Epoxidation of Olefins by a Water-Soluble Iron(III) Porphyrin Complex and Hydroperoxides in Aqueous Solution

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Elucidation of the mechanism of oxygen atom-transfer reactions by monooxygenase enzymes and metal complexes has been the major goal of bioinorganic and oxidation chemistry.[1] In recent studies, use of hydroperoxides in the catalytic oxygenations of organic substrates by iron(III) porphyrin complexes has drawn particular attention, since the reactions with such oxidants are more biologically relevant than those with other oxygen atom donors such as iodosylbenzene, peroxyacids, periodate, NaOCl, and $KHSO_5$.[2] Traylor and co-workers first succeeded in using hydrogen peroxide and *tert*-butyl hydroperoxide in olefin epoxidation reactions by iron porphyrins in hydroxylic solvent system (*i.e.*, CH_3OH solution).[3] We also showed that an electronegatively-substituted iron(III) porphyrin complex catalyzes the epoxidation and the hydroxylation of hydrocarbons by H_2O_2 in aprotic solvent (*i.e.*, acetonitrile solution).[4] In aqueous solution, however, the epoxidation of olefins with the oxidants such as H_2O_2 and *t*-BuOOH has not been successful,[5] although Meunier and co-workers reported the olefin epoxidations in water with biologically irrelevant oxidants like $KHSO_5$.[6,7] We now report that a water-soluble iron porphyrin complex catalyzes the epoxidation of olefins with H_2O_2 and *t*-BuOOH in buffered aqueous solutions. A high-valent iron(IV) oxo porphyrin cation radical complex is proposed as a reactive intermediate responsible for the olefin epoxidation.

The epoxidation of CBZ (CBZ=carbamazepine) by H_2O_2 and *t*-BuOOH was performed in the presence of a water-soluble iron(III) porphyrin complex, (*meso*-5,10,15,20-tetrakis(2,6-difluoro-3-sulfonatophenyl)porphinato)iron(III) [Fe(TDFPPS)] (Figure 1),[8] in aqueous solution.[9] The CBZ epoxidation by $KHSO_5$ was also carried out for comparison.[6] As the results of the epoxidation reactions were shown in Figure 2, the conversion of the substrate was high at relatively low pH values (*vide infra*) and the resulting product
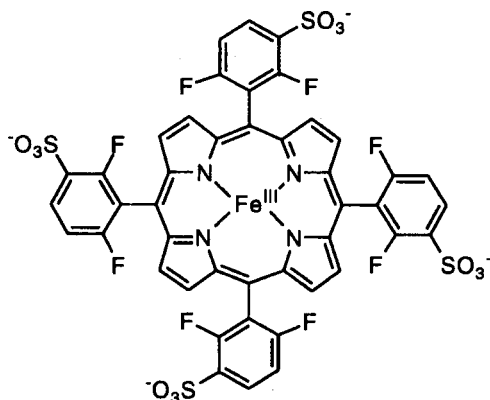
was identified to be CBZ-10,11-oxide in all the reactions of H_2O_2, *t*-BuOOH, and $KHSO_5$. Formation of the oxide product was not detected in the absence of the iron porphyrin complex.

In order to characterize the nature of the epoxidizing intermediate formed in the reactions of H_2O_2 and *t*-BuOOH, we studied the following reactions: (1) stereoselectivity in *cis*-stilbene and *trans*-stilbene epoxidations, (2) intermolecular competitive epoxidation between *cis*-stilbene and *trans*-stilbene and between *cis*-stilbene and CBZ, (3) epoxidation of CBZ in isotopically labeled water, $H_2^{18}O$. We then compared the reactivity patterns obtained in these reactions to those obtained from the identical reactions performed with $KHSO_5$, since it has been shown previously that high-valent iron(IV) oxo porphyrin cation radical species are generated in the reactions of iron porphyrins and $KHSO_5$.[6,7a] The results are listed in Table 1. In the *cis*- and *trans*-stilbene epoxidations, the substrates disappeared completely, and *cis*-stilbene oxide was formed in the *cis*-stilbene epoxidation and *trans*-stilbene oxide was the product in the *trans*-stilbene epoxidation. From the results of the *cis*-stilbene epoxidation, we were able to rule out the involvement of both peroxyl radicals (ROO·) and $(Porp)Fe^{IV}=O$ as epoxidizing agents in the reactions of H_2O_2 and *t*-BuOOH, since these species should oxidize *cis*-stilbene nonstereospecifically.[10] In the intermolecular competitive epoxidation reactions,[11] we found that the ratios of the products (*i.e.*, *cis*-stilbene oxide to *trans*-stilbene oxide and *cis*-stilbene oxide to CBZ-10,11-oxide) were identical within the experimental error. Interestingly, equal amounts of *cis*- and *trans*-stilbene
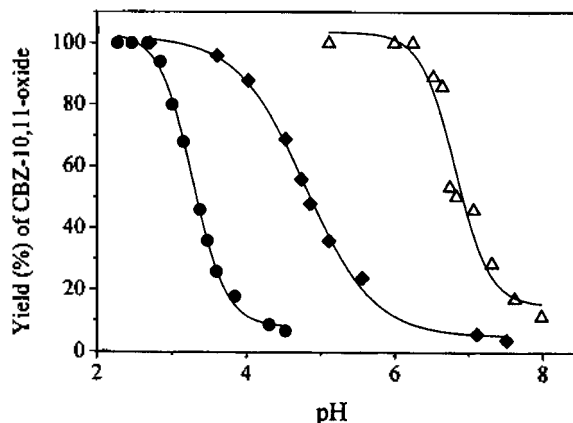

