

# Intermediates in the Epoxidation of Alkenes by Cytochrome P-450 Models. 5. Epoxidation of Alkenes Catalyzed by a Sterically Hindered (*meso*-Tetrakis(2,6-dibromophenyl)porphinato)iron(III) Chloride

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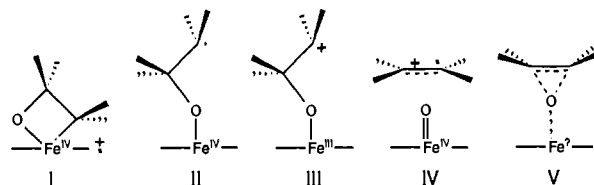
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**Abstract:** Sterically hindered (*meso*-tetrakis(2,6-dibromophenyl)porphinato)iron(III) chloride ( $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ ) was prepared and used as a catalyst for epoxidation of nine structurally different alkenes.  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  is an extremely efficient catalyst for epoxidation, and nearly quantitative yields of epoxides were obtained in all cases. Computer graphics docking experiments show that alkenes can approach the iron-oxo moiety of the iron(IV)-oxo porphyrin  $\pi$  cation radical ( $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})(\text{X})$ ) from above the oxygen and distal to the iron, but with various angles of approach. With the exception of terminal alkenes, the bulky *o*-bromo substituents prevent interaction of alkenes with the iron or pyrrole nitrogens of the porphyrin ring. With alkyl-substituted terminal alkenes various degrees of porphyrin N-alkylation accompany epoxidation. Selectivity for N-alkylation parallels the selectivity observed with microsomal cytochrome P-450. Arguments are presented that support either a concerted or a radical mechanism for N-alkylation by terminal alkenes. Formation of a metallaoxetane intermediate in the epoxidation reaction via a  $2a + 2s$  cycloaddition is discounted on the basis of (i) docking experiments, which show that all but terminal alkenes are unable to approach the iron(IV) moiety, and (ii) examination of X-ray-based computer graphics constructed metallaoxetane structures formed from  $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O}) + \text{cis-stilbene}$  or 2,3-dimethyl-2-butene regardless of whether the porphyrin ring is flat, ruffled, or saucer shaped. Evidence for rate-determining formation of the carbon radical  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}\text{-O-C-C}^\cdot$ , carbocation  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}\text{-O-C-C}^+$ , and the solvent-caged intimate pair  $/(\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})\cdots\text{alkene}^{+\cdot}/$  in alkene epoxidation is considered. A mechanism that best correlates the results of epoxidation studies for both  $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})(\text{X})$  and  $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}(\text{O})(\text{X})$  involves a rate-determining formation of a charge-transfer complex by partial electron transfer from the alkene to the hypervalent porphyrin metal-oxo species.

Several intermediates have been proposed in the epoxidation reactions catalyzed by metalloporphyrins (Chart I).<sup>1</sup> These include metallaoxetane (I),<sup>1b-d</sup> carbon radical (II),<sup>1c-h</sup> carbocation (III),<sup>1i-m,2a</sup> and the ion pair  $/(\text{Porph})\text{M}^{\text{IV}}(\text{O})\cdots\text{alkene}^{+\cdot}/$  (IV),<sup>1l,m</sup> Concerted insertion of oxygen into the alkene double bond (V)<sup>1n-q</sup> should also be considered.

We have been engaged in studies directed toward the elucidation of the mechanism of epoxidation reactions.<sup>2-4</sup> In this study we examine the epoxidation of a number of alkenes using (*meso*-tetrakis(2,6-dibromophenyl)porphinato)iron(III) chloride ( $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ ) as the catalyst and  $\text{C}_6\text{F}_5\text{IO}$  as oxygen-transfer agent. Bulky *o*-bromo substituents provide steric hindrance with alkene substrates to a degree that allows all but terminal alkenes

Chart I



to interact only with the iron-bound oxygen. We show that (i)  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  is the most efficient catalyst reported thus far for the epoxidation of alkenes, including terminal alkenes, (ii) rearrangement products that arise from the pathways parallel to epoxidation are largely absent, (iii) N-alkylation of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  is observed only with terminal alkenes bearing alkyl substituents, and (iv) proposed metallaoxetane intermediates are not on the reaction path to epoxidation. Knowledge gained from this and previous studies<sup>2-4</sup> suggests a mechanism of epoxidation that involves the rate-limiting formation of an intermediate with a small degree of electron transfer from the alkene to  $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})(\text{Cl})$  (a charge-transfer (CT) complex), followed by an unsymmetrical concerted oxygen transfer to form epoxide plus  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ . Porphyrin N-alkylation and substrate rearrangements are the result of competition to epoxidation by parallel reactions that stem from the CT complex.

## Experimental Section

**Materials.** The solvent  $\text{CH}_2\text{Cl}_2$  used throughout this study was of the highest purity and its preparation has been described previously as grade A.<sup>5</sup> 2,6-Dibromobenzaldehyde was prepared according to a literature procedure<sup>6</sup> [ $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  10.26 (s, 1 H, aldehyde), 7.64 (d, 2 H,  $J = 8.5$  Hz, *m*-H), 7.24 (t, 1 H,  $J = 8.5$  Hz, *p*-H); mp 90–91 °C (lit.<sup>7</sup> mp 90.5 °C)]. *meso*-Tetrakis(2,6-dibromophenyl)porphyrin ( $\text{Br}_8\text{TPPH}_2$ ) was prepared and coarsely purified according to

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a literature procedure.<sup>8</sup>  $\text{Br}_8\text{TPPH}_2$  is only slightly soluble in most solvents suitable for chromatography, which made its purification tedious. Further purification was achieved by column chromatography on silica using first  $\text{CHCl}_3$  to elute fast-moving impurities, followed by elution of  $\text{Br}_8\text{TPPH}_2$  with 10% ethanol in  $\text{CHCl}_3$ . This required a large volume of solvent, which also partially dissolved silica. After evaporation to dryness,  $\text{Br}_8\text{TPPH}_2$  was extracted from silica by using a Soxhlet apparatus and  $\text{CH}_2\text{Cl}_2$  as solvent. The  $\text{Br}_8\text{TPPH}_2$ , which crystallized in the bottom part of Soxhlet apparatus, was filtered off and dried in high vacuum. This material was used without further purification. The UV/vis spectrum was characterized by two Q-band peaks at 590 and 516 nm and a sharp Soret peak at 422 nm. (*meso*-Tetrakis(2,6-dibromophenyl)porphinato)iron(III) chloride ( $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ ) was prepared by metalation of  $\text{Br}_8\text{TPPH}_2$  (200 mg, 0.16 mmol) with  $\text{FeCl}_2$  (100-fold excess) in 50 mL of refluxing DMF/toluene, 3/1 (v/v), under nitrogen atmosphere for a period of 24 h. The reaction mixture was cooled, diluted with water, and extracted with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  layer was thoroughly washed with water and evaporated to dryness to give crude  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ . Final purification was achieved in the following manner: Chromatography on silica using  $\text{CH}_2\text{Cl}_2$ /ethyl acetate/methanol, 100/10/1, separated the majority of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  from an unidentified faster moving impurity. The resulting purified  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  was dissolved in  $\text{CH}_2\text{Cl}_2$ , treated with  $\text{HCl}$ (gas) until no changes were evident in the UV/vis spectrum, and chromatographed on acidic (HCl) alumina, using as the eluent  $\text{CH}_2\text{Cl}_2$  previously stirred over concentrated HCl. A single band of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  separated nicely. Recrystallization from  $\text{CH}_2\text{Cl}_2$ /pentane gave 120 mg of pure  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  [ $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 500 MHz)  $\delta$  80.7 (s, 8 H, pyrrole H), 13.6 (s, 4 H, Ph *m*-H), 12.5 (s, 4 H, Ph *m*-H), 8.2 (s, 4 H, Ph *p*-H); UV/vis,  $\lambda$ , nm (log  $\epsilon$ ) 647 (3.57), 582 (3.58), 513 (4.09), 422 (5.02), 368 (4.63); mass spectrum,<sup>9</sup> laser desorption, calcd for  $\text{C}_{44}\text{H}_{20}\text{N}_4\text{Br}_8\text{FeCl}$  1335.2, obsd  $m/e$  1335 ( $\text{M}^+$ ), 1300 ( $\text{M}^+ - \text{Cl}$ ), 1220, 1140, 1060, 980, 900, 820, 740 (consecutively weaker signals due to the losses of Br's); the signals are clusters of peaks due to Br isotope distribution]. To ensure that our product is not a mixture of compounds containing a variable number of bromines, an experiment was performed in which after  $\text{CO}_2$  laser desorption all ions except the  $m/e$  1300 were ejected, followed by the 308-nm excimer laser photodissociation of the  $m/e$  1300 fragment. An identical peak distribution pattern with somewhat altered intensities was observed, consistent with the proposed structure.<sup>9</sup>

