High-Yield Epoxidations with Hydrogen Peroxide and *tert*-Butyl Hydroperoxide Catalyzed by Iron(III) Porphyrins: Heterolytic Cleavage of Hydroperoxides

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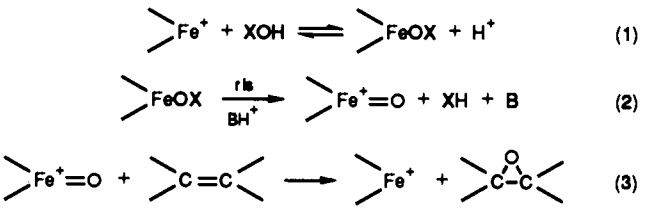
Abstract: The reactions of hydrogen peroxide or *tert*-butyl hydroperoxide with cyclooctene and norbornene, catalyzed by iron(III) tetrakis(pentafluorophenyl)porphyrin chloride and other electronegatively-substituted porphyrins, produce 60–100% epoxide yields. The epoxynorbornane yield has the same ratio of exo/endo isomers as is obtained using pentafluoroiodosylbenzene, an oxidant which produces the iron(IV) radical cation (oxene) intermediate. These results demonstrate heterolytic cleavage of these peroxides in the catalyzed reaction. We use the fast-reacting pentafluoroiodosylbenzene (or *m*-chloroperbenzoic acid) to produce the oxene in the presence of *tert*-butyl hydroperoxide. Under these conditions, the hydroperoxide does not react directly with the iron(III) porphyrin. The same loss of epoxide stereochemistry and reduction in yield were previously submitted as evidence for homolytic cleavage; this earlier explanation is invalid. Formerly, iron(III) tetraphenylporphyrin chloride and iron(III) tetramesitylporphyrin chloride failed to produce high epoxide yields or significant stereospecificity. These results are explained as follows: hemin-derived oxenes highly prefer hydroperoxide oxidation to epoxidation. This preference is much lower for electronegatively-substituted hemins, pointing the way to high epoxide yields. Previous evidence for homolysis of hydroperoxide bonds in these catalytic reactions is shown to accord with heterolysis; definitive evidence for heterolysis of hydrogen peroxide and hydroperoxides in protic solvents is presented.

Introduction

The importance of metalloporphyrin-catalyzed oxidations in biological systems and their potential as industrial catalysts have brought considerable attention to these reactions.[1-3] Since the first biomimetic porphyrin epoxidation was studied,[4] such catalysts have been improved from giving a few epoxidation turnovers accompanied by catalyst loss to 10^5 turnovers without severe catalyst loss.[5,6] Many of the properties of the enzymes cytochrome P-450 and horseradish peroxidase have been mimicked.[7-10]

Most of these studies employed oxidants such as iodosylbenzenes or peracids, although hypochlorite and monoperoxysulfuric acid have also been used.[11,12] Attempts to employ hydrogen peroxide or dioxygen have met with rather limited success[13-17] as compared to the high-turnover, high-yield processes developed with iodosylbenzenes, for example. One cause of the failure to achieve efficient use of hydrogen peroxide (or *tert*-butyl hydroperoxide) derives from the interference of radical-producing side reactions.[13] For example, the consequences of the production of *tert*-butoxyl radicals in the presence of *tert*-butyl hydroperoxide are well-known. A chain decomposition of the hydroperoxide occurs along with the free-radical processes associated with the particular substrate.[18-20] In short, the very clean epoxidation or hydroxylation reaction with iodosylbenzene becomes a mess with hydrogen peroxide or alkyl hydroperoxides.

The mechanism of epoxidation, except for minor details, is currently thought to proceed as follows[1,21-23] (>Fe^+ represents an iron(III) porphyrin cation, chloride etc.):



(1) Mansuy, D. *Pure Appl. Chem.* **1987**, *59*, 759–770.
(2) *Cytochrome P-450: Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1986.
(3) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411–1456.
(4) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032–1033.
(5) Collman, J. P.; Hampton, P. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 2977–2986.
(6) Traylor, T. G.; Hill, K. W.; Fann, W.-P.; Tsuchiya, S.; Dunlap, B. E. *J. Am. Chem. Soc.* **1992**, *114*, 1308–1312.
(7) Tabushi, I.; Koga, N. *Tetrahedron Lett.* **1979**, 3681–3684.
(8) (a) McMurry, T. J.; Groves, J. T. In ref 2, pp 1–28. (b) Groves, J. T.; Kruper, W. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7613–7615. (c) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *Ibid.* **1980**, *102*, 6375–6377.
(9) (a) Traylor, T. G.; Nakano, T.; Dunlap, B. E.; Traylor, P. S.; Dolphin, D. *J. Am. Chem. Soc.* **1986**, *108*, 2782–2784. (b) Traylor, T. G.; Miksztal, A. R. *Ibid.* **1989**, *111*, 7443–7448.
(10) Lindsay Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1009–1015.
(11) (a) Guilmet, E.; Meunier, B. *Tetrahedron Lett.* **1980**, *21*, 4449–4450. (b) Meunier, B.; Guilmet, E.; De Carvalho, M.-E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668–6676.
(12) (a) De Poorter, B.; Meunier, B. *Nouv. J. Chim.* **1985**, *9*, 393–394. (b) De Poorter, B.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1735–1740.
(13) (a) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462–8470. (b) Mansuy, D.; Battioni, P.; Renaud, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1255–1257.
(14) (a) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Chem. Soc., Chem. Commun.* **1989**, 779–780. (b) Banfi, S.; Maiocchi, A.; Montanari, F.; Quici, S. *Gazz. Chim. Ital.* **1990**, *120*, 123–130.
(15) Rocha Gonsalves, A. M. d'A.; Johnstone, R. A. W.; Pereira, M. M.; Shaw, J.; do N. Sobral, A. J. F. *Tetrahedron Lett.* **1991**, *32*, 1355–1358.
(16) Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1991**, *113*, 3595–3596.
(17) Jones, P.; Mantle, D.; Wilson, I. *J. Chem. Soc., Dalton Trans.* **1983**, 161–164 (and references therein).
(18) *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons: New York, 1973; Vols. 1 and 2, pp 113, 204.
(19) Kropf, H.; Spangenberg, J.; Gunst, A.; Hinrichsen, J. *Liebigs Ann. Chem.* **1980**, 1923–1938.
(20) Factor, A.; Russell, C. A.; Traylor, T. G. *J. Am. Chem. Soc.* **1965**, *87*, 3692–3698.
(21) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7834–7836.
(22) (a) Traylor, T. G.; Xu, F. *J. Am. Chem. Soc.* **1988**, *110*, 1953–1958. (b) Traylor, T. G.; Xu, F. *Ibid.* **1987**, *109*, 6201–6202.
(23) Traylor, T. G.; Lee, W. A.; Stynes, D. V. *J. Am. Chem. Soc.* **1984**, *106*, 755–764.

