Biommetic Oxidations by Synthetic Metallo-porphyrins.

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Cytochrome P-450 is the general term of a large class of monooxygenases, widely present in nature. Its prosthetic group is Fe(III)-protoporphyrin IX, in which a thiolate group of a cysteine occupies one of the axial coordination sites of the metal. These enzymes exploit molecular oxygen as the oxidant, by introducing one oxygen atom into the substrate while the second oxygen atom is eliminated as water. The activation of molecular oxygen occurs via one electron reduction of the metal through electron transfer chain starting from NADPH.

A first approach to build up a simpler and equally efficient "artificial oxidant" involved the use of a series of single oxygen donors (PhIO, $NaIO_4$, H_2O_2, organic peracids, etc..) instead of the reductive dioxygen activation. Oxidations occur via Fe(IV) oxene porphyrinato cation radical, which is the reactive species.

A further important step has been the use of Fe(III) and Mn(III) complexes of synthetic tetraaryl porphyrins, which are capable of catalyzing mono-oxygenation reactions in a similar way. Although an ideal model would associate to the metalloporphyrin a thiolate group as axial ligand, the latter can be effectively substituted by heterocyclic nitrogen bases. Both the porphyrin ring and the axial ligand undergo oxidative demolition under the reaction conditions, and this degradation is particularly evident with poorly reactive substrates.

The chemical stability of metallo-porphyrins can be noticeably improved by introducing sterically hindering and/or electron withdrawing substituents both in the meso-phenyl rings and in the pyrrolic moieties of tetraaryl porphyrins. Several difficulties arise in the reductive dioxygen activation with Fe(III) and Mn(III)-porphyrins, and in the direct use of O_2 in the presence of Ru-porphyrins.

On the contrary by using simple and inexpensive oxidants, such as $HOCl/ClO^-$ and 30%-H_2O_2 under aqueous-organic two-phase conditions at 0°C, alkene epoxidations and/or alkane hydroxylations can be easily obtained.

When the NaOCl aqueous phase is at pH 9.5-10.5 a phase transfer (PT) catalyst is not required. The addition of small amounts of lipophilic heterocyclic nitrogen bases as axial ligands (L) increase the oxidation rates. Optimum amounts of ligand depend on the porphyrin, the pH of the aqueous medium and the presence of a PT catalyst. In the epoxidation of reactive alkenes catalysed by chemically robust porphyrins in the absence of L, several thousands of turnovers (up to 100,000) can be obtained.

Lipophilic carboxylic acids and heterocyclic bases strongly enhance oxidations promoted by 30%-H_2O_2. Alkene epoxidations and alkane hydroxylations are completed in a few minutes at 0°C, at initial rates up to 125 turnovers/min.

Highly structured porphyrins bearing heterocyclic bases or carboxylic groups covalently attached by a flexible chain have been synthetized. These catalysts are often very efficient, and their robustness towards the oxidants is increased by introducing chlorine atoms in the o-o'-positions of meso-aryl groups. Several recent reports on asymmetric oxygenations catalyzed by metallo-porphyrins will be also discussed.

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- Porphinoids, e.g. the red pigment of blood and the green pigments of plants, are essential catalysts in all spheres of life.

- Their deep colour indicates the existence of low energy electronically excited states, hence their easy involvement in redox reactions.

- Porphinoids, and the related corrinoids, firmly complex transition metal ions.

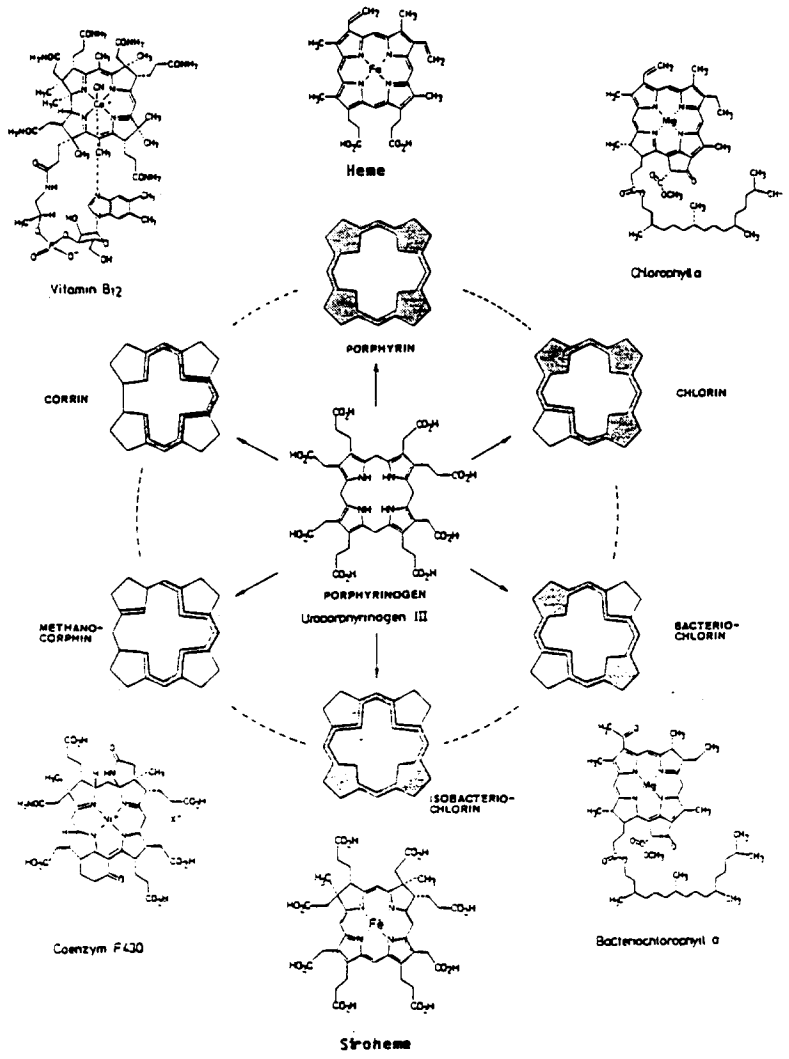
- In a circular and planar array, 4 nitrogen atoms surround a coordination hole with a diameter of ca. 4Å.

