The Porphyrin Handbook

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Shape-Selective Oxidation by Metalloporphyrins

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I. Introduction

Discriminating between one site and another on a molecule and distinguishing among many similar molecules presents a challenge to both industrial and biological chemistry. Shape-selective catalysis of hydrocarbon re-forming and other reductive processes have been extremely successful (most notably with zeolites and related microporous solids), and has formed the basis for important industrial processes.[1,2] Oxidative processes with organic substrates also has an important place in both biological and industrial processes.[3–7] The uniqueness of enzymes in such reactions is their ability to direct the oxidation to specific substrates and at specific sites on these substrates.[8] Regioselectivity often originates from discrimination based on the size and shape of substrate molecules, that is, shape selectivity arises from both steric repulsions and van der Waals attractions. Dipole–dipole, hydrogen bonding, ion pairing and other weak forms of bonding provide other sorts of interactions to induce selective binding, specific substrate orientation and regioselectivity. Nonetheless, the creation of shape-selective *oxidation* catalysts is still in an early stage of development.

Although there has been a huge effort to develop the field of supramolecular chemistry,[9] the vast majority of this work has concentrated on molecular recognition, that is, the design of host-guest systems that exhibit specificity in binding substrates. Few such systems, however, have been designed to actually do something to the substrate once it has been bound.

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Molecular recognition is not enough. There must be *two* goals for researchers interested in mimicking the specificity typical of enzymatic reactions—not only the design and synthesis of chemical species capable of molecular recognition, but also the inclusion in such hosts of a reactive center that can produce a regioselective or enantioselective chemical transformation on the guest substrate.

In the absence of steric restraints, regioselectivity in oxidations generally is heavily influenced by thermodynamics. For example, in the hydroxylation of alkanes by metalloporphyrins, product distribution analyses are consistent with a radical intermediate formed by hydrogen atom abstraction.[10,11] Hydroxylation selectivities are therefore dominated by C–H bond strengths[12] (Table 1), and the rates of oxidation are tertiary C–H bonds much faster than secondary, which are much faster than primary (that is, $3° \gg 2° \gg 1°$). In epoxidations, the active oxidant is extremely electrophilic and therefore preferentially attacks the most electron-rich (that is, the most substituted) double bond.[13]

In principle, however, regioselectivities can be controlled by kinetic access to reactive sites by specificity in substrate binding. In this fashion, various metalloproteins can yield products dramatically different than those expected from simple bond strengths. The most important enzyme used for catalytic oxidation of organic compounds is cytochrome P450, and intense efforts have been made to generate similar catalytic behavior with transition metal macrocycle or chelate complexes. The synthetic versatility of the porphyrins makes them especially attractive for the construction of enzyme analogues through the elaboration of the superstructure of the macrocycle.[14–17] In terms of the enzyme specificity, some of the isozymes of P450 and the nonheme, iron-containing proteins known as ω-hydroxylases, are especially impressive.

This chapter begins with an overview of oxidation catalysis by heme proteins and by synthetic porphyrins. This is followed by an examination of the regioselectivity of enzymatic oxidation of hydrocarbons, especially those enzymes responsible for primary alcohol synthesis from the terminal hydroxylation of alkyl chains (for example, cholesterol, fatty acids and *n*-alkanes). The bulk of the chapter is a description of the development of synthetic oxidation catalysts based on metalloporphyrins whose superstructure takes on the enzymatic role of substrate discrimination.

Table 1. Selected Bond Dissociation Energies

H–C bond	Bond type	Bond dissociation energy (kJ mol^{-1})
H–C_6H_5	Phenyl	464
H–CH_3	Methane	438
H–C_2H_5	Primary	420
H–*n*–C_3H_7	Primary	417
H–$CH_2C(CH_3)_3$	Primary	418
H–$CH(CH_3)_2$	Secondary	401
H–C_6H_{11}	Secondary	400
H–$C(CH_3)_3$	Bertiary	390
H–$CH_2C_6H_5$	Benzyl primary	368
H–$CH(CH_3)C_6H_5$	Benzyl secondary	357
H–$C(CH_3)_2C_6H_5$	Benzyl tertiary	353
H–$CH_2CH{=}CH_2$	Allyl primary	361
H–$CH(CH_3)CH{=}CH_2$	Allyl secondary	345

Source: Handbook of Chemistry and Physics, 71st ed.; Lide, D. R., Ed. CRC Press, Boca Raton, 1991.

Table 2. List of Abbreviations

C_nPBP	*n*-carbon picnic-basket porphyrin
m-CPBA	*meta*-chloroperoxybenzoic acid
Pc	Phthalocyanine
PXLPBP	*p*-Xylyl strapped picnic-basket porphyrin
salen	*N*,*N*′-bis(salicylideneamino)ethane
T(2′,6′-DHP)P	5,10,15-20-Tetrakis(2′,6′-dihydroxy phenyl)-porphyrinate
T(3′,5′-DHP)P	5,10,15-20-Tetrakis(3′,5′-dihydroxyphenyl)-porphyrinate
T(4-HDP)P	5,10,15,20-Tetrakis(4′-hexadecyloxyphenyl)-porphyrinate
TBNAPP	5α,10β,15α,20β-Tetrakis[(*S*)-2-(carboxymethyl)-1,1-binapthyl-2′-carboxyamidophenyl]porphyrinate
TBNP	5α,10β,15α,20β-Tetrakis-[(*R*)-1,1′-binapth-2-yl]-porphyrin
TDCPP	5,10,15,20-Tetrakis(2′,6′-dichlorophenyl)porphyinate
TMP	5,10,15,20-Tetramesitylporphyrinate; 5,10,15,20-Tetrakis(2′,4′,6′-trimethylphenyl)porphyrinate
TMPyP	5,10,15,20-Tetrakis(*N*-methylpyridinium-4′-yl)-porphyrinate
TPP	5,10,15,20-Tetraphenylporphyrinate
TPPyP	5,10,15,20-Tetra-4′-pyridylporphyrinate
TTMPP	5,10,15,20-Tetrakis(2′,4′,6′-trimethoxylphenyl)-porphyrinate
TTPPP	5,10,15,20-Tetrakis(2′,4′,6′-triphenylphenyl)-porphyrinate

II. Hydrocarbon Oxidation by Metalloporphyrins

A. CYTOCHROME P450

1. Overview

Oxidations in biological systems are catalyzed by various classes of enzymes, including dehydrogenases, dioxygenases, peroxidases and monooxygenases.[5] Of these, the dehydrogenases do not directly involve redox chemistry of dioxygen or its products. Instead, they catalyze the removal of two hydrogen atoms from a substrate to form either a ketone or a carboxylic acid. The large majority of biological oxidations involve dioxygen. The dioxygenases use O_2 and insert both oxygen atoms into substrate, as shown in eq 1.

$$R_2CH{-}CHR_2 + O_2 \longrightarrow R_2C(OH){-}C(OH)R_2 \qquad (1)$$

A large fraction of enzymes responsible for oxygen utilization are heme proteins. The hydroperoxidases (Figure 1) consist of the subclasses of peroxidases, catalases and the monooxygenase P450. The peroxidases catalyze the one-electron oxidation of a large variety of substrates, including cytochrome *c*, halide anions and various organic substrates, as generalized in eqs. 2 and 3. Two intermediate oxidation states of the enzyme are seen during this process: (1) com-

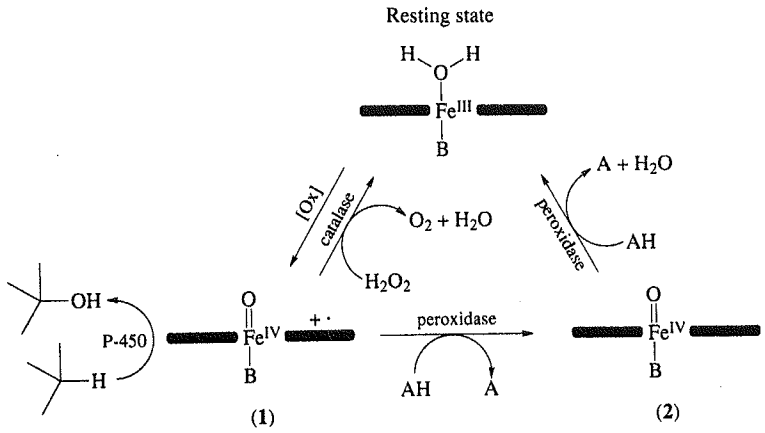


Figure 1. Catalytic cycles of the hydroperoxidases.

pound I (CpdI), which is two oxidation equivalents above the Fe(III) resting state and (2) compound II (CpdII), which is one oxidation equivalent above Fe(III). Catalase converts H_2O_2 to O_2 and H_2O, through a CpdI-type intermediate.

$$AH_2 + H_2O_2 \longrightarrow A + 2H_2O \quad (2)$$

$$2AH_2 + H_2O_2 \longrightarrow 2AH + 2H_2O \quad (3)$$

Monooxygenases catalyze the insertion of one oxygen atom, which was derived from the reductive activation of dioxygen, into a substrate as shown for example in eq 4. Not all monooxygenases are heme proteins, or even metalloproteins. Cytochrome P450, the best studied of this general class of oxidation enzymes, is a heme protein closely related to the peroxidases. It is the diverse and highly regioselective reactions of various forms of cytochrome P450 that has motivated most of the effort to produce the bioinorganic analogues that are the primary focus of this chapter.

$$RH + O_2 + 2e^- + 2H^+ \longrightarrow ROH + H_2O \quad (4)$$

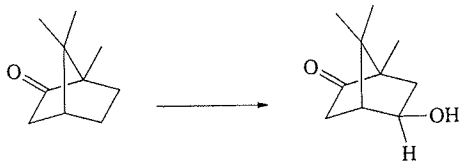
2. Regioselectivity

Cytochrome P450s are a class of heme-containing monooxygenases that transfer an oxygen atom from dioxygen to various organic substrates.[14] In mammalian systems, these include cholesterol and other steroids, prostaglandins and a variety of xenobiotics. P450 is also responsible for the carcinogenesis of otherwise unreactive molecules such as benzene. The types of reactions catalyzed by P450s are extremely diverse, as shown in Figure 2, and include aliphatic and arene hydroxylations, alkene epoxidation, N-oxidation, S-oxidation, and N-, O- and S-dealkylation.[18] Cytochrome P450 is found in prokaryotes, and both higher and lower eukaryotes. These enzymes contain an iron protoporphyrin IX (PPIX) prosthetic group, with unusual axial ligation of the thiolate of a proximal cysteine.

The catalytic cycle of P450 involves several discrete steps[19] and is shown in Figure 3. The resting state of the heme is a water-bound six-coordinate low-spin iron(III) complex. Substrate binding results in loss of water coordination leaving a high-spin five-coordinate iron(III) complex. One-electron reduction (usually from an Fe–S protein) gives the five-coordinate iron(II) heme that can bind O_2 to give the superoxo-bound iron(III) complex. A second one-electron reduction results in cleavage of the O–O bond and presumed formation of a short-lived iron-oxo intermediate. The iron-oxo species is proposed to be an Fe^{IV}=O porphyrin π-radical cation similar to the CpdI of peroxidase or catalase. For hydroxylations, the iron-oxo species is thought to abstract a hydrogen from the substrate generating a hydroxo-bound iron complex. Rapid recombination of the substrate radical with the hydroxo-complex generates the product.[20] This step also regenerates the water-bound six-coordinate complex after the product leaves the active site.

There are often distinct substrate specificities associated with different forms of P450 and other monooxygenases, varying both from species to species and from isozyme to isozyme. This diversity of specificity requires tailored interactions between the protein's binding site and substrate. Examples include $P450_{cam}$,[21] $P450_{\omega\text{-}2}$,[21,22] ω-hydroxylases,[23–26] the liver microsomal enzymes involved in cholesterol and prostaglandin biosynthesis[27] and fatty acid metabolism.[28]

The best studied of these is a bacterial P450 from *Pseudomonas putida*, $P450_{cam}$, which oxidizes camphor to 5-exo-hydroxycamphor exclusively, both in vivo and in reconstituted enzyme systems (eq 5).[21]



(5)

The extreme regioselectivity of this reaction is caused, in part, by the match in shape between the substrate and the enzyme binding site and in part to a hydrogen bond between tyrosine-96 and the camphor carbonyl (Figure 4).[29] Mutant P450s, unable to form this hydrogen bond with camphor, show less selectivity with a wider range of products,[30] as does the native enzyme with camphane and thiocamphor, neither of which can form the important hydrogen bond.

In order to probe the effect of steric interactions on the specificity of hydroxylation, Atkins and Sligar altered two

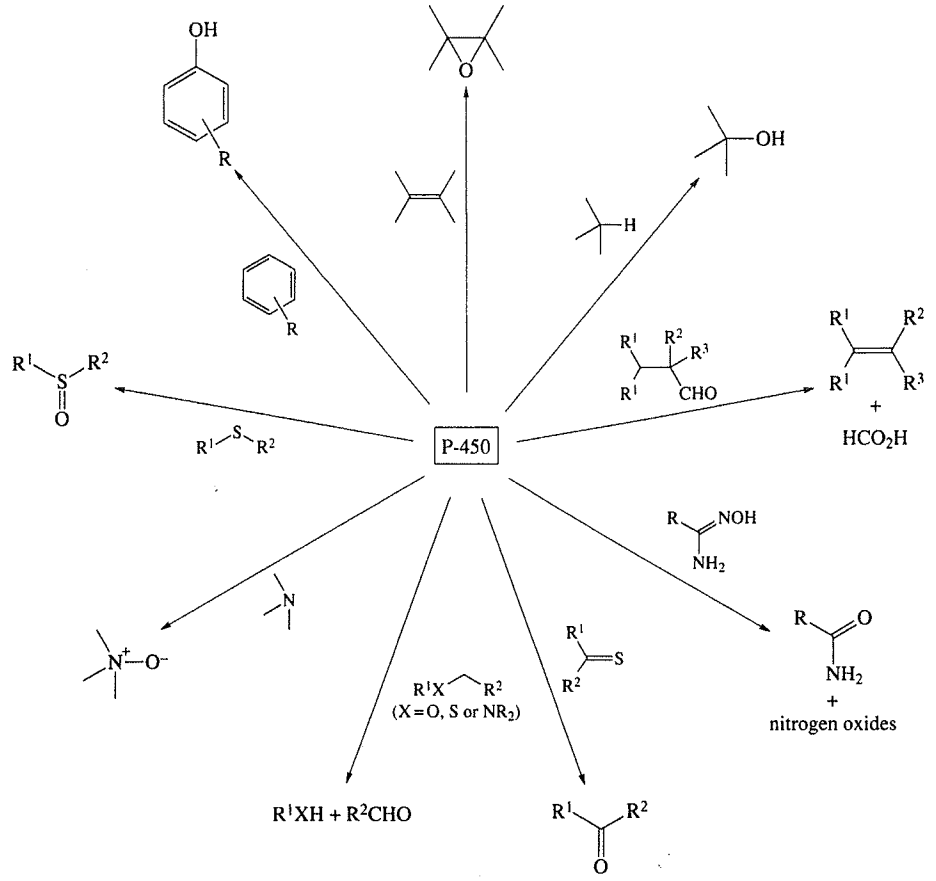


Figure 2. Main types of oxidations catalyzed by P450. Adapted from *Cytochrome P450: Structure, Mechanism and Biochemistry, 2nd ed*; Ortiz de Montellano, P. R., Ed.; Plenum Publishing: New York, 1995. © 1995 Plenum Publishing.