All alkenes were purchased from Aldrich and rigorously purified by the appropriate method (sublimation, distillation, or vacuum transfer). Liquid alkenes were passed consecutively through short columns of basic and neutral alumina immediately prior to use.  $\text{CH}_2\text{Cl}_2$  solutions of alkenes were prepared under nitrogen atmosphere and used fresh. Commercially available epoxides (Aldrich) used as GC and HPLC standards were purified to homogeneity before use, as established by GC or HPLC. Other epoxides were prepared by MCPBA epoxidation of the alkenes<sup>3c</sup> and purified by flash chromatography on silica, followed either by recrystallization or by vacuum transfer. Purity and identity of epoxides were verified by  $^1\text{H}$  NMR; purity was also verified by GC or HPLC.  $\text{C}_6\text{F}_5\text{IO}$  was available from a previous study.<sup>2a</sup> Iodometric assay showed that  $\text{C}_6\text{F}_5\text{IO}$  was >98% pure.<sup>10</sup>

HPLC and GC methods of product analysis have been described previously.<sup>2a,5</sup>

**Reactions of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  with  $\text{C}_6\text{F}_5\text{IO}$  in the Presence of Alkenes.** All reactions were carried out under nitrogen atmosphere in grade A  $\text{CH}_2\text{Cl}_2$  at room temperature. The general procedure follows.  $\text{C}_6\text{F}_5\text{IO}$  was weighed out in 1-mL Whatman vials, small magnetic stirrers were added, and the vials were transferred into a nitrogen-filled glovebox. A freshly prepared solution of alkene was added first, followed by addition of the solution of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ . Total volume of reaction mixtures was between 0.6 and 1.0 mL. Vials were crimped with Teflon-coated serum caps, and rapid stirring was initiated.  $\text{C}_6\text{F}_5\text{IO}$  is only slightly soluble in  $\text{CH}_2\text{Cl}_2$  and the reaction mixture is heterogeneous until completion. The time required for the reaction mixture to clear was dependent on the amount of  $\text{C}_6\text{F}_5\text{IO}$  and the concentration of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ . At  $[(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})] = 1.0 \times 10^{-4}$  M, the reaction time was about 10 min per 100 turnovers. Upon completion of reactions, UV/vis spectra of reaction mixtures were recorded, and product analysis was performed.

**Instrumentation.** UV/vis spectra were recorded and manipulated on the Cary-14 UV/vis spectrophotometer interfaced with a Zenith ZF-

**Table I.** Epoxide Yields with  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  Catalyst and  $\text{C}_6\text{F}_5\text{IO}$  Oxygen Donor in Grade A<sup>5</sup>  $\text{CH}_2\text{Cl}_2$  at Room Temperature

| alkene                    | alkene concn, M | catalyst turnover | epoxide yield, <sup>a,b</sup> % |
|---------------------------|-----------------|-------------------|---------------------------------|
| 2,3-dimethyl-2-butene     | 1.0             | 200               | 99 (1)                          |
|                           | 0.1             | 170               | 98                              |
|                           | 0.01            | 200               | 92                              |
| norbornene                | 1.0             | 250               | 99 <sup>c</sup> (4)             |
|                           | 0.1             | 140               | 93                              |
|                           | 0.01            | 100               | 82                              |
| <i>cis</i> -stilbene      | 0.25            | 125               | 99 <sup>d</sup> (3)             |
|                           | 0.05            | 60                | 94                              |
|                           | 0.025           | 45                | 93                              |
| <i>trans</i> -stilbene    | 0.14            | 175               | 4 (3)                           |
|                           | 0.025           | 170               | 4                               |
| styrene                   | 1.0             | 25–200            | 97 (5)                          |
|                           | 0.125           | 165               | 95                              |
|                           | 0.025           | 60                | 80                              |
| 2,4,4-trimethyl-1-pentene | 1.0             | 100               | 99 (6)                          |
|                           | 0.2             | 100               | 96                              |
|                           | 0.05            | 100               | 92                              |
| vinylcyclohexane          | 0.5             | 225               | 97 (3)                          |
|                           | 0.05            | 100               | 84                              |
| 1-hexene                  | 1.0             | 10–200            | 97 (2)                          |
|                           | 0.1             | 150               | 83                              |
|                           | 0.01            | 100               | 71                              |
| 1-octene                  | 1.0             | 100               | 86 (7)                          |
|                           | 0.2             | 100               | 88                              |
|                           | 0.05            | 100               | 72                              |

<sup>a</sup>Yields are based on oxidant, under the assumption that it was 100% pure. <sup>b</sup>Numbers in parentheses are epoxide yields obtained in the absence of catalyst. <sup>c</sup>The *exo*-/*endo*-norbornene oxide ratio was 6.8. <sup>d</sup>Less than 0.1% *trans*-stilbene and 0.5–1.5% *trans*-stilbene oxide were observed.

248-81 computer equipped with OLIS (On Line Instrument Systems, Inc.) software designed for collection and manipulation of spectral data. GC analyses were performed on a Varian Model 3700 gas chromatograph with flame ionization detector using a 0.2 mm  $\times$  25 m WCOT Vitreous  $\text{SiO}_2$  column and interfaced with a Hewlett-Packard 3392A integrator. HPLC analyses were done with two Perkin-Elmer Series 10 pumps, a Perkin-Elmer Series 10 LC Controller, Lichrosorb  $\text{SiO}_2$  column (4.6  $\times$  250 mm), and a Schoeffel Spectroflow Monitor (Model SF770) at 254 nm, interfaced with a Hewlett-Packard 3392A integrator.