Heme: Fe-porphyrinate

Chlorophyll a: Mg-chlorinate

Coenzym F-430: Ni-corphinate

Vitamin B-12: Co-corrinate.



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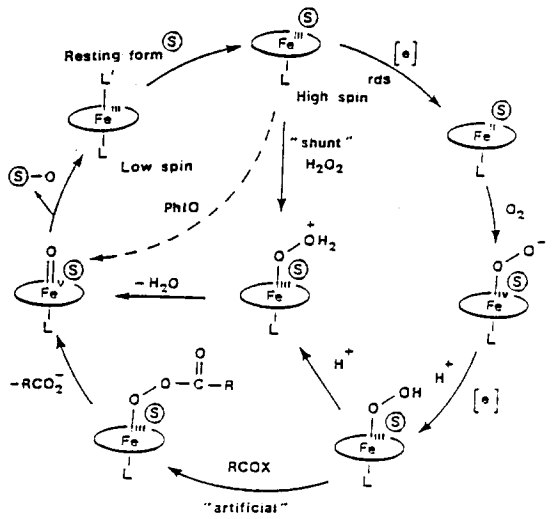
These enzymes eploit molecular oxygen as the oxidant, by introducing one oxygen atom into the substrate while the second oxygen atom is eliminated as water.

$$RH + O_2 + 2e^- + 2H^+ \xrightarrow{\text{P-450}} ROH + H_2O$$

DIOXYGEN ACTIVATION

(catalytic cycle of Cytochrome P-450)



The activation of molecular oxygen occurs via one electron reduction of the metal through electron transfer chain starting from NADPH.

When oxygen-donors are used the reaction follows the so called "shunt pathway".

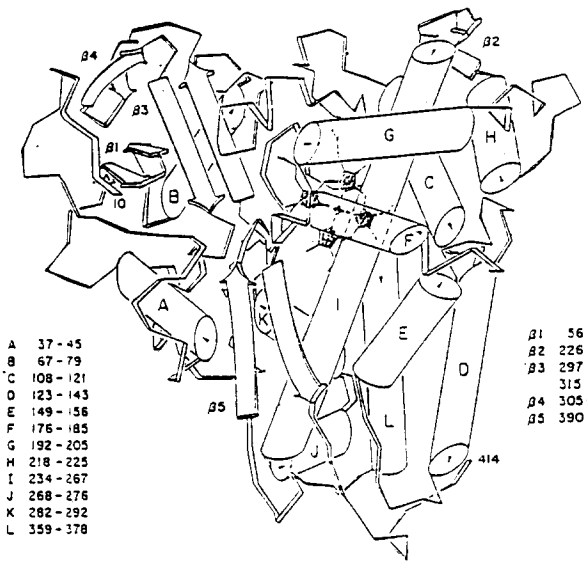
The most plausible structure of the active intermediate, porphyrinato iron (V) oxene 1, was first suggested by Groves (1979).

1 2

Spectroscopic measurements strongly suggest that the cation radical 2 of porphyrinato Fe(IV) oxene is the most dominant limiting structure.

STRUCTURE OF CYTOCHROME P-450

from "Pseudomonas Putida" (T.L. Poulos, 1985)

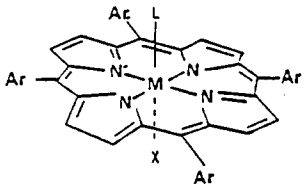


A	37 - 45
B	67 - 79
C	108 - 121
D	123 - 143
E	149 - 156
F	176 - 185
G	192 - 205
H	218 - 225
I	234 - 267
J	268 - 276
K	282 - 292
L	359 - 378

β1	56 - 62
β2	226 - 233
β3	297 - 301
	315 - 320
β4	305 - 312
β5	390 - 400

Artificial oxidant: Single oxygen donors (PhIO: Ullrich, 1976; Groves, 1979) instead of the reductive dioxygen activation.

Artificial catalysts: a) metal complexes (M = Mn, Fe, etc..) of synthetic tetraaryl porphyrins (Tabushi, Groves, et al., since 1979).
b) Heterocyclic nitrogen bases as axial ligands (L) (imidazoles, pyridines).
c) Single oxygen donors.

