Nature of the Epoxidizing Intermediates in the Epoxidation of Olefins by Hydrogen Peroxide, *tert*-Butyl Hydroperoxide, *m*-Chloroperbenzoic Acid, and Iodosylbenzene Catalyzed by Iron(III) Porphyrin Complex

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The consensus mechanism for olefin epoxidation by iron porphyrin complexes with peracids involves high-valent iron oxo complexes as an intermediate for oxygen atom transfer to organic substrates.[1] In the cases with hydroperoxides, Traylor and coworkers recently suggested that high-valent iron oxo species, which is generated by the heterolytic O-O bond cleavage of Fe-OOR (R=H, $C(CH_3)_3$), is the reactive species for olefin epoxidation, on the basis of observation that high epoxide yield and stereospecificity are obtained in the epoxidation reactions.[2] In contrast, Bruice *et al.* proposed that the O-O bond of hydroperoxides is cleaved homolytically by iron porphyrin complexes and the resulting ROO· is the epoxidizing agent.[3] In the present Communication, we report, based on the studies of intermolecular competitive reactions, that the intermediate responsible for the olefin epoxidation by hydrogen peroxide, *tert*-butyl hydroperoxide, and *m*-chloroperbenzoic acid is the high-valent iron oxo species and that the epoxidizing intermediate generated in the iodosylbenzene reaction is different from that formed in the reactions of H_2O_2, *t*-BuOOH, and MCPBA. A stable (F_{20}TPP)Fe^{IV}=O complex, which has been characterized by UV-vis, EPR, and ^{1}H NMR spectroscopic methods, is found to be present during the epoxidation reaction by iodosylbenzene.

We carried out intermolecular competitive reactions[4] in the oxidation of organic substrates with various oxidants such as H_2O_2, *t*-BuOOH, MCPBA, and PhIO in the presence of an electronegatively-substituted iron porphyrin complex, (*meso*-tetrakis(pentafluorophenyl)porphinato)iron(III) chloride [Fe(F_{20}TPP)Cl], in order to investigate the nature of the intermediates responsible for oxygen atom transfer. From the studies of relative reactivities of substituted styrenes to styrene in the iron porphyrin complex-catalyzed epoxidations, different ρ values for Hammett plot for the PhIO reaction and for the H_2O_2, *t*-BuOOH, and MCPBA reactions were obtained (see Figure 1). It is of interest to note that the ρ values obtained in the latter reactions were close to the ρ value of −1.9 determined in the styrene epoxidations by iron(IV) oxo porphyrin cation radical species.[5] In addition, from the intermolecular competitive reactions between cyclooctene and cyclooctane, epoxide was obtained as the sole product in the reactions of H_2O_2, *t*-BuOOH, and MCPBA, whereas PhIO reaction gave a good amount of alcohol product (Table 1). Evidently, the same reactivity patterns observed in the H_2O_2, *t*-BuOOH, and MCPBA reactions indicate the involvement of a common high-valent iron oxo complex for olefin epoxidation (see Scheme 1).[2,6] The results from

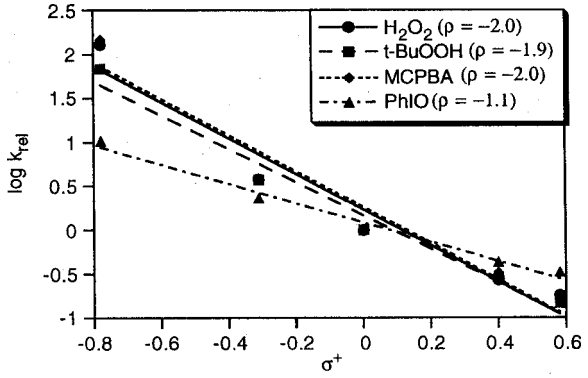
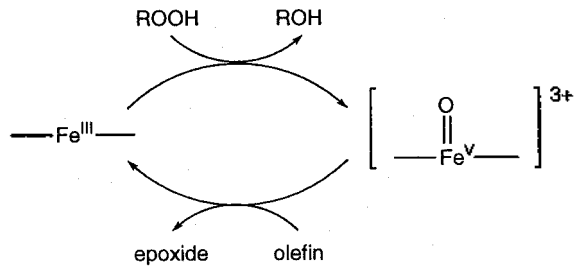


Figure 1. Relative reactivities of substituted styrenes to styrene. Reactions were run in a solution containing Fe(F_{20}TPP)Cl (2.5×10^{-3} mmol), styrene (0.25 mmol), and substituted X-styrene (0.25 mmol, X=*para*-OCH_3, *para*-CH_3, *meta*-Cl, *para*-CF_3) in a mixture (5 mL) of CH_3OH-CH_2Cl_2 (3 : 1). Oxidant (0.15 mmol) was added to the reaction solution, and the solution was stirred for 1 h at ambient temperature. The relative reactivities were determined by the following equation, $k_x/k_y=\log(X_f/X_i)/\log(Y_f/Y_i)$ where X_i and X_f are the initial and final concentrations of substituted styrenes and Y_i and Y_f are the initial and final concentrations of styrene.