**Molecular modeling studies** were performed on Silicon Graphics Iris 4D/60 workstation using Polygen programs Quanta and CHARMM.

## Results

**Epoxidation studies** were carried out in grade A<sup>5</sup>  $\text{CH}_2\text{Cl}_2$  under nitrogen at room temperature using  $\text{C}_6\text{F}_5\text{IO}$  as the oxygen-transfer agent and (*meso*-tetrakis(2,6-dibromophenyl)porphinato)iron(III) chloride ( $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ ) as the catalyst. Epoxide yields are shown in Table I. In the absence of alkenes, the catalyst is completely bleached with a 100-fold excess of  $\text{C}_6\text{F}_5\text{IO}$ .

**The ratio of *exo*- to *endo*-norbornene oxide** determined by GC was  $6.8 \pm 0.5$ .  $^1\text{H}$  NMR spectrum<sup>11</sup> of the reaction mixture run in  $\text{CD}_2\text{Cl}_2$  (norbornene: $\text{C}_6\text{F}_5\text{IO}$ : $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl}) = 150:100:1$ ) showed only the absorptions corresponding to the unreacted norbornene and *exo*- and *endo*-epoxides in the same ratio as determined by GC.

**N-Alkylation of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ .** When terminal alkenes are employed, UV/vis spectra of spent reaction solutions show a change of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  to the corresponding N-alkyl derivatives.<sup>12</sup> The extent of N-alkylation was dependent on the catalyst turnover number and the steric demand of the alkene. Aside from terminal alkenes, no spectral changes were observed upon completion of the reactions, with the exception that at high catalyst turnover a small portion of chloride axial ligand was exchanged for hydroxide. N-alkylation of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  was studied in detail using 1-hexene as substrate. At  $[1\text{-hexene}] = 1.0$  M and  $[(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})] = 1.0 \times 10^{-4}$  M, the  $[\text{C}_6\text{F}_5\text{IO}]$

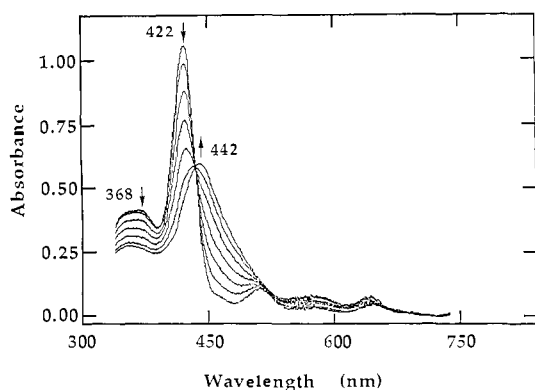
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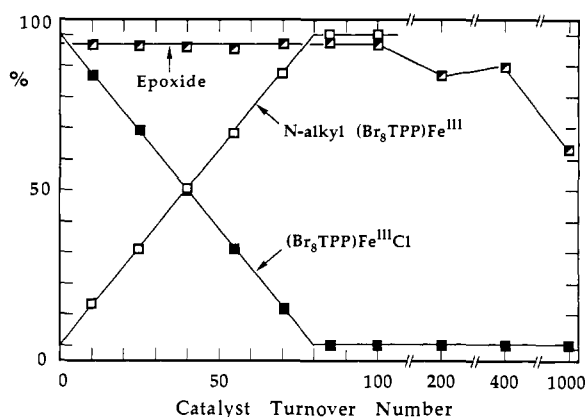
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**Figure 1.** Initial UV/vis spectrum of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  (1-mm cell; Soret  $\lambda_{\text{max}} = 422$  nm) and spectra taken upon completion of the reaction of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  with various concentrations of  $\text{F}_5\text{C}_6\text{IO}$  in the presence of 1-hexene (1 M). With increase in catalyst turnover number (ratio of  $[\text{F}_5\text{C}_6\text{IO}]/[(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})]$ ) from 10 to 100, the spectrum of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  is seen to give way to that of *N*-alkyl- $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}$  (Soret  $\lambda_{\text{max}} = 442$  nm) with an isosbestic point at 436 nm.



**Figure 2.** Plots of percentage of the intact  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  and *N*-alkyl- $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}$  and the yield of 1,2-epoxyhexane upon completion of the reaction of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  ( $1.0 \times 10^{-4}$  M) with various concentrations of  $\text{F}_5\text{C}_6\text{IO}$  in the presence of 1-hexene (1 M). Catalyst turnover (ratio of  $[\text{F}_5\text{C}_6\text{IO}]/[(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})]$ ) varies from 10 to 1000.

was such that the catalyst turnover number varied from 10 to 1000. Spectra of spent reaction mixtures at catalyst turnovers ranging from 10 to 100 are shown in Figure 1. Spectra obtained between 80 and 100 catalyst turnovers are identical and characteristic of reported spectra of *n*-alkyl iron(III) porphyrins.<sup>12</sup> Each spectrum was deconvoluted to give the final concentrations of the intact and *N*-alkylated  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ , by using the spectrum at 100 turnovers as that for *N*-alkylated  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ . The plot of the concentrations of each porphyrin species and the epoxide yield at different catalyst turnovers is shown in Figure 2. It is evident from Figure 2 that, when 1-hexene is a substrate,  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  is completely *N*-alkylated at 80 turnovers. Thus, the frequency of *N*-alkylation is 1 in every 80 turnovers of catalyst. At higher catalyst turnovers (>200) the spectrum of *N*-alkylated  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  shows further changes, and the epoxide yield decreases from 96% at 100 turnovers to 63% at 1000 turnovers. The *N*-alkylation turnover number determined at 1.0 M vinylcyclohexane was 130, and at 1.0 M 2,4,4-trimethyl-1-pentene it was 280. At lower concentrations of terminal alkenes some destruction of the *N*-alkylated  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}$  is observed, resulting in somewhat lower apparent alkylation turnover numbers. This is due, in part, to the low reactivity of terminal alkenes, which makes the porphyrin a relatively better substrate for oxidation compared to the alkene. Experiments using 25–250 catalyst turnovers with styrene as a substrate showed, by UV/vis spectral examination, no *N*-alkylation at all. The only spectral change observed was a small decrease of absorbance at 368 nm, which corresponds to conversion of  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$  to  $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{OH})$  by exchange of  $\text{Cl}^-$  for  $\text{OH}^-$  ligand. This ligand ex-

change gradually increased with the increasing number of catalyst turnovers.

