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# On the Mode of Epoxidation by the Tetraphenylporphinatoiron(III)–Iodosylbenzene System[1)]

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Epoxidation of cholesteryl acetate by a nonradical reagent system such as *m*-chloroperbenzoic acid, $Mo(CO)_6$–$^t$BuOOH, or $Fe(ClO_4)_3$–$H_2O_2$ was highly α-stereoselective. In contrast, a radical reagent system such as Fe(*acac*)$_3$–$^t$BuOOH, $KO_2$–$^t$BuBr, or biacetyl–$O_2$-***hv***, showed high β-selectivity. The stereoselectivity in the epoxidation of cholesteryl acetate seems, therefore, to be a useful indication of the mode of reaction. On this basis, epoxidation may occur through a radical process in the tetraphenylporphinatoiron(III)chloride–iodosylbenzene system. Earlier studies with stilbene had failed to clarify the mechanism in this system.

**Keywords**——cholesteryl acetate; stereoselectivity of epoxidation; stilbene; nonradical process; radical process; *meso*-tetraphenylporphinatoiron(III)chloride; iodosylbenzene

A unique hemoprotein, cytochrome P-450, participates in the biosynthesis of physiological substances and in the metabolism of these substances, drugs, and other xenobiotics.[2)] The mechanism of oxygen activation by this protein has been the subject of extensive investigation. Since the oxygenation of substrates has been shown to occur at an iron porphyrin site, various chemical models of cytochrome P-450 have been studied, including metalloporphyrin derivatives.[3)] Recently, the oxygenations of substrates such as olefins, aromatic compounds, and hydrocarbons with iodosylbenzene (PhIO) mediated by tetraphenylporphinatoiron(III)–chloride (Fe(III)TPPCl) were examined as model reactions, and the results of hydroxylation and epoxidation were similar to those with cytochrome P-450.[4–6)] Groves *et al.*[4)] reported the stereospecific epoxidation of stilbenes with the Fe(III)TPPCl–PhIO system, which proceeds by a nonradical concerted mechanism, as does that with organic peracids. They also assumed that active oxygen species of radical character participates in the hydroxylation with the same model system.[7)] Lindsay Smith and Sleath[6)] reported the radical ferryl ion (Fe-O·) as the active species in the Fe(III)TPPCl–PhIO system, which produces stereospecific epoxidation of stilbene; the intermediate radical of the substrate in its solvent cage is, prior to equilibration of the radical isomers, rapidly closed to form the oxirane ring. Thus, the mechanism of epoxidation with the Fe(III)TPPCl–PhIO system could not be elucidated with stilbene, which has often been used as a substrate for investigating the mode of oxygenation reactions.

In a series of studies on the oxygenation of cholesteryl acetate, we found that the nonradical reagent, *m*-chloroperbenzoic acid (MCPBA), gave highly α-stereoselective epoxidation and, in contrast, high β-selectivity was obtained with the tris (acetylacetonato) iron (III) (Fe(*acac*)$_3$)–ROOH system, in which the epoxidation proceeded through a radical process.[8,9)] Triplet carbene of radical character showed β-selective addition.[10)] These results prompted us to confirm that the stereoselectivity in the epoxidation of cholesteryl acetate can be regarded as a reliable indication of the mode of reaction (radical or nonradical process). In

this paper, we describe the epoxidation reactions with some usual reagents and with the Fe(III)TPPCl–PhIO system, and a mechanism is proposed.

## Results and Discussion

### Epoxidation *via* a Nonradical Process

The epoxidations of stilbene (**1**) and cholesteryl acetate (**3**) were examined with the well-known agent, MCPBA,[11] and the $Mo(CO)_6$–$^t$BuOOH system, which produces the metal complex of hydroperoxide as an epoxidizing agent[12] (Table I). Both *cis*- and *trans*-stilbenes were epoxidized stereospecifically, completely retaining their original configuration. The epoxidation of cholesteryl acetate by the reagents showed high α-selectivity; these epoxidizing agents gave the β-epoxide in the ratio ($\beta/\alpha+\beta$) of 0.33 or 0.36, respectively.[13] The stereoselectivities were not affected by the presence of a radical scavenger, butylated hydroxytoluence (BHT), in the reaction mixtures. The reaction in the $Fe(ClO_4)_3$–$H_2O_2$–$CH_3CN$ system, which was proposed to involve both radical and nonradical processes, also selectively gave the α-epoxide of cholesteryl acetate, showing a ratio of 0.33, which decreased to 0.17 when BHT was added to the reaction mixture.[14] Thus, the α-stereoselectivity is clearly high when cholesteryl acetate is epoxidized *via* a nonradical process.