Table 1. Competitive Reactions between Cyclooctene and Cyclooctane with Various Oxidants Catalyzed by Fe(F_{20}TPP)Cl[a]

Oxidant	Yield of products (%)		Total yield (%)	Ratio (ol/oxide)
	cyclooctene oxide	cyclooctanol		
H_2O_2	62	0	62	0
t-BuOOH	50	trace	50	0
MCPBA	88	trace	88	0
PhIO	27	21	48	0.78

[a]Reactions were run in a solution containing Fe(F_{20}TPP)Cl (2.5×10^{-3} mmol), cyclooctene (0.1 mmol), and cyclooctane (10 mmol) in a mixture (5 mL) of CH_3OH-CH_2Cl_2 (3 : 1). Oxidant (0.1 mmol) was added to the reaction solution, and the solution was stirred for 1 h at ambient temperature.



Scheme 1.

the competitive reactions also suggest that the active species generated in the PhIO reaction was different from that formed in the H_2O_2, *t*-BuOOH, and MCPBA reactions. The smaller ρ value and high yield of alcohol product resulted in the PhIO reaction indicate that the intermediate species generated in this reaction has a greater reactivity than the

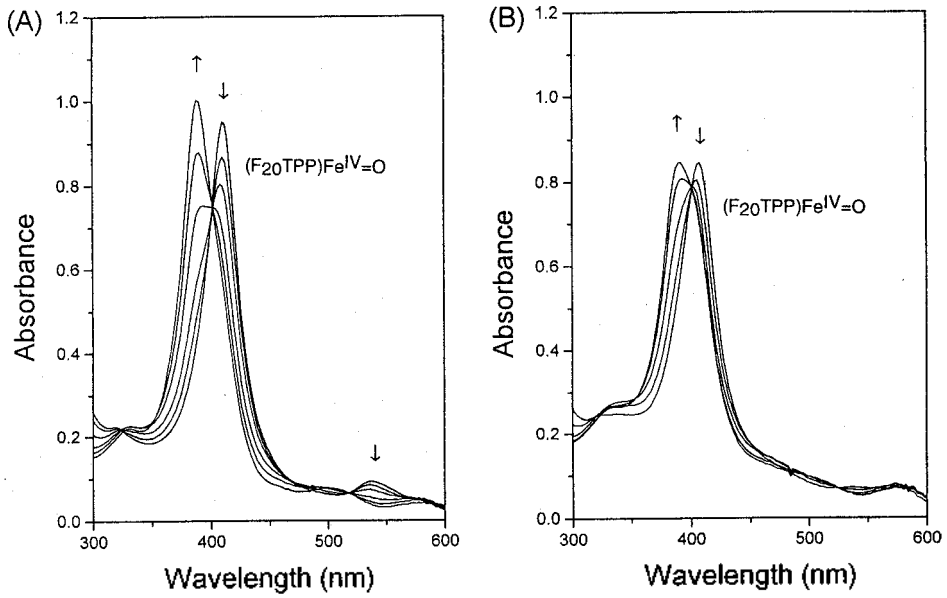


Figure 2. UV-vis spectral changes obtained during the reaction of Fe(F_{20}TPP)Cl and PhIO (A) in the absence (spectra were taken at 30 s, 5 min, 12 min, 19 min, 22 min, 24 min) and (B) in the presence (spectra were taken at 30 s, 3 min, 7 min, 11 min, 15 min) of cyclohexene at room temperature. Reaction conditions: Fe(F_{20}TPP)Cl (2.5×10^{-3} mmol), cyclohexene (2 mmol), and PhIO (0.2 mmol) in a mixture (5 mL) of CH_3OH-CH_2Cl_2 (3 : 1). The small glitches in the spectra are due to the HP spectrophotometer.

high-valent iron oxo complex formed in the reactions of H_2O_2, *t*-BuOOH, and MCPBA toward oxygenation of hydrocarbons.