**Molecular modeling studies** were performed in order to examine the feasibility of some of the proposed intermediates and the sterically allowed orientation of the reactants. The structure of iron-oxo porphyrin  $\pi$  cation radical ( $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})(\text{X})$ ) is not known, and two template X-ray structures were used as possible models: (i) *meso*-(tetraphenylporphinato)iron(III) chloride ( $(\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ )<sup>13a</sup> and (ii) chloro(*meso*-tetraphenylporphinato)iron(III) hexachloroantimonate  $\pi$  cation radical ( $(^+\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})(\text{SbCl}_6)$ ).<sup>13b</sup> Model i is justified on the basis of same spin multiplicity ( $^3/2$ ) as in the catalase and horseradish peroxidase oxidants and by the fact that porphyrin radical cations are most likely flat in solution.<sup>14</sup> Model ii was considered because it shows the degree to which the porphyrin ring can deviate from planarity. *o*-Bromo substituents on the phenyl rings were appended with the fixed bond distance of 1.85 Å, and an Fe–O bond was created with the length of 1.64 Å.<sup>15</sup> Due to the steric interaction of bromine atoms with pyrrole carbons, the phenyl groups can rotate to a minimal dihedral angle of 70° with respect to the plane of the porphyrin ring. Although this relieves some steric interaction with the incoming substrate, considerable steric restrictions are still present. For modeling of the putative metallaoxetane intermediate, two template X-ray structures were considered: (i) iridium azametallacyclobutane ( $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{CH}_2\text{CMe}_2\text{NH}_2^+)$ )<sup>16a</sup> (bond lengths in the four-membered ring: Ir–C = 2.11 Å, C–C = 1.52 Å, C–N = 1.51 Å, N–Ir = 2.12 Å) and (ii) platinum oxametallacyclobutane ( $(\text{As}(\text{C}_6\text{H}_5)_3)_2\text{Pt}(\text{C}_2(\text{CN})_2\text{O})$ )<sup>16b</sup> (bond lengths in the four-membered ring: Pt–C = 2.10 Å, C–C = 1.58 Å, C–O = 1.36 Å, O–Pt = 2.05 Å). Both structures have similar bond lengths and angles in the relevant four-membered ring, and the slightly more relaxed  $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{CH}_2\text{CMe}_2\text{NH}_2^+)$  was used as the actual template for the proposed iron–metallaoxetane. Structures of metallaoxetane ring systems derived from *cis*-stilbene and 2,3-dimethyl-2-butene were constructed by fixing the structure of the four-membered ring according to the aforementioned X-ray structure and energy minimizing the orientation of the substituents. Assembly of the putative porphyrin metallaoxetanes was carried out by superimposing the metal of the porphyrin and that of metallaoxetane, followed by readjustment of the substituent positions to provide minimal steric interactions, by rotation to positions of minimal energy. The structures of alkenes used in docking experiments were obtained by CHARMm energy minimization. Mutual orientation of alkenes and  $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})$  was obtained by allowing alkene and  $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})$  to achieve the position of van der Waals minimum energy and then bringing them closer together until the energy of interaction reached  $\sim 0.6$  kcal/mol (*RT* at room temperature).<sup>4</sup>

## Discussion

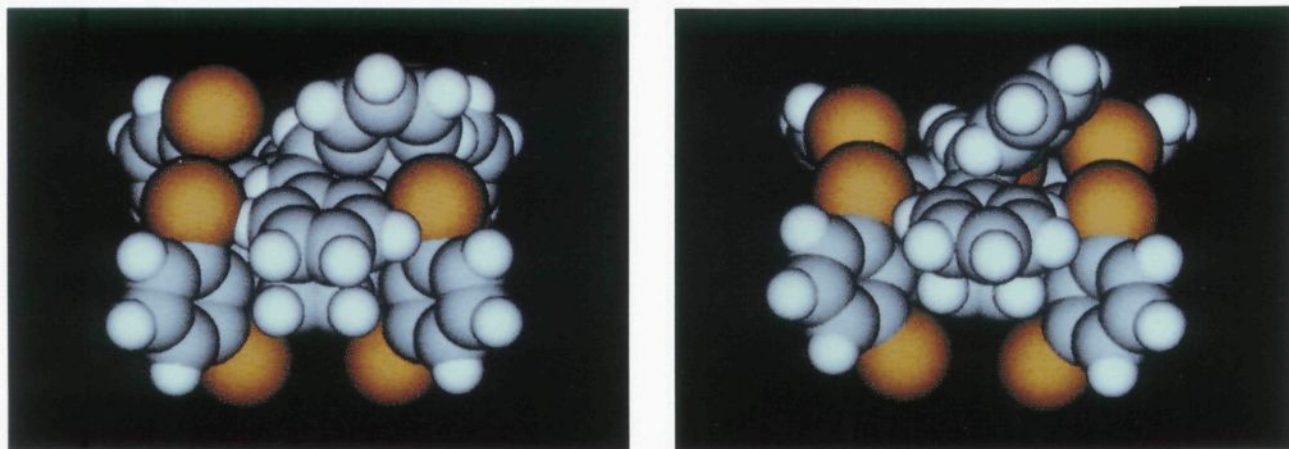
In this study the sterically hindered (*meso*-tetrakis(2,6-dibromophenyl)porphinato)iron(III) chloride ( $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$ ) was used as the catalyst for epoxidation of alkenes by  $\text{C}_6\text{F}_5\text{IO}$ . With the exception of *trans*-stilbene, high yields of epoxides—including those from terminal alkenes—were observed (Table I). Lack of formation of epoxide with *trans*-stilbene is attributed to severe steric restrictions in the approach of this alkene to the epoxidizing  $(^+\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})(\text{Cl})$  species.

