

in vivo by mammalian glycosyltransferases in the Leloir pathway, are now accessible by practical synthetic approaches. The sugar moieties are either commercially available at acceptable prices or, in case of Neu-5-Ac, accessible by convenient methods. Procedures for synthesis of the nucleoside phosphate sugars, based on enzymatic or chemoenzymatic methodologies, are now practical in gram quantities and larger (Table II). Although not all of these syntheses are trivial, and some presuppose substantial synthetic expertise, the availability of the nucleoside phosphate sugars is no longer the factor that limits the application of glycosyltransferases in preparative carbohydrate chemistry. At present, the major limitations are access to a broad spectra of glycosyltransferases and limited knowledge on the breadth of the substrate specificity for the enzymes that are available.

Appreciation of the biological importance of glycoconjugates is growing rapidly. We believe that the resulting demand for synthetic materials in fundamental and applied research and the unique ability of enzymatic methods to carry out synthetic modification of delicate biological structures (proteins, organelles, living cells) will encourage the application of glycosyltransferases to the synthesis of more complex carbohydrate structures. Enzymatic glycosyl transfers can offer an efficient complement to nonbiological synthetic chemistry for the syntheses of structures such as N-linked glycoproteins (via dolichol-bound intermediates), O-linked glycoproteins, and glycolipids.

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Mechanism of Alkene Epoxidation by Iron, Chromium, and Manganese Higher Valent Oxo-Metalloporphyrins

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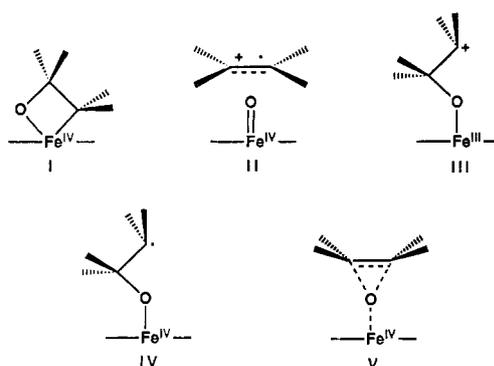
Cytochrome P-450 enzymes catalyze a number of important metabolic reactions. This large class of enzymes also includes members whose role is the oxidative degradation of xenobiotic compounds and unwanted products of normal metabolism. Cytochrome P-450 enzymes catalyze, among other reactions, the epoxidation of alkenes.¹ A reasonable assumption is that the oxidant is an enzyme-bound hypervalent iron-oxo porphyrin. From this assumption ensued investigations directed toward the elucidation of the mechanisms of oxidation of alkenes by such species. We present here an account of our studies using iron, chromium, and manganese tetraphenylporphyrins.²

Deliberations concerning the mechanism of epoxidation have revolved around questions of the intermediacy of metalla-oxetane I,³⁻⁵ π -radical cation II,⁶⁻¹⁰ carbocation III,⁷⁻¹³ and carbon radical IV¹⁴⁻²⁰ as opposed to concerted "oxene" insertion (V)²¹⁻²⁴ (Chart I).

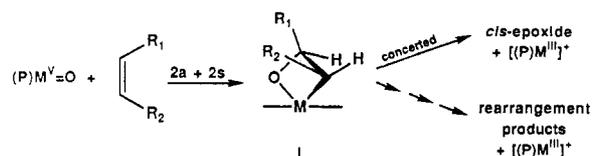
Drazen Ostovic was born in Croatia in 1956. He received his B.S. degree in pharmacy from the University of Zagreb (1979), working with Prof. Stanko Borcic, and his Ph.D. in chemistry from the University of Minnesota (1985), working with Prof. Maurice M. Kneevoy. He carried out postdoctoral work in Prof. Thomas C. Bruce's laboratory at the University of California at Santa Barbara. Since 1989 he has been working in the Pharmaceutical Chemistry Group at Merck Research Laboratories.

After dropping out of high school to serve in the military, Thomas C. Bruce attended the University of Southern California (B.S., 1950; Ph.D., 1954) and received his postdoctoral training at UCLA. Prior to moving to the University of California at Santa Barbara in 1964, Professor Bruce held faculty positions at Yale, Johns Hopkins, and Cornell Universities. His research has involved the study of the mechanisms of reactions of biochemical interest; it has been recognized by a number of awards.

Chart I



Scheme I



The stereochemistry of epoxide products relates directly to the mechanism of epoxidation. The nature of

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(1) *Cytochrome P-450: Structure, Mechanism, and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum: New York, 1986.

other products may not be relevant to the mechanism of epoxidation if these side products arise from reactions which are parallel to and competing with the epoxidation reaction. However, much of the evidence which has been used in support of the involvement of intermediates I-IV is based on the structures of products other than epoxide. As an example, using (F₂₀-TPP)Fe^{III}(Cl), (Cl₈TPP)Fe^{III}(Cl), and (Cl₈TPP)-Mn^{III}(Cl) as catalysts and C₆F₅IO as oxygen donor for the epoxidation of *cis*-stilbene, the following products were obtained: *trans*-stilbene, benzaldehyde, *cis*-stilbene oxide, *trans*-stilbene oxide, diphenylacetaldehyde, and deoxybenzoin. In addition, *cis*-stilbene destruction was found to exceed the equivalents of C₆F₅IO oxidant employed, suggesting radical condensation products as well.¹² The numerous products can be accommodated by schemes in which they either are formed from intermediates on the way to epoxide or are products of reaction paths parallel to and competing with epoxidation.

