Biomimetic catalysts for selective oxidation in organic chemistry

D. MANSUY

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, URA 400 CNRS, Université René Descartes, 45 rue des Saints Pères, 75270 Paris Cédex 06, France.

__Abstract__: Major advances have been made towards efficient catalytically active model systems for cytochrome P-450 during these last ten years. Some recent developments of this field are described . This include (i) examples of application of these biomimetic systems to compounds of biological interest, (ii) the use of Mn-porphyrins to catalyze the transfer of a nitrogen atom into organic substrates, and (iii) the preparation and catalytic properties of metalloporphyrins supported on mineral matrices.

INTRODUCTION

The finding of efficient catalysts for the selective insertion of one oxygen atom from oxygen donors like alkylhydroperoxides, hydrogen peroxide or dioxygen itself into various organic molecules (eq.1), under mild conditions, remains a difficult challenge in organic chemistry. This is particularly true if one thinks to the hydroxylation of inert C-H bonds of alkanes or to the selective hydroxylation of aromatic compounds.

$$RH + AO \xrightarrow{\text{Catalyst}} ROH + A \qquad (\text{eq. 1})$$
$$(AO = ROOH, H_2O_2 \text{ or } O_2)$$
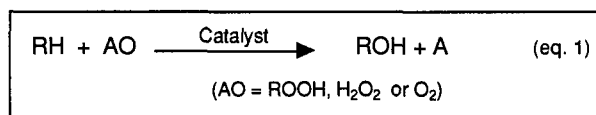
A possible approach in this field is to mimic biological systems. Enzymes called monooxygenases are able to catalyze such monooxygenation reactions under very mild conditions. Many of these monooxygenases are using an hemeprotein called cytochrome P-450. These cytochromes are ubiquitous in living organisms and have been found to play at least two key roles. First, they catalyze many oxidation steps involved in the biosynthesis or biodegradation of endogenous substrates such as steroid hormones, fatty acids or prostaglandins. Second, they play a central role in the oxidative metabolism of exogenous compounds such as drugs or other environmental products, allowing their elimination out from living organisms.[1]

Synthetic models for these cytochromes P-450 should have at least three main interests : (i) for the catalysis of selective oxidations in organic synthesis, (ii) for the prediction of the oxidative metabolism of drugs, agrochemicals or other xenobiotics and (iii) for the preparation of large amounts of hydroxylated metabolites of drugs or of other compounds of biological interest.

The research of synthetic catalysts which could act as models for cytochromes P-450 has attracted the interest of many groups during this last decade (for recent reviews on this subject, see references 2-7).In fact, most efforts have been devoted to the construction of homogeneous catalysts based on metalloporphyrins. Thus, the first part of this paper will consist in a brief overview illustrating the main steps that have led to the development of new efficient homogeneous catalysts as models of cytochrome P-450. Examples of the application of these systems for the oxidation of compounds of biological interest will also be given. In a second part, it will be shown that very similar metalloporphyrin catalysts can be used not only for the transfer of oxygen atoms but also for the selective transfer of nitrogen atoms into substrates. Finally, in the last part, recent results towards the development of more practical model catalysts supported on inorganic matrices will be described.

