ııllıllıllıllıllıllıllıll
Review
ıllıllıllıllıllıllıllıll

Recent Progress of Metalloporphyrin-catalyzed Oxidation and Oxygenation*

Tadashi Okamoto**, Ken Sasaki***, and Masahiko Tachibana****

Metalloporphyrin-catalyzed oxidation is one of the most attractive topic in biomimetic chemistry. Recent progress in this field is reviewed from biological, synthetic, and mechanistic aspects. The biochemical figure of cytochrome P-450, representative metalloporphyrin-containing oxidation catalyst in biological systems, are summarized in the former part of this article. The last part covers important studies concerning 1) synthesis of chemical analogues of P-450, 2) biomimetic oxidation and oxygenation with synthetic metalloporphyrin catalysts by various oxidants, especially molecular oxygen, and 3) mechanism of oxygen transfer to organic substrates from meltalloporphyrin in higher oxidation states.

KEY WORDS: Metalloporphyrin/ Oxidation/ Oxygenation/ Cytochrome P-450/ Molecular oxygen/

1. INTRODUCTION

The use of molecular oxygen, the most important oxidizing agent used in biological systems, is an attractive subject for synthetic organic chemists. Reactions of singlet organic compounds with triplet molecular oxygen, however, are generally difficult without some change of their spin states because of the spin exclusion.[1] Thus, "substrate activation" or "oxygen activation" is necessary for the successful oxygenation of organic compounds. In biological systems "monooxygenases" have been known that reductively activate molecular oxygen to ensure oxidations and oxygenations of a wide variety of organic substrates.[2,3] In particular, the molecular mechanism of the reactions of cytochrome P-450's, typical heme containing monooxygenases, has been the subject of attention for over a decade.[4-8] The present review describes the outline of catalysis of cytochrome P-450 and the recent development of the chemical simulation of the protein using synthetic metalloporphyrins.

---

* This review article is dedicated to Emeritus Professor Shinzaburo Oka on the occasion of his retirement.
** 岡本　忠 : 1st Department, Ibaragi Research Laboratory, Hitachi Chemical Co. Ltd. Higashi-cho, Hitachi, Ibaragi 317.
*** 佐々木　健 : Department of Polymer Science and Engineering, Kyoto Institute of Technology, Sakyo-ku, Kyoto 606.
**** 橘　雅彦 : Laboratory of Organic Unit Reaction, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611.

2. CYTOCHROME P-450

Cytochrome P-450 is the general term of monooxygenases with iron(III) pro-toporphyrin(IX) (heme, Figure 1) as a prosthetic group, which exists mainly in liver microsome and adrenal mitochondria.[9-11]
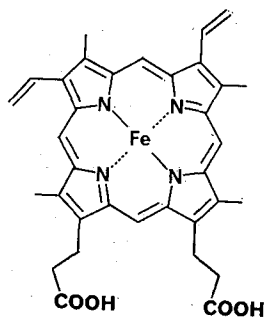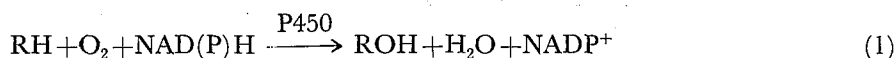

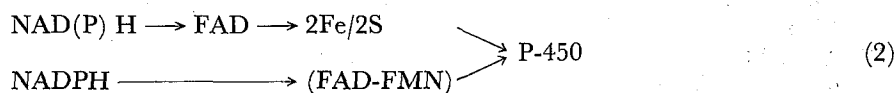Fig. 1. Structure of protoporphyrin (IX) (Heme).

These enzymes catalyze the O-O bond fission of the molecular oxygen at the active site by using electrons derived from NAD(P)H, and mediate the wide variety of significant oxygenation reactions responsible for steroid metabolism, drag detoxification, and so on.

$$RH + O_2 + NAD(P)H \xrightarrow{P450} ROH + H_2O + NADP^+ \tag{1}$$

Interesting reactions in synthetic organic chemistry such as selective hydroxylation of unactivated alkanes, O-dealkylation of ethers, N-dealkylation of tertiary amines, and epoxidation of olefins are promoted by P-450 under very mild reaction conditions.

Microsomal P-450's are generally responsible for drug and toxin metabolism with low substrate specificity. The molecular weights of highly purified ones are about 50000. P-450's in adrenal cortex which are responsible for the processes of steroidal hormone biosynthesis have very high substrate specificity and the reactions are stereo- and regioselective. These two types of enzymes utilize NADPH as an electron source. P-450$_{CAM}$ (camphor-5-exo-hydroxylase) obtained by d-camphor induction of *Pseudomonas putida* has been highly purified and crystallized. The major difference of P-450$_{CAM}$ from other membrane-bound P-450's is its water-solubility and the use of NADH as an electron source.[15] The reaction of this enzyme is also regio- and stereospecific.

Two principally different processes for transferring electrons from NAD(P)H to the active site of P-450 have been found as shown in eq. (2): in bacteria and mitochondria, both FAD-flavoprotein and iron-sulfur protein are involved,[15-18] while in liver microsome, only FAD-FMN flavoprotein mediates the direct reduction of the iron-center without the help of other proteins.[19-22]

$$NAD(P)H \longrightarrow FAD \longrightarrow 2Fe/2S$$
$$\hspace{13em} \searrow \text{P-450}$$
$$NADPH \longrightarrow (FAD\text{-}FMN) \nearrow \tag{2}$$

2.1 Molecular Structure

Recently, extensive X-ray crystallographic studies have been performed with P-450$_{CAM}$, including both substrate-binding and non-binding forms (Figure 2).[23-25]
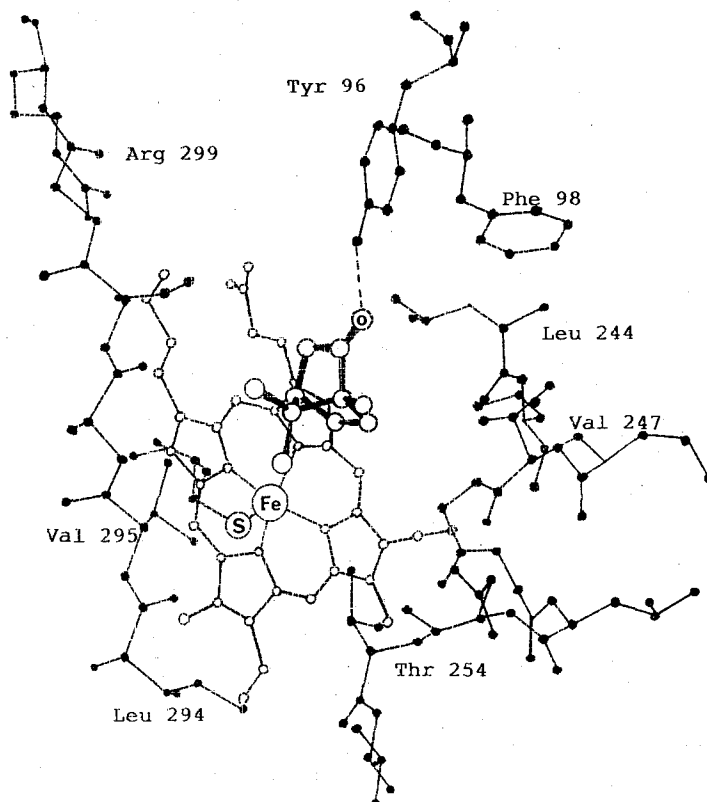

Fig. 2. Structure of the active site around the heme of camphor bound P-450$_{CAM}$.

Iron(III) protoporphyrin(IX), the active site of O$_2$ activation and oxygenation of organic compounds, is fixed by hydrogen bonds between the propionate moieties of heme and Arg 112, Arg 299, and His 355 of the apoenzyme. Iron center of heme is ligated with thiolate anion of Cys 357 as the fifth axial ligand. The active site domain around the heme prosthetic group is highly hydrophobic, except for the presence of tyrosine residue in a distant position from the metal center, for the purpose of fixation of camphor.[23] Analysis of camphor non-binding form reveals that a few molecules of water are present in the active site domain which are freely exchangeable each other because of weak interaction with the iron center.[25] It is considered that the elimination of the coordinated water from the domain by the substrate binding is the driving force of spin interconversion from low spin Fe(III) to high spin state.[26-30]

2.2 Mechanism of Catalysis

Cytochrome P-450 is reduced by the two electrons from NADPH (or NADH in P-450$_{CAM}$) via P-450 reductase which contain of FAD-FMN or iron-sulfur cluster at the active site and activates molecular oxygen for use in oxygenation of the organic substrate accompanied with formation of one molecule of water per consumed dioxygen. The mechanism of catalysis of P-450, though it is a multi-step process and very complex, has been accepted as shown in Scheme 1.
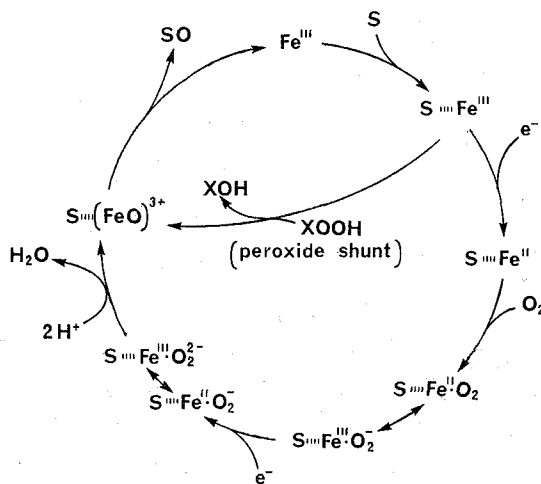
Scheme 1.

The catalytic cycle shows the following feature in each step:[5-7]

1. Binding of substrate to give a high spin ferric complex.

2. Reduction of Fe(III) to Fe(II) by P-450 reductase.

3. Binding of O_2 to the Fe(II) center generating low spin Fe(II)-O_2^- complex.

4. A second reduction of the low spin oxy complex to give peroxo species, Fe(III)-O_2^{2-}.

5. Heterolysis of O-O bond to genreate the reactive oxidant formally depicted as [FeO]$^{3+}$ and one molecule of water.

6. Oxidation or oxygenation of the substrate which results in formation of the product and regeneration of ferric resting state of the enzyme.

Since the rate-determining step is the electron transfer process and intermediates responsible for oxygenation reaction might be unstable, no direct evidence of the subsequent processes after the second electron transfer has been obtained. Thus, although oxoiron(IV) porphyrin cation radical or oxoiron(V) complex has been suggested, exact nature of reactive species is not yet clarified.

The binding and reduction of O_2 in the native P-450 catalytic cycle could be circumvented by the use of exogenous oxygen sources such as ROOH,[31] PhIO,[32-34] NaIO$_4$,[35-37] and peracids.[32,38] These processes require neither NADPH nor O_2, and inhibition by carbon monoxide was not observed.[38,39] Thus, it is suggested that these processes, referred as "peroxide shunt" in Scheme 1, proceed via the reaction

of the two electron oxidants with ferric P-450, which directly generates the reactive species $[FeO]^{3+}$ without reduction of Fe(III) and subsequent oxy-Fe(III) by electrons from NADPH.[38] These oxidant-dependent reactions are quite similar to these of H_2O_2 dependent peroxidases (Scheme 2).
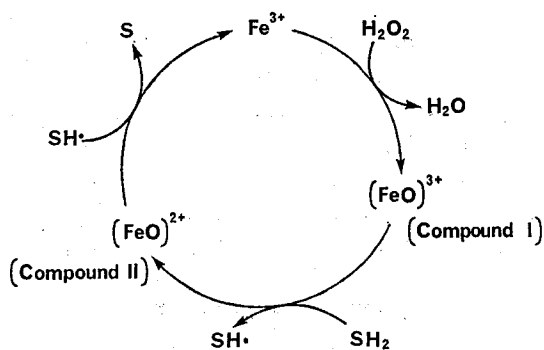

Scheme 2.