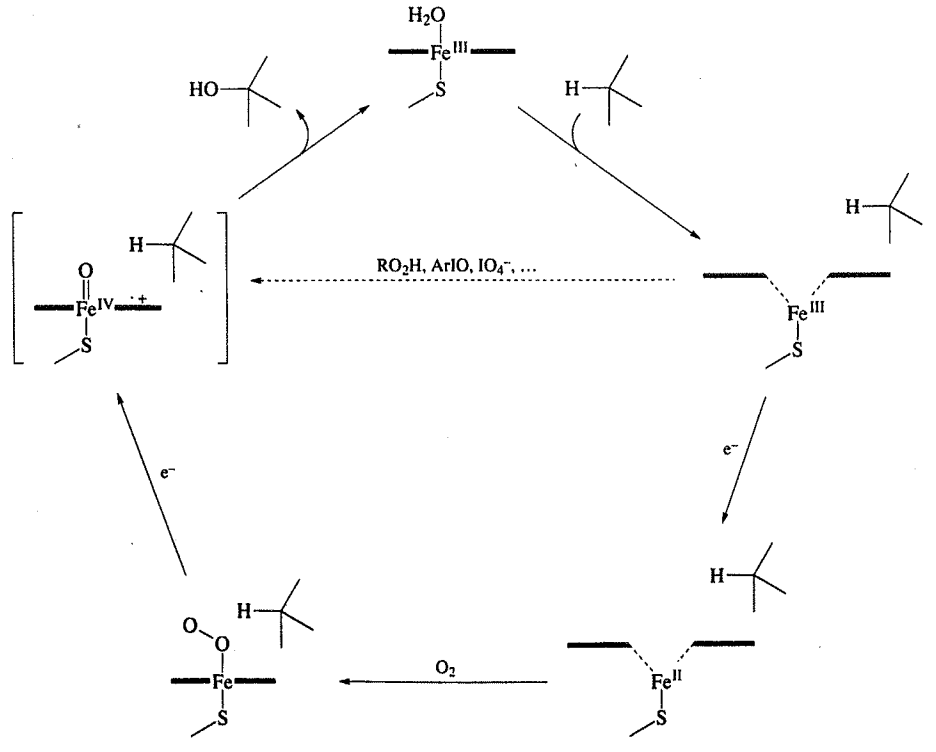


Figure 3. P450 reaction cycle.

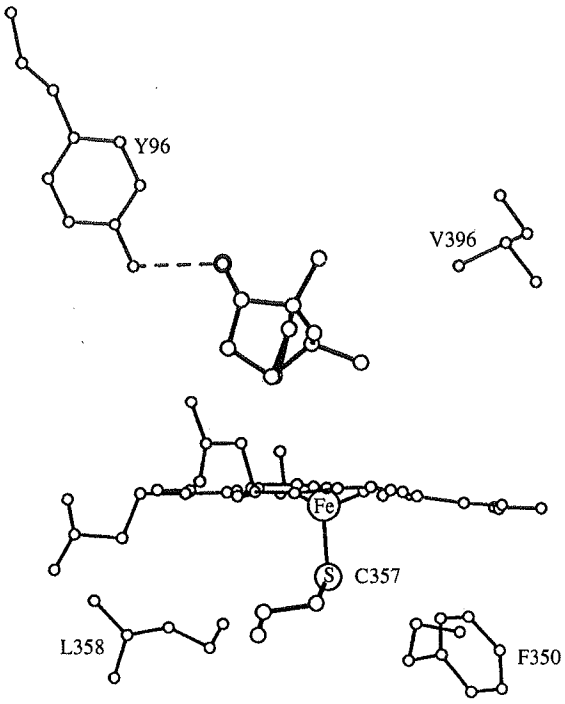


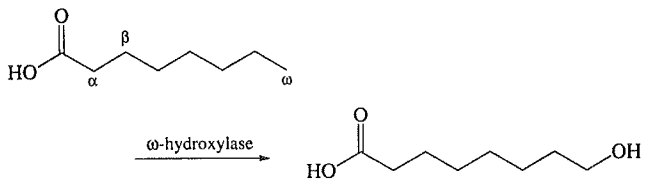
Figure 4. Active site of $P450_{cam}$. Reprinted with permission from *Bioinorganic Chemistry*; Bertini, I.; Gray, G. B.; Lippard, S. J.; Valentine, J. S., Eds. University Science Books: Mill Valley, CA, 1994. © 1994 University Science Books.

of the residues in $P450_{cam}$ that have interactions with the substrate, valine-247 and valine-295.[30] Site specific mutagenesis of valine-247 to alanine (which has less steric bulk) results in lower selectivity of hydroxylation and greater product distributions. Valine-295 was mutated to isoleucine, which resulted in increased selectivity of hydroxylation for both 1-methylnorcamphor and norcamphor and no change for camphor versus the native enzyme. Thus, the increased steric bulk of isoleucine versus valine holds the smaller molecules more tightly in the pocket than the native enzyme.

Fowler *et al.* have produced a single site mutant of $P450_{cam}$ (tyrosine-96 to alanine) that is able to bind diphenylmethane.[31] While the rate of hydroxylation was diminished eightfold compared to native $P450_{cam}$, it was highly regioselective for the aromatic hydroxylation of diphenylmethane to produce *p*-hydroxydiphenylmethane.

Another bacterial enzyme, $P450_{\omega\text{-}2}$ from *Bacillus megaterium*, catalyzes the hydroxylation of the ω-1, ω-2 and ω-3 carbons of fatty acids (that is, the methylenes at the end of the alkyl tail). $P450_{\omega\text{-}2}$ also hydroxylates the ω-1, ω-2 and ω-3 positions of alcohols and amides but not the terminal methyl groups of any substrate.[22,32,33] Miura and Fulco suggested that the substrate is held in place by strong interactions with the protein at the ends of the molecule but has more freedom in the central portion.[33] This binding model would account for the enzyme's inability to hydroxylate the terminal carbon, given the substantial difference in bond dissociation energies for 1° and 2° C–H bonds (see Table 1). Unlike the nonheme and heme-containing ω-hydroxylases, this enzyme will not hydroxylate alkanes. The reason $P450_{\omega\text{-}2}$ is unable to hydroxylate alkanes is unknown, but is likely caused by poor binding.

In higher organisms, the enzymes involved in fatty acid metabolism often exhibit high regioselectivity. The initial hydroxylation of straight-chain saturated fatty acids is a good example. Three types of initial oxidation are seen in vivo, α-hydroxylation, β-hydroxylation and ω-hydroxylation (positions shown in eq 6).[28] These three reactions are performed by several different enzymes in various locations.



(6)

β-Hydroxylation is the most common pathway for fatty acid metabolism and is catalyzed by a number of different enzymes, each of which is specific for a particular substrate chain length, and all of which operate on fatty acid Coenzymes (CoA) esters.[28] α-Hydroxylation of the free fatty acids in most animal tissues takes place when the β-position of the fatty acid is blocked.[34] α-Hydroxylation in the brain is responsible for the formation of cerebronic acid (1-hydroxy-$C_{24}H_{49}O_2$) from lignoceric acid (n-$C_{23}H_{47}CO_2H$).[35] In plants, α-hydroxylation of free fatty acids is a major pathway for the breakdown of fatty acids.[34]

Biosynthesis of steroid hormones from cholesterol[25] by mammalian isozymes of P450 also show a high degree of regioselectivity. The reactions include hydroxylation at C-20 and C-22 of cholesterol, hydroxylation at C-11 of either 11-deoxycorticosterone or 11-deoxycortisol, hydroxylation of C-17 of progesterone and subsequent side-chain cleavage, which generates androstenedione and C–C bond cleavage of 20,22-dihydroxycholesterol which genearates pregnenolone.

Another class of P450s capable of high regioselectivities are the fatty acid ω-hydroxylases,[25] which hydroxylate long-chain fatty acids exclusively at the terminal methyl group. ω-Hydroxylation in animals, catalyzed by a P450,[36,37] is more common for long-chain ($>C_{20}$) fatty acids, but is not the major pathway for their breakdown. In plants, ω-hydroxylation of free fatty acids is more important and seems also to be catalyzed by a P450.[38] Work on the site-specific mutagenesis of human fatty acid ω-hydroxylase has shown that its selectivity and activity are both very sensitive to alteration of the binding site.[36] It may also be possible to provide the necessary reduction equivalents for fatty acid ω-hydroxylases electrochemically, which will be critical for pharmaceutical or industrial applications of P450 catalysis.[37]

The effects of halo-substitution of benzene hydroxylation by P450 show the interplay of electronic and steric control in regioselectivity. Koerts *et al.*[39] concluded that, for the fluorobenzenes studied, the main factors directing the regioselectivity of their aromatic hydroxylation are the nucleophilic chemical reactivity of the site to be hydroxylated and the steric influence of the substituent ortho with

respect to the site of hydroxylation. The steric effects are negligible for fluoro, chloro, and cyano substituents, but become significant for bromo and iodo substitution.

Our understanding and ability to model the active site of P450 and its interactions with substrates now permits at least rational attempts at *de novo* design. The ability to engineer P450 for specific bioremediation needs is likely to see success in the near future.[40]

B. SYNTHETIC METALLOPORPHYRINS

1. Mechanisms of Oxidation

There are two distinct aspects of mechanisms of hydrocarbon oxidation by P450 and its analogues. The first deals with O_2 activation, a reaction that nature handles easily, but which still provides major difficulties in synthetic analogue chemistry. The second concerns the actual substrate oxidation and the reactions of highly oxidized metal intermediates with various hydrocarbons.

Our understanding of the details of the enzymatic activation of O_2 by $P450_{cam}$ has been significantly advanced by Sligar and coworkers,[40–42] using a combination of site-specific mutagenesis and kinetic solvent isotope effects. They were able to provide convincing evidence for a charge relay model of protonation of the bound O_2. This protonation involves the distal tyrosine and aspartic acid residues that lie near the coordinated O_2, as shown in Figure 5.

Isotope labeling experiments by Sligar and coworkers[43] suggested a two-step mechanism for the hydroxylation of camphor by the high-valent iron-oxo species of $P450_{cam}$. Deuterium isotope experiments demonstrated stereochemical scrambling during the hydrogen abstraction step but no scrambling in the hydroxylation step. If the mechanism had involved a concerted oxygen insertion, deuterium scrambling would have been seen for the hydroxylation.

In general, the active species in metalloporphyrin oxidations is thought to be a high-valent metal-oxo species, usually generated by reaction of a metal(III) porphyrin

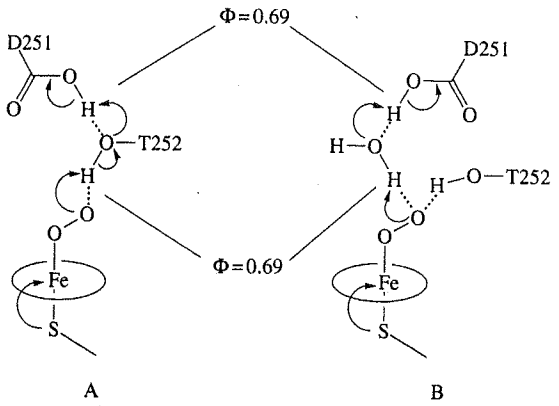


Figure 5. Charge relay models for the activation of O_2 and formation of a oxo complex in $P450_{cam}$. Reproduced with permission from Aikens, J.; Sligar, S. G. *J. Am. Chem. Soc.* **1994**, *116*, 1143 © 1994 American Chemical Society.

complex with an oxygen atom donor (for example, iodosylbenzene, peroxyacids, etc.). Groves and coworkers[10,20] has proposed that hydrocarbon hydroxylation with metalloporphyrin catalysts proceeds via a radical pathway in a "rebound" mechanism. In this mechanism (Figure 6), an oxygen atom is transferred from an oxidant to the metalloporphyrin to form a high-valent metal-oxo species. Hydroxylation has generally been assumed to occur from radical abstraction of a hydrogen from the substrate by an oxy-ferryl (Fe=O), analogous to the less-reactive CpaI of the hydroperoxidases, which form a metal hydroxide complex and substrate radical. The metal hydroxide complex then rapidly transfers the hydroxyl group back to the substrate. In 1998, however, Collman and coworkers presented some rather strong kinetic evidence that there is an agostic intermediate.[44] Other, less plausible intermediates have also been suggested.[45]

Significant controversy remains, however, over the mechanisms of epoxidation of olefins by metalloporphyrin catalysts.[46–49] Several intermediates have been proposed for the oxygen transfer from a high-valent metal-oxo species to an alkene, as shown in Figure 7. The uppermost pathway, involving a concerted addition of the oxygen atom from the metalloporphyrin to the double bond, appears to be most favored. As discussed later in this chapter (Section III.C), shape selectivity studies have demonstrated that there are in fact multiple pathways possible in these oxidations, which explains, in part, the lack of consensus in these complex mechanistic issues.

The nature of the transition state also remains open. Groves and Nemo[50] proposed that the preferred geometry of the interaction between an alkene and the metal-oxo intermediate should be side-on, based on orbital interactions. This side-on geometry for substrate approach, however, may not be exclusive. Epoxidation still occurs with sterically bulky metalloporphyrin catalysts on substrates that are unable to approach the metal-oxo moeity in a side-on fashion.[51,52]

2. Metalloporphyrin-Catalyzed Oxidations

In attempting to mimic the reactivity of heme proteins, many researchers have used metalloporphyrins to catalyze a variety of hydrocarbon oxidations with various oxygen donors.[6,50–54] Metalloporphyrin-catalyzed oxidations include hydroxylation, epoxidation, N-oxidation and cleavage of 1,2-diols. The largest bulk of reports have been with Mn(III), Fe(III), Ru(III), or Cr(III) porphyrins, in that order. Mn(III) complexes are generally preferred in terms of rates and efficiency. Mn(III), Ru(III) or Fe(III) complexes will catalyze both epoxidation and hydroxylation reactions; Cr(III) complexes are competent only for epoxidation.

An enormous range of oxidants have been used as oxygen atom transfer reagents to the metalloporphyrins.[53] These include iodosylbenzenes, peroxyacids, hypochlorite, chlorite, hydroperoxides, *N*-oxides, hydrogen peroxide, monoperoxyphthalate and potassium monopersulfate (Oxone™). Iodosylbenzene was one of the very first oxidants and remains in use because it is often mechanistically cleaner than some alternatives. Some work has also been accom-

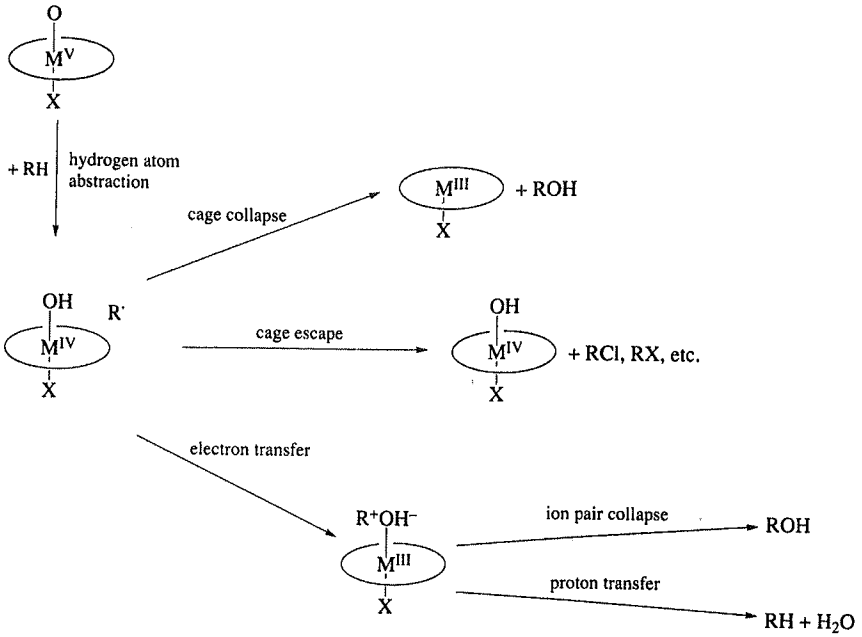


Figure 6. Rebound mechanism of metalloporphyrin-catalyzed hydroxylations.