### Epoxidation *via* a Radical Process

Three systems, which are known to function in a radical fashion, were employed for the epoxidation of *cis*- and *trans*-stilbenes and cholesteryl acetate, and the results are summarized in Table II. These three were the illuminated biacetyl–$O_2$ system,[15] the $^t$BuBr–$KO_2$ system,[16,17] which produces *tert*-butyl hydroperoxyl radical, and the $Fe(acac)_3$–$^t$BuOOH system, in which both peroxyl and alkoxyl radicals were proposed to act as the attacking species.[8] Since the C–C bond is capable of free rotation in the radical intermediate (Chart 2),

Table I. Stereoselectivity of Epoxidation *via* a Nonradical Process

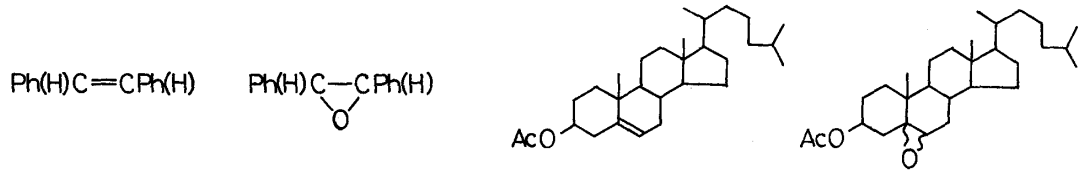
| | 1 | 2 | | 4 | |
|---|---|---|---|---|---|
| | | Yield (%) | *cis* : *trans* | Yield (%) | $\beta/\alpha+\beta$ |
| MCPBA | *trans* | 70 | 0 : 100 | 100 | 0.33 |
| | *cis* | 78 | 100 : 0 | | |
| $Mo(CO)_6$–$^t$BuOOH | *trans* | 100 | 0 : 100 | 100 | 0.36 |
| | *cis* | 84 | 100 : 0 | | |

Figures are the means of three runs in benzene.

Table II. Stereoselectivity of Epoxidation *via* a Radical Process[a]

| | 1 | 2 | | 4 | |
|---|---|---|---|---|---|
| | | Yield (%) | *cis* : *trans* | Yield (%) | $\beta/\alpha+\beta$ |
| $Fe(acac)_3$–$^t$BuOOH[b] | *trans* | 50 | 4 : 96 | 13 | 0.72 |
| | *cis* | 45 | 4 : 96 | | |
| Biacetyl-$O_2$–*hν* | *trans* | 89 | 1 : 99 | 94 | 0.70 |
| | *cis* | 94 | 1 : 99 | | |
| $^t$BuBr–$KO_2$[c] | *trans* | 10 | 5 : 95 | 14 | 0.75 |
| | *cis* | 8 | 6 : 94 | | |

*a*) Figures are the means of three runs in benzene. *b*) See ref. 8*b*. *c*) See ref. 17.




1 2 3 4

Chart 1

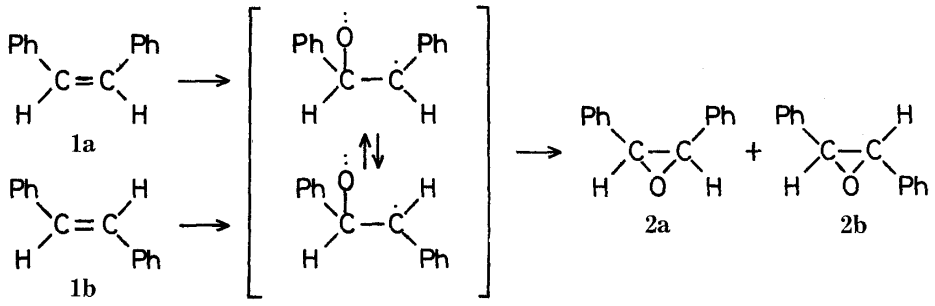



Chart 2

the epoxidation of stilbenes was nonstereospecific and the isomer ratio of *cis*- and *trans*-epoxides ranged from 1 : 99 to 6 : 94. The epoxidation of cholesteryl acetate was, in contrast to that *via* a nonradical process, highly $\beta$-stereoselective, and the ratio ($\beta/\alpha+\beta$) ranged from 0.70 to 0.75. The stereoselectivity in the epoxidation of cholesteryl acetate was, thus, shown to depend on the mode of reaction; a nonradical or radical process leads to $\alpha$- or $\beta$-selectivity, respectively.

These results suggest that the stereoselectivity in the epoxidation of cholesteryl acetate may be used as an indicator of the mode of reaction. Since free rotation of the C(5)–C(6) bond is impossible in the radical intermediate formed from cholesteryl acetate, the stereoselectivity in its epoxidation may be independent of the rate constant of the radical reaction in a solvent cage. Cholesteryl acetate may, therefore, be superior as such an indicator to stilbenes, for which the solvent cage participates in the reaction mechanism.

