Haber–Weiss mechanism,⁶⁾ and these radicals are responsible for the epoxidations of **1** and **3** and for the allylic oxidation of **3**, respectively.⁷⁾ Therefore, such radicals produced by a similar mechanism seem to participate in the oxygenations of **1** and **3** by the Fe(III)TPPCL (0.1 mM)–*t*-BuOOH system. However, the mode

TABLE I. Stereoselectivity of Epoxidation of *cis*-Stilbene

System	Epoxide	
	Yield (%) ^{a)}	<i>cis</i> : <i>trans</i>
Fe(III)TPPCL (0.1 mM)– <i>t</i> -BuOOH ^{b)}	3	2:98
Fe(III)TPPCL (10 mM)– <i>t</i> -BuOOH ^{b)}	0.3	82:18
Fe(III)TPPCL (10 mM)– <i>t</i> -BuOOH–BHT ^{b, d)}	0.03	88:12
Fe(acac) ₃ – <i>t</i> -BuOOH ^{b)}	49	4:96
Fe(III)TPPCL–PhIO ^{b)}	35	90:10
MCPBA ^{c)}	0	
Fe(III)TPPCL (10 mM)–MCPBA ^{c)}	2	83:17
MCPBA–collidine ^{c)}	0	
Fe(III)TPPCL (10 mM)–MCPBA–collidine ^{c)}	15	84:16
Fe(III)TPPCL (10 mM)– <i>t</i> -BuOOH–collidine ^{b)}	0.6	83:17

a) Based on substrate. b) 25 °C, 1 h. c) –35 °C, 1 h. d) 60 mM BHT.

TABLE II. Oxygenations of Cholesteryl Acetate

System	Yield (%) ^{a)}				Epoxidation (%)
	4 ($\beta/\alpha+\beta$)	5	6	7	
Fe(III)TPPCL (0.1 mM)- ^t BuOOH ^{b)}	0.1 (0.75)	0.6	0.3	0.1	9
Fe(III)TPPCL (10 mM)- ^t BuOOH ^{b)}	1 (0.75)	19	3	0.6	4
Fe(acac) ₃ - ^t BuOOH ^{b)}	1 (0.75)	77	3	11	11
Fe(III)TPPCL-PhIO ^{b)}	19 (0.72)	0	5	0	79
MCPBA ^{c)}	76 (0.33)	0	0	0	100
Fe(III)TPPCL (10 mM)-MCPBA ^{c)}	26 (0.54)	0.2	2	0	92
MCPBA-collidine ^{c)}	1	0	0	0	100
Fe(III)TPPCL (10 mM)-MCPBA-collidine ^{c)}	25 (0.75)	0.5	4	0	85
Fe(III)TPPCL (10 mM)- ^t BuOOH-collidine ^{b)}	2 (0.75)	9	4	2	12

a) Based on substrate. b) 25 °C, 1 h. c) -35 °C, 1 h. d) 60 mM BHT.

Fig. 1. Effect of the Concentration of Fe(III)-TPPCL on the Epoxidation of *cis*-Stilbene

The concentration of *tert*-butyl hydroperoxide was 200 mM. The yields of products were calculated on the basis of Fe(III)TPPCL. ○, the yield of *cis*-epoxide; △, the yield of *trans*-epoxide; ●, the ratio of *cis*-epoxide.

Fig. 2. Effect of the Concentration of ^tBuOOH on the Epoxidation of *cis*-Stilbene

The yields of products were calculated on the basis of Fe(III)TPPCL. The concentration of Fe(III)TPPCL was 10 mM. ○, the yield of *cis*-epoxide; △, the yield of *trans*-epoxide; ●, the ratio of *cis*-epoxide.

of the epoxidation of **1** by the Fe(III)TPPCL-^tBuOOH system was found to depend on the concentration of Fe(III)TPPCL; the stereoselectivity increased with increase in the concentration of Fe(III)TPPCL, though the total yield of the epoxides decreased, probably due to radical-induced decomposition of ^tBuOOH (Fig. 1).⁸⁾ As shown in Table I, the ratio of **2a** to **2b** reached 82:18 at 10 mM Fe(III)TPPCL. The effects of ^tBuOOH concentration on the mode of the reaction are shown in Fig. 2. The yield of epoxides increased with increase in the concentration of ^tBuOOH up to 200 mM and remained constant over the range of 200–400 mM. The ratio of **2a** and **2b** remained nearly unchanged over the range of 10–400 mM ^tBuOOH, indicating that the mode of the epoxidation is not affected by the concentration of ^tBuOOH. The oxygenation of **3** by the Fe(III)TPPCL-^tBuOOH system was also carried out at 10 mM Fe(III)TPPCL, and the results were compared with those at 0.1 mM Fe(III)TPPCL

