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METALLOPORPHYRINS AS MODELS FOR THE CYTOCHROMES P-450

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CONTENTS

A. THE CYTOCHROMES P-450

The P-450 cytochromes are ubiquitous membrane bound mono-oxygenase enzymes that homogeneously catalyse oxygen atom transfer to entrapped non-polar substrates. The binding of carbon monoxide to the enzyme produces a split in the 420 nm Soret band to yield bands at 364 and 450 nm [1,2]. The absorption at 450 nm distinguishes the haemoprotein from all others and so provides its name [3]. More recently, it has been established that dioxygen binding effects similar spectral changes [4]. In fact, these enzymes are not cytochromes as their main function is oxygen atom transfer rather than electron transport.

The catalyst reductively activates dioxygen by using NADPH as an electron source. One oxygen atom is then reduced to water and the other atom is transferred to a substrate, resulting in the hydroxylation of alkanes and arenes, the epoxidation of alkenes and the formation of *N*-oxides and *S*-oxides from amino and sulphur compounds. Other P-450 reactions include *N*-dealkylation, *O*-dealkylation and reductase-like dehalogenation of halocarbons. These reactions [5] are summarized in Table 1. The enzyme is also

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TABLE 1
Typical P-450 reactions [5]

Reaction type	Simplified example	Typical substrate
Aliphatic hydroxylation	Cyclohexane → cyclohexanol	Pentobarbital
Aromatic hydroxylation	Benzene → phenol	Phenobarbital
Alkene epoxidation	Cyclohexene → cyclohexene oxide	Aldrin
N-Dealkylation	$CH_3N(H)CH_3 \rightarrow CH_3NH_2 + H_2C{=}O$	Methadone
O-Dealkylation	$C_6H_5OCH_3 \rightarrow C_6H_5OH + H_2C{=}O$	Codeine
Oxidative deamination	$(CH_3)_2CHNH_2 \rightarrow (CH_3)_2C{=}O + NH_3$	Amphetamine
S-Oxidation	$CH_3SCH_3 \rightarrow (CH_3)_2S{=}O$	Chlorpromazine
Reductive dehalognation	$C_6H_5CH_2Br \rightarrow C_6H_5CH_3$	Halothane

responsible for oxidative cleavage of carbon–carbon bonds in the biosynthesis of certain steroids. Cytochrome P-450 enzymes have been isolated from a variety of mammalian tissues, insects, plants, yeasts and bacteria. Mammal sources include the liver, kidney, lung, nasal membrane, brain, intestinal mucosa, bladder, testis, adrenal cortex, aorta and blood platelets [6]. The liver contains the greatest concentration of P-450 cytochromes.

Substrates processed by P-450 include endogenous compounds such as steroids, fatty acids, leukotrienes and prostaglandins, as well as exogenous drugs, pesticides, anaesthetics, solvents and chemical carcinogens. These substrates are rendered partially water soluble for further metabolism or excretion. In contrast to its beneficial roles in biosynthesis, metabolism and detoxification, cytochrome P-450 may be the initiator of many chemical carcinogens. The epoxide produced from vinyl chloride by hepatic P-450 has been shown to cause tumours, and benzpyrene, found in charred or burned organic material (e.g. cigarette smoke), is oxidized in the lung to a highly carcinogenic diol-epoxide [6,7]. Carcinogenesis may also be a consequence of the escape of free radicals generated in the catalytic cycle. The reductive anaerobic and oxidative metabolism of halothane produces metabolites that are responsible for the renal and hepatic toxicity of this widely used anaesthetic [34].

Multiple forms or isoenzymes of P-450 have been discovered, each having a slightly different reactivity and substrate selectivity [8]. Microsomal P-450 isoenzymes display broad and overlapping substrate specificity, while mitochondrial and bacterial P-450 cytochromes are generally more specific [6].

Substrates themselves can initiate the production of specific isoenzymes. The high incidence of liver cancer amongst alcoholics has been attributed to increased levels of the ethanol-inducible cytochrome P-450$_j$ and variations in drug tolerance across a population may arise from different levels of the appropriate P-450 enzyme (genetic, sex, age and environment-related polymorphism [9,10]). Polymorphism in a cigarette smoke-inducible isoenzyme may explain variations in lung cancer risk.

The most extensively studied mammalian P-450 has been the phenobarbitol-inducible form from rabbit liver, P-450$_{LM2}$. However, the bacterial camphor-hydroxylating enzyme from *Pseudomonas putida* was the first P-450 to be purified and crystal structures have recently been reported [11–13] for the resting and substrate bound states of P-450$_{cam}$. Cytochrome P-450$_{cam}$ is an asymmetrically shaped haemoprotein resembling a triangular prism that is about 30 Å thick with a maximum dimension of around 60 Å. The structure is dominated by 12 helical segments that are arranged in three layers stacked one on top of the other with a protoporphyrin IX haem sandwiched between. The helical topography of the protein is very similar to that found in globins and cytochrome c peroxidase [14]. The camphor binding site is lined with hydrophobic residues and the substrate is buried about 4 Å from the porphyrin plane, directly adjacent to the O_2 binding site (see Figs. 1–3). A reversible cap admits and protects the substrate from the external milieu. The iron porphyrin is a nearly independent entity, as it is in other haemoproteins, that

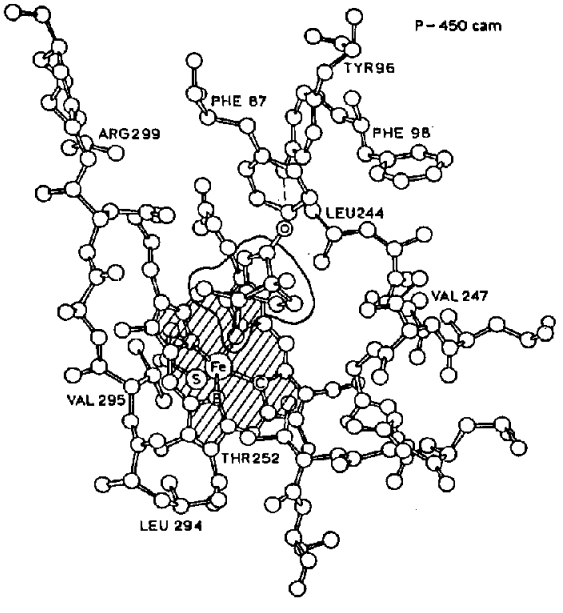


Fig. 1. Crystal structure of P-450$_{cam}$ reaction site [149]. Reproduced with permission.

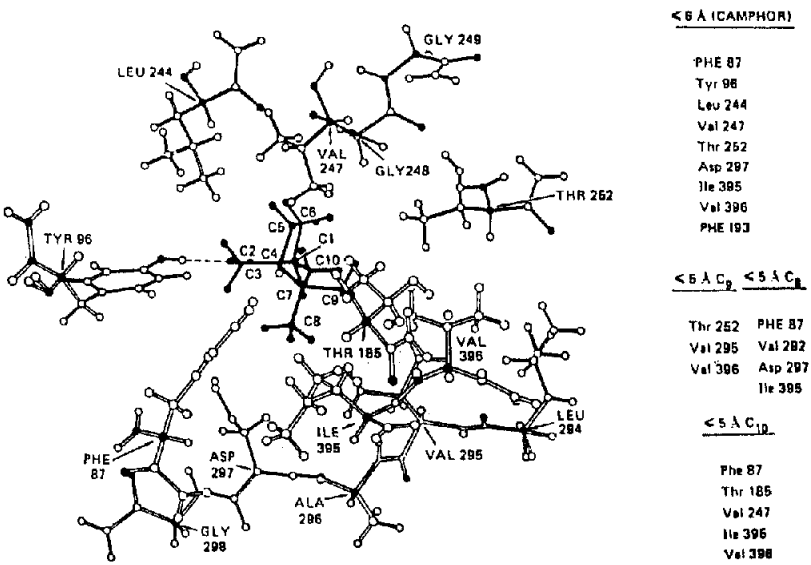


Fig. 2. P-450$_{cam}$ binding site crystal structure [36]. Reproduced with permission.

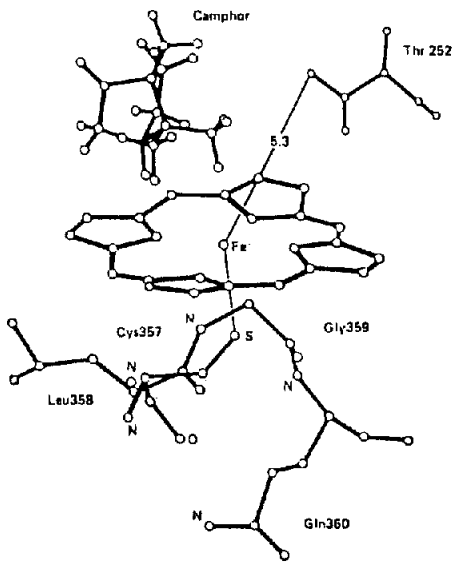


Fig. 3. Cutaway of P-450$_{cam}$ reaction site crystal structure [36]. Reproduced with permission.

is attached to the protein by a single amino acid cysteine residue. The sulphur atom of this residue is in close contact with the backbone oxygen and nitrogen atoms of a contiguous helical tetrapetide sequence. Electron density maps of the substrate-free enzyme indicate a network of five water molecules in the

substrate binding site, one of which is close enough to the iron to be a second axial ligand. The network of water molecules is maintained by hydrogen bonding that imparts a significant hydroxide-like character to the ligated water molecule.

Sequencing studies using recombinant DNA techniques have revealed large homologous regions among the P-450 proteins [36]. The structure of the active site and the reaction cycle are now believed to be the same in all P-450 cytochromes, both eukaryotic and prokaryotic [14]. Recombinant DNA methods have also been used to synthesize the protein in an active form and consequently the enzyme has become a candidate for modification through site-specific mutagenesis. Such techniques have revealed an active site feature essential for efficient reduction and activation of dioxygen [15]. A deformation in a long proximal α-helix vitally controls the juxtaposition of oxygen and substrate. The helix also assists in the maintenance of the network of water molecules in the oxygen binding pocket. Site-directed mutagenesis has also been used to manipulate the regiospecificity of the hydroxylation of several bicyclic substrates [16]. A single mutation is sufficient to convert the specificity of $P\text{-}450_{coh}$ from coumarin to steroid hydroxylation [17].

The pictorial representation of the reaction cycle shown in Fig. 4 is taken from a 1987 paper by Mansuy [18]. In its resting state, P-450 is in equilibrium between a hexacoordinate low-spin Fe(III) complex and a high-spin pentacoordinate Fe(III) complex. On substrate binding, the equilibrium shifts to favour the high-spin pentacoordinate state as the hydroxy-like water ligand

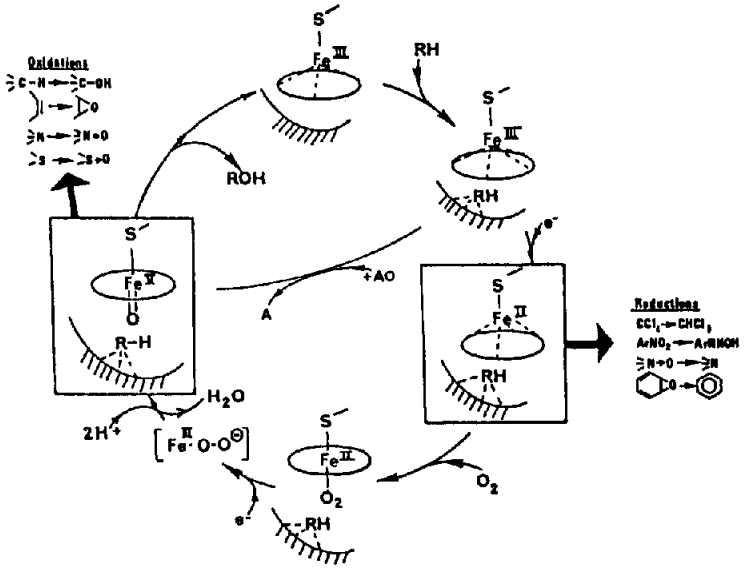


Fig. 4. P-450 reaction cycle [18]. Reproduced with permission.

is displaced. The change of spin state facilitates the uptake of an electron, and subsequent dioxygen binding forms a stable low-spin hexacoordinate intermediate. A second electron is then taken and heterolytic cleavage liberates water to form an active oxoiron intermediate that is responsible for the rate-limiting step of substrate oxidation and product release. As Mansuy points out, crystal structures have been reported for iron porphyrin models of the first four intermediates in the reaction cycle. The reactive oxo intermediate is the least understood component of the oxidation process.

The diagram indicates that P-450 can behave as a reductase and it also suggests that molecules bearing reductively activated oxygen can provide a shunt in the reaction cycle and eliminate the need for NADPH. Such oxygen sources include alkyl hydroperoxides, peracids, periodate, hypochlorite, hydrogen peroxide, amine oxides and iodosoarenes. The P-450 cytochromes, under appropriate conditions, can in fact function as peroxygenase, peroxidase, catalase and chloroperoxidase enzymes, all of which have the same protoporphyrin IX prosthetic group, as do the globins. Peroxidase enzymes catalyse substrate oxidation at the expense of peroxide reduction, but without oxygen transfer to the substrate (eqn. (1)). In contrast, peroxygenases do transfer oxygen, but with homolytic O–O cleavage rather than the heterocleavage of peroxidase (eqn. (2)).

$$RH_2 + XOOH \rightarrow R + XOH + H_2O \quad (1)$$

$$RH + XOOH \rightarrow ROH + XOH \quad (2)$$

Catalase is related to peroxidase in that it catalyses the reduction of peroxide and its function is the dismutation of hydrogen peroxide to dioxygen and water. The chloroperoxidase enzymes catalyse the peroxidase-dependent halogenation of organic substrates.