I – THE DEVELOPMENT OF VERY EFFICIENT OXIDATION CATALYSTS BY MIMICKING CYTOCHROME P-450

Under physiological conditions, cytochromes P-450 catalyze the monooxygenation of a wide range of substrates by using dioxygen and a reducing agent (NADPH or NADH). The corresponding long catalytic cycle is very schematically depicted in Fig.1. It involves the reduction of its resting ferric state to the ferrous state, the binding of O_2 to the Fe(II) state, the one-electron reduction of the Fe(II)-O_2 intermediate and the formation of the so-called active oxygen complex which is believed to be a high-valent iron-oxo complex.[1] This iron-oxo complex, formally Fe(V)=O, is able to deliver its oxygen atom into many substrates and achieves the hydroxylation of alkanes, the epoxidation of alkenes and of aromatic rings, the S-oxidation of thioethers and the N-oxidation of amines. The
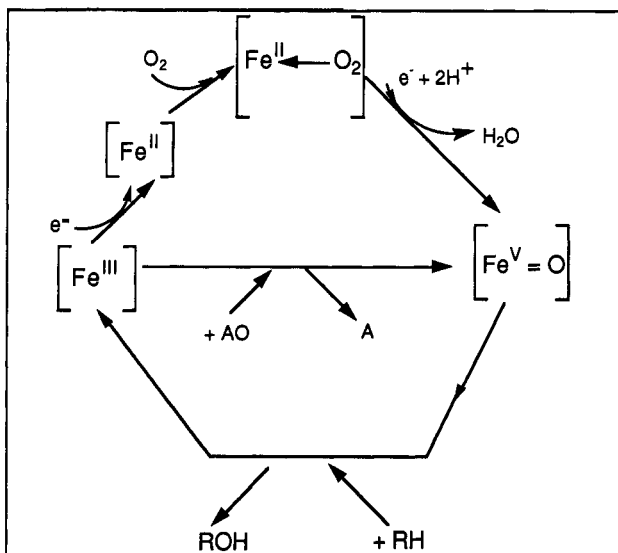
Fig. 1 : Catalytic cycles of cytochrome P-450 using either
$O_2+ 2e^-+ 2H^+$ or an oxygen atom donor AO

long catalytic cycle, which is the only one found *in vivo,* is, a priori, very difficult to mimic by using simple metalloporphyrin catalysts. However, it has long been recognized that cytochromes P-450 may perform similar oxidations by using single oxygen atom donors such as peracids, hydroperoxides or iodosylarenes, instead of O_2 and NADPH. This shortened catalytic cycle should be easier to mimic. In fact, it is clear that the difficulty to construct a catalytically active model system for cytochrome P-450 will be critically dependent upon the oxygen atom donor that will be used.

The objective of this paper is not to give a complete review of the model systems described so far in the literature, but simply to illustrate with some examples the development of this field during these last ten years. One may distinguish four main steps. The first one was the discovery, mainly thanks to the pioneer work of J.T. Groves et al.,[8] that a simple system involving iodosylbenzene as an oxygen atom donor and Fe(TPP=tetraphenylporphyrin)Cl as a catalyst was able to perform all the reactions catalyzed by cytochrome P-450 with very similar characteristics at least from a qualitative point of view (eq.2) :
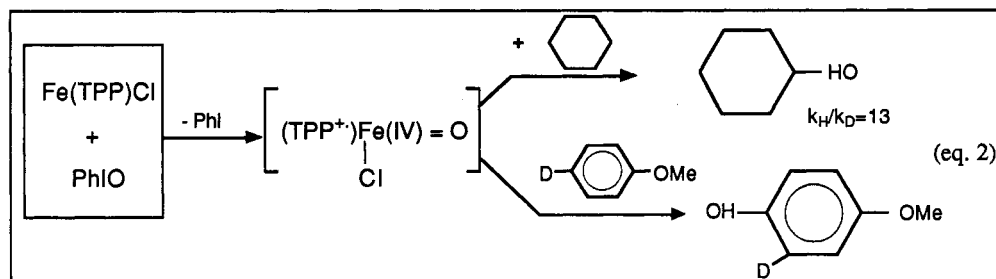
Unfortunately, simple iron-tetraarylporphyrins like Fe(TPP)Cl are too rapidly oxidatively destroyed during the reactions so that it is difficult to use them for preparative chemistry. Thus, in a second main step towards efficient models, major improvements of the catalytic activities were obtained by using Fe(III) or Mn(III) complexes of polyhalogenated tetraarylporphyrins like TDCPP = tetra-2,6-dichlorophenylporphyrin[9] (Fig.2). For instance, Fe(TDCPP)Cl catalyzes alkene epoxidation by C_6F_5IO with initial rates as high as 300 turnovers per second[10], and more than 100,000 turnovers can be achieved without appreciable destruction of this catalyst. More recently, even more robust polyhalogenated Mn(III)- and Fe(III)-porphyrins, like Fe[tetrakis-2,6-dichlorophenyl) octabromoporphyrin]Cl, have been prepared and used as very efficient catalysts for hydrocarbon oxidation.[11]