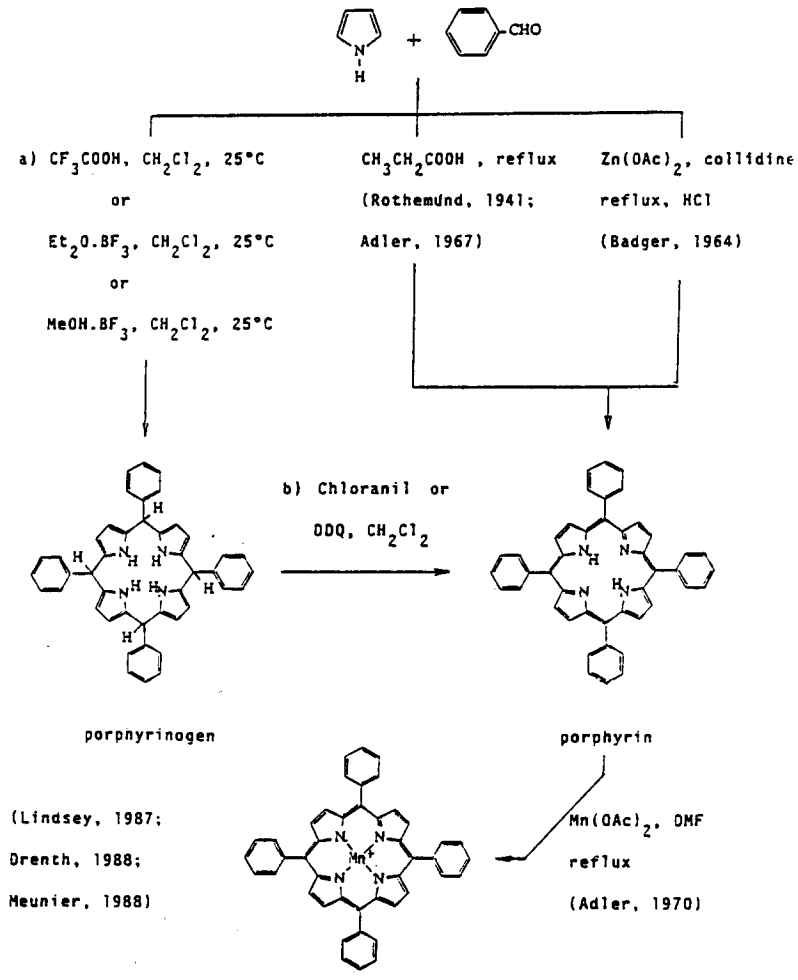


OXIDANTS: C_6H_5IO, C_6F_5IO, ROOH, $KHSO_5$, RCO_3H, $NaClO_2$, etc...

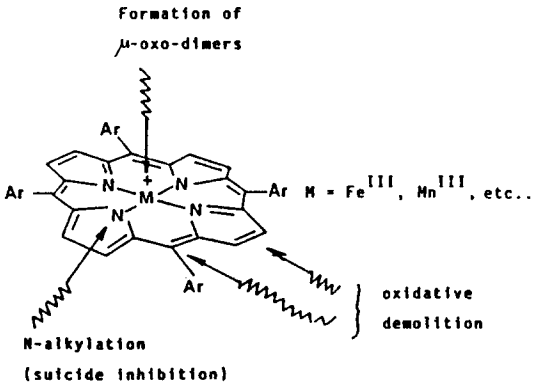
$O_2 + 2e^-$, O_2, $ClO^-/HOCl$, H_2O_2

Problems to be solved in order to obtain effective synthetic models of cytochrome P-450:

1) Synthesis
2) Chemical stability
3) Catalytic efficiency



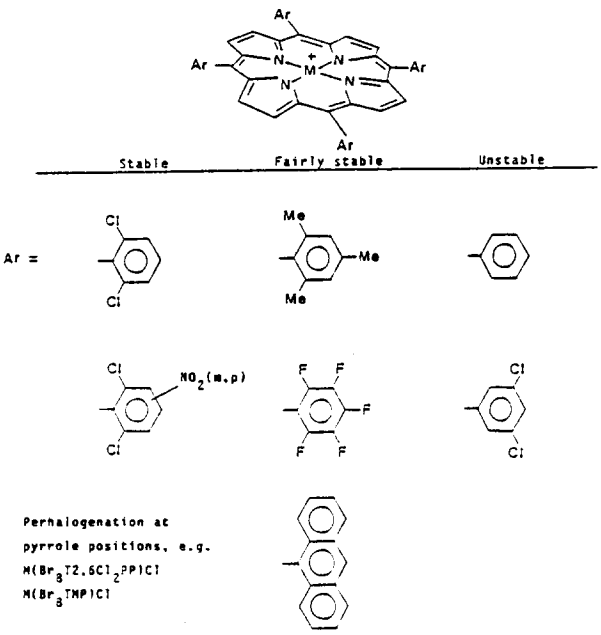
Porphyrin deactivation



STABILITY OF METALLO-PORPHYRINS

1) Intrinsic structural factors
2) Complexed metal
3) Oxygen donor
4) Reactivity of substrate
5) Oxygen donor/substrate ratio

STABILITY OF METALLO-PORPHYRINS (INFLUENCE OF SUBSTITUENTS)

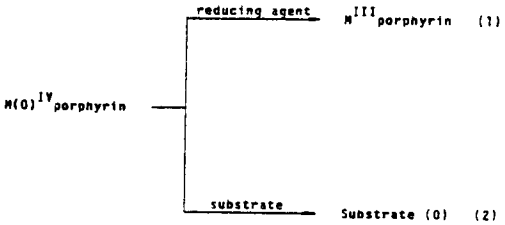


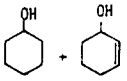
Highly reactive substrates and a high molar excess of substrate with respect to the oxidant strongly favour the porphyrin survival.

REDUCTIVE DIOXYGEN ACTIVATION

Fe(III) and Mn(III) synthetic tetraarylporphyrins catalyze the transfer of one oxygen atom from O_2 to hydrocarbons in the presence of reducing agents.

Catalytic efficiency and yields often very low due to the lack of separation between the active-oxygen species and the reducing agent.