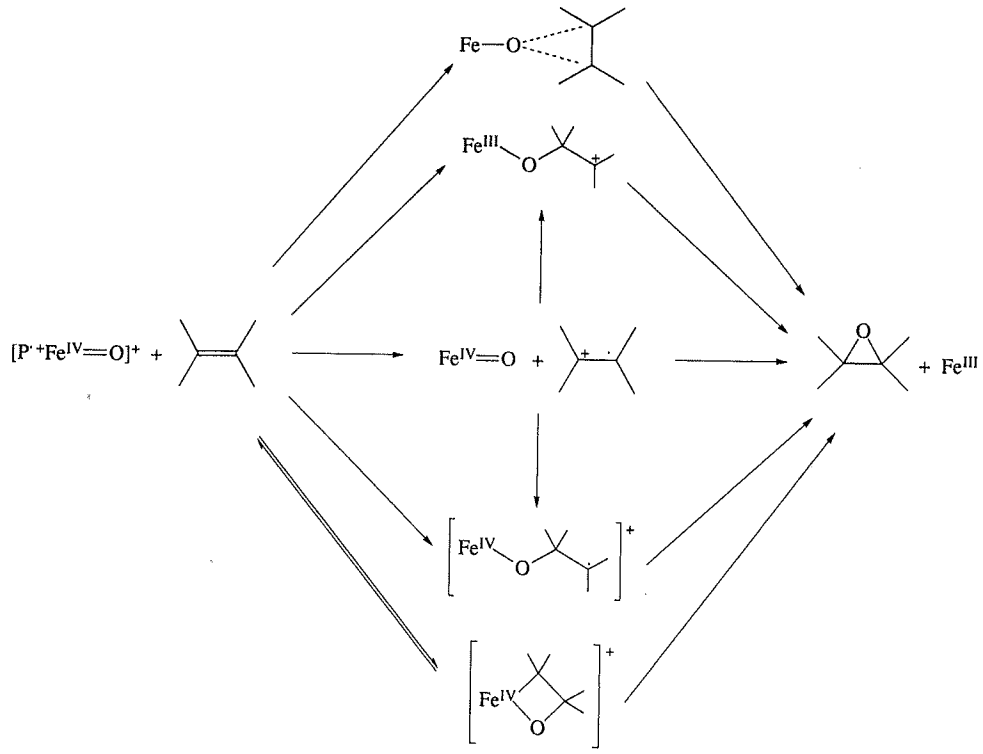


Figure 7. Proposed mechanisms for epoxidation with metalloporphyrins.

plished using various reductants (especially borohydrides) with O_2 to produce substrate oxidation. Other macrocycles have been investigated to a lesser extent[55,56] (especially for asymmetric epoxidation, as discussed later). Porphyrins, especially those with electron-withdrawing substituents, appear to have a strong advantage with respect to stability.

In order to use any catalyst for oxidation of hydrocarbons, the catalyst be oxidatively robust compared to the substrate. Unfortunately, simple metalloporphyrins are readily decomposed under oxidizing conditions. This oxidative degradation occurs readily at the meso ring position (the methine carbons), and in fact this is the route used for the catabolism of heme in vivo.[57] Both electronic and steric factors can be manipulated to improve the oxidative robustness of metalloporphyrins. The use of electron-withdrawing substituents on the porphyrin periph-

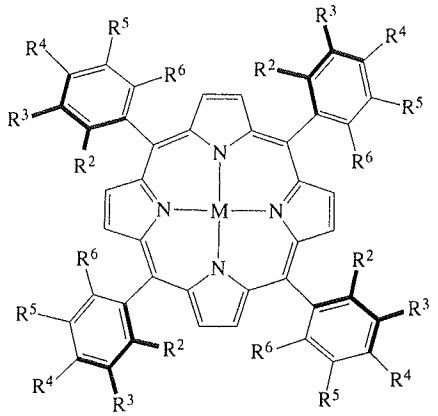


Figure 8. Peripherally substituted metalloporphyrins. M(TPP): $R^2=R^3=R^4=R^5=R^6=H$; M(TDCPP): $R^3=R^4=R^5=H$, $R^2=R^6=Cl$; M(T(3′,5′-DHP)P): $R^2=R^4=R^6=H$, $R^3=R^5=OH$; M(T(2′,6′-DHP)P): $R^3=R^4=R^5=H$, $R^4=R^6=OH$; M(TMP): $R^3=R^5=H$, $R^2=R^4=R^6=CH_3$; M(TTMPP): $R^3=R^5=H$; $R^2=R^4=R^6=OCH_3$; M(TTPPP): $R^3=R^5=H$; $R^2=R^4=R^6=C_6H_5$.

ery (Figure 8), especially halogenated and perhalogenated phenyl porphyrins,[58–62] has proved very successful in producing robust catalysts. Steric protection of the meso position of the porphyrin has also been used effectively.[17,50,63–67] In practice, however, these are not entirely separate approaches, because nearly all of the electron-withdrawing substituents will also contribute significant steric protection to the metalloporphyrin.

A semi-quantitative comparison of the rates of porphyrin degradation in these systems is enlightening. In dilute solutions of manganese tetraarylporphyrins (approximately 10 μM), the half-lives of the metalloporphyrins upon addition of a large excess of oxidant are independent of oxidant concentration, but strongly dependent on steric encumbrance at the meso position: Mn(TPP)(OAc) has a half-life of 5 minutes, Mn(TTMPP)(OAc) of 10 min, and Mn(TTPPP)(OAc) of 25 hours.[66] Thus, steric protection of the periphery of metalloporphyrins can substantially enhance the oxidative robustness of the catalyst.

III. Shape-Selective Oxidation of Hydrocarbons

Two general approaches have been used to create regioselective catalysts. The first involves the synthesis of homogeneous catalysts that have a superstructure designed to recognize and bind incoming substrates, or at least to limit orientation of their access to the metal site. The second uses a heterogeneous environment to restrict substrate orientation or access by using either a solid heterogeneous catalyst (for example, a microporous solid with a simple metal complex imbedded within it) or a microheterogeneous liquid–liquid system (for example, a complex imbedded in a lipid bilayer).

In general, both hydrocarbon hydroxylation and alkene epoxidation have been examined for most of these approaches. By far, hydroxylation is the more demanding of the two, both from the thermodynamic differences required to induce selectivity and in the oxidative stability of the catalyst required to prevent self-degradation. It is worth noting that the presence of a large excess of easily oxidized substrate (for example, alkene) will provide kinetic protection against oxidative destruction of the catalyst.

A. HOMOGENEOUS CATALYSTS

1. Hydroxylation

Selective hydroxylation presents the most troublesome challenge to catalytic oxidation. The thermodynamics of selectively replacing a C–H bond with a C–OH unit are exceedingly difficult to control for three reasons. (1) The bond strength of the C–H bond places high demands on the stability of the catalyst to avoid self-oxidation. (2) The susceptibility of oxidized products to further oxidation is severe, leading ultimately to complete combustion. (3) The most relevant reason is that most organic substrates have multiple C–H bonds, so selectivity becomes an especially important but difficult goal. Thus, there is inherently an important role for shape-selective hydroxylation of hydrocarbons.

In hydroxylations, regioselectivity is essentially under thermodynamic control in the absence of other steric restraints. Radical-based oxidations show little or no regioselectivity beyond that based on bond strengths. For this reason, hydroxylation selectivities are generally dominated by C–H bond strengths (see Table 1). The expected rates of oxidation are therefore allylic C–H > benzylic $> 3° \gg 2° \gg 1°$, and there is no significant preference for one 2° site over another 2° site, and so on.

Catalytic selectivity during hydroxylation can be modified by controlling access of the incoming substrate to the active oxidant. For example, with sterically bulky catalysts, access of an alkane to the metal would be restricted to the more exposed C–H bonds, giving rise to shape selectivity. Because the most exposed C–H bonds will be the least substituted ones (for example, $1° > 2° > 3°$), the possibility for reversal of selectivities by steric means is therefore established. A second approach is to build polar, hydrogen-bonding or other specific weak-bonding interactions into the catalyst superstructure to direct substrate orientation.

The most difficult substrate for the demonstration of regioselectivity by any catalyst must be alkyl chains, which lack any functionality or polarity with which the catalyst may differentiate one site from another. Only relatively modest differences in shape make one methylene distinct from another. Even more challenging is the selection of terminal methyl groups. Nonetheless, the selective oxidation of alkyl chains and alkanes remains an important scientific and commercial goal, because the terminal hydroxylation of alkyl chains is an important metabolic pathway in mammals as well as in bacteria, and because alkanes could become inexpensive chemical feedstocks.

Metalloporphyrins with sterically demanding superstructures have been used to induce substantial selectivity in some hydroxylation reactions. As one would expect, such selectivity is not seen with unhindered or modestly hindered metalloporphyrins,[50,63–66,68–72] such as complexes of TPP

or TTMPP. In these cases, only very modest shape selectivity proved possible. Slight regioselectivity for hydroxylation of one secondary carbon versus another was observed, but no significant terminal hydroxylation and production of primary alcohols occurred. These subtle differences in shape selectivity were demonstrated by noting the production of 2-ols relative to 3-ols from *n*-alkane hydroxylation, for a large number of substituted metalloporphyrin systems, as shown in Figure 9. In this graph, if there is no discrimination between one secondary site and another, the normalized [2-ol] / [3-ol] ratio would be 1.0, as observed for unhindered metalloporphyrins. As the level of steric restraint increases, however, this ratio can become considerably greater than one.

The selectivity for the most accessible secondary site is greatest for the extremely hindered, bis-pocket porphyrin, TTPPP, even for substrates as small as pentane.[66] For this porphyrin, the calculated pocket dimensions from molecular modeling (Figure 10) are 4.0 Å across by 5.0 Å deep (measured from the van der Waals surfaces[64,66]). This pocket size suggests that shape selectivities should increase as the alkane chain length increases, preventing side-on entrance to the metal-oxo species, which proves to be the case.

Regioselectivity among primary sites of different steric environments may be exhibited in the hydroxylation of branched alkanes. 2,2-Dimethylbutane [$(CH_3)_3CCH_2CH_3$] is an especially interesting case, because it has both a 2° site and two quite different 1° sites. This substrate is shaped like a fist with a sore thumb, and as such is well suited as a probe for shape selectivity. The secondary alcohol is the predominant product (> 90%) for catalysis by either Mn(TPP)(OAc) or Mn(TTMPP)(OAc). With the deeply pocketed Mn(TTPPP)(OAc), however, the steric inaccessibility of the 2° site is quite pronounced and 3,3-dimethylbutan-2-ol becomes only a minor product (< 25%). Even more striking is the selectivity shown in favor of the most exposed methyl group (to form 3,3-dimethylbutan-1-ol) and against the

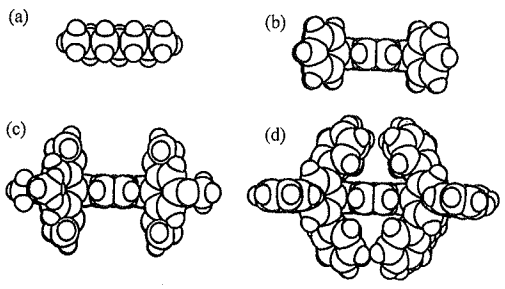


Figure 10. Molecular models of sterically hindered porphyrins; for scale, heptane (a) is also shown. The porphyrins represented are the unhindered TPP (b) the moderately hindered TTMPP (c) and the deeply pocketed TTPPP (d) For clarity, atomic radii shown are only 0.8 of the van der Waals radii. Reprinted with permission from Suslick, K. S. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley & Sons: New York, 1989; pp 219–241 © 1989 John Wiley & Sons, Inc.

hindered *tert*-butyl group methyls (to form 2,2-dimethylbutan-1-ol). The ratio of the primary alcohols, weighted for their total number of hydrogens, increases from 0.3 to 0.89 to 34 for Mn(TPP)(OAc), Mn(TTMPP)(OAc) and Mn(TTPPP)(OAc), respectively. Thus, 2,2-dimethylbutane may enter the pocket of Mn(TTPPP)(OAc) with only one orientation to minimize the steric interaction between the bulky *tert*-butyl group and the triphenylphenyl substituents on the porphyrin's periphery. This very specific, enzyme-like, shape selection of the substrate by the catalyst gives rise to the impressive preference for hydroxylation of the sterically most accessible methyl group.

The ability to produce oxidation catalysts selective for methyl group hydroxylation remains an economically important challenge. The most important goal in this research is clearly the hydroxylation of terminal methyl groups in *n*-alkanes. In order to make meaningful comparisons between various alkane substrates, a primary selectivity index is defined for Figure 11 as the ratio of the concentration of primary alcohol to secondary alcohols, normalized for the respective number of hydrogens.

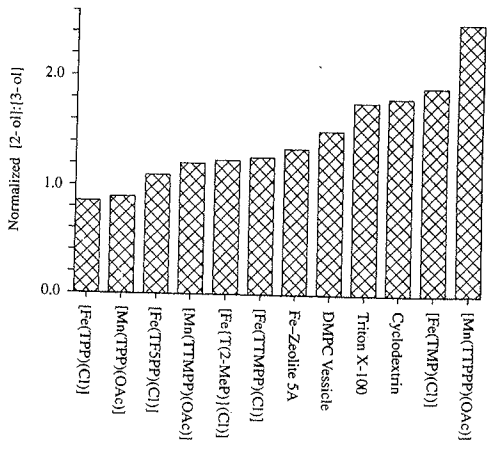


Figure 9. Secondary versus secondary C–H hydroxylation in pentane: ω-1 selectivity as a function of steric hindrance of the catalyst. Reprinted with permission from Suslick, K. S. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley & Sons: New York, 1989; pp 219–241 © 1989 John Wiley & Sons, Inc.

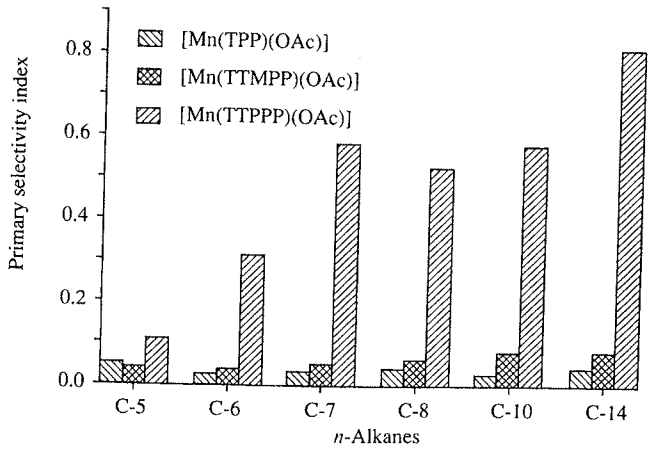


Figure 11. Shape selectivity for hydroxylation of the terminal methyl of *n*-alkanes vs. chain length, normalized for relative numbers of hydrogens. Reprinted with permission from Suslick, K. S. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley & Sons: New York, 1989; pp 219–241 © 1989 John Wiley & Sons, Inc.

As expected, unpocketed and shallow-pocketed porphyrins give nearly exclusively 2° alcohols upon hydroxylation of *n*-alkanes. Using Mn(TTPPP)(OAc) and various oxygen donors, Suslick and coworkers were able to direct hydroxylation to the primary carbons of alkanes.[65,66] When Mn(TPP)(OAc) is used as the hydroxylation catalyst, the products are primarily 2° alcohols (95–99%) which would be predicted using relative C–H bond strengths. Using Mn(TTPPP)(OAc) as the catalyst increases the yield of 1° alcohols, up to 26% with *n*-heptane as the substrate. Also seen was a decrease in the percentage of ω-2 and ω-3 oxidation, indicating that these positions are less able to access the manganese-oxo center. Relatively large increases in the primary selectivity index are observed from pentane to hexane to heptane, after which much smaller increases are observed with each added methylene unit. Thus, heptane marks the size cutoff for the "side-ways" entry of *n*-alkanes into the pocket of this porphyrin, and alkanes of larger size are restricted in their entry to an end-on approach. Even more difficult will be the selection for primary over tertiary hydroxylation, because of the large difference in bond dissociation energies; this remains largely unsuccessful at this time, even in the most hindered systems.