**Epoxidation with Metal(III)TPPCl–Iodosylbenzene Systems**

The reaction of stilbene with the Mn(III)TPPCl–PhIO system gives isomeric epoxides through the radical process, which allows free rotation of the C–C bond in the transition state.[18] The epoxidations with the Fe(III)TPPCl[4,6] and Cr(III)TPPCl[19]–PhIO system are, on the other hand, known to be stereospecific owing to the participation of the solvent cage. In the epoxidation of *cis*- and *trans*-stilbenes with the Mn(III)TPPCl–PhIO system, the formation of the *trans*-epoxide was predominant and was independent of the solvent (*e.g.* dichloromethane, benzene, and chlorobenzene). The epoxidation in this system was, thus, clearly shown to proceed in a radical fashion, as has been reported.[18] When the substrate was cholesteryl acetate, epoxidation was, as expected, highly $\beta$-stereoselective showing a ratio ($\beta/\alpha+\beta$) of 0.77—0.88 (Table III). Since the epoxidizing species formed in the Mn(III)-TPPCl–PhIO system is known to have a highly radical character,[16] the above-mentioned features of cholesteryl acetate remained unchanged when the metal(III)TPP complex was the attacking species.

In the title reaction, stilbene mainly gave the epoxide retaining its original geometry, but the stereoisomer was also obtained, and was presumably formed through the free rotation of the C–C bond in the radical intermediate. Cholesteryl acetate, however, was clearly characteristic, showing high $\beta$-stereoselectivity (Table IV). The Cr(III)TPPCl–PhIO system

gave results similar to those of the title reaction system when stilbene and cholesteryl acetate were employed as substrates (Table V). Thus, the radical species probably participates in the title reaction and the epoxidation with the Cr(III)TPPCl–PhIO system. In the reaction of Cr(III)TPPCl with PhIO, and active species, O=Cr(V)TPPCl, was shown to be formed by oxygen atom transfer from PhIO to Cr(III)TPPCl.[20] Thus, the Fe(III)TPPCl–PhIO system is assumed to give, in a similar fashion, an active species capable of epoxidizing an olefin *via* a radical process.

In this study, it was revealed that the epoxidation of cholesteryl acetate is α- and β-stereoselective when the reactions proceed through nonradical and radical processes, respectively. Although the reason for this characteristic of cholesteryl acetate remains unknown, the stereoselectivity in the epoxidation of cholesteryl acetate may be an important indicator for characterizing the mode of reaction.

TABLE III. Stereoselectivity of Epoxidation by Mn(III)TPPCl and PhIO

| Solvent | 1 | 2 | | | 4 | |
|---|---|---|---|---|---|---|
| | | Yield (%) | *cis* : | *trans* | Yield (%) | β/α+β |
| $CH_2Cl_2$ | *trans* | 23 | 1 : | 99 | 24 | 0.88 |
| | *cis* | 37 | 33 : | 67 | | |
| PhH | *trans* | 16 | 0 : | 100 | 24 | 0.79 |
| | *cis* | 41 | 25 : | 75 | | |
| PhCl | *trans* | 20 | 0 : | 100 | 18 | 0.77 |
| | *cis* | 34 | 33 : | 67 | | |

Figures are the means of three runs.

TABLE IV. Stereoselectivity of Epoxidation by Fe(III)TPPCl and PhIO

| Solvent | 1 | 2 | | | 4 | |
|---|---|---|---|---|---|---|
| | | Yield (%) | *cis* : | *trans* | Yield (%) | β/α+β |
| $CH_2Cl_2$ | *trans* | 3 | 0 : | 100 | 12 | 0.78 |
| | *cis* | 23 | 87 : | 13 | | |
| PhH | *trans* | 13 | 0 : | 100 | 25 | 0.83 |
| | *cis* | 26 | 94 : | 6 | | |
| PhCl | *trans* | 14 | 7 : | 93 | 31 | 0.72 |
| | *cis* | 31 | 90 : | 10 | | |

Figures are the means of three runs.

TABLE V. Stereoselectivity of Epoxidation by Cr(III)TPPCl and PhIO

| Solvent | 1 | 2 | | | 4 | |
|---|---|---|---|---|---|---|
| | | Yield (%) | *cis* : | *trans* | Yield (%) | β/α+β |
| $CH_2Cl_2$ | *trans* | 4 | 0 : | 100 | 3 | 0.75 |
| | *cis* | 14 | 77 : | 23 | | |
| PhH | *trans* | 2 | 0 : | 100 | 1 | 0.71 |
| | *cis* | 10 | 89 : | 11 | | |
| PhCl | *trans* | 4 | 0 : | 100 | 2 | 0.89 |
| | *cis* | 13 | 87 : | 13 | | |

Figures are the means of three runs.