(2) Abbreviations. In studies which involve oxidation of metalloporphyrins, chemists stabilize the porphyrin ring by substituting phenyl groups at the 5-, 10-, 15-, and 20-positions: tetraphenylporphyrin (TPP), tetrakis(2,6-dichlorophenyl)porphyrin (Cl₈TPP), tetrakis(2,6-dibromophenyl)porphyrin (Br₈TPP), tetrakis(pentafluorophenyl)porphyrin (F₂₀TPP), tetrakis(2,4,6-trimethylphenyl)porphyrin (TMP). Two 1⁻oxidations of the Cr^{III} species with oxygen transfer provide chromium(V)-oxo porphyrins [(TPP)Cr^V(O), (Cl₈TPP)Cr^V(O), (Br₈TPP)Cr^V(O), etc.], while 2e⁻ oxidation above the Fe^{III} state with oxygen transfer generates the iron(IV)-oxo porphyrin π -cation radicals [(⁺TPP)Fe^{IV}(O), (⁺Cl₈TPP)Fe^{IV}(O), (⁺Br₈TPP)Fe^{IV}(O), etc.].

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Metallaoxetanes I Are Not Required Intermediates in Epoxidation

Formation of I was proposed to occur by a 2a + 2s cycloaddition reaction and then to give way to epoxide plus metal(III) porphyrin via a concerted reductive elimination (Scheme I).³⁻⁵ Though alternate rationales have been advanced for the spectral and kinetic observations offered in support of the accumulation of I, the occurrence of I as a low-concentration steady-state intermediate remained in contention.³⁰ The requirement for the formation of I may be questioned on the basis of the fact that *trans*-stilbene oxide is sometimes the major product in the epoxidation of *cis*-stilbene with catalysis by manganese(III) porphyrins. Both support for the intermediacy of I and arguments against it have been based upon the nature of non-epoxide products. The proposed requirement of I as an intermediate in epoxidation is best assessed by observing whether epoxidation occurs when metal(III) porphyrin catalysts are used which sterically prohibit the formation of I.

All *cis*-alkenes, including terminal alkenes, are cleanly epoxidized when (Br₈TPP)Fe^{III}(Cl) is used as catalyst with C₆F₅IO as oxidant to generate the (⁺Br₈TPP)-Fe^{IV}(O) epoxidizing species. Though almost quantitative yields of epoxide are obtained, approach of the alkene to the iron-oxo reaction center is restricted by the bulk of the eight *o*-bromo substituents. We have used molecular modeling to determine whether formation of I is possible upon reaction of alkene with (⁺Br₈TPP)Fe^{IV}(O).^{27,28}

o-Bromo substituents were appended, with the fixed Br-C bond distance of 1.85 Å, on the phenyl rings of the X-ray structures of both flat (^{3/2} spin) (TPP)-Fe^{III}(Cl)³¹ and extremely "dished" (⁺TPP)Fe^{III}(Cl)-(SbCl₆)³² and the phenyl rings were rotated to energy minima. For the dished structure the iron is 0.46 Å out of the plane defined by porphyrin pyrrole nitrogens and 0.99 Å out of the plane defined by pyrrole β -carbons. The iron metallaoxetane ring was set in place upon these two extreme conformational structures. For computer construction of the putative metallaoxetane intermediate, two template X-ray structures were considered: (i) iridium azametallacyclobutane (Cp*(PMe₃)Ir(CH₂CMe₂NH₂⁺))³³ and (ii) platinum oxametallacyclobutane ((As(C₆H₅)₃)₂Pt(C₂(CN)₄O)).³⁴ Both structures had similar bond lengths and angles in the relevant four-membered ring, and the slightly more relaxed Cp*(PMe₃)Ir(CH₂CMe₂NH₂⁺) 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 iron of the porphyrin and the iridium of the metallaoxetane, followed

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by readjustment of the substituent positions to provide minimal steric interactions by rotation to positions of minimal energy.