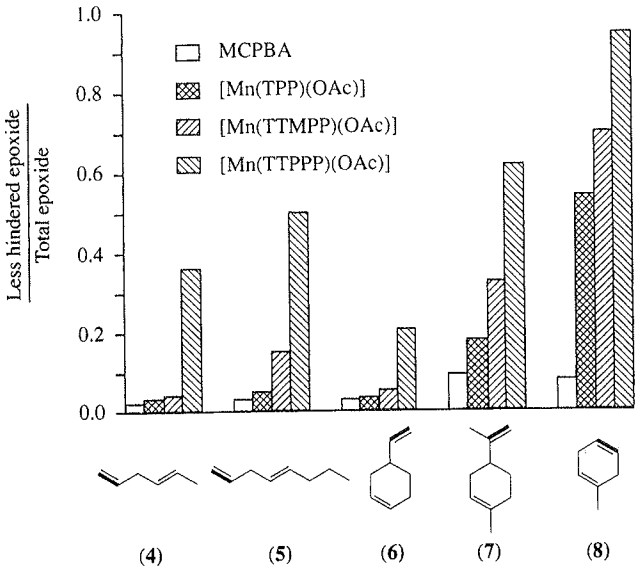


Figure 12. Intramolecular shape selectivity for nonconjugated diene epoxidation. The less hindered double bond is highlighted in the drawing. Reprinted with permission from Suslick, K. S. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley & Sons: New York, 1989; pp 219–241 © 1989 John Wiley & Sons, Inc.

2. Epoxidation

This same sort of shape selectivity can be extended to alkene epoxidation, as well. In general, there are two classes of probes for such selectivity: *intra*molecular and *inter*molecular. Intramolecular probes require the oxidation of (nonconjugated) dienes in which the double bonds are sterically and electronically inequivalent. Alternatively, intermolecular competition between two differently shaped alkenes is a more general, but perhaps less unambiguous probe from a mechanistic perspective.

A number of researchers have examined the effect of small steric restraints and electronegative substitution on the regioselectivity of some alkene epoxidations[73–77] and the related catalyzed cyclopropanation.[78] For norbornene oxidation, the exo to endo ratio is exquisitely sensitive to steric and electronic factors. Just the addition of an *ortho*-chloro substitution [as in 5,10,15,20-tetrakis(2′,6′-dichlorophenyl)-porphyinate] (TDCPP) will give a 10-fold decrease in the production of *exo*-epoxynorbornane.[73] Another intramolecular test case is epoxidation of the cis versus trans double bonds of the symmetric 1,5,9-*trans*,*cis*,*trans*-dodecatriene. The comparison of TMP complexes to TPP shows a 10- to 15-fold increase in selectivity for the cis epoxide.[50,76] The facile epoxidation of *cis*-stilbene, when compared with the very low reactivity of the sterically demanding *trans*-stilbene (even with unhindered porphyrins), is another example of the importance of steric concerns with bulky substrates.

In order to compare more highly selective catalysts, one must relax the steric demands of the substrates. To this end, a series of nonconjugated dienes of varying shapes and sizes have been developed as intramolecular probes of shape selectivity[63,64,67] in analogue to the shape-selective hydroxylation of alkanes. The same series of unpocketed, shallow-pocketed and deeply pocketed porphyrins were used as catalysts for the epoxidation of these dienes. In all cases, Mn(TTPPP)(OAc) exhibits enhanced selectivity for epoxidation of the most exposed double bond of the substrate (Figure 12). Even with sterically undemanding, straight-chain dienes, Mn(TTPPP)(OAc) shows a substantial preference for epoxidation at the terminal position. As expected, this selectivity for terminal epoxidation increases as the steric bulk of the diene increases, similar to the trend discussed for the hydroxylation of *n*-alkanes by these same catalysts. The shape selectivity originates from the steric demands of the superstructure of the metalloporphyrins. Consistent with this, the ratio of enhancement for terminal epoxidation of linear, nonconjugated dienes is very similar to that observed for hydroxylation of *n*-hexane versus *n*-octane.

Limonene (**7** in Figure 12) and its structural analogue 4-vinyl-1-cyclohexene (**6** in Figure 12) are very useful chiral starting materials for many organic syntheses.[79] With standard oxidants available for epoxidation of these molecules [such as *meta*-chloroperoxybenzoic (*m*-CPBA)], ring epoxidation occurs exclusively, rather than external epoxidation. Likewise, ring epoxidation dominates with the unhindered Mn(TPP)(OAc) and the modestly hindered Mn(TTM-PP)(OAc). The extremely hindered Mn(TTPPP)-(OAc), however, enhances the epoxidation of the external double bond, and for the more sterically demanding limonene, external epoxide is the major product formed.[67] Even higher selectivity is observed in the epoxidation of 1-methyl-1,4-cyclohexadiene (**5** in Figure 12), where epoxidation of the sterically less-hindered double bond with Mn(TTPPP)-(OAc) accounts for 95% of the product.

In a versatile and elegant synthetic approach to the creation of shape-selective catalysts, Collman and coworkers[15,16,80,81] have used a variety of manganese(III) picnic-basket porphyrins (PBPs) (Figure 13) to regioselec-

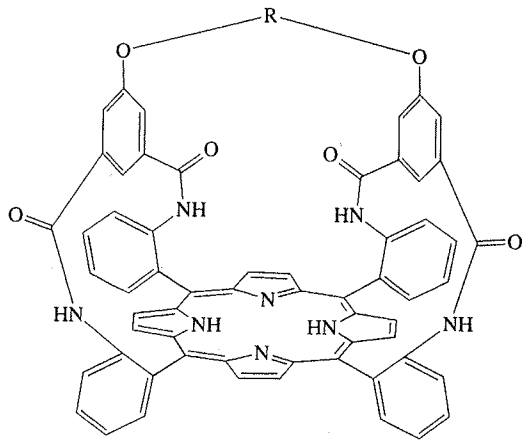


Figure 13. Picnic-basket porphyrins and their intermolecular shape selectivity. Adapted from Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404 © 1993 American Association for the Advancement of Science.

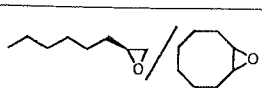
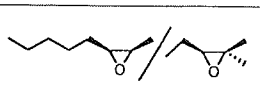
tively epoxidize olefins. With this class of complexes, a variety of pockets can be designed and optimized for specific substrates. For this class of catalysts, however, the open face of the porphyrin must be blocked with a large axial ligand, such as 3,5-di-*tert*-butylphenoxide. The greatest selectivities (Table 3) were seen using the C_6- and *p*-xylyl PBPs (C_6PBP and PXLPBP, respectively). The ratios of epoxidation were greater than a 1000/1 for *cis*-2-octene compare with cyclooctene for Mn(PXLPBP) as the catalyst. Selectivity for a disubstituted double bond over a trisubstituted double bond was also explored using *cis*-2-octene and 2-methyl-2-pentene. For either Mn(C_6PBP) or Mn(PXLPBP), the ratio of epoxidation for these two olefins was more than 1000/1. Selectivity for terminal olefin epoxidation versus internal olefin epoxidation was examined using 1-octene and cyclooctene. Modest selectivities were obtained using Mn(C_6-PBP) and Mn(PXLPBP). Collman and coworkers noted that some reaction occurs with cyclooctene, possibly indicating slow oxidation at the open face of the porphyrin complex.[80]

Moore, Suslick, and coworkers synthesized a new class of sterically hindered dendrimer-metalloporphyrins for use as shape-selective catalysts.[82–84] A series of oxidatively robust poly(phenylester) and poly(phenylamide) dendrimers was prepared through a convergent synthesis (Figure 14). Monodendrons were appended either to the meta positions of 5,10,15,20-tetrakis(3′,5′-hydroxyphenyl)porphinatomanganese(III) chloride or to the ortho positions of 5,10,15,-20-tetrakis(3′, 6′-hydroxyphenyl)porphinatomanganese(III) chloride to provide extreme steric protection of the metal center (Figure 15). These complexes are from 4,000 to 12,000 atomic mass units (amu), so they are comparable in size to small-heme proteins.

These complexes have been examined as regioselective oxidation catalysts for the epoxidation of dienes and of alkene mixtures of 1-alkene and cyclooctene. Although access from the top is extremely restricted in all of the dendrimer-metalloporphyrins, the *meta*-phenyl-substituted complexes show a significant side opening (10 Å and 7 Å, van der Waals surface to surface, for the first and second generation dendrons, respectively). The meta-substitution causes the dendrons to sweep away from the metal site before branching back over it. This limits the degree of regioselectivity that can be achieved with meta-substitution of a tetraphenylporphyrin. Consequently, the shape selectivity observed for these dendrimer-metalloporphyrins is good, but still surpassed by the bis-pocket porphyrin, TTPPP.

In contrast, ortho-substitution provides an extremely hindered active site and is an extraordinary shape-selective oxidation catalyst. An amide-linked, oxidatively robust monodendron [3, 5-bis(4′-*tert*-butylphenylamido)benzoic acid] was used to esterify all eight of the *ortho*-phenyl positions of 5, 10, 15, 20-tetrakis(2′, 6′-hydroxyphenyl)porphinatomanganese(III) chloride to create a highly hindered metal center. To probe the potential this dendrimer-metalloporphyrin as a shape-selective oxidation catalyst, selectivities of were determined for both intermolecular and intramolecular epoxidations. Epoxidation of 1/1 intermolecular mixture of 1-alkenes and *cis*-cyclooctene and of nonconjugated dienes were carried out with iodosylbenzene as the oxygen donor. The Mn(III) dendrimer-porphyrin complex showed excellent shape selectivity relative to the unsubstituted Mn(TPP)Cl, comparable to the best previous (nondendrimer) catalysts (Figures 16 and 17). Molecular modeling studies on the dendrimer-porphyrin delineate the steric control around the porphyrin periphery and show that substrate access to the metal is limited to a approximate 0.5-

Table 3. Intermolecular Shape Selectivity with the Picnic-Basket Porphyrins[80]

	Epoxide ratio			
Catalyst				
Mn(TPP)(OAr)	1.2	1.1	0.03	0.9
Mn(TMP)(OAr)	14.4	0.7	0.04	2.5
Mn(C_2PBP)(OAr)	0.4	1.1	0.05	1.3
Mn(C_4PBP)(OAr)	1.0	2.1	0.4	1.8
Mn(C_6PBP)(OAr)	70	67	1.7	> 1000
Mn(PXYLPBP)(OAr)	29	> 1000	7.0	> 1000
Mn(C_8PBP)(OAr)	12.7	1.6	0.06	21.1
Mn(C_{10}PBP)(OAr)	8.8	0.2	0.04	17.9

Source: Collman, J. P.; Zhang, X.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 5356.

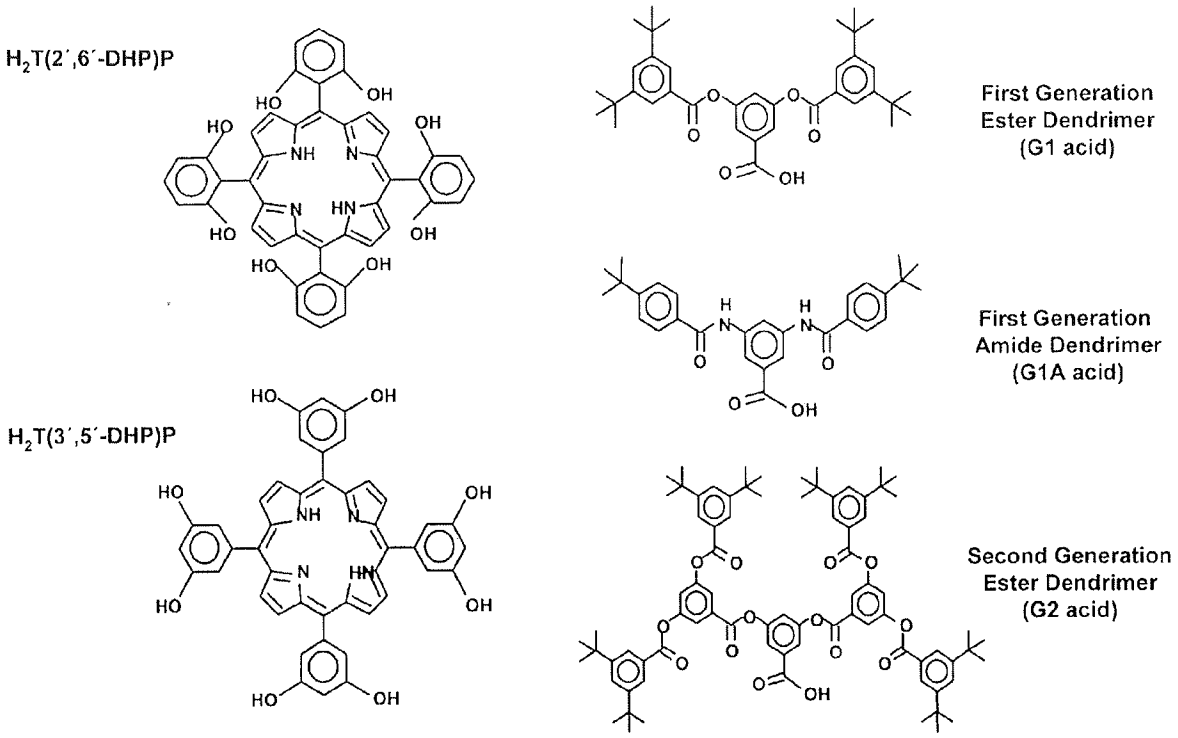


Figure 14. Chemical structures of monodendrons, porphyrin precursors, and sterically hindered dendrimer-porphyrins.

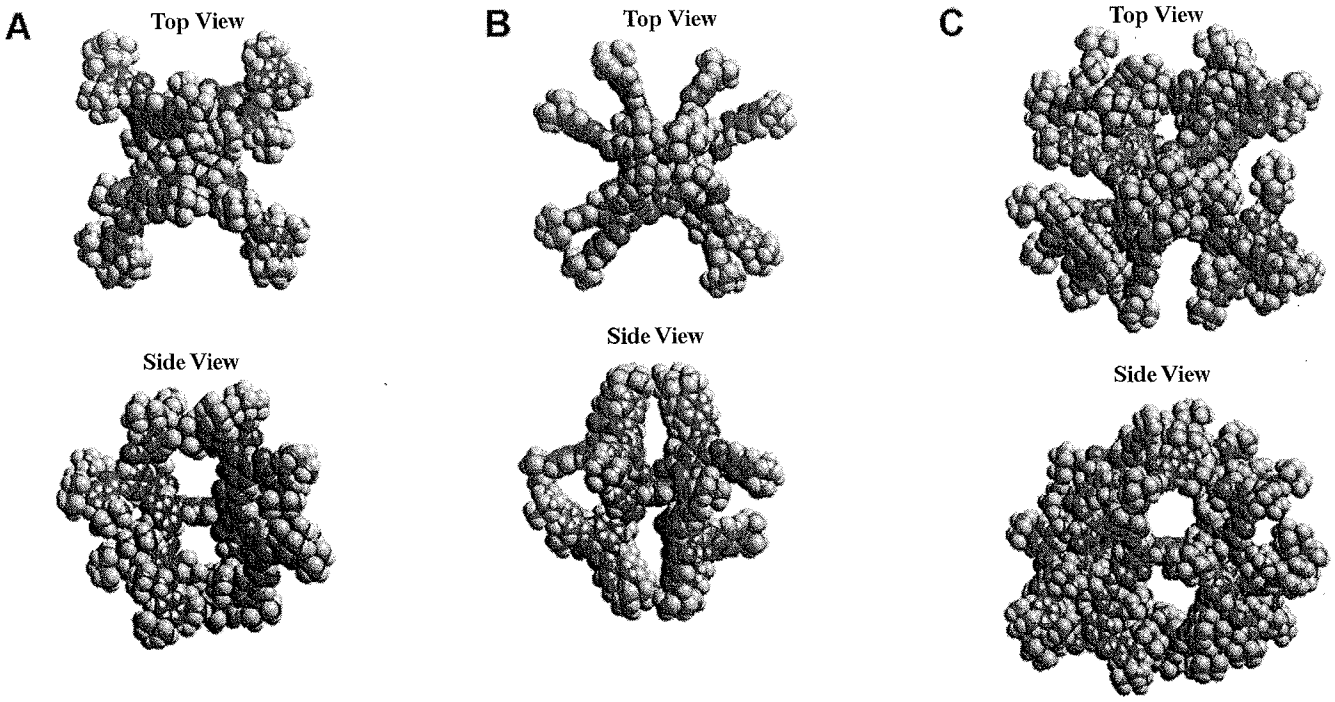


Figure 15. Molecular models of dendrimer-porphyrins. A: *meta*-substituted $H_2T(3',5'\text{-}G1P)P$. B: *ortho*-substituted $H_2T(2',6'\text{-}G1AP)P$. C: *meta*-substituted second generation dendrimer-porphyrin $H_2T(3',5'\text{-}G2P)P$.

nm gap between the dendrimer substituents (Figure 18). Thus, there is substantial steric control of substrate access to the metal site and that the limited access available is side-on to the oxo-manganese intermediate.