Chart 1

(Table II). Though the yields of α -epoxide (**4a**), β -epoxide (**4b**) and the allylic oxidation products (**5**, **6**, and **7**) were higher at 10 mM than at 0.1 mM Fe(III)TPPCL, stereoselectivity in the epoxidation was independent of the concentration of Fe(III)TPPCL. Therefore, the main epoxidizing agent produced in the Fe(III)TPPCL-*t*-BuOOH system at 10 mM Fe(III)TPPCL is concluded to be neither nonradical nor radical (other than the ferryl ion), since nonradical and radical reagents catalyze α -selective epoxidation of **3** and nonstereoselective epoxidation of **1**, respectively.^{1b)}

Possible reaction mechanisms between Fe(III)TPPCL and *t*-BuOOH are assumed to be: (i) bonding of ROOH to Fe(III)TPPCL, followed by homolytic cleavage of the O–O bond in the complex to give an alkoxyl radical and hydroxo ferryl ion complex (quasi-Fenton mechanism), (ii) heterolytic cleavage of the O–O bond in the complex to afford the ferryl ion (ferryl ion mechanism) (Chart 2). An alkoxyl radical is unable to epoxidize an olefin, though the radical can abstract a hydrogen atom from a hydrocarbon. The hydroxo ferryl ion (Fe(IV)–OH) may not oxidize an organic compound. On the other hand, the ferryl ion (Fe(IV)–O $\cdot$) which is formed in the reaction between Fe(III)TPPCL and PhIO, is capable of epoxidizing an olefin as well as abstracting a hydrogen atom from a hydrocarbon. Since the stereoselectivities in the epoxidations of **1** and **3** by the Fe(III)TPPCL-*t*-BuOOH system were similar to those by the Fe(III)TPPCL-PhIO system (Tables I and II), the ferryl ion produced by heterolytic cleavage may participate as a main epoxidizing agent in the oxygenations of **1** and **3** by the Fe(III)TPPCL (10 mM)-*t*-BuOOH system.

1. quasi-Fenton mechanism

2. ferryl ion mechanism

: porphyrin ring

Chart 2

Though the ferryl ion may also participate in the allylic oxidation of **3** with Fe(III)TPPCL-*t*-BuOOH, the extent of the allylic oxidation was greater than that with the Fe(III)TPPCL-PhIO system. Further, the ratio of epoxides to the allylic oxidation products

from the reaction with the Fe(III)TPPCL-^tBuOOH system was similar not to those with the Fe(III)TPPCL-PhIO system but to those with the Fe(acac)₃-^tBuOOH system. Thus, in competition with the heterolytic cleavage of the O–O bond in the complex of Fe(III)TPPCL-^tBuOOH (ferryl ion mechanism in Chart 2), the homolytic cleavage (quasi-Fenton mechanism) seems to occur to give ^tBuO· (responsible for the allylic oxidation of **3**). An alkoxyl radical can induce the decomposition of ROOH to give the alkylperoxy radical, leading to nonstereoselective epoxidation of **1** and β -selective epoxidation of **3**. In the oxygenation by the Fe(III)TPPCL-^tBuOOH system, such radical-induced decomposition may occur to give ^tBuOO·, which may participate partially in the nonstereoselective epoxidations of **1** and β -selective epoxidation of **3**. In fact, the stereoselectivity in the epoxidation of **1** by the Fe(III)TPPCL-^tBuOOH system increased in the presence of a radical scavenger, di-*tert*-butylhydroxytoluene (BHT), and closely resembled that obtained with the Fe(III)TPPCL-PhIO system (Table I). It is, therefore, assumed that the Fe(III)TPPCL-^tBuOOH system produces the ferryl ion and ^tBuO· as active oxidants through heterolytic and homolytic cleavages of the O–O bond in the complex of Fe(III)TPPCL and ^tBuOOH, respectively.