Examination by computer graphics of the constructed *cis*-diphenylmetallaioxetanes and the tetramethylmetallaioxetanes shows that phenyl and methyl substituents are invaginated into both the porphyrin ring and the *o*-bromo substituents. These drastic steric effects do not depend upon the porphyrin being planar or dishd. In order to avoid these severe steric interactions, the Fe-C and Fe-O bond lengths of the metallaioxetane rings must be extended to unreasonable values of >3.2 Å. We concluded that metallaioxetanes cannot be required intermediates in alkene epoxidation by hypervalent metal-oxo porphyrin species.²⁸

π -Carbocation Radical II Cannot Be a Required Intermediate in Epoxidation. The Nature of the Rate-Limiting Step

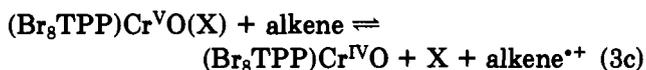
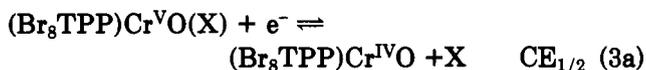
The bimolecular rate constants (k_2) have been determined for reaction of alkenes with relatively stable Cr^V-oxo tetraphenylporphyrins.²⁵ The reduction potentials for $1e^- + \text{Cr}^{\text{V-oxo porphyrin}} \rightarrow \text{Cr}^{\text{IV-oxo porphyrin}}$ ($\text{CE}_{1/2}$) and $1e^- + \pi\text{-radical cation (II)} \rightarrow \text{alkene (AE}_{1/2})$ have also been established. The linear correlation between $\log k_2$ for the reaction of five variously substituted Cr^V(O) tetraphenylporphyrins with norbornene vs ($\text{CE}_{1/2}$) is given by eq 1:

$$\log k_2 = 9.03(\text{CE}_{1/2}) - 8.57 \quad (1)$$

The linear free energy relationship between $\log k_2$ for reaction of 16 alkenes with $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{X})$ and $\text{AE}_{1/2}$ is shown in eq 2 and Figure 1.²⁶ The electro-

$$\log k_2 = -2.99(\text{AE}_{1/2}) + 4.02 \quad (2)$$

chemical emf values for $1e^-$ oxidation of an alkene by $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{X})$ ($\text{CE}_{1/2} = 0.880$ V vs SCE), eq 3c, are equal to the sum $\text{CE}_{1/2} + \text{AE}_{1/2}$ (eqs 3a,b). The standard free energies (ΔG°) for the equilibria of eq 3c are obtained from the emf values. The free energies of activation (ΔG^\ddagger) for reaction of $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{X})$ with alkenes are obtained from k_2 values by use of the Eyring equation.³⁵



One can judge the feasibility of the carbocation radical (II, Chart I) as intermediate by comparison of the ΔG° and ΔG^\ddagger values. The dashed line in Figure 1 separates those alkenes for which $\Delta G^\ddagger < \Delta G^\circ$ (free energy content of II exceeds that of the transition state for the rate-limiting step) and those for which $\Delta G^\ddagger > \Delta G^\circ$ (free energy of transition state exceeds that of II). It is important to understand that when $\Delta G^\ddagger < \Delta G^\circ$ the reaction of eq 3c cannot be involved in the oxidation of alkene by $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{X})$ and the carbocation radical II cannot be an intermediate nor can it be a product formed from a competing reaction. With about one-half of the alkenes investigated, $\Delta G^\ddagger < \Delta G^\circ$. In the reaction of $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O} + 1\text{-octene}$, intermediate II