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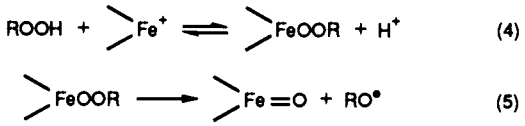
In those cases where X is a good leaving group (PhIO, RCO_3H, HCl, or $HOOSO_3^-$), this reaction proceeds smoothly. The indicated heterolytic cleavage is well established.[9a,23,24] In those cases where $X^- = HO^-$ or RO^-, low to zero yields of epoxide have been reported, and products of the hydroperoxide decomposition, derived from alkoxyl or hydroperoxyl radicals, are seen.[13,25]

The nature of the reactions leading to alkoxyl and hydroperoxyl radicals has been studied extensively with both heme proteins[26] and simple hemins.[25,27] Because products derived from alkoxyl radicals have been observed even in the presence of specific traps for the "oxene" species (and inhibitors of radical chain reactions) and because preformed hemin hydroperoxides give radical products,[28] most of the work has been interpreted in terms of homolysis in the first step. In one case, exclusive homolysis of *tert*-butyl hydroperoxide was suggested.[25] In most other studies, competitions between heterolytic and homolytic cleavage were proposed.

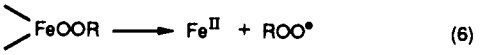
For these reasons, researchers seem to despair at achieving efficient epoxidation with hydrogen peroxide because it has been established that the oxoiron species (>Fe=O) of eq 5 does not



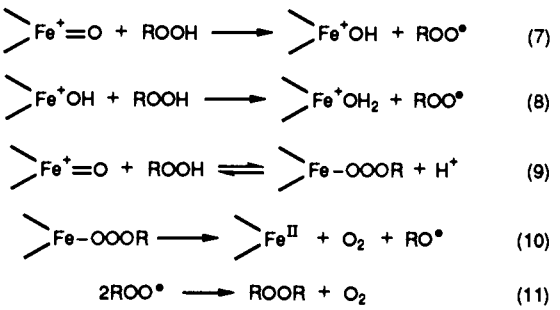
epoxidize alkenes, even though it does react with phosphines.[29-31] In fact, the failure to obtain epoxide has been taken as evidence for the homolytic cleavage in eq 5 since the oxene ($>Fe^+=O$) epoxidizes alkenes but the oxoiron (>Fe=O) does not.[25,27b,32-35]

In our kinetic studies, we found that the known heterolytic process in eq 2, where $X^- = RCOO^-$, responds to changes in leaving group (RO^-) stability,[23] buffer catalysis,[23] protic solvent acidity,[36] proximal basicity,[23] internal acid catalysis,[23,37,38] and solvent–deuterium isotope effects[36] in the same way as do reactions of *tert*-butyl hydroperoxide ($X^- = t\text{-}BuO^-$) or hydrogen peroxide ($X^- = HO^-$). This provides strong evidence for similarities in mechanisms. Using phenylperacetic acid, the sensitive probe for homolytic cleavage, we established that there is no homolytic cleavage of peracids in these solutions.[23] This led to the conclusion that hydroperoxides and hydrogen peroxide also react by heterolytic O–O bond cleavage. Therefore, we were not discouraged by poor epoxidation with hydrogen peroxide. In our view, this problem arose from side reactions after the metal oxidation rather than from a fundamental flaw in this first step. By avoiding these competitive side reactions of the oxene species ($>Fe^+=O$), we should achieve high yields of epoxidation with hydrogen peroxide.[31]

Let us consider the possible sources from which alkoxyl radicals might be derived: direct reactions or, more importantly, post-heterolytic reactions. One possibility, which we consider rather unlikely, is electron transfer (inner or outer sphere, eq 6).



However, several highly-probable reactions can occur after heterolysis, the first of which, hydroperoxide oxidation (eq 7), we have documented.[22b] Reaction 11 is part of the well-known termination process in autoxidation reactions.[39,40] Reactions 9 and 10 were postulated by Hager et al.[41] to explain their ^{18}O-labeling experiments with chloroperoxidase. Therefore, either reaction 7 or something equivalent to reaction 9 could lead to alkoxyl radicals. If this were the case, then simple iron porphyrins could react with hydroperoxides to give high-yield epoxidations after all—if subsequent side reactions could be avoided.



We now report that this is the case. We have used a commercially-available hemin, iron(III) tetrakis(pentafluorophenyl)porphyrin chloride, hydrogen peroxide, and cyclooctene to obtain 86% yields of epoxide at a set turnover of about 200, with little loss of catalyst. *Some hemins yielded ~100%*! We offer this and other data as evidence that hydrogen peroxide reacts with hemins by the same mechanism as does iodosylbenzene or peracids, that is, by *heterolytic cleavage of the O–O bond.*

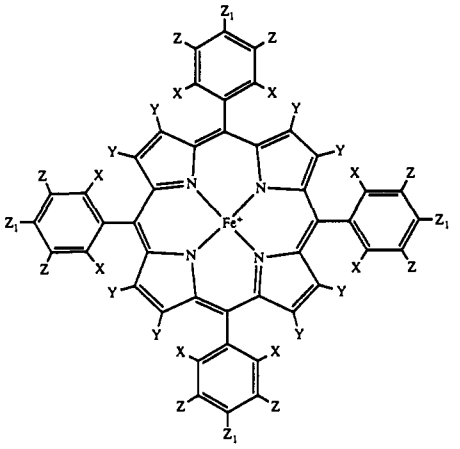
A study of hydroperoxide reactions with the high-valent iron species of eq 2 ($>Fe^+=O$) also provides explanations of previous failures to obtain efficiently-catalyzed epoxidations[22,25] and demonstrates that some prior evidence for homolytic cleavage of the O–O bond is actually consistent with heterolytic cleavage.

Experimental Section

Instruments. Ultraviolet–visible spectra were obtained with a Kontron-810 spectrophotometer interfaced with Celerity or Zenith computers. Product analyses were performed on a Varian 3700 gas chromatograph with flame detection and an 80/100 Supercoport-packed column. Response factors were determined relative to dodecane for all products. Some products were made from the alkenes using MCPBA.