Horseradish peroxidase (HRP) reacts with H_2O_2, generating a stable oxidized intermediate complex, Compound I,[40,41] the iron center of which is in the same oxidation state with that of the proposed reactive intermediate of P-450. Compound I has been characterized as an oxoiron(IV) porphyrin cation radical species by spectroscopic studies including Mossbauer,[42] EPR,[43] ENDOR,[44] EXAFS,[45] NMR,[46] and MCD.[47] The reactive species in P-450 represented by $[FeO]^{3+}$ has been also believed as an oxo-Fe(IV) porphyrin cation radical from the two facts: "peroxide shunt" pathway is also effective in the P-450 catalytic cycle as in the peroxidase process, and the reactions by P-450 catalysis are simulated by synthetic metalloporphyrins which can be oxidized to oxo-Fe(IV) cation radical.

The catalytic behavior of HRP, however, is quite different from that of P-450: HRP does catalyze successive one-electron oxidations but does not catalyze oxygenation reactions.[48] The difference has been discussed on the basis of the differences in the structure of active site domain[8] and in the fifth axial ligand, which is imidazole of histidine in HRP[49] whereas is unusual thiolate of cystein in P-450.[23,24]

3. SIMULATION OF METALLOPORPHYRIN CONTAINING OXYGENASES

As described above, cytochrome P-450 possessing iron(III) protoporphyrin(IX) as the active site performs the reductive activation of dioxygen leading to oxygenation of many organic substrates. The catalytic action of transition metal salts for autoxidation of organic molecules has been known since the dawn of chemistry. However, the role of metal salts in these classical reactions has been established as generation of free radical species in the radical chain processes. On the contrary, biological oxidation and oxygenation have been recognized as the processes through the cleavage of high energy O-O bond. Thus, free radical chain reactions as autoxidation could be ruled out from the enzymatic oxygenation mechanism. Udenfriend system composed of Fe(II), EDTA, O_2 and ascorbic acid (AA) as the electron source

has been reported in 1954 as the model system for the biological aromatic hydroxylation by using molecular oxygen.[50]

$$C_6H_6 \xrightarrow[\text{O}_2,\ \text{AA}]{\text{Fe(II), EDTA}} C_6H_5OH \tag{3}$$
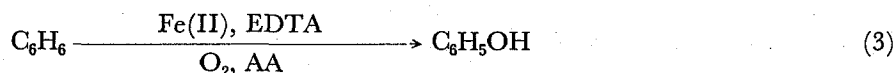
The system also promoted hydroxylation of aliphatic hydrocarbons and expoxidation of olefins albeit in very low yields. Recently, Lindsay-Smith concluded that the mechanism of this oxygenation system was, however, quite different from that of biological oxygenation, catalysed by cytochrome P-450 in particular, on the basis of the measurement of deuterium isotope effect and experiments using $^{18}O_2$.[51,52] In this section we will describe recent progress of metalloporphyrin catalyzed oxygenation of organic substrates in relation to cytochrome P-450.

3.1 Metalloporphyrin complexes in higher oxidation states

In this decade, a number of papers reported about synthesis and characterization of complexes which can be regarded as models of oxidized forms of heme proteins.

Groves et al. reported that (Fe(TMP)Cl, Figure 3) was oxidized by m-chloroperbenzoic acid (mCPBA) at $-78°C$ to give a green complex.[53]
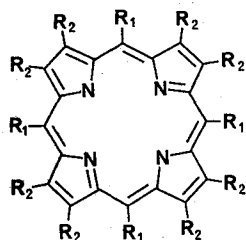
abbrev.	R_1	R_2
TPP	C_6H_5-	H
TMP	$2,4,6\text{-Me}_3C_6H_2-$	H
TFPP	C_6F_5-	H
TDCPP	$2,6\text{-Cl}_2C_6H_3-$	H
TPPS	$4\text{-SO}_3HC_6H_4-$	H
TPFPP	C_6F_5-	F

Fig. 3. Abbrevations of synthetic porphyrins used in this article.

This complex, of which absorption bands appear in long wavelength region and aryl protons shift to low field region in ^1H-NMR, is proved to be oxo-iron(IV)porphyrin cation radical,[53-56] consistent with results such as the isomer shift in Mossbauer spectra, magnetic moments, and EXAFS studies, which estimated the Fe-O bond distance as 1.6 A.[57] These physicochemical properties are quite similar to that observed in HRP Compound I. Furthermore, the fact that the cation radical has the ability of epoxidizing of norbornene at low temperature (Scheme 3) is considered to be a clue suggesting that it should be the catalytically active species in iron porphyrin-oxidant systems corresponding to the high-valent heme in the active species of P-450.[53]

Fe(IV) porphyrin complexes so far reported has, with no exceptions, oxo- or alkoxo- axial ligands which should be required for the stabilization of the Fe(IV)
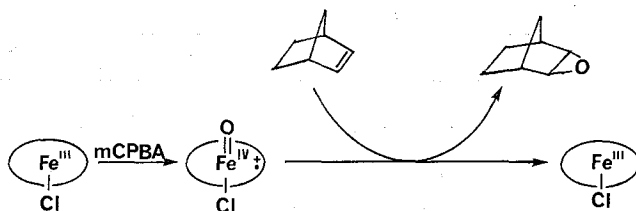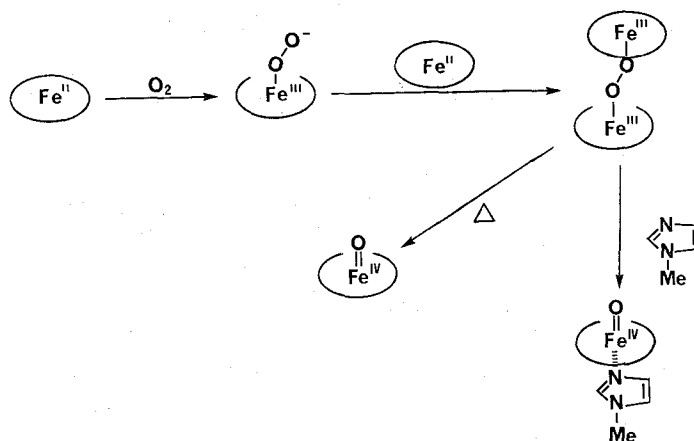
Scheme 3.

center.[56]   In general, one electron oxidation of Fe(III) prophyrins by the oxidants results in electron loss from the porphyrin ring, not from the metal center.[58,59]   The approach of strong electron donating ligands to ghe resulted iron(III) porphyrin cation radical causes electron transfer from metal to ligand, generating Fe(IV) porphyrins.[55]

$$\tag{4}$$
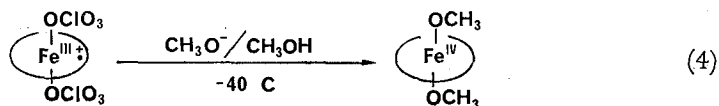
In table I are summarized the oxidized form of metalloporphyrin complexes as well as the oxygenated metalloporphyrin complexes in relation to catalytic activity of P-450.

Oxoiron (IV) porphyrin complex isoelectronic to HRP compound II is known to be produced through a O-O bond scission of an intermediate formed from Fe(II) porphyrin and molecular oxygen.   Weiss et al. reported the generation of $Fe(IV)=O(por)$ by the reaction of CO_2 with $Fe(II)O_2^-$ or $Fe(III)O_2^{2-}$, which was formed by successive one-electron reduction of $Fe(II)O_2$ complex.[67]   The generation of Fe $(IV)=O(por)$ species is also reported by Balch et al. either through cleavage of μ-peroxoiron(III)(TPP) dimer when treated with N-MeIm[65] or through thermal cleavage of μ-peroxoiron(III)TMP dimer (Scheme 4).[63]   The same authors reported

Scheme 4.

(175)

Table 1. Metalloporphyrin Complexes Related to the P-450 Catalytic Cycle.

compound	preparation	identification[b]	ref.
Fe(II) TpivPP(O_2)	Fe(II) Tpiv PP+O_2	vis, Moss	60
Fe(II) TPP(O_2)	Fe(II) TPP+KO_2	vis, EPR	61, 56
	Fe(II) TPP+O_2+e^-		62
[Fe(III) TMP]$_2$ O_2	Fe(II) TMP+O_2	NMR	63
Fe(III) TMP$^{+\cdot}$(ClO_4)$_2$	FeTMP(ClO_4)$_2$+Fe(ClO)	vis, Moss	59
		HNMR	64
O=Fe(IV) TPP(NMeIM)	[FeTPP]$_2$$O_2$+NMeIm	HNMR	57
	(−50°C)		65
		Moss	66
O=Fe(IV) TMP	[FeTMP]$_2$$O_2$	HNMR	63
	(−30C°)		
O=Fe(IV) Tpiv PP	FeTpivPP(O_2)+CO_2−e^-	Moss	67
O=Fe(IV) TMP$^{+\cdot}$	FeTMPCl+mCPBA	vis	53
	(−78°C)	EPR(silent)	54
		EXAFS	55
		Moss	56
			57
	Fe(III) TMP$^{+\cdot}$−e^-	HNMR	68
	(−78°C)		
O=Fe(IV) PP(IX)		vis, RR	69
Fe(IV) TEP(OMe)$_2$	FeTMPOMe+mCPBA	HNMR, Moss	54
	in MeO$^-$/MeOH		
	FeTMP$^{+\cdot}$(ClO_6)$_2$		57
	+MeO$^-$(−50°C)		
Mn(II) TPP(O_2)	MnTPP+O_2	vis, EPR	70
Mn(III) TPP$^{+\cdot}$	MnTPPX+Cl_2	EPR	
Mn(III) TMP$^{+\cdot}$	MnTMPCl+OCl_2^-	NMR	71
	(−78°C)		
Mn(IV) TPP(X)$_2$ X=OI(OAc) Ph	MnTPP+PhIO	vis, Xray	72
			73
			74
			75
Mn(IV) TPP(OMe)$_2$	MnTPP+PhIO	vis	76
	in MeO$^-$/MeOH		77
O=Mn(V) TEP	MnTMOCl+OCl^-	vis	78
	(−80°C)	HNMR	
	MnTMP+mClPhCOCl	vis	79
	+KO_2+OH^-	HNMR	
	(−78C°)		
O=Cr(V) TPP	CrTPPCl+PhIO	vis, EPR	80–82
	+tBuNH$_2$		
O=Cr(IV) TPP	CrTPP+NO	vis	83
	O=Cr(V) TPP−e^-		84
			85

[a] Abbrevations used throughout this article for porphyrin dianons exept for those referred in Figure 3: TpivPP; α, α, α, α-meso-tetrakis (o-pivalamidophenyl) porphyrin, PP; protoporphyrin (IX), T (Chol) PP; α, β, α, β-meso-testrakis (o-(3-hydroxycholenylamido)-phenyl) porphyrin, TTPPP; meso-tetrakis (2, 4, 6-triphenylphenyl) porphyrin, TDMDCPP; meso-testrakis (2, 4, 6-trichloro-3, 5-dimethylphenyl)porphyrin; TMPyPP; meso-tetrakis(N-methyl-4-pyridyl)

that further one-electron oxidation of (TMP)Fe(IV)=O by halogens or by iron (III) porphyrin cation radical generates (TMP$^+$)Fe(IV)=O cation radical.[68] The neutral Fe(IV)=O species, though its chemical reactivity has not thoroughly examined, does not epoxidize olefins but induces oxygenation of phosphines to phosphine oxides,[86] which in quite different from that of highly reactive cation radicals whose chemical reactivity is rather well known.

