Metalloporphyrins as Versatile Catalysts for Oxidation Reactions and Oxidative DNA Cleavage

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Received April 22, 1992 (Revised Manuscript Received July 30, 1992)

Contents

1. Introduction

A. Aims and Scope

The past decade should be considered as the decisive period for the development of oxidation reactions catalyzed by synthetic metalloporphyrin complexes. A

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Bernard Meunier was born in Poitiers, France, in 1947. He studied chemistry at the University of Poitiers before moving to the University of Montpellier to obtain a first doctorate with Robert Corriu. He joined Hugh Felkin in 1973 at the Institut de Chimie des Substances Naturelles at Gif-sur-yvette and obtained his second doctorate in 1977. Following postdoctoral works in crystallography with Keith Prout at Oxford University and Claudine Pascard at Gif-sur-yvette, he moved to the Laboratoire de Chimie de Coordination du CNRS at Toulouse in 1979, where he is presently as CNRS research director. His early research interests included catalytic activation of Grignard reagents by nickel and titanium complexes in organosilicon chemistry, preparation and reactivity of inorgano-Grignard reagents, coupling reactions catalyzed by iron complexes. Since 1979 his current research subjects are focused on oxidations catalyzed by metalloporphyrins using bleaching agents as primary oxidants (NaOCl and $KHSO_5$), ligninase models, molecular pharmacology of antitumor agents (ellipticines and bleomycine), DNA cleavage by manganese porphyrins, and synthesis of cytotoxic hybrid molecules (metalloporphyrin vector).

computer-search in the Chemical Abstracts files using a combination of the following three key words /porphyrin/oxidation/catal/ from 1979 to 1990 indicates that 496 papers appeared in this field with a regular increase every year (Figure 1). In the area of oxidations catalyzed by transition-metal complexes,[1,2] synthetic metalloporphyrins occupy a particular place: they are analogues of the prosthetic group of heme-containing enzymes which selectively catalyze various oxidation reactions with the same transition metal (iron) and the same macrocyclic ligand (protoporphyrin IX); however, in the chemical system, selectivity is obtained by choosing among all possible different metals and ligands. Biological oxidations by heme enzyme can be classified as follows: oxygenations of organic substrates catalyzed by cytochrome P-450,[7] oxidations by peroxidases,[8] oxidative halogenations by chloroperoxidases,[9] and hydrogen peroxide dismutation by catalase.[10]

[An oxygenation reaction is regarded as an incorporation of one (monooxygenase) or two (dioxygenase) oxygen atoms in the substrate and an oxidation reaction as an electron abstraction (one, two, or four electrons) from the substrate and transfer to the oxidant which acts as final electron acceptor (if dioxygen is the oxidant, a one-, two-, or four-electron oxidation generates superoxide anion, hydrogen peroxide, or water, respectively and if hydrogen peroxide is the enzyme cofactor, a two-electron process gives water). The concept of oxygenation was initially proposed by Lavoisier[3] for chemical oxidations. The term of oxygenase was initially introduced by Bach and Chodat[4] for enzymes and resurrected by Hayaishi.[5] (For a recent survey in biological oxidation systems, see reference.)[6]]

The control of the catalytic activity of these heme enzymes, in terms of substrate specificity, chemoselectivity, oxidant activation, or oxidation rate, is not

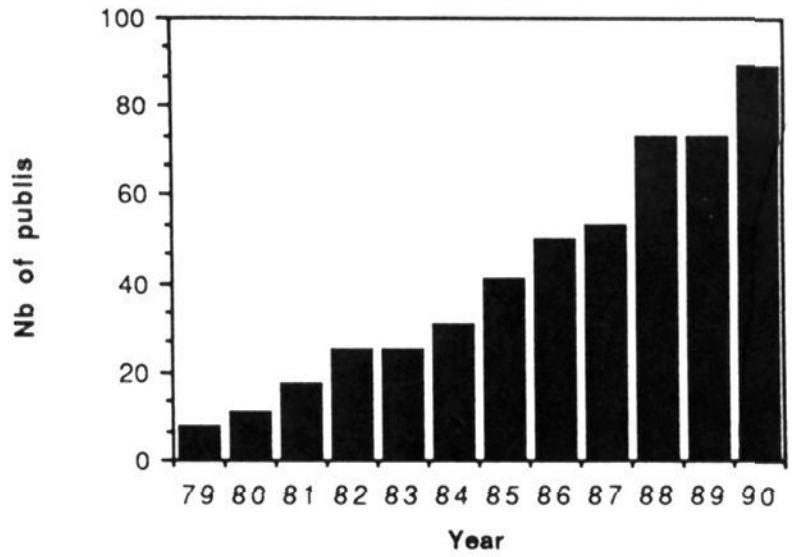


Figure 1. Number of publications per year filed by Chemical Abstracts related to the following three key words: /porphyrin/oxidation/catal/ over the period 1979–1990.

due to the metal itself or the tetrapyrrole ligand but to the proximal ligand, the distal amino acid residues and the protein itself. In cytochrome P-450 a cysteinato ligand is attached to the iron, and there are no close contacts with amino acids in the distal site,[7,11,12] whereas in peroxidases histidine is the proximal ligand while distal amino acids, close to the prosthetic group, are present to favor the heterolytic cleavage of the O–O bond of hydrogen peroxide by a push–pull mechanism.[8,11] Similar distal residues are present in catalase but in this case the proximal ligand is a tyrosine residue.[10]

Recent advances in the field of monooxygenases concern the three-dimensional structure of cytochrome P-450 from *Pseudomonas putida*[12] and the cloning of various P-450 genes.[13] X-ray studies on P-450 which crystallized with or without the camphor substrate indicate how a hydrogen bond interaction of the 2-keto group with Tyr-96 and weak hydrophobic interactions with Phe-87, Leu-244, Val-247, Thr-252, and Val-295 are sufficient to organize the exact fitting of the substrate inside the active site, then making possible the specific hydroxylation at the 5-exo position. More or less simultaneously, the complete amino acid sequence of cytochrome P-450s was described by Fujii-Kuriyama et al. by using recombinant DNA technology.[13] The cloning and the sequencing of corresponding cDNAs allowed the prediction of the amino acid sequence of more than a hundred cytochromes P-450, which can be more easily compared and classified.[14]

The availability of cDNAs allows the evaluation of the catalytic role of specific amino acids by site-directed mutagenesis studies. The simple mutation of Phe-209 by Leu in the cytochrome $P\text{-}450_{coh}$ which catalyzes the 7-hydroxylation of coumarin is sufficient to obtain a 15 α-hydroxylase activity such as that afforded by $P\text{-}450_{15\alpha}$, the enzyme catalyzing the 15 α-hydroxylation of testosterone derivatives.[15] These two enzymes differ by only 11 amino acids on the same total of 494 residues. By manipulating three active site residues in cytochrome P-450, Val-295, Val-247, and Tyr-96, Atkis and Sligar demonstrated that only the mutation at Tyr-96 has an important effect on the loss of hydroxylation specificity.[16]

So, on the one hand protein engineering is going to produce monooxygenases with predictable regio- and stereospecificity but with limitations inherent to enzymes of this category, viz. cofactor regeneration and difficulty in immobilizing a multienzyme system, while

on the other hand we have the development of new generations of synthetic metalloporphyrins which are able to reproduce and mimick all these different heme-enzyme-mediated reactions: oxygenation, oxidation, oxidative chlorination, and dismutation. This similarity is one of the obvious driving forces for studying metalloporphyrin-catalyzed reactions. The second one arose from the necessity of producing valuable chemicals from oil derivatives by selective oxygenation reactions. Yet, this is not the case at the present time since most of the reactions performed at the industrial scale are based on autoxidation reactions.[17-20] Small amounts of cobalt or manganese salts are catalysts for oxidation of saturated hydrocarbons by molecular oxygen at mild temperatures (70–150 °C), the key step being the fast reaction of free organic radicals with molecular oxygen to yield hydroperoxides and other oxygenated molecules such as peroxides, alcohols, ketones, aldehydes, and acids. Autoxidation reactions, by producing free radical organic intermediates, overcome the spin conservation selection rule which is against the direct reaction of triplet dioxygen with singlet hydrocarbons,[21,22] but they give a mixture of different products and reasonable selectivities are only obtained at low substrate conversions.[19]

Among the selective reactions which are not accessible by currently used autoxidation catalysts, one can note: (i) the selective hydroxylation of saturated alkanes to alcohols, (ii) the stereospecific activation of a saturated prochiral C–H bond to create a C–O bond and a chiral center, and (iii) the asymmetric epoxidation on non-activated olefins. An important achievement over the last decade was the highly stereoselective epoxidation of allylic alcohols by the Sharpless reaction which is based on titanium(IV) isopropoxide, an alkyl hydroperoxide and diisopropyl tartrate.[23,24]

In this review article, mainly based on the literature between 1985 and May/June 1991 (earlier literature is available in several accounts[25-30]), we attempt to present a comprehensive view of two main topics of different size in terms of number of references: the first one will be devoted to the chemical aspects of metalloporphyrin-catalyzed oxidations and the second one to the oxidative DNA cleavage by activated metalloporphyrins. The chemical oxidations are classified by the type of catalytic reactions: epoxidations in section II, hydroxylations in section III, and various organic molecule oxidations in section IV. All these sections are subdivided with respect to the oxidant (iodosylbenzene, hypochlorite, dioxygen, hydrogen peroxide, alkyl hydroperoxides, monopersulfate, etc.) and the metal of the metalloporphyrin (iron, manganese, etc.). Reactions catalyzed by chiral metalloporphyrins or supported metalloporphyrins are reported in sections V and VI. A particular section (VII) is devoted to the characterization of high-valent metal–oxo porphyrin complexes which are the active species in those catalytic oxygenation and oxidation reactions. Oxidative DNA cleavage data are presented in section VIII, and finally, recent advances in the preparation of porphyrin ligands are described in section IX. The abbreviations used throughout this review are listed in section XI (we tried to observe as strictly as possible the IUPAC recommendations on the tetrapyrrole nomenclature[31], i.e. the name porphin, as well as α, β, γ, and δ for the meso positions have not been used).

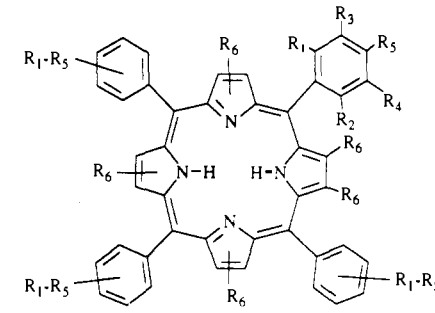


Figure 2. Structures of various synthetic hydrophobic porphyrin ligands. H_2TPP: R_1–R_5 = H, R_6 = H. H_2TMP: R_1 = R_2 = R_5 = Me, R_3 = R_4 = H, R_6 = H. H_2TPFPP: R_1–R_5 = F, R_6 = H. H_2TDCPP: R_1 = R_2 = Cl, R_3–R_5 = H, R_6 = H. H_2Br_8TDCPP: R_1 = R_2 = Cl, R_3–R_5 = H, R_6 = Br. H_2Cl_8TDCPP: R_1 = R_2 = Cl, R_3–R_5 = H, R_6 = Cl. H_2Br_8TMP: R_1 = R_2 = R_5 = Me, R_3 = R_4 = H, R_6 = Br. $H_2Cl_{12}TMP$: R_1 = R_2 = R_5 = Me, R_3 = R_6 = Cl, R_4 = H. H_2F_8TPFPP: R_1–R_5 = F, R_6 = F.

B. Early Works (1979–1980) on Oxygenation Reactions Catalyzed by Metalloporphyrin Complexes

Before beginning in the detailed report on metalloporphyrin-catalyzed oxidations, early works published in 1979 and 1980 will be summarized. Within 10 papers, the concept of the association of a simple oxygen atom donor with a synthetic metalloporphyrin was introduced in the field of catalytic oxidation, a rather crowded area.

In 1979, Groves et al. published the first article on the use of iodosylbenzene as simple oxygen atom donor in olefin epoxidations and alkane hydroxylations,[32] catalyzed by Fe(TPP)Cl (see Figure 2 for porphyrin structures).

$$\text{olefin (or alkane)} + \text{PhIO} \xrightarrow{\text{Fe(TPP)Cl}} \text{epoxide (or alcohol)} + \text{PhI}$$

Cyclohexene preferentially gives cyclohexene oxide, but the allylic oxidation product, cyclohexenol, is also detected (epoxide/allylic alcohol ratio = 3.6/1). Adamantanol, a paradigm molecule to evidence a C–H activation reaction, is oxidized to a mixture of adamantanol-1 and -2 without subsequent oxidation of adamantanol-2 to the corresponding ketone. This behavior is expected for a good cytochrome P-450 model. Thus the high-valent metal–oxo porphyrin complex has a pronounced "oxygenase character", rather than an "oxidase character", at least when an alkane is present in a large excess in the reaction medium. In the case of a heme oxygenase, the hydrophobic pocket of the active site largely helps to switch between these two activities. The entrance of the alkane inside the hydrophobic site of the enzyme triggers the oxygen activation cycle and, furthermore, the released hydroxylated substrate, a hydrophilic molecule, is then a poor competitor with respect to the alkane substrate for the uptake by the hydrophobic pocket of P-450.

meso-Tetraarylporphyrins are suitable synthetic ligands in these PhIO oxidations catalyzed by metalloporphyrins (Figure 2). Flat ligands, such as protoporphyrin IX or octaethylporphyrin, with no substituents at meso positions are more reactive toward meso cleavage via the formation of a *meso*-hydroxyporphyrin derivative.[33] Not only iron, but also chromium[34] and

manganese[35,36] TPP complexes are able of catalyzing the oxygen atom transfer from PhIO to an olefin or an alkane.

Cr(TPP)Cl stereospecifically catalyzes the epoxidation of *cis*-olefins, including *cis*-stilbene, but allylic oxidation products are the main reaction products in cyclohexene oxidation.[34] Mn(TPP)Cl, in contrast with the corresponding iron complex, gives a mixture of the cis and trans isomers in the case of *cis*-stilbene (*cis*-/*trans*-epoxide ratio = 38/62). This loss of stereochemistry can be explained by the formation of a carbon-centered radical with a life time long enough to allow isomerization by a C–C bond rotation (Figure 3).[35,36] In alkane activation catalyzed by Mn(TPP)Cl, the product distribution argues for the presence of fairly long-lived free alkyl radicals as precursors of both alcohol and halide products.[36]

Diluted aqueous solutions of sodium hypochlorite, NaOCl, can be used as oxygen atom source in the Mn(TPP)OAc-catalyzed oxidation of benzylic alcohol to benzaldehyde[37] or the epoxidation of styrene.[38]

$$PhCH{=}CH_2 + NaOCl \xrightarrow[CH_2Cl_2/H_2O]{Mn(TPP)OAc/R_4N^+Cl^-} PhCH(O)CH_2 + NaCl$$

This catalytic epoxidation with NaOCl is performed in a biphasic system (dichloromethane, water). A phase-transfer agent is necessary to increase the concentration of OCl^- ions in the organic phase where the catalyst is soluble.

The third early approach to oxygenations catalyzed by metalloporphyrin was proposed by Tabushi by using molecular oxygen in the presence of sodium borohydride[39] or a tetraalkylammonium borohydride.[40]

$$\text{cyclohexene} \xrightarrow[Mn(TPP)Cl]{O_2/NaBH_4} \text{cyclohexanol (80\%)} + \text{cyclohex-1-en-3-ol (20\%)}$$

No cyclohexene oxide is detected in this attempt to mimick the "long cycle" of cytochrome P-450, the epoxide being quickly reduced to the corresponding alcohol.

When an alkyl hydroperoxide is used as oxygen atom source in an oxygenation reaction catalyzed by a metalloporphyrin, the major difficulty is to avoid the production of RO• radicals by either homolytic cleavage of the peroxidic O–O bond or other pathways.[41]

$$[por\text{–}M^{III}] + ROOH \rightarrow [por\text{–}M^{IV}\text{–}OH] + RO^{\bullet}$$

In this case, an alkane hydroxylation reaction is observed because of the hydrogen atom abstraction from alkane C–H bonds by RO•, but olefin epoxidations are not catalyzed, an observation which supports the belief that a metal–oxo porphyrin complex is not directly involved in these ROOH alkane hydroxylations. This hypothesis was confirmed later by using different metalloporphyrin complexes having restricted access to the metal–oxo species.[42]

The different metal derivatives of H_2TPP constitute the *first generation of metalloporphyrin catalysts* used in oxygenation reactions. The second generation of tetraarylporphyrins is represented by *meso*-tetrakis(pentafluorophenyl)porphyrin, H_2TPFPP,[43] *meso*-tetramesitylporphyrin,[44,45] H_2TMP, and *meso*-tetrakis(2,6-dichlorophenyl)porphyrin, H_2TDCPP,[46,47] and related ligands where alkyl or halogen substituents have been introduced at the ortho, meta, or para positions of the phenyl groups of the macrocycle meso positions, in order (i) to provide steric effects, i.e. a cage effect or an open-well effect, to avoid the formation of catalytically inactive μ-oxo complexes and/or (ii) to enhance the electrophilicity of the metal–oxo entity by electron-withdrawing substituents on phenyl rings.

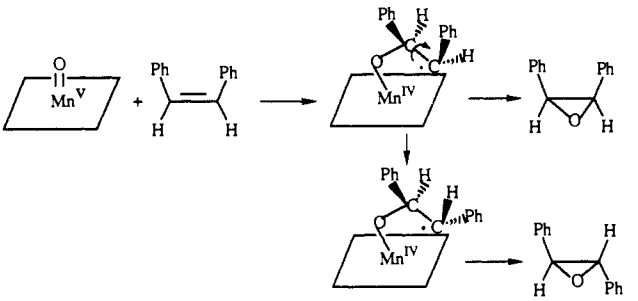


Figure 3. Isomerization procedure during the *cis*-stilbene epoxidation by the PhIO/Mn(TPP)Cl system.

$$[por\text{—}M^{n+1}{=}O] + [por\text{—}M^{n-1}] \rightarrow [por\text{—}M^{n}\text{—}O\text{—}M^{n}\text{—}por]$$
(μ-oxo dimer)

The third generation is an extension of the previous idea by having bromine, chlorine, or fluorine atoms at the β-positions of pyrroles such as *meso*-tetrakis(2,6-dichlorophenyl)-β-octabromoporphyrin, H_2Br_8TDCPP,[48] *meso*-tetrakis(2,6-dichlorophenyl)-β-octachloroporphyin H_2Cl_8TDCPP,[49] *meso*-tetramesityl-β-octabromoporphyrin, H_2Br_8TMP,[50] *meso*-tetrakis(2,4,6-trimethyl-3-chlorophenyl)-β-octachloroporphyrin, $H_2Cl_{12}TMP$,[50a] and a "Teflon" ligand, *meso*-tetrakis(pentafluorophenyl)-β-octafluoroporphyrin, H_2F_8TPFPP.[51] The structures of these different porphyrins are shown in Figure 2 and references given in the present paragraph correspond to articles where these ligands where first mentioned in catalytic oxidations (two groups are cited in the case of independent reports which appeared the same year). New methods for efficient syntheses of these porphyrin ligands will be detailed in section IX.

II. Olefin Epoxidations Catalyzed by Metalloporphyrins

The epoxidation of olefins is still an attractive reaction which is greatly used in organic synthesis.[52-54] In one reaction, two C–O bonds are created as well as two chiral centers in the case of an asymmetric epoxidation reaction.[24] The peracid method is widely used in organic syntheses but is limited to the preparation of nonacid sensitive epoxides. The transition-metal-catalyzed epoxidation of olefins by alkylhydroperoxides is currently performed at the industrial scale (Halcon process, i.e. propene epoxidation with *t*-BuOOH and a molybdenum catalyst)[55] or in the production of fine chemicals with the Sharpless reaction[24] (for recent review articles on epoxidative reactions catalyzed by transition-metal complexes, see refs 55 and 56). In this context there is a place for metalloporphyrin-catalyzed epoxidation for the following reasons: (i) a large variety of oxidants

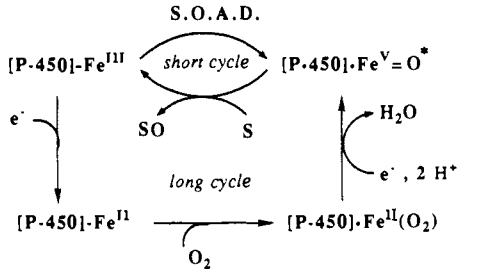


Figure 4. Generation of a "short" cytochrome P-450 catalytic cycle with oxygen atom donors (SOAD = PhIO, NaOCl, etc) as opposed to the "long" cycle with molecular oxygen and electrons. (*The exact iron oxidation state in active P-450 is still an open question, see text. The alternative proposal is an iron(IV)–oxo porphyrin radical cation as in HRP compound I.)

can be used (iodosylbenzene, hypochlorite, organic or inorganic peroxides, molecular oxygen, and an electron source), (ii) a wide range of reaction conditions can be employed (mono- and biphasic systems and, in both cases, soluble or supported catalysts), and (iii) the design of sophisticated porphyrin ligands allows shape-selective epoxidations as well as the asymmetric epoxidation of simple olefins (see section V).

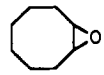
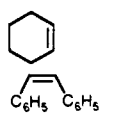
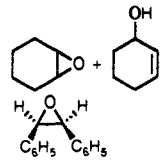
The recent advances in this section will be presented according to the oxidant serving as oxygen atom donor with the metalloporphyrin catalyst. More than two-thirds of the references on metalloporphyrin-catalyzed reactions deal with olefin epoxidations. In fact, this is now the most achieved reaction catalyzed by synthetic porphyrin complexes. This reaction is stereospecific for aliphatic olefins, highly regioselective, diverse with regard to the oxygen atom sources which can be used, effective with respect to yield and exceptionally fast when carried out with the appropriate metalloporphyrin catalysts.

A. Epoxidation with PhIO and Related Oxidants

Iodosylbenzene, PhIO, is easily prepared from NaOH hydrolysis of iodobenzene diacetate[57] (commercially available) which is more stable than iodobenzene dichloride.[58] Iodobenzene diacetate is prepared by peracetic acid oxidation of iodobenzene.[59] In addition, ^{18}O-labeled iodosylbenzene can be prepared by the hydrolysis of iodobenzene dimethoxide with $H_2{}^{18}O$.[60] (Since the 9th Collective Index (1972–1976) of Chemical Abstracts Service, PhIO is named iodosylbenzene instead of iodosobenzene. We shall use the term iodosylbenzene throughout this article.)

Iodosylbenzene was initially used as a single oxygen atom donor in reactions catalyzed by cytochrome P-450 at a period of time when the exact nature of active species of heme monooxygenases was a matter of debate.[7b,61,62] In the absence of molecular oxygen and NADPH, oxygen surrogates such as PhIO, $NaIO_4$, H_2O_2, or ROOH were used to reproduce the main reactions, hydroxylation or O-dealkylation reactions, catalyzed by cytochrome P-450. The hypothesis of a high-valent ferryl species Fe^V=O as reactive entity in enzyme-catalyzed oxidations was then considered as a reasonable possibility (see Figure 4 for a schematic representation of the catalytic cycle of cytochrome P-450 and the possible shunt with simple oxygen atom donors such as iodosylbenzene). After these brief remarks on the use of PhIO in cytochrome P-450 mediated oxidations, olefin epoxidations with PhIO catalyzed by metalloporphyrins will be detailed according to the nature of the central metal atom.

Table I. PhIO Olefin Epoxidations Catalyzed by Fe(TPP)Cl[a] (from ref 44; copyright 1983 American Chemical Society)

	Fe(TPP)Cl		93%
	Fe(TTP)Cl		84%
	Fe(TTP)Cl		67%, 3%
	Fe(TPP)Cl		0%[b]
	Fe(TPP)Cl Fe(TTP)Cl FePPIX-DME Fe(TPP)Cl		55%, 15% 67%, 15% 22%, 5% 77%[c]

[a] Yield based on iodosylbenzene consumed. [b] On standing with iodosylbenzene alone, cyclohexenone produced small amounts of epoxide. [c] *trans*-Stilbene oxide was not produced.

(Fe^V=O is a formal representation of the active species of cytochrome P-450 with the only merit of indicating that this species is two redox equivalents above the resting state of the enzyme (Fe^{III}). Fe^{IV}–O· is another possible structure, as well as (Por·$^+$)Fe^{IV}=O as in compound I of peroxidases. However, recent resonance Raman excitation profile spectroscopic data seem to indicate that the active species in P-450 does not resemble that of horseradish peroxidase.[63] The cysteine sulfur ligand of cytochrome P-450 may play an important role, not only in the dioxygen cleavage step, but also in the stabilization of an oxy radical character of the metal–oxo entity when formulated as Fe^{IV}–O·. However, the active species of chloroperoxidase, which also presents a cysteinato residue as proximal ligand, is recognized as being a (Por·$^+$)Fe^{IV}=O entity.[64] Thus, the hydrophobic pocket of the P-450 active site might also contribute to the electronic configuration and the nature of the active species. For a presentation of isolated high-valent metal–oxo porphyrin complexes, see section VII.)

1. Iron Porphyrins

The PhIO epoxidation of olefins catalyzed by Fe(TPP)Cl is stereospecific, *cis*-olefins give only *cis*-epoxides.[32,44] Dienes are oxidized to corresponding monoepoxides and norbornene gives 67% of the *exo*-epoxide and only 3% of the *endo*-epoxide (see Table I). A remarkable feature of the PhIO/Fe(TPP)Cl catalytic system is the high reactivity of *cis*-olefins compared the trans isomers.[44] *meta*-Chloroperbenzoic acid epoxides *cis*- and *trans*-stilbene at equal rates at room temperature, whereas the *cis*-epoxide is formed 15 times faster than the *trans*-epoxide in the metalloporphyrin-catalyzed epoxidation. This selectivity results from nonbonding interactions between the olefinic substrate and the phenyl groups at the meso positions of the macrocycle. The selectivity in favor of the *cis*-olefin is enhanced when TMP is the ligand, but highly reduced in the case of the flat iron–protoporphyrin catalyst.[44,65]

As expected for an electrophilic high-valent iron-oxo species as active intermediate, a fully methylated olefin such as 2,3-dimethyl-2-butene, i.e. a very electron-rich olefin, is 200 times more reactive than 1-octene.[66] A Hammet treatment of data obtained with para- and meta-substituted styrenes gives a ρ value of −0.93, slightly below the ρ value found in the peracid epoxidation of olefins.[67]

The stability of this iron–TPP catalyst is greatly enhanced when pentafluorophenyl substituents occupy the meso positions of the porphyrin ring.[43] Not only is Fe(TPFPP)Cl a more efficient catalyst in olefin epoxidation, it also displays a significant NIH shift (72% of deuterium retention) during the oxidation of *p*-D-anisol to *p*-methoxyphenol.[43] (For a review article on the deuterium shift observed in arene oxide intermediates generated by monooxygenases, the so-called NIH shift, see ref 68.) An even more robust iron catalyst is Fe(TDCPP)Cl, the iron(III) derivative of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin. When associated with iodosylpentafluorobenzene, C_6F_5IO,[69] up to 10 000 molecules of norbornene oxide can be produced per molecule of catalyst.[46] (***Caution***: An explosion has been reported during one preparation of iodosylpentafluorobenzene: see Collman, J. P. *Chem. Eng. News* **1985**, March 18, 2. For a detailed preparation of C_6F_5IO, see ref 99a.) This oxidant reacts directly with only very electron-rich olefins, but the reaction with iron(III) porphyrins is much more rapid, even in dichloromethane where this material is insoluble (iodosylbenzene is also insoluble in this solvent). Homogeneous solutions of C_6F_5IO (up to 0.03 M) can be obtained in a mixture of dichloromethane, methanol, and water (80/18/2).[70] In this case the reactive species is not iodosylpentafluorobenzene itself, but an adduct with one molecule of alcohol which has a peracid-like structure.

$$C_6F_5IO + ROH \rightleftharpoons C_6F_5I(OH)OR$$

This adduct reacts very slowly with olefins, but is a very efficient oxygen atom donor to iron porphyrins.[46]

Many studies are available concerning the mechanism of PhIO olefin epoxidations catalyzed by iron porphyrins. They can be classified in three different categories: (i) isolation of high-valent iron porphyrin intermediates (see section VII), (ii) product analyses, or (iii) kinetic studies. From data presented in section VII, all discussions on product analyses and kinetic studies implicate a high-valent iron–oxo porphyrin radical cation, $(Por^{\bullet+})Fe^{IV}=O$, as oxidizing species which reacts with an olefin by different possible reaction pathways: (i) a direct oxygen atom transfer, (ii) a free radical addition followed by a fast ring closure, (iii) an electrophilic addition and fast ring closure, (iv) a reversible metallaoxetane formation, and (v) an electron transfer followed by a collapse to a radical or to a carbocation (all these routes are depicted in Figure 5).[71]

Product Analyses. With iodosylbenzene and Fe(TPP)Cl, norbornene gives mainly the exo epoxide,[44] but with iodosylpentafluorobenzene as oxidant, the ratios of *exo*- to *endo*-norbornene oxides vary from 38/1 with Fe(TPP)Cl as catalyst to 23/1 with Fe(TMP)Cl and 9/1 with Fe(TDCPP)Cl.[71]

The increase of *endo*-norbornene oxide with very reactive iron catalysts suggests that besides a direct attack of the iron–oxo species on norbornene, there is

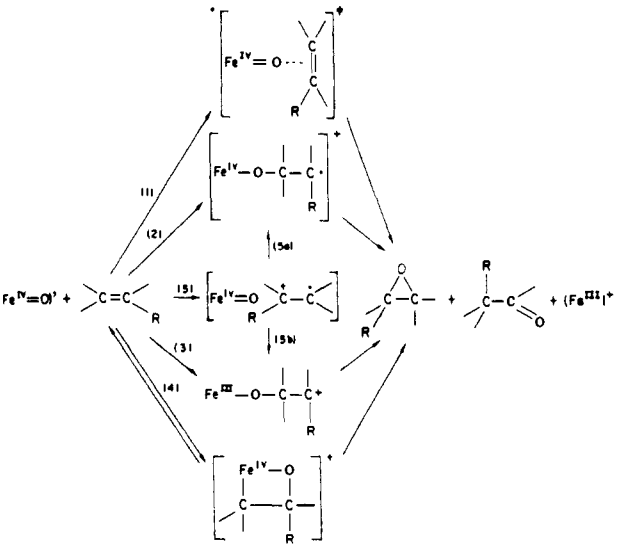
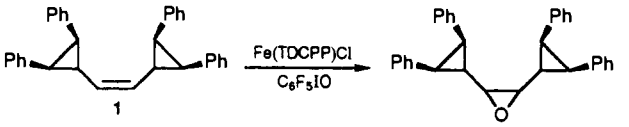


Figure 5. Different possible reaction pathways in the reaction of a high-valent iron–oxo porphyrin intermediate with an olefin: direct oxygen atom transfer (eq 1), free radical addition followed by fast ring closure (eq 2), electrophilic addition and fast ring closure (eq 3), reversible metallaoxetane formation (eq 4), and electron transfer followed by a collapse to a radical (eq 5a) or to a carbocation (eq 5b). Reproduced from ref 71a. Copyright 1986 American Chemical Society.