Materials. Dichloromethane (Fisher) was distilled from calcium hydride. Hydrogen peroxide (30%) and *tert*-butyl hydroperoxide (70%, Aldrich) were analyzed and used as received. *cis*-β-Methylstyrene, 1,4-diphenylbutadiene, cyclooctene, norbornene, cyclohexene, 2-cyclohexen-1-ol, 2-cyclohexen-3-one, and *exo*-2,3-epoxynorbornene were used as received from Aldrich Chemical Co. Pentafluoroiodosylbenzene (PFIB) and *m*-chloroperbenzoic acid (MCPBA, Aldrich) were prepared or purified

(24) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8443–8452.
(25) Bruice, T. C. *Acc. Chem. Res.* **1991**, *24*, 243–249.
(26) (a) Yumibe, N. P.; Thompson, J. A. *Chem. Res. Toxicol.* **1988**, *1*, 385–390. (b) Thompson, J. A.; Wand, M. D. *J. Biol. Chem.* **1985**, *260*, 10637–10644.
(27) (a) Dix, T. A.; Marnett, L. J. *J. Am. Chem. Soc.* **1983**, *105*, 7001–7002. (b) Labeque, R.; Marnett, L. J. *J. Am. Chem. Soc.* **1989**, *111*, 6621–6627. (c) Dix, T. A.; Marnett, L. J. *J. Biol. Chem.* **1985**, *260*, 5351–5357. (d) Dix, T. A.; Marnett, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 6744–6746. (e) Dix, T. A.; Fontana, R.; Panthani, A.; Marnett, L. J. *J. Biol. Chem.* **1985**, *260*, 5358–5365.
(28) Arasasingham, R. D.; Cornman, C. R.; Balch, A. L. *J. Am. Chem. Soc.* **1989**, *111*, 7800–7805.
(29) Chin, D.-H.; La Mar, G. N.; Balch, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 5945–5947.
(30) Peterson, M. W.; Rivers, D. S.; Richman, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 2907–2915.
(31) Traylor, T. G.; Fann, W.-P.; Bandyopadhyay, D. *J. Am. Chem. Soc.* **1989**, *111*, 8009–8010.
(32) Hirao, T.; Ohno, M.; Ohshiro, Y. *Tetrahedron Lett.* **1990**, *31*, 6039–6042.
(33) Smith, J. R. L.; Lower, R. *J. Chem. Soc., Perkin Trans. 2* **1991**, 31–39.
(34) He, G.-X.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 2747–2753.
(35) Mansuy, D.; Bartoli, J.-F.; Chottard, J.-C.; Lange, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 909–910.
(36) Traylor, T. G.; Xu, F. *J. Am. Chem. Soc.* **1990**, *112*, 178–186.
(37) Ciccone, J. P. Doctoral Thesis, University of California, San Diego, CA, 1989.
(38) Traylor, T. G.; Ciccone, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 8413–8420.
(39) Bartlett, P. D.; Hiatt, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 1398–1405.
(40) Traylor, T. G.; Russell, C. A. *J. Am. Chem. Soc.* **1965**, *87*, 3698–3706.
(41) Hager, L. P.; Doubek, D. L.; Silverstein, R. M.; Lee, T. T.; Thomas, J. A.; Hargis, J. H.; Martin, J. C. *Oxidases and Related Redox Systems*; King, T. E., Mason, H. S., Morrison, M., Eds.; University Park Press: Baltimore, MD, 1973; Vol. 1, pp 311–332.



Compound	X	Y	Z	Z_1	Reference
1	F	F	F	F	42
2	Cl	Ph	H	H	43
3	F	H	F	F	44
4	Cl	H	H	H	45
5	Cl	Br	H	H	46
6	Me	H	H	Me	47

Figure 1. Iron(III) porphyrin chlorides.

as previously described.[22,23] The iron(III) porphyrin/chlorides discussed below are from studies referenced in Figure 1.

Kinetic Studies. The competitive kinetic studies using 1,4-diphenylbutadiene as a reporter substrate were carried out as previously described.[22] Conditions for each experiment appear with the figures.

Oxidations. Generally, the catalyst and substrates were made to concentration from standard solutions, and the oxidant was added from a standard solution (in the same solvent) to start the reaction. Aliquots of solution were withdrawn at indicated times—or after about $^1/_2$ h—and analyzed by gas chromatography.

Results

Epoxidation with Hydrogen Peroxide. We first explored the hemin-catalyzed epoxidations with hydrogen peroxide (0.2 M) in dichloromethane/methanol (1/3), which was both a polar and a good solvent for the catalyst and substrate. At a catalyst concentration of 10^{-3} M, the maximum possible turnover is 200. The solution of catalyst (10^{-3} M), substrate (1.5 M), and hydrogen peroxide (0.2 M, added last) was analyzed after 10 min and after 1 h at 25 °C by gas chromatography. The results were the same. Product yields of cyclooctene, norbornene, and cyclohexene oxidation are shown in Table I. Epoxide yields of up to 100% were obtained, with regiochemistries identical to those of iodosylbenzene epoxidations.

A similar study with *tert*-butyl hydroperoxide is shown in Table II. Again, very high yields of epoxides were produced. Even at equimolar concentrations of *t*-BuOOH and cyclooctene, the epoxide yield was 70%. Under some conditions the yield was ~90%!

Table III compares the reaction of various oxidants (catalyzed by hemin **3**) with norbornene. As we have previously reported, this reaction produces exo and endo epoxides as well as the rearrangement product cyclohexene-4-carboxaldehyde. All four oxidants gave essentially the same product ratios. The yield of the hydrogen peroxide reaction (80%) was between those of the PFIB and MCPBA reactions. The low yield from the PFIB reaction could result from incomplete reaction in the absence of water.

Table I. Hydrogen Peroxide Oxidations Catalyzed by Various Hemins[a]

hemin (see Figure 1)	yield (%) epoxycyclooctane	epoxynorbornane	epoxycyclohexane
1	~100	64 (22)[b]	80[c]
2	~100	60 (5)	83[d]
3	86	50 (22)	80
4[c]	76	64 (9)	37[e]
5	61		
6	2		

[a] Conditions: catalyst, 10^{-3} M; H_2O_2, 0.2 M; substrate, 1.5 M; solvent, CH_2Cl_2/MeOH (25/75 by volume); temp, 25 °C; yields based upon H_2O_2. [b] Exo/endo ratios are given in parentheses. Identical exo/endo ratios of epoxynorbornanes were obtained with pentafluoroiodosylbenzene as oxidant. [c] No alcohol or ketone was produced. [d] An additional yield of alcohol (17%) plus ketone was observed. [e] An additional yield of alcohol (2.5%) plus ketone was observed.