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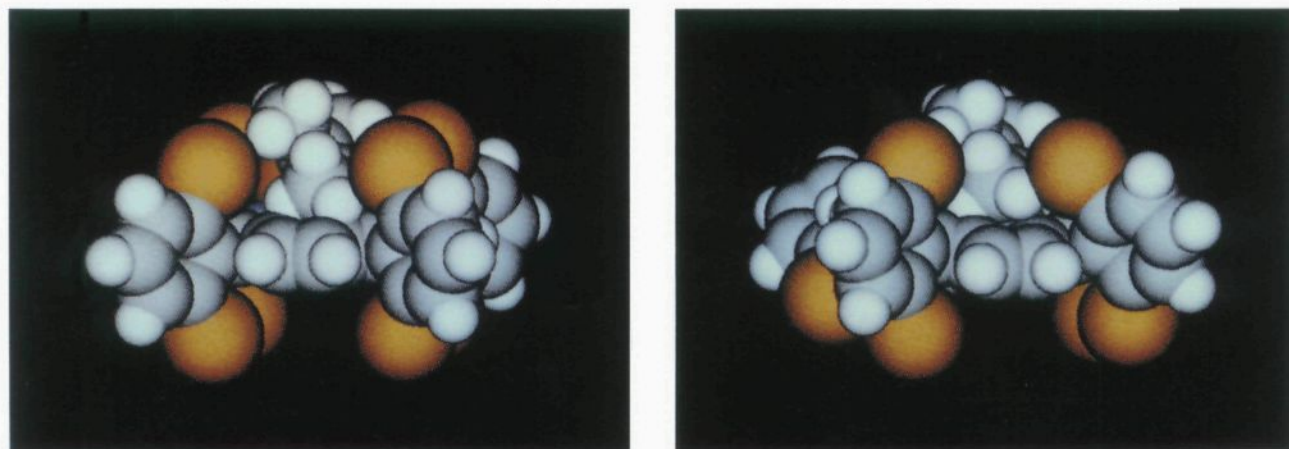
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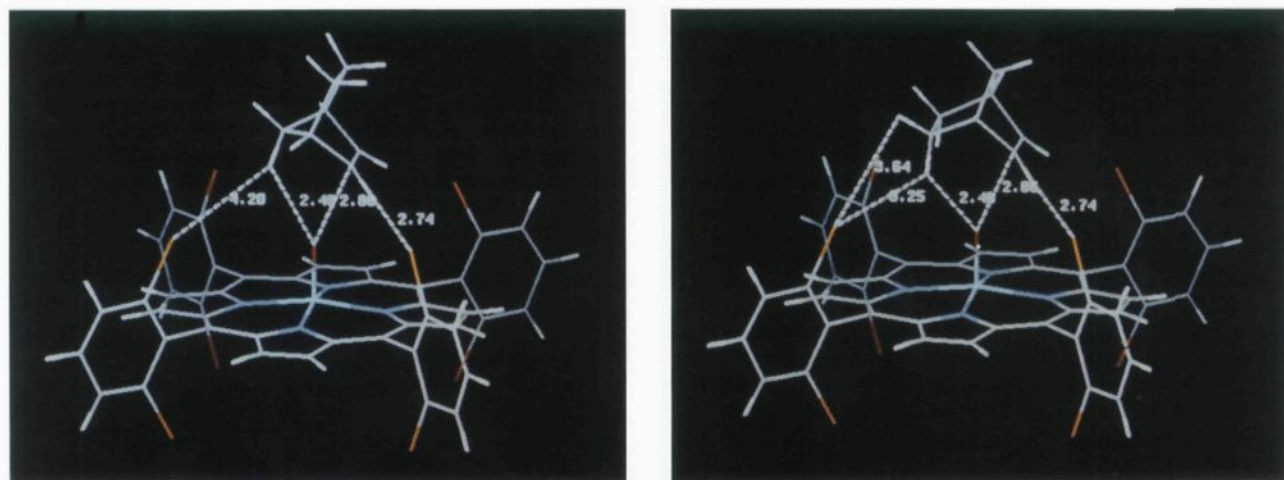
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**Figure 3.** Computer-generated space-filling models (CPK) of iron porphyrin derived *cis*-diphenylmetallaioxetane using (A, left) (TPP)Fe<sup>III</sup>(Cl)<sup>13a</sup> ("flat") and (B, right) (\*TPP)Fe<sup>III</sup>(Cl)(SbCl<sub>6</sub>)<sup>13b</sup> ("saddle shaped") as a templates for the structure of the porphyrin moiety. The template for the structure of the metallaioxetane four-membered ring was taken from the X-ray structure of ref 16a. Serious steric interactions are evident in both structures. The carbon atoms of the porphyrin pyrrole moiety and the phenyl ring of the *cis*-stilbene moiety are interacting at  $R/R_0$  (actual distance/van der Waals distance) down to 0.61 in A and 0.59 in B. Also, hydrogens and carbons on the phenyl ring of the *cis*-stilbene moiety are interacting with the porphyrin *o*-bromo substituents,  $R/R_0 = 0.66$  in A and 0.73 in B. Oxygen of the metallaioxetane moiety is at a  $R/R_0 = 0.77$  with two porphyrin nitrogens.

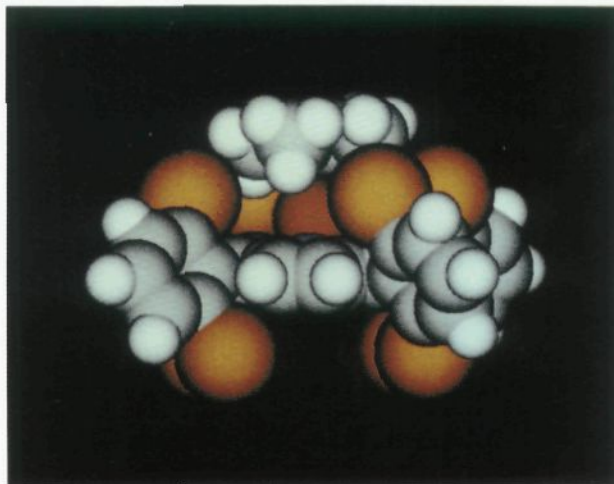
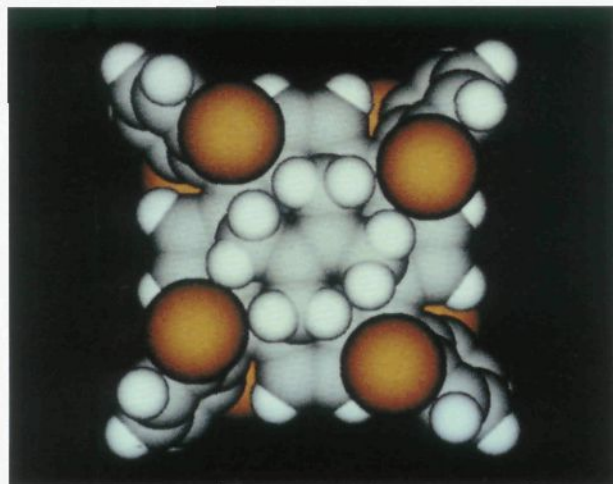


**Figure 4.** Computer-generated space-filling models (CPK) of iron porphyrin derived tetramethylmetallaioxetane using (A, left) (TPP)Fe<sup>III</sup>(Cl)<sup>13a</sup> ("flat") and (B, right) (\*TPP)Fe<sup>III</sup>(Cl)(SbCl<sub>6</sub>)<sup>13b</sup> ("saddle shaped") as a templates for the structure of the porphyrin moiety. The template for the structure of metallaioxetane four-membered ring was taken from the X-ray structure of ref 16a. Serious steric interactions are evident in the structures of both views A and B. The carbon atoms of the porphyrin pyrrole moiety and the methyl group hydrogens of the 2,3-dimethyl-2-butene moiety are interacting at  $R/R_0$  (actual distance/van der Waals distance) down to 0.56 in A and 0.52 in B. Also, the methyl group hydrogens of the 2,3-dimethyl-2-butene moiety are interacting with the porphyrin *o*-bromo substituents,  $R/R_0 = 0.79$  in A and 0.73 in B. Oxygen of the metallaioxetane moiety is at  $R/R_0 = 0.77$  with two porphyrin nitrogens and one porphyrin carbon.

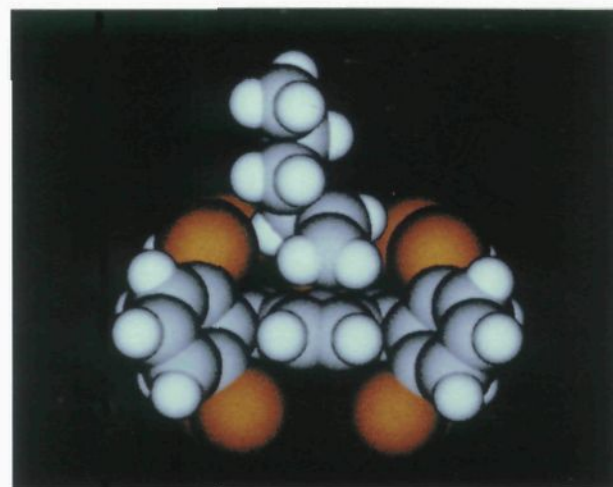


**Figure 5.** Computer-generated stick models of norbornene docked on (\*Br<sub>8</sub>TPP)Fe<sup>IV</sup>(O): (A, left) attack of oxygen from the exo side (interaction energy = 0.71 kcal/mol), and (B, right) attack of oxygen from the endo side (interaction energy = 0.69 kcal/mol). The relevant interatomic distances are shown. The view was chosen such that the interaction of norbornene double-bond hydrogens with the *o*-bromo substituents on the porphyrin phenyl groups is evident. X-ray structure of (TPP)Fe<sup>III</sup>(Cl)<sup>13a</sup> was used as a template for the structure of the porphyrin moiety, and the structure of norbornene is a CHARMm-minimized structure.