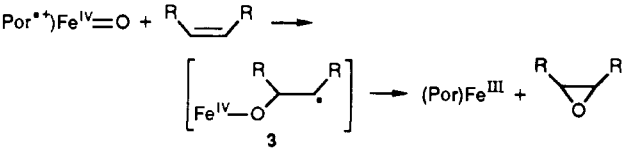
a pathway involving an electron transfer from the olefin to the high-valent metalloporphyrin followed by a radical collapse to give a carbocation intermediate with a metal–carbon bond (eq 5b in Figure 5).[71] This mechanism also explains the formation of small amounts of *cis*-cyclooctene oxide and cycloheptanecarboxaldehyde in the *trans*-cyclooctene epoxidation by iodosylxylene and Fe(TPP)Cl.[72] In a search for radical intermediates in PhIO epoxidations of olefins catalyzed by iron porphyrins, Bruice and Castellino used the cis olefinic substrate 1 with *trans*-2,*trans*-3-diphenylcyclopropyl substituents to trap possible olefin radical cation intermediates resulting from an electron transfer from the olefin to the high-valent iron–oxo complex (eq 5b, Figure 5).[73]



1

2 (yield = 89%)

The only detected product of the C_6F_5IO oxidation catalyzed by Fe(TDCPP)Cl was the corresponding *cis*-epoxide **2**, devoid of *trans*-epoxide or products resulting from the opening of a cyclopropyl radical to a homoallylcarbinyl radical which occurs with a rate constant > 10^{10} s^{-1}. This experiment suggests that a neutral radical species like **3** cannot be a discrete intermediate in the iodosylbenzene epoxidation catalyzed by iron porphyrins.[73] The same conclusion is also valid for manganese complexes. In addition, these experiments ruled out free organic radical intermediates.

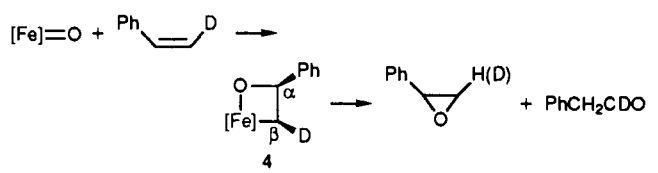


3

Collman et al. provide experimental support for a concerted oxygen-transfer mechanism in the study of the oxygenation of styrene by iron (or manganese) porphyrin complexes.[74] Phenylacetaldehyde is a pri-

$$PhCH{=}CH_2 \xrightarrow[C_6F_5IO]{Fe(TDCPP)Cl} PhCH(O)CH_2 + PhCH_2CHO \quad (13{:}1)$$

mary oxygenation product and does not arise from epoxide isomerization (see also refs 44 and 75 for previous reports on phenylacetaldehyde formation). Only 1-*d*-phenylacetaldehyde was observed in the oxygenation of *cis*-β-deuteriostyrene, suggesting that the aldehyde resulted from a stereoselective migration of the β-hydrogen atom of a metallaoxetane intermediate **4**.



4

This metallaoxetane was initially proposed in kinetic studies in the NaOCl/Mn(Por)Cl system (see section II.B.2) and extended to the case of PhIO/Fe(Por)Cl.[74b] Such a metallaoxetane intermediate was previously proposed by Sharpless et al. to explain the formation of epoxides, chlorohydrins and dichlorides in the oxidation of olefins by chromyl chloride.[76] Metallaoxetane structures have also been proposed in (i) the addition of a ketone to titanium or tantalum methylene complexes,[77] (ii) the insertion of an iron atom into the C–O bond of ethylene oxide[78] (the reverse reaction compared to the epoxide formation), and (iii) the oxidation of a 1,5-cyclooctadiene–rhodium complex[79] (oxametallacyclobutanes were characterized by an X-ray diffraction study with tantalum[77b] and rhodium[79]). An exhaustive and pertinent study on metallaoxetanes in oxygen-transfer reactions has been recently reported by Jorgensen and Schiott.[80]

In metalloporphyrin-catalyzed epoxidations, a metallaoxetane is not a long-lived intermediate, since the breakdown rate constant should be above 10^{-12} s^{-1}, but it can still be considered as a possible candidate as transition state.[80,81]

Kinetic Studies. Different possible mechanisms have been supported by kinetic studies: (i) a concerted mechanism with a metallaoxetane intermediate (its breakdown to epoxide being the rate-determining step)[75] or (ii) an electron transfer from the olefin to the metal–oxo complex (the rate-determining step being the formation of the high-valent iron–oxo species).[82]

More recently, Bruice and Ostovic proposed a mechanism involving as rate-determining step the formation of a charge-transfer complex by partial electron transfer from the olefin to the high-valent iron–oxo species[83] (see Figure 6). This attempt to provide a unified view on the mechanism of olefin epoxidations by PhIO/Fe(Por)Cl also includes the formation of *N*-alkylporphyrins which are observed in the case of terminal olefin epoxidations (see below).

The approach angle of the olefin with respect to the iron–oxo bond has also been discussed. Groves initially proposed that the olefin approaches the iron–oxygen bond with a small angle from the side in order to

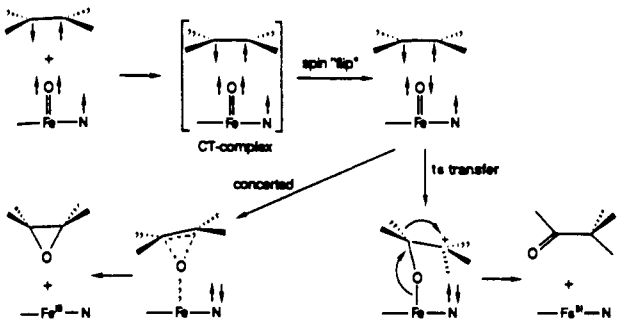


Figure 6. Formation of a charge-transfer complex between the olefin and the high-valent iron–oxo species in the olefin epoxidation by PhIO/Fe(Por)Cl. Reproduced from ref 83. Copyright 1989 American Chemical Society.

maximize the interaction of olefin π orbitals with singly occupied π-antibonding orbitals (d_{xz} and d_{yz} orbitals) of the iron–oxo moiety. With the aid of computer graphics, Bruice proposed that olefins can approach the iron–oxo entity from the top, especially in the case of sterically hindered porphyrin ligands.[84] This type of approach has also been proposed by Breslow in the case of metalloporphyrin carrying binding groups.[85] However, the molecular structure determined by an X-ray study of a complex containing a styrene oxide molecule coordinated via the oxygen atom to a sterically hindered ruthenium(II) porphyrin reveals an angle of 49° of the epoxide ring with respect to the mean porphyrin plane.[86a] This adduct provides an idea of the possible approach angle of an olefin to a metal–oxo species, even if the porphyrin is a so-called hindered ligand.[86b]

Catalytic Epoxidations in Phospholipid Bilayers. Among the efforts to formulate regioselective and stereoselective oxidation systems with metalloporphyrins as catalysts, the use of vesicle bilayers has been studied by Nolte and Groves, using iron or manganese porphyrins. The two reports on manganese porphyrins and molecular oxygen will be presented in section III.C.2.

The condensation of 3β-hydroxy-5-cholenic acid with α,β,α,β-*meso*-tetrakis(*o*-aminophenyl)porphyrin followed by metalation with an iron salt provides the membrane-spanning metalloporphyrin depicted in Figure 7.[87] The orientation (parallel or perpendicular?) and the position of the porphyrin plane (how deep is the porphyrin plane?) within the membrane bilayer was determined by ESR spectroscopy using the copper and the cobalt porphyrin analogues, respectively.[88]

The pillared steroidal iron porphyrin in bilayer vesicles is able to catalyze the regioselective epoxidation of sterols on the side chain using iodosylbenzene as oxidant. The Δ^5 double bond of stigmasterol is more reactive than that on the side chain with homogeneous porphyrin catalysts, but in the present case, only the Δ^{22} double bond is epoxidized.[87,88]

At the end of this section devoted to metalloporphyrin-catalyzed epoxidations with iodosylbenzene, we will discuss briefly two points: the epoxide formation in olefin oxidations by PhIO activated by iron salts and the N-alkylation of porphyrin in terminal olefin epoxidations.

The olefin epoxidation by iodosylbenzene and metalloporphyrin catalysts is due to the formation of an active metal–oxo species; however, it should be noted that iodosylbenzene is also a strong oxidant of olefinic

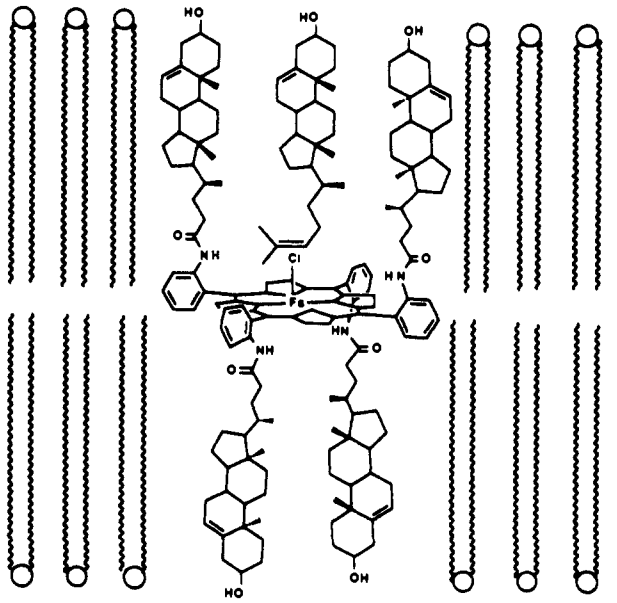


Figure 7. Membrane metalloporphyrins as selective oxidation catalysts in synthetic vesicules. Reproduced from ref 87. Copyright 1987 American Chemical Society.

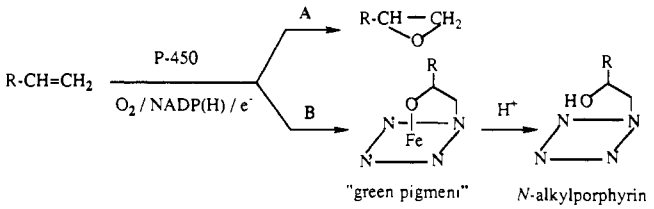


Figure 8. Two metabolic pathways in the epoxidation of terminal olefins by cytochrome P-450 enzymes: epoxide formation (route A) and heme N-alkylation (route B, the "green pigment" of hepatic porphyrias).

substrates in reactions catalyzed by non-heme metal complexes. These oxidations are related to the chemistry of iodine(III) compounds where triflate iron complexes are suitable catalysts.[89] Finally, PhIO and synthetic iron porphyrins were largely used to study the mechanism of heme N-alkylation during epoxidation of terminal olefins.

Porphyrin N-Alkylation. Epoxides are usually formed in cytochrome P-450 mediated olefin oxidations. However, it is known that the oxidation of particular olefins, such as terminal alkenes, leads to an irreversible inactivation of the enzyme. This loss of enzyme activity is due to a suicidal process involving the formation of heme N-alkylated residues ("green pigments").[90,91] This reaction corresponds formally to a pyrrole alkylation by the epoxide (see Figure 8).

The same N-alkylation of synthetic porphyrins is observed during terminal olefin epoxidation by PhIO/Fe(TDCPP)Cl[92] or by PhIO/Fe(TPP)Cl.[93] The reaction mixture changed from brown to green-brown with the concomitant disappearance of the Soret band to the profit of a new band at 435 nm or at 447 nm with Fe(TDCPP)Cl or Fe(TPP)Cl as catalyst, respectively. The green product can be demetalated in acid medium and purified by chromatography. The *N*-alkylporphyrin is isolated in good yield (>50%).[92] A bis-*N*-alkylporphyrin iron complex has been produced by the direct reaction of a iodonium ylide, a carbon analogue of iodosylbenzene, and characterized by X-ray crystallography.[94] The formation of *N*-alkylporphyrin is observed not only in terminal olefin epoxidations, but also in the epoxidation of *trans*-1,2-disubstituted olefins such as *trans*-2-hexene,[95] 1,1-disubstituted olefins, and also styrene itself.[96]

Olefin partition numbers (molar ratio of epoxide versus N-alkylated porphyrin complex, i.e. route (a) versus route (b) in Figure 8), have been measured for different olefinic substrates. These partition coefficients are highly dependent on the olefin structure: 100 for 1-decene, 800 for methylenecyclohexane, and 10 000 for styrene. For allylisopropylacetamide, a suicide inhibitor of cytochrome P-450, the partition coefficient is around 200.[96] The *N*-alkylporphyrin structure is also dependent on the nature of the porphyrin ligand used in oxidation of terminal olefins. For instance, with the iron complex of *meso*-tetra(*p*-chlorophenyl)porphyrin, PhIO and 1-butene, an unstable *N*-alkylporphyrin is produced (60% yield) with an unexpected structure. Mass spectra and proton NMR data confirmed that the *N*-alkyl chain structure was **5** and not **6**.[97] **5** is probably the overoxidation

[Por–*N*]–CH(COOH)–CH_2–CH_3 **5**

[Por–*N*]–CH_2–CH(OH)–CH_2–CH_3 **6**

product of the iron complex precursor of compound **6**. *N*-Alkylporphyrin derivatives of synthetic metalloporphyrin are not always a dead end in catalytic oxidations, especially with disubstituted olefins. Traylor et al. have demonstrated that the *N*-alkylporphyrin derivative formed in the norbornene epoxidation by C_6F_5IO/Fe(TDCPP)Cl is also a catalyst of the epoxidation reaction and can reversibly return to the non-N-alkylated catalyst.[98] Kinetic data suggest that the iron *N*-alkylporphyrin complex or its oxidized form is not an intermediate in the main epoxidation catalytic cycle, but is formed and acts in an alternate catalytic cycle (see Figure 9).

As for olefin epoxidations, different mechanisms have been proposed for the formation of *N*-alkylporphyrins. An acyclic intermediate[98] or a more concerted process involving a putative metallaoxetane[99] have been evoked (Figure 10). (See ref 99b for an exhaustive discussion on the different possible mechanisms of metalloporphyrin-catalyzed epoxidations and *N*-alkylporphyrin formation.)

Despite the absence of direct evidences for the formation of metallaoxetane porphyrin structures, this hypothesis cannot be definitively ruled out and remains a convenient proposal in different metal–oxo-mediated oxidations of olefins, including some particular aspects of olefin epoxidations catalyzed by monooxygenases, e.g. the 95% loss of deuterium label when *cis*-1-deuteriopropene is oxidized by cytochrome P-450.[100]

Related Macrocyclic Catalysts. Iron phthalocyanin catalyzes the PhIO epoxidation of an estradien-17-one derivative in a very selective manner. The desired α epoxide is the major reaction product (α/β epoxide ratio = 10/1).[101] Iron bipyridine containing macrocycles[102] or iron Schiff bases[103] are also able to catalyze olefin epoxidations with PhIO.

2. Manganese Porphyrins

Because manganese porphyrins are less biologically relevant complexes in the modeling of heme oxygenases, fewer reports deal with PhIO olefin epoxidations catalyzed by manganese porphyrins, compared to the large number of articles devoted to iron porphyrin

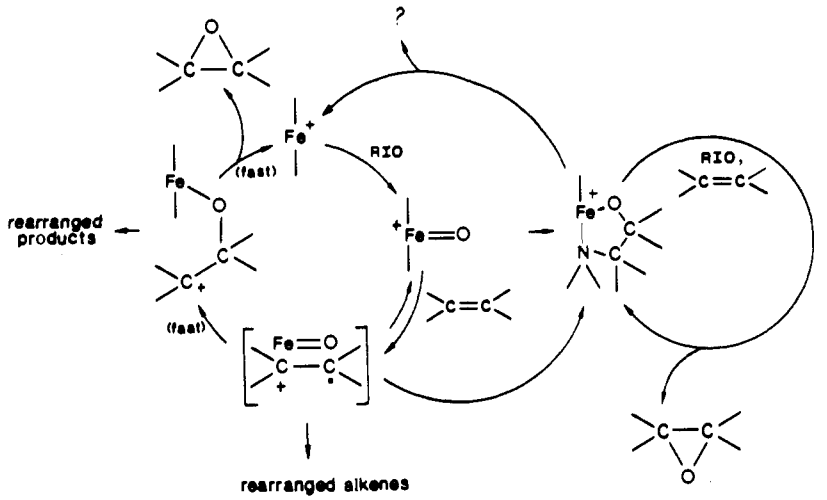
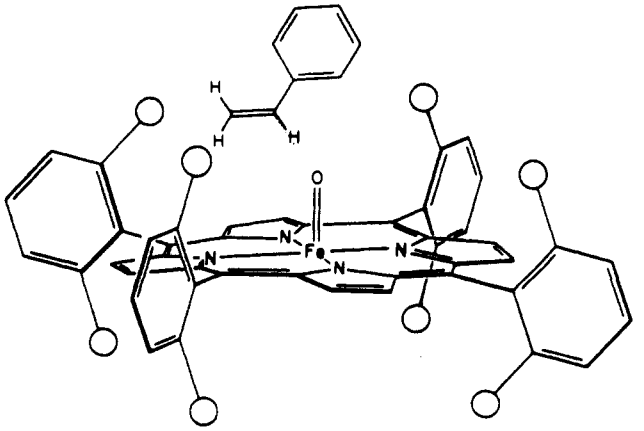
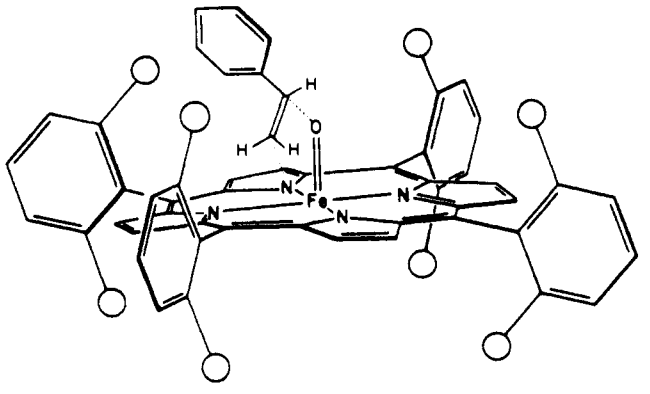


Figure 9. Formation of reversible *N*-alkylporphyrin complexes in the norbornene epoxidation by PhIO/Fe(TDCPP)Cl. Reproduced from ref 98. Copyright 1987 American Chemical Society.



Transition-state geometry **A** for epoxide formation.



Transition-state geometry **B** for *N*-alkylhemin formation.

Figure 10. Possible transition-state geometries for epoxide formation (A) or *N*-alkylporphyrin formation (B). Reproduced from ref 99b. Copyright 1990 American Chemical Society.

complexes. Yet, manganese porphyrin complexes are efficient catalysts of olefin epoxidations with iodosylbenzene.[36] A large loss of stereoselectivity is observed in the *cis*-stilbene epoxidation, where the *trans*-epoxide is the predominent product.[36] *cis*-Stilbene has been used as mechanistic probe in metalloporphyrin-catalyzed epoxidations with different oxygen atom sources (NaOCl, O_2 and electrons, $KHSO_5$, etc.) to evidence the radical character of high-valent manganese–oxo species in these catalytic oxidations.[104] (A d^2 high spin Mn^V=O should have triplet character.)

Besides both stilbene oxides, a significant amount of diphenylacetaldehyde is observed in the epoxidation of *cis*-stilbene.[104] In a mechanistic study, Traylor and Miksztal[71b] found that manganese porphyrins gave larger *exo-endo*-epoxide ratios (35 to 395; low ratios with TDCPP-type ligands and high ratios with TPP-type ligands) than those observed with corresponding iron complexes (6 to 86) in the catalytic epoxidation of norbornene with iodosylpentafluorobenzene as oxidant (in the *m*-CPBA epoxidation of norbornene the *exo-endo*-epoxide ratio is 960). These data suggest that the ET mechanism proposed by Traylor is less pronounced for manganese porphyrin catalysts compared to those of iron.

Shape-selective oxygenation is a favorite domain for metalloporphyrin catalysts. (See below in sections II.B. and II.A. for shape-selective catalysts used by Suslick et al. in NaOCl olefin epoxidation or PhIO alkane hydroxylation reactions.) A dramatic case of selectivity has recently been observed by Collman et al. in the PhIO epoxidation of *cis*-2-octene versus *cis*-cyclooctene.[105] Using the "picnic-basket" manganese porphyrin catalyst, the epoxide ratio, linear substrate versus cyclic substrate, reached 1000 instead of 1.1 with Mn(TPP)OR and 0.7 with Mn(TMP)OR catalysts. Finally, cyclic dienones are efficiently epoxidized to the corresponding epoxides by PhIO/Mn(TPP)Cl (yield = 72–82%).[106]

Related Macrocyclic Catalysts. Kochi et al. have developed the use of manganese Schiff base complexes as catalysts of olefin epoxidations with PhIO as oxidant.[107] The presence of electron-withdrawing groups (Cl or NO_2) on ligand aromatic rings enhances the catalytic activity of the Mn^{III}(salen) catalysts. A small difference in catalytic activity (a factor of 10) is observed between the most reactive olefin, *p*-methoxystyrene, and the least reactive one, 1-octene. Manganese amide complexes catalyze the epoxidation of olefins with PhIO as oxygen atom source.[108]

Hill and Brown have also demonstrated that polyoxometalates substituted with manganese or cobalt, $(n\text{-}Bu_4N)_4H(Mn\text{ or }Co)PW_{11}O_{39}$, are efficient catalysts for olefin epoxidations with iodosylbenzene derivatives.[109] In cyclooctene epoxidations, the catalytic activity of these so-called inorganic porphyrins is higher than with Mn(TPP)Cl or Mn(TDCPP)Cl.[110]

3. Other Metalloporphyrins (Cr, Co, Ru, and Os)

Olefin epoxidations catalyzed by chromium porphyrins are stereospecific,[34] but these complexes are less active that the corresponding iron complexes,[71b] and a large amount of allylic oxidation is observed in the case of cyclic olefins.[111] PhIO/Cr(TPP)Cl is in fact a good catalytic system for the oxidation of alcohols to aldehydes or ketones.[112]

Cobalt porphyrins are poor catalysts of the PhIO olefin epoxidation, and the corresponding nickel complexes are nearly inert.[113]

Metalloporphyrins of the iron triad have been tried as catalysts in PhIO olefin epoxidations. Ruthenium octaethylporphyrin is a poor catalyst[114] whereas Os(TPP)(PBu^n_3)Br is slightly more efficient.[115] Allylic oxidation of cyclohexene is important with both ruthenium and osmium porphyrin complexes.

Related Macrocyclic Catalysts. Chromium salen complexes are also able to catalyze the PhIO olefin epoxidation.[116,117] These complexes catalyze the PhIO oxidation of alkynes to diones.[118] Cobalt[119] and nickel[120] salen complexes have also been reported as catalysts of olefin epoxidations. Optically active nickel cyclams catalyze olefin epoxidations in a nonenantioselective manner.[121]

4. Oxidants Related to PhIO

Epoxidations using iodosylpentafluorobenzene have been described in the preceding section. So this section will be essentially devoted to (tosylimino)iodobenzene, PhI=N—Ts. This compound is a nitrene source potentially able to generate high-valent metal–nitrene porphyrin complexes. The use of PhI=N—Ts was initially reported by Breslow et al. in the tosylimidation of cyclohexane catalyzed by Mn(TPP)Cl or Fe(TPP)Cl,[122] and later with cytochrome P-450 itself.[123]

The metalloporphyrin-catalyzed aziridination of olefins with PhI=N—Ts has different characteristics compared to the PhIO epoxidation reaction. Mansuy et al. indicate that the catalytic aziridination of *cis*-stilbene by Fe(TPP)Cl is not stereospecific, the *trans*-aziridine being the major isomer.[124,125] Besides aziridine, a large amount of the corresponding epoxide is produced by the fast reaction of residual water with the high-valent iron–nitrene intermediate. It should be noted that the stereoselectivity of the *cis*-2-hexene aziridination is highly dependent on the axial ligand of the catalyst precursor, poor with Cl^- but high with ClO_4^-.[125]

B. Epoxidations with NaOCl and Related Hypochlorites Catalyzed by Manganese Porphyrins and Other Metalloporphyrins

Sodium hypochlorite solutions are usually prepared by chlorination of sodium hydroxide (for the first report on the preparation of a hypochlorite solution, see ref 126).[127] Chemical properties of aqueous solutions of sodium hypochlorite depend essentially on the solution pH value.[128] Commercially available solutions are stable at very alkaline pH values, 12–13, and OCl^- is the major species.

$$2NaOH + Cl_2 \rightarrow NaOCl + NaCl + H_2O$$

At room temperature the equilibrium constant is equal to 7.5×10^{15}. By lowering the pH of hypochlorite solutions, hypochlorous acid, HOCl, becomes the main reactive chlorinated species. At pH 9.0, only 3% of chlorine is available as HOCl, but at pH 7.5 and 5.0, it is 50% and 99.7%, respectively.[128] HOCl is a chlorinating and oxidizing agent (see ref 129 for the haloform reaction and refs 130–132 for more recent data). Lowering the pH of hypochlorite solutions also favors the formation of radical species which leads to vigorous and sometimes explosive chain reactions.[133]

For more than a decade, oxidations of manganese porphyrin complexes by sodium hypochlorite were carried out in order to understand the mechanism of water oxidation in photosynthesis.[1-34,135] In 1979, Tabushi reported the NaOCl oxidation of benzylic alcohol to benzaldehyde catalyzed by Mn(TPP)Cl.[37] At the same period, we were working independently on the search for macrocyclic complexes to catalyze the olefin epoxidation reaction using NaOCl as oxygen atom source. We found in fact that porphyrin ligands were more suitable than Schiff base macrocycles in catalyzed epoxidations[38,136] (see Table II). The association of NaOCl with chiral Schiff base complexes was found by Jacobsen et al. as being one of the most efficient systems for the asymmetric epoxidation of nonactivated olefins (see section V).

Because of higher catalytic activities of metalloporphyrins compared to salen-type complexes, most of the studies reported during the last decade have been focused on metalloporphyrins and, more precisely, on manganese derivatives.

$$PhCH{=}CH_2 + NaOCl \xrightarrow[R_4N^+Cl^-/H_2O/CH_2Cl_2]{Mn(TPP)Cl} PhCH(O)CH_2 + NaCl$$

Very small amounts of manganese porphyrin catalyst can be used (catalyst/olefin molar ratios range from 0.025% to 2.5% in typical experiments).[38,136] The catalytic oxygen-transfer reaction occurs in the organic phase, and the phase-transfer agent is present simply to transfer OCl^- as ammonium salt into the dichloromethane solution. In very fast epoxidation reactions the oxidant transfer can be the rate-limiting step.

Table II. Epoxidation of Styrene with NaOCl Catalyzed by Porphyrin or Schiff Base Complexes (catalyst/olefin molar ratio = 2.5%)[a] (from ref 136; copyright 1984 American Chemical Society)

complex	conversion, %[b]	yield in styrene oxide,[b] %
Cr(TPP)Cl (2)	24 (18)	8 (6)
Mn(TPP)OAc (1a)	80[c] (68)	36[c] (28)
Mn(TPP)Cl (1b)	75 (62)	35 (24)
Fe(TPP)Cl (3)	33 (18)	2 (2)
Co(TPP)Br (4)	53 (42)	6 (6)
Mn(salpr)OAc (5)	22 (5)	0 (0)
Mn(salphen)OAc (6)	17 (8)	4 (2)
Mn(salphen)Br (7)	28 (20)	6 (4)
Co(salphen)(O_2) (8)	38 (18)	8 (4)
$VO(acac)_2$	3–4	0
$Mn(OAc)_3$	3–4	0
none	3–4	0

[a] Reactions are carried out in air at room temperatures as described in the Experimental Section in ref 136. [b] Conversion and yield are determined after a reaction time of 3 h. Results corresponding to 1 h are indicated in parentheses. [c] The same reaction run under inert atmosphere (nitrogen) gives 76% of conversion after 3 h and 40% yield.

Manganese porphyrins with a trimethylammonium substituent on the para position of one of the phenyl rings have been used as catalysts in the absence of a tetraalkylammonium salt.[137]

This catalytic epoxidation can be performed indifferently under air or nitrogen atmosphere without noticeable modifications in epoxide selectivity. The origin of the oxygen atom of the epoxide was investigated using LiOCl in $H_2{}^{18}O$ in the epoxidation of *p*-methoxystyrene catalyzed by Mn(TPP)OAc.[136] The absence of incorporation of ^{18}O labeling into the epoxide suggested that the oxygen exchange of hypochlorite anions with water was slow compared to the catalyzed oxygen atom transfer. These data also confirmed that the origin of the epoxide oxygen atom was the hypochlorite itself.

The most striking features of these catalytic epoxidations with manganese porphyrins are the remarkable improvement of the rate, chemo- and stereoselectivity of the reaction by addition of pyridine derivatives in the reaction mixture.[136,138-140] Because the chemoselectivity is improved, a large number of different olefins can be epoxidized with NaOCl in good yields, e.g. terpenes, steroid olefins.[141,142] Dienes are epoxidized to the corresponding monoepoxides.[136,142]

Pyridine can be replaced by imidazole derivatives,[143] but these axial ligands are less robust with respect to oxidation than pyridine derivatives. In fact, 4-*tert*-butylpyridine is one of the best possible axial ligands considering all the various parameters: nitrogen basicity, lipophilicity, and oxidation resistance.[144-146]

The role of pyridine as axial ligand ("proximal effect") was confirmed by using an elaborate porphyrin ligand with a pyridine moiety attached by one or two tethers[147-149] (see Figure 11). With these manganese porphyrin complexes having only one attached pyridine in axial position, all the effects on the reaction rate, product selectivity and stereoselectivity which are usually obtained by addition of 5–20 equiv of free pyridine in the catalytic medium are reproduced. The "proximal effect" of pyridine in these catalyzed epoxidation reactions can be considered as the preliminary approach in the modeling of proximal and distal effects involved in the chemical properties of hemoproteins such as cytochrome P-450, peroxidases, and catalase. For further developments concerning the proximal effects in metalloporphyrin-catalyzed oxygenations, see section II.C on the role of imidazole or phenoxo ligands in H_2O_2 epoxidation reactions (see also ref 149b for a review article).