Efforts were made to elucidate the reaction of the iron porphyrin complex with PhIO using spectroscopic methods. When PhIO was added to the solution of Fe(F_{20}TPP)Cl at room temperature, a new iron porphyrin complex with optical bands at 410 nm (Soret) and at 540 nm was formed. The iron porphyrin intermediate showed no strong EPR signals at 4 K in frozen methanol-dichloromethane (3 : 1) solution. The ^{1}H NMR spectrum of this complex in CD_3OD-CD_2Cl_2 (3 : 1) at -40 ℃ showed pyrrole β-proton signal at 1.2 ppm and the chemical shift was temperature dependent.[7] Based on the UV-vis, EPR, and NMR spectroscopic studies, the iron porphyrin species was assigned to be (F_{20}TPP)Fe^{IV}=O.[8] This iron porphyrin complex decomposed to regenerate iron (III) porphyrin with clear isosbestic behavior as the reaction proceeded further (see Figure 2-A). The rate of disappearance of the iron(IV) oxo porphyrin complex did not depend much on the presence of substrate (see Figure 2-B), and the distinct UV-vis spectral changes were not observed in olefin epoxidation reactions by H_2O_2, *t*-BuOOH, and MCPBA. We therefore propose that the different reactivity for the PhIO reaction might arise from the involvement of iron(IV) oxo porphyrin complex for the reaction with PhIO to generate a more reactive oxygenating intermediate, *i.e.* Fe^{IV}-OIPh complex.[9] Further mechanistic studies as well as the identification of the intermediate for the PhIO reaction are currently under investigation in this laboratory.

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References

1. (a) Ortiz de Montellano, P., Ed. *Cytochrome P-450: Structure, Mechanism and Biochemistry*; Plenum Press: New York, 1986. (b) Montanari, F.; Casella, L., Eds. *Metalloporphyrins Catalyzed Oxidations*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1993. (c) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411-1456. (d) Fujii, H. *J. Am. Chem. Soc.* **1993**, *115*, 4641-4648. (e) Sugimoto, H.; Tung, H.-C.; Sawyer, D. T. *J. Am. Chem. Soc.* **1988**, *110*, 2465-2470. (f) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884-2886.
2. (a) Traylor, T. G.; Kim, C.; Richards, J. L.; Xu, F.; Perrin, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 3468-3474. (b) Traylor, T. G.; Tsuchiya, S.; Byun, Y.-S.; Kim, C. *J. Am. Chem. Soc.* **1993**, *115*, 2775-2781. (c) Traylor, T. G.; Fann, W.-P.; Bandyopadhyay, D. *J. Am. Chem. Soc.* **1989**, *111*, 8009-8010.
3. (a) Almarsson, O.; Bruice, T. C. *J. Am. Chem. Soc.* **1995**, *117*, 4533-4544. (b) He, G.-X.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 2747-2753. (c) Murata, K.; Panicucci, R.; Gopinath, E.; Bruice, T. C. *J. Am. Chem. Soc.* **1990**, *112*, 6072-6083.
4. (a) Valentine, J. S.; Nam, W.; Ho, R. Y. N. In *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Barton, D. H. R.; Martell, A. E.; Sawyer, D. T., Eds.; Plenum Press: New York, 1993; pp 183-198. (b) Machii, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1995**, *117*, 6691-6697. (c) Watanabe, Y.; Yamaguchi, K.; Morishima, I.; Takehira, K.; Shimizu, M.; Hayakawa, T.; Orita, H. *Inorg. Chem.* **1991**, *30*, 2581-2582.
5. Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 507-508.
6. (a) Fujii, H. *Chem. Lett.* **1994**, 1491-1494. (b) Yamaguchi, K.; Watanabe, Y.; Morishima, I. *J. Chem. Soc., Chem. Commun.* **1992**, 1721-1723. (c) Nanthakumar, A.; Goff, H. M.

J. Am. Chem. Soc. **1990**, *112*, 4047-4049.
7. It was found that a small amount of $Fe^{IV}(F_{20}TPP)(OCH_3)_2$ has also been formed. The pyrrole β-proton signal of the dimethoxyiron(IV) porphyrin complex appeared at −26 ppm at −40 ℃: Groves, J. T.; Quinn, R.; McMurry, T. J.; Nakamura, M.; Lang, G.; Boso, B. *J. Am. Chem. Soc.* **1985**, *107*, 354-360.
8. (a) Bell, S. E. J.; Cooke, P. R.; Inchley, P.; Leanord, D. R.; Lindsay Smith, J. R.; Robbins, A. *J. Chem. Soc. Perkin Trans. 2* **1991**, 549-559. (b) Arasasingham, R. D.; Cornman, C. R.; Balch, A. L. *J. Am. Chem. Soc.* **1989**, *111*, 7800-7805. (c) Gold, A.; Jayaraj, K.; Doppelt, P.; Weiss, R.; Chottard, G.; Bill, E.; Ding, X.; Trautwein, A. X. *J. Am. Chem. Soc.* **1988**, *110*, 5756-5761. (d) Shin, K.; Goff, H. M. *J. Am. Chem. Soc.* **1987**, *109*, 3140-3142.
9. Mn^{IV}-OIPh complexes have been shown to oxygenate alkenes and alkanes. (a) Smegal, J. A.; Schardt, B. C.; Hill, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 3510-3515. (b) Smegal, J. A.; Hill, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 3515-3521.