Table II. Cyclooctene Epoxidation with *t*-BuOOH Catalyzed by $(F_{20}TPP)FeCl$ (**3**)[a]

concn (M) *t*-BuOOH	concn (M) cyclooctene	epoxide yield (%)[d]	concn (M) *t*-BuOOH	concn (M) cyclooctene	epoxide yield (%)
0.01	0.3	52[b]	0.2	0.2	67[b]
0.01	0.6	57[b]	0.3	0.3	70[b]
0.05	0.3	70[b]	0.3	0.2	85[c]
0.1	0.3	89[b]	0.3	0.1	100[c]
0.2	0.6	86[b]			

[a] Conditions: $(F_{20}TPP)FeCl$ (**3**), 10^{-3} M; solvent, CH_2Cl_2/CH_3OH (25/75 by volume); room temperature. Reaction times (20–90 min) did not change epoxide yields. [b] Based upon oxidant. [c] Based upon akenes. [d] Small amounts (1.5–4%) of cyclooctanone were detected.

Table III. Norbornene Oxidation with Various Oxidants Catalyzed by $(F_{20}TPP)FeCl$ (**3**)[a]

oxidants	exo/endo	exo/aldehyde	aldehyde/endo	exo + endo + aldehyde yield (%)
PFIB	23	5.1	4.4	75
H_2O_2[b]	22	3.5	6.1	80
t-BuOOH	25	4.2	6.1	59
MCPBA	24	4.4	5.5	100

[a] Conditions: norbornene, 1.5 M; oxidant, 0.2 M; $(F_{20}TPP)FeCl$ (**3**), 1×10^{-3} M; solvent, CH_2Cl_2/MeOH (25/75 by volume); temp, 25 °C. [b] H_2O_2, 0.02 M.

Reactions of Hydroperoxides with High-Valent Iron Intermediates. In order to understand previous failures of hydroperoxides to produce good epoxide yields, we have designed peracid and iodosylbenzene epoxidation experiments which prevent direct reaction of the hydroperoxides with the catalyst. This is possible because hydroperoxides react with hemins about 100 times slower than do peracids or iodosylbenzenes.[23] Table IV shows the epoxide yields obtained after about 30 s in various PFIB (or MCPBA)/*tert*-butyl hydroperoxide mixtures. There is no appreciable hydroperoxide/hemin reaction in the first 30 s.[23] The hydroperoxide causes drastic reduction in epoxide yields (compare entry 1 with entries 8–10 in Table IV). This cannot result from homolytic cleavage because the observed reaction of hydroperoxides—regardless of whether it is heterolytic or homolytic—is too slow to be involved. Therefore, the decreased yield results from reactions of ROOH with the oxene (>Fe^+=O), as in eqs 7 and 9. This means that free-radical epoxidation is not very efficient in this system. Because tetramesitylhemin (**6**) has been commonly employed in reactions suggested to proceed by homolytic cleavage, it was also used in this study.

Kinetic Studies of Competitions between Alkenes and Hydroperoxides. An alternative method—using iodosylbenzene to

(42) Tsuchiya, S.; Seno, M. *Chem. Lett.* **1989**, 263–266.
(43) Tsuchiya, S. *Chem. Phys. Lett.* **1990**, *169*, 608–610.
(44) Chang, C. K.; Ebina, F. *J. Chem. Soc., Chem. Commun.* **1981**, 778–779.
(45) Traylor, P. S.; Dolphin, D.; Traylor, T. G. *J. Chem. Soc., Chem. Commun.* **1984**, 279–280.
(46) Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338–1339.
(47) Cheng, R.-J.; Latos-Grazynski, L.; Balch, A. L. *Inorg. Chem.* **1982**, *21*, 2412–2418.

Table IV. Epoxidation of *cis*-β-Methylstyrene with Perfluoroiodosylbenzene (PFIB), *m*-Chloroperbenzoic Acid (MCPBA), *tert*-Butyl Hydroperoxide (*t*-BuOOH), and Mixtures of These Oxidants Using (TMP)FeCl (**6**) as the Catalyst[a]

concn of oxidants (M)				total	cis epoxide/
PFIB	MCPBA	*t*-BuOOH	time	yield (%)	trans epoxide
0.01	0	0	40 s	56	17.8
			50 min	57	17.5
0	0.025[b]	0	50 s	20.8	5.7
			40 min	20.8	5.8
0	0	0.025	38 s	1.7	0.6
			40 min	2.2	0.1
0	0.025[c]	0.05	40 s	8.9	2.7
0.01	0	0.0025	37 s	40	17.4
0.01	0	0.005	40 s	22	11.0
0.01	0	0.01	40 s	2.4	0.5

[a] Conditions: (TMP)FeCl (**6**), 1×10^{-3} M; *cis*-β-methylstyrene, 0.1 M; solvent, dichloromethane/methanol/water (35/64.7/0.3 by volume); temp, 25 °C. [b] 80% **6** destroyed. [c] 20% **6** destroyed.

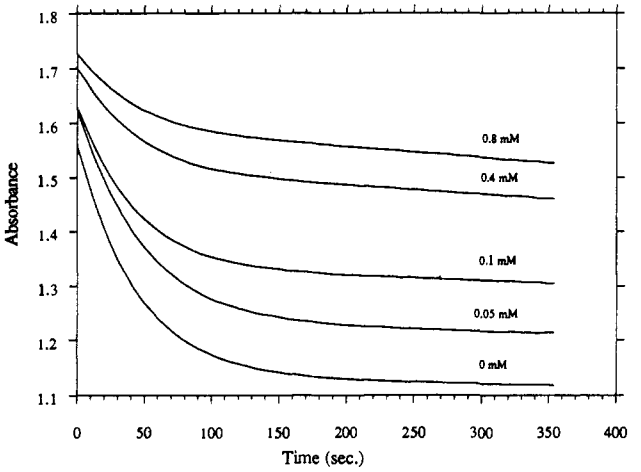
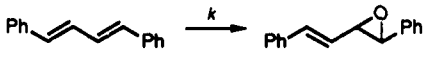


Figure 2. Plots of absorbance at 329 nm vs time for solutions of 10^{-4} M (TMP)FeCl (**6**), 2×10^{-4} M MCPBA, and 2.71×10^{-4} M 1,4-DPBD in CH_2Cl_2/MeOH (25/75 by volume) at room temperature. Concentrations of *t*-BuOOH are indicated.

rapidly prepare the oxene—was previously introduced to demonstrate that hydroperoxides compete with alkenes for the oxene.[22] With this technique, the rate of epoxidation could be followed by observing the disappearance of the 348-nm absorbance of 1,4-diphenylbutadiene (eq 12).