It must be noted that the success of the proximal effect with pyridine and a manganese porphyrin is based on the fact that the association constants K_1 and K_2 favor the existence of the pyridine monoadduct as the major species in catalytic conditions (see ref 148 for a detailed discussion on this point). This situation is not

$$M(Por)X + 2L \overset{K_1}{\rightleftharpoons} [M(Por)(L)]^+X^- + L \overset{K_2}{\rightleftharpoons} [M(Por)(L_2)]^+X^-$$

the case for iron porphyrin complexes where the major species in solution is the bis-pyridine adduct (because $K_2 > K_1$). Hence no axial position is available for the activation of the oxygen atom donor. Iron porphyrin complexes can take advantage of the proximal effect

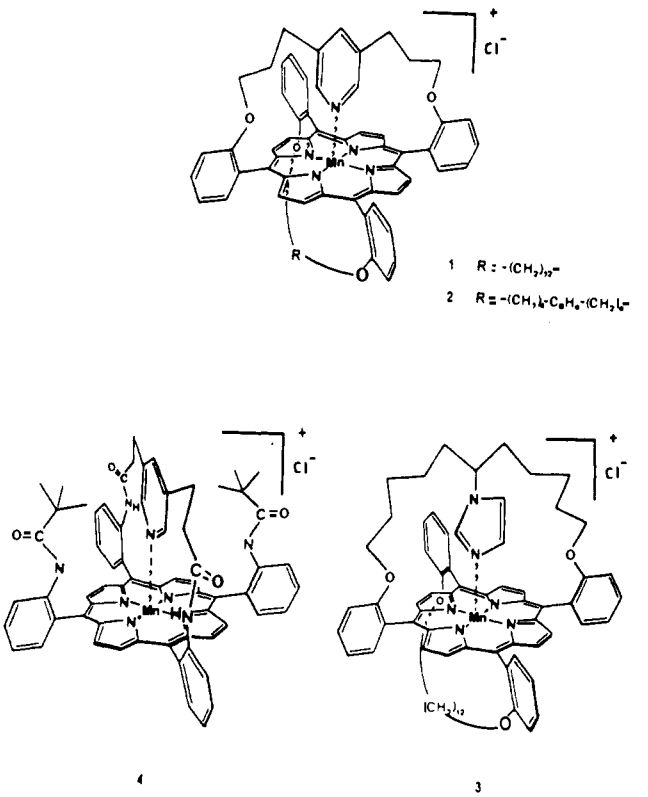
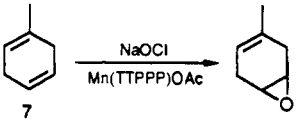


Figure 11. Structures of "basket-handle" manganese porphyrins used to confirm the requirement of only one pyridine axial ligand to produce a "proximal effect" in catalytic olefin epoxidations with NaOCl as oxidant. Reproduced from ref 148. Copyright 1988 American Chemical Society.

when one side of the macrocyclic ligand with sterically hindered substituents can block the coordination of the second nitrogen ligand. This case was demonstrated by Naruta and Muruyama with an iron binaphtylporphyrin in PhIO olefin epoxidations.[150] With NaOCl only sterically hindered iron porphyrins gave high catalytic activities in the epoxidation of styrene or cyclohexene.[151]

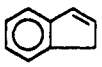
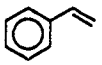
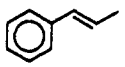
These so-called sterically hindered porphyrin ligands have been largely used in the case of manganese complexes. The cage effect can be created by alkyl groups at the ortho and ortho' positions of the *meso*-phenyl groups[45,152,153] or by halogen atoms at the same position.[47,154-156] In this case an enhanced selectivity of the catalytic activity is observed because of the increase of the electrophilicity of the high-valent manganese–oxo species. Good yields are obtained in the catalytic epoxidation of nonreactive substrates such as terminal olefins.[47,154] With an extremely hindered bis-pocket manganese complex based on the *meso*-tetrakis(2,4,6-triphenylphenyl)porphyrin ligand, Suslick et al. observed an enhanced selectivity for the epoxidation of the exocyclic double bond of 4-vinylcyclohexane and limonene.[157] In the case of 1-methyl-1,4-cyclohexadiene (7), the same shape-selective catalyst gave almost the exclusive epoxidation of the disubstituted double bond.



7

All these epoxidation reactions were initially reported with commercial bleach solutions which are highly basic

Table III. Saturation Kinetics Parameters (V_{max} and K_m) in Olefin Epoxidations by the LiOCl/Mn(Por)Cl System (from ref 163; copyright 1985 American Chemical Society)

olefin	Mn(TPP)Cl K_M(rel), M	Mn(TPP)Cl V_{max}, turnovers s^{-1}	Mn(TMP)Cl K_M, M	Mn(TMP)Cl V_{max}, turnovers s^{-1}
	1.0	1.0	0.02	4
	1.0	1.0	0.04	5
	1.5	3.1	0.08	8
	2.1	1.5	0.8	11
	0.32	0.37	8	6
	1.8	1.4	*a*	*a*

[a] Could not be determined.

(pH = 12–13). Montanari et al.[158] reported that highly efficient catalytic epoxidations can be obtained by adjusting hypochlorite solutions to pH 9.5 with diluted HCl (for other reports on metalloporphyrin-catalyzed epoxidations with NaOCl at pH 9.5, see also ref 156a, 159, and 160). At lower pH values (7 or 8.5), the epoxide selectivity decreased and significant amounts of chlorinated products were detected.[158,161]

Kinetic Studies. The kinetics of the OCl^-/Mn(Por)Cl epoxidation system has been extensively studied, and controversial reports have appeared for 6 years.[162–164] Because of its well-defined chemical composition, LiOCl is recommended in kinetic studies as hypochlorite oxygen atom donor after a treatment with $BaCl_2$ to remove sulfate.[163]

Saturation kinetics were reported by Collman et al. for the epoxidation of different olefins (styrene, cyclic olefins, or aliphatic alkenes) using Mn(TPP)Cl or Mn(TMP)Cl as catalyst and 4′-(imidazol-1-yl)acetophenone (a rather oxidizable imidazole derivative) as axial ligand.[162,163] In these conditions (high olefin concentrations), the epoxidation reaction was determined to be first order in manganese porphyrin catalyst and independent of hypochlorite and olefin concentrations.

However, different olefins are epoxidized at different rates, suggesting that the olefin must be involved in the rate-determining step. This kinetic scheme is classic in enzymology and is described by the Michaelis–Menten equation:

$$\text{activated Mn catalyst} + \text{olefin} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{intermediate}] \xrightarrow{k_2} \text{Mn}^{III}\text{ catalyst} + \text{epoxide}$$

The two Michaelis–Menten parameters, V_{max} and K_m ($V_{max} = k_2$[catalyst] and $K_m = (k_{-1} + k_2)/k_1$; if $k_{-1} \gg k_2$, then K_m can be regarded as the dissociation constant of the olefin from the intermediate) have been measured for different olefins (Table III).

The possible intermediate in these saturation kinetics was tentatively described as a metallaoxetane complex. (See Figure 12 for the catalytic cycle proposed by Collman et al.[163] and ref 164 for new views on this catalytic cycle.) Saturation kinetics were also observed in olefin epoxidations with NaOCl[165] or with iodosylbenzene derivatives[74] and iron porphyrin catalysts. (See section II.A.1 for kinetic studies on metalloporphyrin-catalyzed olefin epoxidations with PhIO or C_6F_5IO.)

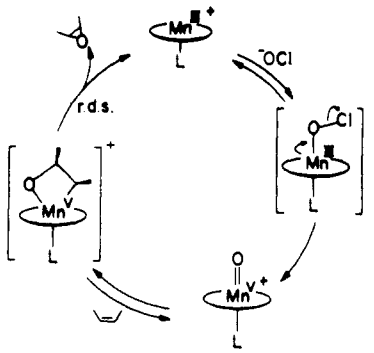


Figure 12. Proposed catalytic cycle for olefin epoxidations by "OCl^-/Mn(Por)Cl". Reproduced from ref 163. Copyright 1985 American Chemical Society.

The biphasic nature of the OCl^-/Mn(Por)Cl system did not facilitate kinetic studies, and conflicting interpretations were proposed by Nolte et al.[166–171] and Bruice et al.[172,173] Using Mn(TPP)Cl, a rather fragile catalyst, Nolte et al. proposed that the epoxidation of cyclohexene is zero order in substrate.[186,167] Depending on the NaOCl concentration, the reaction order in oxidant varies between zero and one. They proposed that the rate-determining step is the conversion of the manganese(III) complex with a hypochlorite axial ligand to a high-valent manganese–oxo porphyrin, this complex reacting quickly with the olefin substrate or, in a reversible process, with the manganese(III) precursor to give a Mn^{IV}–O–Mn^{IV} μ-oxo dimer.[170] This step might explain the saturation behavior in alkene concentration and is modified by the presence of pyridine or styrene in the reaction mixture.[168,169] In order to avoid any possible artefact due to the biphasic system, Bruice et al. investigated the kinetics of a homogeneous system where the hypochlorite is transferred into dichloromethane with an ammonium salt in a pretreatment step. In these conditions, second-order rate constants for the oxygen transfer from hypochlorite to the manganese complex were determined.[172,173]

$$[\text{Mn}]^{III} + \text{ClO}^- \xrightarrow{k_1} \text{active } [\text{Mn}]^{V} \qquad k_1 = 10^5\ \text{M}^{-1}\ \text{s}^{-1}$$

$$[\text{Mn}]^{III} + \text{active } [\text{Mn}]^{V} \xrightarrow{k_2} 2[\text{Mn}]^{IV} \qquad k_2 = 10^8\ \text{M}^{-1}\ \text{s}^{-1}$$

$$\text{active } [\text{Mn}]^{V} + \text{norbornene} \xrightarrow{k_3} [\text{Mn}]^{III} + \text{epoxide} \qquad k_3 = 10^4\ \text{M}^{-1}\ \text{s}^{-1}$$

These data were obtained with Mn(TMP)Cl. As a result, rather than the μ-oxo dimer formation proposed by Nolte, Bruice found that a very fast comproportionation reaction exists between the high-valent manganese(V) species and the manganese(III) porphyrin precursor.

In a recent article, Collman reexamined "saturation kinetics" studies and pointed out that a large number of oxidant molecules are wasted in side reactions,

Table IV. Percent Conversion and Product Yields in Olefin Oxidations by NaOCl/Ni(salen) (from ref 178; copyright 1988 American Chemical Society)

substrate	% convsn[a]	epoxide[b]	PhCHO[c]	selectivity[d]
styrene	98	44	6	45
(*Z*)-β-methylstyrene	100	84[e]	10	84
(*E*)-β-methylstyrene	100	89[e]	0	89
(*Z*)-stilbene	45	12[e]	12	27
(*E*)-stilbene	80	46[e]	0	58
cyclohexene	87	23		26
norbornene	94	30[f]		32

[a] Disappearance of starting material after 5 h. [b] Based on starting alkene. [c] Remainder of product is $PhCO_2H$. [d] Epoxide yield/% conversion. [e] (*E*)-Epoxide only. [f] *exo*-Epoxide only.

especially at low olefin concentrations and when the axial ligand used is easily oxidized.[164] These facts contribute to misinterpretations of kinetic data in the hypochlorite–manganese porphyrin system. The rate-determining step is now believed to be the formation a high-valent manganese–oxo species, and Collman proposed to abrogate the proposition of a metallaoxetane as intermediate in these metalloporphyrin-catalyzed epoxidations with hypochlorite as oxygen atom donor.

It should be noted that further advances on the mechanism of this reaction will require a full characterization of a manganese(V)–oxo species which probably exists (see section VII for preliminary studies) and will provide some information on the possible formation of a Mn^{III}–OCl porphyrin complex. Up to now, no transition-metal complex with a hypochlorito ligand has been isolated and characterized. (For some attempts using aluminum, gallium, or iridium porphyrins, see ref 174.)

Related Catalytic Systems. In addition to the large amount of data available in NaOCl epoxidation reactions catalyzed by manganese porphyrin catalysts, Bressan and Morvillo reported the use of ruthenium and osmium bidentate phosphorus complexes as catalysts[175a] (for other oxidations, see ref 175b). The "NaOCl/Mn(Por)Cl" system is also very efficient in the oxidation of sulfides to sulfones.[176] Whereas nickel porphyrins are completely inactive in olefin epoxidations with NaOCl as oxidant, nickel salen or cyclam complexes can be used as catalysts[177-180] (Table IV). A reverse reactivity is observed for stilbene isomers: the trans isomer is more reactive than the cis isomer.[178] High turnover rates are obtained when the pH value of the hypochlorite solution is lowered to a value of 9.3.[180] Chlorine radicals are catalytically produced[181] and the mechanism of these oxidations using NaOCl and nickel salen catalysts is still under investigation.[182] Finally, transition-metal phthalocyanins are poor epoxidation catalysts when associated with NaOCl as oxygen atom source.[183]

C. Epoxidations with O_2

This section and the following one will focus on the modeling of the monooxygenase catalytic cycle with synthetic metalloporphyrins. (For an early report on the role of cobalt or iron porphyrin in autoxidation reactions, see reference 184.) Since the stoichiometry of a monooxygenase-mediated oxygenation requires two electrons and two protons to reduce the second oxygen atom of dioxygen to water, most of the works reported in the two following sections involve an electron source: borohydride, hydrogen and colloidal platinum, zinc or electrons from an electrode. (For a detailed review article, see ref 29.) In some of these reactions, epoxides are not the major reaction product because of their fast reduction in situ by borohydrides.

Attempts have been made to avoid the sacrificial use of electrons in these catalytic oxygenations with molecular oxygen by using ruthenium porphyrin complexes or by photochemical activation of oxygenated metalloporphyrins.

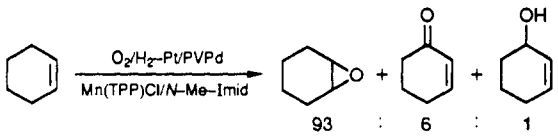
1. Borohydrides, H_2-Colloidal Platinum, or NADPH as Electron Sources

The first attempt to mimic cytochrome P-450 mediated epoxidation reactions was reported by Tabushi in 1979.[39] Cyclohexene is oxidized to cyclohexanol and 2-cyclohexen-1-ol (ratio = 80/20) in the presence of dioxygen, sodium borohydride, and a catalytic amount of Mn(TPP)Cl. Cyclohexene oxide is not detected because of its fast reduction to cyclohexanol by sodium borohydride. This metalloporphyrin-catalyzed reaction is complicated by a free-radical chain autoxidation pathway which can be suppressed by addition of a free-radical scavenger such as 2,6-di-*tert*-butyl-*p*-cresol.[39] This successful modeling of the "reductive dioxygen activation" by metalloporphyrins can be repeated with a soluble tetraalkylammonium borohydride, in dichloromethane[40] or in a mixture of benzene and ethanol.[185] The $O_2/NaBH_4/Mn(TPP)X$ system can also be supported on silica or cellulose (see section VI, works of Tanaka and Sakurai). Another modification was the introduction of cysteine in the reaction mixture which provides a thiolato ligand to manganese or iron porphyrins.[186,187] The main oxidation products are still the unsaturated alcohol and the ketone. Both compounds are the main products in the cyclohexene oxidation catalyzed by isolated rat hepatocytes.[186]

In these reactions catalyzed by manganese complexes, the active species is supposed to be a metal–oxo species. This is not the case when the cyclohexene oxidation with sodium borohydride and oxygen is catalyzed by rhodium(III) porphyrins.[188] The main product being cyclohexanol, this reaction can be regarded as a catalytic hydration of olefins.[189] The oxygenation of olefins under reductive conditions is also catalyzed by Co^{II}(TPP). Styrene derivatives are converted to the corresponding benzylic alcohols in high yields (70–98%).[190,191] The catalytic cycle of this reaction probably involves a cobalt–alkyl complex which then reacts with molecular oxygen.

A similar reaction pathway was also proposed by Shimizu et al. for manganese porphyrin-catalyzed olefin oxidations when Mn(TPP)Cl is replaced by *meso*-tetrakis(*p*-sulfonatophenyl)porphyrinatomanganese-(III), Mn^{III}(TPPS).[192] The same authors have also reinvestigated the product distribution in Mn(TPP)Cl-catalyzed oxidations.[193] Styrenes mainly afford the Markovnikov hydration products, e.g. benzylic alcohols and dimers. Both *cis*- and *trans*-stilbene were oxidized to benzylic alcohol and benzil. The introduction of a hydrogen atom from $NaBH_4$ at the β-position of benzylic alcohols in the catalytic oxidation of styrenes was checked by using deuterated reagents.[193] These data suggest that the main route is in fact the formation of an alkylmanganese complex arising from the reaction

of a manganese(II) complex with the olefin and not the reductive activation of dioxygen to produce a metal–oxo species. In fact, the latter mode of dioxygen activation should provide epoxides as major olefin oxidation products. This outcome was observed when borohydride was replaced by H_2 and colloidal platinum by Tabushi in a search for a cleaner reductant.[194]



Colloidal platinum supported on poly(vinylpyrrolidone) (PVPd) is a very efficient catalyst for the reduction of metalloporphyrins and metalloenzymes by molecular hydrogen.[195]

Pseudo-second-order rate constants for the reduction of Mn(TPP)Cl and cytochrome *c* are 8×10^7 and 1.5×10^5 M^{-1} s^{-1}, respectively.[29] When oxygen is present, colloidal platinum can also catalyze the hydrogen reduction of O_2 to H_2O_2, but when O_2/H_2–Pt is replaced by H_2O_2 in a manganese porphyrin mediated olefin oxidation, only a very small amount of epoxide is detected, suggesting then that the cyclohexene oxide formed in the O_2/H_2–Pt/Mn(TPP)Cl system is effectively the result of a catalytic reductive activation of molecular oxygen leading to a manganese–oxo species as active intermediate.[29] This catalytic system epoxidizes geraniol acetate at the trisubstituted double bond and not at the allylic position (1000–2000 epoxide molecules are produced per catalyst molecule).[196]

Delicate and precise protein–protein interactions between cytochrome P-450 and its associated reductase are tuning the electron flux from NADPH to the active site of the enzyme and only two electrons are delivered per catalytic cycle. This idealized situation is not easily reproduced by a chemical process where a metal–oxo species is generated in the presence of an electron source. So, besides olefin oxidation products, water is also generated by direct reduction of the metal–oxo porphyrin complex (Figure 13).[197]

In the same work Tabushi also measured the acceleration of the O–O bond cleavage in $Fe^{II}(T_{piv}PP)(O_2)$ by protonation and electron transfer. With the only assistance of a coordinated imidazole, the O–O cleavage rate is 1.9×10^{-4} M^{-1} s^{-1}, whereas it is 4.4×10^2 M^{-1} s^{-1} in the presence of protonated imidazole and 1.8×10^9 M^{-1} s^{-1} when electrons are present as well.[197] In $Fe^{II}(T_{piv}PP)(O_2)$, the complex resulting from the activation of molecular oxygen by $Fe^{II}(T_{piv}PP)$, the O–O bond cleavage can be assisted by addition of carboxylic acid anhydride. This reaction was also studied by Khenkin and Shteinman.[198]

In order to reduce the formation of water molecules for each epoxide molecule produced (ratio H_2O/epoxide = 1/0.03 in the present case), a NADH analogue, *N*-methyldihydronicotinamide (MeNAH) was used as electron source in the presence of FMN (flavine mononucleotide). The rate of epoxide formation increased by a factor of 6 while the ratio H_2O/epoxide fell to 2.[199] Attachment of flavine to α-cyclodextrin provided a promising model for flavoprotein.[200] The last project of Tabushi was the design of a superstructured manganese porphyrin with a flavo-α-cyclodextrin covalently bonded directly to the porphyrin ligand.[29]

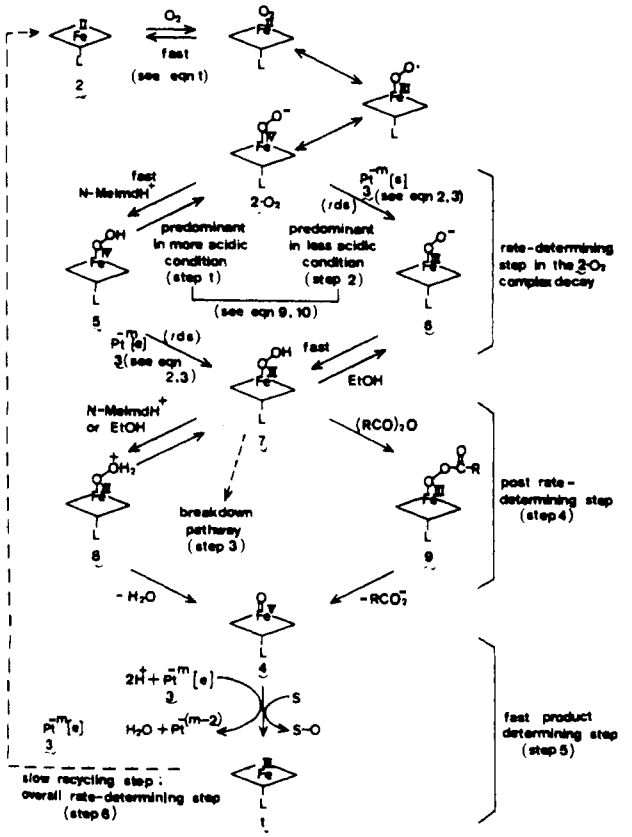


Figure 13. Different pathways in the reductive O_2 activation in the "O_2/H_2-Pt/Fe(T_{piv}PP)/imidazole" system. Reproduced from ref 197. Copyright 1985 American Chemical Society.

2. Metal Powder, Ascorbic Acid, or Aldehyde as Reductant

Udenfriend's reagent, a mixture of dioxygen, ascorbic acid, and Fe(EDTA), is able to hydroxylate arenes to phenols under mild conditions.[201] This early model of oxygenases can also produce alcohols from alkanes and epoxides from olefins, but in moderate yields.[202] (The term "oxenoid" was introduced in the later article under the pressure of one referee, but Hamilton was proposing that the terminal oxygen atom of the $Fe(O_2)$ complex had this "oxenoid" character and was responsible for the oxygen atom insertion into substrates, the remaining oxygen atom bound to iron being reduced to water. Later on, the use of single oxygen atom donors helped to clarify this mechanism.)

When Fe(EDTA) is replaced by Mn(TPP)Cl, many different organic substrates are oxidized in a biphasic medium (benzene/buffered water pH 8.5).[203] Styrene is epoxidized accompanied by formation of phenylacetaldehyde while *cis*-stilbene gives a mixture of *cis*- and *trans*-stilbene oxides (cis/trans = 0.14/0.23), whereas *cis*-2-hexene oxide is stereospecifically formed from the corresponding *cis*-olefin. Product distribution and stereoselectivity are very similar to those of PhIO/Mn(TPP)Cl or NaOCl/Mn(TPP)Cl system, suggesting that manganese–oxo species are also involved in the present case.[204]

Ascorbic acid can be replaced by other reductants, such as zinc amalgam with methylviologen as electron-transfer agent[205] or zinc powder in acetic acid.[206] The Shilov system will be commented in section III.C since primary data reported deal with alkane hydroxylation. In the second case, viz. zinc/acetic acid (a larger volume of data is available on olefin epoxidation) *N*-meth-

ylimidazole is a required cofactor. More surprisingly, Mn(TPP)Cl is a better catalyst than Mn(TMP)Cl or Mn(TDCPP)Cl in the epoxidation of cyclooctene, with catalytic activities being 75, 11, and 10 mol of epoxide produced per mole of catalyst in 30 min, respectively. On the basis of zinc, epoxide yields are ca. 50%, a rather good yield with respect to the electron source.[206]

In a search for a propylene oxide preparation catalyzed by metalloporphyrin catalysts, Haber and Mlodnicka reported the oxidation of propylene in the presence of propionaldehyde and molecular oxygen in ethylacetate.[207a] First-row metalloporphyrin complexes (Cr, Mn, Fe, Co, and Ni) were examined as potential catalysts. Only Mn(TPP)Cl, Fe(TPP)Cl, and Co(TPP) are active. Propionaldehyde is autoxidized to perpropionic acid via a free radical intermediate since carbon dioxide is also formed. Propylene oxide probably results from a catalyzed oxygen atom transfer from perpropionic acid. This cooxidation reaction was also observed with cyclohexene.[207b] The epoxidation of olefins with molecular oxygen and aldehydes is likewise catalyzed by nickel(II) acetylacetonate derivatives[208a] or by nickel(II) Schiff base complexes.[208b] The cooxidation of an olefin and *N*-hydroxyphthalimide by molecular oxygen is also catalyzed by Mn(TPP)Cl.[209] The influence of pyridine on the stereoselectivity of *cis*-stilbene epoxidation suggests in this case that a manganese–oxo complex may be involved.

3. Electrochemical Reduction

Murray reported in 1986 an efficient electrocatalytic epoxidation reaction using Mn(TPP)Cl in dichloromethane, with *N*-methylimidazole as axial base and tetrabutylammonium perchlorate as supporting electrolyte.[210] The reductive electrolysis was performed at −0.4 V versus NaCl-SCE at a glassy carbon plate electrode and cyclooctene epoxide was the only detectable product from the corresponding olefin. The catalytic activity is good: 1.7 cycles min^{-1} giving a product distribution similar to that described for systems based on single oxygen atom donors.[211] Little manganese porphyrin decomposition is observed which is not the case when a manganese Schiff base complex is used in these electrocatalytic olefin epoxidations.[212]

Manganese(III) [triphenyl-*p*-*N*-pyrrolylphenyl]porphyrin can be electropolymerized onto carbon tissue electrodes by repeated potential scans from −1.0 to +1.5 V.[213] Voltammograms of these modified carbon electrodes in aerobic conditions indicate that O_2 binding occurs on a reduced Mn(II) porphyrin, as also suggested by Murray et al.[210] At a constant potential of −0.5 V, cyclooctene is electrocatalyzed in air with these Mn-TPP-coated electrodes to cyclooctene oxide.[213]

These electrochemical epoxidations involve an initial electroreduction of the manganese porphyrin followed by O_2 binding, the passage of a second electron and the heterolysis of the O–O bond to give rise to the high-valent Mn–oxo species. Recently, Murray described a new electrochemical approach to olefin epoxidation by generating H_2O_2 by electroreduction of O_2 on electrodes coated with a film of poly[Ru(vbpy)$_3$] (vbpy = 4-methyl-4′-vinylbipyridine), the generated H_2O_2 then reacts with Mn(TPP)Cl, Mn(TMP)Cl, or Mn(TPFPP)Cl to create a manganese–oxo complex.[214] At high concentrations of olefin and manganese porphyrin, the current efficiency for epoxide production is nearly 100%. At low olefin concentrations, a catalase-like decomposition of H_2O_2 is observed. Co^{II}TMPyP can also be used in the electrocatalytic epoxidation of olefins.[215] In these epoxidations catalyzed by cobalt complexes in the presence of benzoic anhydride, the nature of the active cobalt species (a $cobalt^{IV}$–oxo or a $cobalt^{III}$–perbenzoato complex?) is an open question. The main advantage of these electrochemical oxygenation reactions with manganese porphyrin catalysts is to supply reducing equivalents by a controlled electrochemical potential in a more easily adjustable manner than with chemical reductants.

4. Without Reductant, Case of Ru(TMP)(O)$_2$

The main goal in catalytic olefin epoxidations is to use both oxygen atoms of molecular oxygen to produce selectively epoxides without using reducing agents as co-factors, i.e. via the following abiotic reaction:

$$2\,R{-}CH{=}CH{-}R' + O_2 \xrightarrow{\text{catalyst}} 2R{-}CH(O)CH{-}R'$$

Such a reaction is particularly important for the large scale production of various epoxides. Today, ethylene oxide is produced from ethylene and dioxygen by heterogeneous catalysis at high temperature (160–250 °C).[216] The catalyst consists of reduced silver particles dispersed on alumina. In this widely used process, ethylene and, to a less extent, ethylene oxide are consumed to CO_2 and H_2O. Even with doped silver catalysts the selectivity of the epoxidation reaction is around 75–80% and this process is limited to ethylene. (For a recent contribution on the possible role of silver–oxo species in ethylene epoxidation, see ref 217.) Even Halcon-type processes where an alkane (isobutane) and an olefin (propylene) are co-oxidized by molecular oxygen in the presence of an epoxidation catalyst (Mo^{VI} complex) suffer from the drawback of producing a coproduct (*tert*-butyl alcohol). Both compounds, propylene oxide and *tert*-butyl alcohol, do not have necessarily the same demand at the same time in the chemical market.

In the field of metalloporphyrin-catalyzed olefin epoxidations with molecular oxygen, the breakthrough was reported by Groves and Quinn in 1985. Ru^{VI}(TMP)$(O)_2$[218] catalyzes the aerobic epoxidation of olefins at room temperature and normal pressure.[219]

Measurement of oxygen uptake during the oxidation of cyclooctene indicated that 2 mol of epoxide were produced per mole of molecular oxygen consumed. The epoxidation reaction is stereospecific and can be applied to different olefins: cyclooctene, styrenes, norbornene. The main limitation is the rather low catalytic activity: 16–45 mol of epoxide are produced per mole of ruthenium catalyst in 24 h. Detailed studies explain how both oxygen atoms of O_2 are used[219,220] (see Figure 14).