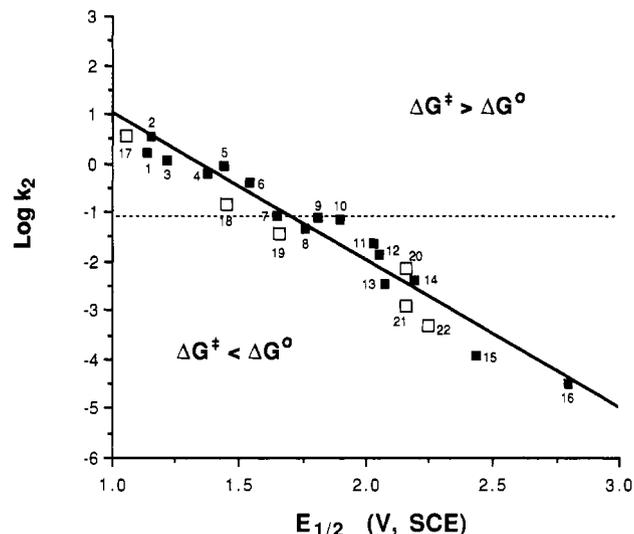


Figure 1. Plot of the log of the second-order rate constants (k_2 , $\text{M}^{-1} \text{s}^{-1}$) for the reactions of a series of alkenes with $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{X})$ vs $E_{1/2}$ (SCE) for $1e^-$ oxidation of the alkenes. The dashed line separates the reactions into two groups. Above the dashed line, values of the free energies of activation (ΔG^\ddagger) exceed the standard free energy (ΔG°) for the formation of alkene-derived π -carbocation radicals (II in Chart I) plus $\text{Cr}^{\text{IV-oxo porphyrin}}$ such that the formation of II is allowed. Below the dashed line, values of $\Delta G^\circ > \Delta G^\ddagger$, and the stability of II plus $\text{Cr}^{\text{IV-oxo porphyrin}}$ is less than that of the transition state so that II cannot be formed. Experimental results (\square) have been taken from ref 47, while other experimental results (\blacksquare) are from ref 25. The alkenes are as follows: (1) 1,4-diphenyl-1,3-butadiene; (2) 4-methoxystyrene; (3) 1,1-diphenylethylene; (4) 4-methylstyrene; (5) 2,3-dimethyl-2-butene; (6) *cis*-stilbene; (7) styrene; (8) 4-acetoxystyrene; (9) cyclohexene; (10) norbornene; (11) *cis*-cyclooctene; (12) 4-cyanostyrene; (13) *cis*-2-pentene; (14) cyclopentene; (15) 1-hexene; (16) 1-octene; (17) *trans-p,p'*-dimethoxystilbene; (18) (*Z*)-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene; (19) *trans*- β -methylstyrene; (20) *trans*-5-decene; (21) *trans*-2-pentene; (22) *trans*-2-hexenyl acetate. The $\log k_2$ values for *trans*-stilbene and *trans-p,p'*-dicyanostilbene exhibit large negative deviations due to steric effects (discussed in ref 47).

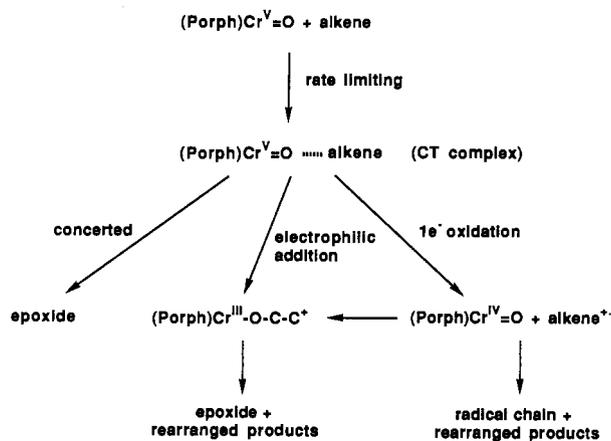
is >20 kcal/mol less stable than the transition state. For II to exist as an intermediate in the solvent-caged pair $[(\text{Br}_8\text{TPP})\text{Cr}^{\text{IV}}\text{O} + 1\text{-octene } \pi\text{-cation radical}]$, it would be required that the 1-octene π -cation radical be stabilized relative to the solvent-separated pair by up to $20 + Y$ kcal/mol [where $Y = \Delta G^\ddagger$ for reversion of solvent-caged intermediates to solvent-separated $\text{alkene}^{++} + (\text{Br}_8\text{TPP})\text{Cr}^{\text{IV}}\text{O}$]. The possibility of a change in mechanism from one involving formation of II to another does not seem likely since there is no break in the plot of Figure 1. This conclusion that the mechanism does not involve rate-limiting $1e^-$ transfer to form II is also supported by the slope of Figure 1.

For $1e^-$ transfer reactions, the dependence of rate constants on potential can be placed into one of three categories: (i) if the diffusion together of the reactants is rate limiting, $\log k_2$ is independent of the difference in potential between reactants ($\Delta E_{1/2}$) (slope = 0); (ii) in the other extreme, $1e^-$ transfer is so endothermic that $\log k_2$ is directly proportional to $\Delta E_{1/2}$ for the overall $1e^-$ transfer (slope = -16.6 V^{-1}); and (iii) the intermediate region where $\log k_2$ for rate-limiting $1e^-$ transfer is dependent on $\Delta E_{1/2}$ with the slope dependent upon degree of electron transfer in the transition state, changing from 0 to -16.6 V^{-1} .^{36,37} The slope of the plot

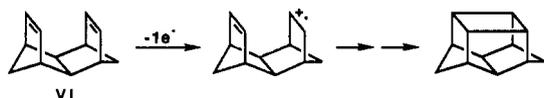
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Scheme II



Scheme III

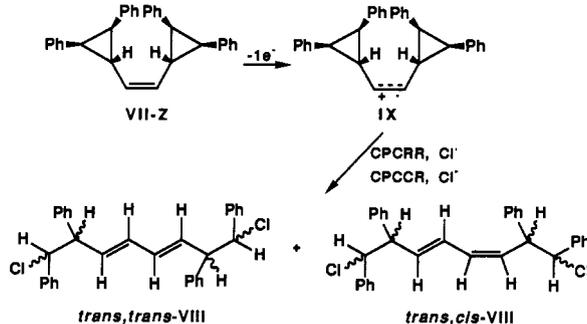


of $\log k_2$ vs $E_{1/2}$ of Figure 1 is -2.99 V^{-1} , which would correspond in a conventional Brønsted plot ($\log k_2$ vs $\log K_{\text{eq}}$) to a slope $\alpha = -0.18$. Thus, in the reaction of $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}$ with alkenes, the transition state is reached when there is very little electron transfer. Such a situation would be equivalent to rate-determining formation of a charge-transfer (CT) complex.