1  Mn^{III}-TPP, $NaBH_4$ / O_2, C_6H_6-EtOH →  4:1 Tabushi, 1979 ≈2c/h

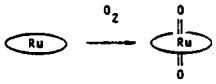
2 " Mn^{III}-TPP, $Bu_4N^+BH_4^-$ / O_2, CH_2Cl_2 → " Pereé-Fauvet, 1981 1.6 c/min

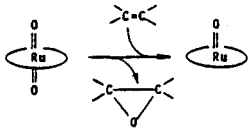
3  Mn^{III}-TPP, N-Me-IM / O_2, H_2, Pt-coll., EtOH →  Tabushi, 1984 0.6-3.0 c/h

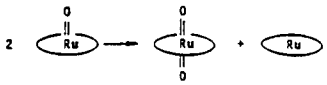
4  Fe^{III}-TPP, Ac_2O, Zn/Hg / O_2, MeCN →  Shilov, 1987 2.2 c/min

5  Mn^{III}-TPP, N-Me-IM / O_2, Zn, AcOH →  (50% su Zn) Mansuy, 1987 2.5 c/min

$Ru(O_2)$-TETRAARYLPORPHYRIN

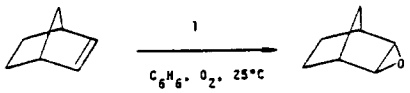




2 

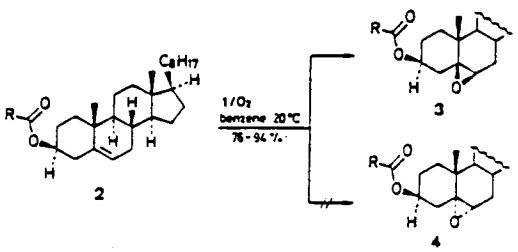
Catalytic aerobic epoxidation is eventually terminated by the formation of a Ru(II)(CO)porphyrin. The source of the carbonyl ligand is the substrate.

(Groves 1984, 1989).



45 turnovers/d

Groves (1985)



5h-7d : 72-94%

Marchon (1988)

1 = Ru(TMP)(O_2)

$(CH_3)_3C\text{-}H + O_2 \xrightarrow[80°C,\ 7\ bar]{Fe(TF_5PP)X} (CH_3)_3\text{-}OH$ 90% select.

2000 turn. in 6 h

$CH_3CH_2CH_3 + O_2 \xrightarrow[125°C,\ 70\ bar]{Fe(TF_5PP)X,\ benzene} CH_3\text{-}\underset{OH}{CH}\text{-}CH_3 + CH_3COCH_3$

0.8 : 1

870 turn. in 3 h

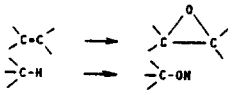
Lyons (1989).

C_6H_5IO

(Ullrich, 1976;
Groves, 1979)

Drawbacks

Fe(III) and Mn(III)porphyrins - expensive



- polymeric, almost insoluble in most organic solvents

Ar-H ⟶ Ar-OH - no kinetic measurement

C_6F_5IO

(Traylor, 1985)

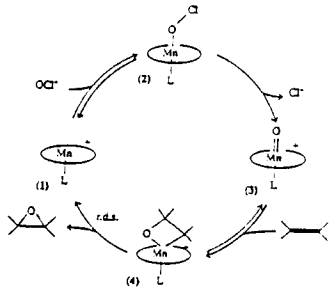
Drawbacks

- Soluble under certain conditions
- Very efficient oxidant
- In alkene epoxidations up to 10,000 turnovers, with initial rate as high as 300 turn./sec.

- highly expensive
- highly unstable (can explode).

Alkene epoxidations promoted by ClO^-/HOCl under two-phase conditions

- Tabushi (1979): NaOCl, H_2O-CH_2Cl_2, Q^+X^-
- Meunier (1982): NaOCl, H_2O-CH_2Cl_2, Q^+X^-
  heterocyclic base as axial ligand
- Montanari (1985): NaOCl at pH 9.5-10.5 (HOCl as oxidant)
  H_2O-CH_2Cl_2 without Q^+X^-
  lipophilic heterocyclic base as axial ligand



Collman, Meunier (1984)

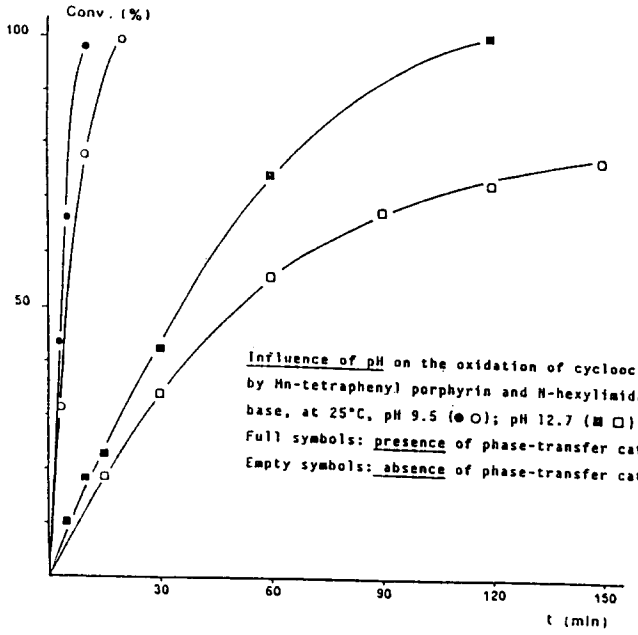
INFLUENCE OF pH AND OF PHASE-TRANSFER CATALYST (Q^+X^-)

Epoxidation rates progressively increase by lowering the pH of the aqueous NaOCl solution from 12.7 to 9.5

pH	oxidant in the organic phase	
	Q^+X^-	—
12.7	ClO^-	—
10.5	ClO^- + HOCl	HOCl
9.5	ClO^- + HOCl	HOCl

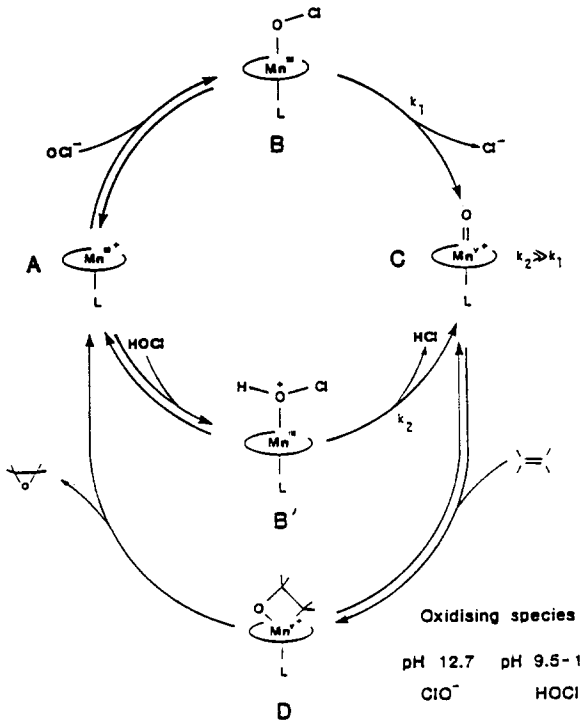
HOCl is a very weak acid (pK_a = 7.54).