**Figure 6.** Computer-generated space-filling models (CPK) of 2,3-dimethyl-2-butene docked on top of  $(^*Br_8TPP)Fe^{IV}(O)$ . Inspection of view A (left) shows that 2,3-dimethyl-2-butene can be fit into the niche created by the bromo substituents. Inspection of view B (right) shows that 2,3-dimethyl-2-butene can be docked only on top of the oxygen. The minimal sterically allowed angle of approach is  $40^\circ$ . The interaction energy is 0.63 kcal/mol. X-ray structure of  $(TPP)Fe^{III}(Cl)^{13a}$  was used as a template for the structure of the porphyrin moiety, and the structure of 2,3-dimethyl-2-butene is a CHARMM-minimized structure.



**Figure 7.** Computer-generated space-filling model (CPK) of the docking of 1-hexene on  $(^*Br_8TPP)Fe^{IV}(O)$  with the geometry suitable for concerted N-alkylation ( $C_1-N$  bond distance, 2.93 Å;  $C_2-O$  bond distance, 2.93 Å). X-ray structure of  $(TPP)Fe^{III}(Cl)^{13a}$  was used as a template for the structure of the porphyrin moiety, and the structure of 1-hexene is a CHARMM-minimized structure.

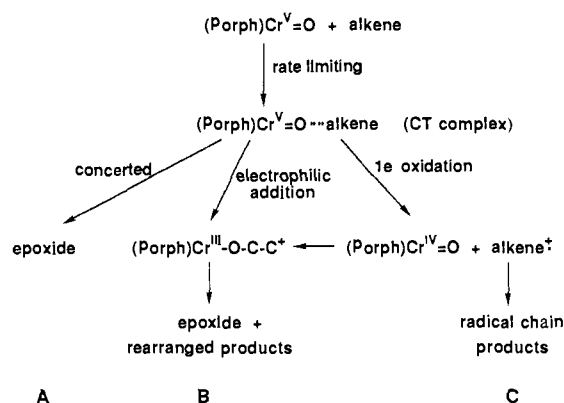
The four structures of Chart I have been proposed as intermediates in alkene epoxidation.<sup>1</sup> It has been shown in an earlier publication from this laboratory that the intermediacy of the carbon radical species (II) would require its collapse, to epoxide plus iron(III) porphyrin, to occur with a rate constant of  $>10^{12} s^{-1}$ .<sup>2b</sup> Such a finding excludes II as a discrete intermediate in epoxidation. The metallaoxetane intermediate (I) has been proposed to be formed by a  $2a + 2s$  cycloaddition reaction and to give way to epoxide plus iron(III) porphyrin via a concerted reductive elimination.<sup>1b-d</sup> Evidence for accumulation of I as an intermediate in epoxidation has been challenged.<sup>17</sup> The question remains as to the viability of I as a steady-state intermediate in the epoxidation reaction. To address this question we have turned to the use of molecular modeling (see Results).

The constructed structures of putative metallaoxetanes formed from the  $(^*Br_8TPP)Fe^{IV}(O)$  moiety and the alkenes *cis*-stilbene and 2,3-dimethyl-2-butene are shown in Figures 3 and 4. Examination of the *cis*-diphenylmetallaoxetane structure (Figure 3) shows that one phenyl ring is invaginated into both the porphyrin ring and the *o*-bromo substituents. For the tetramethylmetallaoxetane structure (Figure 4), two of the methyl groups are deeply penetrated into the porphyrin plane. In order to avoid these unfavorable steric interactions, the Fe-C and Fe-O bond lengths must be extended to unreasonable values of  $>3.2$  Å. Both *cis*-stilbene and 2,3-diphenyl-2-butene epoxidize in almost quantitative yields (Table I). In order to further elaborate on this point, an extremely "dished" structure of  $(^*Br_8TPP)Fe^{IV}$  was constructed in which the iron was 0.46 Å out of plane defined by porphyrin nitrogens and 0.99 Å out of plane defined by pyrrole  $\beta$ -carbons. The *cis*-stilbene metallaoxetane moiety was then docked on this porphyrin structure to the closest sterically allowed position that still satisfies a metallaoxetane geometry. In this case more reasonable bond distances were achieved (Fe-C = 2.72 Å and Fe-O = 2.37 Å; this is a minimal Fe-O distance sterically allowed by O-N<sub>pyrrole</sub> repulsions even when Fe is 0.46 Å out of the plane defined by porphyrin nitrogens; compare to Pt-O = 2.05 Å and Pt-C = 2.10 Å, the distances in the X-ray structure of a known metallaoxetane<sup>16b</sup>). Also, with this porphyrin model, a *trans*-stilbene porphyrin metallaoxetane with the identical geometry of the four-membered ring can be constructed without any additional steric interactions, suggesting that *trans*-stilbene should also epoxidize via metallaoxetane. This, however, is not observed (Table I). These results (and docking studies, *vide infra*) exclude metallaoxetanes as required intermediates in alkene epoxidation by hypervalent metal-oxo porphyrin species.

The intermediacy of the ion pair IV has been proposed on the basis of the formation of rearranged products in the course of epoxidation.<sup>11m</sup> Hypervalent oxo-metalloporphyrins are good oxidants, and isomerization and rearrangement of alkenes through their carbocation radicals is reasonable for the alkenes with low oxidation potentials.<sup>1m,3b</sup> However, the alkene-derived carbocation radical of IV may or may not be on the reaction path to epoxidation. Observation that epoxidation of norbornene provides unusually low ratios of *exo*- to *endo*-norbornene oxides has been offered in support of the formation of carbocation radical and carbocation intermediates.<sup>11</sup> The mechanism would involve an initial *le* transfer from alkene to  $(^*Porph)Fe^{IV}(O)(X)$ , followed by more or less indiscriminate collapse of the intimate ion pair

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Scheme I



IV to *exo* and *endo* carbocations, which would yield both *exo*- and *endo*-epoxides. The observed trend was that the lower *exo/endo* ratios were obtained with catalysts of increasing oxidation potential and increasing steric demand of the ortho substituents on the tetraphenylporphyrin moiety. Increased reactivity (oxidation potential) itself can explain lower selectivity. Computer graphics docking experiments have been employed (Figure 5) to assess steric factors involving norbornene H-C<sub>2</sub> and H-C<sub>3</sub> interactions with *o*-bromo substituents vs *syn* H-C<sub>5</sub>, *syn* H-C<sub>6</sub> (*endo*), and *syn* H-C<sub>7</sub> (*exo*) interactions with iron(IV)-bound oxygen. The interactions of the *syn* H-C<sub>7</sub> (*exo* attack), *syn* H-C<sub>5</sub>, and *syn* H-C<sub>6</sub> (*endo* attack) with ortho substituents on the porphyrin phenyl groups are sterically unimportant, and their interactions with the oxygen remain invariant, while the steric interactions of ortho substituents on the porphyrin phenyl groups with H-C<sub>2</sub> and H-C<sub>3</sub> (double-bond hydrogens) become more demanding with increase in size of the substituent. Thus, an additional steric factor is present, making the usual *exo/endo* selectivity less pronounced. The observed change in the ratio of *exo*- to *endo*-norbornene oxide can be explained by these electronic and steric effects. Thus, norbornene<sup>+</sup> is not required as an intermediate in order to explain the experimental results. However, only the intermediacy of Fe<sup>III</sup>-O-C-C<sup>+</sup> (III) can explain the formation of the small amounts of norcamphor and cyclohexene-4-carboxaldehyde during metalloporphyrin-catalyzed epoxidation of norbornene.<sup>11,m</sup> In (Br<sub>8</sub>TPP)Fe<sup>III</sup>(Cl)-catalyzed epoxidation of norbornene we detect no other products but *exo*- and *endo*-norbornene oxide.