The catalyst precursor Ru^{VI}(TMP)$(O)_2$ (with two *trans*-oxo ligands) transfers one oxygen atom to the olefinic substrate and the resulting mono-oxo ruthenium complex, Ru^{IV}(TMP)(O), disproportionates (rate-limiting step) to generate the epoxidizing agent Ru^{VI}(TMP)$(O)_2$ and Ru^{II}(TMP) which reacts with molecular oxygen to produce the intermediate Ru^{IV}(TMP)(O) complex. TMP is the unique porphyrin ligand suitable in these ruthenium porphyrin-catalyzed aerobic epoxidations. [We found in our laboratory that Br_8TMP

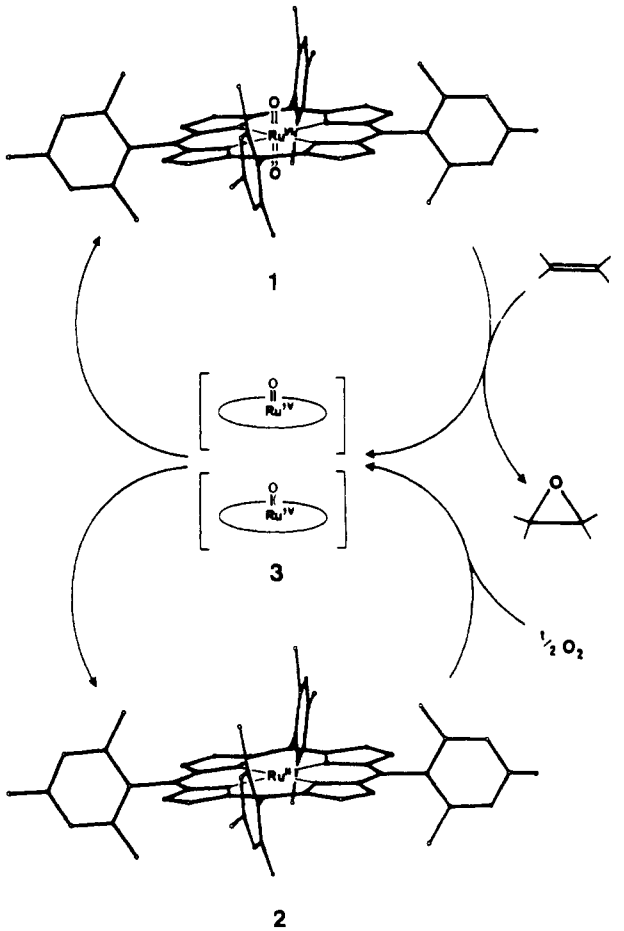


Figure 14. Mechanism of the O_2 olefin epoxidation catalyzed by a ruthenium porphyrin complex. Reproduced from ref 219. Copyright 1985 American Chemical Society.

does enhance the rate of these ruthenium-catalyzed epoxidations. (P. Hoffmann, unpublished data.)] 5-Cholestene derivatives are epoxidized by the O_2/Ru(TMP)$(O)_2$ system to their corresponding 5β,6β-epoxides.[221,222] For steroids having C=C bonds on the B cycle and on the lateral chain, epoxidation of the internal double bond is preferred.[223]

5. Photochemical Activation

Few examples of photochemical epoxidation of olefins with molecular oxygen and metalloporphyrins as catalysts have been reported. The photoassisted reduction of molecular oxygen to hydrogen peroxide by Mo^V(TPP)(OMe)(O) was initially reported by Ledon et al. in 1981,[224] but the photochemical epoxidation of olefins by niobium and molybdenum porphyrins was reported later by Murakami et al.[225] In the case of niobium, the photoactivation of Nb_2(Por)(μ-oxo)$_3$ leads to a monomer, Nb(Por)(O)(O–O•), the proposed active complex. The recycling of the catalyst probably occurs via a niobium dimer complex which allows the use of both oxygen atoms of dioxygen. These reactions are slow, since 20 to 80 catalytic cycles only are obtained within 12 h. Titanium and vanadium porphyrins are also poor catalysts in photochemically induced olefin epoxidations.[226] Richman et al. have shown that both continuous or flash photolysis produce a photochemical disproportionation of μ-oxo-bis(tetraphenylporphyrinato)iron(III) to generate the ferrous complex and the ferryl Fe(TPP)(O).[227] Catalytic photooxidation of cyclohexene yields 2-cyclohexen-1-one with more than 1000 cycles.

Table V. Olefin Epoxidations by O_2 Catalyzed by Mn(Br_8TMP)Cl in the Presence of Pyridine or 4-*tert*-Butylpyridine[a] (from ref 228; copyright 1991 American Chemical Society)

olefin	mol % catalyst	[axial ligand]/[cat.][b]	epoxide yield, %	turnover no.
cyclooctene	1.0	0	4.8	5
	0.33	52	12	37
	1.1	33	29	28
	3.1	49	38	12
trans-stilbene	0.8	36	11	13
	3.0	52	14	5
cis-stilbene	1.1	34	34 (cis) + 7.8 (trans)	39
styrene	1.1	31	26	24
1-octene	1.0	35	7	7
trans-2-hexene	1.0	35	6.4	7
cis-2-hexene	1.0	35	21 (cis) + 3 (trans)	25
cis-3-heptene	1.1	32	24	21

[a] In all cases, the olefin conversion was above 94–98%. Reaction time, 15–40 min at room temperature. For more experimental details, see text of ref 228. Yields are based on the starting olefin. [b] Pyridine was used as axial ligand in the case of cyclooctene, stilbene, styrene, and 4-*tert*-butylpyridine for 1-octene, 3-heptene, and 2-hexene.

6. Ozone

To our knowledge, the only report on the use of ozone as single oxygen atom donor in metalloporphyrin-catalyzed epoxidations is our recent work using Mn(Br_8TMP)Cl and Fe(Br_8TMP)OAc as catalysts.[228]

$$O_3 + M^{III}(Por)X \rightarrow M^V(Por)(O)X \quad [\text{or } Me^{IV}(Por^{\bullet+})(O)X] + O_2$$

Whereas Mn(TMP)Cl and Mn(TDCPP)Cl are quickly destroyed by ozone, Mn(Br_8TMP)Cl is oxidized to a high-valent manganese–oxo complex with a Soret band at 456 nm. The main results of olefin epoxidations by ozone with Mn(Br_8TMP)Cl are reported in Table V. As expected for a metalloporphyrin-catalyzed epoxidation, *cis*-olefins are more reactive than the corresponding trans isomers. The epoxidation is not stereospecific, but the *cis*-epoxide remains the major isomer in the epoxidation of *cis*-hexene and *cis*-stilbene (*cis*-/*trans*-epoxide ratio = 7 and 4.3, respectively). Besides epoxides, products of the direct olefin ozonolysis (aldehydes and carboxylic acids) are also observed.

D. Epoxidations with H_2O_2

Hydrogen peroxide is now a cheap oxidant produced by many different companies using the anthraquinone autoxidation process originally carried out in the 1940s.[229,230] Two main reasons drive the fast-growing production of hydrogen peroxide, and both are related to environmental considerations: (i) water is the side product of H_2O_2 after an oxidation reaction, and (ii) no chlorinated residues can be formed in bleaching methods, in contrast to processes using chlorine-containing oxidants. For these reasons, hydrogen peroxide is considered as a clean oxidant.

However, hydrogen peroxide is often too reactive in transition-metal-catalyzed oxidations. The main reaction pathway is the homolytic cleavage of the weak

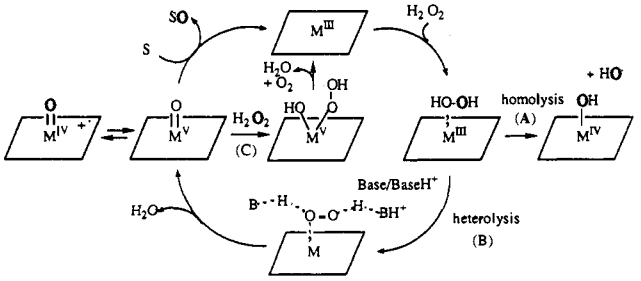


Figure 15. Different possible reaction pathways in the activation of H_2O_2 by metalloporphyrins: (A) = homolytic pathway with generation of HO·, (B) = heterolytic pathway with generation of a metal–oxo species, and (C) = addition of a second molecule of H_2O_2 to produce molecular oxygen and water (catalase reaction).

O–O bond: only 50 kcal/mol are involved in the generation of hydroxyl radicals from H_2O_2.[229] These Fenton-type reactions involve a fast nonselective addition of hydroxyl radicals to aromatic substrates with intermediate radicals reacting with molecular oxygen.[231,232]

$$[Fe]^n + H_2O_2 \rightarrow [Fe]^{n+1}\text{–OH} + HO^\bullet$$

The desired activation route in the case of synthetic metalloporphyrins is the heterolytic mode which leads to the generation of a high-valent metal–oxo porphyrin complex and a water molecule (pathway B of Figure 15). The two undesirable routes are the homolytic cleavage of H_2O_2 (pathway A) or the reaction of a second molecule of H_2O_2 with the metal–oxo complex to produce molecular oxygen and water (the catalase route, pathway C in Figure 15). The different factors involved in the oxidation of iron porphyrins with hydrogen peroxide have been reported by Bruice[233] and Traylor.[234] The rate-limiting step is the cleavage of the O–O bond and of one O–H bond in an intermediate where H_2O_2 is coordinated to M^{III}(Por). Traylor favors a general-acid catalysis and Bruice a general-base catalysis. Manganese and iron complexes are efficient catalysts for the dismutation of hydrogen peroxide to molecular oxygen and water.[235,236] No singlet dioxygen is formed in these transition-metal-catalyzed dismutation reactions.[237]

Metalloporphyrin dimers[238] or monomers[239] are also efficient H_2O_2 dismutation catalysts. Two heme enzymes, catalase and peroxidase, handle hydrogen peroxide as oxidant. Both enzymes are able to generate a high-valent iron–oxo porphyrin radical–cation active species (compound I).[240] With the same oxidant, the catalytic activity of these two hemoproteins is completely different: catalase is highly efficient for hydrogen peroxide dismutation,[10] whereas peroxidases have no catalase activity and are very active in one- or two-electron oxidations of various organic substrates.[8]

In these heme enzyme reactions different selectivities (heterolytic versus homolytic activation of H_2O_2, electron abstraction versus dismutation for the iron(IV)–oxo porphyrin radical–cation intermediate) result from the addition of different factors, viz. the nature of the proximal ligand (histidine in peroxidase, tyrosine in catalase), distal amino acid residues (histidine and arginine in the case of cytochrome *c* peroxidase[241] or histidine and asparagine in catalase[10]) and the protein channel for the arrival of hydrogen peroxide and protein–substrate interaction sites in the case of peroxidases.

Table VI. Imidazole and 2- or 4-Methylimidazoles Are Suitable Cocatalysts in the Mn(TDCPP)Cl-Catalyzed Epoxidation of Cyclooctene with Hydrogen Peroxide[a] (from ref 247; copyright 1988 American Chemical Society)

	yield of epoxide, %		H_2O_2 consumed, %	
cocatalyst	after 1 h	after 24 h	after 1 h	after 24 h
Im	91	91	100	100
2-CH_3-Im	94	94	100	100
4-CH_3-Im	90	90	100	100
1-CH_3-Im	51	85	59	100
benzimidazole[b]	9	45	21	66
1,2,4-triazole	8	20	25	63
pyridine	30	73	52	100
2,6-di-*t*-Bu-pyridine	1	5	16	33
Et_3N	51	51	100	100
i-$PrNH_2$	42	42	100	100
$(C_6H_{11})_2NH$	39	39	100	100

[a] Progressive addition of 2 equiv (relative to alkene) of H_2O_2 (30% in H_2O, diluted 10 times in CH_3CN) over 0.5 h, at room temperature, to a cyclooctene/imidazole/Mn(TDCPP)Cl mixture (40:10:1) in CH_2Cl_2/CH_3CN (1:1) under aerobic conditions. Final concentration of Mn(TDCPP)Cl = 3 mM. Yield based on starting cyclooctene. [b] In this case, a partial precipitation of the catalyst was observed.

Using synthetic manganese and iron porphyrin complexes having a nitrogen ligand or an oxygen ligand in the proximal position, we recently proposed that tyrosine is present in catalase to inhibit any possible oxygen atom transfer reaction from the metal–oxo to a distal amino acid residue of the protein in order to avoid an oxidative degradation of the protein.[242,243]

The first report of a metalloporphyrin-catalyzed oxygenation reaction with H_2O_2 involving metal–oxo chemistry describes the formation of sulfoxides from sulfides catalyzed by Fe(TPP)Cl in acetonitrile.[244] The

$$\text{Ph–S–CH}_2\text{–R} \xrightarrow[H_2O_2/CH_3CN]{\text{Fe(TPP)Cl/imidazole}} \text{Ph–SO–CH}_2\text{–R}$$

presence of imidazole was necessary to observe an efficient catalytic reaction. A S-dealkylation side reaction was also observed, which is consistent with cytochrome P-450 type chemistry. An early report on the H_2O_2 hydroxylation of phenylalanine to tyrosine catalyzed by Fe^{III}(TMPyP) in water (7 cycles/h) implied that this reaction might be related to the catalytic formation of hydroxyl radicals.[245]

The key role of imidazole in metalloporphyrin-catalyzed oxygenations with H_2O_2 was also evidenced by Mansuy et al. in olefin epoxidations.[246,247] Imidazole, 2-methylimidazole, and 4-methylimidazole are efficient cocatalysts in the epoxidation of cyclooctene with H_2O_2 and Mn(TDCPP)Cl as catalyst[247] (Table VI). Good epoxidation yields are obtained with the H_2O_2/Mn(TDCPP)Cl/imidazole system. Robust metalloporphyrins such as Mn^{III}(TDCPP)Cl are not degraded when hydrogen peroxide is progressively added to the reaction mixture.

Using a basket-handle manganese porphyrin complex with one imidazole in proximal position (see Figure 11, complex 3) as catalyst with or without added free imidazole in the reaction mixture, evidence was provided in these metalloporphyrin-catalyzed oxygenation reactions on the role of imidazole both as proximal ligand and as acid-base catalyst at the distal site to favor the heterolytic cleavage of the peroxidic O–O bond.

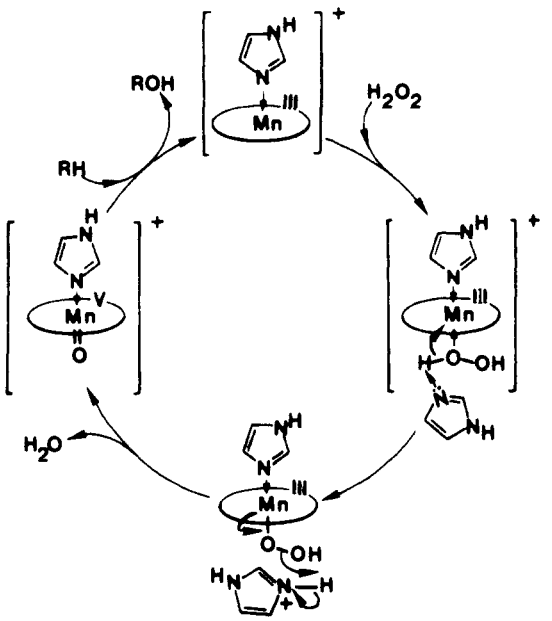


Figure 16. Possible roles in olefin epoxidations with H_2O_2 catalyzed by manganese porphyrins. Reproduced from ref 247. Copyright 1988 American Chemical Society.

(See Figure 16 for a proposed catalytic cycle in olefin epoxidations.)

In olefin epoxidations with H_2O_2/Mn(TDCPP)Cl reaction rates are strongly enhanced by addition of lipophilic carboxylic acids (e.g. benzoic or hexanoic acid) and lipophilic imidazole or pyridine axial bases (e.g. *N*-hexylimidazole or 4-*tert*-butylpyridine).[248,249] The pH of commercial 30% H_2O_2 (pH 2–3) must be adjusted to 4.5–5.0 by addition of sodium carboxylate to observe the highest catalytic activities. With a 200/200/1/1/1 molar ratio for cyclooctene/H_2O_2/benzoic acid/*N*-hexylimidazole/Mn(TDCPP)Cl in a CH_2Cl_2/30% H_2O_2 two-phase medium at 0 °C, cyclooctene oxide is quantitatively formed within 10 min.[248,249]

Yields of Mn(TPP)Cl-catalyzed olefin epoxidations with hydrogen peroxide are improved by addition of orthoquinones[250] (including methoxatin, the coenzyme PQQ of amine deshydrogenases).[251] A H_2O_2–orthoquinone adduct was proposed as active oxidant in this catalytic epoxidation. Adducts of hydrogen peroxide with tertiary amine *N*-oxides, urea, or sodium carbonate have also been used as a convenient source of anhydrous H_2O_2.[252] However, a small amount of water is necessary to favor the release of H_2O_2 in the organic phase, otherwise the biphasic reaction (solid–liquid) is too slow. The same authors have also reported the high catalytic activity of β-perhalogenated metalloporphyrins in olefin epoxidations with hydrogen peroxide.[253] In addition, they found that Mn(Cl_8TDCPP)Cl can be attacked by HO• leading to a black insoluble manganese porphyrin complex having a Cl atom replaced by an oxygen atom (m/z = 1199 instead of 1218 for the original complex).[253]

Molybdenum porphyrin complexes do not catalyze the dismutation of hydrogen peroxide and they act as olefin epoxidation catalysts, but their catalytic activities remain weaker than the ones of manganese porphyrins.[254] Turnover rates range from 2 to 5 cycles/h. 1,5-Cyclooctadiene is selectively epoxidized to the corresponding monoepoxide. One limitation is the necessary use of anhydrous hydrogen peroxide. A 30% aqueous H_2O_2 solution can be used as oxygen atom source if Mo^V(TPP)(O)Cl is replaced by molybdenum β-halogenated porphyrin complexes (Figure 17).[255]

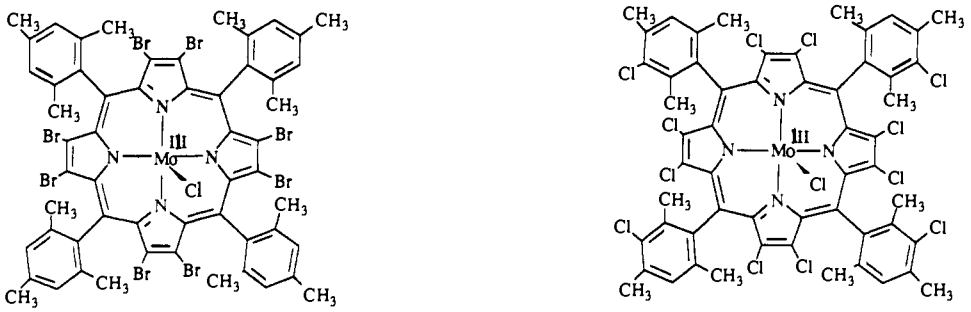
E. Epoxidations with ROOH

Alkyl hydroperoxides are easily produced by autoxidation of alkanes having one tertiary C–H bond (isobutane, cumene). These oxidants are very good oxygen atom donors in olefin epoxidation catalyzed by molybdenum, vanadium, or titanium complexes.[1a,256] Alkyl hydroperoxides are also the oxidants of choice for the Sharpless asymmetric epoxidation of allylic alcohols,[23,24] but, as with hydrogen peroxide, the major problem in the activation of alkyl hydroperoxides by manganese or iron porphyrins is to avoid the homolytic cleavage of the O–O bond. Such a process generates an alkoxy radical RO• which is able to abstract one hydrogen atom from alkanes, but is unable to produce epoxides. (The absence of epoxides in a transition-metal-mediated olefin oxidation with ROOH is the signature of a mechanism where metal–oxo species can be ruled out.) The factors involved in heterolytic versus homolytic O–O bond cleavage have been extensively investigated by different research groups.

In the absence of a nitrogen axial ligand, iron(III) porphyrins mainly cleave alkyl hydroperoxides via a homolytic process generating an oxoiron(IV) complex and alkoxo radical.[257–259] Activation of 10-hydroperoxyoctadeca-8,12-dienoic acid by Fe(TPP)Cl produce 10-oxodec-8-enoic acid and 10-oxooctadeca-8,12-dienoic acid. Both products are derived from an alkoxy radical intermediate generated by the homolytic cleavage of the starting alkyl hydroperoxide or possibly by homolysis of a (Por)FeOOR intermediate complex.[260] Alternatively, Traylor et al. favor the formation of an (alkylperoxo)iron(III) complex followed by a heterolytic cleavage to give rise to an oxoiron(IV) porphyrin and to the corresponding alcohol. The latter reaction is acid catalyzed.[234,261] NMR studies indicate that activation of *t*-BuOOH by Fe^{II}(TTP) produces an (alkylperoxo)iron(III) complex which yields (*N*-MeIm)-Fe^{IV}(TTP)(O) after addition of *N*-methylimidazole.[262] Activation of alkyl hydroperoxides by manganese porphyrins is greatly enhanced by nitrogen base ligation and produces oxomanganese(V) porphyrins and the corresponding alcohols.[263,264] (Association constants of imidazole, *N*-methylimidazole, 4′-(imidazol-1-yl)acetophenone, 3,4-dimethylpyridine, and 2,6-dimethylpyridine have been reinvestigated and are available in ref 263.)

The first reports on metalloporphyrin-catalyzed olefin epoxidations with alkyl hydroperoxides described the use of molybdenum complexes. Both *t*-BuOOH and CumOOH were associated with Mo^V(TPP)(O)OMe in catalytic olefin epoxidations.[265] Reaction rates are slightly slower than with *t*-BuOOH/$Mo(CO)_6$. Ti^{IV}(TPP)(O) can also catalyze olefin epoxidations with *t*-BuOOH.[266] The peroxo complex Ti(TPP)(O_2) which is formed during the reaction is unable to oxidize olefins. Thus, the active species is probably the *cis*-hydroxo(alkylperoxo)titanium(IV) porphyrin complex.

In the presence of imidazole, Mn(TPP)Cl catalyzes the epoxidation of various olefins (styrene, cyclohexene, *cis*-stilbene) with cumyl hydroperoxide as oxygen atom source.[267] Here, Fe(TPP)Cl is less efficient than the corresponding manganese complex. As for PhIO epoxidations catalyzed by metalloporphyrins, *cis*-olefins are more reactive than *trans*-olefins and preliminary



$Mo^{III}(Br_8TMP)Cl$ $Mo^{III}(Cl_{12}TMP)Cl$

Figure 17. Structures of two halogenated molybdenum porphyrins: $Mo^{III}(Br_8TMP)Cl$ and $Mo^{III}(Cl_{12}TMP)Cl$.

UV–visible data indicate that a high-valent manganese–oxo species with a Soret band at 426 nm is generated by addition of CumOOH to Mn(TPP)Cl at low temperature. Manganese Schiff base complexes in the presence of imidazole or pyridine can also catalyze the olefin epoxidation with alkyl hydroperoxides.[268]

The mechanism of olefin epoxidations with ROOH and Fe(TDCPP)Cl as catalyst was investigated by Traylor et al. using the *exo-endo*-norbornene oxide ratio as probe.[269] This ratio is 15 with *t*-BuOOH as oxidant (18 and 13 with H_2O_2 and C_6F_5IO, respectively) and suggests that the active iron–oxo species is similar whatever the oxidant used. However, Bruice recently reported that the oxidation products of *cis*-stilbene by *t*-BuOOH/Fe(TDCPP)Cl are *trans*-stilbene oxide as major product and diphenylacetaldehyde, deoxybenzoin, and PhCH[OO(*t*-Bu)]CH[O(*t*-Bu)]Ph as side products.[270] This author concludes that these reaction products are derived from an initial reaction of *t*-BuOO•, rather than $Fe^{IV}(Por^{\bullet+})(O)$, with *cis*-stilbene. However, it should be noted that the two latter studies on epoxidations with *t*-BuOOH were not performed with Mn(TDCPP)Cl and imidazole, the efficient association in catalytic oxygenation reactions, and, hence, the reaction mechanisms are probably more related to cage-controlled metal–oxo chemistry than to free-radical chemistry.

F. Epoxidation with $KHSO_5$ and Related Oxidants

Potassium monoperoxysulfate (or monopersulfate) is an efficient water-soluble oxygen atom donor stable at pH < 6 and at pH 12.[271] The point of minimum stability is at pH 9 where HSO_5^- and SO_5^{2-} concentrations are equal.[272]

At very acid pH (< pH 1), HSO_5^- hydrolyzes to hydrogen peroxide. Potassium monopersulfate is a stable inorganic peroxide obtained by crystallization from a mixture of potassium sulfate and potassium monoperoxysulfate into a triple salt: $2KHSO_5, KHSO_4, K_2SO_4$, which is available under the names of Oxone, Caroat, or Curox from DuPont, Degussa, or Interox, respectively. This white powder (active oxygen content = 5.2%) is 96% pure, is free of hydrogen peroxide and can be used without further purification. $KHSO_5$ itself is obtained by neutralization with potassium carbonate of H_2SO_5 (Caro's acid) which is produced from hydrogen peroxide and sulfuric acid.[272] Water solutions of $KHSO_5$ are relatively stable with a loss of active oxygen of only 5% in 3 days. Potassium monopersulfate is becoming a widely used oxidant in organic chemistry for the preparation of pyridine *N*-oxides,[273] β-lactam intermediates,[274] and sulfones,[275] for the oxidation of quinones,[276] amino acids,[277] or pyrimidine, and purine bases,[278,279] and for olefin epoxidations or alkane hydroxylations via the intermediate formation of a ketone dioxirane[280,281] or directly for water-soluble alkenes in aqueous methanol.[282]

This efficient single oxygen atom donors, based on peroxidic derivatives, have a nonsymmetrical oxygen–oxygen bond. This arrangement is also the case for organic peracids, such as *m*-chloroperbenzoic acid. The X-ray structure of $KHSO_5$ confirms the existence of a short and nonsymmetrical O–O bond[283] (1.460 Å compared to 1.497 Å in solid H_2O_2) with a hydrogen atom on one side and an SO_3^- group on the other side (the sulfate entity is the leaving group in the case of heterolytic cleavage of the O–O bond).

We discovered the ability of $KHSO_5$ to behave as a single oxygen atom donor in the epoxidation of olefins catalyzed by metalloporphyrins.[284,285] Another example of epoxidation by potassium monopersulfate catalyzed by transition-metal complexes was recently reported by Strukul et al.,[286] but no metal–oxo chemistry is involved in these platinum-mediated reactions.

Simple aliphatic olefins are soluble only in organic solvents while potassium monopersulfate is a water-soluble oxygen source. Consequently, the catalytic epoxidation reactions have been performed in a biphasic system, namely buffered water/dichloromethane. Usually a phosphate buffer is sufficient to keep the pH value around 7 during the catalytic oxygen transfer reaction which occurs in dichloromethane with hydrophobic metalloporphyrins such as M(TPP)OAc, M(TMP)Cl, M(TDCPP)Cl, Mn(Br_8TMP)Cl or Mn(Cl_{12}TMP)Cl, where M is Mn or Fe.

$$\text{olefin} + KHSO_5 \xrightarrow[\text{phase-transfer agent, buffered } H_2O/CH_2Cl_2]{M^{III}(Por)Cl/4\text{-R-pyridine}} \text{epoxide}$$

In these reactions, 0.1–1.25% of catalyst is used with respect to the olefin, while 10–100 equivalents of 4-R-pyridine (R = Me or 4-*t*-Bu) are used with respect to manganese complexes (manganese complexes when associated to a proximal ligand, usually a pyridine derivative, are more efficient catalysts than the corresponding iron porphyrins). Moreover, any stable tetraalkylammonium salt is suitable as phase-transfer agent.[287] High catalytic activities are observed, e.g. for cyclohexene with Mn(TPP)OAc/4-*tert*-butylpyridine as catalyst, 80% yield of cyclohexene oxide is obtained within 5 min (the epoxide yield is below 2% in a control experiment without metalloporphyrin), corresponding to a turnover rate of 13 cycles min^{-1}. This activity is

based on epoxide formation. More recently, with the manganese complex of *meso*-tetramesityl-β-octabromoporphyrin, Mn(Br$_8$TMP)Cl, up to 40 cycles min^{-1} are reached.[50b] With Mn(Cl$_{12}$TMP)Cl, even a *trans*-olefin like *trans*-stilbene is easily epoxidized (turnover rate = 90 min^{-1}).[288]

As in the NaOCl epoxidation catalyzed by manganese porphyrin complexes[140,148] 4-substituted pyridines act as a "push-ligand" in the proximal position.[287] Because of the strong oxidation properties of $KHSO_5$, pyridine ligands are partially oxidized to *N*-oxides during the catalytic epoxidation. Fortunately, this reaction occurs at slower rates than the epoxidation itself, always leaving a sufficient amount of intact 4-R-pyridine in the organic phase to act as proximal ligand.[287] In oxidations with potassium monopersulfate, imidazole derivatives cannot be used as proximal ligands because of their rapid degradation.

Aliphatic *cis*-olefins are stereospecifically epoxidized, whereas *cis*-stilbene, an olefin sensitive to epoxidation by a radical pathway, gives mainly the *cis*-epoxide with a small amount of the trans isomer (*cis*-*trans*-epoxide ratio = 80/20). With Mn(TPP)OAc as catalyst, the decreasing order of reactivity is tetramethylethylene > *cis*-stilbene > cyclohexene > styrene > 1-methylcyclohexene > *trans*-stilbene > *cis*-2-hexene > *trans*-2-hexene[287] (terminal olefins are also epoxidized[285]). With Mn(Br$_8$TMP)Cl as catalyst, the $KHSO_5$ epoxidation of 1-octene is performed at 1 cycle min^{-1} [50b]).

Labeling experiments performed with a solution of $KHSO_5$ in $H_2{}^{18}O$ indicated that no ^{18}O was incorporated during cyclohexene epoxidation by $KHSO_5$/Mn(TPP)OAc.[287] This result strongly suggests (i) that $KHSO_5$ is the oxygen source in these metalloporphyrin-catalyzed epoxidations and (ii) that the oxygen transfer rate from the high-valent metal–oxo species is faster than the exchange with the oxygen atom of $H_2{}^{18}O$. (For recent informations on oxygen atom exchanges in catalyzed epoxidation reactions, see refs 289–291.)