Mn porphyrin complexes also hydroxylate hydrocarbons in the presence of PhIO.[87,88] Although the active species of the reaction is estimated to be Mn(V), its identification has not yet been done, while Mn(IV) species, which is more stable than Mn(V), can be isolated in several cases.[72-77] Groves et al. observed Mn(V) species in the reaction of (TMP)Mn(III) with superoxide at −78°C in the presence of benzoic anhydride and hydroxide ion, and confirmed the progress of epoxidation of olefins coexisting in the system.[79] Meunier discussed the generation of Mn(V) species from the reaction of (TMP)Mn(III) with hypochlorite at low temperature.[78]

Generation of oxo-Fe(IV) cation radicals resulted from the reaction of iron porphyrins with peracids such as mCPBA is shown to proceed via heterolysis of O-O bond[89,90] after the ligation of ArCOO$^-$ to Fe(III) in dichloromethane (Figure 4).[90]

On the othre hand, in toluene, homolytic cleavage predominates generation of ArCOO$^\bullet$ and subsequent alkylation of the heme taking place.[91] Bruice et al. carried out kinetic studies on the reaction of Fe(III) porphyrins with a number of peracids and peroxides, employing t-butylphenol as the trapping reagent of Fe=O spe-
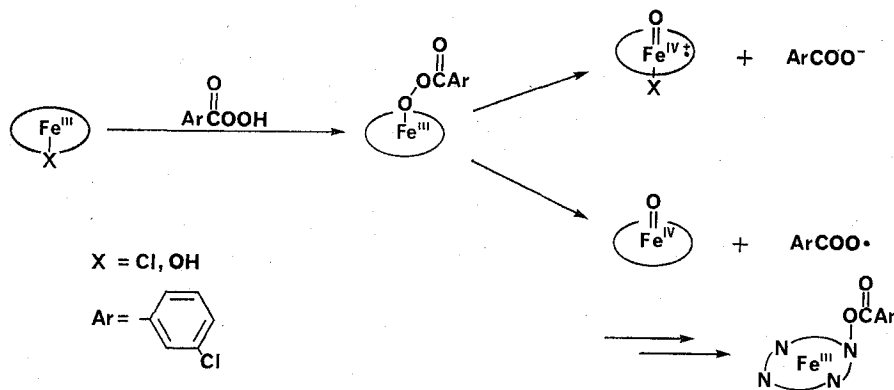

Fig. 4. Heterolysis and homolysis routes in mCPBA oxidation of Fe(III) complex.

porphyrin, for other reagents: PhIO; iodosylbenzene, F$_5$PhIO; pentafluoroiodosylbenzene, XyIO; m-xylyliodosylbenzene, mCPBA; m-chloroperbenzoic acid, CmOOH; cumenehydroperoxide, tBuOOH; t-butylhydroperoxide, NO; N, N-dimethylaniline-N-oxide derivatives, Im; imidazol, N-MeIm, N-methylimidazol, AcPhIm; 4-imidazoylacetophenone, ImPh$_2$; 1,5-diphenylimidazol, AA; ascorbic acid, BA; benzoic anhydride, PVA; polyvinylalchol, MNAH; 1-methyl-3-carbamoyl-1,4-dihydropyridine, BNAH; 1-benzyl-3-carbamoyl-1,4-dihydropyridine.

b Abbreviations of the physical methods used for the identiofication of the compounds: vis; visible absorption spectroscopy, Moss; Mossbauer spectroscopy, EPR; electron paramagnetic resonance spectroscopy, NMR; nuclear magnetic resonance spectroscopy, HNMR; proton NMR, EXAFS; extended X-ray absorption finestructure spectroscopy, RR; resonance Raman spectroscopy, X-ray; X-ray crystallography.

cies.[92] They have noticed that the bending of the Bronsted plot of the rate constants around the pKa value of 11. On the basis of the experimental results they estimated that the homolytic mechanism prevails the peroxides having pKa value greater than 11. Similar relationship between oxidant's pKa and the rate constants is also observed in the case of (TPP)Mn(Im) complexes,[93] not in the case of Cr(TPP) where only heterolysis occurred.[94] These results agree with the contribution of O-O bond homolysis in P-450 reactions especially when peroxides are involved in the reaction.[95] Considering that the native P-450$_{CAM}$, the active site of which is surrounded by *hydrophobic* residues,[23] undergoes *heterolysis* as the major reaction, it is noteworthy that in *hydrophobic* solvents *homolytic* cleavage is predominant to heterolysis in the reaction of the model complexes.

There have been discussions concerning the exact electronic distribution of oxo-Fe (IV) cation radical. Recently Sugimoto et al. examined oxidation of (TDCPP) Fe(III) with monooxygen donors at low temperature.[96] They concluded on the basis of magnetic and electrochemical measurements of the product complexes that the oxidized intermediate should be well characterized as an oxygen atom covalently bound to Fe(II) cation radical center. They also discussed that stereospecific formation of exo-epoxide in the reaction with norbornene is consistent with concerted insertion of a singlet oxygen of "oxene-porphyrin" into pi-bond of olefin, and rules out the possibility of high-valent iron formation, which would give mixed products through electron transfer reaction.

Some papers suggest the generation of oxo-Fe(IV) porphyrin cation radical by oxidation of Fe(II) complex with molecular oxygen. Khenkin et al. reported that Fe(II)O$_2^-$, generated by the reduction of Fe(II)O$_2$, derived an EPR-silent green complex upon treatment with acetic anhydrode at $-50°C$, though furhter investigations had not been presented.[97] Tabushi et al. found that reduction of the picket-fence porphyrin Fe(II)-O$_2$ complex by H$_2$/Pt in the presence of benzoic anhydride caused epoxidation of cyclooctene under acidic conditions, suggesting Fe(V) as the active species.[98] The analysis of the rate constants, however, has indicated that the rate determining step is the reduction of Fe(II)O$_2$ to Fe(III)O$_2^{2-}$, hence no furhter information about the subsequent reactions could be given from the kinetic study. In the absence of the substrate to be oxidized, a rapid reduction of high-valent active catalyst by the excess reductant took place which is considered to be the main degradation pathway of the reductant. All the systems reported so far require acid anhydrides for the cleavage of O-O bond without exceptions,[99] which does not necessarily mean the participation of the carboxylate group in the catalytic oxygenation process, the contribution of which is once proposed during the course of activation of O$_2$ by P-450 in the heme pocket of the enzyme.[23] Thus, it should be concluded that a proton catalyzed cleavage of O-O bond, which is sometimes believed as the process occurring in P-450, has not yet been confirmed in the model systems.

3.2 Simulation of metalloporphyrin mediated oxygenations[100,101]

3.2.1 Peroxide dependent reactions

Groves et al. have reported in 1979 that (TPP)FeCl-iodosylbenzene(PhIO) sys-

Table 2. Summary of P-450 Model Systems Dependent on Exgenous Oxidants.

oxidant	catalyst	additives	reaction	ref.
PhIO	(TPP) FeCl	—	epoxidation hydroxylation	102–109
	(TFPP) FeCl	—	arom. hydroxylation epoxidation hydroxylation and aromatization	110 111, 112, 113 114
	(TPP) Fe, Mn	—	O-dealkylation N-dealkylation $S \rightarrow S=O$	51, 52 104 105
	(TPP) Fe, Mn, Co, Cr		hydroxylation	115
	(TPP) MnCl		epoxidation hydroxylation	87, 88, 116, 117
		Im, Py	epoxidation hydroxylation	118
	(TTPPP) MnOAc	—	hydroxylation	119
	(TFPP) MnCl	—	epoxidation	120
	(TDCPP) MnCl	Im	epoxidation	121
	(picnbask) Mn	ImPh$_2$	epoxidation	122
	(binappor) Mn	ImPh$_2$	epoxidation	123
	(T (Chol) PP) Mn	—	hydroxylation	124, 125
F$_5$PhIO	(TFPP) FeCl	—	epoxidation	126
	(TDCPP) FeCl	—	epoxidation	127, 128
XyIO F$_5$PhIO	(TPP) FeCl	—	epoxidation	129, 130
OCl$^-$	(TDMDCPP) FeCl	—	epoxidation	131, 132
	(TPP) MpCl	—	epoxidation	133, 134, 135
		py	epoxidation	136, 137, 138, 139
	(TPP) MnCl	AcPhIm	epoxidation	149
		—	CHOH $\rightarrow$ CHO	141
		—	hydroxylation	142
	(TMP) MnCl	—	epoxidation	143
CmOOH tBuOOH	Fe, Co (TPP)	—	hydroxylation	144
CmOOH	Fe, Mn (TPP) Cl	Im	epoxidation	145
tBuOOH	(TPP) MnCl	Im	epoxidation	146
CmOOH	(TPP) FeCl	—	O-dealkylation	147
	(TPP) Mo (=O) OMe	—	epoxidation	148, 149
H$_2$O$_2$	(Pors) Mn	Im	epoxidation	150
	(TMPyP) Fe	—	hydroxylation	151
	(TPP) FeCl	—	$S \rightarrow SO$	152
NO	(TPP) FeCl	—	N-dealkylation	153
	(TFPP) FeCl	—	N-dealkylation	154
	(TPP) Fe, MnCl	—	epoxidation	155, 156
		—	hydroxylation	157
		—	N-dealkylation	158
	(TPP) Fe$_2$O	—	epoxidation	159
	(TPP) MnCl	Im	N-dealkylation	160
	(TPP) CrCl	—	diol cleavage	83
KHSO$_5$	(TFPP) Mn	—	epoxidation	161
		—	hydroxylation	162

^{a} abbreviations used: see Figure 3 and footnote of Table I.

tem is effective for stereospecific epoxidation of olefins and hydroxylation of saturated hydrocarbons.[102] This system is the first model reaction of peroxide-dependent cytochrome P-450. In the self-hydroxylation of a strapped-porphyrin iron complex by PhIO the distribution of the hydroxylated positions on the strap moiety clearly indicated that the oxygenation reactions were performed by the coordinated oxygen on the central metal[103] but not by such free radical species as Fenton reagent (Fe(II)/H$_2$O$_2$).

This PhIO-dependent oxygenation system was extended to the wide variety of P-450 type oxygenations such as O-dealkylation of ethers,[51,52] N-dealkylation of tertiary amines,[104] and oxygenation of sulfides.[105] Furthermore, various metalloporphyrin-based oxidant systems other than iron porphyrin-PhIO system have been developed; Fe, Mn and Cr porphyrins as catalysts and ClO$^-$, hydroperoxides, H$_2$O$_2$, amine-N-oxides and KHSO$_5$. These studies are summarized in Table II.

Simple tetraphenyl- and tetraaryl-porphyrin metal complexes, especially iron complexes which were often used in the first stage of the studies, were too unstable under the oxidative conditions to give high catalyst turnover numbers. It has been considered that the catalyst deactivation was brought about by an electrophilic attack to the meso position of porphyrin ring by oxidizing species.[163] More effective catalysts resistant to the oxidative degradation have been designed and prepared by introduction of electronegative groups such as F$^-$ and Cl$^-$ as the substituents of phenyl rings and/or by the steric protection of meso positions.[110,111,121,164,165] Recently, more stable catalyst was obtained by perfluorination of all the hydrogens of the porphyrin ((TPFPP)FeCl), which induces aromatic hydroxylation by H$_2$O$_2$ without significant degradation of the catalysts.[166]

Applications of metalloporphyrin catalyzed oxygenation to regio- or stereo-selective epoxidation of unfunctionalyzed olefins were reported. The use of iron porphyrins modified by a chiral binaphtyl groups[167] or strapped porphyrins with the chiral
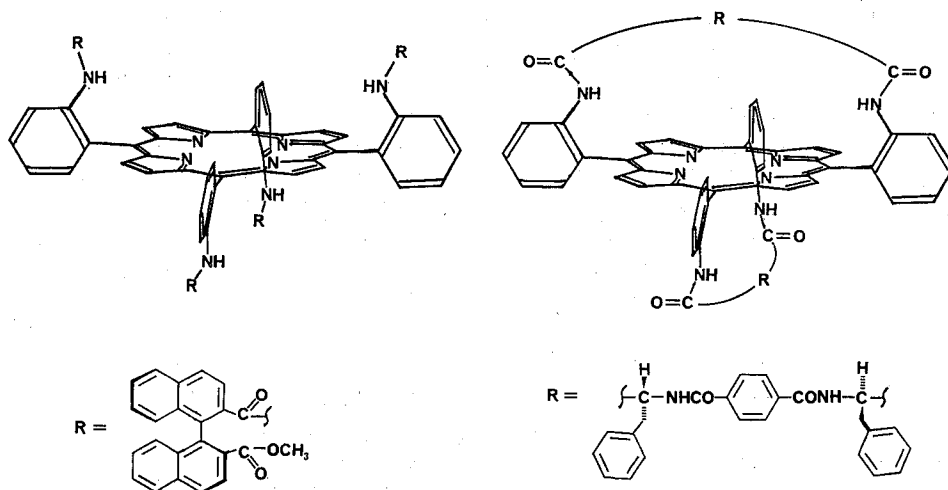

Fig. 5. Modified porphyrin ligands for asymmetric epoxidation.

groups derived from amino acids[168] in shown in Figure 5 is rewarded by about 50% e.e. inthe epoxidation of styrene. Recently, Groves and co-workers have prepared a membrane bound porphyrin modified by cholesterol derivative ((TCholPP)FeCl).[124,125] The oxygenation of cholesterols by the iron or manganese complex proceeded with high regioselectivity at the side chain of cholesterol derivatives.