Epoxidation of **1** and **3** by the Fe(III)TPPCL-MCPBA System

Recently, the mode of cleavage of the O–O bond in metalloporphyrin-ROOH complexes has been discussed on the basis of kinetic analysis of the reactions between metalloporphyrins and a series of ROOH including percarboxylic acids (R = acyl).⁴⁾ These kinetic studies suggested that the mode of cleavage depends on the structure of the peroxide; the ease of heterolytic cleavage increases as R in ROOH becomes more electron-withdrawing. Thus, the oxygenations of **1** and **3** were carried out with the Fe(III)TPPCL-MCPBA system, in which the heterolytic cleavage seems to be favorable. The results obtained are summarized in Tables I and II. Since **1** and **3** are epoxidized by MCPBA alone at 25 °C *via* a nonradical process,⁹⁾ inhibition of these epoxidations is necessary to characterize the mode of oxygenation by the Fe(III)TPPCL-MCPBA system. Though MCPBA did not epoxidize **1** at –30 °C, the epoxidation of **3** proceeded even at –30 °C. The epoxidations of both **1** and **3** were inhibited almost completely by addition of γ -collidine (2,4,6-trimethylpyridine). Collidine can act as a base, but cannot coordinate to iron porphyrin because of its steric hindrance.¹⁰⁾ Thus, collidine seems not to have any effect on the mode of the oxygenation by the Fe(III)TPPCL-MCPBA system. In fact, the presence of γ -collidine did not alter the mode of oxygenation of **1** and **3** by the Fe(III)TPPCL-^tBuOOH system. In the oxygenations of both **1** and **3** by the Fe(III)TPPCL-MCPBA system at –30 °C in the presence of γ -collidine, the extents of epoxidation increased significantly as compared with the results obtained with the Fe(III)TPPCL-^tBuOOH system. Since the yields of epoxides in both reactions exceeded 100% on the basis of Fe(III)TPPCL, the iron played a catalytic role. Furthermore, the product distributions and stereoselectivities in the epoxidations closely resembled those with the Fe(III)TPPCL-PhIO system. Therefore, the Fe(III)TPPCL-MCPBA system may give Fe–O· as a main active oxygen through the heterolytic cleavage of the O–O bond in the Fe(III)TPPCL-MCPBA complex. This conclusion is in agreement with those of Lee and Bruce⁴⁾ and Traylor *et al.*¹⁰⁾

From the results obtained in this study, it may be concluded that the mode of oxygenation by the Fe(III)TPPCL-peroxide system depends on the concentration of Fe(III)TPPCL as well as the structure of the peroxide. In the presence of catalytic amounts of Fe(III)TPPCL (0.1 mM), ^tBuOOH decomposes *via* a free radical chain reaction to give ^tBuO· and ^tBuOO·, which are responsible for allylic oxidation and epoxidation, respectively. At a high concentration (10 mM of Fe(III)TPPCL), however, the O–O bond in the Fe(III)TPPCL and ^tBuOOH complex cleaves both heterolytically and homolytically. The former leads to Fe–O· and the latter to ^tBuO· as active oxygen species. On the other hand, when MCPBA is used instead of ^tBuOOH, Fe–O· is formed as a main active oxygen species through the

heterolytic cleavage of the O–O bond in the Fe(III)TPPCL–MCPBA complex.

The mechanism of camphor hydroxylation by the lipoate–cytochrome P-450 system has been reported to involve acylation of heme-bound dioxygen by the carboxylate of lipoate.¹¹⁾ It is of interest that oxygenation by the Fe(III)TPPCL–MCPBA–collidine system, a chemical model for the enzymatic reaction, proceeds with the ferryl ion (Fe–O·) as an attacking species. Our results suggest that P-450-catalyzed oxygenation involves both heterolytic and/or homolytic cleavage of the O–O bond in the oxidant, depending on its structure.