One might have been concerned that the use of a sterically restrictive superstructure to alter the regioselectivity of the catalysts would also substantially diminish their activity. Fortunately, this proves not to be the case.[83]

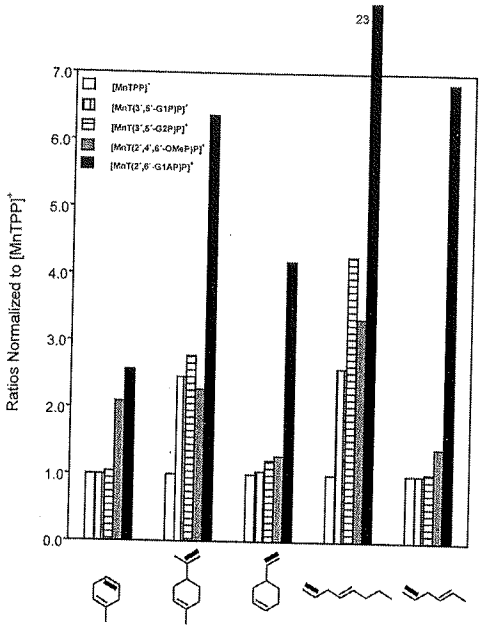


Figure 16. Intramolecular selectivities (ratio of epoxidation of the least hindered to most hindered double bond) for catalytic epoxidation of various non-conjugated dienes by manganese(III) dendrimer-porphyrins, normalized to $[Mn(TPP)]^+$. The most sterically accessible double bond of each diene is indicated by heavy lines. Estimated errors are 6% relative.

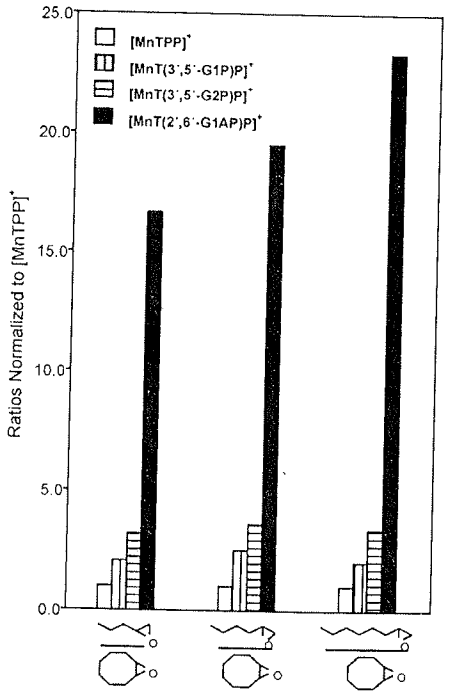


Figure 17. Intermolecular selectivities for catalytic epoxidation of 1-alkenes relative to *cis*-cyclooctene, normalized to $[Mn(TPP)]^+$. Estimated errors are 5% relative.

Turnover numbers for the *ortho*-dendrimer-metalloporphyrin, Mn(T(2′,6′-G1AP)P)Cl are typically 1–2 sec^{-1}, which is only modestly slower than those for the unhindered Mn(TPP)Cl, which are typically 3–4 sec^{-1}. While these

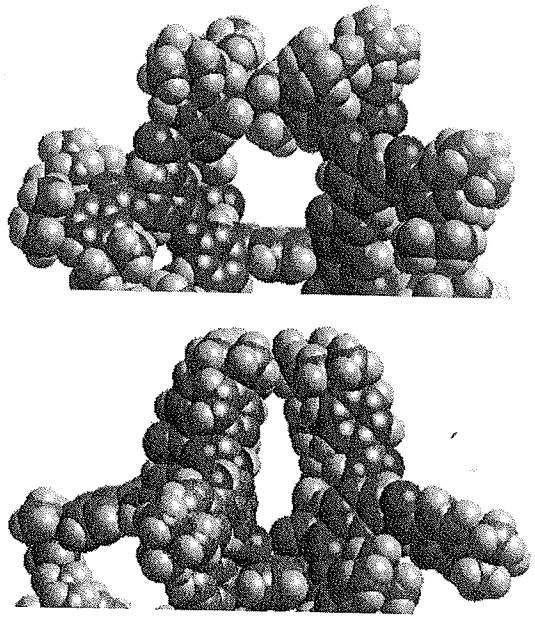


Figure 18. Molecular models showing an enlarged side view of the binding sites of dendrimer porphyrins. A: *meta*-substituted $H_2T(3',5'$-G1P)P. B: *ortho*-substituted dendrimer-porphyrin $H_2T(2',6'$-G1AP)P. Note the open cavity of 10 Å versus a narrow slit of 5, respectively; in both cases, top access to the porphyrin is completely blocked.

rates are not large compared to some catalytic systems, they are of the same order as the rates of oxidation seen with P450. Yields in terms of oxidant used are also a matter of potential concern. In all cases studied, the yields based on oxidant consumed are very good and range between 70% and 80%.[83]

Although catalytic oxidation studies probe shape selectivity in a kinetic sense, one can also examine steric pocket effects on equilibria. To this end, molecular recognition of metal-binding ligands by these dendrimer-metalloporphyrins was probed using nitrogenous bases of varying shapes and sizes.[84] The *ortho*-dendrimer Zn porphyrin has a narrow binding site sterically constrained by the dendrimer substituents and shows remarkable selectivity differences between linear and nonlinear amines, with changes greater than 10^4 in equilibrium binding constants. In contrast, the *meta*-dendrimer Zn porphyrins, which have more open binding sites, do not show selectivity and instead actually increase severalfold binding of all bases relative to Zn(TPP). Thermodynamic parameters for ligation have also been determined: the steric control of binding of bulky ligands in these systems is primarily enthalpic. The K_{eq} values of the ortho-substituted system were exquisitely sensitive to the shape and size of the substrates. Linear amines (4-phenylpyridine or dodecylamine) were bound a bit more strongly by the dendrimer-porphyrins than by Zn(TPP) itself, because of attractive interactions between the ligand and the aromatic dendrons and to solvation effects. In the case of nonlinear amines, however, differences in K_{eq} of 10^3–10^5 were observed among the dendrimer-metalloporphyrins.

Other studies have emphasized the steric demands of the substrates, rather than those of the catalysts. Large, complex

substrates often have substantial differences in steric accessibility from site to site within the substrate. For a wide range of natural products, sterically unencumbered ruthenium porphyrins have been shown to be regioselective, as well as stereoselective, epoxidation catalysts.[85–90] Marchon and Ramasseul used *trans*-dioxo(tetramesitylporphyrinato)ruthenium(VI) [(Ru(TMP)$(O)_2$)] to catalyze epoxidation of steroids. Yields of the $\Delta^{5,6}$-epoxide were from 76% to 94%.[85–88] Formation of the β-epoxide predominated with reported selectivities from 92% to 99%; $\Delta^{5,6}$ selectivity was reported for steroids with more than one double bond, although stereoselectivity was lost with some substrates.[88,89] An extensive examination of the selectivity of ruthenium porphyrins in the epoxidation of dienes, especially natural product dienes, was published by Hirobe and coworkers.[90] These workers have produced an efficient catalytic system using aromatic *N*-oxides as the oxidant; in some cases, turnover numbers above 10^5 were observed. High selectivities for cis versus trans double bonds were observed. In β-acetoxy-substituted dienes, a strong preference was shown for the most electron-rich, trisubstituted double bond, which means that steric control is not dominant even with the tetramesitylporphyrin ruthenium complex.

3. Comparisons to Enzymatic Selectivity

Direct comparisons of the regioselectivities of various monooxygenase enzymes and the biomimetic oxidation catalysts just discussed are difficult because of the variations of one isozyme to another, to limited biochemical data on a range of chemically useful substrates and to the weak binding of many nonnatural substrates in enzyme active sites. The best comparisons are made with the ω-hydroxylases, of which there are two classes: (1) a nonheme iron monooxygenase found in bacteria,[24] and (2) specific isozymes of P450 found, in bacteria, yeast, plants and mammalian mitochondria.[21,25,26] With in vivo substrates (for example fatty acids and cholesterol steroids), the regioselectivities can be quite striking.[91] The ratio of $\omega/(\omega-1)$ hydroxylation of capric acid by kidney P450, for example, can be as high as 20, which represents an extreme example of kinetic control of product formation.

Although several forms of P450 have been isolated (especially from bacterial sources) that give terminal hydroxylation of *n*-alkanes, data are seldom given for the amounts of secondary alcohols that may also be produced. Data are available[91–94] for the hydroxylation of hexane and heptane by rat liver microsomal P450. As one might expect, the regioselectivities shown for these *n*-alkanes are not nearly as high as those shown for fatty acids. The primary selectivity, as defined earlier, of rat liver microsomal P450 (uninduced) is 0.16 for hexane and 0.26 for heptane, as compared to 0.32 and 0.59, respectively, for Mn(TTPPP)(OAc). Upon treatment with phenobarbital, different and less selective isozymes of P450 are induced, with primary selectivities of 0.03 for hexane and 0.10 for heptane.

Certain isozymes of the heme protein P450 are capable of dramatic regioselective epoxidation, as well.[95] A comparison of the selectivities for epoxidation of limonene and of 4-vinyl-1-cyclohexene can be made between the synthetic metalloporphyrins and limonene-induced rat liver microsomal P450. As the steric demands of the active site of the oxidizing system increase from uncatalyzed *m*-CPBA to the very bulky Mn(TTPPP)(OAc), the selectivity for external epoxidation dramatically increases and Mn(TTPPP)(OAc) is nearly as selective as the native enzyme.

Thus, for the most successful homogeneous catalysts, regioselectivities for simple substrates are comparable with those of native P450s. Although the details of the steric interactions undoubtedly differ between the enzyme and our synthetic analogues, the total steric interaction must be quite similar in magnitude for both Mn(TTPPP)(OAc) and various isozymes of P450. A comparison of the relative size and shape of binding sites in the enzymes with the synthetic analogues should prove interesting as more structures become available.

B. HETEROGENEOUS AND MICRO-HETEROGENEOUS CATALYSTS

Less work has been done with heterogeneous catalysis for shape-selective oxidation, in part because such systems are inherently more difficult to characterize than the homogeneous catalysts already discussed. Nonetheless, this approach retains much promise. There are two classes of catalysts in this area: (1) microheterogeneous systems that use micelles or lipid bilayers to achieve a steric isolation of the catalytic center, and microporous solids with interior catalytic sites (usually zeolites). Each will be considered in turn.

1. Micellar or Bilayer Structures

A number of researchers have incorporated porphyrins into micellar or bilayer structures, and there have been two reports of the use of such systems to induce shape-selective oxidation. The first is an intriguing, but often overlooked, note by Shilov and coworkers.[96] These researchers used a long-tailed iron porphyrin complex [tetrakis(4′-hexadecyloxyphenyl)porphyrin, H_2(T(4-HDP)P] incorporated into Triton X-100 micelles or phospholipid vesicles to hydroxylate hexane. The preference for $\omega-1$ hydroxylation to give 2-hexanol is good in both cases, as shown in Figure 11. Terminal hydroxylation occurs, albeit to a limited extent. The primary selectivity index is 0.04 for the micellar system and 0.10 for the vesicles, as compared to 0.31 for the bis-pocket porphyrin, Mn(TTPPP)(OAc). Even more remarkable, however, is the effect of added β-cyclodextrin to Fe[T(4-HDP)P]Cl; in this system, the [2-ol]/[3-ol] ratio is reasonably good, but the terminal hydroxylation is amazing, with a primary selectivity index of 0.47. The origin of this effect has not been explained, and the effect of substrate or oxidant also requires further examination.

Metalloporphyrins have also been incorporated into lipid bilayer vesicles for both O_2 binding and oxidation.[97,98] Groves and coworkers have succeeded in using the system represented in Figure 19 to regioselectively epoxidize sterols and fatty acids.[20,99,100] Electron paramagnetic

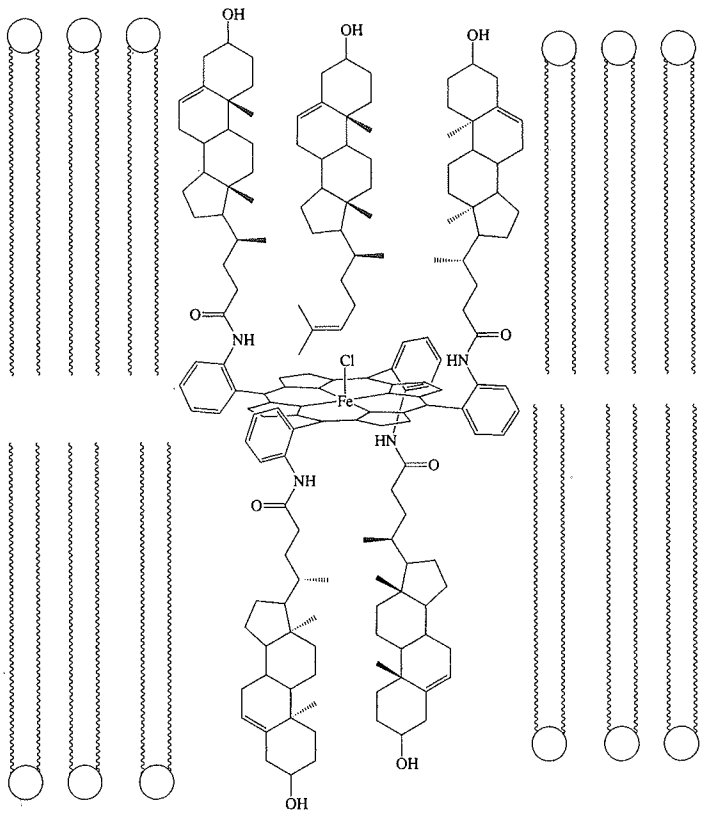


Figure 19. Idealized molecular assembly of a tetra-sterol-substituted porphyrin and desmosterol as substrate in a phospholipid bilayer. Reproduced with permission from Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1989,** *111,* 2900 © 1989 American Chemical Society.

resonance (EPR) experiments demonstrated that the porphyrin was oriented perpendicular to the phospholipid bilayer chains. Given a sufficiently large sterol, the selectivity for the more extended double bond can be significant. In the case of simple diene fatty acids, however, the selectivities are relatively modest. Alkanes are apparently not effective substrates. Self-poisoning of the catalyst is also a problem with these systems, because the products appear to remain in the binding site and certainly in the bilayer.