Magnesium Monoperoxyphthalate or MMPP. This water-soluble organic peracid displays the same behavior with metalloporphyrins as potassium monopersulfate.[292,50b] As noted above olefin epoxidations are greatly enhanced by the presence of 0.1–1% of metalloporphyrin catalysts in biphasic solutions (water/dichloromethane). With Mn(TMP)Cl as catalyst and MMPP as oxygen source, the catalytic activity in cyclooctene epoxidation is 55 times that observed with potassium monopersulfate.[288]

G. Epoxidations with Other Oxygen Atom Donors

1. Amine N-Oxides

Bruice et al. found that *N*,*N*-dimethylaniline *N*-oxide derivatives were able to transfer their oxygen atom to synthetic iron[293,294] and manganese[295] porphyrin complexes, but *N*,*N*-dimethylanilines which are left after the oxygen atom transfer are not innocent molecules with respect to generated high-valent metal–oxo porphyrin complexes. These tertiary amines are good substrates and are easily demethylated by an oxidative process.[293] *p*-Cyano-*N*,*N*-dimethylaniline *N*-oxide is a better single oxygen atom donor to Fe(TPP)Cl than *N*,*N*-dimethylaniline *N*-oxide.[296] Both *N*-oxides are also able to activate cytochrome P-450.[297]

Olefins are epoxidized by *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide with Fe(TPP)Cl as catalyst.[295] As expected, the best epoxidation yield was observed for tetramethylethylene, a highly electron-rich olefin which is a better substrate for the iron–oxo species than the tertiary amine. Kinetic data indicate that the rate-determining step is the oxidation of Fe^{III}(Por)Cl by the *N*-oxide and not the olefin epoxidation.[298,299] The second-order rate constant for the oxidation of *meso*-[tetrakis(2,6-dimethylphenyl)porphyrinato]iron(III) chloride by *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide is 1.7 M^{-1} s^{-1}, 3.3-fold lower than for Fe(TPP)Cl (5.5 M^{-1} s^{-1}). With a hindered porphyrin ligand, the activation step is slower than with TPP, but epoxide yields are better, because of the reduced ligand degradation.

The oxidation rate of manganese porphyrins by amine *N*-oxides is highly enhanced by an axial nitrogen ligand.[295,300] Ligation of imidazole to *meso*-[tetrakis(2,6-dimethylphenyl)porphyrinato]manganese(III) increases its oxidation rate by 166-fold.[300] Hill et al. also reported olefin epoxidations with *N*-methylmorpholine *N*-oxide catalyzed by Mn(TPP)Cl.[301] *cis*-Stilbene gives a mixture of *cis*- and *trans*-epoxides and benzaldehyde (yield = 19, 13, and 6%, respectively). *trans*-Stilbene is oxidized to *trans*-stilbene oxide, but a small amount of *cis*-stilbene oxide is observed (yield = 14% for trans and 3% for cis). In addition, *N*-methylmorpholine *N*-oxide gives a stable bis-adduct with Mn(TPP)ClO_4 which has been characterized by X-ray crystallography. The manganese–axial oxygen distance is 2.14 Å. For comparison, the Mn–O distance is 2.26 Å in Mn^{III}(TPP)(2,6-lutidine *N*-oxide)ClO_4[302] and 2.11 Å in [Mn^{III}(TPP)aquo]triflate.[303]

Pyridine *N*-oxides are unable to behave as oxygen donors with manganese or iron porphyrin complexes,[139] but they react with ruthenium porphyrins. Ru^{VI}(TMP)(O)$_2$ or Ru^{II}(TMP)CO can be used as catalyst precursor in olefin epoxidation with different pyridine *N*-oxides.[304] 2,6-Disubstituted pyridine *N*-oxides are the best oxidants in ruthenium porphyrin catalyzed epoxidations. Pyridine *N*-oxide itself is not suitable as oxygen source, because the generated pyridine is a strong binding axial ligand and inhibits the catalytic activity. The proposed catalytic cycle involves a dismutation of Ru^{IV}(TMP)O to Ru^{VI}(TMP)(O)$_2$ and Ru^{II}(TMP), as previously reported by Groves et al.,[219] Ru^{VI}(TMP)(O)$_2$ being the oxygen transfer complex for olefin oxidation and Ru^{II}(TMP) reacting with lutidine *N*-oxide to regenerate Ru^{IV}(TMP)O.[304]

2. m-CPBA

m-Chloroperbenzoic acid, *m*-CPBA, is one of the favorite peracids used at laboratory scale to perform oxidation and epoxidation reactions. Commercial forms of *m*-CPBA contain *m*-chlorobenzoic acid as contaminant which also reduces the shock sensitivity and hazardous nature of the material in condensed phase.

This oxidant is an efficient oxygen atom donor which has been widely used to generate high-valent iron–oxo porphyrin complexes (see section VII). With a highly hindered iron porphyrin like Fe^{III}(TTPPP)OH, an (acylperoxo)iron(III) porphyrin complex can be generated and characterized at room temperature.[305] An excess of *m*-CPBA produces the high-valent green iron–oxo complex Fe^{IV}(Por$^{\bullet+}$)(O) (see section VII). (Acylperoxo)manganese(III) porphyrin complexes can also be prepared by addition of *m*-CPBA to Mn^{III}(TMP)OH at −40 °C. Homolytic cleavage of the O–O bond is

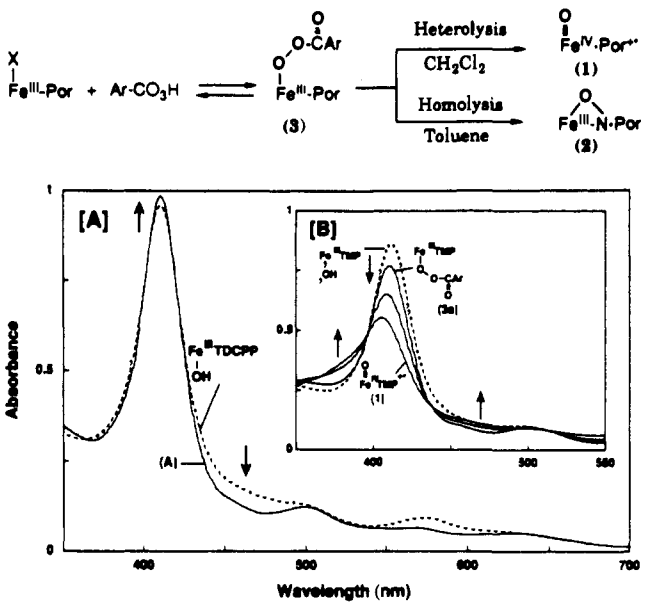


Figure 18. Solvent effect on the O–O bond cleavage of an intermediate (acylperoxo)iron(III) porphyrin complex generated by oxidation of an iron porphyrin with *m*-CPBA. Reproduced from ref 314. Copyright 1991 American Chemical Society.

favored under basic conditions leading to Mn^{IV}-(TMP)(O)OH (the complex is probably negatively charged) and to RCOO• which quickly decarboxylates under these conditions.[306] In the absence of base, the heterolytic cleavage of the O–O bond generates Mn^{V}(TMP)(O).

Because *m*-CPBA is an epoxidizing agent by itself, very few articles are devoted to metalloporphyrin-catalyzed olefin epoxidations with *m*-CPBA as oxygen atom source. In addition, an early report on oxidation of *N*-nitrosodibenzylamines catalyzed by Fe(TPP)Cl or Mn(TPP)Cl indicated that better yields were obtained for reactions carried out with PhIO than with *m*-CPBA.[307] The oxygen transfer step from oxidant to metalloporphyrin is fast and should not be incriminated for poor catalytic oxidations.

Measurements of transfer rates are available for manganese,[263,308] iron,[309,310] chromium,[309] and cobalt.[311] But *m*-CPBA can also oxidize iron porphyrins to catalytically inactive iron(III) porphyrin *N*-oxide complexes.[312,313] Actually, the decomposition of the intermediate (acylperoxo)iron(III) porphyrin to the reactive $Fe^{IV}(Por^{\bullet+})(O)$ (heterolytic O–O bond cleavage) or to the inactive iron(III) porphyrin *N*-oxide (homolytic O–O bond cleavage) is largely controlled by solvent effects[314] (see Figure 18). Recently, Watanabe et al. have evidenced a solvent effect on the O–O bond cleavage of the intermediate peracid–metal complex. The heterolytic cleavage is favored in dichloromethane, whereas the homolytic pathway is observed in toluene.[314] In addition, *m*-CPBA was also used in iron porphyrin-catalyzed oxidations of alkenes like hexamethyl(Dewar benzene) which are known to produce rearranged molecules after $1e^-$ oxidation reactions.[315]

3. Oxaziridines

Oxaziridines have also been used as oxygen atom donors in Mn(TPP)Cl-catalyzed olefin epoxidations.[316] Oxygen transfer rates to chromium and iron porphyrin complexes have been measured.[317]

4. Perchlorate and Periodate

Photochemical epoxidations have been reported with perchlorate or periodate as oxygen atom source and irradiation of manganese(III) tetraphenylporphyrin at wavelength corresponding to the Soret band.[318] Catalytic activities are low: 1–15 for the turnover numbers.

III. Alkane Hydroxylations Catalyzed by Metalloporphyrins

Most of the hydrocarbons recovered from crude oil are unfortunately burned to carbon dioxide and water. In the near future, viz. three or four decades, saturated hydrocarbons should be mainly used as raw material for the manufacturing of chemicals. Controlling the oxidation of saturated hydrocarbons to alcohols or ketones is not an obvious process, since these partially oxidized intermediates are themselves more easily oxidized than starting hydrocarbon substrates. The exothermicity of the oxidation of ethane to ethanol is 40 kcal/mol, whereas it is 49 and 70 kcal/mol for the oxidation of ethanol to acetaldehyde and of acetaldehyde to acetic acid, respectively.[18] However, the kinetics of oxidation reactions are unfavorable at low temperatures, and the selective production of alcohols or ketones by partial oxidation of alkanes requires a strict kinetic control of these reactions. This feat is achieved in living organisms by metalloenzymes such as methane monooxygenase (MMO) or cytochrome P-450. MMO, produced by methanotrophic bacteria, is able to generate selectively methanol from methane with molecular oxygen and NADH as cofactor,[319] whereas the latter, with a heme as prosthetic group, catalyzes the hydroxylation of various exogeneous or endogeneous substrates in many living organisms, from plants to mammals.[7] For all these reasons, the discovery of new catalytic hydroxylation reactions, able to operate at mild temperatures, is a challenging area in oxidation chemistry. Two main directions have been explored during the last decade: (i) the use of bimetallic (or cluster) catalytic precursors in order to mimic methane monooxygenase,[320,321] (the Gif system developed by Barton et al. has been recently linked to this field[322]) and (ii) the use of metalloporphyrins to catalyze the hydroxylation of alkanes. The latter aspect will be the only area developed in the present review article. (For alkane activation by low-valent organometallic complexes, by gas-phase systems, by polyoxometalates, or by mercury photosensitization, see refs 323, 324, 325 and 326, respectively.)

A. Hydroxylations with PhIO

1. Iron Porphyrins

Cyclohexane oxidation by PhIO and *meso*-(tetra-*o*-tolylporphyrinato)iron chloride, Fe(TTP)Cl, mainly affords cyclohexanol (31%, based on oxidant) and cyclohexanone (6%). The hydrogen–deuterium isotope effect for this cyclohexane hydroxylation reaction was found to be as high as 12.9 ± 1.[327] This high primary isotope effect is compatible with a rate-determining step being the hydrogen atom abstraction by a high-valent iron–oxo species. A fast rate constant for the "oxygen rebound" step explains why high retention of configuration (but not complete retention of configuration, see refs 327b and 334b) is observed in hydroxylations catalyzed by cytochrome P-450 or by P-450

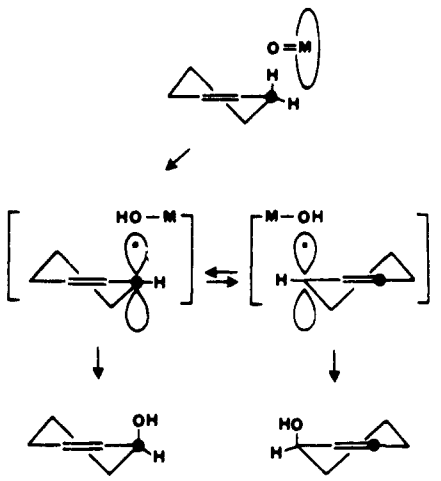


Figure 19. Allylic rearrangement in hydroxylations catalyzed by iron porphyrin complexes. Reproduced from ref 329. Copyright 1984 American Chemical Society.

models based on metalloporphyrin. (For a recent article on kinetic investigations of the "oxygen rebound" rate constants, see ref 328. These values range from 1 to 5 $\times 10^{10}$ s^{-1}.)

The radical character of metalloporphyrin-catalyzed hydroxylation is also supported by the allylic rearrangement observed in the allylic hydroxylation of olefins[329] (Figure 19).

Even in the case of benzylic hydroxylation, the key step is the abstraction of a hydrogen atom, not an electron abstraction from the aromatic ring.[330] The yield of the metalloporphyrin-mediated hydroxylation is better in a hydrophobic medium (dichloromethane or benzene) than in methanol or acetonitrile.[331] The yields and product distribution in hydrocarbon oxidations are markedly affected by the nature of porphyrin ligands. Higher yields are observed with iron porphyrins having bulky phenyl substituents at the meso positions of the macrocycles.[332,333] Kinetic measurements show that bulky catalysts are protected against bimolecular self-destruction by these hindered phenyl substituents.[333]

The third generation of porphyrin catalysts with chlorine or bromine atoms at the β-pyrrolic positions of the macrocycle is highly efficient in hydroxylation of linear alkanes[334a] or norbornane derivatives.[334b] The regioselectivity of the linear alkane hydroxylation, i.e. the 2-/3-/4-ol distribution ratio in the case of heptane oxidation, is close to that expected from a statistical reactivity, suggesting that the metal–oxo species is probably too reactive to have hydroxylase activity which can be modulated by cage effects (see below for shape-selective hydroxylations with manganese porphyrin catalysts).

2. Manganese Porphyrins

A series of manganese and iron porphyrins with sterically protected ligands have been studied by Suslick et al. in the alkane hydroxylation with iodosylbenzene as oxidant. Shape-selective oxygenation reactions have been observed with a very sterically hindered catalyst, Mn(TTPPP)OAc (TTPPP = *meso*-tetrakis(2,4,6-triphenylphenyl)porphyrinato ligand).[335a,b] The latter catalyst enhances the ω-hydroxylation of aliphatic alkanes while the regioselectivity in alcohol formation is comparable to that found for cytochrome P-450 enzymes which catalyze the hydroxylation of the terminal methyl group in fatty acids or alkanes.[335b] On the basis of the use of covalently attached templates introduced by Breslow in the 1970s, Grieco reported the remote hydroxylation of 17β-methyl-5α-androstane-3α,17α-diol from 17β-methyl-5α-androstan-3α-ol.[335c] The manganese complex of the *meso*-tetrakis(2,6-dinitrophenyl)porphyrin is also an efficient catalyst for alkane hydroxylation.[336] Few studies have been devoted to kinetic isotope effects (KIE) in alkane hydroxylations catalyzed by manganese porphyrins. A low KIE value, $k_H/k_D = 3.5$, was initially reported by Suslick,[335b] and we found, in a detailed study involving cyclohexane as substrate and various manganese porphyrin catalysts (Table VII), that there is a general tendency toward obtaining low intermolecular isotope effects with these catalysts (k_H/k_D = 1.8 to 2.6) compared to iron porphyrins (k_H/k_D = 7.7–9.0).[337] The electronic structure of the high-valent manganese–oxo species responsible for the hydrogen atom abstraction from the alkane substrate is different from that of the corresponding iron entity. The "oxygen rebound" rate constant is also probably slower than in the iron case, thus allowing the organic radical to escape from the solvent cage, making possible the formation of carbon–halogen or carbon–nitrogen bonds in some cases.[338]

Table VII. Kinetic Isotope Effects in Cyclohexane Hydroxylation (C_6H_{12} vs C_6D_{12}) with Different Oxidants and Metalloporphyrin Catalysts (from ref 337)

run	oxidant	metal	ligand	KIE[a]
1	$K^+HSO_5^-$	Mn	TMP	3.1
2		Mn	Cl_{12}TMP	3.4
3		Mn	TDCPP	2.1 ± 0.2
4		Mn	Br_8TMP	2.3 ± 0.3
5		Fe	TDCPP	1.5 ± 0.7
6		Fe	Br_8TMP	1.2 ± 0.4
7	n-$Bu_4N^+HSO_5^-$	Mn	TDCPP	2.8 ± 0.6
8		Mn	Br_8TMP	4.9 ± 0,2
9		Fe	TDCPP	2.3 ± 1.2
10		Fe	Br_8TMP	2.9 ± 1.3
11	C_6H_5IO	Mn	TDCPP	2.6 ± 0.4
12		Mn	Br_8TMP	1.8 ± 0.3
13		Fe	TDCPP	9 ± 3
14		Fe	Br_8TMP	7.7 ± 0.6

[a] KIE is calculated as $(C_6H_{12}$ conv/C_8H_{16} conv$)_H/(C_6D_{12}$ conv/C_8H_{16} conv$)_D$. For details on the experimental conditions, see ref 337.

3. Other Metalloporphyrins

Chromium porphyrin complexes are less efficient hydroxylation catalysts than the corresponding manganese derivatives.[339] Osmium complexes are also poor hydroxylation catalysts,[340] whereas aluminum porphyrins are completely inactive.[341]

B. Hydroxylations with NaOCl and Other Hypochlorites

1. Manganese and Iron Porphyrins

The first report of an alkane hydroxylation with NaOCl as oxidant was published by Tabushi in 1979, using Mn(TPP)Cl as catalyst.[37] In adamantane oxidation, the main products detected in the dichloromethane phase were chloroadamantanes (1-AdCl = 47% and 2-AdCl = 21%) and adamantanols as minor

products (1-AdOH = 17% and 2-AdOH = 11%). Less than 4% of adamantanone was detected.[37] Mn(TMP)Cl and Mn(TPFPP)Cl complexes were found to be better catalysts, giving adamantanols as the main reaction products.[342]

However, we found that NaOCl is a poor oxygen atom donor in metalloporphyrin-catalyzed hydroxylation reactions compared to $KHSO_5$ which is also used as oxygen atom donor in a biphasic catalytic system (see section III.E). The poor capacity of NaOCl/Mn(Por)Cl to hydroxylate hydrocarbons is not due to the biphasic nature of the reaction mixture, but more presumably to the nature of the high-valent manganese–oxo species generated by NaOCl.

Very high values have been reported by Shilov et al. for kinetic isotope effects in the NaOCl cyclohexane hydroxylation catalyzed by Fe(TMP)Cl, viz. 21.0 ± 1.9.[343] This tunneling contribution was observed only in benzene, while lower k_H/k_D values were measured in benzonitrile (10.2) and in chlorobenzene (10.0).

2. Other Complexes

Nickel salen complexes efficiently catalyze the chlorination of saturated alkanes when basic aqueous solutions of sodium hypochlorite are used as oxidant.[181] The chloroalkanes/oxygenated hydrocarbons ratio ranges from 10 to 33. The mechanism of this nickel-catalyzed hydrocarbon chlorination might be related to the aryl–halogen exchange catalyzed by nickel porphyrin complexes in the presence of sodium hypochlorite at pH 9.[182] Free chlorine radicals might be responsible for these chlorination reactions with nickel playing the role of catalytic initiator.

3. Related Oxidants

Sodium hypobromite is another suitable oxidant in manganese porphyrin catalyzed hydroxylations.[342] Lithium hypochlorite can also be used in adamantane hydroxylation catalyzed by ruthenium biphosphine complexes.[344] However, ethers are the best substrates for the latter catalytic system. They are quickly converted to esters (or lactones in the case of cyclic ethers).

Sodium chlorite, $NaClO_2$, is also a suitable oxidant in metalloporphyrin-catalyzed oxidations of alkanes.[345] With the same manganese porphyrin, turnover numbers with $NaClO_2$ are 200 times those observed with NaOCl. Sodium chlorate, $NaClO_3$, is inactive in these metalloporphyrin-catalyzed hydroxylations.

C. Hydroxylations with O_2

1. Autoxidation Reactions

Alkane autoxidations are usually performed at the industrial scale with cobalt or manganese complexes which are cheaper than metalloporphyrins. However, early reports indicated that manganese porphyrin[346] or phthalocyanine[347] can catalyze the autoxidation of indoles or tryptophan with a product distribution different from that observed in a free-radical autoxidation reaction.[347] Lyons and Ellis recently reported that chromium, manganese or iron complexes of *meso*-tetraphenylporphyrin with one azido as axial ligand were efficient catalysts for the autoxidation of isobutane to *tert*-butyl alcohol.[348] Reactions were operated at 80 °C under 100 psig of O_2 in benzene solutions and selectivities in alcohol ranged from 88 to 92%, the only side product being acetone. Better catalytic activities were obtained when perfluorophenylporphyrin derivatives were used. With Fe(TPFPP) as catalyst, 12 000 catalytic cycles where reported for the formation of *tert*-butyl alcohol from isobutane with a selectivity of 95%.[349] This reaction is catalyzed at room temperature by the iron complex of *meso*-tetrakis(pentafluorophenyl)-β-octabromoporphyrin. The catalytic activity is unchanged after 74 h.[350] ***Caution***: It should be mentioned that these catalytic oxidations must be carried out in a barricaded laboratory since reaction conditions are close to explosion limits. The proposed mechanism involves the initial reduction of the iron(III) porphyrin complex to iron(II), formation of a μ-oxoiron complex which disproportionates to an iron(IV)–oxo able to react with isobutane via hydrogen atom abstraction. Four important critera have been reached in this metalloporphyrin-catalyzed alkane oxidation: (i) O_2 is the oxygen atom source, (ii) no coreductant is necessary, (iii) selectivity in alcohol is high, and (iv) catalytic activities over 12 000 cycles are obtained without destruction of the catalyst precursor. For these reasons, this oxidation of isobutane catalyzed by iron porphyrin complexes might have a real future as new chemical process.

2. O_2 and an Electron Source

Many studies on metalloporphyrin-catalyzed alkane hydroxylations have been devoted to the modeling of the catalytic cycle of cytochrome P-450 which involves the NAD(P)H-dependent reductive dioxygen activation to give the active high-valent iron–oxo species.

The first attempt of modeling the reductive dioxygen activation cycle with synthetic metalloporphyrin was reported by Tabushi using H_2/colloidal Pt as electron donor.[194] Adamantane was oxidized to 1-adamantanol, 2-adamantanol, and 2-adamantanone (ratio, 44/5/3, respectively) with Mn(TPP)Cl as catalyst. By using 1,3-dideuterated adamantane, the kinetic isotope effect for the bridgehead hydrogen was found to be 3.3.[194] With manganese porphyrin catalysts, kinetic isotope effect values are always lower than those observed with iron porphyrin complexes. With a manganese porphyrin catalyst and PhIO as oxidant, a k_H/k_D value of 3.5 was reported by Suslick.[335b] Using H_2/colloidal Pt as electron source and Mn(TPP)Cl, Tabushi reported the catalytic hydroxylation of benzene (or substituted benzene) to phenol (or substituted phenol).[351] However, catalytic activities are very weak: 1.8–4.2 molecules of phenol/molecule of manganese porphyrin.

Sodium ascorbate was also used as electron source in a biphasic system (benzene/buffer pH 8.5) and manganese porphyrins as catalysts.[203,204] Cyclohexane is mainly oxidized to cyclohexanone and cyclohexanol (ratio, 30/4). At lower pH (7.4), the oxidation reaction rate decreases. These biphasic reactions with ascorbate as the electron source provide mild conditions for the manganese catalyst. The complex is not destroyed after 3 h at room temperature. However, the main limitation is the large consumption of ascorbate and dioxygen in the metalloporphyrin-catalyzed production of water. (For a detailed study of this side reaction in reductive dioxygen activation procedures, see ref 197.) The O_2/ascorbate system was used by Groves to achieve the selective C-25 hydroxylation of cholesterol with a

membrane-spanning manganese porphyrin positioned in a synthetic bilayer.[352] Ascorbate can be replaced by zinc powder and acetic acid[206] or by zinc amalgam, acetic anhydride, and methylviologen as mediator.[205] Electrons can also be provided by electrochemistry.[353] Electrocatalytic oxidation of cyclooctane and tetralin was achieved by using supported polypyrrole-MnTPP catalyst in the presence of 1-methylimidazole and benzoic anhydride with acceptable catalytic efficiency (78 and 560 cycles h^{-1} for cyclooctane and tetralin, respectively) and faradaic yield (1.5 and 28%, respectively).

Aniline hydroxylation was reported using β-mercaptoethanol and hemin solubilized in aqueous medium via poly(ethylene oxide alkylamine) micelles.[354] The para/ortho hydroxylation ratio is 1.2–1.5.

The C–C bond cleavage of side chains of various steroids is an important biosynthetic pathway to hormones which is catalyzed by cytochrome $P\text{-}450_{sec}$. This reaction was performed on diol models using Fe(TPP)Cl, molecular oxygen, and a 1,4-dihydropyridine as electron source.[355] Two aldehyde molecules are produced. When O_2/dihydropyridine is replaced by *tert*-butyl hydroperoxide, a free radical C–C bond cleavage is observed which is suppressed by diphenylpicrylhydrazyl, a radical trap, which is not the case when using O_2 and the reductant.

Activation of metalloporphyrins by the superoxide anion $O_2^{\bullet-}$ is another way to generate high-valent metal–oxo species in the presence of an acyl chloride.[356] With Fe(TPP)Cl or Mn(TPP)Cl as catalysts, *cis*-1,2-dimethylcyclohexane is hydroxylated with 87% of retention of configuration.[357]

3. Photooxidations

Unactivated C–H bonds can be functionalized by irradiation with a Hg lamp in the presence of catalytic amounts of an ammonium salt of decatungstate, $W_{10}O_{32}^{4-}$, under argon.[358] Photooxidation of cycloalkanes can be performed with iron halogenated porphyrin complexes like Fe^{III}(TDCPP)OH under irradiation between 350 and 450 nm.[359] It must be noted that the main oxidation product is the ketone, not the alcohol. No epoxide is formed when this photooxidation is performed with an olefin, suggesting that no iron–oxo species is involved in the catalytic cycle. The proposed mechanism suggests that HO• radicals, generated by photoactivation of the iron–hydroxo porphyrin complex, are the active species. The resulting organic radical can recombine with the iron(II) complex to form an iron(II)–alkyl complex which reacts with O_2 to give rise to an iron(III)–peroxoalkyl complex. The latter compound decomposes to ketone and regenerates Fe^{III}(TDCPP)OH.[359] The quantum yield of the key step, i.e. the reduction of Fe^{III}(TDCPP)OH to Fe^{II}(TDCPP), is weak: 10^{-4}.[360] However 100–170 catalytic cycles can be obtained before the catalyst destruction.

The photocatalytic cleavage of 1,2-diols was efficiently performed with the iron complex of the 2,6-dichloro-substituted derivative of *meso*-tetrakis(4-methylpyridiniumyl)porphyrin, [Fe(TDCMPyP)]-$(Cl)_5$.[361] Because of the presence of chloro-substituents in ortho and ortho′ positions of the pyridinium groups, a shape selectivity is observed in photooxidation product distribution.

D. Hydroxylations with H_2O_2

The association of hydrogen peroxide with ferrous iron, the Fenton reagent, is able to perform the hydroxylation of aromatic derivatives and alkanes. (For a review article on Fenton reagent chemistry, see ref 231.) The hydroxyl radical is the actual oxidant in all these systems where hydrogen peroxide is reduced through a one-electron process by a low-valent transition-metal salt or complex. HO• generates free organic radicals by a very fast hydrogen atom abstraction from a large variety of organic substrates. The rate constants for this reaction range from 10^7 to 10^{10} L mol^{-1} s^{-1}.[231] Limitations of the Fenton reaction are the absence of selectivity (molecular oxygen is also involved in hydroxylation with the Fenton reagent[362]) and the required presence of a large amount of ferrous salt. However, early attempts indicate that stereospecific aliphatic hydroxylations can be performed when using hydrogen peroxide and ferrous perchlorate in dry acetonitrile.[363]

Low catalytic activities of metalloporphyrins were reported in the hydroxylation of phenylalanine[364] and benzene derivatives,[365] but high conversions of alkanes to alcohols and ketones were obtained when using manganese porphyrin catalysts in the presence of imidazole.[247,366] Hydrogen peroxide was slowly added to a dichloromethane/acetonitrile mixture (1:1) containing the alkane, Mn(TDCPP)Cl (2.5% with respect to hydrocarbon) and imidazole (24 equiv with respect to Mn porphyrin).[366] Under these experimental conditions, 54% of cyclohexane was converted within 2 h at room temperature to cyclohexanol and cyclohexanone (yields based on oxidant, 30% and 10%, respectively). The role of imidazole has been discussed in section II.D. Chromium complexes are less active than manganese derivatives in alkane hydroxylations with hydrogen peroxide as oxidant.[367]

The manganese porphyrin catalyzed hydroxylation is strongly accelerated by addition of small amounts of a carboxylic acid such as benzoic acid, a nitrogen base still being present[368] although this base could be a 4-substituted pyridine and not necessarily an imidazole derivative. These reactions are performed in a two-phase system (dichloromethane/30% aqueous hydrogen peroxide). A super-structured halogenated manganese porphyrin with an imidazole ligand and a carboxylic acid tethered to the macrocycle itself has been designed by Montanari et al. in order to confirm the role of imidazole (proximal ligand) as well as carboxylic acid (intramolecular activation of coordinated hydrogen peroxide).[369] Polyhalogenated metalloporphyrins with brominated, chlorinated, or fluorinated β-pyrrole positions are robust enough to catalyze aromatic hydroxylations. A "Teflon" iron porphyrin complex, Fe(F_8-TPFPP)Cl, is able to catalyze the oxidation with hydrogen peroxide of benzene to phenol at room temperature (55 catalytic cycles were reached within 2 h).[370]

Mn(Br_8TDCPP)Cl is an efficient catalyst for the H_2O_2 oxidation of anisole to *o*- and *p*-hydroxyanisole, with some O-demethylation also being observed.[371] The only recent report on the hydroxylation of methane with hydrogen peroxide was dealing with a ruthenium complex of 2,9-dimethyl-1,10-phenanthroline.[372]

E. Hydroxylations with ROOH

When alkyl hydroperoxides are used as oxidants in hydroxylations catalyzed by metalloporphyrins, two

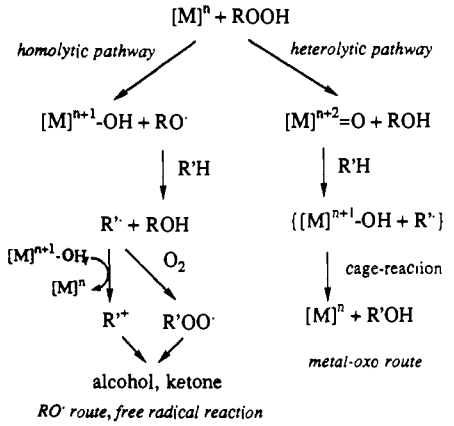


Figure 20. Two possible mechanisms in alkane oxidations by alkyl hydroperoxides catalyzed by metalloporphyrins: homolytic versus heterolytic pathway.

modes of C–H activation can be observed: (i) one due to the homolytic cleavage of the peroxidic O–O bond with RO• as active species or (ii) one due to a metal–oxo species resulting from the heterolytic cleavage of the O–O bond by the metalloporphyrin catalyst (Figure 20). The "RO• route" is not modulated by the porphyrin ligand, and in fact, these pathways are autoxidation reactions (products are dependent on the presence of molecular oxygen), whereas the "metal–oxo route" is dependent on the porphyrin ligand (i.e. shape-selective hydroxylations can be observed) and generally not dependent on molecular oxygen.