(12)

Adding a second, competing substrate, such as another alkene, decreased the initial rate of reaction 12 and the total change in absorbance but did not affect the pseudo-first-order rate constant because oxene formation was the rate-limiting step.[22] Nevertheless, relative rates of substrate reactions could be measured with this technique using either of the changes mentioned. Using MCPBA instead of PFIB, we now employ this method to determine the relative rates of reaction of hydroperoxides (versus alkenes) with the species >Fe⁺=O.

Figure 2 shows a series of rate curves for 1,4-diphenylbutadiene epoxidation in various concentrations of *tert*-butyl hydroperoxide (tetramesitylhemin chloride (**6**) was the catalyst). Clearly, the hydroperoxide competes with the diene for the high-valent intermediate. The rate constant for reaction of *tert*-butyl hydroperoxide with the oxene (eq 7) is about 1.3 times that for the diene and about 100 times larger than that for norbornene. This is in agreement with earlier results where PFIB was the oxidant.[22] A similar reactivity was found for hydrogen peroxide. This result explains the low yield (Table I) obtained with this catalyst and is consistent with the results in Table IV. All of

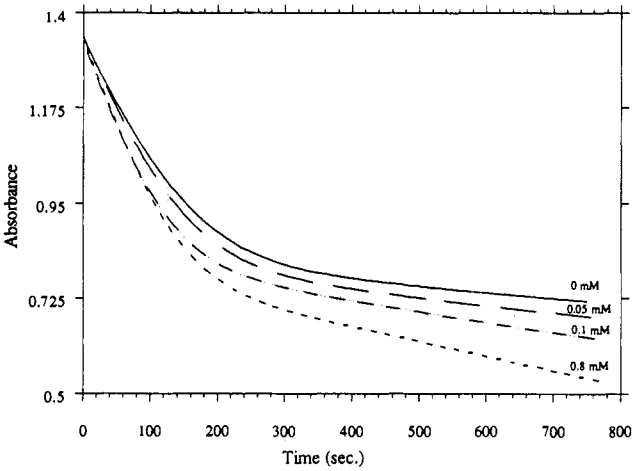


Figure 3. Plots of absorbance at 329 nm vs time for solutions of 5×10^{-6} M (F_{20}TPP)FeCl (**3**), 1.3×10^{-4} M MCPBA, and 2.3×10^{-4} M 1,4-DPBD in CH_2Cl_2/MeOH (25/75 by volume) at room temperature. Concentrations of *t*-BuOOH are indicated.

these reactions employed peracids or iodosylbenzene. It is certainly not necessary to postulate that homolytic cleavage is responsible for the low epoxide yields. Cleavages of the iron intermediates (>Fe–OX) are exclusively heterolytic.

An entirely different result was obtained with tetrakis(pentafluorophenyl)hemin (**3**). Figure 3 shows the kinetic plots obtained with this catalyst using the method of Figure 2. Notice that the hydroperoxide does *not* compete with the diene. Instead, a small increase in rate and yield of epoxide is seen. Therefore, the competition of ROOH and the diene is very dependent upon the hemin structure.

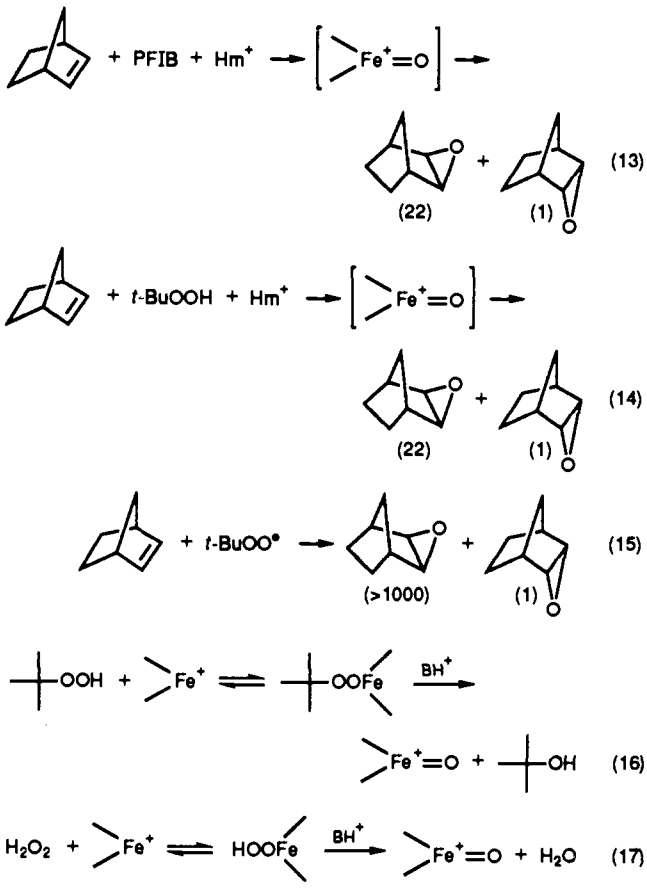
Stereochemical Studies. The loss of stereospecificity in hemin-catalyzed epoxidations of *cis*-stilbene (which sometimes occurs when hydroperoxides are used as oxidants, for example) is indicative of peroxyl radical formation and is often given as evidence for homolytic cleavage.[27b,34] We tested whether this could be valid evidence in the experiments discussed above. Carrying out hemin-catalyzed oxidations of *cis*-β-methylstyrene with MCPBA or PFIB in the presence and absence of *tert*-butyl hydroperoxide affords the cis/trans epoxide ratios and yields given in Table IV. Clearly, the presence of *tert*-butyl hydroperoxide in a catalyzed epoxidation reaction involving exclusive heterolysis leads to predominant loss of stereochemistry. It is especially noteworthy that *tert*-butyl hydroperoxide alone, or in a PFIB mixture where the oxidation is carried out by PFIB only, gives similar losses of stereochemistry (compare the fifth and last entries in Table IV).