The thiolate axial ligand and non-polar binding site are central to the unique and diverse character of the P-450 cytochromes. Access to the binding site is substrate-selective and the site itself maintains stereo- and regioselectivity. In 1976, Dawson et al. [19] suggested that the relatively polarizable thiolate ligand might push electron density onto the *trans* position of the active catalyst, thereby weakening the O–O bond and facilitating its heterolytic cleavage and the formation of a reactive oxoiron intermediate. Four years later, White and Coon [20] suggested that the axial ligand could also enhance homolytic cleavage and this has led to the macromolecular anthropomorphism that "DNA may be selfish, but P-450 appears to be schizophrenic". Evidence in support of the release of electron density through the iron atom into the *trans* ligand is discussed in the 1987 review by Dawson and Sono [5]. The authors point to the greater *trans* electron density of P-450 when compared with the histidine imidazole-coordinated myoglobin, and

this is reflected in the lower reduction potential of the P-450 Fe(III)/Fe(II) couple.

The binding site of the globins is similar to that of P-450 and so lacks the acid/base residues of histidine and arginine that the peroxidases and catalases employ in charge-stabilizing the heterolytic rupture of the RO–OH bond. So with a histidine ligand and a non-polar reaction cavity, globins cannot stabilize the charge separation required for heterolytic fission, a fission that would, of course, undermine the principle function of these haemoproteins. On the other hand, the chloroperoxidase enzymes have a thiolate ligand in common with P-450, but differ in having a peroxidase-like binding site.

The high reactivity of the active oxidant of P-450 has precluded its isolation and definitive characterization. In fact Dawson and Sono [5] point out that no compelling evidence has yet appeared to show that intermediates beyond oxy-P-450 actually participate in the catalytic cycle. However, it is generally accepted that a ferryl or oxenoid Fe(IV) porphyrin π cation radical is ultimately responsible for the oxygen atom transfer and this intermediate is designated P-450-I. The peroxidases and catalases form stable intermediates that have been extensively studied [21]. Horseradish peroxidase (HRP) reacts with hydrogen peroxide to form a 2-electron oxidized complex which is designated as compound I or HRP-I:

$$\mathrm{HRP} + \mathrm{H_2O_2} = \mathrm{HRP\text{-}I} + \mathrm{H_2O} \tag{3}$$

$$\mathrm{HRP\text{-}I} + \mathrm{AH_2} = \mathrm{HRP\text{-}II} + \mathrm{AH}\cdot \tag{4}$$

$$\mathrm{HRP\text{-}II} + \mathrm{AH}\cdot = \mathrm{HRP} + \mathrm{A} + \mathrm{H_2O} \tag{5}$$

Compound I has been definitively characterized as an oxoiron(IV)porphyrin π radical cation [22,23] and the one-electron reduced derivative, Compound II is a neutral oxoiron(IV) complex. The discovery that P-450 exhibits peroxidase activity has encouraged the belief that the two enzymes have analogous reaction cycles that utilize similar intermediates. Iron porphyrin model compounds that are capable of substrate hydroxylation or epoxidation have supported this analogy. There is now compelling evidence that a compound I-type intermediate plays a fundamental role in oxidations catalysed by iron porphyrin model compounds [21].

However, it would appear that the peroxidase–cytochrome P-450 analogy has been exaggerated for historical reasons [24]. Largely, this has been due to poorly matched comparisons of the peroxidase activity of the two enzymes. Further, the peroxidases are not effective catalysts of substrate hydroxylation or epoxidation and the products of peroxidase-catalysed reactions are largely determined by the solution chemistry of the initial single-electron oxidation product. Electron transfer occurs on the enzyme, but the subsequent reactions of the electron-deficient substrate derivative occur in solution. The reactivity

of thiolate ligands has, to date, prevented their use in functional iron porphyrin model compounds. The model compounds that are able to hydroxylate and epoxidize substrates efficiently are porphyrin derivatives with substituted aryl *meso* residues that protect this vulnerable position from reactions that become possible upon formation of a porphyrin π cation radical (the models are discussed in subsequent sections). The protection of the *meso* positions that is built into the catalytically competent model compounds is not available to the peroxidases or to the cytochromes P-450 (however, the substrate binding site of P-450 proteins would prevent electron transfer occurring at the porphyrin periphery).

The thiolate axial ligand is essential to the physical and functional character of the P-450 cytochromes. Removal of the cysteinate ligand results in both the loss of the unique spectral properties and of the mono-oxygenase activity of the haemoprotein [25]. In 1980, Ullrich [26] described a P-450-dependent intramolecular rearrangement of nitromethane to formaldehyde for which the thiolate ligand was found to be essential. Consequently, he proposed that the thiolate ligand was uniquely able to stabilize the active oxygenase catalyst by preventing the formation of a porphyrin π cation radical. The IEH calculations of Hanson et al. [1,27,28] and the IEH, MNDO, MINDO and INDO model calculations of Loew et al. [29–36] have provided considerable insight into the role of the thiolate axial ligand. These calculations have established their credibility by providing quantitative simulations of the electronic spectra of carboxy [27] and oxy-P-450 [29] and accurately describing the experimentally characterized HRP-I [33,37,38] and HRP-II [37] compounds. Loew et al.'s [36] modelling of substrate binding site interactions and their consequences for product distributions has resulted in the re-evaluation of published experimental results. It seems that the thiolate ligand is unique in having valence orbitals of sufficient energy to mix with the equatorial ligand system, and as a consequence of this the orbitals of a bound oxygen atom or molecule also mix with the equatorial ligand orbitals. Mixing of the axial and equatorial ligand orbitals does not occur in the imidazole (histidine) or thiol coordinated complexes.

The calculations show that the unusual electronic spectra of the carbon monoxide or dioxygen-bound ferrous state of the enzyme arise from extensive mixing of anionic sulphur p_z orbital with the bonding porphyrin a_{2u} π orbital. Differences in the oxy and carbonyl P-450 complexes arise from the fact that electron transfer to the O_2 ligand is greater than to the CO ligand, thereby resulting in a d^5 low-spin iron configuration in the oxy complex and a d^6 low-spin configuration in the carbonyl complex. An admixture of O π^* and $d\pi^*$ orbitals splits the degenerate porphyrin e_g^* LUMO orbitals to give a low-lying virtual orbital with significant oxygen character that is not found in the carboxy complex. A description of the formally diamagnetic oxy P-450

complex was obtained with an electron distribution corresponding to an Fe(III,d^5)–O_2^- configuration. Addition of the second electron changes the spin state to a quartet or sextet as the electron is placed on the macrocycle, with one and possibly two unpaired electrons then being in the $e_g(\pi)^*$ orbitals. Protonation was found to weaken the O–O bond, making it more easily cleaved with the loss of OH^- or water.

Loew et al. [33,36] have contrasted imidazole and thiolate ligation to a model HRP-1-type complex. The calculations again show that the sulphur ligand induces mixing of the equatorial and axial ligand orbitals and this is apparent in the very different characters of the two intermediate types. The oxygen atom of HRP-I carries a partial spin and a full negative charge and the complex is characterized as an Fe(IV)=O porphyrin $a_{2u}(\pi)$ cation radical with a quartet spin state ($S=3/2$). In sharp contrast, P-450-I is an Fe(IV, $S=1$)–O· quartet oxy radical complex having little unpaired spin on the macrocycle and only a partial negative charge on the oxygen atom. Loew et al. interpret the electrophilic reactivity of P-450-I as a consequence of overlap control driven by a low-lying acceptor orbital with significant oxygen character. The calculations show that the Fe–O bond of P-450-I is longer and weaker than in HRP-I and the metal ion of P-450-I lies below the porphyrin plane, towards the cysteine ligand (as was found in the crystal structures), whereas the metal is located in the porphyrin plane of HRP-I.

The mechanism of the P-450 reactions has been studied by using molecular probes. The hydroxylation of saturated methylene units is accompanied by epimerization and a large isotope effect, $k_H/k_D = 10–12$. This was first observed in the hydroxylation of *exo-exo-exo-exo*-tetradeuterionorbornane by $P\text{-}450_{LM}$. Hydroxylation of selectively deuterated cyclohexenes occurs with allylic scrambling. These observations are depicted in Fig. 5, which is taken from a recent review by Groves and McMurray [21]. It is interesting to note that the large isotope effect has led to the suggestion that tunneling may contribute to the effect, although this has recently been countered [39] by the separation of primary and secondary isotope effects.

The results of the molecular probe studies strongly suggest that oxidation proceeds with preferential hydrogen abstraction by the oxoiron intermediate, followed by scrambling or epimerization of the caged alkyl radical and subsequent radical recombination. Loew et al. [35] proposed a similar mechanism based on INDO calculations that also described epoxidation as an asymmetric addition to the double bond in a two-step radical reaction (Fig. 6). Riley and Hanzlik [40] suggested, in 1989, that the P-450 cytochromes might be able to effect benzylic oxidation through a single electron abstraction.

While there is a general acceptance of the hydroxylation mechanism, the details of the P-450 epoxidation mechanism have yet to be resolved. Enzyme-catalysed epoxidations are known to be stereospecific, but can occur with

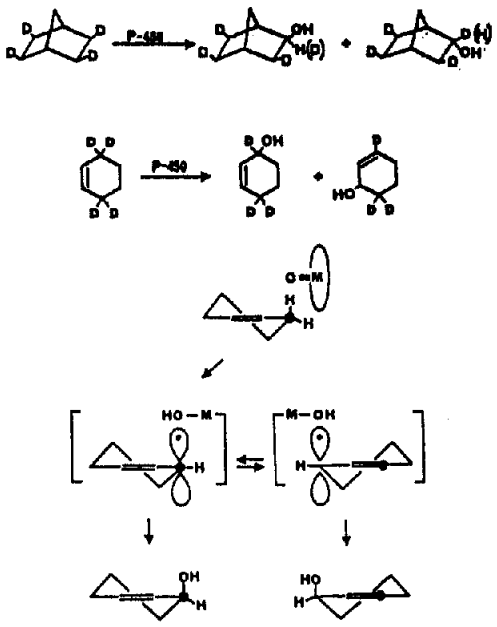


Fig. 5. Free radical effects in P-450 hydroxylations [21].

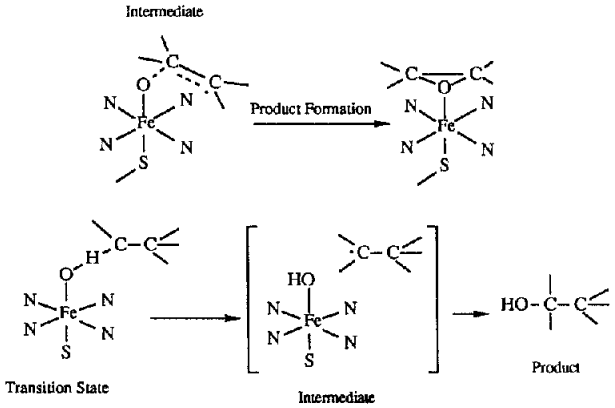


Fig. 6. Proposed epoxidation and hydroxylation mechanism [35].

simultaneous residue migration. The major product obtained from trichloroethylene is chloral (2,2,2 trichloroacetaldehyde) and the distribution of products depends on the isoenzyme utilized [41]. Groves et al. [42] have demonstrated that deuterium exchange with solvent water occurs in the P-450-catalysed epoxidation of propene and Miller and Guengerich earlier found that hydrogen exchange occurred between vinylidene chloride and water [41]. In addition, Ortiz de Montallano et al. [43,44] found that terminal

alkene and alkyne epoxidation led to the formation of *N*-alkylhaemins that rendered the catalyst inactive (suicide labelling). In 1984, Guengerich and MacDonald [45] presented a mechanistic review of P-450 behaviour and the scheme shown in Fig. 7 is taken from this review. The P-450 experimental evidence discounts an exclusively concerted insertion mechanism and is in accord with the two-step theoretical modelling of Loew. Functional models have been used to explore the mechanisms of hydroxylation and epoxidation and they have revealed additional possibilities that are discussed in following sections.

In 1987, Coon and Vaz [46] who were the first to purify P-450_{LM}, discovered that liver P-450 'leaks', with a significant portion of the NADPH reduction of oxygen leading to H_2O_2 production by a 2-electron oxidase reaction and water formation by the 4-electron oxidase reaction. Reductive removal of the powerful oxidant in the absence of a substrate may be a form of enzyme self-defence. In the same year, Atkins and Sligar [47] reported that the cytochrome oxidase-like reduction of dioxygen to water was much

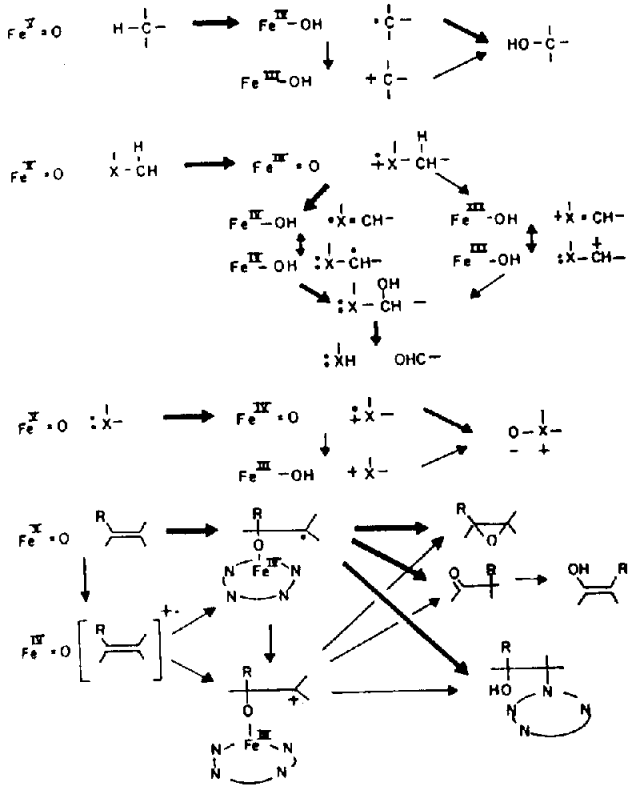


Fig. 7. Proposed unified reaction mechanism (X = heteroatom) [45]. Reproduced with permission.

faster for P-450_{CAM} than for the hepatic P-450. They suggested that water is formed from the 2-electron reduction of the reactive oxoiron intermediate.