3.2.2 Reactions with Molecular Oxygen

Cytochrome P-450 in native system activated the molecular oxygen in the presence of electron source, NAD(P)H, to oxygenate many of organic compounds. Most of metalloporphyrin-mediated reactions reported so far were dependent on the exogenous oxidants referred as the "peroxide shunt" which was a by-path route in the P-450 catalytic cycle. The reactions catalyzed by metalloporphyrins in combination with reducing agents and O_2 should be important for understanding of the native enzymatic reaction pathway. However, only limited numbers of successful reactions have been reported so far as shown in Table III.

The first example of oxygenation by metal·oporphyrin-O_2 was hydroxylation of cyclohexane mediated by hemine-thiosalicylic acid-O_2 system, reported by Belova et al.[169] Subsequently, allylic oxidation by (TPP)Fe(III)-O_2,[170] and aromatic hydroxylations by hemin-O_2-thiol[171] or thio ester[172] were reported, but no mechani-

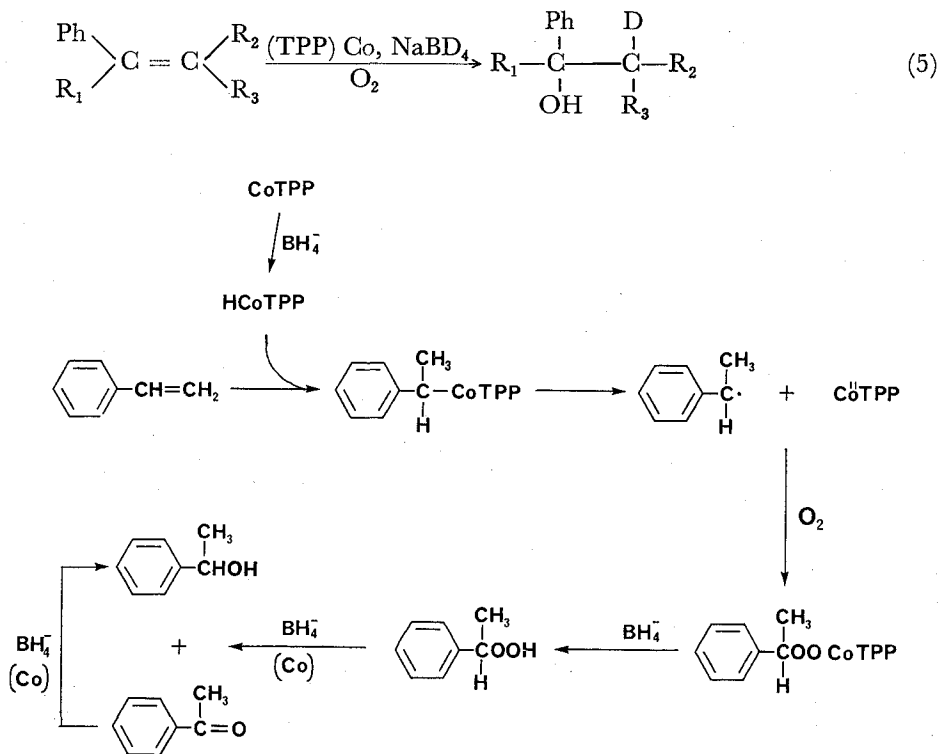Table 3. Summary of O_2 Dependent Reactions with Reducing Agents.[a]

catalyst	reductant	additive	reaction	ref.
Hemin	thiosalicylic acid	—	hydroxylation	169
(TPP) FeCl	—	—	allylic oxidn.	170
	thiol	—	arom. hydroxylation	171
	thioester	—	arom. hydroxylation	172
	NaBH₄		olefin to alcohol	173, 174
	BNAH		C-C cleavage of diol	175, 176
(TPP) Mn	NaBH₄	—	olefin to alcohol	177
	Et₄BH₄	—	olefin to alcohol	178
	BH₄/AA	cystein	olefin to alcohol epoxidation	179
	BH₄	Avicel	hydroxylation. of oleic acid	180
	H₂/Pt/PVA	BA/N-MeIm	epoxidation	181
	H₂/Pt/PVA	BA/N-MeIm	regioselective epoxn.	182
	H₂/Pt/PVA	BA/N-MeIm	arom. hydroxylation	183
	AA	—	epoxidation	184, 185
	e⁻	BA/N-MeIm	epoxidation	186
	Zn	AcOH	epoxidation	187
(TPPS) Mn	MNAH/FMN	BA/N-MeIm	epoxidation	188
	NaBH₄	—	olefin to alcohol epoxidation hydroxylation	189
(T (Chol) PP) Mn	AA		hydroxylation	190
(TPP) Co	NaBH₄		olefin to alcohol	191

[a] abbreviations used: see Figure 3 and footnote of Table I.

stic studies were performed in detail so far.

Major difficulty in simulating P-450 reactions lie in the chemical systems themselves where highly reactive couples, oxidants and reducing agents, coexisted. This drawback is easily overcome in the enzymatic systems in which reaction sites are protected by the proteins, whereas the difficulty remains in model systems. The first successful attempt in this context has been reported by Tabushi in 1979, performing the oxygenation of cyclohexene to cyclohexanol and cyclohexanone utilizing molecular oxygen catalyzed by (TPP)MnCl in the presence of $NaBH_4$ as a reducing agent.[177] Only trace amount of cyclohexene oxide corresponding to the type of product by P-450 catalysis was obtained. The oxygenation of olefins by analogous systems using Mn,[178] Fe,[173,174] Co [174,191] or Rh[192] porphyrin complexes as the catalyst in combination with BH_4^- as the reducing agent were also reported, but major products in these systems were corresponding saturated alcohols and ketones.

Okamoto and Oka suggested that some of oxygenation of olefins by these systems should involve "olefin activation" but not "oxygen activation" in related to cytochrome P-450.[191] Investigation of selective conversion of aryl-conjugated olefins to arylethanols mediated by (TPP)Co with BH_4 under O_2 was carried out by using BD_4 as the reducing agent. Deuterium incorporation in the reactions of styrene was observed not only at the R_1 and R_2 positions of the product but also in recovered styrene.

$$\begin{matrix} Ph \\ R_1 \end{matrix} \!\!\! \Big> C = C \!\!\! \Big< \begin{matrix} R_2 \\ R_3 \end{matrix} \xrightarrow[O_2]{(TPP)\,Co,\ NaBD_4} \underset{\underset{OH\quad R_3}{|\qquad |}}{R_1 - \overset{Ph}{\underset{|}{C}} \!\!-\!\!-\!\! \overset{D}{\underset{|}{C}} \!-\! R_2} \qquad (5)$$
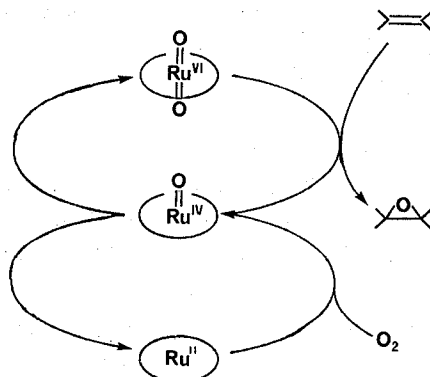

Scheme 5.

This result, though unexpected in the processes of O_2 activation, is easily explained by the reversible insertion of hydride-cobalt complex, resulted in the reaction of (TPP)Co with BH_4^- to styrene, affording alkylcobalt complexes. Consequently, the mechanism shown in Scheme 5 was proposed.

Homolysis of the alkylcobalt bond to alkyl radical was followed by the formation of alkylperoxy-cobalt complex. Subsequent decomposition of the complex by reducing agent gave oxygenation products. Although the mechanisms of Mn or Fe porphyrin mediated reactions were not clarified so far, it is quit probable that some of these reaction followed a similar reaction mechanism.

Tabushi has reported another Mn-porphyrin-O_2-reducing agent system, (TPP) Mn-H_2/Pt-O_2. Using colloidal platinum on polymer support for mediating electron transfer from H_2, (TPP)Mn-catalyzed epoxidation of olefins proceeded successfully.[181] The epoxidation of nonconjugate dienes was regioselective[182] and this system was also effective for the hydroxylation of aromatic compounds.[183] Addition of N-MeIm as the axial ligand and acid anhydride to the reaction system was essential for successful reaction. The relative reactivities of sevral olefins were nearly identical to that of (TPP)Mn-PhIO system, suggesting that high valent Mn-oxo complexes were also the reactive oxidant in this aerobic system.[181] A detailed kinetic investigation of this catalytic system by using iron(II) "picket fence porphyrin" dioxygen complex revealed that the rate-determinig tstep is the second electron transfer to Fe-O_2 complex assisted by H^+. N-MeIm and acid anhydride did not contribute to the r.d.s.[98] Oxygen atom is donated not only to substrate but also to the reducing agent, H_2, probably by reactive iron species, though it has been neither detected nor characterized. The relative rate of H_2O formation to epoxidation was 17.7. Mansuy et al. carried out (TPP)Mn-catalyzed oxygenation of elefins and hydrocarbons by using ascorbate as the reducing agent.[184,185] The overconsumption of reductant was also observed in Mansuy's system similarly in Tabushi's one, and the epoxide formation was only about 1 mol to 100 mol consumption of ascorbate. It was indicated that electrochemical reduction[186] and Zn dust[187] was also effective as the electron source for (TPP)Mn-catalyzed epoxidation of olefins, but no furhter information was obtained.

Groves and co-worker have reported an interesting epoxidation system using only O_2 without any exogenous reductant. (TMP)Ru catalyzed the epoxidation by introducing each oxygen atoms of dioxygen to olefin. Two molecules of epoxide were obtained from one molecule of O_2.[193] The reactions were explained by the mechanism involving disproportionation of Ru(IV)=O porphyrin to Ru(II) and Ru (VI)(=O)$_2$, which was responsible for the epoxidation (Scheme 6).

Cytochrome P-450 in the native enzymatic system utilizes NAD(P)H as the ultimate electron source. Hence, there have been efforts for using N-substituted nicotineamide derivative which has the same dihydropyridine structure as NAD(P)H. It is known that these NAD(P)H analogs transfer the hydrogen atom at C-4 position of ring as a net H^- to carbonyl functions and C-C double bonds activated by electron withdrawing groups.[194,195] Furthermore, Okamoto and co-workers indicated the ability of these compounds for reducing of Fe(III) $(CN)_4^{196,197}$ and the other
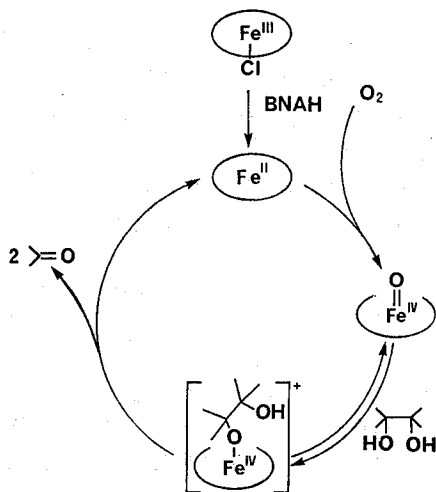
Scheme 6.
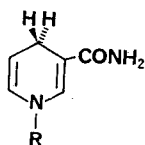
R = nPr: PNAH
    CH$_2$Ph: BNAH
    Me: MNAH

transition metals[198] by stepwise one-electron reduction.

The first application of NAD(P)H analogs to the metalloporphyrin-catalyzed reactions was also accomplished by Okamoto et al. Aerobic C-C bond cleavage of 1,2-diols with aromatic groups was successfully catalyzed by (TPP)FeCl in the presence of BNAH as the reducing agent.[175] This bond cleavage reaction was first O_2-dependent model system of cytochrome P-450$_{scc}$ which was responsible for cholesterol side chain cleavage in the steroidal hormone biosynthesis.[199–201] The reaction was highly selective for C-C bond cleavage affording aldehydes or ketones in nearly quantitative yields. Unproductive consumption of the reductant observed in the other systems was very little. Detailed kinetic analyses of the reaction[176] showed that the kinetics are quite similar to that of epoxidation of olefins by Mn or Fe porphyrin-ClO$^-$ system;[202,203] Michaelis-Menten kinetics and reversal tendency of reactivity for a series of substrates in individual reactions and competitive ones. Finally, on the basis of these observations and spectroscopic identification of intermediate complexes, the mechanism of the reaction through iron(IV)-monoalcholato complex was proposed (Scheme 7).