Discussion

It is now established that the oxene species of eq 2 (>Fe⁺=O) epoxidizes alkenes[24,31] and the oxoiron species of eq 5 (>Fe=O) does not.[29-31] Therefore, the quantitative (or nearly quantitative) yields of epoxide reported in Tables I and II constitute definitive evidence for heterolytic cleavage of hydrogen peroxide and *tert*-butyl hydroperoxide in methanol solvents. This conclusion is further strengthened by the regiochemistry of norbornene epoxidation (exo/endo = 22, eq 14), which can be accomplished only by the oxene species (eq 13).[9b,31]

The exo/endo ratio for the epoxidation of norbornene with *t*-BuOOH, being within experimental error of the ratio obtained with PFIB or MCPBA, indicates that there is none (<4%) of the peroxyl radical epoxidation (eq 15) suggested by Bruice et al.[34] Therefore, the yields of epoxynorbornane (59% from *t*-BuOOH and 80% from H_2O_2) are from heterolytic cleavage to the oxene (eqs 16 and 17).

In the case of cyclooctene, we have no direct test for the extent of peroxyl radical epoxidation. However, the similarity in



reactivities of norbornene and cyclooctene toward the oxene generated from PFIB makes it very likely that these alkenes follow the same pathway in this reaction. Additionally, we find that norbornene reacts with *tert*-butyl hydroperoxyl radical about 6 times faster than does cyclooctene. Therefore, the yields of epoxycyclooctane from oxidations with H_2O_2 (86%) and *t*-BuOOH (89%) are derived from heterolytic cleavage of the oxidants to the oxene.

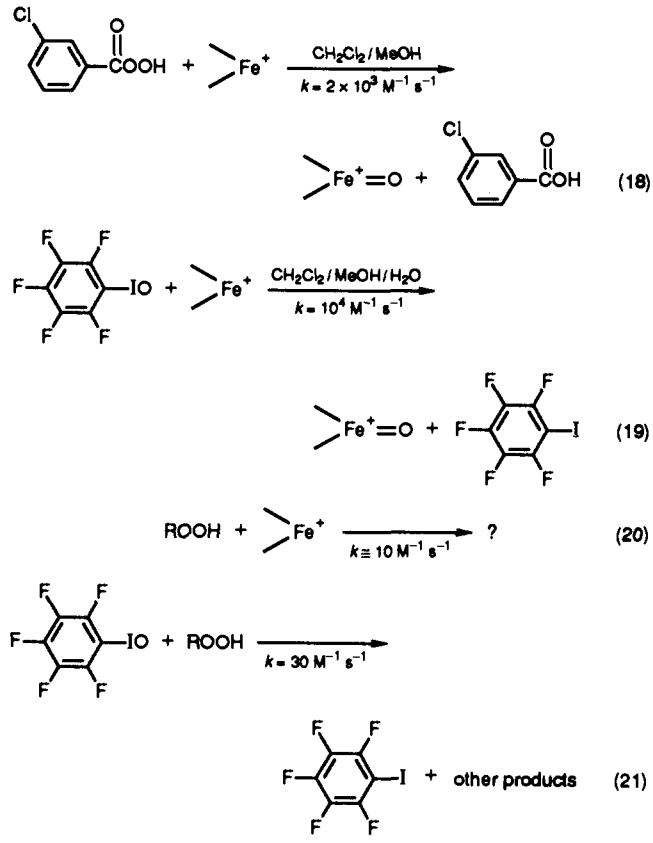
Catalyst **4** purportedly reacts with *tert*-butyl hydroperoxide by exclusive homolysis.[34] However, the 76% yield of epoxide, which does not arise from oxidation with *t*-BuOO•, supports the supposition that this catalyst reacts by heterolysis and indicates that previous work[34] is misinterpreted.

Several reports of hemin reactions with hydroperoxides and hydrogen peroxide, using catalysts and solvents similar (and sometimes identical)[34,48] to those used here, have been interpreted as homolytic reactions. Therefore, we have reinvestigated some of the evidence offered in support of homolytic cleavage of these oxidants. Four principal lines of evidence have been considered incompatible with heterolytic cleavage of hydroperoxides: (1) low or zero yields of epoxide from alkenes;[25] (2) loss of stereospecificity in stilbene reactions where some epoxide is obtained;[27b,34] (3) production of ketones and other products derived from the alkoxyl radical, RO·, which is from the parent hydroperoxide, ROOH;[27a,49] (4) a break in the kinetic plot, log $k_{reaction}^{ROOH}$ versus pK_A^{ROH}, at $pK_A^{ROH} \cong 11$.[27a,50]

We now ask whether these four observations are compatible with heterolytic cleavage and design experiments which show that all are consistent with reactions of the oxene, i.e., with heterolytic cleavage of hydroperoxides. We will show elsewhere that the third and fourth pieces of evidence are consistent with heterolytic cleavage.[51] In this paper, we treat the first two observations and develop definitive ways of answering the question of consistency with heterolysis.

In order to determine the chemical basis of reported low yields and loss of stereospecificity of epoxidation with hydroperoxide (catalyzed by hemins), we have chosen to compare (Table I) two hemins—(F_{20}TPP)FeCl (**3**) and (TMP)FeCl (**6**)—which give high (86%) and low (2%) epoxide yields, respectively, with hydrogen peroxide.

Our approach to these problems, presented briefly in a previous publication,[22b] is as follows: If we can produce the oxene species in an unequivocal manner in the presence of the hydroperoxide under usual hydroperoxide conditions, while at the same time preventing the direct reaction of the hydroperoxide with the hemin, we can determine whether the four observations mentioned above can be due to reactions which occur after the first step rather than to homolytic cleavage in the first step. In this way, we can see whether any or all of the results attributed to homolysis can be obtained from reactions of the oxene with the hydroperoxide. Since we seem to have unequivocal evidence *for* heterolysis (high epoxide yield), a demonstration that other observations are compatible with heterolysis would make a very strong case *against* homolysis in these reactions. Equations 18–21 show how we accomplish these ends using known reactions of peracids and pentafluoroiodosylbenzene with tetramesitylhemin (**6**), the catalyst used in other studies.[9a,22]



Since peracids do not react with hydroperoxides and the reactions of PFIB with hydroperoxides (eq 21) are slow compared to reactions with the hemin and since both MCPBA and PFIB react with the hemin 200 times faster than does *t*-BuOOH or H_2O_2, we can easily produce the oxene in the presence of hydroperoxides and stop the reaction before significant direct reaction of the hydroperoxide with the oxene occurs.

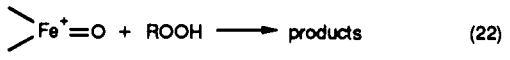
(48) Catalyst **4** is the same as that purported to react by homolysis in methylene chloride.[14]

(49) Panthananickal, A.; Weller, P.; Marnett, L. J. *J. Biol. Chem.* **1983**, *258*, 4411–4418.