Nolan [48], in 1986, and Niedercorn et al. [49], in 1987, reported thiolate ligated model compounds that reproduce the spectral features of cytochrome P-450. A number of other spectroscopic studies have appeared in the chemical literature since then [50–52]. Spectroscopic investigations of P-450 behaviour have revealed a rich organometallic chemistry, some of which is outlined in Mansuy's 1987 review paper [18] and more detail is given in a review of the same year by Dolphin and Setsune [53]. Both papers refer to model compounds that have been crucial in the elucidation of P-450 organometallic chemistry.

The reductive metabolism of compounds containing carbon–halogen bonds, such as DDT and the widely used anaesthetic halothane ($CF_3CHBrCl$), results in a red shift of the Soret band of P-450. The spectral changes reflect the formation of either σ-alkyl Fe(III) or carbene–Fe(II) [54] bonds and these changes have been accurately simulated by INDO calculations [34]. The formation of such bonds may play an important role in controlling the outcome of P-450 oxidations. Green pigments formed during many P-450 reactions are the result of *N*-alkylation [18,53,55,56] of the haem unit and this can result in "suicidal" inactivation of the catalyst. Nitrogen analogues of Fe(II)–O_2 and Fe(V)–O have also been detected and nitrene has been catalytically inserted into hydrocarbon bonds. The rich coordination chemistry of P-450 and its models is summarized in Fig. 8, again taken from Mansuy's 1987 review [18].

B. FUNCTIONAL CYTOCHROME P-450 MODEL SYSTEMS

(i) Iron porphyrin models

The discovery that the binding and reduction of dioxygen could be circumvented by employing exogenous oxygen sources, such as ROOH [57], $NaIO_4$

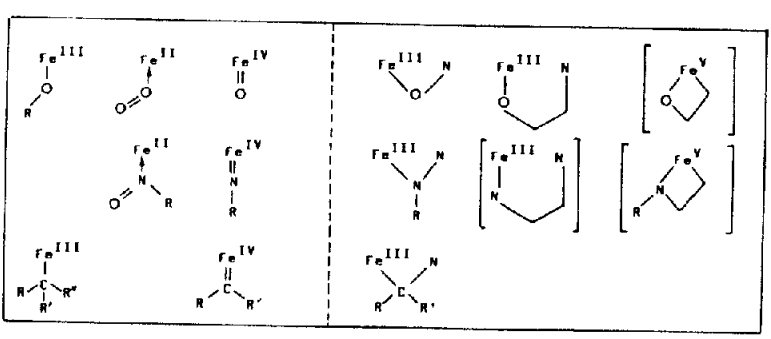


Fig. 8. P-450 coordination chemistry [18].

[58] and PhIO [59], gave considerable impetus to the development of functional model systems for cytochrome P-450. In 1979, Groves et al. [60,61] described a simple Fe(III)TPPCl–iodosobenzene system that mimicked a number of P-450 features. Cyclohexene was epoxidized [60] with a yield of 55%, however only an 8% yield of cyclohexanol was obtained from cyclohexane [60] (yields based on the oxygen source). The catalyst itself was found to be vulnerable to oxidative degradation. The reaction of *cis*- and *trans*-stilbene with iodosobenzene using dimethylferriprotoporphyrin IX chloride as the catalyst gave the corresponding *cis* and *trans* oxides with complete retention of configuration. However, when FeTPPCl was used as the catalyst, only the *cis* isomer underwent conversion and this provided a dramatic demonstration of the effect of steric constraints on catalyst function. This was reinforced three years later when Lindsay-Smith and Sleath [62] showed that FeTPPCl brought about stereospecifically *syn* epoxidations. Increased yields were found for substrates with electron-releasing substituents, while polycyclic hydrocarbons were epoxidized in low yields and aromatic hydroxylation did not occur.

Four months after Groves reported the use of FeTPPCl as a functional P-450 model, Chang and Kuo [63] described the first use of steric effects as a means of avoiding catalyst degradation. They used the μ-oxo dimer of a strapped derivative of octamethylporphyrinatoiron(III) chloride as an oxidation-resistant model catalyst and, in the same paper, presented the first low-temperature study of model catalyst intermediates. Protohaemin chloride and octaethylporphinatoiron(III) chloride in methylene chloride both formed a green compound on addition of iodosoxylene and the optical spectrum of the solution at $-45°C$ was similar to that of catalase compound I. The magnetic moment of the compound was measured in solution by the Evans method and was found to be 4.9 BM and accordingly a high-spin Fe(IV) configuration was proposed. Given that oxidized iron porphyrins are known to be unstable in methylene chloride above $-50°C$ [64], the green complex may have been a decomposition product. Compound I-like complexes are ferromagnetically coupled low-spin Fe(IV, $S=(1)$) π cation $S=(1/2)$ radicals.

In 1981, Groves et al. [65] reported the isolation of a green intermediate from the oxidation of tetramesitylporphyrinatoiron(III) chloride with *m*-chloroperoxybenzoic acid in methylene chloride–methanol at $-78°C$. In the presence of the green compound, norbornene was converted to norbornene oxide with a 78% yield, based on the oxidant. The methanol-ligated intermediate has been definitively characterized [22,23] as an oxo Fe(IV) porphyrin π cation radical that strongly resembles HRP-I in its physical characteristics. Groves points out that oxidation of CrTPPCl with *m*-chloroperoxybenzoic or iodosobenzene yields an oxo Cr(V) complex. This is not unreasonable as the valence *d* orbitals of Cr lie well above the porphyrin ligand HOMO,

whereas those of Fe and the macrocycle HOMO have somewhat similar energy. The ability of the HRP-I-like complex to function as a monooxygenase has reinforced the general belief that HRP-I and P-450-I have essentially the same valence structure. In 1989, an oxoferryl porphyrin π cation radical derivative of [*meso*-tetrakis(2,6-dichlorophenyl)porphinato]iron(III), $FeTP_{2,6\text{-}Cl}P^+$, was characterized [66] and found to have only weak ferromagnetic coupling between the metal and equatorial ligand spin sites. A similar interaction occurs in HRP-I.

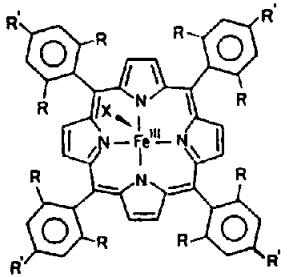
In 1988, Sawyer and co-workers [67] isolated another green compound, in this case from the reaction of [tetrakis(2,6-dichlorophenyl)porphinato]-iron(III) perchlorate, $FeTP_{2,6\text{-}Cl}PClO_4$, with *m*-chloroperbenzoic acid, pentafluoroiodosobenzene or ozone in acetonitrile at $-35°C$. The compound was described as an efficient catalyst for the stereospecific epoxidation of alkenes and this was attributed to a concerted oxygen insertion into the alkene. Sawyer pointed out that a number of valence bond formulations are possible for compound I-like complexes and these resonant structures, together with the optical spectrum of the green compound and a magnetic moment of 4.8 BM, were used to justify a $[(Por^{\cdot -})Fe(II)O]^+$ formulation for the intermediate. The unconventional formulation for this presumably *trans* acetonitrile-coordinated oxoiron complex requires more detailed spectroscopic support, particularly from NMR and Mossbauer spectroscopies. The evidence presented can alternatively be interpreted as indicating an oxoFe(III, $S=3/2$) porphyrin π cation radical complex. We have used $[FeTPP(H_2O)_2]ClO_4$ in conjunction with iodosobenzene in acetonitrile and found it to be a poor P-450 model [68].

In 1981, Goff and co-workers explained the axial ligand independence of the first two oxidation potentials of $FeTPP^+$ for the following set of ligands: F^-; Cl^-; Br^-; I^-; ClO_4^-; SO_4^{2-}; NO_3^-; N_3^-; NCS^-; OPh^-; *p*-$CH_3C_6H_4SO_3^-$. Both oxidations are centred on the equatorial ligand and do not involve the metal and are thus independent of the axial ligands. The two oxidation potentials differ by several hundred mV and this is generally true of other TPP metal complexes. However, as Bruice and co-workers [64] and Groves et al. [70] have demonstrated, the hydroxy and methoxy ligands shift the site of the first oxidation from the porphyrin ligand to the metal, so that after the second oxidation an Fe(IV) porphyrin π cation radical is formed. The iron porphyrin redox potentials given in Table 2 are taken from the 1985 paper of Bruice and co-workers [64]. Balch and co-workers [71] showed in 1980 that imidazole stabilizes the oxoFe(IV) porphyrin state.

Surprisingly, both oxidations occur at similar potentials and the same behaviour is found in HRP, in fact the second HRP oxidation has a slightly lower redox potential than the first and this was attributed by Traylor et al. [72] in 1984, to a change of spin states upon the first oxidation (high to low).

TABLE 2

Porphyrin redox potentials [64]



X	R	R'
1-Cl	H	H
1-OMe	H	H
2-Cl	Me	Me
2-OH	Me	Me
2-OMe	Me	Me
3-Cl	Me	H
3-OH	Me	H
4-Cl	Cl	H
4-OH	Cl	H
4-OMe	Cl	H
5-Cl	F	H
5-OH	F	H
5-OMe	F	H

Porphyrin	Fe(III)P/Fe(IV)P	Fe(III)P/Fe(III)P^{+}	Fe(IV)P/Fe(IV)P^{+}	Fe(III)P^{+}/Fe(III)P^{2+}	Fe(IV)P^{+}/Fe(IV)P^{2+}
1-Cl		1.24		1.55	
1-OMe	1.11		1.16		1.64
2-Cl		1.13		1.49	
2-OH	1.01		1.14		1.58
2-OMe	1.01		1.13		1.56
3-Cl		1.18		1.51	
3-OH	1.07		1.19		1.60
4-Cl		1.43		1.75	
4-OH	1.26		1.44		1.73
4-OMe	1.26		1.44		1.73
5-Cl		1.50			
5-OH	1.38		1.52		
5-OMe	1.38		1.52		

P = porphyrin.

The paper by Traylor et al. stresses the ligand distinction between HRP and P-450 and describes the use of a protohaemin containing a pendant proximal imidazole axial ligand as a catalyst for the oxidation of phenol with peracids and hydroperoxides as oxygen sources. The model showed no hydrogen abstraction or oxygen insertion activity and phenol oxidation occurred solely through electron transfer to the oxidized metalloporphyrin. An analysis of HRP data leads to the proposition that peroxidases also operate through an outer sphere process, with the edge of the porphyrin π cation radical intermediate providing a conduit for electron transfer. Traylor et al. suggest that HRP reactions occur on the periphery because of limited access to the porphyrin nucleus, whereas P-450 has a substrate-binding site directly adjacent to the porphyrin core. A correlation was found between substrate oxidation potential and model catalyst activity and the model used by Traylor et al. was found to oxidize substrates with a potential of less than 1 V; interestingly, the same limiting potential has been noted for HRP. Readily epoxidized substrates, such as phenanthrene with potentials greater than 1 V were not oxidized. The catalyst described by Traylor et al. was seen as a good model for HRP. We have suggested [68] that intermediate complexes of the type characterized by Groves et al. might reasonably be regarded as HRP-I models that are able to function effectively as monooxygenase models because of the protected meso positions of the porphyrin ligand. The *meso* position is a principle point of spin accumulation upon electron loss from the porphyrin a_{2u} HOMO.

In 1981, Chang and Ebina [73] described the first model catalyst that incorporated electronic and steric protection of the oxidation-vulnerable *meso* position [74] of the porphyrin ligand. The use of tetrakis(pentafluorophenyl)porphinato iron(III) chloride ($FeTP_{2,3,4,5,6\text{-}F}PCl$) converted cyclohexene to cyclohexene oxide in 95% yield, cyclohexane was oxidized to cyclohexanol with a 71% yield and P-450 like NIH shifts (the migration of groups from the *para* to the *meta* position [75]) were observed in aromatic oxidations. The manganese derivative of the porphyrin ligand, $MnTP_{2,3,4,5,6\text{-}F}PCl$, gave very similar results. In 1989, Ellis and Lyons [76] reported the use of $FeTP_{2,3,4,5,6\text{-}F}P^+$ complexes as effective catalysts for the aerial oxidation of propane to isopropyl alcohol and acetone (in nearly equal quantities), with up to 640 turnovers. The oxidation reactions proceeded without the need of a co-reductant, a feature reported for ruthenium porphyrin catalysts in 1985 by Groves and Quinn [77]. The report by Ellis and Lyons points out that the $(FeTP_{2,3,4,5,6\text{-}F}P)_2O$ dimer displays activity comparable with that of monomeric $FeTP_{2,3,4,5,6\text{-}F}P^+$ complexes. We have found that $(FeTPP)_2O$ and FeTPPCl exhibit similar behaviour when used as catalysts for the epoxidation of cyclohexene [68].