Implication of Secondary Structure of Bradykinin in Membrane Mimic Solution Investigated by NMR Spectroscopy

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Bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is a linear peptide hormone with diverse physiological properties such as vasodilation and pain mediation.[1] Most peptide hormones interact with their specific receptors in the cell membrane. However, identification of hormone receptors has proved difficult and there are few examples of structural analysis from a receptor/hormone complex. The cell membrane receptor for bradykinin has not been isolated, but recent evidence indicates that the pain receptors are localized in the dorsal root and trigeminal regions of the guinea pig nervous system.[2] In general, peptide hormones first interact with membranes and form nascent secondary structure prior to binding to the receptor. The solution conformation of a bradykinin was investigated by 1D and 2D proton NMR spectroscopy and it was reported that bradykinin has disordered conformation in water[3] and two β turns in DMSO (dimethyl sulfoxide).[4] Futhermore, the interaction of the bradykinin with SDS micelle has been reported as the conformational changes of the C-terminal tetrapeptide fragment, Ser-Pro-Phe-Arg, made strong interactions with monomeric SDS.[5,6] We used a simple TFE (trifluoroethanol)/water binary solvent system to mimic the biological membrane. The hydrophobic character of TFE provides a similar environment to a membrane for bradykinin.

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Table 1. Chemical shift values of backbone and side chain protons of bradykinin[a]

	NH	αH	βH	γH	δH	Others
Arg 1		4.26	1.90	1.68	3.13	scNH[b] 7.20
Pro 2		4.71	2.38, 1.89	1.97	3.68, 3.43	
Pro 3		4.40	2.23, 1.87	2.01	3.76, 3.61	
Gly 4	8.08	3.92, 3.79				
Phe 5	7.79	4.55	3.00			
Ser 6	7.76	4.65	3.81, 3.69			
Pro 7		4.27	2.0, 1.53	1.41, 1.73	3.50, 3.45	
Phe 8	7.51	4.60	3.21, 2.82			
Arg 9	7.67	4.24	1.83, 1.70	1.57	3.16	scNH 7.12

[a]The Chemical shifts are given in ppm and are referenced to the residual methylene protons of TFE (3.88 ppm, 298 K). [b]side chain NH

Bradykinin was purchased from Sigma and used without further purification, since no minor constituents could be detected by NMR spectroscopy. The peptide was dissolved in water/TFE-d_3 and pH was adjusted to 3 by adding HCl and NaOH solution. All NMR spectra were recorded on the BRUKER 500 MHz NMR Spectrometer at ambient temperature. Assignments were performed by sequential assignment strategy.[7] TOCSY (total correlation spectroscopy) was used for spin system identification, and ROESY (rotating-frame noe spectroscopy) was used to determine sequential connectivities and other medium range NOE's. The full assignment values are given in Table 1. As is implied in its primary structure, bradykinin has high probability of tight turns. In Figure 1, the fingerprint region of ROESY spectra is shown. The sequential connectivities are broken due to the lack of amide protons in three prolines. For proline, the δ proton was used instead of missing amide proton to confirm the sequential connectivities. The NOE between δ protons of Pro 7 and amide proton of Phe 8 implies there might be a turn structure in the C-terminal fragment. The distance between the δ proton of a proline and the amide proton of an adjacent residue is equivalent to the distance between amide protons of neighboring residues. The NOE's between amide protons can be used to identify α helix and β turns. In α helix, there must be sequential NH-NH NOE connectivities not less than three residues long. However, the NOE connectivity in this peptide implies a turn-like structure. The type of the turn could not be determined due to the spectral overlap caused by other NOE's. 1D temperature variation experiment showed further evidence of the existence of a turn. 1D spectra were recorded at 5 K interval from 278 K to 323 K. The temperature coefficient values are shown in Table 2. These values can be used as a measure of solvent accessibility. Generally, temperature coefficient ($d\delta/dT$) values of <0.003 ppm K^{-1} are indicative of solvent-shielded and presumably hydrogen-bonded amide protons, and the values >0.005 ppm K^{-1} are attributed to the amide protons