The objective of the third main step in the development of efficient model catalysts was to use oxidants simpler and more readily available than iodosylarenes. Systems based on Mn-porphyrins and ClO^- or $KHSO_5$ have been found useful for hydrocarbon oxidations,[2] whereas systems using alkylhydroperoxides ROOH and Fe- or Mn-porphyrins were reported to involve, at least in part, oxidizing species such as $ROO \cdot$ and $RO \cdot$ and to give results different from those obtained with PhIO and the same catalysts.[12] Hydrogen peroxide is a particularly interesting oxygen atom donor as it is very much readily available and gives water as a reaction product. A very efficient system using H_2O_2 diluted in H_2O and catalytic amounts of the robust Mn(TDCPP)Cl catalyst was recently described to reproduce most cytochrome P-450 reactions.[13] This system requires the presence of a catalytic amount of imidazole which was shown to act both as a ligand of Mn and as a base catalyst. It involves a Mn(V)=O active species and achieves the epoxidation of alkenes,[13,14] the hydroxylation of alkanes[13,15] and the hydroxylation of aromatic compounds like anisole or naphtalene. Some examples are given in Fig.3 to show that this system is able to convert alkenes, with almost quantitative formation of epoxides in a stereospecific manner, and alkanes with formation of the corresponding alcohols and ketones in good yields.
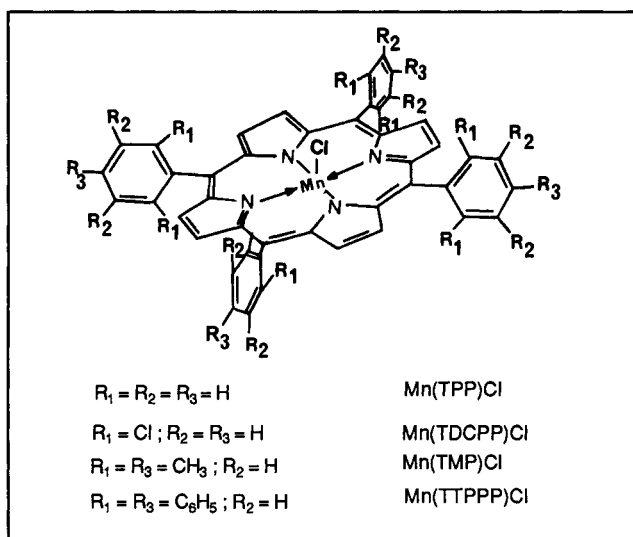
R₁ = R₂ = R₃ = H   Mn(TPP)Cl