When stilbene was used as a substrate, the mode of the title reaction was not clear owing to the possible participation of a solvent cage. However, cholesteryl acetate showed high β-stereoselectivity in the epoxidation with the Fe(III)TPPCl–PhIO system, suggesting that the title reaction proceeds by a radical mechanism. Thus, the attacking species formed in the title reaction may be the ferryl ion, which is assumed to be highly radical in character, as reported in studies on hydroxylation.[7] Since oxygenation by cytochrome P-450 has recently been reported to proceed by a radical mechanism,[2] it is of interest that epoxidation with Fe(III)TPPCl–PhIO, a chemical model of the enzymatic reaction, also proceeds by a radical mechanism.

## Experimental

**General Methods**——Gas chromatograms were taken on a Shimadzu GC-4CM PF machine. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were measured with a JEOL JNM-FX 100 FT spectrometer at 100 Mz with tetramethylsilane as an internal standard in $CDCl_3$. Determination of the yield and the epimeric ratio of the cholesterol epoxide were carried out by the reported methods using an Iatron TFG-10 Thinchrograph (TLC-FID) and a $^1$H-NMR spectrometer, respectively.[9]

**Materials**——Iodosylbenzene and M(III)TPPCl (M = Mn, Fe, Cr) were prepared by the methods of Lucas *et al.*[21] and Adler *et al.*,[22] respectively. Cholesteryl acetate and authentic samples (**2** and **4**) were prepared by the usual methods. Other reagents were purchased from commercial sources.

**Epoxidation of Stilbenes by MCPBA**——A benzene solution (6 ml) of stilbene (117 μmol) and MCPBA (130 μmol) was allowed to stand for 24 h at room temperature. A portion (0.4 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 and the residue was redissolved in 0.1 ml of acetone containing benzophenone as an internal standard. This solution was subjected to gas liquid chromatography (GLC) (column: 2% OV 225, 2 m × 3 mm i.d.; column temp. 150 °C) for determination of the yield and the isomer ratio of the epoxide.

**Epoxidation of Cholesteryl Acetate by MCPBA**——A benzene solution of cholesteryl acetate and MCPBA was treated as described above. The reaction mixture was diluted with AcOEt and the soltion was washed with saturated aqueous $Na_2SO_3$, sat. aq. $NaHCO_3$ and sat. aq. NaCl, then dried on anhydrous $Na_2SO_4$, filtered and finally evaporated to dryness. The residue was subjected to TLC-FID and $^1$H-NHR measurements. The yield and the epimeric ratio of the epoxide were determined according to the general methods.

**Epoxidation of Stilbenes by the Biacetyl–$O_2$-*hν* System**——A benzene solution (5 ml) of stilbene (115 μmol) and biacetyl (575 μmol) was stirred with bubbling oxygen and irradiated for 1.5 h with a 500 W tungsten lamp at 17 °C. After usual work up, the yield and the isomer ratio of the epoxide were determined by the GLC method as described above.

**Epoxidation of Cholesteryl Acetate by the Biacetyl–$O_2$-*hν* System**——A mixture of cholesteryl acetate, biacetyl, and benzene in the same amounts was treated as described above. The reaction mixture was worked up as usual and the residue thus obtained was chromatographed over silica gel (1 g) to remove biacetyl prior to determination of the yield and the epimeric ratio of the epoxide by the general methods.

**Epoxidation of Stilbenes by the Metal(III)TPPCl–PhIO System**——Iodosylbenzene (47 μmol) was added to a mixture of stilbene (122 μmol), M(III)TPPCl (3.40 μmol; M = Mn, Fe, Cr), and organic solvent (0.5 ml). The reaction mixture was vigorously stirred for 1 h at 20 °C under an Ar atmosphere. A portion (0.1 ml) of the reaction mixture was worked up as described above and the yield and the isomer ratio of the epoxide were determined by the GLC method.

**Epoxidation of Cholesteryl Acetate by the M(III)TPPCl–PhIO System**——Iodosylbenzene (94 μmol) was added to a mixture of cholesteryl acetate (224 μmol), M(III)TPPCl (6.80 μmol; M = Mn, Fe, Cr), and organic solvent (1.0 ml). The reaction mixture was treated as described above and a portion of it was subjected to TLC-FID to determine the yield of the epoxide. The remainder of the reaction mixture was subjected to chromatography on silica gel (1 g) and eluted with *n*-hexane (5 ml), benzene (10 ml), and $CHCl_3$ (10 ml). The $CHCl_3$ eluate was evaporated to dryness and the residue was used for determining the epimeric ratio of the epoxide by the $^1$H-NMR method.

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## References and Notes

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