Earlier, in 1984, Traylor and co-workers [78] had reported high turnover

numbers and good yields of epoxides from *meso*-tetra(2,6-dichlorophenyl)-porphyrinatoiron(III) chloride and *meso*-tetra(pentachloro)phenyl]porphyrinatoiron(III) chloride ($FeTP_{2,6\text{-}Cl}PCl$ and $FeTP_{2,3,4,5,6\text{-}Cl}PCl$) used in conjunction with pentafluoroiodosylbenzene. This system was also able to hydroxylate aromatic substrates. The epoxidation of 10 000 norbornene molecules for each catalyst molecule over 20 min (8 turnovers s^{-1}) demonstrates the competence of these catalysts. Cyclohexane was converted to cyclohexanol with a 73% yield. The catalytic system was made homogeneous [79] by using an 80:18:2 methylene chloride–methanol–water solvent combination. This solvent made the catalytic system kinetically accessible and turnover rates as high as 300 (epoxides/catalyst) s^{-1} were obtained. The oxidation reactions were found to be first order in iodosoarene and catalyst concentration, but independent of alkene concentration and structure. Interestingly, the rate was essentially the same for iodosobenzene and pentafluoroiodosobenzene and this was attributed to the formation of a peracid-like compound, in analogy to the conversion of iodosobenzene to dimethoxyiodobenzene reported by Schardt and Hill [80].

$$R\text{–}I\text{–}O + HOR' = R\text{–}I(OH)OR' = R\text{–}I(OR')_2$$

Rate dependence on solvent effects and a general acid catalysis were also noted.

In 1982, Mansuy et al. [81] increased the yield of cyclohexanol obtained from cyclohexane, using the FeTPPCl catalyst, to 19% by changing the solvent from methylene chloride to benzene, thereby minimizing oxene loss through solvent oxidation. Mansuy also reported regioselectivity in *n*-heptane hydroxylations catalysed by basket handle porphyrins; two basket handle porphyrins that have been used by Mansuy et al. [81,82] are shown in Fig. 9.

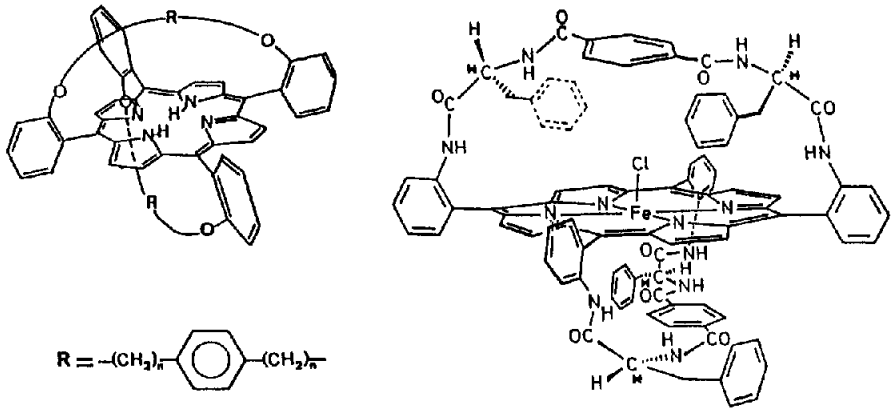
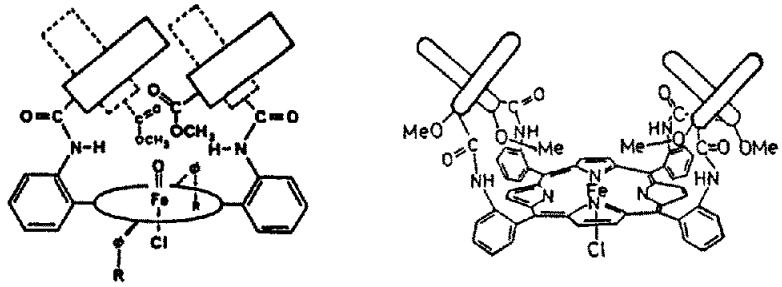


Fig. 9. Basket handle porphyrins [81,82]. Reproduced with permission.

In 1985, Nappa and Tolman [83] presented a detailed study of catalyst activity, regioselectivity, substrate selectivity and stereoselectivity in alkane hydroxylations catalysed by substituted iron tetraphenylporphyrins. The paper introduced a new class of picket fence porphyrins that are distinguished by fluorination of the pickets; *meso*-α^4-tetrakis(heptafluorobutryamidophenyl)porphinato iron(III) chloride. This catalyst oxidized cyclohexane to cyclohexanol with a yield of 37% from 20 turnovers. Catalyst decomposition at the end of some cyclohexane oxidation reactions was determined quantitatively by optical spectroscopy: $FeTP_{4\text{-}MeO}PCl$, 93%; FeTPPCl, 88%; $FeTP_{4\text{-}Me}PCl$, 86%; $FeTP_{2\text{-}Cl}PCl$, 74%; $FeTP_{2\text{-}Me}PCl$, 71%. Variation in the axial ligand in FeTPPX caused the yields of cyclohexanol in the oxidation of cyclohexane to decrease in the series: F^-, 12%; Cl^-, 10%; Br^-, 8%; MeO^-, 8%; ClO_4^-, <1%. Across this series, the Fe(III)/Fe(II) potential was found to be 0.5, −0.29, −0.21, not measured, 0.22 and the Fe(III)P/Fe(III)$P^+\cdot$ potential was found to be independent of X. The higher cyclohexanol yield of FeTPPF was then attributed to more effective stabilization of high metal oxidation states. The addition of pyridine was found to lower the yield of cyclohexanol from FeTPPCl to 7% and this was explained as being a consequence of catalyst inactivation on formation of $[FeTPP(py)_2]Cl$. However, the authors also mention that pyridine enhances the cyclohexanol yields of MnTPPCl. The cyclohexane oxidations also produced small amounts of cyclohexane oxide and apparently this is derived from the formation of cyclohexene during the oxidation reaction. The authors further describe a competitive oxidation of iodosobenzene to iodoxybenzene.

High shape and regioselectivity using sterically hindered chloro-tetrakis(2,4,6-triphenylphenyl)porphinatoiron(III), $FeTP_{2,4,6\text{-}Ph}PCl$ was reported by Suslick et al [84] in 1986. This followed the 1983 demonstration by Groves and Nemo [61] of *cis/trans* selectivity found using tetrakis(5,10,15,20-tetramesitylporphyrinato)iron(III) chloride as a model catalyst. The report contained mechanistic speculation and a molecular orbital account of the observed stereoselectivity of hindered tetra-aryl porphyrin models.

Asymmetric induction was observed in 1983 by Groves and Myers [85] for the catalytic epoxidation of substituted styrenes with a chiral iron porphyrin (Fig. 10) (a)). Four years later, Naruta and Maruyama [86] reported olefin epoxidation within the restricted cavity of a binaphthyl picket fence porphyrin (Fig. 10 (b)) in the presence of a bulky imidazole derivative. Significantly, the oxidation did not occur in the smaller cavity of $FeT_{piv}PPCl$. The results tabulated by Naruta and Maruyama reveal that, in the absence of the imidazole ligand, $FeT_{piv}PPCl$ performs the epoxidation of cyclooctene with surprising efficiency, although the authors make no comment on this finding. Also interesting was the finding that bis ligation by the bulky imidazole derivative was not significantly hindered by the pickets of $FeTP_{piv}PCl$, while



(a) (b)

Fig. 10. (a) Chiral picket fence porphyrin [85]. (b) Binaphthyl picket fence porphyrin [86] (reproduced with permission).

alkoxy groups on the pickets of the binaphthyl porphyrin that protruded over the porphyrin centre did hinder bis ligation. Naruta also indicated that oxygen atom transfer from iodosobenzene to the catalyst was not a rate-limiting process. In the same year, Groves and Neumann [87,88] described the use of membrane-spanning steroidal metalloporphyrins in synthetic vesicles as site-selective catalysts (Fig. 11). In 1989, Groves and Viski [89] reported the asymmetric hydroxylation of ethylbenzene catalysed by a chiral binaphthyl iron porphyrin.

In 1979, Groves et al. [60] introduced *N*,*N*-dimethylaniline *N*-oxide as an oxygen source. Athough giving lower product yields, the *N*-oxide is more

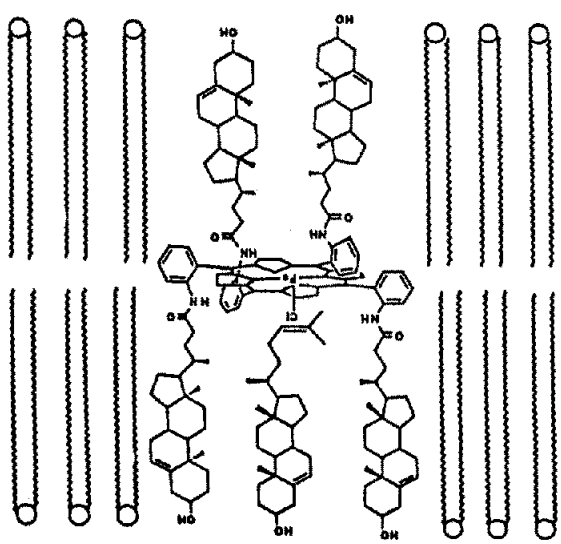


Fig. 11. Synthetic vesicle catalyst [87,88].

soluble in organic solvents than the polymeric iodosobenzene and does not cause porphyrin degradation. In 1982, Bruice and Nee [90] introduced *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide as a soluble oxygen source that gave yields typical of iodosobenzene. This oxygen donor provided the basis of a series [91] of detailed kinetic studies of oxygen atom transfer with metalloporphyrins: MnTPPCl and C_2-capped MnTPPCl in 1984 [92]; FeTPPCl [93] in 1985; $FeTP_{2,6\text{-}Cl}PCl$ [94] in 1986; $FeTP_{2,6\text{-}Me}PCl$ [95] also in 1986; $MnTP_{2,6\text{-}Me}PCl$ [96] in 1987; C_2-capped $FeTPPSbF_6$ [97] in 1987; $FeTP_{2,3,4,5,6\text{-}F}PCl$ [91] in 1987 and $FeTP_{2,6\text{-}Br}PCl$ in 1989 [98]. These investigations established that the rate-determining step in the catalytic process is the oxygen atom transfer from the *N*-oxide to the catalyst. High epoxide yields were obtained from the $TP_{2,6\text{-}Me}P$-based catalysts and the $FeTP_{2,6\text{-}Br}PCl$ catalyst (80–97%). Lower yields of alkene oxides from the remaining halogenated catalysts, which have been shown to be better oxidants, were attributed to greater levels of oxidation products of the oxygen donor. The $FeTP_{2,6\text{-}Br}PCl$ catalyst was found to be a particularly efficient catalyst of alkene epoxidation, being able to epoxidize terminal alkenes in high yield. The use of C_2-capped $FeTPPSbF_6$ produced a pentacoordinate oxo complex, the cap cavity being unable to accommodate a *trans* axial ligand. The reaction of *meso*-tetrakis(2,6-dimethyl-3-sulphonatophenyl)-porphyrinato-iron(III) hydrate with various acyl and alkyl hydroperoxides in water was described in 1989 [99].

In 1985, Collman et al. [100] found that epoxidation rates were independent of olefin concentration, but different substrates were oxidized at different rates and this implied the presence of a reversible oxo-olefin intermediate. Again it was suggested that oxygen atom transfer from iodosoarene to catalyst was not a rate-limiting process. In the same year, Tabushi et al. [101] detailed a kinetic study using a picket fence porphyrin and H_2–colloidal platinum as a reductive P-450 system.

In 1982, it was shown that aliphatic hydroperoxides as oxygen donors for iron porphyrin catalysts give product distributions typical of Fenton's reagent rather than the cytochrome P-450-like distributions produced by iodosobenzene, *N*-oxides and percarboxylic acids [58,59,63,73,102–107]. Cytochrome P-450 induces heterolytic cleavage of the O–O bond whereas the model systems appeared to cause a Fenton-like homolytic scission to produce $RO\cdot$, which is unable to epoxidize alkenes. Two years later, Mansuy et al. [108] discovered that hydroperoxide-catalysed epoxidation does occur in the presence of imidazole and manganese porphyrins performed more efficiently than their iron counterparts. Charge donation from the *trans* axial ligand apparently facilitates heterolytic rupture of hydroperoxides. Homolytic fission catalysed by P-450 model complexes produces an HRP-II-like active intermediate with only one oxidizing equivalent, while heterolytic fission generates

an HRP-I-like oxidant. In 1985, Bruice and Lee [109] suggested that the nature of the bond cleavage in hydroperoxides depends on the acidity of the hydroperoxide, those with a $pK_a < 11$ for the corresponding leaving group (ROH) undergoing heterolytic cleavage. In 1987, Traylor et al. [110–113] reported rather different results from those of Bruice and Lee and rationalized the discrepancies by proposing a unifying mechanism in which hydroperoxides scavenge HRP-I intermediates to produce HRP-II intermediates and alkylperoxy radicals. That is, Traylor et al. suggest that hydroperoxides undergo heterolytic rupture, but that subsequent reactions produce products characteristic of homolytic fission. In 1989, Labeque and Marnett [114] described the homolytic cleavage of 10-hydroperoxyoctadeca-8,12-dienoic acid catalysed by $FeTPP^+$. At the present time, it would appear that both types of fission are possible; the preponderance of either a homolytic or heterolytic mechanism being dependent on the character of the catalyst (and its axial ligands), the nature of the hydroperoxide and solvent conditions. Perhaps reassuringly, the same duality is found in native enzymes.

Khenkin and Shteinman, in 1982, discussed the formation of peroxoiron-porphyrins that are capable of alkane and alkene oxidations when used in the presence of acylating agents. A mechanistic account of the reactions was presented in 1984 [115] and it was shown that the acylating agent permits heterocleavage of the O–O bond in the peroxo complex. An improved P-450 analogue was described by Khenkin et al. [116] in 1987. In this system, oxygen coordinated to tetrakis(pivalamidophenyl)porphinato iron(III), Fe (III)$TP_{piv}P$, is reduced by zinc amalgam in the presence of methylviologen acting as an electron transport system with acetic anhydride providing the acylating agent needed for generation of the reactive oxoiron(IV) intermediate. The model shows similarities to Tabushi's earlier system. The use of riboflavin as an electron transfer agent in a reductive ironporphyrin-catalysed oxygen activation system was described by Sakurai et al. [117] in 1989. In the following year, Fukuzumi et al. [118] described the use of 10-methylacridan as a stable NADH model providing electrons for the metalloporphyrin-catalysed reduction of dioxygen. Weiss and co-workers [119,120] have modelled the dioxygen binding and subsequent reduction stages of the P-450 catalytic cycle with an iron picket fence porphyrin and reaction of the ferrous porphyrin dioxygen adduct with carbon dioxide produced an iron(IV)-oxo porphyrin derivative. In 1989, Weiss et al. [121] described the solvent-dependent formation of an oxoferryl porphyrin or oxoferryl porphyrin π cation radical from the protonation of a peroxoiron(III) picket fence porphyrin (see Fig. 12). The physical properties of a number of ferryl porphyrin complexes are summarized in a 1988 paper by Gold et al. [122].