One interesting approach uses the orientation of a porphyrin molecule in a thermotropic nematic liquid crystal to control substrate access to the metal. The alignment of a porphyrin with mesogenic substituents was determined by time resolved EPR spectroscopy of the triplet state of the free base porphyrin. The Mn(III) complexes of TPP and of the mesogenic porphyrin then were used as catalysts for the epoxidation of alkenes using iodosobenze as oxidant. Reaction yields and regioselectivity for enlongated substrates such as *cis*-stilbene and 4-vinylbiphenyl were somewhat dependent on the alignment of the alkene and its carbon-carbon double bond relative to the director and metalloporphyrin catalyst.

2. Microporous Solids

Various workers have explored the use of modified zeolites as shape-selective heterogeneous oxidation catalysts.[72,102–108] These systems have potential advantages in terms of oxidative robustness, but their selectivities are in many cases less than those of the better homogeneous systems. For example, Herron and Tolman used a modified small-pore zeolite, Fe(II)/Pd(II) exchanged zeolite 5A ($Si/Al \simeq 1.2\%$), to hydroxylate alkanes in the presence of H_2/O_2 mixtures.[104] Good shape selectivity was observed for product *extracted* from within the zeolite: [2-ol]/[3-ol] ratios were comparable with moderately hindered porphyrins (Figure 11), and the primary selectivity index for terminal hydroxylation of octane was very high. There are four considerations, however, that significantly limit the utility of this system. (1) In the absence of a surface poison (such as 2,2′-bipyridine), most oxidation occurs in a *nonselective* fashion on the surface of the zeolite, with little terminal hydroxylation in the total product distribution. The reported product analyses only examined product caught in the interior of the zeolite. (2) Product formed in the interior of the zeolite is permanently trapped there, and must be extracted by *dissolution of the zeolite* in concentrated sulfuric acid. (3) The catalyst is self-poisoning; because product is entrapped, substrate cannot continue to have access to the catalytic sites (turnovers are 0.3/Fe). (4) More than 95% of the H_2 is used in the formation of H_2O rather than substrate oxidation. If a larger pore zeolite host is used (such as ZSM-5), the products can be removed without zeolite dissolution, but the selectivities are reduced. In spite of these concerns, microporous inorganic solids have tremendous potential for future industrial application to selective oxidation catalysis.

Incorporating bioinorganic complexes into solid supports has received some attention as well. The "ship-in-the-bottle" approach synthesized the metallomacrocycle complex within the confines of a large-pore zeolite, isolating and entrapping the catalytic center. Iron phthalocyanines (Pcs) prepared in situ within a zeolite have been examined as an alkane hydroxylation system.[102,103] The number of turnovers observed were quite low because the zeolite pores become clogged with product. No terminal hydroxylation was observed. For octane with the most selective zeolite (type Y with 0.13 wt% Fe), the $\omega - 1$ selectivity was 1.33, which may be compared to moderately hindered porphyrins. A modification of this work by Belgian workers has incorporated similar Fe(Pc) complexes inside zeolite Y and imbedded the zeolite in a silicone polymer.[102] In spite of publicity and rather audacious claims, the effects on selectivity through this approach are quite modest.

Balkus *et al.* used a perfluorinated Ru(Pc) as the seed for the growth of zeolite NaX around it.[110] Metal complex loadings were approximately 1 complex per 125 zeolite supercages. This approach has the advantage of starting with pure metal complex and apparently does not lead to blockage of the zeolite pore structure, at least at the low loadings used in this study. Fluorination of the Ru(Pc) complex dramatically improved the lifetime of the catalyst and encapsulation in the zeolite prevented bimolecular reactions to form μ-oxo dimers, which are catalytically less active. Oxidation of cyclohexane to cyclohexanone occurred at slow turnover rates of roughly 0.03 s^{-1} with no deactivation after 20,000 turnovers (corresponding to 70% conversion of cyclohexane). A roughly 10-fold selectivity was seen for cyclohexane over cyclododecane hydroxylation to the ketones, which reflects steric demands of diffusion of substrate (or product) through the zeolite pores. Intramolecular selectivities have not yet been determined but will be very interesting in probing the immediate environment of the catalytic site.

Other groups have attached oxidatively robust porphyrins to silica surfaces[111] or incorporated them into layered phosphonates,[112,113] again with very modest alteration of selectivity. Mansuy and coworkers have generated "metalloporphyrinosilicas" by cocondensation of halosilanes with trifluorosilyl-substituted iron porphyrins.[114] The specific areas of these materials are $\approx 60\ m^2/g$. These are efficient catalysts for alkene epoxidation by PhIO or *tert*-BuOOH and alkane hydroxylation by PhIO. Relatively modest shape selectivity for alkenes was observed in some cases.

Also interesting is the work of Mansuy and coworkers on manganese porphyrins intercalated into various layered minerals.[115] The tetracationic 5,10,15,20-methylpyridylporphyrin manganese complexes intercalated into Montmorillonite clay produce an oxidatively robust catalyst that is quite efficient for alkane hydroxylation. It is interesting that there are significant intermolecular selectivities found, for example, in competitive oxidation of adamantane versus *n*-alkanes, but very little intramolecular regioselectivity within a single alkane. This result suggests that diffusion of substrate into the porphyrin site is controlled by the layered mineral, but that the active site near the metalloporphyrin is relatively unconstrained.

Finally, a brief mention will be made of the so-called Gif reaction,[48] which has an expanding repertiore of variations, but basically uses an iron salt, zinc and O_2 in a pyridine/acetic acid suspension to form ketones from nonactivated methylene groups in hydrocarbons. The system does not generally attack either primary or tertiary carbons. Although the selectivity is quite high, it does not appear that this is a case of *shape* selectivity, but must represent an unusual mechanistic requirement. The reaction pathways of this reaction are under continued investigation, and they remain controversial.[116–119] Many unusual speculations have been made concerning the mechanism of the Gif reaction,[45] but it appears most likely that a free radical mechanism involving hydroperoxyl intermediates is responsible for its unusual selectivity.[118]

C. SHAPE SELECTIVITY AS A MECHANISTIC PROBE

The presence and degree of shape selectivity can be used as a mechanistic probe of various porphyrin-catalyzed oxidations. The detailed mechanisms of hydroxylation and of epoxidation are different, and the discussion will be divided accordingly.

The shape-selective hydroxylation of an alkane with various oxidants in the presence of a sterically hindered metal complex can demonstrate whether the hydroxylation reaction occurs at the metal center or in the bulk solution. For example, when iodosylbenzene, pentafluoroiodosylbenzene or *m*-CPBA are used as oxidants with hindered manganese porphyrins, the primary alcohol selectivities are all very similar, which indicates that these three oxidants generate the same catalytically active species at the metal.[66] A high spin d^2, Mn(V)-oxo complex is the generally accepted intermediate.[20,120] For iodosylbenzene oxidations, it had also been suggested that the active hydroxylating agent might be a metalloporphyrin-iodosylbenzene complex.[121] This hypothesis, however, is inconsistent with the constancy of the primary selectivity index observed with iodosylbenzene, pentafluoroiodosylbenzene and *m*-CPBA. μ-Oxo dimer species can also be ruled out as the catalytic species, because these sterically hindered complexes cannot form dimers. Thus, the active oxidant in all likelihood is the terminal oxo complex.

In contrast, while *tert*-butylhydroperoxide acts as an efficient oxidant for alkane hydroxylation, alkane regioselectivity is independent of the steric demands of the manganese porphyrin catalyst. Therefore, with this oxidant, hydroxylation is not taking place at the metal center; rather, it must be due to a free radical chain pathway initiated by the metalloporphyrin. The regioselectivity for *n*-heptane hydroxylation by this radical chain shows little primary product, and the predominant secondary product is at the $\omega - 1$ methylene position similar to radical chlorination.[66]

Shape selectivity is observed for both Mn and Fe porphyrins, indicating that substrate oxidation occurs in close proximity to the metal center. Primary selectivity, however, is diminished for iron relative to manganese porphyrin complexes. The diminution in selectivity must be caused by differences in the steric constraints present during the transition state of H-atom abstraction; in the transition

state more C–H bond breaking is occurring in the Fe system than in the Mn. This conclusion is confirmed by the relative isotope effects observed for Fe (k_H/k_D = 11.5 for P450 and 12.9 for Fe(TPP)Cl with iodosylbenzene)[122] as compared with Mn (k_H/k_D = 3.5).[66] The difference in the transition states reflects inherent electronic differences between the two different oxometalloporphyrin intermediates.

The cost in free energy of the steric contact generated between substrate and metalloporphyrin during hydroxylation can be calculated from the relative rates of 1° versus 2° alcohol production. For TTPPP relative to TPP with either Mn or Fe, this calculated energy is 1.6–1.7 kcal/mol for *both* metal systems during the hydroxylation of *n*-alkanes longer than pentane.

For alkene epoxidation catalyzed by metalloporphyrins, several reaction intermediates have been proposed, as discussed earlier in this chapter (Section II.B). As shown in Figure 7, these include long-lived metallooxetane intermediates, metal-bound radical or carbocation intermediates from electron transfer mechanisms, or direct oxygen atom transfer. In addition, radical autoxidation (mostly at allylic positions) via radical chain pathways can be initiated by metalloporphyrins. The substantial selectivity observed with Mn(TTPPP)(OAc) is essentially independent of oxidant used and is insensitive to the addition of nitrogenous bases.[64,67] These results are consistent with initial oxygen atom transfer from the oxidant to form a monomeric Mn^V=O and demonstrate that epoxidation proceed through very similar transition states for all of these systems. It is interesting that selectivity is not significantly altered by addition of ligands (such as imidazoles). Although these ligands hasten the reaction of the metalloporphyrin with the oxidant in forming the active oxidizing species,[76] surprisingly, they do not significantly alter the geometry or energetics of the transition state.

The Fe(III) complexes of these porphyrins also show shape selectivity for epoxidation, albeit less so than Mn. The transition state for epoxidation by Fe must be less sterically demanding relative to Mn, just as in the case of hydroxylation. This may mean that there is a ring open radical or carbocation intermediate, as expected from an electron transfer mechanism, or simply that there is a less compact transition state in a concerted atom transfer. For epoxidations involving iron porphyrins and peroxyacids, there is a striking solvent dependence on the regioselectivity.[123] Furthermore, for conjugated dienes, the regioselectivity is nearly independent of the steric demands of the metalloporphyrin.[67] Thus, the observed regioselectivities argue that under different conditions several different mechanisms are probably operable, which may help resolve some of the apparent literature conflicts in this area.

Steric constraints have also been used to discriminate between active sites in metalloproteins. Shteinman, for example, has discussed the differences in mechanisms between P450 and soluble methane monooxygenase in terms their putative oxidizing intermediates.[124] He argues that a bridged intermediate bis-μ-oxo-diiron(IV) species, in which both oxygen atoms are derived from the dioxygen molecule in methane monooxygenase would have a stronger steric selectivity for substrates compared to the putative terminal oxenoid species in P450, in keeping with the unusual selectivity observed in alkane oxidation by methane monooxygenase.

D. REGIOSELECTIVITY BASED ON POLARITY

Oxidation of polar substrates directed by the polarity of substituents built into the catalyst structure has been relatively little explored for either heterogeneous or homogeneous systems. For example, the substrate specificity observed in the previously discussed (Section III.B) phospholipid bilayer work of Groves and coworkers is likely to originate from both polarity and shape selectivity.[99] A few examples do exist for polarity selectivity in homogeneous systems.

Ogoshi and coworkers have used a cyclodextrin-sandwiched porphyrin and singlet molecular oxygen to selectively oxidize linoleic acid to the 13-hydroperoxy derivative with a very high degree of regioselectivity.[125] Oxidation with the cyclodextrin porphyrin seems to take place in the pocket. The preference for $\Delta^{12,13}$ oxidation can be explained because that double bond is furthest from the carboxylic acid end. They have also used the iron derivative of the cyclodextrin porphyrin to epoxidize nonpolar alkenes in aqueous solution using iodosylbenzene as the oxygen donor.[126] Yields of epoxide are from 14% for norbornene to 55% for cyclohexene; in contrast, the yield of cyclohexene epoxide using a simple water-soluble iron porphyrin as the catalyst was less than2%. This result can be attributed to the affinities of the hydrophobic substrates for the nonpolar pocket of the cyclodextrin. The high yield of cyclohexene oxide compared with norbornene oxide may reflect the size of the cyclodextrin pocket.

Several groups have used cationic, water-soluble porphyrins as selective oxidants for the cleavage of nucleic acids. The discussion will be brief here, because substantial reviews have been published elsewhere.[127] Tetrakis(*N*-methylpyridinium-4-yl)porphyrinatomanganese(III) [that is, Mn(TMPyP)$^+$] has been used with $KHSO_5$ and KO_2 to cleave supercoiled double-stranded DNA.[128–130] H_2(TMPyP) had been previously shown to have a high affinity for DNA because of to its positive charge.[131] The manner of cleavage is thought to be similar to that of bleomycin-Fe(III), although Mn(TMPyP) is not able to intercalate into DNA.[132] Mn(TMPyP) has been shown to bind in the minor groove of A-T–rich regions of DNA.[133] To enhance DNA binding and cleavage, Meunier and coworkers have used several cationic metalloporphyrin-ellipticine complexes as cleavage agents.[133] The ellipticine moiety intercalates into the DNA near the A-T region where the metalloporphyrin binds, providing a two-pronged hold on the DNA. In a similar fashion, site-specific cleavage reagents based on Mn porphyrins have been developed for both DNA[134] and RNA[135] scissions.

IV. Enantioselective Oxidations

Enantioselective oxidations are not precisely within the purview of this chapter; the topic is examined in greater

detail elsewhere in the literature.[7,136–139] Nonetheless, enantioselective oxidations are intimately related to issues of shape selectivity, so a brief discussion is appropriate here. The increasing importance of enantioselective reactions for the synthesis of pharmaceuticals continues to drive the exploration of chiral epoxidation catalysts.[140] Several systems, based on superstructured porphyrins or *N,N′*-bis (salicylileneamino)ethane(salen) complexes, are proving highly successful for the asymmetric epoxidation of various substrates.[15,136–139]

Groves and coworkers pioneered metalloporphyrin catalysts with chiral pockets and succeeded with the iron(III) complex of the sterically hindered vaulted binapthyl porphyrin (Figure 20) [5α,10β,15α,20β-tetrakis[(S)-2′-(carboxymethyl)-1, 1′-binapthyl-2-carboxyamidophenyl]porphyrin (TBNAPP) to enantioselectively hydroxylate alkanes, epoxidize alkenes, and oxidize sulfides.[141–143] Hydroxylation of a variety of alkyl-substituted aromatics showed enantioselectivities from 40% enantiomeric excess (ee) to 72% *ee* with product yields ranging from 19% to 72%. Enantioselectivities seem to be higher with lower yields. Hydroxylations using Mn(TBNAPP)Cl showed much higher yields, up to 98%, but lower stereoselectivities, 12–26% *ee*, and lower alcohol to ketone ratios relative to Fe(TBNAPP)Cl.[143] From mechanistic studies of stereoselectivity in hydroxylation of pure enantiomers of 1-*d*-ethylbenzene, Groves and Viski concluded that the hydrogen abstraction step controls the stereochemistry of the major hydroxylation product.[142] Groves and coworkers have also examined the origins of chiral induction by NMR T_1 relaxation techniques.[144] A new chiral vaulted porphyrin with (*S*)-binaphthyl-L-alanine straps across both faces of a porphyrin was synthesized and characterized. (*R*)-styrene oxide was obtained in greater than 90% *ee* in the initial stages of styrene epoxidation with this vaulted porphyrin with C_6F_5IO as oxidant. The transition state for olefin epoxidation with high-valent metal-ore species was modeled by coordinating epoxides to paramagnetic copper complexes of the corresponding ligands. The epoxide enantiomer that better fit the chiral cavity of the catalyst, as revealed by T_1 relaxation measurements, was also the major product of catalytic olefin epoxidation. These results are consistent with the "lock-and-key" mechanism of asymmetric catalysis by metalloporphyrins. However, a chiral Cu salen complex showed no differentiation in terms of T_1 relaxation rates between the enantiomers of *cis*-β-methylstyrene oxide in spite of its high enantioselectivity for catalytic epoxidation.[144]

Mansuy *et al.*[145] has used the chloroiron(III) complex of various picket-fence and basket-handle porphyrins (Figure 20) to selectively epoxidize *para*-chlorostyrene with yields of 35–50% and enantioselectivities of 12–50% ee. O'Malley and Kodadek[146] has used the manganese(III) chloride complex of a chiral wall porphyrin (Figure 21), 5α, 10β, 15α, 20β-tetrakis-[(*R*)-1,1′-binapth-2-yl]porphyrin (TBNP) to enantioselectively epoxidize several styrene derivatives. Enantioselectivities for these epoxidations were from 15% *ee*, for *trans*-β-methylstyrene, to 40% ee, for *cis*-β-methylstyrene. No epoxide yields were reported.