Experimental

General Methods—Gas chromatograms were taken on a Shimadzu GC-4CM machine. Proton nuclear magnetic resonance (¹H-NMR) spectra were measured with a JEOL JNM-FX 100FT spectrometer at 100 MHz with tetramethylsilane as an internal standard in CDCl₃. Determinations of the yield and the epimeric ratio of **2a** and **2b** were carried out by the reported gas liquid chromatography (GLC) method (column, 2% OV 225 (2 m × 3 mm i.d.); column temp., 150 °C).^{1b)} The epimeric ratio of **4a** and **4b** was determined by the ¹H-NMR method previously reported.¹²⁾ Radioactivity was measured with a Packard Tri-Carb 460C. For thin-layer chromatography (TLC), silica gel (Wakogel B-5F) was used as an adsorbent.

Materials—Fe(III)TPPCL was prepared by the method of Adler *et al.*¹³⁾ Cholesteryl acetate (**3**) and authentic samples (**4**–**7**) were prepared by the methods reported previously.¹⁴⁾ [4-¹⁴C]cholesteryl acetate (5.0 × 10⁴ cpm/mg) was prepared from [4-¹⁴C]cholesterol (60.0 mCi/mmol, from Japan Radioisotope Association) by the cited method.¹⁵⁾ ^tBuOOH (Nakarai Chem. Co.) was purified by distillation under reduced pressure. The purity was determined to be 94% by iodometry. Other reagents were purchased from commercial sources and were used without purification.

Oxygenation of **1 in the Fe(III)TPPCL–^tBuOOH System**—A chlorobenzene solution (1.0 ml) of **1** (0.12 mmol), Fe(III)TPPCL (0.1 or 10 μmol) and ^tBuOOH (0.20 mmol) was stirred for 1 h at 25 °C under an argon atmosphere. A portion (0.1 ml) of the reaction mixture was subjected to chromatography on silica gel (1 g) and eluted with benzene (10 ml). The benzene eluate was evaporated to dryness. The residue was redissolved in 0.1 ml of acetone containing benzophenone as an internal standard. The solution was subjected to GLC for determination of the yield and the isomer ratio of the resulting epoxides. The effect of BHT or γ-collidine was tested by addition of 0.06 mmol of BHT or 0.23 mmol of γ-collidine. Under the same conditions, the effect of various concentrations of Fe(III)TPPCL (0.1–10 mM) or ^tBuOOH (10–2000 mM) on this reaction was examined at 200 mM ^tBuOOH or 10 mM Fe(III)TPPCL, respectively.

Oxygenation of **3 in the Fe(III)TPPCL–^tBuOOH System**—A chlorobenzene solution (1.0 ml) of **3** (4-¹⁴C labeled, 0.12 mmol), Fe(III)TPPCL (0.1 or 10 μmol) and ^tBuOOH (0.20 mmol) was stirred for 1 h at 25 °C under an argon atmosphere. A portion (20 μl) of the reaction mixture was diluted with benzene containing carrier steroids (**3**–**7**), subjected to TLC and developed with benzene–ethyl acetate (19:1, for **4**, **5**, and **6**) or *n*-hexane–benzene (6:4, × 3, for **3** and **7**). The steroids on the TLC plates were visualized with iodine vapor. After the iodine had evaporated, the corresponding zones were scraped into counting vials. The radioactivities were measured for the determination of the product distribution. For the determination of the epimeric ratio of the epoxides (**4a** and **4b**), an unlabeled substrate was used for the oxygenation. The epoxides were separated from the reaction mixture in a similar manner, and the epimeric ratio was determined by the ¹H-NMR method.¹²⁾

Epoxidation of **1 or **3** by MCPBA**—MCPBA (0.10 mmol) was added to a chlorobenzene solution (1.0 ml) of **1** or **3** (0.12 mmol), and the mixture was allowed to stand at –30 °C for 1 h under an argon atmosphere. The reaction mixture was worked up, and the product distribution and the epimeric ratio of the epoxides were determined. Under the same conditions, the oxygenation of **1** or **3** with MCPBA was carried out in the presence of γ-collidine (0.23 mmol).

Oxygenation of **1 or **3** in the Fe(III)TPPCL–MCPBA System in the Presence of γ-Collidine**—MCPBA (0.10 mmol) was added to a chlorobenzene solution (1.0 ml) of **1** or **3** (0.12 mmol), Fe(III)TPPCL (0.01 mmol) and γ-collidine (0.23 mmol). The mixture was allowed to stand at –30 °C for 1 h under an argon atmosphere, then treated as described above for the determination of products and the epimeric ratio of the epoxides.

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References and Notes

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