Tabushi has successfully extended the strategy of using NAD(P)H analogs as a reducing agent to olefin epoxidation in the presence of FMN as an electron mediator.[188] It is known that FMN is present in an active site of liver microsomal cytochrome P-450 reductase and that the reduction of Fe(III) porphyrins to Fe(II) state by BNAH was accelerated by the addition of FMN or modification of porphyrin ligand by FMN.[204] Thus, epoxidation of cyclohexene catalyzed by water soluble Mn porphyrin was performed by using excess MNAH in the presence of catalytic amount of FMN. Addition of N-MeIm and benzoic anhydride was also essential for the reaction as is the case for the H$_2$/Pt system. The contribution of high valent
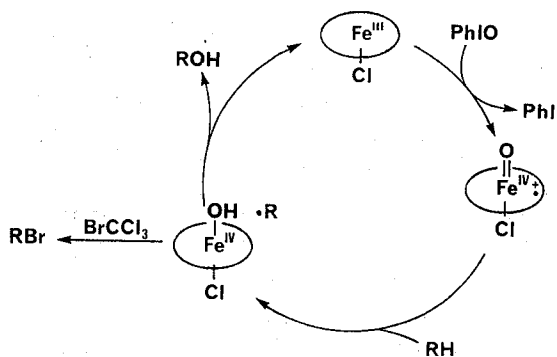
Scheme 7.

oxo-Mn species to the reaction was suggested on the basis of the reactivity orders of a series of olefins.[188]

3.3 Mechanism of Oxygenation of Organic Substrates

The hydroxylation of alkanes and the epoxidation of alkenes catalyzed by P-450 are attractive reactions for synthetic organic chemistry. Extensive studies in this field have provided some mechanistic clue for understanding the oxygenation of organic compounds.

Hydroxylation of saturated hydrocarbons mediated by synthetic metalloporphyrins as well as biological P-450s was suggested as a process of free radical recombination in the solevnt cage. Groves and co-workers have postulated the mechanism of ferric porphyrin-catalyzed oxygenation by PhIO as follows: the hydrogen atom of substrate is abstracted by Fe(IV) cation radical, followed by in-cage recombination of Fe(IV)=O with alkyl radical producing oxygenated product (Scheme 8).[107]
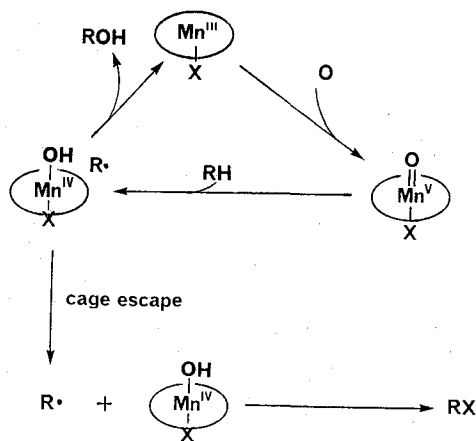

Scheme 8.

Supporting evidence was;
1) allylic rearrangement during cyclohexene oxidation.[205]
2) large deuterium isotope effect $(k^H/k^D \approx 12)$.[107]
3) in the presence of $BrCCl_3$, reaction of cycloheptane produced cycloheptyl bromide in addition of normal oxygenation products.[107]
4) 3° positions of admantane were predominantly hydroxylated.[107]
5) hydorcarbon with cyclopropane ring rearranged to ring opening product by the reaction.[107]
Similar observations were also given in hydroxylation reactions using enzymatic P-450, suggesting the participation of a hydrogen atom abstraction-recombination mechanism.[206]

Manganese porphyrin catalyzed hydroxylations have been also postulated to be a process of similar mechanism, albeit there is slightly different feature from iron-catalyzed reactions (Scheme 9). In (TPP)MnX catalyzed-hydroxylation significant amounts of halogenated alkanes were formed as the by-product in addition to normal hydroxylated product.[207,208] These findings were explained by the increased number of free radical species escaping from in-cage metal-radical pair and reacting with counter anion ligated to metal center.[115]
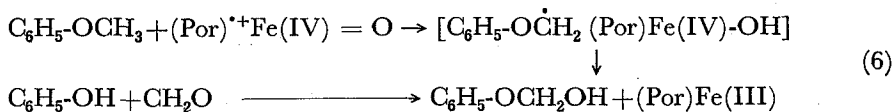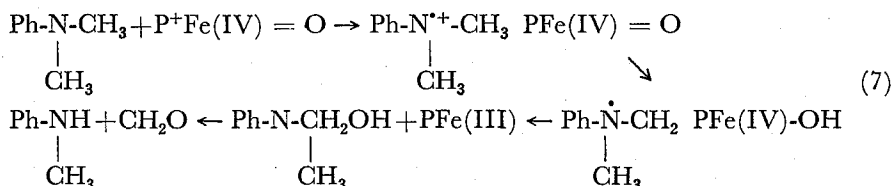

Scheme 9.

Such a halogenation or pseudohalogenation product remarkably increased when aqueous NaX (X=halide anion or pseudohalide anion such as azide) is added to the reaction mixture. Electron releasing substituents on the phenyl rings of porphyrin ligand promoted halogenation of substrates.[115] It is note worthy that the difference of centerred metal, Mn or Fe, was reflected to the reactivity in the 5-exo-hydroxylation of camphor by P-450$_{CAM}$. Sligar et al. prepared P-450$_{CAM}$ having Mn protoporphyrin (IX) as the prosthetic group and carried out oxyganations of camphor and 5,6-dehydrocamphor by this enzyme.[209] Interestingly, this reconstructed P-450$_{CAM}$ did not promote the hydroxylation of camphor, but did only the epoxidation of 5,6-dehydrocamphor. Thus, in the biological system, iron porphyrins were quite important for the hydroxylation activity.

The hydrogen atom abstraction-recombination process was also suggested in O-dealkylation of ethers on the basis of large deuterium isotope effect in the demethylation of anisole.[51,52]

$$C_6H_5\text{-}OCH_3 + (Por)^{\cdot+}Fe(IV) = O \rightarrow [C_6H_5\text{-}O\overset{\cdot}{C}H_2 \ (Por)Fe(IV)\text{-}OH]$$
$$\downarrow \tag{6}$$
$$C_6H_5\text{-}OH + CH_2O \xrightarrow{\hspace{3cm}} C_6H_5\text{-}OCH_2OH + (Por)Fe(III)$$

Bruice and coworkers found the function of soluble, monomeric dimethylaniline-N-oxide derivatives as oxygen donors in ferric porphyrin catalyzed oxygenations.[83,153,155,156,159] Self N-dealkylation of dimethylaniline, produced by the oxygen transfer from N-oxide to metalloporphyrins, have been investigated in detail.[157,158] Kinetic analyses including deuterium isotope effect[154,210] and product analyses[154,211] indicated the process proceeds through aminium cation radical formation via one-electron oxidation of nitrogen atom of amine moiety by elecrophilic oxoiron species.

$$\begin{array}{ccc}
Ph\text{-}N\text{-}CH_3 + P^+Fe(IV) = O \rightarrow & Ph\text{-}N^{\cdot+}\text{-}CH_3 \ PFe(IV) = O \\
\mid & \mid & \searrow \\
CH_3 & CH_3 & \\
Ph\text{-}NH + CH_2O \leftarrow Ph\text{-}N\text{-}CH_2OH + PFe(III) \leftarrow & Ph\text{-}\overset{\cdot}{N}\text{-}CH_2 \ PFe(IV)\text{-}OH \\
\mid & \mid & \mid \\
CH_3 & CH_3 & CH_3
\end{array} \tag{7}$$

The mechanism of epoxidation is now controversial and remains to be solved. The following pathways were considered as possible ones (Figure 6).
A) Concerted oxygen insertion into the double bond.
B) Initial formation of a cation radical intermediate by electron transfer from alkene pi bond to the iron-oxo species and following decomposition of intermediate to epoxide.
C) Initial formation of metal-bound neutral radical by electrophilic attack of oxometal species to olefin following decomposition to epoxide.
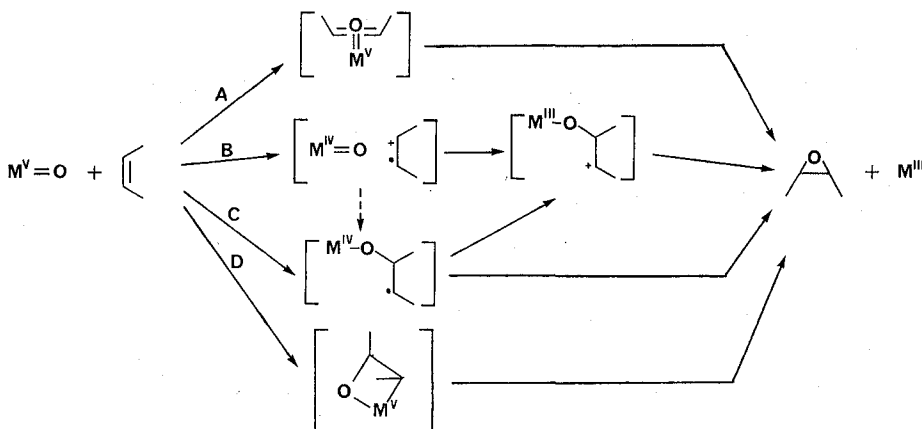

Fig. 6. Proposed mechanisms of the epoxidation of alkenes catalyzed by metalloporphyrins.

D) Initial formation of a metallaoxetane intermediate by addition of metal-oxo bond to alkene and following collapse to the epoxide.

Path (A) was proposed by Groves in the early stage of studies. Retention of the stereochemistry of olefin during the reaction,[106] the oxenoid character of the iron bound oxygen[96] and MNDO molecular orbital calculation[212] support this pathway.

Kinetic investigation of Mn(TPP)Cl-catalyzed epoxidation using LiOCl as the oxidant and 4'-imidazoyl acetophenone as the axial ligand in a two-phase system by Collman and co-workers revealed that the reactions of several alkenes proceeded at different rates and the rates were independent to the concentrations of alkenes.[202,203] A competitive reaction of two different substrates indicated a turnover of the reactivities compared with that of independent one. These results were consistent with the Michaelis-Menten mechanism; reversible formation of an intermediate by the reaction of reactive catalyst with substrate followed by rate-determining product formation. Similar kinetic behavior was also observed in the epoxidation with (TFPP) FeCl-LiOCl system.[126] Metallaoxetane, which is well-known in a number of reactions promoted by transition metals,[213] was proposed as a possible intermediate. Presence of metallaoxetane intermediate was also confirmed in the rearrangement of β-deuteriostyrene to deuteriophenylacetoaldehyde.[120] In this context, it is noteworthy that Groves and co-workers spectroscopically observed an uncharacterized intermediate in the reaction of oxoiron(IV) porphyrin cation radical with olefin at low temperature.[214]

On the contrary, Traylor and co-workers have investigated the epoxidation of olefins with ferric porphyrin systems, (TFPP)FeCl or (TDCPP)FeCl-F$_5$PhIO-ROH, and postulated the reaction mechanism involving cation radical intermediate which is produced by one electron oxidation of alkene with high valent oxo-iron species.[127] Such a mechanism was supported by the following evidence:
1) N-alkylated porphyrin was formed during the catalytic reaction.[215]
2) norbornene afforded substantial endo-epoxide with accompanying skeletal rearrangement.[129,216]
3) a linear relationship between the logarithm of the relative rates of epoxide formation and the ionization potential of the alkenes was observed.[128]
4) rearrangements were promoted by cation radical or easily one electron oxidizable substrates were occurred with substrates highly reactive for one-electron oxidation.[129,130]