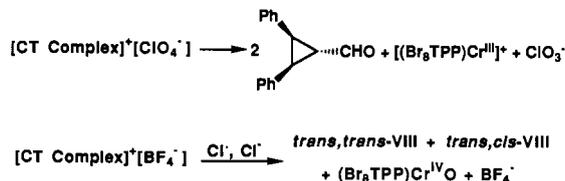
The difference in the slopes of the linear free energy plots of $\log k_2$ vs $\text{AE}_{1/2}$ (alkene is varied, eq 1) and $\log k_2$ vs $\text{CE}_{1/2}$ ($(\text{Porph})\text{Cr}^{\text{V}}\text{O}(\text{X})$ is varied, eq 2) indicates the presence of a perpendicular (Thornton) contribution to the overall Brønsted slope α . On a scale of 0 (dissociative transition state) to 2 (associative transition state), the Thornton contribution to α can be calculated as 0.63, and the Leffler-Hammond contribution to α (measure of a progress along the reaction coordinate) is calculated as 0.37.³⁸ Presuming a $1e^-$ transfer mechanism, the transition state is located ca. 37% along the reaction coordinate and it is somewhat dissociative. This approximation of transition-state structure is not consistent with a full electron transfer (which is endothermic for about one-half of the alkenes studied and therefore requires a late transition state) but is reasonable for rate-limiting formation of a CT complex. An initially formed CT complex could collapse to give $(\text{Br}_8\text{TPP})\text{Cr}^{\text{III}}(\text{X}) + \text{epoxide}$ (Scheme II).

The formation of II can occur on oxidation of alkenes with low oxidation potentials. For example, π -carbocation radicals are intermediates in the oxidative rearrangements of hexamethyl Dewar benzene to hexamethylbenzene and the rearrangement of alkene VI (Scheme III).^{8,9} That the formation of II did not occur in the rate-determining step was shown by examination of the oxidation of VII-Z by $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{BF}_4^-)$ and $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{ClO}_4^-)$ in CH_2Cl_2 solvent.⁵ With $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{BF}_4^-)$, VII-Z provides *trans,trans*- and *trans,cis*-dienes VIII (Scheme IV). With $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{ClO}_4^-)$, VII-Z provides as the major product *trans-2,trans-3*-diphenylcyclopropanecarboxaldehyde (Scheme V). The second-order rate constant (k_2) for

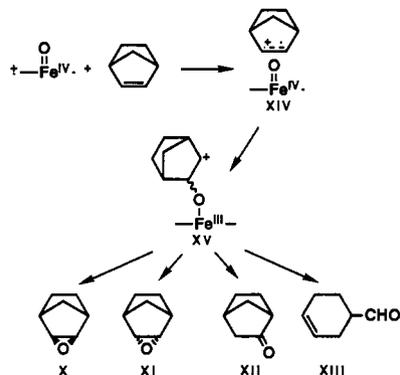
Scheme IV



Scheme V



Scheme VI



oxidation of VII-Z is found to fit the line of Figure 1 and is found to be independent of the ligand X^- when it is BF_4^- or ClO_4^- . We propose the initial rate-determining step to be the following: $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}\text{O}(\text{X}) + \text{VII-Z} \rightarrow [\text{CT}]^+[\text{X}]^-$. When $\text{X}^- = \text{BF}_4^-$: $[\text{CT}]^+ \rightarrow \text{IX}$, and this carbocation radical provides the dienes VIII. In this mechanism, the IX undergoes dual CPCRR and cyclopropylcarbocation to homoallyl carbocation rearrangements (CPCCR) and captures the halogen species generated from the solvent. With $\text{X}^- = \text{ClO}_4^-$, the $[\text{CT}]^+[\text{X}]^-$ species breaks down with ClO_4^- as an oxidant to provide *trans-2,trans-3*-diphenylcyclopropanecarboxaldehyde (Scheme V). The inclusion of the ClO_4^- cooxidant to provide structure $[\text{CT}]^+[\text{ClO}_4^-]$ amounts to an enforced oxidation.

The formation of *exo*-norbornene oxide (X) and *endo*-norbornene oxide (XI) in unusually low *exo/endo* ratios, along with norcamphor (XII) and cyclohexene-4-carboxaldehyde (XIII) on reaction of norbornene with iodosylarenes using several substituted tetraphenylporphyrin and tetrapyrrolylporphyrin iron(III) salts as catalysts, has led to the proposal of a mechanism involving the initial formation of the carbocation radical XIV followed by formation of the carbocation XV (Scheme VI).⁹ When we oxidized norbornene with $(\text{Br}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})/\text{C}_6\text{F}_8\text{IO}$, norbornene oxides were obtained in a combined yield of 99% with an *exo/endo*-norbornene oxide ratio of 6.8/1.²⁷ No other products could be detected. The low ratio of *exo* to