- Reaction rates follow a Michaelis-Menten kinetic equation.
- The r.d.t. of the catalytic cycle is the decomposition of the metal-oxene/olefin adduct (often reported as a metalla-oxetane).

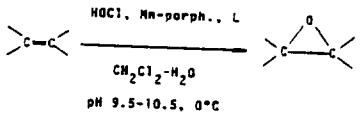


Influence of pH on the oxidation of cyclooctene, catalyzed by Mn-tetraphenyl porphyrin and N-hexylimidazole as extra base, at 25°C, pH 9.5 (● ○); pH 12.7 (■ □).
Full symbols: presence of phase-transfer catalyst.
Empty symbols: absence of phase-transfer catalyst.

MECHANISM of ALKENE EPOXIDATIONS by ClO^- and HOCl

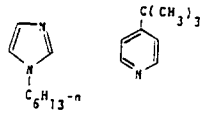


OPTIMUM CONDITIONS FOR ALKENE EPOXIDATIONS PROMOTED BY HOCl



Mn-porph.: L : alkene : HOCl
1 : 0-25 : 200 : 700

Lipophilic axial ligand (L) =



Mono- and bis-coordination constants can be obtained by spectrophotometric measurements.

$$L + P \underset{}{\overset{K_1}{\rightleftharpoons}} PL \qquad (1)$$

$$PL + L \underset{}{\overset{K_2}{\rightleftharpoons}} PL_2 \qquad (2)$$

$$K_1 \cdot K_2 = \beta_2 \qquad (3)$$

$$[PL] = \frac{K_1[L][P_o]}{1 + K_1[L] + \beta_2[L]^2} \qquad (4)$$

$$P_o = P + PL + PL_2$$

- P(L) is by far the most active species.
- The optimum L_o/P_o ratios which afford the maximum initial concentration of P(L) can be calculated from equation (4).

For Mn(T2,6Cl$_2$PP)Cl and N-hexylimidazole:

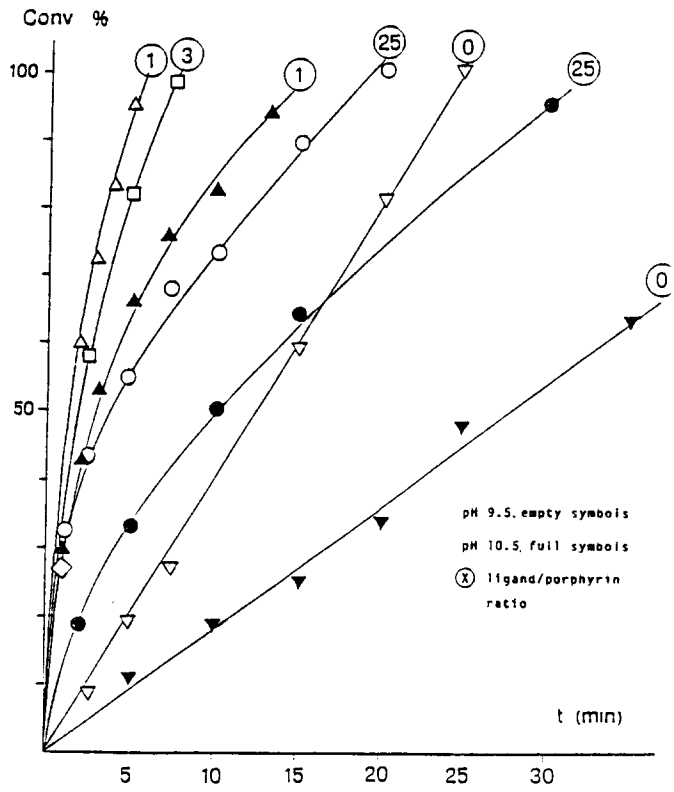
$K_1 = 2000\ (M^{-1})$, $\beta_2 = 2.5 \times 10^6\ (M^{-2})$. Optimum calcd. $L_o/P_o = 1.5$

When the affinity between Mn-oxene and alkene is low (as for 1-dodecene) an excess of ligand is necessary in order to balance its decomposition in the course of reaction.
The same occurs when K_1 and β_2 values are low (as for Mn(TMP)Cl).

At pH >12, a phase-transfer catalyst Q^+X^- is required.
Scarcely solvated and highly reactive anions (ClO^-, Cl^-, OH^-) are transferred by Q^+ into the organic phase.
They displace the heterocyclic ligand (L), so that very high amounts of L are required to avoid the decrease of P(L) concentration.

Influence of L/P ratio on HOCl cyclooctene epoxidation.

Mn(T2,6Cl$_2$PP)Cl; N-hexyl imidazole; 0°C.



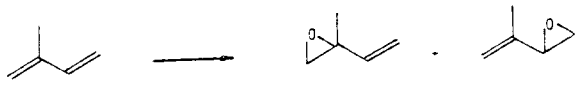
With reactive substrates (e.g. cyclooctene) epoxidations can be carried out at pH 9.5-10.5 (HOCl as oxidant) in the absence of both L and Q^+X^-.
Rates are relatively low, but more than 100,000 turnovers can be realized in 24 h at r.t. without appreciable lost of the porphyrin.