Recently, Bruice and co-workers have investigated side products of the reaction of cis-stilben with (TFPP)FeCl-F$_5$PhIO system in detail (Figure 7).[111] The observed cis to trans isomerization of stilben as well as formation of PhCHO under O$_2$ atmosphere were explained by the reversible formation of cation radical intermediate. Evidence for presence of a carbocation in the reaction pathway leading to epoxide as the intermediate was presented based on the formation of both Ph$_2$CHCHO (Ph group migration) and PhCH$_2$COPH (H migration). The reaction of Z-(1,2-bis(trans-2-trans-3-diphenyl)cyclopropyl)-ethene (DPCPE) with same system carried out for examining the presence of a radical intermediate gave corresponding cis-epoxide at 95% yield without cis-trans isomerization.[112,113] Isolation and characterization of
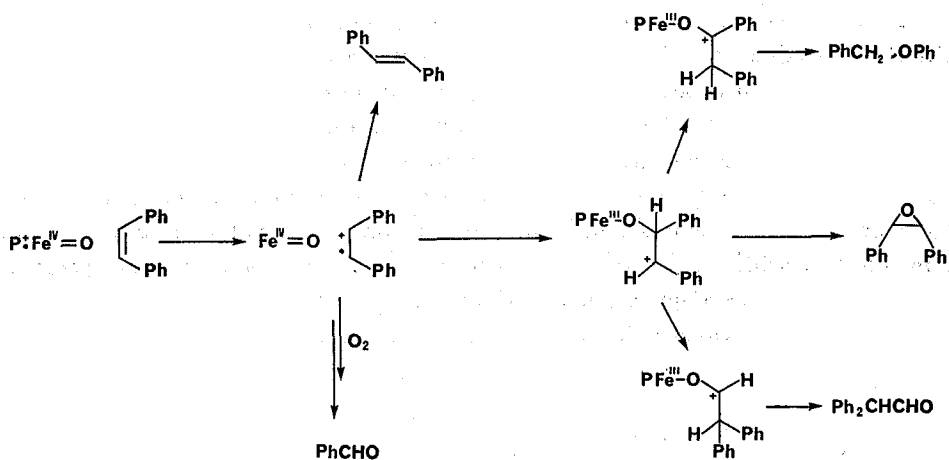
Fig. 7. Proposed pathway for the products in the reaction of cis-stilben.

the side products obtained in only 5% yield showed that they were non-oxygenated hydrocarbons accompanied with ring opening of cyclopropane moiety (Figure 8).
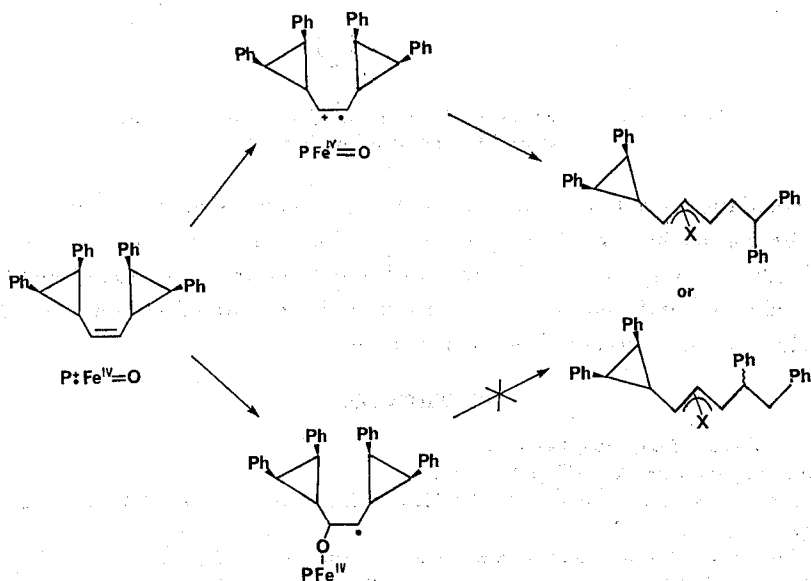

Fig. 8. Proposed route to the non-oxygen cataining products from DPCPE.

The "clock time" of the rearrangement from secondary to secondary benzyl radical is determined as $>2 \times 10^{10}$ based on the kinetics of independent reaction of corresponding cyclopropyl carbinyl radical.[113] The experimental results was consistent with the formation of cation radical species but not the other neutral radicals, suggesting the contribution of cation radical intermediate on the epoxidation processes.[113]

These cation radical processes were, however, postulated only based on the results of the analyses of side products and/or of the reactions with easily oxidazable substrates.   Thus, it is not clear whether these reactions suggesting for cation radical intermediate such as N-alkylation of porphyrin, rearrangement of substrates, and so on arise from the intermediate along the main reaction pathway leading to the epoxide, that is, $1e^-$ oxidation of alkenes is on the epoxidation reaction path, or not. The contribution of metallaoxetane intermediate on the epoxidation path is still remained to be clarified, too.   In this context, Bruice and co-worker recently prepared *meso*-tetrakis(2,6-dibromophenyl)porphyrinato iron complex $(Br_8TPP)FeCl$, Figure 9), the reaction of which will encumbered by the steric bulkiness of *o*-bromo substituents.[217]
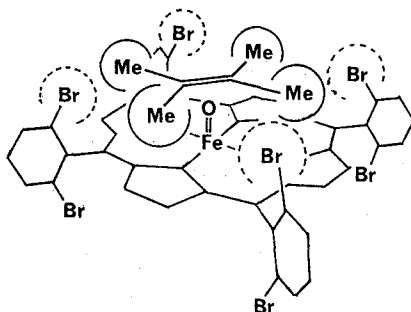

Fig. 9. Proposed structure of the intermediate in the epoxidation
of 2,3-dimethyl-2-butane with $(Br_8TPP)FeCl$.

In the epoxidation reaction with this complex, if high valent iron metal is in the plane of the porphyrin ring, alkenes can be accessible to iorn bound oxygen only from the basal side, and impossible to interact with the metal from the side of Fe-O bond. Clean epoxidation induced by this complex with the dimethyl-2-butene and cis-stilben, disfavors the metalloxetane intermediate.

REFERENCES

(1)   (a) L. Vaska, *Science*, 1963, **140**, 809.
        (b) F. Basolo, *Chem. Rev.*, **179**, 139 (1979).
(2)   E.E. Conn and P.K. Stumpf, In *"Out Lines of Biochemistry"* 5th. ed. John Wiley and Sons: New York, 1987, p 467.
(3)   P. George, In "Oxidases and Related Redox System" vol 1, Chap. 1.
(4)   P.R. Ortiz de Montellano, *"Cytochrome P-450, Structure, Mechanism, and Biochemistry"*, Prenum Press: New York, 1985.
(5)   V. Ullrich, *Topic. Curr. Chem.*, **83**, 68 (1979).
(6)   R.E. White and M.J. Coon, *Ann. Rev. Biochem.*, **49**, 315 (1980).
(7)   F.P. Guengerich, *Acc. Chem. Res.*, **17**, 9 (1984).
(8)   P.R. Ortiz de Montellano, *Acc. Chem. Res.*, **20**, 289 (1987).
(9)   M. Klingenberg, *Arch. Biochem. Biophys.*, **75**, 376 (1958).
(10) D. Garfinkel, *Arch. Biochem. Biophys.*, **77**, 493 (1958).
(11) T. Omura and R. Sato, *J. Biol. Chem.*, **239**, 2370 (1964).
(12) T. Omura and R. Sato, *J. Biol. Chem.*, **239**, 2379 (1964).
(13) K.J. Ryan and L.L. Engal, *J. Biol. Chem.*, **225**, 103 (1957).

(14) R. Estabrook, D.Y. Cooper, and O. Rosenthal, *Biochem. Z.*, **238**, 741 (1963).

(15) M. Katagiri, B.N. Ganguli, and I.C. Gunsalus, *J. Biol. Chem.*, **243**, 3543 (1968).

(16) T. Omura, E. Sanders, R.W. Estabrook, D.Y. Cooper, and O. Rosenthal, *Arch. Biochem. Bio-phys.*, **117**, 660 (1966).

(17) F. Mitani, *Mol. Cell Biochem.*, **24**, 21 (1979).

(18) M. Tanaka, M. Haniu, K.T. Yasunobu, and T. Kimura, *J. Biol. Chem.*, **248**, 1141 (1973).

(19) C.H. Williams and H. Kamin, *J. Biol. Chem.*, **237**, 587 (1962).

(20) T. Iyanagi, F.K. Anan, Y. Imai, and H.S. Msaon, *Biochemistry*, **17**, 2224 (1978).

(21) R.T. Mayer and J.L. Durrant, *J. Biol. Chem.*, **254**, 756 (1979).

(22) J.L. Vermillion and M.J. Coon, *J. Biol. Chem.*, **253**, 2694 (1978).

(23) T.L. Poulos, B.C. Finzel, I.C. Gunsalus, G.C. Wagner, and J. Kraut, *J. Biol. Chem.*, **260**, 16122 (1985).

(24) T.L. Poulos, B.C. Finzel, and A.J. Howard, *J. Mol. Biol.*, **195**, 687 (1987).

(25) T.L. Poulos, B.C. Finzel, and A.J. Howard, *Biochemistry*, **25**, 5314 (1986).

(26) B.W. Griffin and J.A. Peterson, *Biochemistry*, **11**, 4740 (1971).

(27) H. Studt, F. Lichtenberger, and V. Ullrich, *Eur. J. Biochem.*, **46**, 99 (1974).

(28) H. Rein and O. Ristau, *Pharmazie*, **33**, 325 (1978).

(29) J.B. Shenkman, H. Remmer, and R.W. Estabrook, *Mol. Pharmacol.*, **3**, 113 (1967).

(30) S.G. Sligar, D.L. Cinti, G. Gibson, and J.B. Schenkman, *Biochem. Biophys. Res. Commun.*, **90**, 925 (1979).

(31) F.F. Kadlubar, K.C. Morton, and D.M. Ziegler, *Biochem. Biophys. Res. Commun.*, **54**, 1255 (1973).

(32) D.C. Heimbrook and S.G. Sligar, *Biochem. Biophys. Res. Commun.*, **99**, 530 (1981).

(33) F. Lichtenberger, W. Nastainczk, and V. Ullrich, *Biochem. Biophys. Res. Commun.*, **70**, 939 (1976).

(34) A.D. Rahimtula, P.J. O'Brien, H.E. Seifried, D.M. Jeria, *Eur. J. Biochem.*, **89**, 133 (1978).

(35) G. Hrycay, J-.A. Gustafsson, and M. Ingelman-Sundberg, *Biochem. Biophys. Res. Commun.*, **66**, 209 (1975).

(36) E.G. Hrycay, J-.A. Gustafsson, M. Ingleman-Sundberg, and L. Ernster, *FEBS. Lett.*, **56**, 161 (1975).

(37) J-.A. Gustafsson, E.G. Hrycay, and M. Erster, *Arch. Biochem. Biophys.*, **174**, 440 (1976).

(38) G.D. Nordbrom, R.E. White, and M.J. Coon., *Arch. Biochem. Biophys.*, **175**, 524 (1976).

(39) R.E. Miller and F.P. Guengerich, *Biochemistry*, **21**, 1090 (1982).

(40) H.B. Dunford and J.S. Stillmann, *Coord. Chem. Rev.*, **19**, 187 (1976).

(41) W.D. Howson and L.P. Hager, In *"The Porphyrin"*, D. Dolphin, ed. vol 7, Academic Press: New York, 1979, pp 295–332.

(42) C.E. Schults, P.W. Devaney, H. Winkler, P.G. DeBrunner, N. Doan, R. Chiang, R. Rutter, and L.P. Hager, *FEBS. Lett.*, **103**, 102 (1979).

(43) N. Harada, G.T. Miwa, J.S. Walshi, and A.H.Y. Lu, *J. Biol. Chem.*, **259**, 3005 (1984).

(44) (a) J.E. Roberts, B.M. Hoffman, R. Rutter, and L.P. Hager, *J. Biol. Chem.*, **256**, 2118 (1981). (b) J.E. Roberts, B.M. Hoffman, R. Rutter, and L.P. Hager, *J. Am. Chem. Soc.*, **103**, 7656 (1981).

(45) J.E. Penner-Harn, T.G. McMurry, M. Renner, L. Latos-Grazynski, K.S. Eble, I.M. Dabis, A.L. Balch, J.T. Groves, J.R. Dawson, and K.O. Hodgson, *J. Biol. Chem.*, **258**, 12761 (1983).

(46) G.N. LaMar, J.S. deRopp, K.M. Smith, and K.C. Langry, *J. Biol. Chem.*, **256**, 237 (1981).

(47) W.R. Browlett, Z. Gasyna, and M.J. Stillman, *Biochem. Biophys. Res. Commun.*, **112**, 515 (1983).

(48) V. Ullrich, *J. Mol. Cat.*, **7**, 158 (1980).