R₁ = Cl ; R₂ = R₃ = H   Mn(TDCPP)Cl

R₁ = R₃ = CH₃ ; R₂ = H   Mn(TMP)Cl

R₁ = R₃ = C₆H₅ ; R₂ = H   Mn(TTPPP)Cl

Fig. 2 : Formula of some Mn(meso-tetraarylporphyrin)Cl catalysts
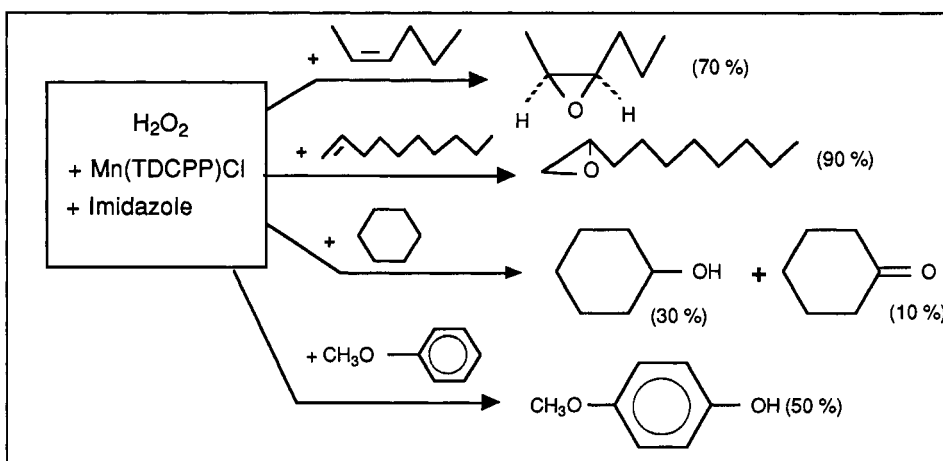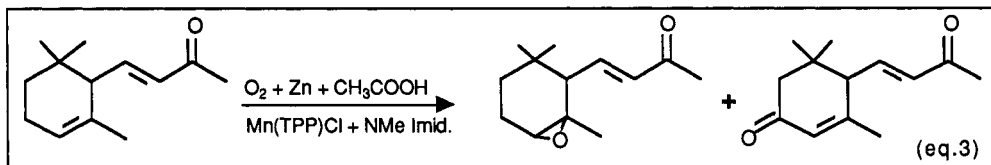used in model systems

Fig. 3 : Examples of oxidations by the H_2O_2-Mn(TDCPP)Cl-imidazole system
(yields based on the starting compound)

Finally, a fourth step in the development of good models for cytochrome P-450 concerns systems using O_2 itself as oxygen atom donor as in the physiologically relevant long catalytic cycle of cytochrome P-450. In this case, a reducing agent must be used. Several model systems using O_2 and various reducing agents in the presence of Mn(III)porphyrins as catalysts have been described in the literature these last ten years.[16] Most of them have relatively low rates and yields based on the reducing agent. More recently, three systems were reported to give at the same time rates (up to 9 turnovers per min) and yields based on the reducing agent (up to 60%) that are not too far from those observed with cytochromes P-4540. Examples of reactions performed by one of these systems, using Zn powder as a reducing agent, CH₃COOH as a proton source, and catalytic amounts of Mn(TPP)Cl and N-methyl-imidazole, are shown in Fig.4.[17]

These successive improvements have led to systems already efficient enough to be used for the preparation of oxidized metabolites of compounds of biological interest like drugs. For instance, the treatment of α–ionone (at the gram level) by the Zn-O_2-Mn(TPP)Cl-N-methyl imidazole system for two hours at room temperature led, after a single column chromatography to remove the Mn-porphyrin catalyst, to the cis and trans epoxides derived from the oxidation of the trisubstituted double bond and to an allylic ketone with yields based on starting α-ionone of 75% and 18% respectively (eq.3).
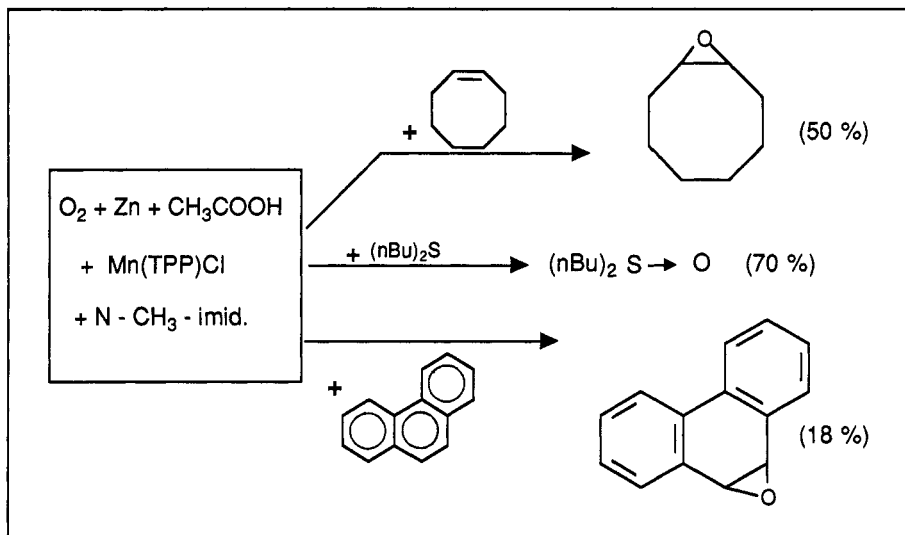