(100)

α-pinene

(100)

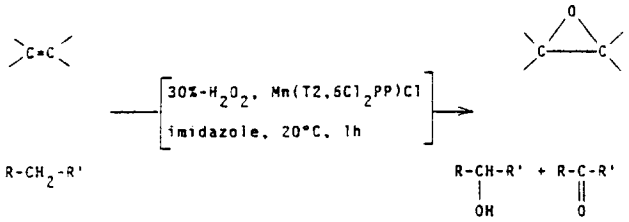
camphene



isoprene (94) (6)

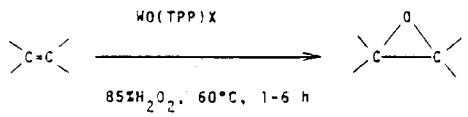
H_2O_2-HYDROCARBON OXYGENATIONS

First reports: Mansuy (1985, 1986)



Drawback: huge amounts of imidazole (up to 60% mol. equiv. with respect to the substrate).

Other reports: Degussa (1989)



H_2O_2 AS SINGLE OXYGEN ATOM DONOR

Very high active oxygen content

readily available

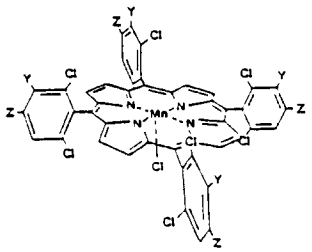
cheap

H_2O as the secondary product

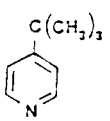
OUR INVESTIGATIONS

Essential requirements are:

- Chemically robust porphyrin (P), e.g.: 1, 2, 3
- Lipophilic carboxylic acid (A), e.g. PhCOOH
- Lipophilic axial ligand (L), e.g. 4, 5



		Y	Z
1	Mn(T2,6Cl$_2$PP)Cl	H	H
2	Mn(T2,6Cl$_2$3NO$_2$PP)Cl	NO_2	H
3	Mn(T2,6Cl$_2$4NO$_2$PP)Cl	H	NO_2



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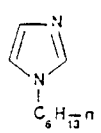

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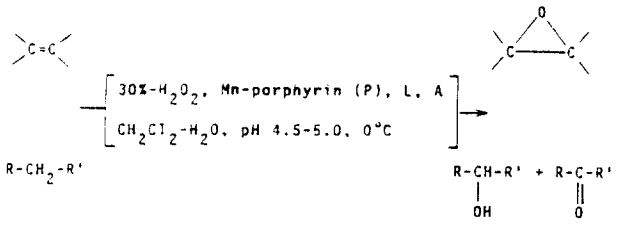


P : L : A : substrate : 30%-H_2O_2 =

1 : 1-2: 5-20 : 200-2000 : 400-4000

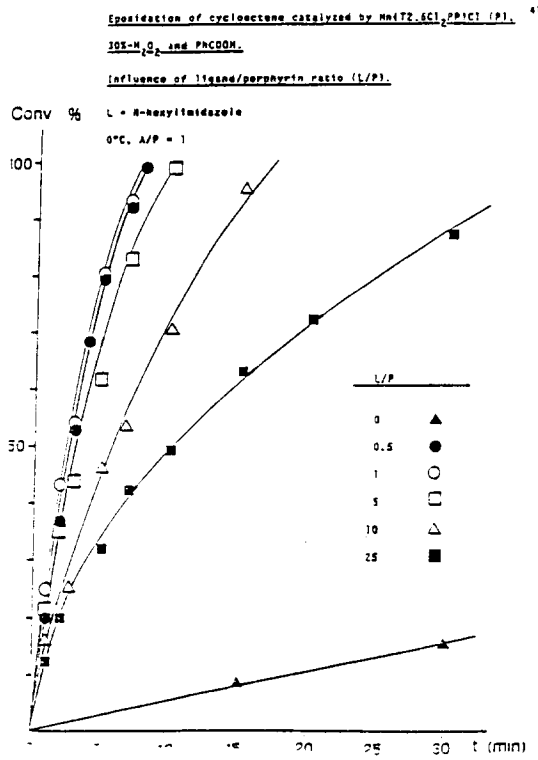
For both alkenes and alkanes:

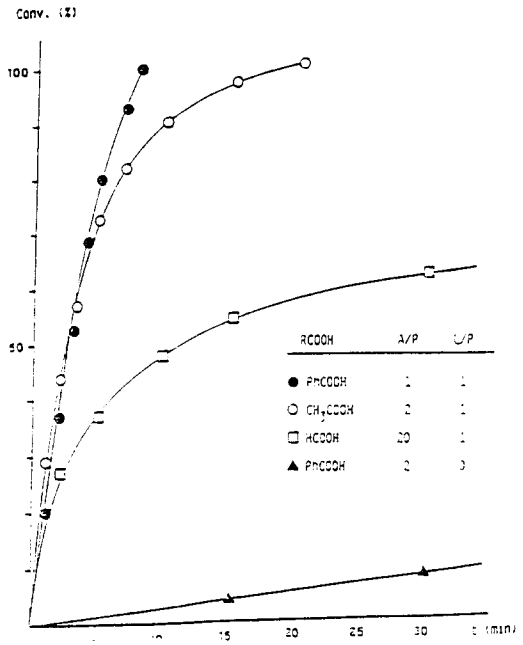
Reaction time: 10-20 min

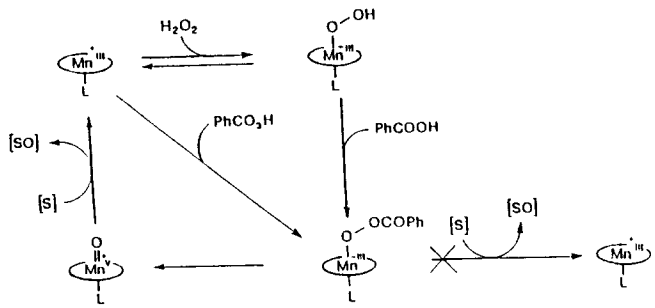
Conversion : up to 100%

Rate (turnovers/min, at 3 min): up to 125

Total turnovers: up to 800.