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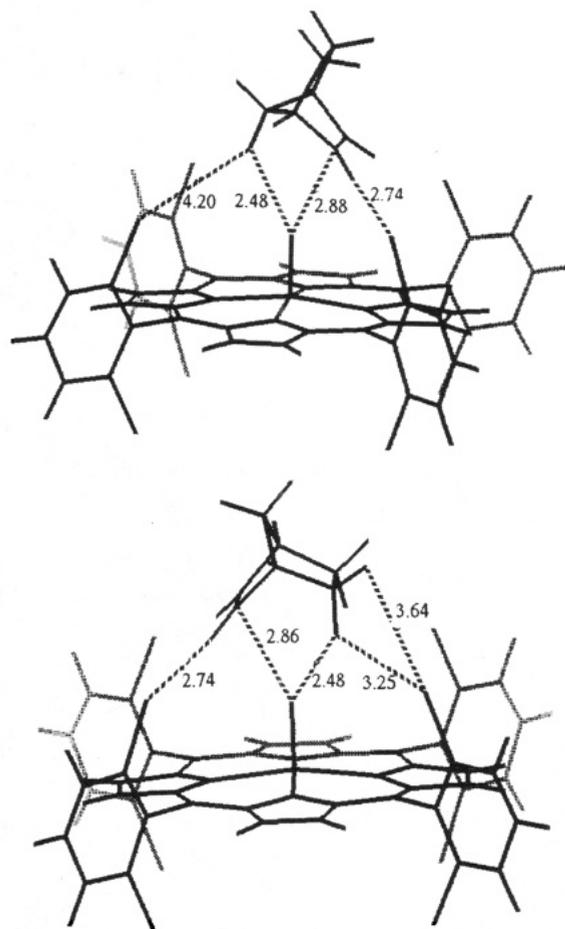
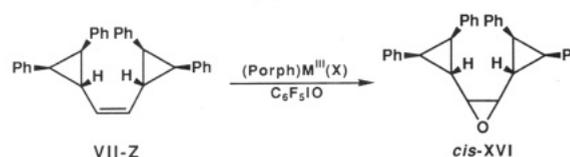


Figure 2. Computer-generated stick models of norbornene docked on $(^{+}\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})$: top, attack of oxygen from the exo side (interaction energy = 0.71 kcal/mol); bottom, attack of oxygen from the endo side (interaction energy = 0.69 kcal/mol).

endo epoxides was interpreted in terms of indiscriminate collapse of XIV to XV.

Computer graphics docking experiments (Figure 2) were used to assess steric factors which influenced the stereochemical outcome of norbornene epoxidation by the $(^{+}\text{Br}_8\text{TPP})\text{Fe}^{\text{IV}}(\text{O})$ oxidant. When the norbornene double bond is positioned within the van der Waals distance from the metalloporphyrin-bound oxygen, the norbornene double-bond hydrogens experience significant steric hindrance from the bulky *o*-bromo substituents on the porphyrin phenyl groups. The conventional endo/exo selectivity in this case would be based only on the interaction of exo and endo hydrogens with the metal-bound oxygen. However, the additional steric interaction between the norbornene double-bond hydrogens and the bulky ortho substituents on the porphyrin phenyl groups makes the usual exo/endo selectivity less pronounced. This steric hindrance becomes more important with an increase in the size of the ortho substituents on the porphyrin phenyl groups, thus diminishing the exo/endo selectivity. The observed change in the ratio of *exo*- to *endo*-norbornene oxide can be explained by these steric effects. Thus, XIV is not required as an intermediate in order to explain experimental results. However, formation of carbocation XV is required to explain the formation of the small amounts of norcamphor and cyclohexene-4-carboxaldehyde. Computer graphics docking experiments have also been used to determine the energy

Scheme VII



minima for the angle and distance of approach of *cis*- and *trans*-alkenes to metallo-oxo porphyrins.^{27,28,48}

Carbocation III Formation Cannot Be Rate Limiting

Electrophilic addition to provide a carbocation (intermediate III, Chart I), wherein the positive charge of III is partially stabilized by interaction with the electron cloud on porphyrin nitrogens, has been proposed in order to explain the presence of rearranged products (i.e., *cis*-stilbene \rightarrow III \rightarrow deoxybenzoin + diphenylacetaldehyde).¹² Plots of $\log k_2$ for the epoxidation of substituted styrenes by either $(\text{Br}_8\text{TPP})\text{Cr}^{\text{V}}(\text{O})(\text{X})$ ²⁵ or $(^{+}\text{TMP})\text{Fe}^{\text{IV}}(\text{O})$ ¹⁷ vs σ^+ provide as slope $\rho^+ = -1.9$. Rate-limiting carbocation formations via electrophilic additions to substituted styrenes are associated with much more negative ρ^+ values [i.e., -3.58 (hydration)³⁹ and -4.8 (bromination)⁴⁰]. These observations do not favor formation of III in the rate-limiting step.

The fact that rearranged products resulting from alkene-derived carbocation radicals II and carbocations III are observed on epoxidation of certain alkenes does not necessitate the involvement of II and III in the reaction path to epoxide. The evidence presented indicates that II is *not* an intermediate on the epoxidation reaction path.