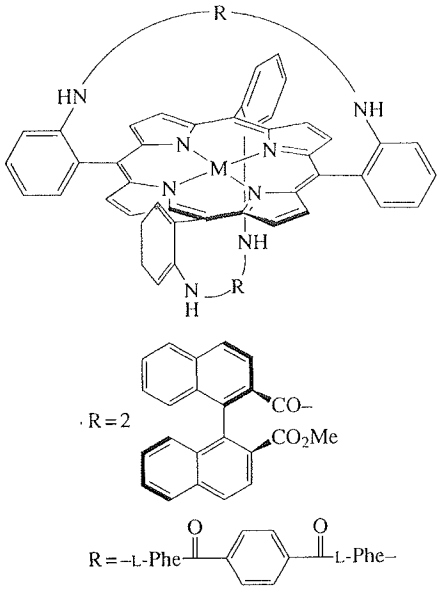


Figure 20. Enantioselective superstructured metalloporphyrins: Groves' vaulted binapthyl porphyrin[141] (upper *R* group) and Mansuy's[145] basket-handle porphyrin (lower *R* group).

Naruta and coworkers[147] have used chloroiron(III) complexes of two twin-coronet porphyrins (Figure 22) as stereoselective epoxidation catalysts. Two possible isomers exist for twin-coronet porphyrins, staggered and eclipsed, which will interact differently with the prochiral substrate. The enantioselectivities of epoxidation of substituted styrenes were from 11% ee, for 4-methylstyrene, to 89% ee, for 2-nitrostyrene. Their results indicate that the twin coronet porphyrin derived from bitetralin is a more selective catalyst than the porphyrin derived from binapthalene because of the added steric bulk of the bitetralin.

Konishi *et al.*[148] have used chloromanganese(III) complexes of chiral-strapped porphyrins to stereoselectively epoxidize alkenes. Unlike the previously discussed chiral porphyrins, which are derivatives of TPP, the strapped porphyrins are derivatives of dihexyldeuteroporphyrin. The stereoselectivities obtained with these porphyrins were from 58% ee for indene oxide to 8% ee for 4-chlorostyrene oxide, using 2-phenylimidazole as the base, with fair to good yields of the epoxides and modest turnover numbers.

Halterman and Jan[149] have prepared a D_4 symmetric porphyrin based on a chiral 5,10,15,20-dimethanoanthracenylporphyrin (Figure 23). With arene-conjugated *cis*-alkenes, good yields of epoxides were obtained with moderate enantioselectivities (41–76% ee). *Trans*-alkanes did not epoxidize well.

Collman and coworkers further developed their PBP series with chiral threitol straps[15,150,151] (Figure 24), complete with X-ray structure of one of the derivatives. This framework is easily modified by the condensation of aldehydes or ketones with the 2,3-diol of the threitol strap, which permits optimization of the chiral pocket for specific substrates. The epoxidation of 1,2-dihydronaphthalene, for example, can be epoxidized in an 88% ee with the Mn derivative of a 1,2-diphenoxyethane-strapped porphyrin. As

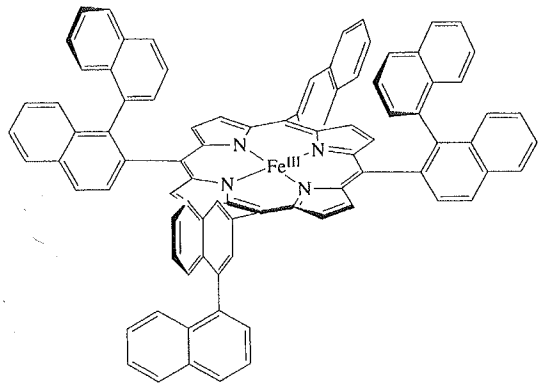


Figure 21. An enantioselective superstructured metalloporphyrin: Kodadek's[146] chiral wall porphyrin. Reproduced with permission from O'Malley, S.; Kodadek, T. *J. Am. Chem. Soc.* **1989**, *111*, 9116 © 1989 American Chemical Society.

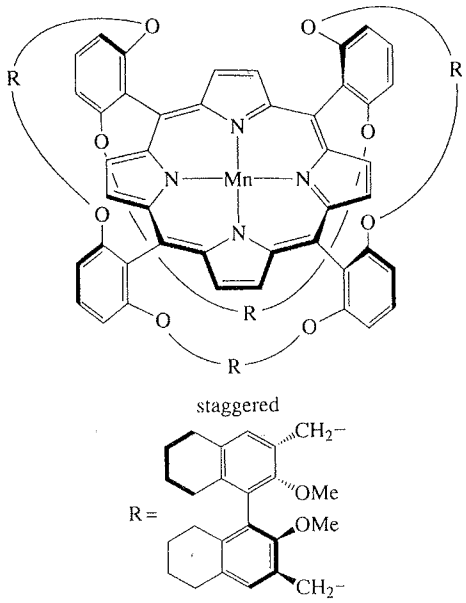


Figure 22. Enantioselective superstructured metalloporphyrins: Naruta's[147] twin-coronet porphyrins. Reproduced with permission from Naruta, Y.; Tani, F.; Ishihara, N.; Maruyama, K. *J. Am. Chem. Soc.* **1991**, *113*, 6865 © 1991 American Chemical Society.

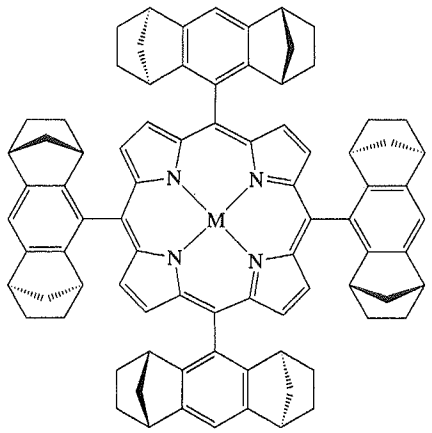


Figure 23. An enantioselective superstructured metalloporphyrin: a D_4 symmetric porphyrin based on a chiral 5,10,15,20-dimethanoanthracenyl porphyrin. Reproduced with permission from Halterman, R. L.; Jan, S.-T. *J. Org. Chem.* **1991**, *56*, 5253.

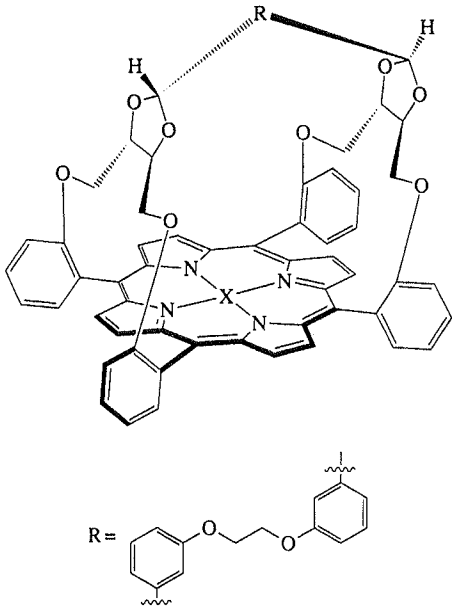


Figure 24. Enantioselective superstructured metalloporphyrins: Collman's picnic-basket porphyrin with chiral threitol straps. Adapted from Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404 © 1993 American Association for the Advancement of Science.

in several other chiral oxidation systems, turnovers are relatively low, and evidence was found for significant hydroxylation of the superstructure after approximately 100 turnovers. Significant differences in enantioselectivities were observed with different oxidants: for example, iodosylbenzene gave the best selectivities frequently with greater than 80% ee, whereas LiOCl or *tert*-BuOOH giving very low selectivities (approximately 10% ee). This may either reflect oxidation of the porphyrin superstructure, possible the participation of a metal-bound oxidant in the epoxidation, or in the case of low ee epoxidation, oxidation from species not bound to the metal.

For metalloporphyrin catalysts, there is one final report of an unusual example of a different class of enantioselective oxidations—carbon-carbon bond cleavage by dioxygen. Ohkubo and coworkers[152] have used chiral manganese porphyrins to catalyze stereoselective cleavage of the carbon-carbon double bond of racemic *N*-acetyltryptophan by dioxygen. Yields of the dioxygenation product are relatively low compared to the percent consumption of substrate, and yields of the other products were not given.

The use of nonporphyrinic tetra-coordinating ligand complexes, usually of salen, has had substantial success because of the high synthetic yields of the catalysts, high product yields and extremely high enantioselectivities. The facile synthesis of salen complexes with a chiral superstructure also provides an easy means to change systematically the catalyst for each class of substrates (Figure 25).

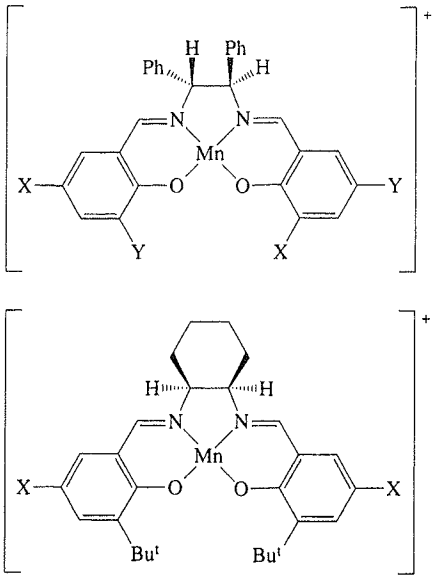


Figure 25. Some enantioselective manganese(III) (*N,N'*-bis(salicylideneamino)ethane) complexes;[136] X = H, CH_3, *tert*-Bu; Y = *tert*-Bu, C*H(Et)(C_6H_5).

The most visible work in this field has been the discoveries by Jacobsen and coworkers of highly enantioselective epoxidation by chiral manganese(III) salen complexes.[136,137,153-159] Katsuki and coworkers have also been active in developing this class of catalysts.[138,160,161] Chiral salen complexes are relatively easily synthesized from substituted ethylenediamines and substituted salicylaldehydes, and there are now more than 100 complexes of this sort that have been tested to various degrees. The most effective of these are derived from chiral *trans*-1,2-diaminocyclohexane. Using inexpensive oxidants (notably sodium hypochlorite solutions), these catalysts are very effective for the chiral epoxidation of conjugated cis-disubstituted and trisubstituted alkenes, and at low temperature, even for terminal alkenes, such as styrene itself. Enantioselectivities are often above 90% ee for otherwise nonfunctionalized *cis*-alkenes. Yields of epoxide generally are above 80%. This work has been extended to the synthesis of chiral *trans*-epoxides from *cis*-alkenes by the simple addition of chiral quaternary amines, but the mechanism for this is unclear at present.[157]

The salen complexes, unfortunately, are not particularly robust, and turnover numbers are typically below 40. Oxidation of the imine groups in the salen complex is the likely source of catalyst degradation. In spite of this, Merck has used one of the Jacobsen catalysts for the synthesis of antihypertensive chromanol derivatives.[140]

Insight into the general mechanism of enantioselectivity has been provided by both the groups of Katsuki[138,161] and of Jacobsen.[137,159] The high enantioselectivities are clearly a consequence of restricting the available approaches of the substrate molecules to the putative metal-oxo intermediate. The most enantioselective catalysts provide only one unhindered (favored) approach for the substrate to reach the metal-oxo center with the other approaches hindered by *tert*-butyl or other sterically restricting groups. Apparently, one must consider $\pi-\pi$ interactions as well, at least in the case of enyne substrates. The stereogenic centers of the salen complexes are much closer to the metal-oxo center than those of porphyrins, which provides for a greater level of interaction with the substrate than in most chiral porphyrin catalysts. Jacobsen and coworkers have found that enantioselectivity in the (salen)Mn-catalyzed asymmetric epoxidation reaction correlates directly with the electronic properties of the ligand substituents, with complexes bearing electron-donating substituents affording highest selectivity.[159] Their conclusion is that enantioselectivity is tied to the position of a transition state along the reaction coordinate, which may hold general implications for the design of asymmetric catalysts, particularly those that effect reactions without substrate binding.

V. Conclusions

A variety of approaches have been developed to create oxidation catalysts that can recognize organic substrates and selectively oxidize specific sites. Sterically hindered metalloporphyrins have proved successful as shape-selective catalysts for hydrocarbon hydroxylation and especially olefin epoxidation. A few catalysts (both homogeneous and heterogeneous) show remarkable enhancements for primary hydroxylation of branched and *n*-alkanes. Such selectivity is unprecedented in non-biological catalysis and often comparable to enzymatic ω-hydroxylase activity. Nonetheless, the absolute level of selectivity for *n*-alkane hydroxylation remains modest. In addition, the turnover rates and catalyst stability for hydroxylation are often relatively low (in both synthetic and enzymatic systems). Clearly, industrial application of this work remains only a future possibility. The situation is distinctly better, however, for regioselective and enantioselective epoxidation.

The presence and degree of shape selectivity is offered as conclusive proof of direct metalloporphyrin involvement during the actual hydroxylation and epoxidation of substrates with some, but not all, oxidants under conditions of homogeneous catalysis. Similar selectivity for both hydroxylation and epoxidation has been observed for several different classes of oxidants, proving metal-based oxidation via a common monomeric intermediate (probably a terminal metal-oxo complex) for these systems.

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REFERENCES

1. *Selectivity in Catalysis*; Davis, M. E.; Suib, S. L., Eds. American Chemical Society: Washington, DC, 1993.
2. *Handbook of Heterogeneous Catalysis*; Ertl, G.; Knozinger, H.; Weitkamp, J., Eds. Wiley & Sons–VCH Publishers: Weinheim, 1997.