A number of papers [72,113,123–128] have discussed proximal, distal and general base effects on the heterolytic cleavage of peracids and hydroperoxides

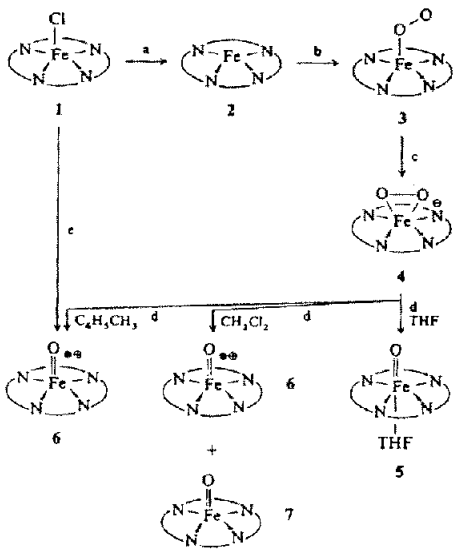


Fig. 12. Solvent-dependent oxidation of a peroxoiron(III) porphyrin [121]. a, Zinc amalgam, room temperature; b, oxygenation, 220 K; c, hydride reduction, 230 K; d, $HBF_4 \cdot Et_2O$, 190 K; e, *m*-chloroperoxybenzoic acid, toluene, 190 K. The steps a and b were carried out in toluene, in CH_2Cl_2, or in tetrahydrofuran. Reproduced with permission.

catalysed by iron porphyrins and peroxidases. Traylor and Xu [113] have related the general catalytic effects of alcohols in model studies to the general acid catalysis by water of O–O bond cleavage in cytochrome P-450. In 1986, Groves and Watanabe [124] described the formation of an acylperoxyiron(III) complex and claimed the first direct observation of an iron-catalysed heterolytic O–O bond cleavage. This bond rupture yielded a low-spin oxo Fe(IV) porphyrin π cation radical, and a surprising homolytic scission that formed a high-spin porphyrin *N*-oxide was described by Groves and Watanabe [129] in 1988. The formation of the *N*-oxide was shown to reduce the epoxidation activity of the catalyst. A theoretical study by Jorgensen [130] in 1987 suggested that the most stable structure for the proposed high-valent oxo intermediate of P-450 is one in which the oxygen is inserted into an iron–nitrogen bond. The paper also described the modelling of alkene epoxidation by such an intermediate. Epoxidation is preceded by olefin coordination to vacant metal *d* orbitals followed by electron transfer from an oxygen *p* orbital to an alkene π^* acceptor orbital. The observation of the decomposition of an acylperoxy complex is significant because, in 1980, Sligar et al. [131] presented evidence indicating that dihydrolipic acid acylates the distal dioxygen of ferrous P-450, thus suggesting that the formation of an acyl peroxide is an intermediate in the enzyme catalytic cycle.

In 1982, Mansuy et al. [132] reported an intermediate-spin iron porphyrin

complex that had a vinylidene moiety inserted into an Fe–N bond. Later, in 1986, Mansuy and co-workers [133] found a high-spin complex with a nitrene group inserted into an Fe–N bond. In 1985, Traylor et al. [134] isolated an *N*-alkyl iron porphyrin derivative of a P-450 model. Suicidal inactivation of cytochromes P-450 in terminal alkene epoxidation involves the formation of a bond between a pyrrole nitrogen and the more substituted carbon of the alkene, and a number of synthetic iron porphyrins have modelled [134,135] this behaviour. In 1987, Mansuy et al. [136] described a catalyst inactivation arising from bonding to the least substituted carbon of the alkene, and an interesting Fe–O–C–C–N_{py} complex was isolated by Mansuy et al. [54] in 1988.

Suslick et al. [137] discovered in 1987 that selective irradiation into the charge transfer band of FeTPPX resulted in photoreduction of the iron atom and liberation of X· (X=Cl, Br, F, I, N_3). In the presence of O_2 and a suitable substrate, photoinitiation of hydrocarbon oxidation was observed. Using cyclohexene as a substrate, the product distribution was typical of allylic oxidation with 23% cyclohexene-3-ol and 77% cyclohexene-3-one being produced and 150 equivalents of product were generated for each equivalent of porphyrin consumed. In 1989, Bartocci et al. [138] reported the $FeTP_{2,6\text{-}Cl}PCl$-catalysed photoreduction of carbon tetrachloride by alcohols, with high quantum yields and turnover numbers (up to 130 000). In contrast, FeTPPCl was found to be a poor catalyst and the difference was attributed to the electronegativity and steric protection of the *meso* position rendered by the chlorine residues of $FeTP_{2,6\text{-}Cl}PCl$. Similar reasoning [68] suggests that the complex characterized as an oxoiron(IV) porphyrin π cation radical by Groves and co-workers in 1981, may best be regarded as an HRP model that can function as a monooxygenase because of the protected *meso* positions of the complex.

In 1988, Miyamato and co-workers [139] described the successful use of *ortho*-substituted TPP iron(III) catalysts in the NaOCl system and differences between these catalysts and their manganese counterparts are related to the respective metal–oxene bond lengths.

(ii) Manganese porphyrin models

Interest in manganese porphyrins as synthetic catalysts for hydrocarbon oxidation was stimulated by simultaneous reports from Hill and Schardt [140] and Groves et al. [141] in 1980; both reports demonstrated that Mn(III)TPPCl was more effective in alkane hydroxylations than Fe(III)-TPPCl. Hill and Schardt obtained a cyclohexanol yield of 26% from cyclohexane using iodosobenzene as the oxygen source and benzene as the reaction solvent. Groves et al. found that epoxidation proceeded with loss of stereo-

chemistry at the double bond and *trans*-stilbene was epoxidized to give the *trans*-oxide only. In contrast, FeTPPCl is an essentially stereoretentive catalyst that does not react with *trans*-stilbene. Groves et al. attributed the differences to the triplet ground state of the purported Mn(V)=O intermediate. In 1982, Gelb et al. [142] demonstrated that manganese provided a reasonable substitute for iron in cytochrome P-450$_{cam}$. Calculations by Yamaguchi et al. [143] suggest that thiolate ligation to manganese porphyrin catalysts may result in a deleterious reduction of the electrophilicity of the active intermediate.

Soon after Hill and Schardt and Groves et al. had presented their results, Tabushi and Koga [144] outlined the first reductive activation of dioxygen utilizing a manganese porphyrin, MnTPPCl, with $NaBH_4$ used as the reducing agent [145]. Cyclohexanol was obtained in 80% yield in the oxidation of cyclohexene and it was apparently derived from the reduction of cyclohexene epoxide formed during the reaction. The system was improved in 1981 [146] by using dihydrogen and colloidal platinum as the electron source and imidazole as an axial ligand; cyclohexene was oxidized to give cyclohexene epoxide as the major product. Aromatic hydroxylations in the presence of an acid and acid anhydride added as an extension to the system were reported in 1986 [147]. A more effective system was announced in the same year by Tabushi and Kodera [148] in which dihydropyridine was used as the reducing agent in the presence of a flavin and a water-soluble manganese porphyrin catalyst. Shortly before his death, Tabushi [149] prepared an entertaining and illuminating review of reductive dioxygen activation by iron and manganese porphyrin model systems. The review was published in 1988 and it includes a description of Tabushi's development of a "super-molecule" that incorporates the essential features of the native enzyme; the molecule has a metalloporphyrin core attached to a flavin-containing cyclodextrin. The assembly displayed self-organization properties and electron transfer rates that exceeded the native P-450 performance, so promising "super-enzymic activity".

As mentioned in the iron model discussion, in 1981 Chang and Ebina reported a very efficient oxidation of alkenes and alkanes with $MnTP_{2,3,4,5,6\text{-}F}PCl$ as the catalyst and iodosobenzene as the oxygen donor. In 1989, Banfi et al. [150–152] presented an evaluation of the performance of the iron and manganese derivatives of some halogenated tetra-aryl porphyrins in the NaOCl system. When the substrate was not present in a protective excess, only the manganese porphyrins showed resistance to self-destruction and the most effective ligand was $TP_{2,6\text{-}Cl}P$. Electron-rich olefin substrates were efficiently oxidized in the presence of pyridine; however, the use of pyridine proved deleterious when less reactive substrates were used, as both equatorial and axial ligands underwent decomposition.

Mansuy et al. [153,154] described another reductive system in 1983 that

utilized sodium ascorbate and MnTPP in a biphasic system. A comparison of the product distributions from the ascorbate and iodosobenzene-driven hydrocarbon oxidations suggested that a manganese-oxo complex was not involved in the biphasic system. By 1987, Mansuy et al. [155] had developed a more impressive model system comprising zinc as the electron source, imidazole as an axial ligand and acetic acid as a proton donor (Mn:1-methylimidazole:AcOH:Zn:substrate = 1:100:150:150:385). Zinc and acetic acid provided simple substitutes for NADPH and H^+ of the enzymatic system. A turnover of 2.5 moles of epoxide per mole of catalyst per minute for cyclohexene compared favourably with an epoxidation turnover of 10 mol min^{-1} for P-450. The reducing agent was replaced in an electrochemical version of the system described by Mansuy et al. [156] in 1988.

In 1979, Tabushi and Koga [157] introduced NaOCl as an oxygen source and used it to fuel the MnTPPCl-catalysed oxidation of cyclohexane in a biphasic system. Application of the new system to alkene epoxidation by Meunier and Guilmet [158] in 1980 was more successful. Control of the reaction rate and stereoselectivity by the axial ligand employed in the system was described in 1983 by Collman et al. [159] and turnover rates of up to 10 s^{-1} were recorded with an imidazole ligand. Control of the product distribution by the macrocycle was described by Meunier and Bortolini [160] in 1984.

In the same year, Meunier et al. [161] published a detailed paper that expanded on preliminary reports, released in 1982 [162,163], of enhanced catalyst performance when pyridine is used as an axial ligand. In the presence of pyridine and a phase transfer catalyst, Mn(III)TPPOAc under aqueous NaOCl returned cyclohexene epoxide in 72% yield after consuming 85% of the substrate in 4 h (yield based on starting quantity of substrate, the ratio of substrate to catalyst being 160). Without pyridine, the same system required 7 h to convert 72% of the substrate with an epoxide yield of 32%. In the absence of pyridine, *trans*-stilbene oxide is the major isomer obtained from *cis*-stilbene epoxidation, whereas the addition of a small amount of pyridine returns the *cis* isomer as the predominant product. Meunier and De Poorter pointed out that commercial bleach provided a cheap source of NaOCl, though differences attributed to variations in hydroxide ion concentration were noted [164]. MnTPPOAc was found to be superior to FeTPPCl, CoTPPBr, CrTPPCl and a number of other transition metal complexes. Oxidative phenolic coupling catalysed by MnTPPOAc using NaOCl or dioxygen was reported by Basoli et al. in 1989 [165].

Again in 1984, Meunier et al. [166] employed a double-bridged porphyrin ligand with pyridine incorporated into one of the bridges and in 1985 Montanari et al. [167] produced two "tailed" manganese porphyrins bearing pyridine or imidazole attached to a pendant arm. The bridged and tailed

porphyrins evolved from the pioneering work of Battersby et al. [168] in which these porphyrins were specifically designed to provide a favourable environment for dioxygen coordination to iron(II). Montanari et al. also reported that lowering the bleach pH from 12.7 to 9.5 significantly improved the oxidation rate and removed the need for a phase-transfer catalyst. There was, however, a small penalty in that metalloporphyrin oxidation increased, although this did not become significant until virtually all of the substrate was consumed. In 1989, Querci and Ricci [169] introduced the water-soluble magnesium monoperoxyphthalate as a cheap oxene source.

Electron-withdrawing substituents on the peripheral phenyl groups were utilized in a 1985 study [170] that introduced potassium hydrogen persulphate as a mono oxygen donor. In 30 min, cyclohexene was completely converted to the epoxide when $Mn(III)TP_{2,3,4,5,6\text{-}F}P^+$ was used as the catalyst in combination with pyridine and persulphate. Just as significantly, terminal olefins could be epoxidized with 60–80% yields. The oxidation of cyclohexane was less spectacular and although 55% of the substrate underwent conversion, the yield of cyclohexanol was only 13%.

Cumyl hydroperoxide was used as an oxygen source for MnTPPCl–imidazole-catalysed epoxidations by Mansuy et al. [108] in 1984. Cyclohexene gave cyclohexene epoxide in 27% yield, with minor quantities of allylic oxidation products. FeTPPCl returned only 3% cyclohexene oxide. The same paper showed that imidazole had the same effect on the performance of the $MnTPP^+$–C_6H_5IO catalytic combination, as pyridine had on the character of the NaOCl–$MnTPP^+$ system. A year later, Mansuy et al. [171] used hydrogen peroxide and the more robust tetra(2,6-dichlorophenyl)porphyrinatomanganese(III) catalyst to obtain a cyclohexene epoxide yield of 91%, with 100% consumption of the substrate. Cyclohexane [172] was oxidized to cyclohexanol with a 30% yield at 54% substrate consumption and the yield increased to 40% when the ratio of alkane to peroxide to catalyst was lifted to 700:40:1 (yields in the single-phase systems are based on the oxygen source). Nitrogen base ligation and hydrogen bonding were shown to be vitally important in oxygen transfer from percarboxylic acids and alkyl hydroperoxides to MnTPPCl in a 1986 paper by Yuan and Bruice [173].