Fig. 1. Structure of Fe(TDFPPS) complex.

Figure 2. Plot of the percent yield of CBZ-10,11-oxide based on CBZ used *vs.* pH of reaction solutions for the catalytic epoxidations of CBZ by H_2O_2 (●), *t*-BuOOH (◆), and $KHSO_5$ (△) carried out in the presence of Fe(TDFPPS) in buffered aqueous solutions.

Table 1. Stereospecificities and Competitive Reactivities Studied in the Epoxidation of Olefins by Fe(TDFPPS)[a]

Oxidant	Products (yields, mM)	
1. *cis*-stilbene epoxidation		
	cis-stilbene oxide	*trans*-stilbene oxide
H_2O_2	0.75	trace[b]
t-BuOOH	0.65	trace[b]
$KHSO_5$	0.76	trace[b]
2. *trans*-stilbene epoxidation		
	cis-stilbene oxide	*trans*-stilbene oxide
H_2O_2	0	0.68
t-BuOOH	0	0.70
$KHSO_5$	0	0.65
3. competitive reaction between *cis*-stilbene and *trans*-stilbene[c]		
	cis-stilbene oxide	*trans*-stilbene oxide
H_2O_2	0.34	0.33
t-BuOOH	0.43	0.43
$KHSO_5$	0.25	0.22
4. competitive reaction between *cis*-stilbene and CBZ[d,e]		
	cis-stilbene oxide	CBZ-10,11-oxide
H_2O_2	0.32	0.10
t-BuOOH	0.31	0.080
$KHSO_5$	0.31	0.10

[a] Reactions were run in a solvent mixture of buffered water (2.5 mL)/CH_3OH (1.0 mL)/CH_3CN (1.5 mL) in order to make the reaction mixture homogeneous. Other reaction procedures were the same as described in ref 9. [b] Less than 0.02 mM was formed. [c] The amounts of oxidants used were as follows: H_2O_2 (1 mM), *t*-BuOOH (2.5 mM), and $KHSO_5$ (0.5 mM). [d] Mixtures of *cis*-stilbene (1 mM) and CBZ (5 mM) were used to improve the accuracy for measuring the amount of CBZ-10,11-oxide product. [e] The amounts of oxidants used were as follows: H_2O_2 (0.5 mM), *t*-BuOOH (1.3 mM), and $KHSO_5$ (0.25 mM).

oxides were formed in the competitive epoxidation between *cis*- and *trans*-stilbenes. In other iron porphyrin-catalyzed epoxidation reactions,[12] only a small amount of *trans*-stilbene oxide was formed due to the steric interaction between the phenyl groups of *trans*-stilbene and the phenyl groups of iron porphyrin complexes. As a result, the competitive epoxidation reactions suggest us that a common intermediate governs the epoxidation of olefins by H_2O_2, *t*-BuOOH, and $KHSO_5$. More significantly, when the CBZ epoxidation was carried out with H_2O_2 in buffered $H_2{}^{18}O$ solution,[13] we found that 33% of oxygen in the oxide product came from solvent water, $H_2{}^{18}O$ (eq. 1). This is the strong evidence that the reactive intermediate generated in the reaction of Fe(TDFPPS) with H_2O_2 is the high-valent iron(IV) oxo porphyrin cation radical.[6,7a,14,15] All the results obtained from the mechanistic studies discussed above clearly demonstrate that a common intermediate is generated in the reactions of H_2O_2, *t*-BuOOH, and $KHSO_5$ and that the intermediate responsible for the olefin epoxidation is a high-valent iron(IV) oxo porphyrin cation radical species.