(49) T. Yonetani, H. Yamamoto, J.E. Erman, J.S. Leigh, and G.H. Reed, *J. Biol. Chem.*, **247**, 2447 (1972).

(50) S. Udenfrient, C.T. Clark, J. Axelrod, and B.B. Brodie, *J. Biol. Chem.*, **208**, 731 (1954).

(51) J.R. Lindsay-Smith, R.E. Piggot, and P.R. Sleath, *J. Chem. Soc., Chem. Commun.*, **55** (1982).

(52) J.R. Lindsay-Smith and P.R. Sleath, *J. Chem. Soc., Parkin Trans.* 2, 621 (1983).

(53) J.T. Groves, R.C. Haushalter, M. Nakamura, T.E. Nemo, and B.J.Evans, *J. Am. Chem. Soc.*, **103**, 2884 (1982).

(54) J.T. Groves, R. Quinn, T.J. McMurry, G. Lang, and B. Boso, *J. Chem. Soc., Chem. Commun.*, 1445 (1984).

(55) J.T. Groves, R. Quinn, T.J. McMurry, G. Lang, and B. Boso, *J. Am. Chem. Soc.*, **107**, 354 (1984).

(56) B. Boso, G. Lang, T.J. McMurry, and J.T. Groves, *J. Chem. Phys.*, **119**, 1122 (1983).

(57) J.E. Penner-Hahm, I.M. Davis, A.L. Balch, J.T. Groves, J.M. Dawson, and K.D. Hodgson, *J. Biol. Chem.*, **258**, 12761 (1983).

(58) R.H. Felton, G.S. Owen, D. Dolphin, and J. Fajer, *J. Am. Chem. Soc.*, **93**, 6332 (1971).

(59) M.A. Phillipi and H.M. Goff, *J. Am. Chem. Soc.*, **104**, 6026 (1982).

(60) J.P. Collman, R.R. Gegne, C.A. Reed, T.R. Halbert, G. Lang, and W.T. Robinson, *J. Am. Chem. Soc.*, **97**, 1427 (1975).

(61) E. McCandlish, A.R. Miksztal, M. Nappa, A.Q. Sprenger, J.S. Valentine, J.D. Stong, and T.G. Spiro, *J. Am. Chem. Soc.*, **102**, 4268 (1980).

(62) C.H. Welborn, D. Dolphin, and B.R. James, *J. Am. Chem. Soc.*, **103**, 2869 (1981).

(63) A.L. Balch, Y.W. Chan, R.J. Cheng, G.N. La Mar, L. Latos-Grazynski, and M.W. Renner, *J. Am. Chem. Soc.*, **106**, 7779 (1984).

(64) P. Gans, G. Buisson, E. Duee, J.C. Marchon, B.S. Erler, W.F. Sholts, and C.A. Reed, *J. Am. Chem. Soc.*, **108**, 1223 (1986).

(65) A.L. Balch, G.N. La Mar, L. Latos-Grazynski, M.W. Renner, and V. Thanabal, *J. Am. Chem. Soc.*, **107**, 3003 (1985).

(66) G. Simmoneaux, W.F. Scholtz, C.A. Reed, and G. Lang, *Biochem. Biophys. Acta,.* **716**, 1 (1982).

(67) M. Schappacher, R. Weiss, R. Montiel-Montoya, A. Trantwein, and A. Tabard, *J. Am. Chem. Soc.*, **107**, 3736 (1985).

(68) A.L. Balch, L. Ratos-Grazynski, and M.W. Renner, *J. Am. Chem. Soc.*, **107**, 2983 (1985).

(69) R.T. Kean, W.A. Oertling, and G.T. Babcock, *J. Am. Chem. Soc.*, **109**, 2185 (1987).

(70) B.M. Hoffman, C.J. Weschler, and F. Basolo, *J. Am. Chem. Soc.*, **98**, 5473 (1976).

(71) K.R. Rodgers and H.M. Goff, *J. Am. Chem. Soc.*, **110**, 7049 (1988).

(72) J.A. Smegal, B.C. Schardt, and C.L. Hill, *J. Am. Chem. Soc.*, **105**, 2920 (1983).

(73) J.A. Smega·, B.C. Schardt, and C.L. Hill, *J. Am. Chem. Soc.*, **105**, 3515 (1983).

(74) J.A. Smegal, B.C. Schardt, and C.L. Hill, *J. Am. Chem. Soc.*, **105**, 3510 (1985).

(75) M.J. Camanzind, B.C. Schardt· and C.L. Hill, *Inorg. Chem.*, **23**, 1984 (1984).

(76) M.J. Camanzind, F.J. Hollander, and C.L. Hill, *Inorg. Chem.*, **21**, 4301 (1982).

(77) I. Willner, J.W. Otvos, and M. Calvin, *J. Chem. Soc., Chem. Commun.*, 964, (1980).

(78) O. Bartorini, M. Ricci, and B. Meunier, *Neuv. J. Chem.*, **10**, 39 (1986).

(79) J.T. Groves, Y. Watanabe, and T.J. McMurry, *J. Am. Chem. Soc.*, **105**, 4489 (1983).

(80) J.T. Groves and R.C. Haushalter, *J. Chem. Soc., Chem. Commun.*, 1165 (1981).

(81) J.T. Groves and R.C. Haushalter, *J. Chem. Soc., Chem. Commun.*, 259 (1981).

(82) S.E. Greager and R.W. Murray, *Inorg. Chem.*, **24**, 3824 (1985).

(83) R.I. Murray and S.G. Sligar, *J. Am. Chem. Soc.*, **107**, 2187 (1985).

(84) J.W. Buchler, K.L. Lay, and V. Ullrich, *Inorg. Chem.*, **21**, 1363 (1982).

(85) J.T. Groves, W.J. Krupper, and R.C. Haushalter, *Inorg. Chem.*, **21**, 1363 (1982).

(86) D.H. Chin, G.N. La Mar, and A.L. Balch, *J. Am. Chem. Soc.*, **102**, 5945 (1980).

(87) J.T. Groves, W.J. Krupper, and R.C. Haushalter, *J. Am. Chem. Soc.*, **102**, 6375 (1980).

(88) C.L. Hill and B.C. Schardt, *J. Am. Chem. Soc.*, **102**, 6374 (1980).

(89) T.G. Traylor, W.A. Lee, and D.V. Stynes, *J. Am. Chem. Soc.*, **106**, 755 (1984).

(90) (a) J.T. Groves and Y. Watanabe, *J. Am. Chem. Soc.*, **108**, 7834 (1986).
　　　 (b) J.T. Groves and Y. Watanabe, *Inorg. Chem.*, **26**, 785 (1987).

(91) J.T. Groves and Y. Watanabe, *J. Am. Chem. Soc.*, **108**, 7836 (1986)

(92) W.A. Lee and T.C. Bruice, *J. Am. Chem. Soc.*, **107**, 513 (1985).

(93) (a) L.C. Yuan and T.C. Bruice, *J. Am. Chem. Soc.*, **108**, 1643 (1986).
　　　 (b) L.C. Yuan and T.C. Bruice, *Inorg. Chem.*, **24**, 986 (1985).

(94) L.C. Yuan and T.C. Bruice, *J. Am. Chem. Soc.*, **107**, 512 (1985).

(95) R.E. White, S.G. Sligar, and M.J. Coon, *J. Biol. Chem.*, **255**, 11108 (1980).

(96) H. Sugimoto, H.-C. Tung, and D.T. Sawyer, *J. Am. Chem. Soc.*, **110**, 2465 (1988).

(97) A.M. Khenkin and A.A. Shiteinman, *J. Chem. Soc., Chem. Commun.*, 1219 (1984).

(98) I. Tabushi, M. Kodera, and Y. Yokoyama, *J. Am. Chem. Soc.*, **107**, 4466 (1985).

(99) S.G. Sligar, K.A. Kennedy, and D.C. Pearson, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 1240 (1980).

(100) T.J. McMurry, and J.T. Groves, *"Metalloporphyrin Models for Cytochrome P-450"*, In *"Cytochrome chrome P-450, Structure, Mechanism, and Biochemistry"*, P.R. Ortiz de Montellano, ed. Prenum Press: New York, 1986.
(101) B. Meunier, *Bull. Chim. Soc. Fr.*, 578 (1986).
(102) J.T. Groves, T.E. Nemo, and R.S. Myers, *J. Am. Chem. Soc.*, **101**, 1032 (1979).
(103) C.K. Chang and M.O. Kuo, *J. Am. Chem. Soc.*, **101**, 7613 (1979).
(104) J.R. Lindsay-Smith and D.N. Mortimer, *J. Chem. Soc., Chem. Commun.*, 64 (1985).
(105) W. Ando, R. Tajima, and T. Tanaka, *Tetrahedron Lett.*, **23**, 1685 (1982).
(106) J.T. Groves and T.E. Nemo, *J. Am. Chem. Soc.*, **105**, 5786 (1983).
(107) J.T. Groves and T.E. Myers, *J. Am. Chem. Soc.*, **105**, 6243 (1983).
(108) J.R. Lindsay-Smith and P.R. Sleath, *J. Chem. Soc. Parkin Trans 2*, 1009 (1982).
(109) J.R. Lindsay-Smith and P.R. Sleath, *J. Chem. Soc. Parkin Trans 2*, 1165 (1983).
(110) C.K. Chang and F. Ebina, *J. Chem. Soc., Chem. Commun.*, 778 (1981).
(111) A.J. Castellino and T.C. Bruice, *J. Am. Chem. Soc.*, **110**, 158 (1988).
(112) A.J. Castellino and T.C. Bruice, *J. Am. Chem. Soc.*, **110**, 1313 (1988).
(113) A.J. Castellino and T.C. Bruice, *J. Am. Chem. Soc.*, **110**, 7512 (1988).
(114) Y. Watanabe and Y. Ishimura, *J. Am. Chem. Soc.*, **111**, 410 (1989).
(115) R.B. Brown, Jr. and C.L. Hill, *J. Org. Chem.*, **53**, 5762 (1988).
(116) J.T. Groves and W.J. Krupper, *J. Am. Chem. Soc.*, **101**, 7613 (1979).
(117) J.T. Groves and W.J. Krupper, *Isr. J. Chem.*, **25**, 148 (1985).
(118) M.J. Nappa and R.J. Mckinney, *Inorg. Chem*, **27**, 3740 (1988).
(119) B.R. Cook, T.J. Reinert, and K.S. Suslick, *J. Am. Chem. Soc.*, **108**, 7281 (1986).
(120) J.P. Collman, T. Kodadek, and J.I. Brauman, *J. Am. Chem. Soc.*, **108**, 2588 (1986).
(121) P. Battioni, J.P. Renaud, J.F. Bartoli, M. Reina-Artiles, M. Fort, and D. Mansuy, *J. Am. Chem. Soc.*, **110**, 8462 (1988).
(122) J.P. Collman, J.I. Brauman, J.P. Fitzgerald, P.D. Hampton, Y. Naruta, and T. Michida, *Bull. Chem. Soc. Jpn.*, **61**, 47 (1988).
(123) Y. Naruta and K. Maruyama, *Tetrahedron Lett.*, **28**, 4553 (1987).
(124) J.T. Groves and R. Neumann, *J. Am. Chem. Soc.*, **109**, 5045 (1987).
(125) J.T. Groves and R. Neumann, *J. Am. Chem. Soc.*, **111**, 2900 (1989).
(126) J.P. Collman, T. Kodadek, S.A. Raybuck, J. Brauman, and L.M. Papazian, *J. Am. Chem. Soc.*, **107**, 4343 (1985).
(127) T.G. Traylor, J.C. Marsters, Jr., T. Nakano, and B.E. Dunlap, *J. Am. Chem. Soc.*, **107**, 5537 (1985).
(128) T.G. Traylor and F. Xu, *J. Am. Chem. Soc.*, **110**, 1953 (1988).
(129) T.G. Traylor, T. Nakano, and B.E. Dunlap, *J. Am. Chem. Soc.*, **108**, 2782 (1988).
(130) T.G. Traylor, Y. Iyanamoto, and T. Nakano, *J. Am. Chem. Soc.*, **108**, 3529 (1986).
(131) S. Banfi, F. Montanari, and S. Quici, *J. Org. Chem.*, **53**, 2863 (1988).
(132) S. Banfi, F. Montanari, and S. Quici, *J. Org. Chem.*, **54**, 1850 (1989).
(133) E. Guilmet and B. Meunier, *Tetrahedron Lett.*, 4449 (1980).
(134) J.A.S.J. Razenberg, A.W. Van Der Made, J.W.H. Smeets, and R.J.M. Nolte, *J. Mol. Cat.*, **31**, 271 (1985).
(135) R.W. Lee and T.C. Bruice, *Proc. Natl. Acad. Sci. U.S.A.*, **85**, 641 (1988).
(136) E. Guilmet and B. Meunier, *Tetrahedron Lett.*, **23**, 2449 (1982).
(137) B. Meunier, E. Guilmet, M.E. De Carvalho, and R. Poilbranc, *J. Am. Chem. Soc.*, **106**, 6668 (1984).
(138) E. Guilmet and B. Meunier, *J. Mol. Cat.*, **23**, 115 (1984).
(139) A.W. Van der Made, and R.J.M. Nolte, *J. Mol. Cat.*, **26**, 333 (1984).
(140) J.P. Collman, T. Kodadek, S.A. Raybuck, and B. Meunier, *Proc. Natl. Acad. Sci. U.S.A.*, **80**, 7039 (1983).
(141) I. Tabushi and N. Koga, *Tetrahedron Lett.*, 3681 (1979).
(142) B. De Porter, M. Ricci, O. Bartorini, and B. Meunier, *J. Mol. Cat.*, **31**, 221 (1985).
(143) W.R. Lee, P.C. Nakagaki, and T.C. Bruice, *J. Am. Chem. Soc.*, **111**, 1368 (1989).
(144) D. Mansuy, J.F. Bartori, J.C. Chottard, and M. Lang, *Angew. Chem. Int. Ed. Engl.*, **19**, 909 (1980).