In 1988, Mansuy et al. [174] presented a comparison of iron and manganese porphyrin catalyst performance in alkene and alkane oxidations with hydrogen peroxide in the presence of imidazole. The oxidation-resistant tetra(2,6-dichlorophenyl)porphyrinatomanganese(III) catalyst gave a significantly better performance in the presence of imidazole than did its iron counterpart. Replacing hydrogen peroxide with iodosobenzene gave identical results, with the manganese catalyst returning a 97% yield of cyclohexene epoxide from cyclohexene and the total yield of alcohols from *n*-heptane oxidation was found to be 65%. Mansuy et al. suggested that imidazole acted

both as a stabilizing ligand and as a base in the hydrogen peroxide system. The influence of the proximal ligand on the dismutation of hydrogen peroxide catalysed by manganese and iron porphyrins was discussed in a 1989 paper by Meunier and co-workers [175,176]. The performance of the catalysts was related to catalase, and oxygen proximal ligation was shown to result in reduced catalase activity and oxygenase ability when compared with an imidazole ligand. Overall, this was seen as being beneficial to the phenoxy ligated native catalase, as limited oxygenase activity would preserve the integrity of nearby amino acid residues. The nitrogenous ligand had a much more pronounced effect on the performance of the manganese catalysts than on the iron catalysts. This difference had also been found in the 1988 comparison of iron and manganese catalyst performance in the NaOCl system by Miyamoto and co-workers [139].

In a 1984 kinetic study [92] that utilized *p*-cyano-*N*-*N*-dimethylaniline *N*-oxide as an oxygen source, Bruice and co-workers stated that, in the absence of an axial ligand, manganese porphyrin catalysis was extremely slow. This conclusion was reached after studying the catalytic epoxidation reactivity of Baldwin et al.'s [177] capped porphyrin (shown in Fig. 13) in benzonitrile. The crystal structure of this porphyrin shows the cap only 4 Å from the porphyrin plane and the halide ligand is located outside the capped cavity. Bruice and co-workers then preclude halide coordination within the cavity, and this means that oxygen donation can only occur in the absence of any other axial ligand. Interestingly, Mansuy et al. [108] found that styrene was oxidized by a catalyst that was capped on both sides when iodosobenzene was used as the oxygen donor. The influence of imidazole ligation to $MnTP_{2,6\text{-}Cl}PCl$ as an epoxidation catalyst fueled by *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide was examined by Bruice and co-workers [96] in 1987. The dramatic change in performance on ligation by the nitrogenous based signalled a significant alteration in electronic character and in opening remarks they attributed such changes to a shift in metal ion spin state from high to low. Bruice and Yuan [178] introduced oxaziridine as an oxene transfer agent in 1985.

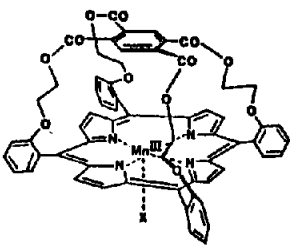


Fig. 13. Baldwin et al.'s capped porphyrin [92,177]. Reproduced with permission.

In 1984, Mansuy et al. [108] compared the regioselectivity of olefin oxidations catalysed by various Fe, Mn, and Cr tetraarylporphyrins with iodosobenzene as the oxygen source. The chromium catalyst, CrTPPCl, was found to be less effective in alkene oxidation than the iron or manganese catalysts, which exhibit similar regioselectivity in catalytic oxidation. The importance of catalyst topology in controlling the competition between allylic oxidation and epoxidation was reinforced. Shape-selective alkane hydroxylations catalysed by sterically hindered iron and manganese porphyrins were discussed in detail in a 1986 paper by Suslick et al. [84]. Again manganese porphyrins were found to be superior, the stereoselectivity of the catalysts compared very favourably with the native enzyme and the behaviour of the catalysts did not depend on the nature of the oxygen source. A robust asymmetric "chiral wall" manganese porphyrin having high catalytic efficiency and moderate enantioselectivity was described by O'Malley and Kodadek in 1989 [179].

In a 1986 study of alkene epoxidation in the NaOCl system, Razenberg et al. [180] discovered that methanol and styrene significantly increase the reaction rate without changing the product distribution. In 1987, Shimizu et al. [181] epoxidized cyclohexene with MnTPPCl and iodosobenzene in methanol and obtained a 60% yield of the product, which is a significant increase from the 40% yield obtained in benzene [154]. Following the 1986 report that styrene increases the rate of oxidation of aliphatic alkenes, Razenberg and co-workers found evidence that the aldehydes formed as a side product in styrene oxidation were responsible for the observed rate enhancement. The evidence was discussed in a 1987 paper [182] and the synergistic effect was tentatively attributed to the reaction of the pentavalent oxomanganese intermediate with a carbonyl residue to form a carbonyl oxide or a dioxirane. Later [183], ketones as well as aldehydes were shown to be rate-enhancing in epoxidations. The synergistic effects of lipophilic carboxylic acids and heterocyclic bases (imidazoles and pyridines) on the $MnTP_{2,6\text{-}Cl}P^+$-catalysed epoxidation of alkenes by hydrogen peroxide in a two phase aqueous methylene chloride system were described by Banfi and co-workers in 1989 [184]. Cyclooctene was completely converted to epoxide with 400 turnovers in 10 min using a 1:1:1 ratio of catalyst to lipophilic acid to base. The authors suggest that the acid assists in the heterolytic cleavage of the O–O bond in the hydroperoxy complex.

In 1988, Collman et al. [185] reported the use of manganese picnic basket porphyrins as P-450 active site analogues (Fig. 14). Picnic basket porphyrins have one face open and the other sterically hindered and the porphyrins used in this study were designed to provide a cavity large enough to be occupied by substrate molecules such as *cis*-2-octene or *trans*-β-methylstyrene. Molecular models showed that the pocket should resemble the cavity in the tetramesi-

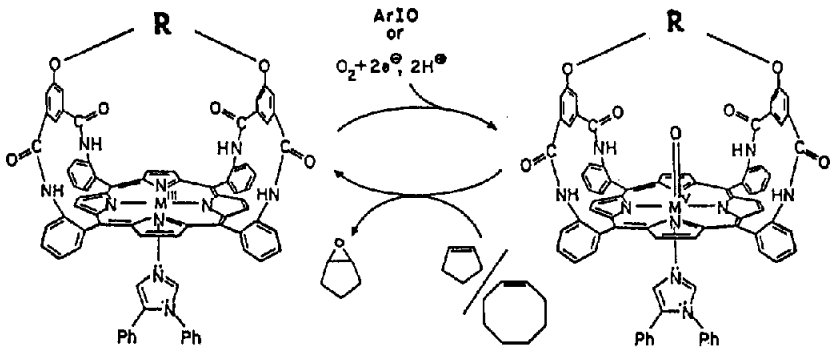


Fig. 14. Collman et al.'s picnic basket strategy [185]. Reproduced with permission.

tyl porphyrin ligand. Surprisingly, the basket porphyrins showed the same *cis/trans* olefin selectivily as Mn(III)TPP and shared the same rate of epoxidation, indicating that oxidation occurred at the open face of the metalloporphyrin. A variety of oxygen donors were used, including PhIO, NaOBr, H_2O_2 and O_2; 1,5-diphenylimidazole was used as the axial ligand and the influence of bromide versus perchlorate counterions was tested. Collman et al. suggested that the rate of oxygen transfer from the donor to the porphyrin was much faster outside the pocket than inside the sterically more demanding cavity. The lack of reactivity with dioxygen could not be explained.

In 1987, Suslick et al. [186] reported the photocatalytic oxidation of hydrocarbons by the perchlorate and periodate derivatives of Mn(III)TPP. Irradiation into the Soret or C.T. bands cleanly converts $MnTPPClO_4$ to MnTPPCl with concomitant oxidation of substrate. Excess perchlorate salts could be used and thermal oxidations were noted for periodate but not perchlorate. Another novel oxygen source was described by Groves and Stern [210] in 1988, when it was found that chloroform stirred under 6 N NaOH, with triethylbenzylammonium chloride as a phase transfer catalyst, forms a carbonyl oxide which has an oxene residue equivalent to that of iodosobenzene (Fig. 15). In 1982, Breslow and Gellman [187,188] reported the catalytic amination of alkanes, using tosylimidoiodobenzene in conjunction with iron and manganese porphyrins.

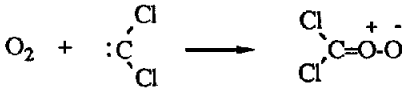


Fig. 15. Carbonyl oxide formation [211].

C. THE CHARACTERIZATION OF HIGH-VALENT COMPLEXES FORMED IN MANGANESE PORPHYRIN-CATALYSED HYDROCARBON OXIDATIONS

Biomimetic oxidative activation of hydrocarbons by manganese porphyrins involves the generation of high-valent manganese oxo complexes. Stable non-porphyrinic oxomanganese(V) complexes have been isolated and structurally characterized [189,190], but to date there has been no isolation and definitive characterization of a pentavalent oxomanganese porphyrin complex. A low-spin nitrido Mn(V) porphyrin complex was characterized structurally and spectroscopically by Hill and Hollander [191] in 1982. An examination of the nitrido Mn(V) and isoelectronic oxo Cr(IV) complexes [192] revealed that the true oxidation state was significantly lower than the formal state as a result of significant electron delocalization from the formally N^{3-} and O^{2-} ligands. The low-spin nitrido complex was shown to be remarkably stable, however Groves and Takahashi [193] found that, when trifluoroacetic anhydride was added to a red solution of the complex in methylene chloride, a new green paramagnetic complex formed that was able to transfer nitrogen to cyclooctene. The change in reactivity was attributed to a change of spin state that was detected by NMR spectroscopy.

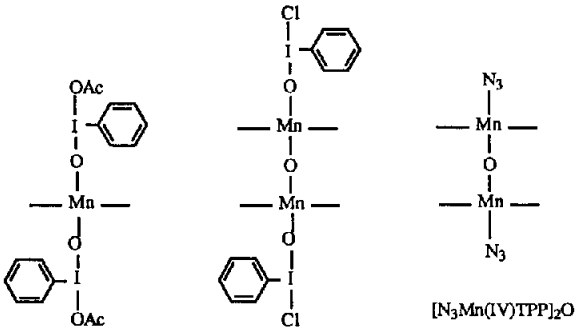
In 1980, Willner et al. [194] reported the isolation of a tetravalent oxomanganese tetraphenylporphyrin complex from the reaction of Mn(II)TPP with iodosobenzene in methanol. The oxo formulation was re-evaluated by Hill et al. [195] in a 1982 paper that described the structural and spectroscopic characteristics of a high-spin $Mn(IV)(OCH_3)_2$ complex that was isolated under the conditions described by Willner et al. It is interesting to note that the analogous iron compound has been shown to be a low-spin complex [64,70].

In 1980, Groves et al. [196] trapped an intermediate from the reaction of MnTPPCl with iodosobenzene and assigned it as a high-spin pentavalent oxomanganese porphyrin, O=Mn(V)TPPCl, capable of the hydroxylation and halogenation of alkanes and epoxidation of alkenes. The pentavalent oxidation state was assigned on the basis of a blue shifted spectrum and a solid state Faraday magnetic moment of 2.9 μ_B.

By 1983, Hill et al. [197–199] had characterized three types of Mn(IV) intermediate obtained from the reaction of iodosobenzene with MnTPPX (Fig. 16):

(i) $[XMn(IV)TPP]_2O$, $X = N_3^-$, OCN^-
(ii) $[YMn(IV)TPP(OIPh)]_2O$, $Y = Cl^-$, Br^- and
(iii) $[PhI(OAc)O]_2Mn(IV)TPP$.

The nitrido complex, $[N_3Mn(IV)TPP]_2O$, was EPR silent and had an effective magnetic moment of 2.0 μ_B. The dimer-containing iodosobenzene was



[PhI(OAc)O]$_2$Mn(IV)TPP [ClMn(IV)TPP(OIPh)]$_2$O

Fig. 16. Intermediates isolated by Hill et al. [197–199].

also found to be EPR silent and had a moment of 1.5 μ_B. The infrared spectra of these two complex types did not contain bands between 1250 and 1300 cm^{-1}, where TPP π cation radical absorptions are believed to occur. Accordingly, the electronic state of the dimers was ascribed to two antiferromagnetically coupled high-spin d^3 Mn(IV) atoms in neutral porphyrins. The dimers were shown to exchange oxygen with water and this suggested a reversible disproportionation to Mn(III) and an oxo Mn(V)-like monomer. The monomer complex, [PhI(OAc)O]$_2$Mn(IV)TPP, was identified as a high-spin d^3 complex containing five oxidizing equivalents.

A detailed study of hydrocarbon functionalization with these complexes suggested the involvement of an ·O–Mn(IV) [200] complex, but only by inference. However, Mn(II)TPP was detected and implicated in the formation of RX during alkane oxidation. The report concluded with the presentation of a detailed mechanism for the oxidation of alkanes catalysed by manganese porphyrins having iodosobenzene as an activated oxygen donor.

An EPR-silent manganese porphyrin complex with a magnetic moment of 2.7 B.M. was prepared from the aqueous alkaline reaction of NaOCl with a water-soluble and TPP-like manganese porphyrin, described by Harriman et al. [201,202] in 1982. The evidence presented by Harriman provided strong support for a monomeric high-spin d^2 Mn(V) oxo complex formulation. The oxidation of manganese porphyrins in methylene chloride was shown to be difficult and electrochemical studies revealed that the solvent was oxidized before a second electron was removed from the metalloporphyrin. Only a Mn(IV) complex could be detected in reactions with iodosobenzene in methylene chloride and this led to the proposition that Mn(V) is a transient state that rapidly decomposes in organic solvents to Mn(IV). Harriman also suggested that the complex isolated by Groves in 1980 was an impure dimer of

the type that had been elaborated by Hill. In 1986, Harriman et al. [203] reported the limited evolution of dioxygen from basic aqueous solutions of oxidized manganese porphyrins.