These two mechanisms have been well evidenced by Mansuy and Momenteau in 1982 in a comparative study using super-structured metalloporphyrins in association with ROOH or PhIO.[41,42] The same two routes have been examined in the activation of 10-hydroperoxy-8,12-octadecadienoic acid by the iron complex of bleomycin (BLM), an antitumor agent able to cleave DNA by hydroxylation of the C–H bond at the 4′-position of deoxyriboses.[373,374] This particular oxidant is a convenient molecule to probe the two possible activation pathways of alkylhydroperoxides (homolytic versus heterolytic) (Figure 21). The homolytic pathway generates an alkoxy radical which decomposes by β-scission to 10-oxo-8-decenoic acid, whereas 10-hydroxy-8,12-octadecadienoic acid is the only product resulting from the heterolytic cleavage of the O–O bond by a metal complex.

Both routes have been observed in the case of iron bleomycin, but whereas the BLM-Fe^{IV}-OH species formed in the homolytic scission of the peroxidic O–O bond is able to perform the N-demethylation of *N,N*-dimethylaniline,[373] it is unable to degrade DNA by activation of sugar C–H bonds.[374] These data also confirm that high-valent metal–oxo species are much more efficient at hydroxylating C–H bonds than RO• species. However, it should be noted that the iron(IV)–hydroxo complex is able to epoxidize olefins when the metal is chelated either by a porphyrin[375] or by bleomycin,[373] but studies with labeled oxidants indicate that 65% of the epoxide oxygen derives from molecular oxygen and 35% from the hydroperoxide, more consistent with a free-radical mechanism than high-valent metal–oxo chemistry.[374] Recent studies by Bruice and Lindsay Smith confirm that the heterolytic scission of ROOH by manganese or iron porphyrin complexes is not the major pathway.[259,376,377]

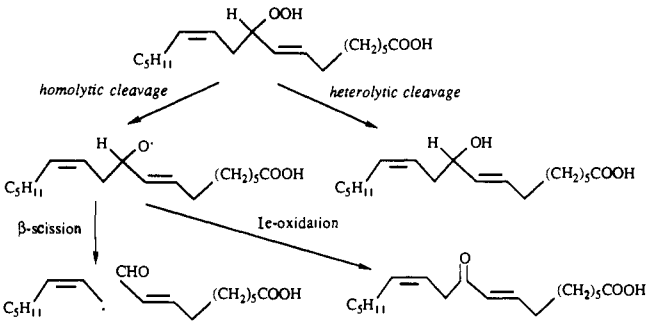


Figure 21. Product probing of the homolytic or heterolytic cleavage routes of 10-hydroxy-8,12-octadecadienoic acid activated by iron bleomycin.

All these data strongly suggest that many hydroxylation reactions with alkyl hydroperoxides in the presence of transition-metal complexes are not due to a metal-centered active species but to a free-radical process initiated by RO•. This mechanism was recognized for cobalt complexes[378] and may or may not be involved in recent works on binuclear iron or manganese complexes.[321,379] Any claims on an "oxygen-rebound" mechanism should be supported by different criteria such as C–O bond formation with retention of configuration, shape-selectivity dependent on metal ligands and use of labeled oxidants to identify the origin of the oxygen atom in products (alcohols or ketones). However, and since very high yields have been obtained in olefin epoxidations by ROOH or H_2O_2 with third generation metalloporphyrin as catalysts, it should be accepted that a metal–oxo route is also possible and is highly dependent on the nature of the catalyst. [Both reaction pathways should probably differ by few kcal/mol and have to be considered of similar mechanistic importance. (T. G. Traylor, personal communication.)]

F. Hydroxylations with $KHSO_5$ and Related Oxidants

Potassium monopersulfate is not only a suitable oxygen atom donor[271] in olefin epoxidations catalyzed by metalloporphyrins (see above, section II.F), but it is also a very efficient oxygen atom source in catalytic hydroxylations of saturated alkanes.[287,380] It must also be noted that dioxiranes generated from $KHSO_5$ and ketones at low temperature are very efficient hydroxylating agents.[280,281]

In the case of metalloporphyrin-catalyzed hydroxylations, reactions are performed in a biphasic system with dichloromethane and buffered or nonbuffered (pH 5–7) water with a small amount of catalyst (0.1 to 2% with respect to alkane). Nonbuffered water solutions of potassium monopersulfate (pH 2) can also be used. Manganese porphyrins associated with 4-*tert*-butylpyridine as axial ligand are more efficient catalysts than the corresponding iron complexes.[287] When brominated or chlorinated tetramesitylporphyrins are used as ligand for manganese, up to 6 catalytic cycles s^{-1} can be reached in the hydroxylation of adamantane, i.e. 40 times the activity of cytochrome P-450.[50b,288] Adamantanols are the major oxidation products and only a small amount of ketone is detected.[289] This is not the case when $KHSO_5$ is used as oxidant in the Gif system, confirming that the mechanism of this alkane ketonization reaction is different from alkane hydroxylations catalyzed by metalloporphyrins.[381] With the $KHSO_5$/Mn porphyrin system, hydroxylations occur with 90% retention of

configuration while isotope effects range from 2.1 to 4.9, depending on the nature of the porphyrin ligand.[287,337] These values confirm that the rate-determining step is the abstraction of a hydrogen atom from alkane, but these values are lower than those observed with the PhIO/Fe porphyrin system. In a detailed study on kinetic isotope effects using various oxidants, porphyrin ligands and iron or manganese as the central metal, we found that KIE values are highly dependent on the oxidant and on the metal center itself[337] (Table VII). These data suggest that high primary KIE values are only obtained with PhIO and iron porphyrins (nonbent transition states), whereas manganese porphyrin associated with PhIO or $KHSO_5$ gives lower KIE values (2 to 5), suggesting that the transition state is more unsymmetric and dependent on the leaving group of the oxidant. (See ref 337 for a detailed discussion on KIE values in metalloporphyrin-catalyzed hydroxylations.) KIE values are also low in the photooxidation of alkanes mediated by polyoxometalates[325] and in the Gif system[382] (k_H/k_D = 2.5 and 2.2, respectively).

A report on hydroxylation at the C_8 position of adenosine 5'-monophosphate with $KHSO_5$ and a water-soluble manganese porphyrin, MnTMPyP, suggests that hydroxylation can also be catalyzed in aqueous solutions.[383] Additional data obtained on the mechanism of DNA cleavage by manganese porphyrins activated by $KHSO_5$ support the hypothesis that hydroxylase activity can be obtained in water solutions with potassium monopersulfate and water-soluble catalysts (see below, section VIII).

Magnesium monoperphthalate also is a very good oxygen atom donor which is highly soluble in water.[384] When used in a biphasic reaction mixture (dichloromethane/water), very high alkane conversions to alcohols can be obtained. In fact, catalytic activities are limited by the oxidant transfer step from water to dichloromethane when halogenated manganese porphyrins are used as catalysts.[337,384]

G. Hydroxylations with Amine *N*-Oxides and Periodate

Few hydroxylation reactions have been reported with amine *N*-oxides. Actually, these reactions are competing with dealkylation of amine *N*-oxide itself. Hydroxylation of cyclohexane was observed using Fe(TPP)Cl and *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide.[296] A minor reaction pathway is the hydroxylation of this aromatic amine *N*-oxide in the ortho position.[299] When using this same oxygen atom donor and Cr(TPP)Cl as catalyst, Sligar reported the oxidative cleavage of 1-phenyl-1,2-ethanediol.[385] Benzaldehyde was the only detected cleavage product.

The photocatalytic oxidation of cyclopentane to cyclopentanone with periodate as oxygen atom source and Mn(TPP)OAc as catalysts has been reported.[318]

IV. Oxidations of Other Organic Substrates

Simple olefins or alkanes are not the only substrates that can be oxidized by metalloporphyrin catalysts. Heme enzymes are not only able to catalyze olefin epoxidation and alkane hydroxylation but also N- or O-dealkylation of aromatic amines or ethers, oxidative chlorination of β-diketones, oxygenation of dialkyl sulfides or electron removal from many different molecules such as phenol derivatives, drugs, or even polymers, e.g. lignin. Some of these various oxidizable molecules have been used as substrates in metalloporphyrin-catalyzed oxidations.

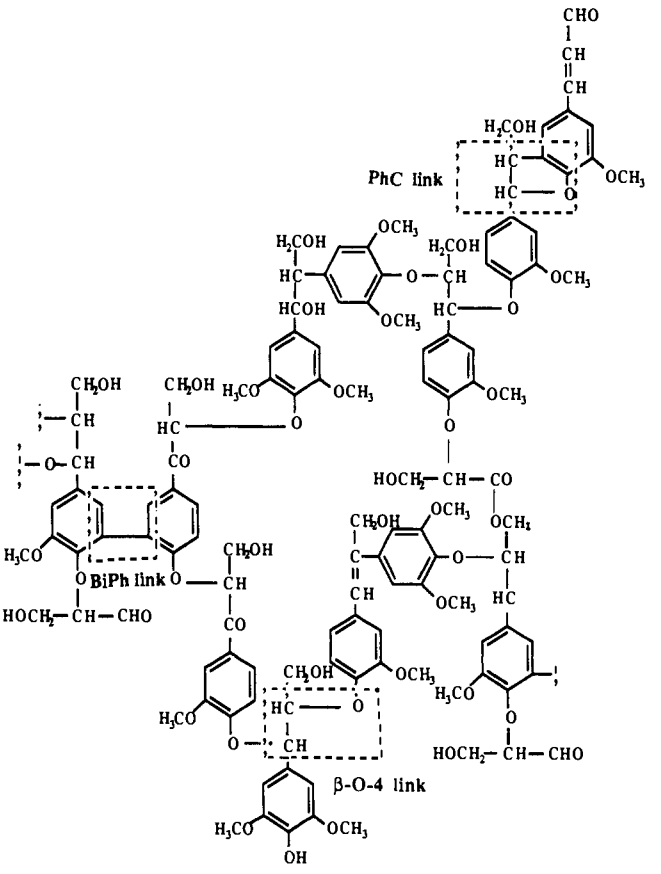


Figure 22. Schematic representation of lignin structure. Polymer reticulation is due to three main types of links: arylglycerol β-aryl ether links (β-O-4 link, 48–50% of the total number of links), biphenyl links (BiPh link, 9–11%), and phenylcoumaran links (PhC link, 9–12%). These three types of links are indicated in dashed lines.

A. Lignin Models

Lignin, cellulose, and hemicellulose are the main plant polymers. Since cellulose is the raw material for the paper industry and because there exists a great need for white paper in our "printer civilization", there is a growing interest in delignification by clean industrial processes. (See Figure 22 for a schematic representation of lignin structure and ref 386 for additional structural details on different lignins.) The classical oxidative chlorine degradation of lignin in white-paper manufacturing produces 4–5 kg of chlorinated phenol residues per metric ton of treated wood pulp.[387,388] For obvious ecological reasons, a clean and efficient process to remove lignin from wood chips is needed. In addition, a mild degradation method of lignin would lead to a renewable source of aromatics, since lignin results from polymerization of substituted hydroxycinnamyl alcohol subunits derived from phenylalanine, this amino acid being produced from CO_2 via the shikimic acid route.[389,390]

The recent purification and characterization of two heme-containing peroxidases produced by a lignilytic fungus, *Phanerochaete chrysosporium*, have stimulated modeling studies in this field. One of these peroxidases is ligninase or LiP.[391] The oxidation capability of this

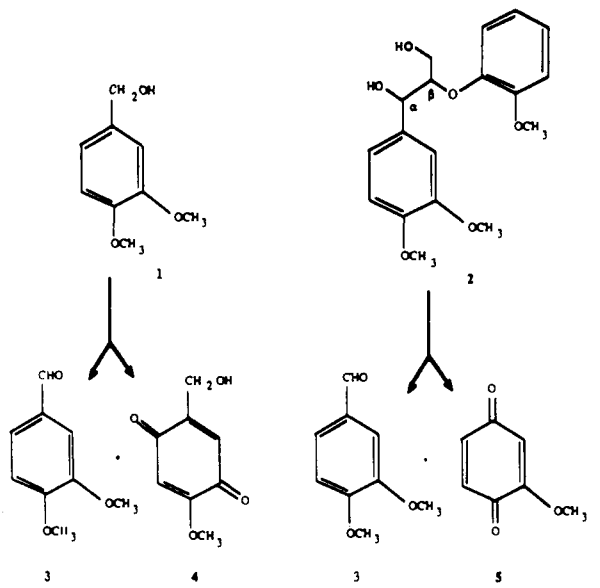


Figure 23. Oxidative degradation of lignin model compounds by the "$KHSO_5$/sulfonated metallorphyrin" system. Reproduced from ref 401. Copyright 1989 American Chemical Society.

peroxidase is much higher than that of horseradish peroxidase,[392] but LiP is a fragile enzyme when exposed to 20 equiv of hydrogen peroxide.[393] The formation of LiP III*, a compound III enzyme form containing one extra molecule of H_2O_2, leads to the irreversible inactivation of the enzyme.[393] A second enzyme mediates lignin degradation through the catalytic oxidation of manganese(II) to manganese(III) chelates and for this reason is called manganese peroxidase or MnP.[394]

Early models of ligninase were based on iron protoporphyrin IX associated with *tert*-butyl hydroperoxide[395,396] or on Fe(TPP)Cl with O_2 and a dihydropyridine as electron source.[397] However, these metalloporphyrins are not water-soluble and are easily destroyed under oxidizing conditions. Sulfonated metalloporphyrins were found to be suitable catalysts in the modeling of ligninase.[398-401] Sodium hypochlorite was used as oxygen atom donor in ligninase models,[398] but this oxidant cannot be developed at the industrial scale because of risky and nondesired aromatic chlorinations when solution pH values decrease below 9. In this respect, potassium monopersulfate seems to be a more suitable oxidant in ligninase modeling. The best oxidant would be hydrogen peroxide, but we found that catalytic activities are lower with this oxidant.[401] The "$KHSO_5$/sulfonated metalloporphyrin" system has been tested with low molecular weight molecules which are used as classical model substrates for ligninase: veratryl alcohol and 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenyl)propane-1,3-diol. The latter compound is a useful organic substrate to check the ability of a peroxidase, or its model, to break C_α–C_β bonds of arylglycerol β-aryl ether linkages, the major type of links present in lignin (see Figure 23). We found that FeTPPS associated with $KHSO_5$ in a mixture of acetonitrile and buffered water at pH 2–3 is highly efficient at cleaving the C_α–C_β bonds by oxidation of propanediol derivatives. Catalytic activities range from 1 to 5 cycles s^{-1}.[400,401] MnTPPS is a slightly less active catalyst but the optimum pH for the catalytic oxidation reaction is 6.[401]

Robust sulfonated iron and manganese porphyrins have also been used as ligninase models: M-TMPS,[50b] M-TDCPPS,[402] and M-Br_8TMPS.[50b] These sterically protected water-soluble complexes are the most promising catalysts. The degradation products of lignin dimer models are similar to those observed in reactions catalyzed by ligninase (see Figure 24). These iron catalysts are able to decolorize Poly B-411,[402] a blue dye which has been used to monitor the activity of ligninase.[403] These sulfonated metalloporphyrins are also efficient ligninase models when supported on ion-exchange resins (see below, section VI.A).

The second peroxidase of *P. chrysosporium* mediates its activity via the oxidation of Mn(II) to Mn(III) chelates (lactates, malonates, tartrates, or citrates). The role of these manganese chelates has also been studied in the decolorization of dyes[404] or oxidation of lignin models[405] catalyzed by these robust water-soluble metalloporphyrins. The mediating efficiency of the manganese chelates is not directly related to their redox potentials, suggesting that ionic interactions between the sulfonated porphyrin catalyst and Mn chelates are key factors in the formation of active Mn(III) intermediates.

The bleaching of lignin itself with these catalysts is possible, but the annual production of millions of tons of white paper requires very cheap catalysts, at least cheaper than sophisticated metalloporphyrins.

However, these water-soluble iron and manganese porphyrins might be useful in the oxidation of other substrates than lignin itself, organic pollutants for example.

B. Pollutants

Microorganisms convert most of the man-made organic chemicals into inorganic products. The biodegradation of these chemicals involves reductive or oxidative steps or successive combinations of both modes of activation. However, some molecules are recalcitrant to biotransformation and are subject to biomagnification and accumulation in plant or animal tissues.[406] Among these compounds, the organic halide pollutants (e.g. DDT and lindane, common names for 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane and 1α,2α,-3β,4α,5α,6β-hexachlorocyclohexane) resist microbial destruction. Actually, a very slow reductive activation of these chlorinated organic molecules has been observed,[407] but this process is unable to prevent their accumulation in soils and waters. The lack of penetration into microorganisms is among the factors making organic molecules recalcitrant to biodegradation. Thus, there is an urgent need for new catalytic processes able to remove recalcitrant molecules from waste waters or industrial effluents in order to avoid their accumulation in the environment.

Partial degradation of DDT was observed when using hemin in the presence of air and cysteine as electron source.[408] Products resulting from a reductive activation of DDT have been observed, including a cysteine–DDT adduct. A similar dehalogenation of lindane was observed when using hemin and dithiothreitol.[409] However, these reactions are poorly catalytic, and expensive reducing agents are over consumed. Oxidation processes are alternative methods to insure the degradation of pollutants. However, enzymes with high redox capabilities are required. This is the case of ligninase from *P. chrysosporium*. This microorganism is able to oxidize organo halide pollutants.[410,411] We

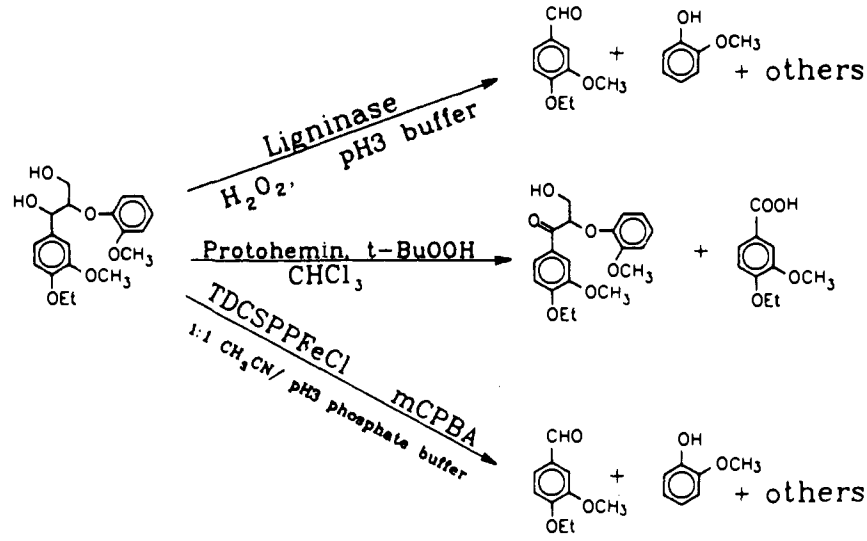


Figure 24. Comparison of product distribution in the oxidation of 4-*O*-ethylguaiacylglycerol β-guaiacyl ether catalyzed by ligninase/H_2O_2, Fe^{III}(TPP)X/*t*-BuOOH/$CHCl_3$ or Fe^{III}(TDCSPP)Cl/*m*-CPBA/H_2O. (Nota bene: TDCSPP corresponds to TDCPPS in the present review article.) Reproduced from ref 402. Copyright 1989 American Chemical Society.

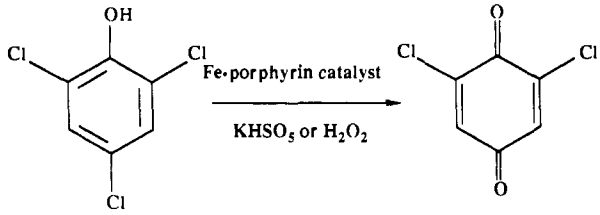


Figure 25. Iron porphyrin catalyzed oxidation of 2,4,6-trichlorophenol, a pollutant from paper mill effluents, to 2,6-dichlorobenzoquinone.

recently reported that lignin models based on sulfonated iron or manganese porphyrins in association with $KHSO_5$ or H_2O_2 are highly efficient in the oxidative transformation of 2,4,6-trichlorophenol, a major pollutant in paper mill effluents,[387] into 2,6-dichlorobenzoquinone (Figure 25).[412] Quinones are easily eliminated from waters by floculation methods. Catalytic activities as high as 20 cycles s^{-1} have been observed (Table VIII). It must be noted that hydrogen peroxide, the "clean oxidant", can be used in this metalloporphyrin-catalyzed pollutant oxidation. The same catalytic systems are also able to oxidize DDT and lindane. By using various methoxylated arene derivatives it has been possible to rank and to compare the redox ability of these biomimetic catalysts with ligninase and horseradish peroxidase (HRP).[412,413] While HRP is unable to oxidize organic molecules with a $E_{1/2}$ potential above 1.2 V (Ag/AgCl), ligninase is active up to 1.4 V and the "$KHSO_5$/Fe porphyrin" system up to 1.7 V.[412] These peroxidase models are also efficient when immobilized into ion-exchange resins, a technology used in water treatment. Consequently, they might have a future in the oxidative degradation of organic pollutants.

Table VIII. Catalytic Oxidation of 2,4,6-Trichlorophenol to the Corresponding *p*-Benzoquinone (from ref 412; copyright 1990 VCH Verlagsgesellschaft mbH)

run	catalyst	% catalyst per substrate	pH	oxidant	yield of quinone within 1 min, %	yield of quinone within 15 min, %
1	FeTPPS	0.3	3.0	$KHSO_5$	95[a]	
2	FeTPPS	0.3	3.0	H_2O_2	11	68
3	FeTPPS	0.1	3.0	$KHSO_5$	90	92
4	FeTMPS	0.3	3.0	$KHSO_5$	95	
5	FeTMPS	0.3	6.0	$KHSO_5$	25[b]	10[b]
6	FeTDCPPS	0.3	3.0	$KHSO_5$	92	
7	FeTPPS-Ad	10	3.0	$KHSO_5$	11	30
8	FeTMPS-Ad	10	3.0	$KHSO_5$	15	36
9	MnTPPS	10	6.0	$KHSO_5$	25[b]	

[a] 89% of quinone in 15 s: catalytic activity = 20 cycles per second. [b] Quinone polymerizes at pH 6.0.

C. Drugs (Metabolization Tests)

The oxidative metabolism of drugs, either exogenous or endogenous, by cytochrome P-450[7a,414] and peroxidases[8a,415] has been extensively studied in the last two decades. A better understanding of biosynthetic pathways (e.g. side-chain degradation of cholesterol, aromatization of the A ring in estrogen biosynthesis) and production of (i) mutagenic intermediates in the biotransformation of polyaromatic molecules, (ii) of toxic or active metabolites of drugs by heme enzymes is now accessible. These data are useful to predict possible behavior of drug candidate molecules. However, isolation of reactive intermediates in enzyme-catalyzed oxidations, even in all-free systems, is not so easy. Cytochrome P-450 monooxygenases are multienzyme systems which are more sophisticated than simple peroxidases, involving a complete set of proteins to insure and control the electron flow from NAD(P)H. Hence, it might be convenient to use biomimetic catalysts to check the behavior of biologically active compounds in oxidative conditions.

Metalloporphyrin models of cytochrome P-450 have been used to catalyze the oxidation of various drugs. The first models used were simple, non-water-soluble iron porphyrins, such as Fe(TPP)Cl. For example, the PhIO/Fe(TPP)Cl system oxidizes (i) antergan[416] to N-demethylated products, (ii) benzo[*a*]pyrene or 2-aminofluorene to mutagens in the Ames assay,[417] (iii) phencyclidine to a piperidine-3-oxo compound,[418] and performs the aromatization of tetralone derivatives.[419] Robust iron porphyrins associated with *m*-CPBA have been used to oxidize polycyclic aromatic hydrocarbons yielding mixtures of phenols and quinones[420] or steroid aldehydes to the corresponding acid derivatives.[421]

Manganese porphyrin complexes were also used in metabolic studies. They catalyze the PhIO oxidation

of nicotine to cotinine and 3-hydroxycotinine, two products identical to those obtained from in vivo metabolism.[422] NaOCl/Mn(TPP)Cl porphyrin was used to couple phenolic benzylisoquinoline alkaloids[423] while CumOOH/Mn(TDCPP)Cl oxidized 1,3-dimethyluracil to 5-hydroxy-1,3-dimethyluracil.[424] Hydroxylation of a nucleotide was previously observed with $KHSO_5$/MnTMPyP and 8-hydroxyadenosine 5′-monophosphate is obtained from AMP.[425] This reaction illustrates the hydroxylase activity of this system which has been largely developed as artificial nuclease for DNA (see below, section VIII).

More recently, we have shown that water-soluble iron and manganese porphyrins, M-TPPS or M-TMPyP, associated with potassium monopersulfate, are able to mimic efficiently the peroxidase oxidation of acetaminophen, a well-known analgesic, and antitumoral ellipticine derivatives.[426] In both cases, the expected quinone-imines are formed in high yields (40–90%) with initial turnover rates similar to those observed with HRP/H_2O_2. Therefore, these electrophilic drug metabolites are easily prepared by using biomimetic catalysts, since they are not quenched by nucleophilic sites of the protein outside, a result usually observed in enzyme-catalyzed oxidations.

D. Sulfur- or Nitrogen-Containing Molecules and Miscellaneous Substrates

Metalloporphyrin-catalyzed oxidations of amines or sulfides which are not considered as drugs are collected in the present section.

Like cytochrome P-450, iron and manganese porphyrins are able to catalyze the oxidative N-dealkylation of tertiary amines. Lindsay Smith et al. have shown that the initial step is a one-electron transfer process when iodosylbenzene is the oxidant, whereas with *tert*-butyl hydroperoxide, the first step is a hydrogen atom abstraction.[427] The first mechanism is also preferred when molecular oxygen is the oxidant.[428] Diaryl sulfides are mainly oxidized to sulfones by PhIO/Fe porphyrins, a small quantity of sulfoxides being likewise formed.[429] Sulfoxides are also the major oxidation product of dialkyl sulfides with NaOCl/Mn(TPP)Cl.[430] In the early work of Oea et al. on sulfide oxidations by H_2O_2/Fe(TPP)Cl/imidazole, they observed only minor S-dealkylation.[244]

The oxidative desulfurization of pentavalent phosphorus derivatives is catalyzed by manganese porphyrins with periodate or iodosylbenzene as oxidants.[431] Manganese and iron porphyrins are very effective catalysts for the PhIO oxidation of nitroso to nitro compounds. Nitrobenzene is formed in 90% yield within 5 min, even at −78 °C.[432]

Dienones are oxidized with PhIO/Mn(TPP)Cl, affording the corresponding epoxide and pyrone derivatives.[433a] Water-soluble metalloporphyrins, Fe- or Mn-TPPS and Fe- or Mn-TMPyP, are efficient catalysts for the chemiluminescent oxidation of luminol or isoluminol with a signal-to-noise ration raising up to 200. The chemiluminescence produced by these synthetic metalloporphyrins is similar to that obtained in reactions catalyzed by a peroxidase like HRP.[433b]

V. Oxidations Catalyzed by Chiral Metalloporphyrins

During the last decade considerable efforts have been devoted to the development of new methods for the preparation of stereochemically pure compounds at the industrial scale.[434] This necessity was first recognized for pharmaceuticals[435] and more recently for agrochemicals.[436] Since biological macromolecules (proteins, nucleic acids) contain a very large number of chiral centers, exogenic chemicals containing stereogenic centers elicit a biological response which depends on the absolute configuration of these chiral centers. The various industrial processes are based on diastereoisomer crystallization, chemocatalytic kinetic resolution and catalytic asymmetric synthesis with chemical catalysts or enzymes.[434] Efficient enantioselective formation of carbon–hydrogen bonds catalyzed by chiral rhodium or ruthenium complexes are now well established.[437] In the field of transition-metal-catalyzed asymmetric carbon–oxygen bond formation, the only example of practical value remains the enantioselective epoxidation of allylic alcohols by the Sharpless method.[23,24] We will see in the present section that asymmetric hydroxylations and epoxidations of nonactivated olefins catalyzed by chiral metalloporphyrins are progressing. Efficient asymmetric dihydroxylation of simple olefins by chiral osmium complexes containing alkaloid ligands has also been recently improved.[438]

A. Asymmetric Hydroxylation Reactions

Cytochrome P-450 monooxygenases are able to perform highly enantioselective olefin epoxidations[439] or hydroxylations.[440] While many reports deal with enantioselective epoxidations catalyzed by chiral metalloporphyrins, very little data are available on the most challenging asymmetric oxidation, viz. the catalytic conversion of an alkane to an optically active alcohol.

The only example has been reported by Groves and Viski using vaulted binaphthyl iron or manganese porphyrins.[441] Ethylbenzene, tetrahydronaphthalene, and 2-ethylnaphthalene were hydroxylated to benzylic alcohols with an enantiomeric excess (ee) of 40, 72, and 68%, respectively. PhIO served as oxidant in these asymmetric hydroxylation reactions. Alcohol yields, based on iodosylbenzene, ranged from 28 to 47%. Using (*R*)- and (*S*)-ethylbenzene-d_1 as substrate, it has been possible to obtain new insight into the mechanism of hydroxylation at a prochiral center. The enantiotopic protons of ethylbenzene are hydroxylated by PhIO/chiral Fe porphyrin. Abstraction of H or D at the *pro-R* site of ethylbenzene by the chiral metal–oxo complex generates an organic radical which recombines with the high-valent hydroxo ligand with complete retention of configuration, whereas when the radical is produced by H or D abstraction at the *pro-S* site, the same C–O bond formation occurs with 40–50% racemization.[441a]

B. Asymmetric Epoxidation Reactions

Optically active binaphthyls have been widely used in building chiral porphyrin ligands. When attached via amide linkages to 5α,10β,15α,20β-tetrakis(*o*-aminophenyl)porphyrin, relatively high ee values (40–48%) were obtained in the iodosylbenzene epoxidation of styrene.[442] Kodadek prepared a "chiral wall" porphyrin ligand by condensation of (*R*)-binaphthaldehyde with pyrrole.[443] The corresponding manganese complex associated with NaOCl produced epoxide in 20–40% ee. This reaction was the first asymmetric epoxidation using a cheap oxidant such as sodium hypochlorite.