Radical IV Is Not a Required Intermediate in Epoxidation

The cyclopropyl substituent is a widely used radical trap. However, the rate constants for the cyclopropylcarbinyl to homoallyl radical rearrangement (CPCRR) of a secondary to a primary radical are too small ($2 \times 10^7 \text{ s}^{-1}$, 30°C ⁴¹) to trap a radical intermediate which collapses to product with a rate constant $>10^{10} \text{ s}^{-1}$. We established, from competitive experiments, that the rate constant for the secondary \rightarrow secondary benzyl CPCRR of the (*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical exceeds the rate constant for CPCRR of secondary \rightarrow primary radical of cyclopropylcarbinyl radical by at least a factor of 10^3 .¹⁹ The alkene (Z)-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene (VII-Z) incorporates the *trans*-2,*trans*-3-diphenylcyclopropyl hypersensitive radical trapping group.

The catalysts employed in the epoxidation of VII-Z were $(\text{F}_{20}\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$, $(\text{Cl}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$, and $(\text{Cl}_8\text{TPP})\text{Mn}^{\text{III}}(\text{OH})$ while $\text{C}_6\text{F}_5\text{IO}$ was the oxidant (Scheme VII).²⁰ The yields of epoxide *cis*-XVI with the various catalysts were as follows: 95% with $(\text{F}_{20}\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$, 90% with $(\text{Cl}_8\text{TPP})\text{Fe}^{\text{III}}(\text{Cl})$, and 84% with $(\text{Cl}_8\text{TPP})\text{Mn}^{\text{III}}(\text{OH})$. Polar products which can be derived from the radical species IV (Chart I) as well as *trans*-alkene (VII-E) and *trans*-epoxide (*trans*-XVI) could not be detected at 0.1% detection limit. Aside from *cis*-XVI,

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very nonpolar, non-oxygen-containing products were obtained in 5–16% yield.

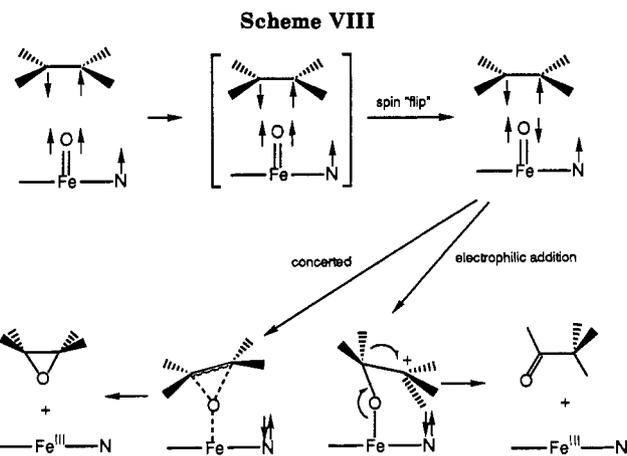
A test for radical intermediates in the epoxidation reaction is based upon the required rate constant for partitioning of the putative radical intermediate to epoxide as compared to other products. Given that the rate constant for CPCRR of the (*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical is $\geq 2 \times 10^{10} \text{ s}^{-1}$ and that the yields of products derived from the radical species I are $< 0.1\%$, the conversion of radical to *cis*-XIV would have a rate constant of $> 10^{12} \text{ s}^{-1}$. The neutral radical species IV cannot be a discrete intermediate in the epoxidation reaction.

Products which could be derived from the cation radical IX are obtained in 5–16% yields. It follows that the rate constant for conversion of IX to epoxide must be $\geq (1-2) \times 10^{11} \text{ s}^{-1}$. A rate constant of about 10^{11} s^{-1} for the recombination of a solvent-caged pair involving IX to provide epoxide is not unreasonable. Recall our conclusion that the formation of IX cannot be rate determining. The nonpolar products could have arisen from a reaction that is parallel to epoxidation.

Experimental Evidence Can Be Interpreted in Favor of a Concerted Mechanism for Epoxidation

In the iron(IV)-oxo porphyrin π -cation radical the iron-bound oxygen is believed to have triplet oxenoid character due to mixing of oxygen p_x and p_y orbitals with d_{xz} and d_{yz} orbitals on the iron, resulting in partial unpaired electron density.²⁹ Concerted oxygen insertion into the alkene double bond would follow rate-limiting formation of a CT complex and a very fast change of spin state. Spin inversion does not pose a problem since efficient changes of spin states and the presence of "spin equilibria" are well documented for iron porphyrins.⁴²⁻⁴⁴ It is known that mixing of spin states and spin inversions are accelerated by the presence of other unpaired spins in an unsymmetrical environment.⁴⁵ The unpaired electron in the porphyrin π -cation radical might just create such an environment at the point where the electron redistribution within the alkene and the oxidant has commenced. This is supported by the fact that $(^+Br_8TPP)Fe^{IV}O(X)$, which has the porphyrin π -cation radical structure, epoxidizes alkenes in almost quantitative yields, while $(Br_8TPP)Cr^{VO}(X)$, which does not have the porphyrin π -cation radical structure, provides substantial yields of rearranged products.