(145) D. Mansuy, P. Battioni, and J.P. Renaud, *J. Chem. Soc., Chem. Commun.*, 1255 (1984).

(146) P.N. Balasubramanian, A. Sinha, and T.C. Bruice, *J. Am. Chem. Soc.*, **109**, 1450 (1987).

(147) D. Mansuy and P.M. Dansette, *Biochem. Biophys. Res. Commun.*, **96**, 433 (1980).

(148) H.J. Ledon, P. Durbut, and F. Varescon, *J. Am. Chem. Soc.*, **103**, 3601 (1981).

(149) H.J. Ledon and F. Varescon, *Inorg. Chem.*, **23**, 2735 (1984).

(150) J.P. Renaud, P. Battioni, J.F. Bartori, and D. Munsuy, *J. Chem. Soc., Chem. Commun.*, 888 (1985).

(151) T. Shimizu, T. Iyoda, and N. Kanda, *J. Chem. Soc., Chem. Commun.*, 1926 (1981).

(152) S. Oae, Y. Watanabe, and K. Fujimori, *Tetrahedron Lett.*, **23**, 1189 (1982).

(153) P. Shannon and T.C. Bruice, *J. Am. Chem. Soc.*, **103**, 4580 (1981).

(154) D. Ostovic, C.B. Knobler, and T.C. Bruice, *J. Am. Chem. Soc.*, **109**, 3444 (1987).

(155) M.W. Nee and T.C. Bruice, *J. Am. Chem. Soc.*, **104**, 6123 (1982).

(156) C.M. Dicken, T.C. Woon, and T.C. Bruice, *J. Am. Chem. Soc.*, **108**, 1636 (1986).

(157) C.M. Dicken, L.M. Lu, M.W. Nee, and T.C. Bruice, *J. Am. Chem. Soc.*, **107**, 5776 (1985).

(158) M.F. Powell, E.F. Pai, and T.C. Bruice, *J. Am. Chem. Soc.*, **106**, 3277 (1984).

(159) C.M. Dicken, P.N. Balasubramanian, and T.C. Bruice, *Inorg. Chem.*, **27**, 197 (1988).

(160) W.H. Wang, D. Ostovic, and T.C. Bruice, *J. Am. Chem. Soc.*, **109**, 3428 (1987).

(161) B. DePorter and B. Meunier, *Nouv. J. Chim.*, **9**, 393 (1985).

(162) B. DePorter, M. Ricci, and B. Meunier, *Tetrahedron Lett.*, **26**, 4459 (1985).

(163) P.S. Traylor, D. Dolphin, and T.G. Traylor, *J. Chem. Soc., Chem. Commun.*, 279 (1984).

(164) T.G. Traylor, J.C. Marsters, T. Nakano, and B.E. Dunlop, *J. Am. Chem. Soc.*, **107**, 5537 (1985).

(165) T.K. Miyamoto, S. Takagi, T. Hasegawa, S. Tsuzuki, E. Takahashi, K. Okude, I. Banno, and Y. Sasaki, *Bull. Chem. Soc. Jpn.*, **60**, 1649 (1987).

(166) (a) S. Tuchiya and M. Seno, *Chem. Lett.*, 263 (1989).
      (b) T.G. Traylor and S. Tuchiya, *Inorg. Chem.*, **26**, 1338 (1987); **27**, 4520 (1988).

(167) J.T. Groves and R.S. Myers, *J. Am. Chem. Soc.*, **105**, 5791 (1983).

(168) J.P. Renaud, P. Battioni, and D. Mansuy, *Nouv. J. Chim.*, **11**, 279 (1987).

(169) V.S. Belowa, L.A. Nikonova, L.M. Raichman, and M.R. Bornkaeva, *Dokl. Akad. Neuk. SSR. (Engl. Ed.)*, **204**, 455 (1972).

(170) D.R. Poulson, R. Vllman, and R.S. Sloane, *J. Chem. Soc., Chem. Commun.*, 186 (1974).

(171) H. Sakurai, *Chem. Pharm. Bull.*, **24**, 1686 (1976).

(172) H. Sakurai, S. Shimomura, and K. Ishizu, *Biochem. Biophys. Res. Commun.*, **101**, 1102 (1981).

(173) T. Santa, T. Mori, and M. Hirobe, *Chem. Pharm. Bull.*, **33**, 2175 (1985).

(174) T. Okamoto, Y. Sasaki, K. Sasaki, and S. Oka, *Bull. Chem. Soc., Japn.*, **60**, 4449 (1987).

(175) T. Okamoto, K. Sasaki, M. Shimada, and S. Oka, *J. Chem. Soc., Chem. Commun.*, 381 (1985).

(176) T. Okamoto, K. Sasaki, and S. Oka, *J. Am. Chem. Soc.*, **110**, 1187 (1988).

(177) I. Tabushi and N. Koga, *J. Am. Chem. Soc.*, **101**, 6456 (1979).

(178) M. Perree-Fauvet and A.J. Gaudemer, *J. Chem. Soc., Chem. Commun.*, 874 (1981).

(179) H. Sakurai, *J. Mol. Cat.*, **47**, 1 (1988).

(180) H. Sakurai, M. Mizu, M. Nishiki, N. Mitsuo, and T. Satoh, *J. Mol. Cat.*, **48**, 175 (1988).

(181) I. Tabushi and A. Yazaki, *J. Am. Chem. Soc.*, **103**, 7371 (1981).

(182) I. Tabushi and K. Morimitu, *J. Am. Chem. Soc.*, **106**, 6871 (1984).

(183) I. Tabushi and K. Morimitu, *Tetrahedron Lett.*, **27**, 51 (1986).

(184) D. Mansuy, M. Fontecave, and J.F. Bartori, *J. Chem. Soc., Chem. Commun.*, 253 (1983).

(185) M. Fontecave and D. Mansuy, *Tetrahedron*, **40**, 4297 (1984).

(186) S.E. Creager, S.A. Raybuck, and R.W. Murray, *J. Am. Chem. Soc.*, **108**, 4225 (1986).

(187) P. Battioni, J.F. Bartoli, P. Ludec, M. Fontecave, and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 791 (1987).

(188) I. Tabushi and M. Kodera, *J. Am. Chem. Soc.*, **108**, 1101 (1986).

(189) M. Shimizu, H. Orita, T. Hayakawa, and K. Takehira, *J. Mol. Cat.*, **45**, 85 (1988).

(190) J.T. Groves and R. Neumann, *J. Org. Chem.*, **53**, 3891 (1988).

(191) T. Okamoto and S. Oka, *J. Org. Chem.*, **49**, 1589 (1984).

(192) Y. Aoyama, T. Watanabe, H. Onda, and H. Ogoshi, *Tetrahedron Lett.*, **24**, 1183 (1983).

(193) J.T. Groves and R. Quinn, *J. Am. Chem. Soc.*, **107**, 5790 (1985).

(194) S. Yasui and A. Ohno, *Bioorg. Chem.*, **14**, 70 (1986).

(195) A. Ohno and S. Ushida, *"Mechanistic Model of Asymmetric Reductions"*, in *"Lecture Notes in Bio-organic Chemistry"*, Beaulieu et al. eds Splinger-Verlag: Berlin 1986, vol. 1.

(196) T. Okamoto, A. Ohno, and S. Oka, *J. Chem. Soc., Chem. Commun.*, 181 (1977).

(197) T. Okamoto, A. Ohno, and S. Oka, *J. Chem. Soc., Chem. Commun.*, 784 (1977).

(198) T. Okamoto, A. Ohno, and S. Oka, *Bull. Chem. Soc. Jpn.*, **52**, 3745 (1979).

(199) M. Shikita and P.F. Hall, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 1441 (1974).

(200) S. Burstein, B.S. Middleditch, and M. Gut, *J. Biol. Chem.*, **250**, 9028 (1975).

(201) R. Hume, R.W. Kelly, P.L. Taylor, and G.S. Boyd, Eur. *J. Biochem.*, **140**, 583 (1984).

(202) J.P. Collman, J.I. Brauman, B. Meunier, S.A. Raybuck, and T. Kodadek, *Proc. Natl. Acad. Sci. U.S.A.*, **81**, 3245 (1984).

(203) J.P. Collman, J.I. Brauman, B. Meunier, T. Kodadek, and S.A. Raybuck, *J. Am. Chem. Soc.*, **107**, 2000 (1985).

(204) J. Tanaka, S. Ohta, and M. Hirobe, *J. Am. Chem. Soc.*, **109**, 7677 (1987).

(205) J.T. Groves and P.V. Sabramanian, *J. Am. Chem. Soc.*, **106**, 2177 (1984).

(206) (a) J.T. Groves, G.A. McMarry, R.E. White, and M.J. Coon, *Biochem. Biophys. Res. Commun.*, **81**, 154 (1978).
(b) R.E. White, J.P. Miller, L.V. Fevreau, and A.J. Bhattachrya, *J. Am. Chem. Soc.*, **108**, 6024 (1986).
(c) P.R. Ortiz de Montellano and R.A. Slearns, *J. Am. Chem. Soc.*, **109**, 3415 (1987).

(207) J.T. Groves, W.J. Krupper, Jr., and R.C. Haushalter, *J. Am. Chem. Soc.*, **102**, 6377 (1980).

(208) C.L. Hill and B.C. Shardt, *J. Am. Chem. Soc.*, **102**, 6384 (1980).

(209) M.H. Gelb, W.A. Toscano, Jr., and S.G. Sligar, *Proc. Natl. Acad. Sci. U.S.A.*, **79**, 5758 (1982).

(210) C.M. Dicken, F.L. Lu, M.W. Nee, and T.C. Bruice, *J. Am. Chem. Soc.*, **107**, 5776 (1985).

(211) T.C. Bruice, C.M. Dicken, P.N. Balasubramanian, T.C. Woon, and F.L. Lu, *J. Am. Chem. Soc.*, **109**, 3436 (1987).

(212) K.A. Jorgensen, *J. Am. Chem. Soc.*, **109**, 698 (1987).

(213) K.B. Sharpless, A.Y. Teranishi, and J.E. Backvall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).

(214) J.T. Groves and Y. Watanabe, *J. Am. Chem. Soc.*, **108**, 507 (1986).

(215) T.G. Traylor, T. Nakano, A.R. Miksztal, and B.E. Dunlop, *J. Am. Chem. Soc.*, **109**, 3625, (1987).

(216) T.G. Traylor and A.R. Miksztal, *J. Am. Chem. Soc.*, **109**, 2770 (1987).

(217) D. Ostovic and T.C. Bruice, *J. Am. Chem. Soc.*, **110**, 6906 (1988).