In 1983, Meunier and Bortolini [204] captured an intermediate from the reaction of $MnTP_{2,4,6\text{-}Me}PCl$ with NaOCl and suggested that it was a tetravalent oxomanganeseporphyrin radical cation. The solid state magnetic moment of the complex was found to be 4.00 μ_B and slight coupling of a high-spin metal $S = 3/2$ state to a ligand radical $S = 1/2$ state was suggested. The infrared spectrum of the complex indicated a porphyrin π radical. The optical spectrum was similar to that of the monomeric Mn(IV) porphyrin complexes isolated and characterized by Hill et al. [195,199]. An EXAFS study reported in 1986 [205] found a metal–oxygen bond length of 1.84 Å, which is significantly longer than the length of 1.64 Å found for the iron intermediate isolated by Groves and co-workers [22,23]. This suggested delocalization of the oxygen–metal bond into the porphyrin ligand, with the oxygen having a significant amount of radical character.

Also in 1983, Groves et al. [206] had reported the formation of an acylperoxymanganese(III) complex that decomposed to form a proposed oxomanganese(V) oxidant. The addition of *m*-chloroperbenzoic acid to a solution of $MnTP_{2,4,6\text{-}Me}PCl$ in methylene chloride containing 2 equivalents of tetramethyl ammonium hydroxide at $-78°C$ resulted in spectral changes on warming to $-30°C$ that were attributed to the formation of a Mn(V) complex. The decomposition of the high-valent complex in the presence of cyclooctene produced an 80% yield of epoxide and $Mn(III)TP_{2,4,6\text{-}Me}P$(*m*-chlorobenzoate), and a titration of the intermediate with iodide revealed two oxidizing equivalents on the complex. In 1987, Weiss and Schappacher [207] also reported a Mn(V) oxo complex; in this case the reaction of carbon dioxide with a manganese(II)-superoxo complex formed a manganese(III)-peroxycarbonate intermediate that underwent heterolysis to a proposed oxo Mn(V) species or homolysis into a Mn(IV) oxo complex. Both of the reported pentavalent oxidation states were assigned principally by spectral comparisons with the optical spectra of previously reported reaction intermediates.

In 1986, Groves and Watanabe [208] observed that the decomposition path to the high-valent state taken by acylperoxo complexes critically depended on the reaction conditions. In the presence of base, the homolytic scission of O–O was demonstrated as a contrast to a heterolytic fission in the presence of acid. The homolytic fission was seen as arising from an electron-donating orbital interaction between ligated hydroxide and peroxy oxygen atoms. A corresponding homolytic fission catalysed by iron porphyrins results in the formation of an inactive *N*-oxide [129]. The behaviour of a freshly prepared basic solution of the high-valent manganese complex was interesting; initially the solution was EPR-silent but after a few minutes at

−78°C, characteristic Mn(IV) porphyrin signals were detected. This would seem to indicate solvent decomposition of an EPR-silent d^2 Mn(V) complex. Such a complex would be expected to be EPR-silent, whether high-spin ($S=1$) or low-spin ($S=0$). Alternatively, the Mn(V) complex may oxidize an hydroxo ligand, perhaps forming a μ-oxo dimer.

In 1987, Groves and Stern [209] discovered that there are two distinct pathways by which manganese porphyrins can epoxidize alkenes. The reaction of $MnTP_{2,4,6\text{-}Me}PCl$ with 1.2 equivalents of *m*-chloroperbenzoic acid at 0°C in methylene chloride with 2 equivalents of methanolic $(CH_3)_4NOH$, resulted in the isolation of a compound identified as an oxomanganese(IV) complex that was formulated as $MnTP_{2,4,6\text{-}Me}P(O)(H_2O)$. Oxygen transfer to alkenes from this surprisingly stable complex was non-stereoretentive and this behaviour was not modified by the presence of pyridine, in fact pyridine lowered the epoxide yield. Repetition of the isolation procedure at −78°C produced the EPR-silent species that had been identified in earlier work and this complex demonstrated a high degree of stereospecificity in olefin oxidation and rapid oxygen exchange with $H_2{}^{18}O$, in contrast to the slow exchange observed for the Mn(IV) complex. The stereospecificity and reaction rate significantly increased in the presence of pyridine, while oxygen exchange was prevented (presumably a consequence of pyridine ligation).

The differences between the proposed Mn(IV) and Mn(V) oxo complexes and their epoxidation reactions were expanded upon by Groves and Stern [210] in a 1988 paper. The high-temperature complex was found to be a mixture of pentacoordinate $Mn(IV)TP_{2,4,6\text{-}Me}P(O)$ and hexacoordinate $[MnTP_{2,4,6\text{-}Me}P(O)(OH)]^-$ and surprisingly the red mixture could be formed simply by aerobic oxidation on adding $(n\text{-}Bu)_4NOH$ to a green methylene chloride or benzene solution of $Mn(III)TP_{2,4,6\text{-}Me}PCl$ containing chloroform. The active oxidant was found to be a carbonyl oxide species (see Fig. 15; it is worth recalling that a carbonyl oxide species has been suggested as the species responsible for the rate-enhancing effects of carbonyl bearing additives) and a phase transfer system was used to produce the complex mixture on a preparative scale.

Much more revealing were the results of ^{18}O-labelling epoxidation experiments, which suggested that the Mn(IV) oxo complex could react slowly to form only the *trans* epoxide of *cis*-β-styrene or disproportionation could occur to give only the *cis*-epoxide from a rapidly reacting and formally Mn(V) oxo complex. The paper concludes by using the *cis*/*trans*-epoxide ratios as a probe of the Mn(V)–Mn(IV) oxo complex distribution in *all* of the oxygen donor systems reported to 1987, both with and without pyridine as an axial ligand. The NaOCl and iodosobenzene systems were found to generate Mn(V)O in the presence of pyridine. In the absence of pyridine, the NaOCl system had varying Mn(IV)–Mn(V) distributions that depended on the batch

of NaOCl used. The effect of pyridine was ascribed to a reduction of the rate of decomposition from Mn(V) to Mn(IV), that is pyridine stabilizes the higher Mn(V) oxidation state.

In 1988, Goff and Rogers [211] reported the magnetic characterization of a number of high oxidation state manganese porphyrin complexes from the reactions of Mn(III)TPPCl with OCl_2, Cl_2 and *m*-chloroperoxybenzoic acid at low temperatures. The compounds were examined by NMR and EPR spectroscopies and significantly no Mn(V) complexes were detected, even in the presence of pyridine or hydroxide ions. However, an unidentified species was observed by NMR at the time of mixing of the reactants and this may be the complex detected by Groves.

The reaction of MnTPPCl or MnTPPOAC with OCl_2 at $-78°C$ permitted the spectroscopic detection of two kinetically favoured intermediates that decomposed to a third thermodynamically favoured derivative. One of the transient intermediates was identified as a manganese(IV) porphyrin π-cation radical, possibly having a bound oxygen atom, and the second thermally more stable intermediate was characterized as an oxoporphinatomanganese(IV) complex. The thermodynamically favoured derivative was demonstrated to be a manganese(III) isoporphyrin complex, the isoporphyrin being formed from the reaction of a manganese(III) porphyrin π-cation radical with chlorine atoms. The isoporphyrin complex did not form in the reaction of Mn(III)TPP and mCPBA unless Cl_2 was added. Isoporphyrin formation with common nucleophiles, such as hydroxide or even the water molecule, requires a doubly oxidized metalloporphyrin ring. Doubly oxidized complexes can be produced by disproportionation of singly oxidized systems. In 1988, Spreer et al. [212] detailed the formation of isoporphyrins from the nucleophilic attack of oxidized water-soluble manganese porphyrins by hydroxide ions and water molecules, so demonstrating that isoporphyrin formation is accessible in other manganese porphyrin oxidation systems.

The isoporphyrin characterized by Goff carried an oxidizing equivalent as the *meso*-chlorine is formally Cl(0). The reaction of this complex with cyclohexene resulted exclusively in allylic oxidation, whereas the oxoMn(IV) complex produced epoxidation. Isoporphyrin formation did not occur in the presence of 4-methyl pyridine, pyridine apparently maintaining a localization of oxidation on the metal, so preventing the formation of a Mn(III) porphyrin cation radical. Quenching of the isoporphyrin formation may also be assisted through chlorine complexation by the pyridine derivative. A twofold excess of hydroxide or tenfold excess of chloride ions resulted in metal rather than ligand oxidation. Metal-centred single-electron manganese porphyrin oxidation in the presence of excess chloride ions had previously been reported by Iwaizumi and Komura [213]. The $MnTP_{2,4,6\text{-}Me}PCl$ catalyst did not form an isoporphyrin complex and Goff attributed this to its more "robust"

character. An alternative explanation is that the complex forms a π cation radical but that the *ortho* phenyl substituents prevent access to the *meso* positions, where spin density in the a_{2u} orbital would accumulate and thereby provide a point of attack.

We have recently found that benzonitrile ligation produces model P-450 reaction characteristics indicative of metal-centred oxidation [68]. This observation, together with the similar effects, mentioned above, for the chloride ion in electrochemical oxidations, contradicts the generally accepted view that strong donor ligands are required for metal-centred oxidations in manganese porphyrins. Accordingly, we have suggested that hexacoordination is sufficient for the prevention of equatorial ligand oxidation and that pentacoordination facilitates electron loss from the porphyrin macrocycle. We have attributed this unusual property of manganese porphyrins to the uniquely similar energies of the metal $e_g(d_{xz},d_{yz})$ orbitals and the porphyrin $e_g(\pi^*)$ virtual orbitals. A further suggestion is that the stereochemical differences noted for the $MnTPP^+$ and $FeTPP^+$ model P-450 catalysts, may also be attributed to a significant interaction between the manganese e_g and porphyrin e_g orbitals. In early 1990, den Boer et al. [214] reported ab initio calculations on oxomanganese porphyrin chloride that show considerable metal–porphyrin orbital mixing at the anti-bonding level.

In 1987, Spreer et al. [215] described an interesting temperature-dependent valence isomerization in $MnTPP(CF_3SO_3)_2$. The single-electron oxidized complex changes from a Mn(III) π cation radical above 100 K to an Mn(IV) porphyrin at lower temperatures. The opposite behaviour has apparently been observed for $MnTPP(Cl)_2$ in which the ground state appears to be the porphyrin radical [216]. In the previous year, Spreer et al. [217] had described the crystal structure of the $MnTPP(Cl)(SbCl_6)$ porphyrin π cation radical and showed that ligation by the methoxide ion resulted in a shift in oxidation site from the porphyrin ligand to the metal ion. In 1982, Kelly and Kadish [218] provided a detailed study of the variation of oxidation and reduction potentials of MnTPPX for $X=ClO_4^-$, I^-, SCN^-, Br^-, Cl^-, and N_3^- in a variety of solvents. The oxidation potentials were found to vary little with counterion and this was interpreted as an indication of porphyrin ligand oxidation.

It seems reasonable to state that by 1989 a fairly detailed picture of the oxidation characteristics of manganese porphyrins had emerged. The two-electron oxidation of pentacoordinate manganese porphyrins initially produces a manganese(IV) porphyrin π cation radical. In contrast, the two-electron oxidation of hexacoordinate manganese porphyrins results in the formation of a very unstable manganese(V) porphyrin complex that, in organic solvents, can only be detected at very low temperatures. At low temperatures, the pentacoordinate manganese(IV) porphyrin π cation radical may decompose

to form a manganese(IV) porphyrin; either through solvent oxidation or the oxidation of residual water. At higher temperatures, the manganese(III) porphyrin π cation radical and manganese(III) isoporphyrin complexes become accessible, provided that the *meso* position is unhindered. The hexacoordinate Mn(V) manganese porphyrin complex decomposes to a manganese(IV) complex, which in turn may disproportionate between Mn(III) and Mn(V), with the cycle then being repeated.

D. OXIDATION MECHANISMS SUGGESTED BY THE IRON AND MANGANESE PORPHYRIN P-450 MODEL SYSTEMS

The mechanism of alkane hydroxylation by the purported Mn(V)=O complex shown in Fig. 17, is based on the detailed mechanism proposed by Hill and Smegal [200]. The escape of radicals results in halogenated and other minor side products. Not explicitly shown in the scheme is the possibility that tertiary substrate radical derivatives may undergo an outer sphere electron transfer to yield a carbocation before product formation. Evidence for free radicals is found in the detection of dicyclohexyl in the oxidation of cyclohexane and cyclohexylbenzene was detected when the reaction was performed in benzene. The effective use of free radical traps and solvent oxidation provide further support for a free radical mechanism. The product distributions in the hydroxylations studied by Hill and Smegal were used to suggest that the free radicals produced during the reaction had long lifetimes. Hill and Smegal recorded EPR evidence for the formation of Mn(II), which may then reduce any trapped Mn(IV) states.