(50) Lee, W. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 513–514. Strikingly, the break in pK_A^{ROH} vs log *k*, offered as evidence for homolytic cleavage, *is also obtained under conditions where we obtain 86% yield of epoxide*![51]

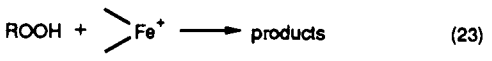
(51) Kim, C. Unpublished results.

This means that eq 22 is the only pathway available for the hydroperoxide/oxene reaction. At this point, the detailed mech-



(22)

anisms of ensuing reactions are not an issue. The question we ask is, In the presence or absence of direct reaction of the hydroperoxide with hemins, do we get similar results? If the observed products are similar for reactions 22 and 23, then the



(23)

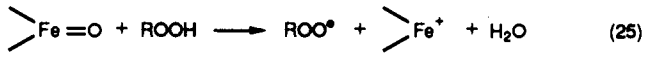
reaction can be explained with heterolytic cleavage in the first step, negating the necessity of a homolytic cleavage reaction.

The question of stereospecificity is addressed in Table VI. Injection of the reaction solution into the gas chromatograph after about 40 s of reaction time stops the epoxidation *before* appreciable direct reaction of the hydroperoxide with the hemin can occur but *after* most of the peracid or PFIB has reacted.

With PFIB or peracid alone, high ratios of cis to trans epoxide (i.e., high stereospecificities) are obtianed. With *tert*-butyl hydroperoxide alone, the trans epoxide dominates (line 5 in Table IV), and cis/trans = 0.6. Addition of an equimolar quantity of *tert*-butyl hydroperoxide (with respect to the other oxidant) to the hemin/PFIB/*cis*-β-methylstyrene reaction mixture, along with termination of the reaction in 40 s, results in an almost identical loss of stereospecificity (last line in Table IV), where cis/trans = 0.5. There is a concomitant loss of epoxide yield. Therefore, reactions 22 and 23 *do* result in the same stereospecificity.

The data in Table IV firmly establish the fact that loss of stereospecificity is completely consistent with heterolytic cleavage. In previous studies,[34] epoxidation of *cis*-stilbene with *tert*-butyl hydroperoxide (catalyzed by tetraphenylhemin chloride) resulted in a predominant production of *trans*-stilbene oxide. This was interpreted as evidence of homolysis—i.e., reaction 5 followed by reactions 24–26.

(24)



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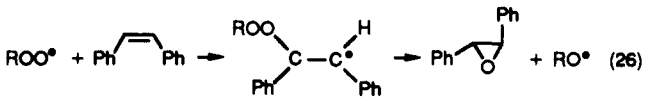


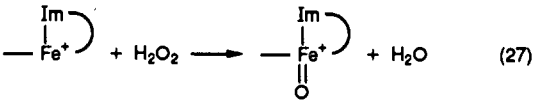
(26)

We now see that this same sequence is efficiently obtained from reaction 7, making the postulate of homolysis unnecessary. The loss of epoxide yield upon addition of ROOH to the pentafluoroiodosylbenzene reaction (last three lines of Table IV) also provides evidence that low epoxide yields (often attributed to homolysis)[34,50] do not require a homolytic explanation. Because we can obtain high epoxide yields with the electronegatively-substituted catalysts **1**–**4**, we can be assured that such catalysts react with hydroperoxides by the heterolytic reaction of eq 2 in hydroxylic solvents. This differs from the kinetically-based explanation by Bruice et al.[25] that similar catalysts (e.g., a tetrasulfonated form of **4**) react by homolysis in water. Their kinetic findings and conclusions are essentially the same for methanol[50] and water and methylene chloride[34] solvents. Therefore, we conclude that heterolytic cleavage occurs under their conditions as well. The kinetic studies will be discussed elsewhere.[51]

These studies and conclusions apply only to hydrogen peroxide and *tert*-butyl hydroperoxide and to the four pieces of evidence mentioned earlier. Other hydroperoxides, such as the unsaturated hydroperoxides studied by Marnett et al.[27] and Thompson et al.,[26] might react differently. In fact, under the conditions where *tert*-butyl hydroperoxide gives 86% yield of epoxide (Table II), α,α-dimethylphenethyl hydroperoxide affords only 16% yield.[51] Additional evidence, such as the absence of a phenol effect (also presented by these authors), is not considered here. These systems are still under study.

Electropositive Hemins. In an early paper, we reported that peracid and hydrogen peroxide reactions with a five-coordinated horseradish peroxidase model (chelated protoheme) were accelerated by better leaving groups (RO^-), by buffers, by covalently-bound neighboring carboxylic acid groups, and by an imidazole in the position trans to the ligated oxidizing agents.[23] We subsequently showed that alcohols catalyze these reactions and that there is a deuterated solvent isotope effect of about 2.[36] These effects are very similar for peracids, hydrogen peroxide, and *tert*-butyl hydroperoxide, and this similarity provides rather strong evidence for similar mechanisms. The results included kinetic studies of microperoxidase, an 11 amino acid peptide catalyst from cytochrome *c*. This catalyst was dissolved in a water/methanol mixture (4/1). Our kinetic results indicated that this compound reacts with hydrogen peroxide by heterolytic cleavage.[36]

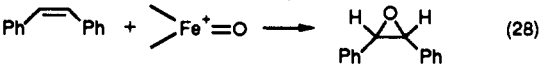
Recently, elegant proof of this heterolytic cleavage has been provided by Van Wart et al.[52] They have reacted the corresponding 8 amino acid peptide hemin (microperoxidase-8) with hydrogen peroxide at low temperature in highly aqueous media. They have shown by UV–visible and Raman spectroscopy that the same series of intermediates occurs in HRP and this microperoxidase. That is, the model compound reacts with hydrogen peroxide to produce the two-electron-oxidized species by heterolysis. Since these microperoxidase structures and chelated hemin, which we used first,[23] are five-coordinated hemin–imidazole complexes, their results definitively confirm all of our kinetically-based findings.



(27)

The reactions of these hemins in methanol, water, and methanol/water proceed by exclusive heterolysis in these biomimetic systems. These studies provide compelling evidence that the more electropositive hemins, such as protohemin and mesohemin, also react exclusively by heterolytic cleavage. Thus, we propose that electronegative hemins without a proximal imidazole, as well as electropositive hemins made more electropositive with a proximal imidazole, react exclusively by heterolysis in alcohol, in aqueous, or in aqueous alcohol solutions.