Asymmetric oxygen insertion, in which the two O-C bonds are formed at different rates but simultaneously as in Scheme VIII, has support in the observation of an inverse secondary isotope effect ($k_H/k_D = 0.93$) for deuterium on the α -carbon and no isotope effect for deuterium on the β -carbon in the epoxidation of styrene by cytochrome P-450.²⁴ After rate-determining formation of 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) electrophilic attack of metal-bound oxygen on the alkene to provide a carbocation intermediate (Scheme VIII).



The latter would be greatly favored by the overlap of p orbitals on the alkene and porphyrin nitrogens.

Support for the concerted mechanism may be found in the following findings: Epoxidation of alkenes by higher valent oxo-metalloporphyrins is stereospecific for the vast majority of alkenes. The formation of *trans*-epoxide from *cis*-alkene when Mn^V -oxo porphyrin is used as oxidant is not uncommon and can be traced to the presence of Mn^{IV} -oxo porphyrin.⁴⁶ The ρ^+ value of -0.93 , determined in competitive experiments, is reported for the epoxidation of series of substituted styrenes by the $(TPP)Fe^{III}(Cl)/C_6H_5IO$ system.¹¹ This value is similar to the ρ^+ values reported for known concerted processes such as carbene insertions into the double bond ($\rho^+ = -0.62$ to -1.61)⁴⁷ or epoxidation with perbenzoic acid ($\rho^+ = -1.2$).⁴⁸

Additional support for the concerted mechanism comes from the fact that the most efficient and selective catalyst is the sterically hindered $(Br_8TPP)Fe^{III}(Cl)$. Bulky *o*-bromo substituents can play a dual role: (i) the steric hindrance prevents the interaction of alkenes with the electron density on the porphyrin ring which can participate in stabilization of the developing positive charge on the alkene and favor an electrophilic mechanism with the formation of a carbocation intermediate and the corresponding rearrangement products; (ii) bromines are heavy atoms, and as such they can facilitate spin-spin interconversions via spin-orbit coupling, which creates a favorable environment for concerted oxygen insertion into the alkene double bond and formation of epoxide.⁴²⁻⁴⁵

Conclusion

Epoxides are one of a number of products formed on oxidation of an alkene. It is appreciated that the mechanism of epoxidation cannot be deduced from a knowledge of the structures of the other oxidation products. They may be formed from reactions which compete with epoxidation. Our approach has been to devise a means by which we could test whether a given species was formed in the rate-determining step (or in some cases, at all) of the epoxidation reaction. Of the various mechanisms proposed for the epoxidation of alkenes by hypervalent iron-oxo and chromium-oxo

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porphyrin species, those which require rate-determining formation (Chart I) of a metallaoxetane (I), an alkene-derived π -cation radical (II), a carbocation (III), and a carbon radical (IV) may be dismissed. It is most likely that the same conclusion can be reached for epoxidations involving manganese-oxo porphyrin species. Alkene oxidation products attributed to the radical nature of Mn^{V} -oxo porphyrins most likely arise due to the major contamination of Mn^{V} -oxo porphyrin by Mn^{IV} -oxo porphyrin. Studies with manganese porphyrins continue. For some much-favored epoxidation process, the formation of a metallaoxetane intermediate (I) along the epoxidation pathway is sterically impossible (shown for hypervalent iron-oxo, chromium-oxo, and manganese-oxo porphyrins). Trapping experiments have shown that the existence of an intermediate carbon radical (IV) would require the latter to possess a lifetime $\leq 10^{-12}$ s. Thus, carbon radical intermediate IV cannot be formed along the pathway to epoxide (shown for hypervalent iron-oxo, manganese-oxo, and chromium-oxo porphyrins). The dependence of the log of the second-order rate constants upon the potential

for reduction of alkene-derived π -cation radicals (II)—equivalent to $\rho_{\text{I}}-\sigma_{\text{I}}$ correlation—as well as a comparison of experimentally available values of ΔG^\ddagger and ΔG° rules out the required intermediacy of II at any step in alkene epoxidation by both hypervalent chromium-oxo porphyrins and iron-oxo porphyrins. The $\rho_{\text{I}}-\sigma_{\text{I}}$ relationship for the epoxidation of styrenes by hypervalent chromium-oxo porphyrins and iron-oxo porphyrins does not support rate-determining carbocation (III) formation. A general picture emerges where charge-transfer complex formation is the rate-limiting step and what follows (epoxidation vs various rearrangement pathways) is dependent on the oxidation potentials of alkene and the active oxidant, the steric and electronic structures of the reactants (which include the steric bulk and geometry of both species and the metal and axial ligand of the metalloporphyrin), as well as the propensity of various substrates to undergo rearrangements.

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