REACTION MECHANISM

Reaction rates follow a Michaelis-Menten Kinetic equation.

Acylperoxy intermediates cannot be the oxidising species in the catalytic cycle. Indeed, (+) camphoric acid and (+) camphorcarboxylic acid afford racemic epoxides from prochiral alkenes.

Optically active epoxides are obtained with the corresponding optically active peroxy-acids alone.

TURNOVER RATES[a] IN ALKANE OXYGENATIONS CATALYZED BY Mn-PORPHYRINS

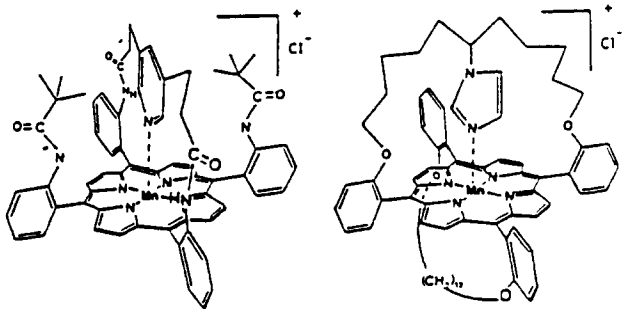
Substrate	30% H_2O_2[b] L-A (our results)	30% H_2O_2[c] $L\text{-}Q^+X^-$ (Mansuy)	$KHSO_5$[c] $L\text{-}Q^+X^-$ (Meunier)	$NaClO_2$[c] $L\text{-}Q^+X^-$ (Collman)	LiOCl[c] $L\text{-}Q^+X^-$ (Meunier)	Mg-monoperoxy-phthalate[c] (Ricci)
adamantane	96 (26)	0.6	3.3	-	-	80
cyclooctane	125 (35)	0.3	-	-	-	-
cyclohexane	50 (9)	0.3	1.3	18	0.04	-

[a] Moles of reacted substrate/moles of catalyst (initial rates).

[b] At 0°C. In parenthesis final rates.

[c] At room temperature.

STRUCTURED PORPHYRINS



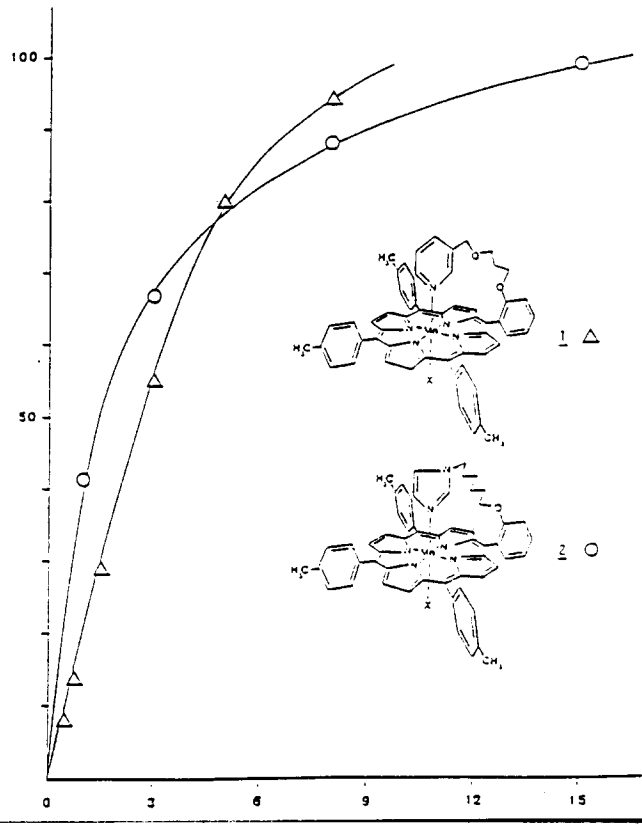
Efficient catalysts in epoxidations promoted by $NaOCl/Q^+X^-$.

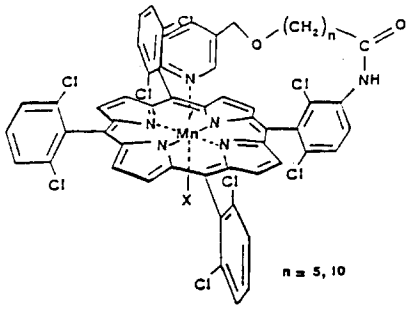
Momenteau, Meunier (1988).

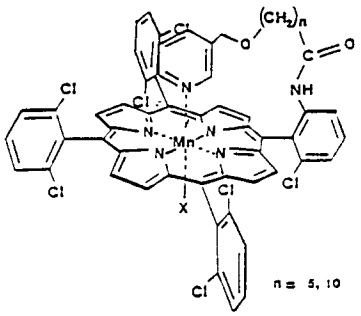
If the imidazole or pyridine axial ligand is connected to the porphyrin through a flexible chain the very high complexation constants between these ligands and Mn(III)tetraarylporphyrins would allow the spontaneous coordination to the metal.