Products of Epoxidation as Mechanistic Probes. Because the reactions of oxenes (>Fe⁺=O) with alkenes have regiochemistry and stereochemistry which differ from those of other epoxidation processes, the nature of the products obtained is used to infer which intermediates are involved. Specifically, the reactions of alkenes with >Fe⁺=O, generated by reacting PhIO with iron(III) porphyrins, show stereospecificity (eq 28) and often involve some type of carbocation rearrangement. These reactions afford both exo and endo epoxynorbornane (eq 29).[9a]



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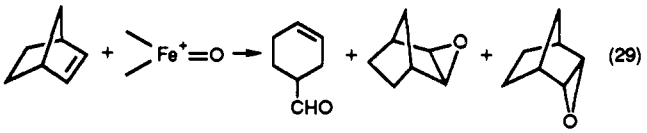
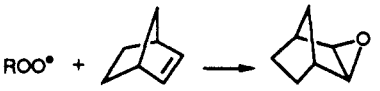


(29)

(52) Wang, J.-S.; Baek, H. K.; Van Wart, H. E. *Biochem. Biophys. Res. Commun.* **1991**, *179*, 1320–1324.

Peracid epoxidations are also stereospecific, but produce no (<0.1% of the total exo yield) endo epoxynorbornane, and do not usually give any rearrangements. Peroxyl radicals add to alkenes with loss of stereospecificity (eq 26) and, when reacted with norbornene, give no endo epoxide or rearrangement (eq 30).[31] Of

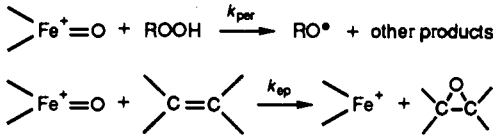


(30)

these probes, only the reaction with norbornene provides direct information about the first intermediate.[9a,b] In contrast to *all* other additions to norbornene, reactions of oxenes (>Fe⁺=O) with norbornene give mixtures of exo and endo products. Also, the mixture composition is specific to the hemin (Table I),[9b] is only slightly dependent upon solvent, and is independent of the type of oxidant. Therefore, comparison of a given oxidant's exo/endo epoxynorbornane product ratios (derived from catalyzed epoxidations) with those for PFIB reveals whether there is peroxyl radical interference and also identifies the intermediate as >Fe⁺=O. No other species has this specificity as a mechanistic probe.

Effect of Hemin Structure on Epoxide Yields, Stereospecificities, and Regiospecificities. The hemin-catalyzed epoxidations using hydroperoxides often result in loss of stereochemistry. It has been noted that the use of electronegatively-substituted hemins, such as **4**, results in greater retention of stereochemistry than that found for tetramesitylhemin or tetraphenylhemin reactions. This difference has been attributed to varying amounts of homolysis and heterolysis, where the electronegative hemins were sometimes assumed to give more heterolysis.[27b,34] Oddly, the addition of 1-methylimidazole to tetraphenylhemin also increases stereospecificity.[34] This is interpreted as an increase in heterolysis due to electron donation by the imidazole. These two interpretations appear to be incompatible.

An alternative explanation can be derived from Figures 2 and 3: tetramesitylhemin prefers reaction 31 to reaction 32 more so than does tetrakis(pentafluorophenyl)hemin.



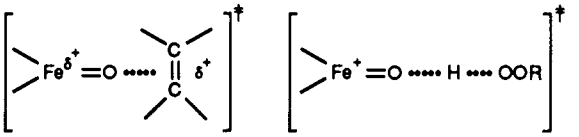
(31)

(32)

Much of the previous evidence offered in support of homolysis has been obtained with tetraphenylhemin or tetramesitylhemin. It is now clear how these results might be obtained.[53] The difference in hemins with regard to the production of peroxyl and alkoxyl radicals lies not in reaction differences of hydroperoxides with iron(III) porphyrins but in the varying efficiencies of hydroperoxide oxidation by the oxene species (eq 31) and how this reaction compares to the oxygen-transfer process (eq 32). This explains many of the discrepancies between our results and those reported elsewhere.

Oxene Selectivity and Porphyrin Structure. Kinetic studies, and the variation in epoxide yields with porphyrin structure, indicate that as the porphyrin is made more electron-deficient, there is a drastic change in the oxene selectivity for epoxidation versus hydroperoxide decomposition (k_{ep}/k_{per}). As the basis of successful epoxidation with hydroperoxides, this change is important and deserves some comment.

One possible explanation is that alkene epoxidation has more electron-transfer characteristics than does hydrogen abstraction (or other reactions of hydroperoxides):



Since the mechanism of the hydroperoxide reaction with the oxene is not known, except for the fact that it has an isotope effect of about 4,[22b] this rationale is, at best, tentative. A second interpretation involves the reasonable assumption that reaction of the oxene with hydroperoxides is near diffusion control, even for (TMP)FeCl, because it is a very fast reaction, with a rate about the same as that with phenols. The slower epoxidation reaction[22a] will be greatly accelerated by making the porphyrin more electron-deficient, simply as a result of having a more electrophilic oxene. Since the rate of the diffusion-controlled reaction cannot be increased, there would be an increase in the k_{ep}/k_{per} ratio.

Both of these possibilities are reasonable, but absolute values of the rate constants (k_{ep} and k_{per}) will be needed in order to establish the basis of this trend.

Conclusions. We report three significant—and perhaps important—findings. (1) High-yield, high-turnover, regiospecific, hemin-catalyzed epoxidations using hydrogen peroxide (or *tert*-butyl hydroperoxide) have been achieved. (2) The decrease in epoxidation stereospecificity in the presence of hydroperoxides occurs after the rate-limiting O–O bond cleavage, showing that loss of stereospecificity is *not evidence for O–O bond homolysis* in the first step. (3) The oxene species (>Fe⁺=O) prefers the oxidation of hydroperoxides to epoxidation. This preference *decreases as the hemin is made more electronegative* by substitutions on the porphyrin. This explains the high yields we obtained and the low yields reported by others; it offers new ways to improve epoxidation reactions. Finally, unequivocal evidence for exclusive heterolyses of *t*-BuOOH and H_2O_2 in reactions with hemins is presented, and previous results are reinterpreted and shown to be consistent with heterolysis.

Acknowledgment. We wish to thank the National Science Foundation (Grant CHE 87-21364) for its support and Professors Lawrence Marnett and Paul Ortiz de Montellano for helpful discussions.

(53) As Lebeque and Marnett[27b] suggest, our epoxidation of norbornene with *tert*-butyl hydroperoxide (catalyzed by tetramesitylhemin) probably proceeds through the peroxyl radical reaction. A check of the exo/endo ratio obtained reveals a value >100, not the expected value of 24. However, this result is still consistent with heterolysis, as we point out in the present work.