Therefore, we conclude unambiguously that reactions of water-soluble iron porphyrin complexes with H_2O_2 and *t*-BuOOH form high-valent iron(IV) oxo porphyrin intermediates in aqueous solution as well as in organic solvent

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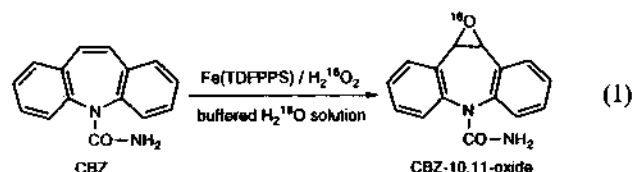
systems.

It is of interest to observe that the yields of the oxide product formed in the epoxidation reactions depend significantly on the pH of the reaction solutions (see Figure 2). The pH effect has also been observed in other metalloporphyrin-catalyzed oxidation reactions with $KHSO_5$ in aqueous solution; however, no clear explanation has been provided for such a phenomenon.[7] The pH dependence of the olefin epoxidation indicates that the generation of the high-valent iron(IV) oxo porphyrin cation radical intermediate is affected by the acidity of the reaction solutions.[16] Three possible mechanisms that may be consistent with this pH effect are (a) general-acid catalysis,[17] (b) a facile $1e^-$ oxidation of $(Porp)Fe^{IV}-OH$ by RO^- "in the cage" at low pHs,[18] and (c) the effect of the nature of the axial ligand bound to metal center (*i.e.*, $(Porp)Fe^{III}(X)_2$, where X represents either H_2O or HO^- depending on the pH of the solution) on the heterolytic *vs.* homolytic O-O cleavage.[19] We have no convincing results to explain such a pH effect at this moment, and detailed mechanistic studies to elucidate the pH dependence of the epoxidation of olefins in aqueous solution are currently under investigation in this laboratory.

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8. Fe(TDFPPS) was obtained from Mid-Century Chemical.

9. In a typical reaction, oxidant (4 mM, 10 mM, and 1 mM for H_2O_2, *t*-BuOOH, and $KHSO_5$, respectively) was added to a reaction solution containing Fe(TDCPPS) (0.04 mM) and CBZ (1 mM, introduced as a 0.1 M solution in methanol) in buffered aqueous solution (5 mL). Reactions at pH 2-3 were performed in formate buffer (0.1 M), at pH 4-5 in acetate buffer (0.1 M), and at pH 6-7 in phosphate (0.1 M), and the pH of the reaction solutions was adjusted by adding either HCl (3 N) or NaOH (3 N) solutions whenever it was necessary. The reaction mixture was stirred in air for 30 min at 25 °C, and then analyzed by Orom Vintage 2000 HPLC equipped with a variable wavelength UV-200 detector. CBZ and its epoxide derivative were separated on Waters Symmetry C18 column, 5 μM, eluted by a mixture of methanol/water, 60:40 (v/v), with retention times of 4.8 and 3.5 min, respectively. Detection was made at 215 nm. Calculation of the conversions of CBZ and the yields of CBZ-10,11- oxide was determined on the corresponding calibration curves of CBZ and the authentic CBZ-10,11-oxide prepared by a literature method. See ref 6 for the preparation of CBZ-10,11-oxide as an authentic sample.

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13. Isotopically labeled water, $H_2^{18}O$, experiment was performed in a buffered solution (0.1 M formate consisted of 200 μL of $H_2^{18}O$ (95% ^{18}O enrichment, Aldrich Chemical Co.) and 40 μL of $H_2^{16}O$) containing Fe (TDFPPS) (0.1 mM) and CBZ (0.4 mM, introduced as a 0.1 M solution in methanol). H_2O_2 (1.6 mM) was added to the reaction solution, and the solution was stirred for 30 min at room temperature. The reaction solution was taken to dryness using a Speed-Vac. Then, CH_3CN (300 μL) was added to the residue followed by filtration. The filtrate was analyzed with VG70- VSEQ mass spectrometer (VG ANALYTICAL, UK) by using the electronic impact method at 70 eV. ^{16}O and ^{18}O compositions in CBZ-10,11-oxide were determined by the relative abundances of mass peaks at m/z=252 for ^{16}O and m/z=254 for ^{18}O.

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