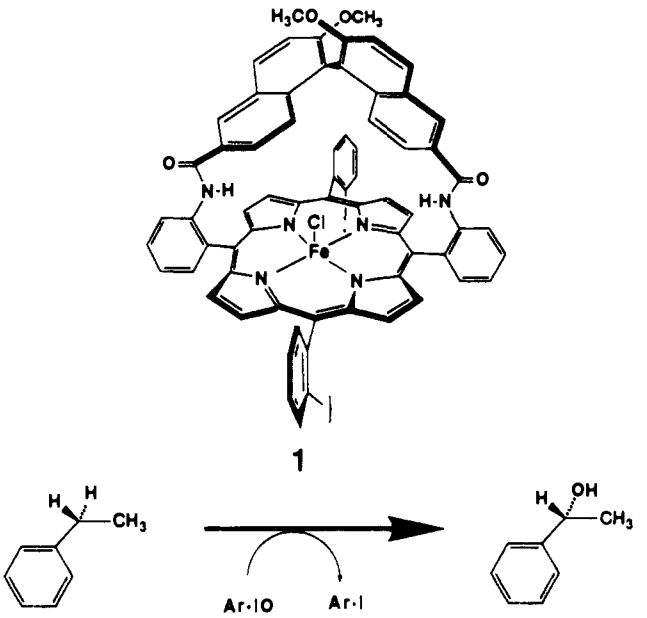


Figure 26. Asymmetric hydroxylation of ethylbenzene catalyzed by a chiral binaphthyl iron porphyrin. Reproduced from ref 441a. Copyright 1989 American Chemical Society.

Using also NaOCl and a D_4-symmetric porphyrin ligand metalated by manganese, Halterman obtained very good epoxide yields (90%) and enantioselectivities ranging from 41 to 76% ee.[444] Naruta and Maruyama designed a "twin-coronet" porphyrin ligand with binaphthyl derivatives as chiral auxiliaries.[445] Each face of the macrocycle is occupied by two binaphthyl units and the ligand has a C_2 symmetry. The highest ee (89%) was obtained in the PhIO epoxidation of 2-nitrostyrene.[445b]

Chiral auxiliaries other than binaphthyls have also been used. L-Phenylalanine residues in basket-handle porphyrin ligands metalated by iron gave 50% ee in the epoxidation of chlorostyrene.[446] Acetylated glucose units can be attached to an ortho-substituted tetraphenylporphyrin. Enantiomeric excesses in the epoxidation of styrene derivatives range from 23 to 33% when using PhIO,[447a] or other oxidants such as NaOCl or $KHSO_5$,[447b] and the manganese or iron complexes of this glucosylated porphyrin. Optical antipodes of chiral strapped manganese porphyrins catalyze asymmetric olefin epoxidations with 42–58% ee values.[447c]

However, the main limitation of these asymmetric epoxidation reactions catalyzed by chiral metalloporphyrins is the multistep synthesis of the chiral ligands accompanied by rather poor yields in some steps. This handicap has been overcomed recently by using chiral Schiff base manganese complexes which are more accessible from readily available chemicals. While Katsuki et al.[448] used chiral manganese salen complexes with four stereogenic centers, two on the central diamine and two on the ortho positions of the phenyl groups, Jacobsen et al. have shown that only the two chiral centers of the diamine are necessary to provide very high enantiomeric excesses with PhIO[449] or NaOCl[450] as oxidant. In the later case, cis-disubstituted olefins are epoxidized with ee values ranging from 89 to 98%. The best diamine appears to be (*S,S*)-1,2-diaminocyclohexane[450b,c] which is commercially available while the suitable hindered salicylaldehyde is easily prepared by formylation of 2,4-di-*tert*-butylphenol.[450a] Two reasons explain the importance of these two bulky

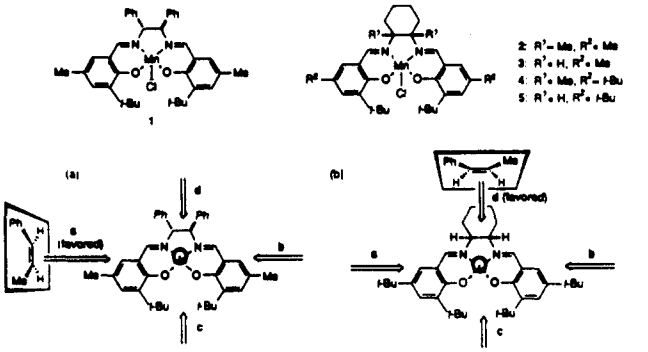


Figure 27. Structures of chiral manganese salen complexes and various possible olefin approaches with respect to the active manganese–oxo species. Reproduced from ref 450b. Copyright 1991 American Chemical Society.

groups on the phenol moieties: (i) they avoid west, south, and east approaches of the prochiral olefin (Figure 27), and (ii) they create a cage effect around the manganese–oxo species thereby reducing the formation of catalytically inactive dimers and ligand bleaching. The later phenomenon was found to be the main limitation of the NaOCl/Mn salen system.[30,136] Application of this new method of preparation of chiral epoxides was recently illustrated in the synthesis of enantiomerically pure epoxychromans.[450c]

C. Other Asymmetric Oxidations

Chiral sulfoxides are useful synthons in organic synthesis. In a stoichiometric reaction, a Sharpless-type reagent provides sulfoxides with ee's as high as 93%,[451] whereas the ROOH oxidation of sulfides catalyzed by chloroperoxidase give ee's ranging from 20 to 91%.[452] With the iron complex of the vaulted binaphthyl porphyrin associated with PhIO, nonsymmetrical disulfides have been oxidized to sulfoxides in good yields, but with ee's ranging from 14 to 48%.[441b] Only a small amount of sulfones is produced. With the "twin coronet" iron porphyrin, ee's are improved in the presence of 1-methylimidazole (23–73%), but the catalytic activity is reduced compared to sulfoxide formation in the absence of nitrogen base.[453] Lower enantiomeric excesses have been obtained with a chiral iron porphyrin or with nonchiral manganese porphyrin attached to bovine serum albumin.[454,455a] The later catalyst was previously used in the stereoselective dioxygenation of tryptophan.[455b] (See also ref 456 for the stereoselective oxidation of tryptophan by a chiral metalloporphyrin.)

VI. Oxidations Catalyzed by Supported Metalloporphyrins

While thousands of articles describe polymer-supported hydrogenation, hydroformylation, hydrosilylation, oligomerization or isomerization catalysts, a limited number of examples concern supported metal complex oxidation catalysts.[457] Sherrington suggested that two main reasons for the slow development of polymer-supported metal complex oxidation catalysts are (i) the infancy of the field of selective homogeneous oxidation metal catalysts compared to reduction and isomerization catalysts and (ii) the assumption that organic polymers would not yield long-lived supports. We will see in this section that efficient supported metalloporphyrin oxidation catalysts have been recently

developed with organic or mineral supports. (For a review article on supported metalloporphyrins as oxygen carriers, see ref 458.) The present section is organized according to the nature of the supports.

In a pioneer work, Nolte and Drenth attached a manganese(III) *meso*-tetrakis(*p*-substitutedphenyl)porphyrin to polyisocyanide prepared by nickel polymerization of a tyrosine-derived isocyanide monomer.[459] The metalloporphyrin content is 1.5 wt % which corresponds to one molecule of catalyst per polymer chain (100 repeating units). These supported manganese porphyrins display good catalytic activity in the NaOCl epoxidation of olefins when 4-methylpyridine is present in the reaction mixture (triphase, dichloromethane/water/polymer). As expected, initial turnover rates are below those observed for soluble catalysts, 95–300 cycles h^{-1}. The NaOCl epoxidation of 2,5-dihydrofuran with a water soluble polymer-bound manganese porphyrin has been reported.[458]

A. Ion-Exchange Resins

Saito et al. reported in 1986 a simple method for the preparation of supported metalloporphyrins using the ability of sulfonated complexes to interact strongly with anion-exchange resins by physical adsorption.[460] The adsorption of metal complexes of *meso*-tetrakis(*p*-sulfonatophenyl)porphyrins onto Amberlite IRA 900 (an ion-exchange resin derived from poly(vinylbenzene) with ammonium groups) is easily performed by shaking the nitrate form of the resin with a solution of M-TPPS in a 1:1 mixture of acetone and water for 10 h at 35 °C. These water-soluble metalloporphyrins are not removed from the polymer by acetone or 1 M sodium chloride.

MnTPPS–Amberlite IRA 900 is a good supported catalyst for the dismutation of hydrogen peroxide.[460a,b] The same supported manganese porphyrin has also a strong peroxidase activity which has been evidenced in the cooxidation of 4-aminoantipyrine and phenol by H_2O_2.[461] The reaction is monitored by UV–visible spectroscopy at 505 nm (λ_{max} of the generated quinoid dye). This method is highly accurate for the titration of diluted hydrogen peroxide solutions.[461,242b] Phenol can be replaced by *N*,*N*-diethylaniline in these peroxidase-like oxidations.[462]

We found that these iron and manganese sulfonated porphyrins supported onto Amberlite are efficient catalysts in the modeling of ligninase. FeTPPS–Amberlite and MnTPPS–Amberlite are much more stable than the corresponding soluble catalysts.[400-401] When MnTPPS–Amberlite–pyridine is reused in the $KHSO_5$ oxidation of veratryl alcohol, the catalytic activity of the second run is 95% of the initial activity.[400] The peroxidase activity of MnTPPS–Amberlite is weak in the absence of pyridine derivatives. In the case of manganese porphyrin, the proximal ligand plays a key role in the formation and reactivity of the high-valent metal–oxo species (see section II.B). However, the presence of free pyridine in the reaction mixture is undesirable. Still, the design of sulfonated porphyrins with a pyridine ligand covalently linked to the macrocycle itself will require a multistep ligand synthesis. In order to combine the two advantageous properties, i.e. the easy adsorption of sulfonated porphyrins onto ion-exchange resins and the proximal effect of pyridine, we found that poly(vinylpyridine) (PVP) answers these criteria.[463] Poly(4-vinylpyridinium) cross-linked with divinylbenzene is a robust and commercially available polymer. A preliminary washing with sodium hydroxide leads to the reticulated polymer with free pyridine units. Sulfonated manganese porphyrins then are easily adsorbed onto poly(vinylpyridine) via the coordination of pyridine, arising from the polymer, to manganese. This modified polymer is subsequently treated with acids or methylating agents to recover the physical adsorption properties of sulfonated groups onto the cationic resin (Figure 28). Data reported in Table IX indicate that very high catalytic activities are obtained in the $KHSO_5$ oxidation of a lignin dimer molecule in the absence of added pyridine.[463] Furthermore, it is possible to recycle the PVP catalysts. In a third reaction with the same sample of MnTMPS–PVP, the catalytic activity was 90% of the first run. An additional advantage is the possibility of using these PVP catalysts at pH values where free pyridine is protonated. The proximal effect with this poly(vinylpyridinium) polymer is not as sensitive to pyridine protonation as it is with Amberlite–type polymers.

MnTMPS–PVP is a suitable catalyst to perform the oxidative chlorination of dimedone.[464] This reaction is catalyzed by chloroperoxidase and is difficult to mimic using simple metalloporphyrins.

The opposite combination, e.g. a cationic porphyrin and a negatively charged ion-exchange resin such as Dowex MSCI, can also be used.[465] Iron *meso*-tetrakis(4-*N*-methylpyridiniumyl)porphyrin adsorbed on Dowex catalyzes the PhIO epoxidation of cyclooctene in methanol.[465b] However, very low catalytic activities are

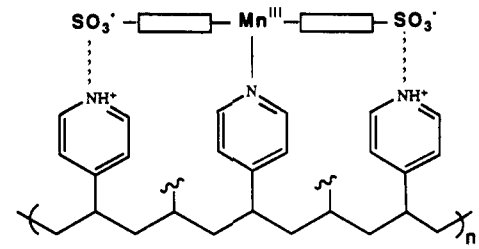


Figure 28. Schematic representation of immobilized sulfonated manganese porphyrins on poly(vinylpyridinium) polymers with a pyridine of the support acting as proximal ligand. Reproduced from ref 463. Copyright 1990 Académie des Sciences.

Table IX. $KHSO_5$ Oxidation of 1-(3,4-Dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol Catalyzed by Sulfonated Manganese Porphyrins in Solution or Supported on Amberlite (Am) or on Poly(vinylpyridinium) (PVP) Polymers (from ref 463)

run	catalyst[a]	ratio of added pyridine to catalyst	substrate conversion in % for a reaction time of *1 min*[b]
1	MnTMPS		5
2	MnTMPS	100	76
3	MnTDCPPS		5
4	MnTDCPPS	100	100
5	MnTMPS-Am	100	46
6	MnTMPS-PVP		61 (63[c])
7	MnTDCPPS-Am	100	59
8	MnTDCPPS-PVP		76

[a] Catalyst/substrate ratio is 10% in all cases. All runs were performed at pH 6.0. [b] 3,4-Dimethoxybenzaldehyde, 2-methoxy-1,4-benzoquinone, and 3,4-dimethoxybenzoic acid were among the major identified products. [c] In this case, the supported catalyst was recovered by filtration after each run, 90% of the original catalytic activity was conserved at the 3rd run.

observed, thus suggesting that interactions of Fe-TMPyP with the sulfonated polymer are aggregations of metalloporphyrin stacked on the resin, rather than dispersion of monomers onto the resin surface. Self-oxidation of the catalyst is favored by stacking effects (for a recent structure determination of FeTMPyP, see ref 466). Much higher catalytic oxygenase activities are obtained when using robust sulfonated manganese porphyrins supported on methylated PVP.[467] Mn-TMPS, MnTDCPPS, $MnBr_8TMPS$, and $MnCl_{12}TMPS$ on PVP are highly efficient catalysts in the epoxidation of cyclooctene or the hydroxylation of cyclooctane by PhIO.

Finally, a robust sulfonated manganese porphyrin such as manganese(III) *meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrin strongly absorbs on colloidal anion-exchange particles in aqueous solution.[468] These colloids are prepared by emulsion polymerization of (chloromethyl)styrenes with divinylbenzene followed by quaternarization with trimethylamine. The resulting particles have a 60-nm diameter. MnTDCPPS is more active in the NaOCl epoxidation of styrene when the catalyst is bound to colloids than alone in aqueous solution.[468]

B. Zeolites

An original approach to selective oxidation of alkanes has been developed by Herron and Tolman using encapsulated metal catalysts into zeolite supercages.[469] Significant shape selectivities have been observed in the PhIO oxidation of alkanes using iron phthalocyanine (Pc) encapsulated in NaX or NaY zeolites. Careful Soxhlet extractions removed all iron catalysts from the zeolite surface. The FePc–zeolite catalysts are able to discriminate between two substrates, e.g. cyclohexane vs cyclododecane.[469a] MnTMPyP can be adsorbed on the surface of a zeolite and used as a selective catalyst for the electrochemical oxidation of di-*tert*-butylphenol.[470] Tetraphenylporphyrin ligands are too large to be encapsulated into zeolites (cage dimension: ~13 Å for Y zeolites), but tetramethylporphyrin has the correct size for an encapsulation within a NaY zeolite. Tatsumi et al. prepared these encapsulated iron tetramethylporphyrins by refluxing pyrrole, acetaldehyde, and Fe(II)-Y zeolite in methanol.[471] These catalysts are active in the H_2O_2 oxidation of cyclohexane to the corresponding alcohol and ketone. Similarly, manganese salen complexes have been encapsulated in NaY zeolites and used in the PhIO olefin epoxidations.[472]

A recent work of Tatsumi indicates that titanosilicate, a zeolite-type structure, is a remarkable shape-selective catalyst in the H_2O_2 oxidation of olefins and alkanes.[473] Linear hydrocarbon oxidation rates are much higher than those of branched and cyclic substrates.

C. Silica

Silica and alumina are attractive supports in catalytic oxidations. They are expected to be completely inert, even under drastic oxidation conditions. Tanaka et al. found that simple Fe(TPP)Cl or Mn(TPP)Cl adsorbed on silica gel or on silica–alumina catalyzed the oxidation of cyclohexene to cyclohexanol and cyclohexenol with molecular oxygen and sodium borohydride as electron source.[474] Sulfides are selectively oxidized to sulfoxides, without formation of sulfones as observed with the corresponding homogeneous catalyst.[475] These neutral metalloporphyrins are believed to be linked to silica via an Si–O–metal bond. However, tetracationic manganese porphyrins such as MnTMPyP are more strongly adsorbed on silica and are very efficient in the PhIO epoxidation of cyclooctene (yield based on oxidant, 95%) and oxidation of cyclohexane to alcohol and ketone (ol/one ratio, 6.5).[476]

Another approach for supported metalloporphyrin on silica is to immobilize the complex via a 3-imidazolyl group linked to surface silicon atoms.[477] The imidazole residues are coordinated in the axial position of metalloporphyrins. Relatively poor yields are observed in the H_2O_2 oxidation of cyclohexane by Mn(TPP)Cl–imidazole–silica catalysts.

D. Clays

Clays have been recently recognized as suitable minerals for supported catalysts.[478] Metalloporphyrins are easily immobilized on clays[479] and they are efficient catalysts for olefin epoxidations or alkane hydroxylations by PhIO.[480] MnTMPyP is more strongly bonded to montmorillonite than to silica. No catalyst release is detected when washing MnTMPyP–clay with organic solvents or water. The catalytic activities of these supported catalysts are higher than those observed with the same metalloporphyrin immobilized on silica. Manganese Schiff base complexes have also been immobilized on a kaolinite clay. Only 10–20 catalytic cycles are obtained in olefin epoxidations with alkyl hydroperoxides as oxidants.[481]

E. Polypeptides

Iron(III) *meso*-5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin has been linked to a modified poly(methyl L-glutamate) via an amide function.[482] This polypeptide-supported iron porphyrin catalyzes the para hydroxylation of aniline by H_2O_2 and olefin epoxidation with $O_2/NaBH_4$. (For the immobilization of metalloporphyrins on proteins and their use in asymmetric oxidations, see reference 455.) When coupled to monomethoxypoly(ethylene glycol) hemin has a high peroxidase activity.[483]

F. Polymerization of Metalloporphyrin Units

Considering the easy addition of nucleophiles to pentafluorophenyl groups of metalloporphyrins,[484] Traylor et al. have developed a new strategy to prepare polymeric polyhalogenated metalloporphyrin catalysts.[485] Treated by sodium sulfite, iron(III) *meso*-tetra(pentafluorophenyl)porphyrin affords a black insoluble polymer which is an efficient catalyst of the cyclohexane hydroxylation by C_6F_5IO.

VII. Characterization of High-Valent Metal–Oxo Porphyrin Complexes

Many stable metal–oxo complexes are known in coordination chemistry. They are often inert and unreactive as oxygen atom transfer reagents at room temperature. This is the case of many oxides or metal–oxo complexes where the metal is highly oxophilic, e.g. titanium, zirconium, vanadium, etc. Since oxygen atom transfer is a crucial step in oxygenation reactions catalyzed by transition-metal complexes or metalloen-

zymes, many works have been devoted to this field for the last 15 years. An exhaustive review article by Holm provides an overview of metal-centered oxygen atom transfer reactions.[1b] Therefore, we will focus our literature survey on high-valent metal–oxo porphyrin complexes and their relation to the nature of active iron–oxo species in heme-enzymes.

Even if everyone agrees on the exact nature of compound I of horseradish peroxidase, there are still some questions to be answered concerning the high-valent iron–oxo in cytochrome P-450, chloroperoxidase or catalase. Is the two-electron oxidized form of these enzymes an iron(V)–oxo or an iron(IV)–oxo porphyrin radical cation like it is in HRP Cpd I? Why is the oxygen atom transfer facile in cytochrome P-450, limited in chloroperoxidase, and absent in catalase? Even if we accept a large influence of the protein residues on the distal site and solvent effects (is a water shell a good screen to avoid intramolecular oxygen atom transfer in catalase or peroxidases?[242b]), many questions still remain on the iron oxidation state, spin state, radical, and/or electrophilic character of the coordinated oxygen atom.

In early articles on metalloporphyrin-catalyzed oxidations of organic substrates, it has been recognized that metal–oxo porphyrin complexes were responsible for most of these reactions: (i) the nature of the porphyrin ligand influences the oxidation reaction features (*meso*-tetraarylporphyrins are better ligands than naturally occurring porphyrins), (ii) when the central metal is able to form strong M=O species at room temperature, no oxygen transfer reaction is observed: vanadium porphyrins are inactive and chromium derivatives are poorly active. Nickel porphyrins are also inactive. In the first cases V=O and Cr=O bonds are too strong to be broken in the presence of the organic substrate. In the second case, no high-valent Ni=O species have been identified so far.

In this context, an accurate knowledge of high-valent oxidation states of heme-protein models should allow a better understanding of the parameters controlling the transfer of a coordinated oxygen atom from a metalloporphyrin to a substrate or the electron transfer from the substrate without oxygen atom transfer. A large number of articles have been devoted to high-valent metalloporphyrins. Consequently, a classification according to the metal has been adopted.

A. Iron–Oxo Porphyrins

1. Chemical Oxidation

m-Chloroperbenzoic acid is a very efficient oxygen atom donor able to generate iron–oxo species even at low temperature. At −78 °C Fe(TMP)Cl reacts with *m*-CPBA in methylene chloride/methanol to produce a "green compound" (Figure 29). At the same temperature PhIO generates a "red compound".[486] Actually, the red derivative is (TMP)Fe^{IV}=O, a model of a peroxidase compound II which can be oxidized by chlorine or bromine[487] to the green derivative (TMP$^{\bullet+}$)Fe^{IV}=O which exhibits a porphyrin radical cation structure like compound I of peroxidases. It is a perferryl derivative which is the one-electron oxidized form of a ferryl compound. The green perferryl porphyrin has been characterized by various physical-chemical methods: UV–visible, NMR, magnetic measurements, Mössbauer, EXAFS, and Raman. The Soret band of (TMP$^{\bullet+}$)Fe^{IV}=O is observed at 405 nm (with a broad band at 645 nm). With TDCPP as ligand the Soret band is at 408 nm.[488] β-Pyrrole protons are observed at −19 ppm for the red ferryl porphyrin complex.[487,489] However, these values are probably highly dependent on the nature of the axial ligand which is not always defined in the various NMR experiments.[489] The magnetic susceptibility of the green compound by the Evans method was found to be 4.2 μ_B, slightly larger than expected for an $S = {}^3/_2$ system.[486] EPR data suggest that a well-separated ground state precludes a total spin $S_t = {}^3/_2$ and suggest that iron and radical spins are weakly coupled in this compound.[488c] Magnetic Mössbauer spectra at low temperatures (4–195 K) and at different magnetic fields (0–6 T) exhibit magnetic features which are different from those of compound I of horseradish peroxidase.[489] These data suggest that the central iron(IV) (S = 1) is tightly coupled to the porphyrin radical cation ($S = {}^1/_2$) in (TMP$^{\bullet+}$)Fe^{IV}=O, whereas the coupling is weaker in HRP compound I. Actually, exchange-coupling constants are dependent on the porphyrin ligand. The J value is >80 cm^{-1} for (TMP$^{\bullet+}$)Fe^{IV}=O and ~1 cm^{-1} for (TDCPP$^{\bullet+}$)Fe^{IV}=O.[488c] By changing the porphyrin ligand to 2,7,12,17-tetramethyl-3,8,13,18-tetramesitylporphyrin, an a_{1u} iron(IV)–oxo radical cation porphyrin complex has been characterized at −78 °C.[488e] Most of the other characterized iron–oxo porphyrin radical cation have the unpaired electron in an a_{2u} orbital.

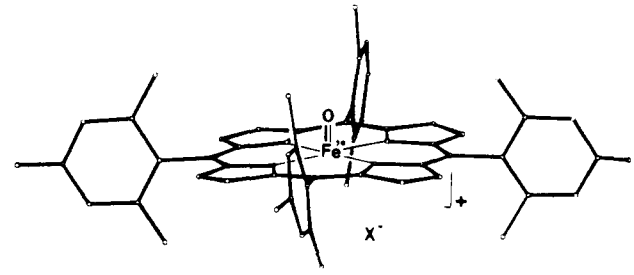


Figure 29. Proposed structure for the green complex (TMP$^{\bullet+}$)Fe^{IV}=O, model of peroxidase compound I. Reproduced from ref 486. Copyright 1981 American Chemical Society.

X-ray absorption, X-ray absorption edge, and extended X-ray absorption fine structure (EXAFS) spectroscopic studies have been performed on these iron–oxo complexes and compared to data obtained on HRP compounds I and II.[490] All edges, for HRP-I, HRP-II, (TMP$^{\bullet+}$)Fe^{IV}=O, and (TMP)Fe^{IV}=O, are similar. EXAFS data indicate the presence of iron–oxygen distances of 1.6 Å in all these derivatives (shorter than an iron–oxygen single bond). Raman resonance spectra indicate that the iron-oxo frequencies are lower than those of stable metal–oxo porphyrin complexes. Vanadium–oxo stretching frequencies range from 980 to 1005 cm^{-1} for (Por)(L)V^{IV}=O, depending on the nature of the axial ligand and the presence or the absence of a radical cation on the porphyrin ligand.[491] The V–O stretching frequency increases by 15 cm^{-1} when a radical–cation is present. In (TMP)(L)Fe^{IV}=O compounds the Fe=O frequency correlates inversely with the strength of the axial ligand trans to the metal–oxo bond: THF (841 cm^{-1}), DMF (829 cm^{-1}), and 1-MeIm (818 cm^{-1}).[488,492] No data are available on the green iron–oxo radical cation complexes due to their

instability during data collection of resonance Raman spectra. However, recent resonance Raman data have been recorded for HRP-I and HRP-II. The Fe=O frequencies are 737 and 776 cm^{-1} for HRP Cpd I and II, respectively.[493a]

The red iron–oxo porphyrin compounds, models of compound II of horseradish peroxidase, are less reactive than the green derivatives.[486] The magnetic susceptibility of (TMP)Fe^{IV}=O is 2.9 μ_B, a value expected for a $S = 1$ system.[486] The Soret band of this iron–oxo porphyrin is observed at 414 nm.[494] (See also ref 488a.) Dimethoxoiron(IV) porphyrins are prepared by addition of sodium methoxide to the corresponding iron(III) radical cation porphyrin complexes.[495] A red shift of the Soret band from 390 to 430 nm was observed. (TMP)$Fe^{IV}(OCH_3)_2$ is EPR silent, and magnetic susceptibility measurements, as well as Mössbauer data, are consistent with an $A = 1$ system for two unpaired electrons (μ_B = 2.9). These rather stable dialkoxoiron(IV) complexes are usually the main species generated by oxidation of iron (or manganese, see below) porphyrins by oxygen atom donors when alcohols are present in the reaction mixture. A ($Por^{\bullet+}$)Fe^{IV}=O complex, claimed to be stable at 8 °C, has recently been prepared by *m*-CPBA oxidation of the iron complex of a porphyrin with twelve phenyl rings. This porphyrin consisted of four 2,6-dichlorophenyl groups at meso positions and eight phenyl substituents at β-pyrrolic positions.[496] It might be possible to obtain an X-ray analysis of this complex. Such data will provide the missing milestone in this field.

Other oxidants are less convenient for the preparation of high-valent iron–oxo porphyrins: dry hydrogen peroxide[497a] destroys iron complexes, even at −30 °C, and *tert*-butyl hydroperoxide generates cationic isoporphyrin compounds with an ROO group attached on one meso position.[498] In the case of hydrogen peroxide, the normal oxygen atom donor of peroxidases, the protein intermediate (compound O) and both high-valent states (compound I and II) have been extensively characterized (see refs 497b and c and references therein).

Dimethyloxirane is also an efficient oxidant to generate (TMP)Fe^{IV}=O.[499] High-valent iron–oxo water-soluble porphyrin complexes have also been generated by potassium monopersulfate in aqueous solutions at pH 9.2 at room temperature.[500a] (Por)Fe^{IV}=O complexes are surprisingly stable in water at ambient temperature. Disproportionation of two ferryl complexes into an iron(III) porphyrin and iron(IV) porphyrin radical cation is postulated. These water-soluble iron–oxo complexes are also easily generated by electrochemical oxidation (see below). Recently Woggon et al. have shown that a high-valent iron–oxo porphyrin complex having an axial thiolato ligand can be generated by molecular oxygen or single oxygen donors.[500b] The concomitant hydroxylation of a C–H bond of a handle of the handle-basket porphyrin is observed as well as the oxidation of the thiol ligand to a sulfonate residue.

2. Electrochemical Oxidation

Hydroxo- or methoxoiron(III) porphyrins with *o*-phenyl substituents to block μ-oxo dimer formation are electrochemically oxidized to generate iron(IV)–oxo porphyrin (one-electron oxidation) or iron(IV)–oxo porphyrin radical cation (two-electron oxidation).[494,501] The oxidation potentials determined by cyclic voltammetry are different in dry[501b] or wet[494] dichloromethane and reported values are controversial. In addition, these values are highly dependent on the nature of the axial ligand. (TPP)Fe^{III}F undergoes a one-electron oxidation at 1.1 V (SCE) whereas the hexacoordinated complex [TPP$Fe^{III}F_2$]$^-$ is oxidized at 0.7 V (SCE).[502] The generated [($TPP^{\bullet+}$)Fe^{IV}=O]F$^-$ reacts with olefins to produce epoxides at low temperature. In the presence of a large excess of fluoride ions the authors suggest that the structure might be a putative iron(V)–oxo complex with the double oxidation centered on the metal.[502c]

Electron-transfer thermodynamics and metal–oxo bond energies of high-valent porphyrin complexes have been extensively studied by Sawyer et al. (in this article, both iron(III)–oxene and iron(IV)–oxo radical cation formalisms have been used).[503] Reported values of metal–oxygen bond energies indicate that the M=O bond is weaker in two-electron oxidized complexes (for ($Por^{\bullet+}$)Fe^{IV}=O and (Por)Mn^{V}=O, $-\Delta G_{BF}$ = 46 and 37 kcal, respectively) than in one-electron oxidized complexes (for (Por)Fe^{IV}=O and (Por)Mn^{IV}=O, $-\Delta G_{BF}$ = 67 and 87 kcal, respectively). All these data have been obtained from electrochemical oxidation of Fe^{III}(TDCPP)Cl or Mn^{III}(TDCPP)Cl.[503] TMPyFe^{IV}=O, a water-soluble iron–oxo complex has been generated by electrochemical oxidation.[504] The Fe=O stretching vibration measured by resonance Raman is found at 812 cm^{-1}.