Rate-determining le oxidation of the alkene has been shown to be improbable in the case of the epoxidation of alkenes with (Br<sub>8</sub>TPP)Cr<sup>V</sup>(O)(X) on the basis that (i) the log of the second-order rate constants (log *k*<sub>2</sub>) for reaction of (Br<sub>8</sub>TPP)Cr<sup>V</sup>(O)(X) with a series of alkenes is a linear function of the le oxidation potential (*E*<sub>1/2</sub>) of the alkenes, suggesting a unified mechanism; but (ii) the standard free energy for le oxidation of approximately half of the alkenes by (Br<sub>8</sub>TPP)Cr<sup>V</sup>(O)(X) to provide (Br<sub>8</sub>TPP)Cr<sup>IV</sup>(O) plus alkene-derived π cation radical appreciably exceeds the free energy of activation for the epoxidation reaction. Alkene-derived π cation radical cannot be an intermediate when the free energy content of this species exceeds the free energy content of the transition states; and (iii) the slope of the correlation line (log *k*<sub>2</sub> vs *E*<sub>1/2</sub>) is 2.99 V<sup>-1</sup>, suggesting a rate-limiting partial electron transfer. The mechanism of Scheme I was proposed.<sup>3b</sup>

Concerning the proposed carbocation intermediate III (Chart I), *cis*-stilbene is a substrate prone to carbocationic rearrangements when less sterically hindered iron(III) porphyrins are used as catalysts.<sup>2a</sup> With (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)iron(III) chloride ((Cl<sub>2</sub>TPP)Fe<sup>III</sup>(Cl)) + C<sub>6</sub>F<sub>5</sub>IO the following yields of products were obtained: *trans*-stilbene, 1.6%; *cis*-stilbene oxide, 40%; *trans*-stilbene oxide, 0.4%; diphenylacetaldehyde, 5.7%; deoxybenzoin, 0.5%.<sup>2a</sup> In the present study, employing the same conditions, (Br<sub>8</sub>TPP)Fe<sup>III</sup>(Cl) + C<sub>6</sub>F<sub>5</sub>IO + *cis*-stilbene provided *cis*-stilbene oxide in 99% yield. The only byproducts observed were minimal amounts of *trans*-stilbene (0.1%) and *trans*-stilbene

oxide (0.5–1.5%). To account for stereochemical retention in epoxidation<sup>1n-q</sup> and carbocation rearrangement products, it has been suggested that the carbocation intermediate III could be partially stabilized by the electron density on porphyrin nitrogens.<sup>2a</sup> Steric hindrance exerted by *o*-bromo substituents reduces such stabilization. Thus, with (Br<sub>8</sub>TPP)Fe<sup>III</sup>(Cl) as catalyst, virtually no rearrangement products are observed when *cis*-stilbene is the substrate. Alkenes other than *cis*-stilbene gave exclusively the corresponding epoxides. This suggests that for successful epoxidation the only interaction needed is that between the alkene double bond and the iron-bound oxygen.

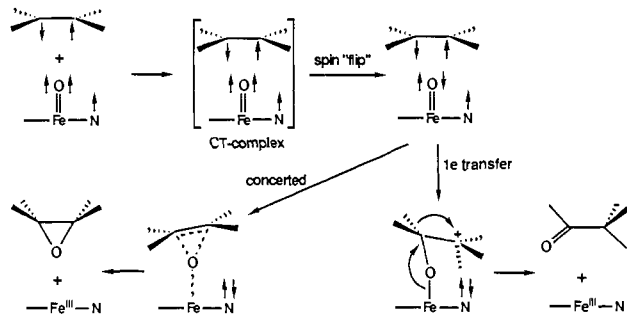
In order to examine this proposal, we performed docking experiments with several alkenes using computer graphics.<sup>4</sup> Mutual orientations of the alkene and (\*Br<sub>8</sub>TPP)Fe<sup>IV</sup>(O)(X) were varied at minimal allowed van der Waals distances in order to examine the energetically feasible orientations of reactants (see Results). The result of a docking experiment with 2,3-dimethyl-2-butene is shown in Figure 6. Inspection of Figure 6 shows that 2,3-dimethyl-2-butene can fit into the niche created by the *o*-bromo substituents. 2,3-Dimethyl-2-butene can be docked *on top* of the oxygen atom with a minimum angle of approach of 40° without serious interactions with *o*-bromo substituents or the porphyrin ring. Similar experiments were performed with norbornene (Figure 5) and *cis*-stilbene. The corresponding allowed angles of approach are 25–85° for norbornene and 45–60° for *cis*-stilbene.<sup>4</sup> (The inability of alkene to approach the iron moiety would tend to rule out the formation of a metallaioxetane by the proposed<sup>1b-d</sup> concerted 2a + 2s cycloaddition.)

Results of the present study, where (\*Br<sub>8</sub>TPP)Fe<sup>IV</sup>(O)(Cl) is the oxidant, can be compared with previous findings for the reaction of (Br<sub>8</sub>TPP)Cr<sup>V</sup>(O)(X) with alkenes. Scheme I was proposed for the (Br<sub>8</sub>TPP)Cr<sup>V</sup>(O)(X) reactions where formation of a charge-transfer (CT) complex is rate limiting.<sup>3b</sup> Rate-limiting CT complex formation has been proposed for the reaction of triplet oxygen atoms with alkenes in the gas phase.<sup>18</sup> One may assume that path A of Scheme I also pertains to epoxidations by (\*Porph)Fe<sup>IV</sup>(O)(X) species. In this instance, formation of a CT complex may or may not be rate limiting. That the ρ<sup>+</sup> of -1.9 pertains to the epoxidation of a series of substituted styrenes by both (Br<sub>8</sub>TPP)Cr<sup>V</sup>(O)(X)<sup>3b</sup> and (\*Me<sub>12</sub>TPP)Fe<sup>IV</sup>(O)(X)<sup>19</sup> is, however, suggestive of like rate-determining steps. The absolute value of ρ<sup>+</sup> (1.9) is too small for the rate-limiting formation of carbocation intermediate.<sup>20</sup> However, similar ρ<sup>+</sup> values are observed in electrophilic reactions that do not involve cationic intermediates, such as carbene addition to a series of substituted styrenes (ρ<sup>+</sup> = -0.4 to -1.6)<sup>21</sup> and epoxidation of substituted stilbenes with perbenzoic acid (ρ<sup>+</sup> = -1.2).<sup>22</sup> For concerted insertion of "oxene", a more negative ρ<sup>+</sup> value is expected than seen in the case of carbene insertion. This would be due to the increased electrophilicity of the metal-bound oxygen compared to carbene. From the sensitivity of styrene epoxidation to electronic effects of substituents, the possibility of a one-step concerted oxygen insertion into the alkene double bond should be considered.