Both Mn and Fe model catalyst studies have provided convincing support for the hydrogen abstraction and recombination mechanism. Groves and Nemo [219] have shown that iron porphyrin catalytic hydroxylations occur with a preference for tertiary alkane oxidation, alkane bromination is found on oxidation in the presence of $BrCCl_3$ and a large isotope effect in cyclohexane hydroxylations ($k_H/k_D = 12.9$) also supports a stepwise free radical mechanism. The detection by Nappa and Tolman [83] of cyclohexene in the hydroxylation of cyclohexane and the finding by Groves and Nemo [219]

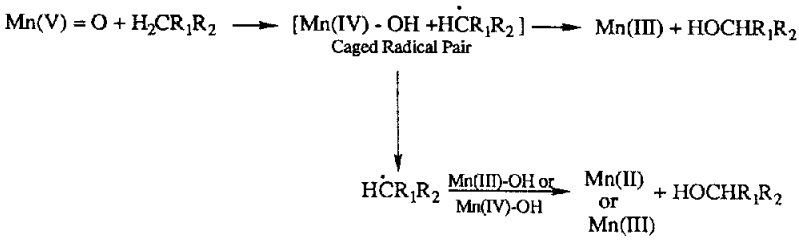


Fig. 17. Hydroxylation mechanism [200].

that the oxidation of cyclohexene in the presence of methanol produced 3-cyclohexenyl methyl ether in addition to epoxide, provides further evidence of the involvement of free radicals. Sorokin and Khenkin [220], in 1990, used tunnelling to explain the strong temperature dependence in aliphatic hydroxylations.

In 1983, Groves and Nemo [219] explained the sensitivity of the model catalyst hydroxylations to relatively small changes in the steric environment of the porphyrin periphery as being a reflection of the stereo-electronic constraints imposed by the oxy character of the singly occupied virtual metalloporphyrin orbital that is responsible for hydrogen abstraction, and this is depicted in Fig. 18. These steric constraints provide an understanding of the ability of some P-450 isoenzymes to synthesize primary alcohols through terminal hydroxylation of alkyl chains (steroids, fatty acids and alkanes). In 1986, Suslick et al. [84] found that the manganese and iron derivatives of the highly encumbered 5,10,15,20-tetrakis(2′,4′,6′-triphenylphenyl)porphyrin ligand exacted greater regioselectivity than some P-450 isoenzymes.

The product distributions and reaction kinetics of epoxidation reactions catalysed by iron and manganese porphyrin P-450 model compounds depend on the steric and electronic character of the substrate, porphyrin ligand, the axial ligand and the solvent. The diverse character of the model systems has resulted in the proposal of a number of reaction paths and intermediates and a summary of these proposals is depicted in Fig. 19. The mechanism by which allylic hydroxylation occurs (Fig. 5) was proposed in a 1984 paper by Groves and Subramanian [221] and the more recent work of Goff and Rodgers

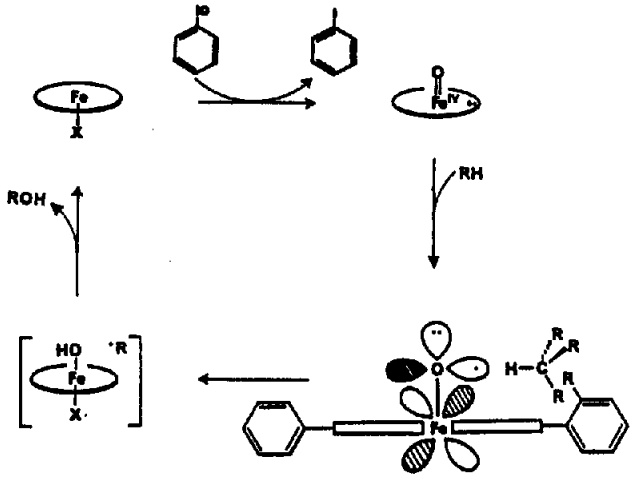


Fig. 18. Sterochemical constraints on hydroxylation [219].

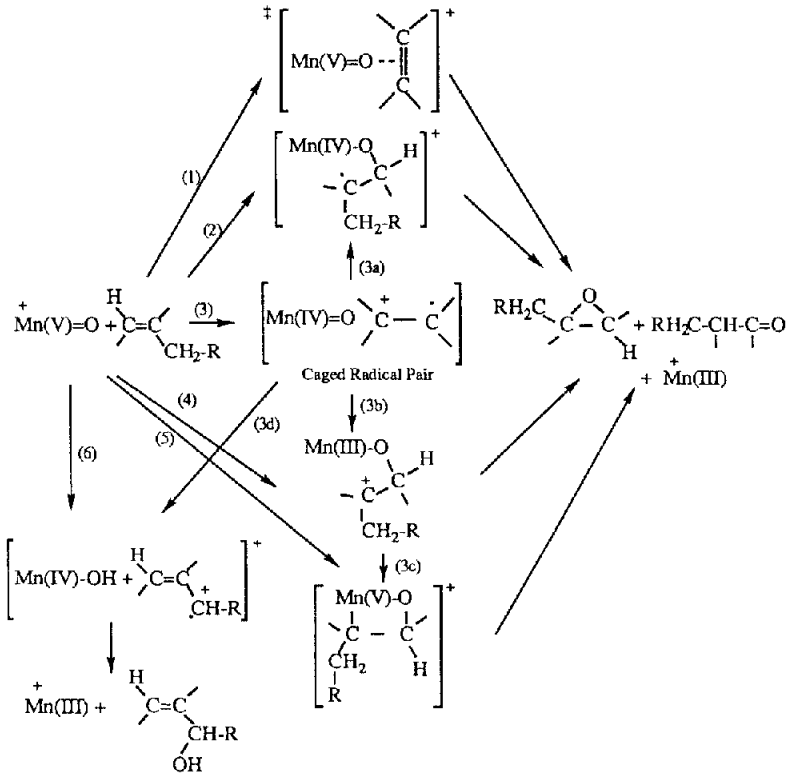


Fig. 19. Possible epoxidation mechanisms.

[211] suggests that the initial electron transfer may occur at the periphery of unprotected porphyrin ligands such as TPP.

During 1988, Castellino Bruice [222,223] reported the use of *cis*-stilbene and (Z)-1,2-bis(*trans*-2-*trans*-3-diphenylcyclopropyl)ethene as substrate probes of the catalytic paths taken by $FeTP_{2,3,4,5,6\text{-}F}PCl$, $FeTP_{2,6\text{-}Cl}PCl$ and $MnTP_{2,6\text{-}Cl}POH$ in dichloromethane with C_6F_5IO as the oxidant. Stereochemical and kinetic evidence is used by them to discount any significant involvement of the metal-bound radical species. The evidence presented by Castellino and Bruice favours the cationic intermediate, which may be formed directly or through collapse of the caged pair. A quasi-closed structure is suggested for the cationic intermediate, which may then form a metallaoxetane. In allowing such a structure, they acknowledge the evidence presented by Collman et al. [224,225] in 1986 that supports a closed intermediate (see Fig. 20). The formation of phenylacetaldehyde in the epoxidation of styrene by $FeTP_{2,3,4,5,6\text{-}F}PCl/C_6F_5IO$ or MnTPPCl/NaOCl/pyridine and a preference for *cis*-hydrogen migration during the aldehyde formation provide evidence to support the reversible 2+2 cycloaddition formation of a

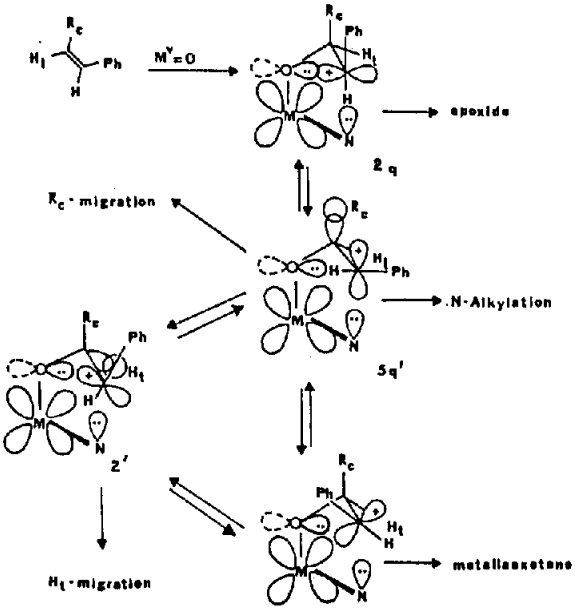


Fig. 20. Castellino and Bruice's styrene oxidation mechanism [222]. Reproduced with permission.

stereoretentive metallaoxetane intermediate. Collman et al. suggest that the metallocycle may collapse in a concerted fashion to yield epoxide or may break down in a stepwise fashion to give the aldehyde via a transition state having radical character. They point out that the two catalytic systems have very similar characters.

In 1984, Collman presented the results of a kinetic study of the MnTPPCl/imidazole/NaCOl system. Michaelis–Menton kinetics suggested the build-up of a reversible catalyst–substrate intermediate in this system, and Collman et al. [226] put forward the metallocycle as that intermediate. After finding that the catalyst is not starved of oxidant in the $C_6F_5IO/FeTP_{2,6\text{-}Cl}PCl$ system, Collman et al. [225] again found that reaction rates suggested the accumulation of an intermediate whose decomposition rate depended on the nature of the substrate. In a 1988 re-examination of the MnTPPCl/NaOCl system employed by Collman, Bruice and co-workers [227] found that if a metallaoxetane is formed, it does not accumulate.

However, in 1986 Groves and Watanabe [228] described the spectral observation of a reversible intermediate that formed rapidly on addition of alkene and *m*-chloroperbenzoic acid to a solution of $FeTP_{2,4,6\text{-}Me}PX$ (X = Cl, or OH) in methylene chloride at $-42°C$. The intermediate decomposed to yield epoxide and the decomposition was dramatically accelerated on addition of methanol or imidazole. The intermediate was too transient to

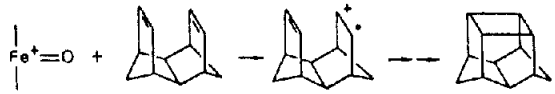


Fig. 21. Traylor and Miksztal's demonstration of single electron alkene oxidation [230].

permit structural characterization. Different spectral changes were found at room temperature by Traylor et al. [229] in 1987, when C_6F_5IO was added to a similar solution of catalyst and alkene. They isolated the complex responsible for the colour changes and showed it to be an *N*-alkylhaemin. The formation of this compound was also shown to be reversible and it was the only transient observed to accumulate. Presumably this compound is a side product of the intermediate observed by Groves and Watanabe.

In the same year, Traylor and Miksztal [230] exquisitely demonstrated that alkenes can undergo a single-electron outer sphere electron transfer to hypervalent oxo iron complexes, and the outcome of the transfer they detailed is shown in Fig. 21. The catalyst used in the demonstration was FeTPPCl and the oxidant employed was either *m*-chloroperbenzoic acid or C_6F_5IO in methylene chloride. The amount of alkene isomerization derived product increased on addition of acetonitrile or perchlorate ions and Traylor and Miksztal suggested that these additives accelerated radical diffusion from the caged pair. Given the unprotected nature of the TPP ligand, the electron transfer may occur at the periphery of the oxidized macrocycle of the active intermediate.

In the following year, Traylor and Xu [231] described a significant correlation between epoxidation reaction rate and alkene ionization potential and reinforced the well-documented correlation between reaction rate and alkene redox potential. Both of these observations were used to support outer sphere electron transfer as the process that initiates alkene oxidation. The catalyst used in this study was $FeTP_{2,6\text{-}Cl}PCl$ in conjunction with *m*-chloroperbenzoic acid or C_6F_5IO in a methylene chloride/methanol/water solvent mixture. Traylor and Xu indicated in this paper that homogeneous and heterogeneous catalytic systems share the described correlations. In 1989, Traylor and Miksztal compared the catalytic epoxidation characteristics of Fe(III), Mn(III) and Cr(III) porphyrins and attributed differences to electron density variations at the metal centre [232] (iron porphyrins being most deficient, then manganese and then chromium). Accordingly, iron porphyrin epoxidations were seen as proceeding through an electron transfer-initiated process, while chromium porphyrins catalysed an electrophilic addition process. Surprise was expressed at the lack of influence of nitrogenous ligands on the iron porphyrin catalytic behaviour. The addition of 1-methylimidazole did not influence the *exo/endo* ratio in norbornene epoxidations driven by iron

porphyrins. A possible explanation is that the catalyst orbital responsible for initiating electron transfer, is sensitive to the type of charge donation from the *trans* axial ligand [68]. In other words, the influence of the *trans* axial ligand may depend on its σ and π donor capacity.

Traylor points out that the principal evidence against metallaoxetane involvement are the skeletal and cation radical alkene rearrangements that accompany model catalyst epoxidations. Collman's argument is that such rearrangements may occur through the breakdown of the metallocycle. In 1986, Traylor et al. [233] monitored the ratios of *exo*- to *endo*-epoxynorbornane obtained from the oxidation of norbornene by a variety of (tetraarylporphyrinato)iron(III) chloride catalysts. The ratios were found to vary from 50 to 3, with the lowest ratios being returned by the most electron-deficient catalysts. These ratios were used to rule out any kind of direct attack on the alkene by the oxo catalyst, as such attack is known to lead exclusively to the *exo* product. The results were suggested as being most consistent with the known behaviour of the 2-norbornyl radical and accordingly the reaction outcomes were rationalized as the result of electron transfer to form a caged pair, with subsequent collapse to form a carbocation. The variation in ratios was explained as a reflection of electronic control of the caged pair exerted by each of the catalysts used.

A reconciliation of the results of the model studies outlined above must admit the possibility of multiple catalytic pathways, the particular product route followed being determined by the geometry and electronic topology of the catalyst and the nature of the substrate suffering oxidation. There remains the possibility that single-electron alkene oxidation and substrate rearrangements are processes independent of the production of epoxide. The only recent support for a direct "singlet oxygen"-like insertion into alkenes from iron porphyrin catalysts comes from the 1988 paper of Sawyer and coworkers [67] that purports the identification of an oxo Fe(II) π cation radical intermediate. Some of the product distributions presented were indeed those expected of a direct and concerted insertion, for instance only *exo*-epoxynorbornane was returned from norbornene when *m*-chloroperbenzoic acid was used as the oxygen source. The product distributions returned by C_6F_5IO are less convincing and, given the incomplete characterization of the intermediate, the significance of these results cannot be assessed.

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