B. Manganese–Oxo Porphyrins

The first well-defined manganese(V) porphyrins were not Mn=O complexes but manganese(V) nitrido porphyrin derivatives resulting from NaOCl or PhIO oxidation of manganese(III) porphyrins in the presence of ammonia.[505,506] Two crystal structures have been published and the M≡N distance is short in both cases, viz. 1.512 and 1.515 Å in (5,15-dimethyl-2,3,7,8,-12,13,17,18-octaethyl-5*H*,15*H*-porphyrinato)nitridomanganese[505b] and *meso*-[tetrakis(*p*-methoxyphenyl)porphyrinato]nitridomanganese, respectively.[506] All these Mn≡N complexes have very sharp Soret bands at 424 ± 2 nm. They are relatively inert molecules, except under two conditions: (i) reaction with $(CF_3CO)_2O$, or (ii) reaction with a chromium(III) porphyrin complex. (TMP)Mn^{V}≡N reacts with trifluoroacetic anhydride at room temperature to give a green paramagnetic complex (high spin d^2) which reacts with an olefin to produce an aziridine (see Figure 30).[507] (OEP)Mn≡N reacts with (TPP)CrCl to produce quantitatively and irreversibly (OEP)MnCl and (TPP)Cr≡N. The reaction is first order in each of the reactants with a second-order rate constant of 48 M^{-1} s^{-1}.[508]

Manganese–oxo complexes are prepared by chemical oxidation when no alcohols or coordinated oxidizable ligands (such as NH_3, see above) are present. Oxidation of Mn(TPP)Cl by PhIO in solutions containing methanol provides the stable dimethoxomanganese(IV) complex Mn(TPP)$(OCH_3)_2$,[509a,b] not a manganese–oxo compound.[509c] When nonhindered manganese(III) tetraphenylporphyrins are oxidized by PhIO in hydrocarbon or halocarbon solvents, several manganese(IV) compounds can be isolated and characterized by X-ray crystallography.[510] Most of these complexes are μ-oxo dimers. The Mn–O–Mn vibration band is in the range

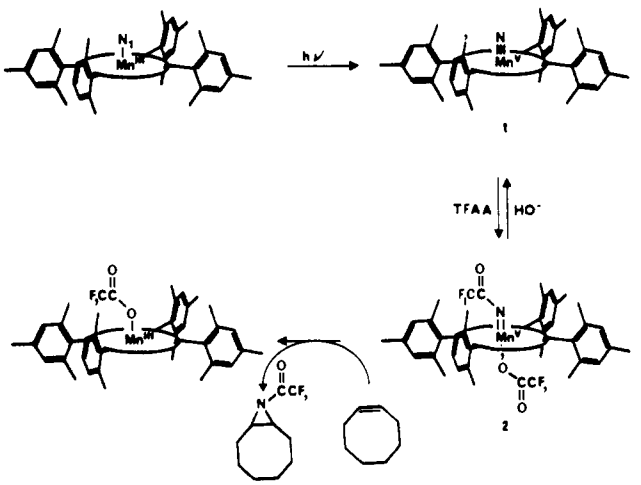


Figure 30. Aziridination of cyclooctene by an imidomanganese(V) porphyrin complex. Reproduced from ref 507a. Copyright 1983 American Chemical Society.

790–800 cm^{-1} and the Mn–O distance is 1.743 Å in $[Mn^{IV}(TPP)N_3]_2O$.[510a] The X-band EPR spectrum of the mixed valence $N_3(TPP)Mn^{IV}$–O–$Mn^{III}(TPP)N_3$ complex is characterized by a pseudo-16-line pattern due to the hyperfine coupling of an $S = {}^3/_2$ Mn^{IV} ion and an $S = 2$ Mn^{III} ion that are strongly antiferromagnetically coupled to give an effective $S = {}^1/_2$ ground state.[510d] By oxidation of Mn(TMP)Cl by NaOCl at room temperature in dichloromethane followed by a fast transfer of the solution in pentane at −78 °C, a brown microcrystalline powder can be isolated.[511] This compound is able to transfer one oxygen atom to an olefin and is reduced to $Mn^{III}(TMP)X$ by two quasi-reversible one-electron steps at $E'_0 = 1.6$ and 1.0 V (Ag/AgCl).[511b] The complex is EPR silent, whereas the one-electron oxidized complex has an EPR spectrum compatible with an Mn(IV) structure. The magnetic susceptibility ($\mu_B = 4.0$) is consistent with a slight antiferromagnetic coupling between the $S = {}^3/_2$ Mn(IV) ion and a radical present on the oxygen ligand (or on the porphyrin ring, although no IR band is detectable at 1260 cm^{-1} as expected for a radical/cation structure). Results of an EXAFS study are compatible with a monomer hexacoordinated manganese porphyrin with a well-defined axial Mn–O ligand ($d = 1.84$ Å, a long Mn^{IV}=O or a Mn^{IV}—OH?) and a water molecule as sixth ligand.[511b] All attempts to grow monocrystals of this high-valent manganese complex failed. The neutral chlorine oxidant OCl_2 is also able to generate high-valent manganese porphyrins.[512] Reaction of Mn(TMP)Cl with OCl_2 in the presence of hydroxide ions yields two different manganese(IV) complexes both of which are able to produce epoxides in the presence of an olefin.

As established in the oxidation of iron porphyrins, *m*-CPBA is a suitable oxidant to generate manganese–oxo species.[513] These compounds result from the decomposition of an intermediate (acylperoxo)manganese(III) complex.[356] $(TMP)Mn^{IV}$=O has been isolated by precipitation with hexane at −78 °C or by chromatography on alumina at −78 °C. The Mn^{IV}=O stretching frequency is at 754 cm^{-1} by FT-IR spectroscopy (this was confirmed by resonance Raman[513c]). Different hexacoordinated manganese(IV)–oxo complexes have been prepared. They differ by the nature of the sixth ligand and their behavior in olefin epoxidation is different. A detailed study based on stereochemistry, oxygen atom exchange with labeled water or molecular oxygen (i) suggests that manganese(IV)–oxo porphyrins are able to epoxidize olefins as well as manganese(V)–oxo species (prepared in situ at −78 °C by *m*-CPBA oxidation), and (ii) confirms that epoxidation stereoselectivity by manganese–oxo entities is dependent on the nature of the sixth ligand.

Another route to prepare manganese(IV)–oxo porphyrins is to treat a manganese(II)–peroxo complex[514] with CO_2 at low temperature. The transient peroxycarbonate complex decomposes to a manganese–oxo derivative.[515] Mn(TMP)X in basic medium is easily oxidized by air to $Mn^{IV}(TMP)(O)$.[513b,516] This complex exhibits a Soret band at 424 nm ($\epsilon = 96\,000$) at −78 °C.[516] Among others, one difficulty in the field of high-valent manganese–oxo porphyrins is that well-defined but different Mn(IV) or Mn(V) complexes, $(TMP)Mn^{IV}(OCH_3)_2$, $(TMP)Mn^{V}(N)$, $(TMP)Mn^{IV}(O)$, have a Soret band in the same range (422 ± 3 nm) which is not conducive to monitoring oxidations of manganese porphyrins (see Table I of ref 516). Irradiation of nitrate or nitrite complexes of manganese(III) porphyrins also produces manganese(IV)–oxo complexes.[517]

High-valent manganese complexes have also been investigated in aqueous solutions.[518] Manganese(III) tetrakis(4-*N*-methylpyridiniumyl)porphyrin, MnTMPy, undergoes facile one-electron chemical or electrochemical oxidation in alkaline solution. The final oxidation product is a manganese(IV)–μ-oxo dimer, $(TMPyP)Mn^{IV}$–O–$Mn^{IV}(TMPyP)$. This dimer reacts with water-soluble olefins, probably via its disproportionation to $Mn^{III}(TMPyP)$ and $Mn^{V}(O)(TMPyP)$. The only example of a stable manganese(V)–oxo complex has been recently published, but the ligand is a macrocyclic tetraamide.[519] The Mn–O distance is 1.555 Å and the stretching frequency 979 cm^{-1}. The complex is a low-spin d^2 square-pyramidal compound.

C. Chromium–Oxo Porphyrins

Chromium(IV)–oxo porphyrin complexes are stable molecules. $(TPP)Cr^{IV}$=O has been prepared by O_2 oxidation of chromium(II) derivatives,[520] by NaOCl or PhIO oxidation.[521,522] This red diamagnetic chromium–oxo complex has a Cr=O bond vibration at 1025 cm^{-1} (metal–oxygen distance, 1.572 Å).[522a] This metal–oxo complex is inert with respect to olefins and alkanes but oxidizes slowly benzylic alcohol to benzaldehyde.[521] However, the product of the one-electron oxidation of $(TPP)Cr^{IV}$=O is reactive toward olefins. Norbornene is epoxidized to *exo*-norbornene oxide by the generated chromium(V)–oxo complex.[523] The mechanism of oxygen transfer from these high-valent chromium complexes to olefins has been studied in detail.[524] Chromium(V)–nitrido complexes have been synthesized by NaOCl oxidation[525] or by irradiation of the chromium(III)–azido porphyrin.[526] These complexes have a d^1 system with strong spin localization in the d_{xy} orbital.

D. Ruthenium–Oxo Porphyrins

$(TMP)Ru^{VI}(O)_2$, a dioxoruthenium(VI) complex, has been prepared by *m*-CPBA oxidation of $(TMP)Ru^{II}(CO)$.[218] This d^2 complex is diamagnetic and the strong IR band at 821 cm^{-1} is assigned to ruthenium–oxo vibrations (for a resonance Raman study, see ref 527).

The corresponding dioxoruthenium(VI) complex with octaethylporphyrin has also been isolated.[528]

VIII. DNA Cleavage by Metalloporphyrins

DNA cleavage by transition-metal complexes is a rapidly growing field for many reasons: (i) first of all, bleomycin, the antitumoral antibiotic discovered by Umezawa et al.[529] is able to cleave DNA via a hydrogen-atom abstraction at the 4′ position of deoxyriboses[530] (this reaction might be mediated by an iron–oxo species[531]), (ii) DNA cleavage by hydroxyl radicals generated by Fe-EDTA (alone[532a,b] or linked to several vectors[532c,d,e]) or by copper nucleases[533] is now recognized as a useful tool in molecular biology, and finally (iii) several cobalt and ruthenium complexes can be used as DNA probes.[534] Porphyrin derivatives have been used in the diagnosis and treatment of malignant diseases. A hemin derivative such as HPD (hematoporphyrin derivative) tends to accumulate specifically in neoplastic tissues and produces irreversible damages via singlet oxygen when the dye is photoactivated by visible light.[535,536] Efforts have been made to prepare new porphyrin derivatives in cancer phototherapy.[537] Manganese(III) *meso*-(*p*-sulfonatophenyl)porphyrin has been used as a tumor-specific contrast-enhancing agent in medical resonance imaging (MRI),[538] where proton relaxation is enhanced by paramagnetic species bound to biological macromolecules. This manganese derivative is found to accumulate in tumor cells and is not demetalated in vivo.[538b]

Cationic porphyrin molecules are able to bind to DNA[539] and RNA.[540] Most of the studies have been focused on free *meso*-tetrakis(4-*N*-methylpyridiniumyl)porphyrin (TMPyP) or on its metalated derivatives (iron, manganese, nickel, palladium, zinc). Several exhaustive review articles in this field are available.[539] The free porphyrin TMPyP intercalates between DNA base pairs, is also able to bind to chromatin in vitro, and tends to localize in the cell nucleus.[541] For the metalated TMPyP derivatives three modes of binding have been recognized: (i) intercalation when metalloporphyrin do not have axial ligands,[539] (ii) outside DNA binding for complexes with axial ligand, and (iii) minor groove binding in the case of MnTMPyP (see below for arguments provided by studies on the molecular aspects of DNA cleavage by activated MnTMPyP). Spectroscopic studies of methylpyridiniumyl metalloporphyrin binding modes to DNA are not facilitated by the porphyrin–porphyrin stacking interactions.[542] Electrochemical or chemical activation of metalloporphyrins is an alternative approach to determine DNA binding constants.[543]

The present section will be focused on recent advances in the oxidative DNA cleavage by iron and manganese porphyrin complexes.

FeTMPyP[544] and hemin[545] have been shown to cause DNA strand scission in the presence of molecular oxygen and a reducing agent, usually a thiol such as dithiothreitol or 2-mercaptoethanol. Potassium superoxide, iodosylbenzene, or potassium monopersulfate can also be used.[546–548] Besides this chemical activation of redox active metalloporphyrins, oxidative photocleavage of nucleic acids by water-soluble zinc porphyrins has also been studied.[549] Photodegradation of super-coiled plasmid pBR 322 DNA to its open circular form by H_2TMPyP or ZnTMPyP suggests that single-strand breaks are more frequent than double-strand breaks. The DNA cleavage efficiency correlates with the quantum yield of singlet oxygen formation. $\Phi(^1O_2)$ is equal to 0.74 and 0.88 for H_2TMPyP and ZnTMPyP, respectively.[549b]

A large volume of data are now available on the binding specificity and on the mechanism of DNA cleavage by MnTMPyP activated by chemical oxidants. Analysis of MnTMPyP-mediated strand scissions on a 139 base-pair fragment of pBR 322 DNA reveals that the minimum metalloporphyrin cleavage site is one A·T triplet (three consecutive A·T base pairs).[547] This DNA binding specificity was confirmed by the DNase I footprinting method.[550] FeTMPyP and ZnTMPyP also bind to AT regions of DNA, whereas NiTMPyP and CuTMPyP were found to bind to both AT and GC regions of the fragments. Preliminary data on $KHSO_5$/MnTMPyP suggest that high-valent manganese–oxo species might be responsible for DNA cleavage. Hydrogen peroxide is at least 3 orders of magnitude less efficient than potassium monopersulfate[551] and breaks are observed in AT regions, at the preferred binding sites of MnTMPyP, suggesting that diffusible hydroxyl radicals are not responsible for the single-strand breaks.[547] These strand scissions are observed on double-stranded DNA at manganese porphyrin concentrations as low as 0.5 nM with short incubation times of 1 min. At low-complex concentration, up to five single-strand breaks per MnTMPyP are observed.[551a] Additional data support the manganese–oxo active species hypothesis: (i) potassium monopersulfate can be replaced by another water-soluble single oxygen atom donor, magnesium monoperoxophthalate[552] and (ii) sugar degradation products result from hydroxylation reactions as expected for in situ generated manganese–oxo porphyrin species.[553,554] 5-Methylene-2-furanone (5-MF) is one of these sugar degradation products and is a marker of DNA hydroxylation at the 1′ carbon of deoxyribose as previously observed by Sigman in DNA breaks mediated by copper phenanthroline.[555] This lesion is mainly observed at GC regions, whereas an hydroxylation at C-5′ is observed in AT-rich regions. In the latter case, furfural is the sugar degradation product.[554] Base release is observed at different stages of the DNA cleavage reaction in these two cases: bases are liberated before the thermal step which is necessary to liberate 5-MF in the case of 1′-hydroxylation, but bases are released only after the thermal step when hydroxylation occurs at the position 5′. The different pathways for oxidative attacks on C–H bonds of DNA by chemical nucleases are depicted in Figure 31. Recently, we found that $KHSO_5$/MnTMPyP preferentially hydroxylates the minor groove-accessible C–H bond at C-5′ on both 3′ sides of A·T base-pair triplets.[556] This fact has been demonstrated in short double-stranded oligonucleotides by HPLC methods and on a ^{32}P-5′-labeled 22-mer. Such selective 5′-hydroxylation by an activated complex located in the minor groove of B-DNA generates a four base-pair shift in strand cleavage as illustrated by Figure 32.

DNA cleavage selectivity can be modulated when porphyrin derivatives are linked to different vectors in order to target their nuclease activity. The vector can be an intercalating agent (acridine,[557] dipyridoimidazole,[558] or 9-methoxyellipticine[559]). The latter derivatives exhibit the essential properties of bleomycin.

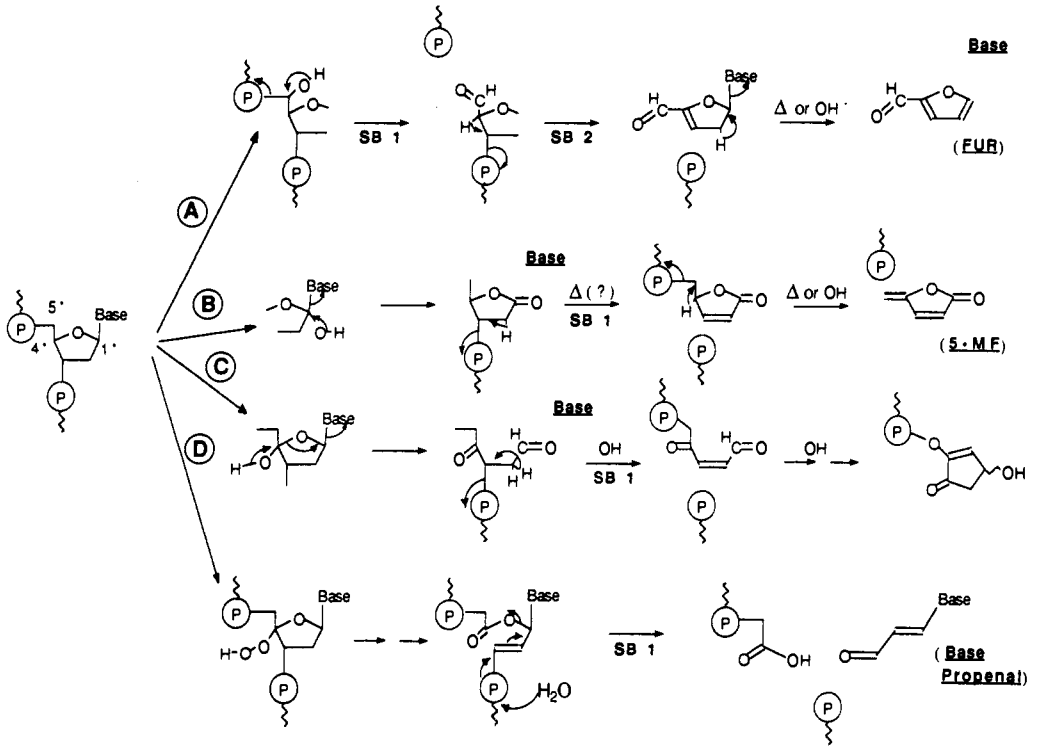


Figure 31. Different pathways for oxidative attacks on C–H bonds of DNA deoxyriboses by chemical nucleases. Reproduced from ref 554b. Copyright 1991 IRL Press Inc.

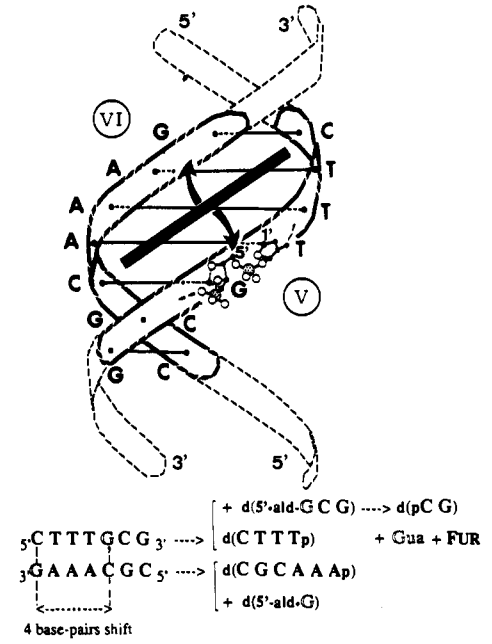


Figure 32. A four base-pair shift in DNA strand scission induced by a preferential attack of $KHSO_5$/MnTMPyP at the 5′-carbon of deoxyriboses on both 3′ sides of an A·T base pair triplet. Reproduced from ref 556. Copyright 1992 National Academy of Science.

They are cytotoxic against leukemia cells in vitro, and their nuclease activity, as well as cytotoxicity, is metal dependent.[559c,d] Because of its DNA affinity, tris-pyridine porphyrin[560] is a suitable motif to be linked to various vectors like oligonucleotides[561] or even to another nuclease motif.[562] The attachment of an efficient DNA cleaver to oligonucleotides might be useful in the development of new antitumoral or antiviral drugs.[563] Recently we have shown that the motif [tris(methylpyridiniumyl)porphyrinato]manganese covalently linked to a 19-mer complementary to the AUG codon region of HIV-1 DNA (5360–5394, according to Wain-Hobson et al.[577]) is able to cleave a 35-mer containing the AUG codon, in the presence of a large excess of salmon sperm DNA, at very low concentrations (5–100 nM). The vectorized cleaver/target ratio was only 1/1. At the same concentrations, the free manganese porphyrin MnTMPyP was unable to cleave the duplex formed by the 35-mer target and the 19-mer vector, in the presence of salmon DNA.[563d]

IX. Recent Advances in Porphyrin Synthesis

A. H_2TMP and H_2TDCPP

Most of the metalloporphyrins used as oxidation catalysts are based on the *meso*-tetraphenylporphyrin ligand family. These porphyrins have a D_4 symmetry and are accessible in a one-step reaction from substituted benzaldehyde and pyrrole. Tetraphenylporphyrin was first synthesized by Rothemund by heating benzaldehyde and pyrrole in pyridine in a sealed bomb at 150 °C for 24 h in low yield (<15%).[564] *meso*-Tetramesitylporphyrin was initially prepared by a modified Rothemund method by Badger et al.[565] A mixture of mesitaldehyde, pyrrole, anhydrous zinc acetate, and pyridine was heated in a stainless steel autoclave at 180 °C for 48 h. The resulting tar was eliminated by filtration and the residue washed with acetone to give the purple ZnTMP complex in 1% yield. Isolation of dipyrromethene derivatives in these syntheses provided some insight into the mechanism of the Rothemund reaction.

Adler and Longo proposed in 1967 a simplified synthesis for *meso*-tetraphenylporphyrin.[566] Benzaldehyde and pyrrole react in refluxing propionic acid within 30 min in aerobic conditions. A 20% yield is commonly obtained for various substituted tetraphenylporphyrins, except for benzaldehydes having substituents in ortho and ortho′ positions. *meso*-Tet-

rakis(2,6-dichlorophenyl)porphyrin is obtained by this method in 1% yield.[567]

The main kinetic product in these Rothemund syntheses of sterically hindered tetraarylporphyrins is not the porphyrin but in fact the dipyrromethene intermediate. The zinc complex of *meso*-(2,6-dichlorophenyl)-5-(*o*,*o*'-dichlorobenzyl)dipyrromethene has been characterized by X-ray crystallography.[568]

Mechanistic considerations served as rational bases for a new method of preparation of H_2TMP and H_2TDCPP based on the formation of the corresponding tetraarylporphyrinogen at low temperature (20–30 °C) followed by a chemical oxidation to the expected porphyrins, *N*,*N*',*N*'',*N*'''-tetraalkylporphyrinogens are sufficiently stable with respect to air oxidation to be easily isolated.[569] The slow step of tetraarylporphyrin formation in the Rothemund or Adler–Longo methods is probably the aerobic porphyrinogen oxidation.[570] Rocha Gonsalves and Pereira found that pyrrole and alkylaldehyde equilibrate to the corresponding porphyrinogen in the presence of a catalytic amount of trifluoroacetic acid. A subsequent oxidation of the porphyrinogen by dichlorodicyanobenzoquinone or *p*-chloranil provides the *meso*-tetraalkylporphyrin ligand in good yields.[570] The same strategy has been applied to H_2TPP synthesis by Lindsey et al.[571] The porphyrin yield is critically dependent on reactant concentrations. With benzaldehyde and pyrrole concentrations at 10 mM, the H_2TPP yield reaches 46%. However, this preliminary work mentioned that this high-yield tetraarylporphyrin synthesis did not work for sterically hindered aldehydes such as mesitaldehyde.[571b]

Fortunately, it was reported that this problem was overcome in optimization procedures independently elaborated by three different groups.[572] Pyrrole and mesitaldehyde are equilibrated to tetramesitylporphyrinogen within 1 h at room temperature in dichloromethane or chloroform in the presence of boron trifluoride–etherate or –methanol. Oxidation by *p*-chloranil or dichlorodicyanobenzoquinone provides H_2TMP in 20–35% yield. The same procedure was extended to the synthesis of *meso*-tetrakis (2,6-dichlorophenyl)porphyrin.[572b,c] The highly hindered *meso*-tetrakis(2,4,6-triphenylphenyl)porphyrin used by Suslick,[157,318] in catalytic oxygenations cannot be prepared by this porphyrinogen method.[572c]

B. Perhalogenated Porphyrins

After TMP- or TDCPP-based complexes, the second-generation metalloporphyrin catalysts and the third-generation catalysts were obtained by halogenation of β-pyrrole positions of H_2TDCPP and H_2TMP porphyrins: H_2Br_8TDCPP[48,573] has been prepared by *N*-bromosuccinimide treatment of ZnTDCPP in carbon tetrachloride at reflux according to a bromination procedure proposed by Callot for H_2TPP.[574] The Soret band of the β-octabromopyrroleporphyrin displays a 48-nm red shift with respect to the starting material, in good agreement with the 6-nm per Br shift found in the bromination of tetraphenylporphyrin. β-Perchlorination of H_2TDCPP was performed by chlorine gas addition at 140 °C in *o*-dichlorobenzene for 5 min.[49] A 22-nm red shift of the Soret band is observed in the case of H_2Cl_8TDCPP.

Bromination of ZnTMP by NBS in refluxing methanol in air provides $ZnBr_8$TMP in high yield. This ionic bromination leaves intact the benzylic positions of mesityl groups.[50,337] When ZnTMP is treated by *N*-chlorosuccinimide under similar conditions, *meso*-tetrakis(2,4,6-trimethyl-3-chlorophenyl)-β-octachloroporphyrin, H_2Cl_{12}TMP, is obtained.[337]

Functionalized polyhalogenated complexes were prepared by selective substitution of the para fluorines of tetrakis(pentafluorophenyl)-β-octabromoporphyrin.[575] The "Teflon" porphyrin, *meso*-tetrakis(pentafluorophenyl)-β-octafluoroporphyrin, was prepared by using cobalt fluoride or silver fluoride as fluorinating agent, but experimental details have yet to be published.[51]

It can be reasonably assumed that most of these second- and third-generation porphyrin ligands will be commercially available in the future to favor the development of oxidation reactions catalyzed by metalloporphyrins.

X. Conclusions and Perspectives

From this survey, it is convincing that metalloporphyrins are very versatile oxidation catalysts which can be used in many different oxidation reactions (olefin epoxidations, alkane hydroxylations, pollutant oxidations, drug metabolization, DNA cleavage, etc.). Synthetic porphyrins are now a meeting point for inorganic chemistry, catalysis, pharmacology, and molecular biology. Combined efforts in such an interdisciplinary area will probably produce new applications of metalloporphyrin chemistry. Very recent data on the catalytic oxidative carbonylation of amines[576] indicate that the field of oxidations catalyzed by metalloporphyrins is still open.

Many articles on metalloporphyrins are dealing with mechanism studies on oxidations catalyzed by these complexes. As general remark on this research field, it must be pointed out that it is tempting to imagine a unique mechanism to account for the formation of different products, but one should keep in mind that several mechanisms (particularly in the case of olefin epoxidations) may be operating depending on the different factors involved in these catalytic oxidations: the oxidant (several oxygen atom donors can be used), the central metal (iron, manganese, etc.), the porphyrin ligand (substituents are modifying steric and electronic effects), the proximal ligand (halide anion, pyridine, or imidazole), and the substrate itself (with high or low redox potential). Conclusions based on particular cases cannot be used to set up a unifying mechanism in these oxidation reactions catalyzed by metalloporphyrins. (For a more exhaustive presentation of these remarks, see refs 81 and 99b.)

The past decade was a decisive period for the start up of oxidation reactions catalyzed by synthetic metalloporphyrin complexes. We can assume that the present decade is going to be dedicated to the development of these catalytic oxidations in the field of fine chemicals since the catalyst cost is far from being negligible at the present time, unless a highly efficient large-scale production of a molecule is based on a metalloporphyrin-catalyzed reaction, forcing the preparation of these complexes to be performed at the industrial scale.

XI. Abbreviations

Am	Amberlite
m-CPBA	*m*-chloroperbenzoic acid
CumOOH	cumyl hydroperoxide
EDTA	ethylenediaminetetraacetic acid
ET	electron transfer
5-MF	5-methylene-2-furanone
NADPH	reduced form of nicotinamide adenine dinucleotide phosphate
N-MeImid	*N*-methylimidazole
OEP	octaethylporphyrin dianion
Por	stands for a nonparticular porphyrinato ligand (for abbreviations of hydrophobic porphyrins, see Figure 2).
PVP	poly(vinylpyridine)
PVPd	poly(vinylpyrrolidone)
TDCMPyP	*meso*-tetrakis(2,6-dichloro-4-*N*-methylpyridiniumyl)porphyrin dianion
TMPyP	*meso*-tetrakis(4-*N*-methylpyridiniumyl)porphyrin dianion
TPPS	*meso*-tetrakis(*p*-sulfonatophenyl)porphyrin dianion
TpivPP	$\alpha,\alpha,\alpha,\alpha$-*meso*-tetrakis[*o*-(pivaloylamino)phenyl]porphyrin dianion
Ts	tosyl
TTP	*meso*-tetra-*p*-tolylporphyrin dianion
TTPPP	*meso*-tetrakis(2,4,6-triphenylphenyl)porphyrin dianion

XII. Acknowledgments

The author is deeply indebted to the work of many collaborators and co-workers whose names are listed in the reference list of this review article. Research works of the Toulouse research group were supported by CNRS, Elf-Aquitaine, Pierre Fabre Médicaments, ARC (Association pour la Recherche contre le Cancer, Villejuif), ANRS (french agency for AIDS research) and the Région Midi-Pyrénées. The first half of the manuscript was written during a summer visit at the Chemistry Department of Princeton University. This stay was included in a collaboration supported by NATO with Profs. John T. Groves and Thomas S. Spiro. Dr. Jeff Lacey is gratefully acknowledged for editing this manuscript.

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