The electronic structure, obtained by theoretical methods for the oxo-iron porphyrins 2e oxidized above the iron(III) state, shows that iron-bound oxygen has a considerable unpaired electron density in its p<sub>x</sub> and p<sub>y</sub> orbitals, which are mixed with d<sub>xz</sub> and d<sub>yz</sub> orbitals on the iron.<sup>23</sup> Thus, the iron-bound oxygen has a partial triplet oxenoid character. If such is the case, a *symmetrical* concerted mechanism can be excluded, since it would be required that an intermediate be formed that could collapse to epoxide only after a spin inversion. Thus, for any concerted mechanism it is necessary to assume an extremely efficient mixing of triplet and

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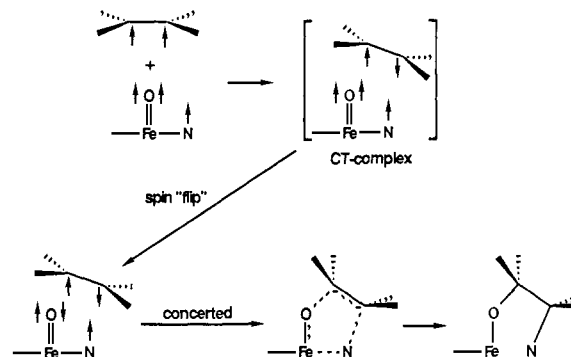
Scheme II



singlet states after the initial CT complex formation. It is known that mixing of spin states and spin inversions is accelerated by the presence of other unpaired spins in an unsymmetrical environment.<sup>24</sup> The unpaired electron in the porphyrin  $\pi$  cation radical might just create such an environment at the point where electron redistribution within the alkene and the oxidant has commenced. Also, a relatively heavy iron is at the reaction site, which can also provide means for efficient mixing of spin states via spin-orbit coupling.<sup>24,25</sup> Efficient changes of spin states and the presence of "spin equilibria" are well documented for iron porphyrins.<sup>25</sup> This indicates that effective means for interconversion of spin states are available in these systems. The most likely mechanism of epoxidation would involve rate-limiting partial  $1e$  transfer from the alkene to  $(^{*}\text{Porph})\text{Fe}^{\text{IV}}(\text{O})(\text{X})$  to form an intermediate CT complex, followed by a very fast change of spin state and concerted oxygen insertion into the alkene double bond. Asymmetric oxygen insertion, in which the two O-C bonds form at different rates but simultaneously, has support in the observation of an inverse secondary isotope effect ( $k_{\text{H}}/k_{\text{D}} = 0.93$ ) for deuterium on  $\alpha$ -carbon and no isotope effect for deuterium on  $\beta$ -carbon in the epoxidation of styrene by cytochrome P-450.<sup>26</sup> After formation of the CT complex and change of spin state, the ratio of epoxide to carbocation rearrangement products would be determined by the relative rates of (i) concerted oxygen insertion to give epoxide and (ii) electron transfer to the porphyrin  $\pi$ -cation-radical moiety to provide III (Scheme II). The later would be greatly favored by the overlap of p orbitals on the alkene and porphyrin nitrogens. The mechanism of Scheme II does not involve the obligatory formation of I, II, III, or IV along the path to epoxidation.

**Porphyrin N-alkylation** observed with terminal alkenes follows the expected trend. Frequency of the N-alkylation event decreases with the steric demand on the alkene. Thus, N-alkylation with 1-hexene occurs once in 80 turnovers in the iron(III) porphyrin catalyst, while for vinylcyclohexane once in 130 turnovers, and for 2,4,4-trimethyl-1-pentene once in every 280 turnovers. This result is consistent with the N-alkylation taking place exclusively at the unsubstituted terminus of the double bond, since selectivity toward vinylcyclohexene and 2,4,4-trimethyl-1-pentene should otherwise decrease much more rapidly compared to 1-hexene. This result, and the fact that styrene does not N-alkylate porphyrin, parallel results obtained with rat liver microsomal cytochrome P-450.<sup>1a,p,27</sup> N-alkylation could be a concerted or a nonconcerted reaction. Formation of an intermediate carbocation on the path to N-alkylation can be excluded. This is so because it would require the formation of a primary carbocation. Radicals, on the

Scheme III



other hand, show much lower preference for substituted vs unsubstituted carbon,<sup>28</sup> suggesting that an initial formation of a carbon radical,<sup>28</sup> followed by the collapse to the N-alkyl porphyrin is possible.<sup>1p,29</sup> It has recently been shown that carbon radicals cannot be discrete intermediates during iron porphyrin catalyzed epoxidation.<sup>2b,c</sup> This, however, does not exclude a radical intermediate in the N-alkylation, but argues that, if radicals are the intermediates in N-alkylation, N-alkylation is a *side reaction* to epoxidation.

Another possible intermediate is the alkene-derived  $\pi$  cation radical (IV). Formation of IV from primary alkenes is energetically unfavorable<sup>3b</sup> since the potentials for their  $1e$  oxidation are quite positive (2.4 V vs SCE for 1-hexene). However, it is these alkenes which exhibit N-alkylation. Styrene, which does not exhibit N-alkylation,<sup>27</sup> has a much lower oxidation potential (1.65 V vs SCE), such that the formation of IV would be much more favorable. This contradiction would tend to eliminate carbocation radical as the plausible intermediate in porphyrin N-alkylation.

Concerted mechanism for N-alkylation of porphyrins is frequently mentioned, but seldom discussed.<sup>1a,p</sup> In the accepted structure of the active oxidant  $(^{*}\text{Porph})\text{Fe}^{\text{IV}}(\text{O})(\text{X})$ ,<sup>23</sup> partial positive charge resides on the porphyrin nitrogens, and partial negative charge on the iron bound oxygen, thus making the O-Fe-N moiety similar to many dipolar molecules that are effective in 1,3 dipolar cycloadditions with alkenes.<sup>30</sup> Also, both the iron-bound oxygen and the porphyrin nitrogen possess unpaired electron density, so that the O-Fe-N moiety has a partial 1,3-diradical character. Thus, after the initial formation of a CT complex between alkene and  $(^{*}\text{Porph})\text{Fe}^{\text{IV}}(\text{O})(\text{X})$  and the subsequent change of spin state, two limiting mechanisms for a concerted N-alkylation are allowed, 1,3 dipolar cycloaddition and 1,3 diradical addition to the alkene. Since N-alkylation also involves reduction of iron and breaking of the Fe-N bond, it is reasonable to assume that neither of the two limiting situations can accurately describe the concerted mechanism of N-alkylation. However, the means for concerted electron redistribution leading to N-alkylation are available. It can be argued that N-alkylation is a concerted reaction that is in competition with epoxidation (Scheme III).

N-alkylation of the porphyrin can compete with the epoxidation only if the steric demands are met. The result of a docking experiment with 1-hexene with a geometry suitable for concerted N-alkylation is shown in Figure 7.

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