3. *Metal Catalyzed Oxidation of Organic Compounds*; Sheldon, R. A.; Kochi, J. A., Eds. Academic Press: New York, 1986.
4. *Activation and Functionalization of Alkanes*; Hill, C. L., Ed. Wiley & Sons: New York, 1989.
5. *Bioinorganic Chemistry*; Bertini, I.; Gray, G. B.; Lippard, S. J.; Valentine, J. S., Eds. University Science Books: Mill Valley, CA, 1994.
6. *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed. Marcel Dekker: New York, 1994.
7. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed. VCH Publishers: New York, 1993.
8. Groves, J. T. *Nature*. **1997**, *389*, 329.
9. *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F.; Eds. Pergamon Press: New York, 1996.
10. Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375.
11. Hill, C. L.; Schardt, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 6374.
12. *Handbook of Chemistry and Physics*, 71st ed.; Lide, D. R., Ed. CRC Press: Boca Raton, 1991; pp 9–95.
13. March, J. In *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed. Wiley–Interscience: New York, 1992; pp 826–828.
14. Suslick, K. S.; Reinert, T. J. *J. Chem. Ed.* **1985**, *62*, 974.
15. Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404.
16. Collman, J. P.; Zhang, X. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Eds.; Pergamon Press: New York, 1996; Vol. 5, pp 1–32.
17. Suslick, K. S.; van Deusen-Jeffries, S. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Eds.; Pergamon: New York, 1996; Vol. 5, pp 141–170.
18. Mansuy, D.; Battioni, P. In *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Marcel Dekker: New York, 1994; pp 99–132.
19. *Cytochrome P450: Structure, Mechanism and Biochemistry, 2nd ed*; Ortiz de Montellano, P. R., Ed.; Plenum Publishing: New York, 1995.
20. Groves, J. T.; Han, Y. Z. In *Cytochrome P450: Structure, Mechanism, and Biochemistry*, 2nd ed.; Ortiz de Montellano, P., Ed. Pergamon Press: New York, 1995; pp 1–45.
21. Sligar, S. G.; Murray, R. I. In *Cytochrome P450: Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Publishing: New York, 1986; pp 429 ff and references therein.
22. Matson. R. S.; Stein, R. A.; Fulco, A. J. *Biochem. Biophys. Res. Commun.* **1980**, *97*, 955.
23. Caron, C.; Mitscher, A.; Riviere, G.; Ricard, L.; Schappacher, M.; Weiss, R. *J. Am. Chem. Soc.* **1979**, *101*, 7401.
24. McKenna, E. J.; Coon, M. J. *J. Biol. Chem.* **1970**, *245*, 3882.
25. Jefcoate, C. F. In *Cytochrome P450: Structure, Mechanism, and Biochemistry*; Ortiz de Montellano, P. R. Ed.; Plenum Publishing: New York, 1986; p 387.
26. Kappeli, O. *Microbiol. Rev.* **1986**, *50*, 244.
27. Fitzpatrick, F. A.; Murphy, R. C. *Pharmacol. Rev.* **1989**, *40*, 229.
28. *Fatty Acid Metabolism and Its Regulation*; Numa, S., Ed.; Elsevier Biomedical: Amsterdam, 1984.
29. Poulos, T. L.; Finzel, B. C.; Howard, A. J. *Biochemistry* **1986**, *25*, 5314.
30. Atkins, W. H.; Sligar, S. G. *J. Am. Chem. Soc.* **1989**, *111*, 2715.
31. Fowler, S. M.; England, P. A.; Westlake, A. C. G.; Rouch, D. R.; Nickerson, D. P.; Blunt, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2761.
32. Ruettinger, R. T.; Fulco, A. J. *J. Biol. Chem.* **1981**, *256*, 5728.
33. Miura, Y.; Fulco, A. J. *Biochim. Biophys. Acta* **1975**, *388*, 305.
34. Mize, C. E.; Steinberg, D.; Avigan, J.; Falls, H. M. *Biochem. Biophys. Res. Commun.* **1966**, *25*, 359.
35. Akanuma, H.; Kisimoto, Y. *J. Biol. Chem.* **1979**, *254*, 1050.
36. Dierks, E. A.; Zhang, Z. P.; Johnson, E. F.; Ortiz de Montellano, P. R. *J. Biol. Chem.* **1998**, *273*, 23055.
37. Faulkner, K. M.; Shet, M. S.; Fisher, C. W.; Estabrook, R. W. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 7705.
38. Soliday, C. M.; Kolattukudy, P. E. *Arch. Biochem. Biophys.* **1978**, *188*, 338.
39. Koerts, J.; Verlaeds, M. C.; Soffers, A. E. M. F.; Vervoort, J.; Rietjens, I. M. C. M. *Chem. Res. Toxicol.* **1997**, *10*, 279-288.
40. Sligar, S. G.; Kellner, D. G.; Maves, S. A. *Curr. Opin. Biotechnol.* **1997**, *8*, 274.
41. Aikens, J.; Sligar, S. G. *J. Am. Chem. Soc.* **1994**, *116*, 1143.
42. Vidakovic, M.; Sligar, S. G.; Li, H. Y.; Poulos, T. L. *Biochemistry* **1998**, *37*, 9211.
43. Gelb, M. H.; Heimbrook, D. C.; Malkonen, P.; Sligar, S. G. *Biochemistry* **1982**, *21*, 370.
44. Collman, J. P.; Chien, A. S.; Eberspacher, T.A.; Brauman J. I. *J. Am. Chem. Soc.* **1998**, *120*, 425.
45. Barton, D. H. R. *J. Mol. Catal. A, Chem.* **1997**, *117*, 3.
46. Traylor, T. G.; Kim, C.; Richards, J. L.; Xu, F.; Perrin, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 3468.
47. Ostovic, D.; He, G.-X.; Bruice, T. C. In *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Marcel Dekker: New York, 1994; pp 29–68.
48. Mirafzal, G. A.; Kim, T.; Liu, J.; Bauld, N. L. *J. Am. Chem. Soc.* **1992**, *114*, 10968.
49. Ostovic, D.; Bruice, T. C. *Acc. Chem. Res.* **1992**, *25*, 314.
50. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.
51. Traylor, T. G.; Mikszal, A. R. *J. Am. Chem. Soc.* **1989**, *111*, 7443.
52. He, G.-X.; Mei, H.-Y.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 5644.
53. Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
54. Bruice, T. C. *Acc. Chem. Res.* **1991**, *24*, 243.
55. Srinivason, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.
56. Busch, D. H. In *Transition metals in Supramolecular Chemistry (NATO ASI Ser. C 448)*; Fabbrizzi, L.; Poggi, A., Eds.; Kluwer Academic Publishers: Dordrecht, 1994; pp 55–80.
57. Rawn, J. D. *Proteins, Energy, and Metabolism*; Neil Patterson: Burlington, 1989; p 622.
58. Traylor, P. S.; Dolphin, D.; Traylor, T. G. *J. Chem. Soc., Chem. Commun.* **1984**, 279.
59. Nappa, M. J.; Tolman, C. A. *Inorg. Chem.* **1985**, *24*, 4711.
60. Traylor, T. G.; Byun, Y. S.; Traylor, P. S.; Battioni, P.; Mansuy, D. *J. Am. Chem. Soc.* **1991**, *113*, 7821.
61. Ellis, P. E., Jr.; Lyons, J. E. *Coord. Chem. Rev.* **1990**, *105*, 181.
62. Hoffman, P.; Labat, G.; Robert, A.; Meunier, B. *Tetrahedron Lett.* **1991**, *31*, 1991.
63. Suslick, K. S. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley & Sons: New York, 1989; pp 219–241.
64. Suslick, K. S.; Cook, B. R. In *Inclusion Phenomena and Molecular Recognition*; Atwood, J., Ed.; Plenum Publishing: New York, 1990; pp 209–215.
65. Suslick, K.; Cook, B.; Fox, M. *J. Chem. Soc., Chem. Commun.* **1985**, 580.
66. Cook, B. R.; Reinert, T. J.; Suslick, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7281.
67. Suslick, K. S.; Cook, B. R. *J. Chem. Soc., Chem. Commun.* **1987**, 200.
68. Mansuy, D.; Bartoli, J.-F.; Momenteau, M. *Tetrahedron Lett.* **1982**, *23*, 2781.
69. Khenkin, A.; Shteinman, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1219.

70. Khenkin, A.; Koifman, O.; Semeikin, A.; Shilov, A.; Shteinman, A. *Tetrahedron Lett.* **1985**, *26*, 4247.
71. Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338.
72. Tolman, C. A.; Druliner, J. D.; Nappa, M. J.; Herron, N. In *Activation and Functionalization of Alkanes*; Hill, C. L., Ed.; Wiley & Sons: New York, 1989; pp 303–360.
73. Traylor, T. G.; Nakano, T.; Dunlap, B. E.; Traylor, P. S.; Dolphin, D. *J. Am. Chem. Soc.* **1986**, *108*, 2782.
74. De Carvalho, M. E.; Meunier, B. *New J. Chem.* **1986**, *10*, 223.
75. Lindsay Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1009.
76. Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000.
77. Ahn, K.-H.; Groves, J. T. *Bull. Korean Chem. Soc.* **1994**, *15*, 957.
78. Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.
79. Szabo, W. A.; Lee, H. T. *Aldrichimica Acta* **1980**, *13*, 13.
80. Collman, J. P.; Zhang, X.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 5356.
81. Collman, J. P.; Zhang, Z.; Lee, V.; Hembre, R. T.; Brauman, J. I. In *Homogeneous Transition Metal Catalyzed Reactions*; American Chemical Society: Washington, DC, 1992; pp 153–62.
82. Bhyrappa, P.; Young, J. K.; Moore, J. S.; Suslick, K. S. *J. Mol. Catal. A* **1996**, *113*, 109.
83. Bhyrappa, P.; Young, J. K.; Moore, J. S.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5708; and unpublished work.
84. Bhyrappa, P.; Vaijayanthimala, G.; Suslick, K. S. *J. Am. Chem. Soc.*, **1999**, *121*, 262.
85. Marchon, J. C.; Ramasseul, R. *J. Chem. Soc., Chem. Commun.* **1988**, 298.
86. Marchon, J. C.; Ramasseul, R. *J. Mol. Catal.* **1989**, *51*, 29.
87. Marchon, J. C.; Ramasseul, R. *Synthesis* **1989**, 389.
88. Tavares, M.; Ramasseul, R.; Marchon, J. C. *Catal. Lett.* **1990**, *4*, 163.
89. Tavares, M.; Ramasseul, R.; Marchon, J. C.; Valleegoyet, D.; Gramain, J. C. *J. Chem. Res.-S.* **1994**, 74.
90. Ohtake, H.; Higuchi, T.; Hirobe, M. *Heterocycles* **1995**, *40*, 867.
91. Ellin, A.; Orrenius, S. *Mol. Cell Biochem.* **1975**, *8*, 69.
92. Frommer, U.; Ullrich, V.; Standinder, H.; Orrenius, S. *Biochim. Biophys. Acta* **1972**, *280*, 487.
93. Morohashi, K.; Sadano, H.; Okada, Y.; Omura, T. *J. Biochem.* **1983**, *93*, 413.
94. Karasevich, E. I. and Khenkin, A. M. *Biokhimiya* **1986**, *51*, 1454.
95. *Assessment of the Use of Single Cytochrome P450 Enzymes in Drug Research*; Waterman, M. R., Hildebrand, M., Eds. Springer-Verlag: New York, 1994.
96. Sorokin, A. B.; Khenkin, A. M.; Marąkushev, S. A.; Shilov, A. E.; Shteinman, A. A. *Dokl. Akad. Nauk. SSSR* **1984**, *279*, 939.
97. Tsuchida, E.; Kaneko, M.; Nishide, H.; Hoshino, M. *J. Phys. Chem.* **1986**, *90*, 2283.
98. Gosling, P. A.; Klein Gebbink, R. J. M.; Schenning, A. P. H. J.; Feiters, M. C.; Nolte, R. J. M. In *Transition Metals in Supramolecular Chemistry (NATO ASI Ser. C 448)*; Fabbrizzi, L.; Poggi, A., Eds.; Kluwer Academic: Dordrecht, 1994; pp 291–308.
99. Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1989**, *111*, 2900.
100. Ungashe, S. B.; Groves, J. T. *Adv. Inorg. Biochem.* **1993**, *9*, 318.
101. Neumann, R. *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A* **1994**, *240*, 33–37.
102. Herron, N.; Stucky, G. D.; Tolman, C. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1521.
103. Herron, N. *J. Coord. Chem.* **1988**, *19*, 25.
104. Tolman, C. A.; Herron, N. *J. Am. Chem. Soc.* **1987**, *109*, 2837.
105. Chang, C. D.; Hellring, S. D. Shape Selective Catalytic Oxidation of Phenol U.S. Patent 4,578,521, 1986.
106. Dessau, R. M. *J. Catal.* **1982**, *77*, 304.
107. Tatsumi, T.; Nakamura, M.; Negishi, S.; Tominaga, H. *J. Chem. Soc., Chem. Commun.* **1990**, 476.
108. Tatsumi, T.; Nakamura, M.; Yuasa, K.; Tominaga, H. *Catal. Lett.* **1991**, *10*, 259.
109. Parton, R. F.; Vankelecom, I. F. J.; Casselman, M. J. A.; Bezoukhanova, C. P.; Uytterhoeven, J. B.; Jacobs, P. A. *Nature* **1994**, *370*, 541.
110. Balkus, Jr., K. J.; Eissa, M.; Levado, R. *J. Am. Chem. Soc.* **1995**, *117*, 10753.
111. Gilmartin, C.; Lindsay Smith, J. R. *J. Chem. Soc., Perkin Trans. 2* **1995**, 243.
112. Deniaud, D.; Schollorn, B.; Mansuy, D.; Rouxel, J.; Battioni, P.; Bujoli, B. *Chem. Mater.* **1995**, *7*, 995.
113. Deniaud, D.; Spyroulias, G. A.; Bartoli, J. F.; Battioni, P.; Mansuy, D.; Pinel, C.; Odobel, F.; Bujoli, B. *New J. Chem.* **1998**, *22*, 901.
114. Battioni, P.; Cardin, E.; Louloudi, M.; Schollhorn, B.; Spyroulias, G. A.; Mansuy, D.; Traylor, T. G.; *J. Chem. Soc., Chem. Commun.* **1996**, 2037.
115. Barloy, L.; Lallier, J. P.; Battioni, P.; Mansuy, D.; Piffard, Y.; Tournoux, M.; Valim, J. B.; Jones, W. *New J. Chem.* **1992**, *16*, 71.
116. Bardin, C.; Barton, D. H. R.; Hu, B.; Rojaswahl, R.; Taylor D. K. *Tetrahedron Lett.* **1994**, *35*, 5805.
117. Minisci, F. Fontana, F. *Tetrahedron Lett.* **1994**, *35*, 1427.
118. Barton, D. H. R.; Hill, D. R. *Tetrahedron Lett.* **1994**, *35*, 1431.
119. Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226.
120. Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.*, **1987**, *109*, 3812.
121. Birchall, T.; Smegal, J. A.; Hill, C. L. *Inorg. Chem.* **1984**, *23*, 1910.
122. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243.
123. Watanabe, Y.; Yamaguchi, K.; Morishima, I.; Takehira, K.; Shimizu, M.; Hayakawa, T.; Orita, H. *Inorg. Chem.* **1991**, *30*, 2581.
124. Shteinman, A. A. *J. Biol. Inorg. Chem.* **1998**, *3*, 325–330.
125. Kuroda, Y.; Sera, T.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 2793.
126. Kuroda, Y.; Hiroshige, T.; Ogoshi, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1594.
127. Murakami, Y., Vol. Ed. *Comprehensive Supramolecular Chemistry; Vol. 4, Bioorganic Systems*; Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D.; Vögtle, F., Eds; Pergamon Press: New York, 1996.
128. Pratviel, G.; Bernadou, J.; Ricci, M.; Meunier, B. *Biochem. Biophys. Res. Commun.* **1989**, *160*, 1212.
129. Fouquet, E.; Pratviel, G.; Bernardou, J.; Meunier, B. *J. Chem. Soc., Chem. Commun.* **1987**, 1169.
130. Raner, G.; Goodisman, J.; Drabrowiak, J. C. In *Metal-DNA Chemistry*; Tullius, T. D., Ed.; American Chemical Society: Washington, DC, 1989; p 74 ff.
131. Praseuth, D.; Gaudemer, A.; Verlac, J.-B.; Kralic, I.; Sissoeff, I.; Guille, E. *Photochem. Photobiol.* **1986**, *44*, 717.
132. Ward, B.; Skorobogaty, A.; Dabrowiak, J. C. *Biochemistry* **1986**, *25*, 7827.
133. Ding, L.; Etemad-Moghadam, G.; Cros, S.; Auclair, C.; Meunier, B. *J. Med. Chem.* **1991**, *34*, 900.
134. Groves, J. T.; Marla, S. S. *J. Am. Chem. Soc.* **1995**, *117*, 9578.
135. Duarte, V.; Sixou, S.; Meunier, B. *J.C.S. Dalton Trans.* **1997**, 4113.
136. Jacobsen, E. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 159–202.
137. Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W.; Hegedus, L.S., Eds.; Pergamon Press: NY, 1995; Vol. 12, pp 1097–1135.
138. Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189.
139. Naruta, Y. In *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Marcel Dekker: New York, 1994; pp 241–260.
140. Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479.
141. Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.