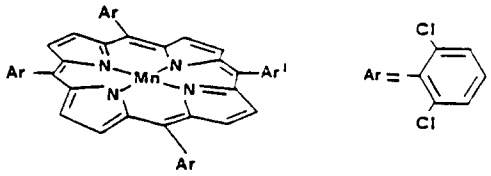
EPOXIDATION OF CYCLOOCTENE catalyzed by "tailed" porphyrins

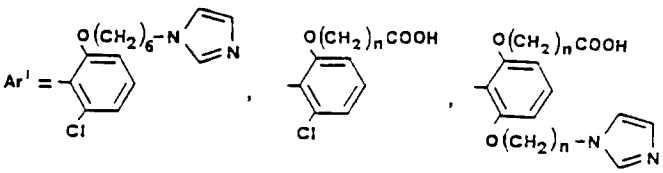
NaOCl, pH 9.5, 0°C









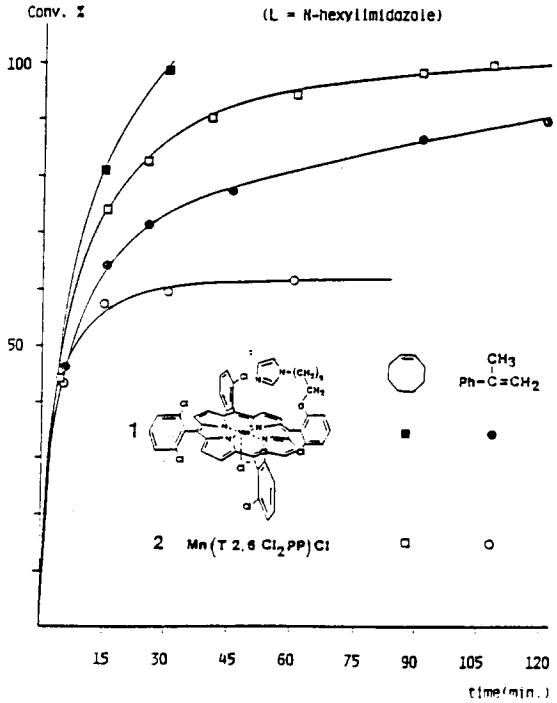


1 2 3

Epoxydations with 30% H_2O_2 at 0°C in CH_2Cl_2-H_2O, catalyzed by Mn-porphyrins 1 and 2.

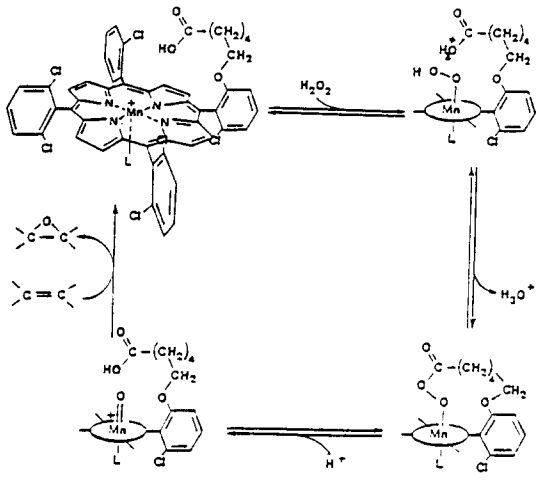
1: PhCOOH: olefin: H_2O_2 = 1:8:1000:2000

2:L:PhCOOH:olefin: H_2O_2 = 1:1:8:1000:2000



Activation of H_2O_2

Covalently anchored carboxylic acids



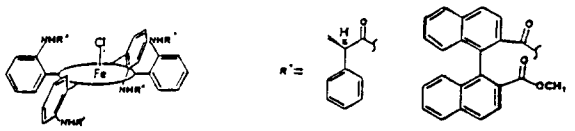
L = N-hexylimidazole

Epoxidation of cyclooctene: 1000 turnovers (45 min., 0°C)

Hydroxylation of cyclooctane: 150 turnovers (45 min., 0°C)

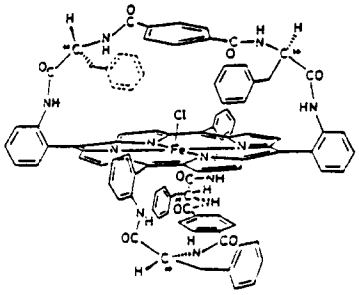
CHIRAL PORPHYRINS

(catalysts for asymmetric epoxidations)



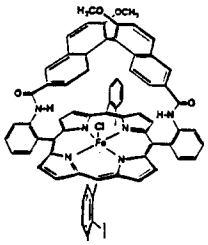
Groves (1983)

e.e. up to 48%.



Mansuy (1985)

e.e. up to 50%.

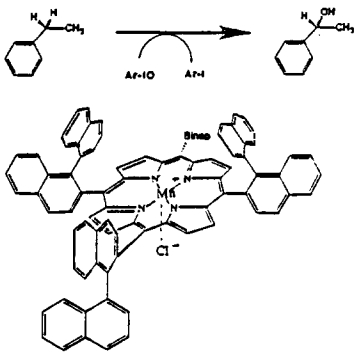


Groves (1990

e.e.

epoxidations : up to 72%

hydroxylations: up to 68%



Kodadek (1989)

e.e. up to 40% in olefin epoxidation

CONCLUSIONS

- Chemically robust metallo-porphyrins are synthetized in satisfactory yields.

- When heterocyclic bases are required as axial ligands, their oxidative demolition is a limiting factor.

O_2 reductive activation. Recent important results have been achieved, however, strong limitations are due to the lack of separation between the oxidant and the reducing agent.

HOCl/ClO^-. Chemically robust metallo-porphyrins are capable of several thousands turnovers (up to 100,000) in the epoxidation of "reactive" alkenes carried out in the absence of axial ligands.

30%-H_2O_2. Highly activated by the synergistic effect of lipophilic carboxylic acids and heterocyclic bases (up to 800 turnovers, initial rates 125 turnovers/min., at 0°C).

- Structured porphyrins in which a axial ligand or a carboxylic acid is connected to a chemically robust porphyrin moiety by a single flexible chain are very effective catalysts in oxygenation reactions promoted by HOCl and/or 30%-H_2O_2.
  More complex structures are less suitable for practical applications.