(eq.3)

Fig. 4 : Examples of oxidations performed by the O_2-Zn-CH_3COOH-Mn(TPP)Cl-N-CH_3-
imidazole system (yields based on starting reducing agent)

A second example to illustrate the use of these model systems for studying drug oxidations concerns tienilic acid, a diuretic and uricosuric drug, the main metabolite of which in humans is 5-hydroxytienilic acid. Very recently, it was found that the C_6F_5IO-Mn(TDCPP)Cl system was able to reproduce this hydroxylation of the thiophene ring of tienilic acid in a highly regioselective manner (eq.4).[7] It is noteworthy that another product formed by this system, the diacid derived from an oxidative cleavage of the thiophene-CO carbon-carbon bond, was also found as a cytochrome P-450-dependent metabolite *in vivo* and *in vitro*.
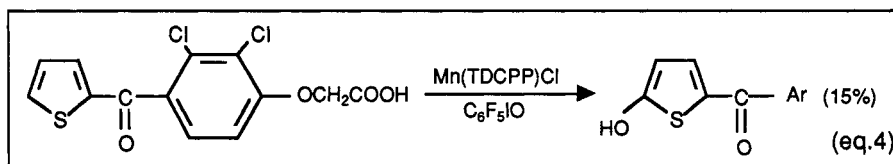
This example shows once more that these model systems reproduce quite well cytochrome P-450 reactions.

II – SELECTIVE TRANSFER OF NITROGEN ATOMS INTO HYDROCARBONS CATALYZED BY METALLOPORPHYRINS

Iron(III) and manganese(III) porphyrins have also been found to catalyze the transfer of the N-tosyl group from PhI=N-tosyl, a nitrogen analog of PhIO, into hydrocarbons.[18-23] In fact, Fe(III)(TDCPP)ClO4 appeared as a catalyst of choice for the N-tosylaziridination of alkenes by PhNTs in a stereospecific manner (Fig.5).[21] On the contrary, Mn(TDCPP)ClO4 appeared as a better catalyst for the insertion of the N-tosyl group of PhINTs into inert C-H bonds of alkanes or into allylic C-H bonds of alkenes (Fig.5).[22]

It seems very likely that the active species involved in these N-tosyl transfers is a high-valent metal=N-tosyl complex, a nitrogen equivalent of the high-valent metal=O complexes which are now well recognized as active species in hydrocarbon monooxygenation by PhIO catalyzed by Fe- or Mn-porphyrins. As the N-tosyl ligand is much more bulky than the oxo ligand, one should expect that the functionalisation of a C-H bond by PhINTs would be more dependent on steric hindrance than its functionalisation by PhIO. In that context, we have recently studied the regioselectivity of the N-tosylamination of heptane by PhINTs in the presence of various Mn(III)-tetraarylporphyrins containing more or less bulky substituents on ortho and ortho'positions of their meso-aryl groups (Fig. 6).[23] Already with the not hindered Mn(III)(TPP), the relative ratio of N-tosylamides coming from functionalisation at position 1,2,3 and 4 of heptane was 13:52:18:17. This ratio is very different from that which was reported for the hydroxylation of heptane by PhIO in the presence of the same Mn-porphyrin (2:38:40:20). Functionalisation of more accessible positions 1 and 2 is much more favored with PhINTs than with PhIO. The relative importance of the N-tosylamination of the much less reactive methyl groups of heptane again increased if one used more hindered Mn-porphyrins like Mn(TDCPP) or Mn(TMP=tetramesitylporphyrin). With Mn(TMP)(CF3SO3), the primary N-tosylamide became the major regioisomer (48%). This regioselectivity in favor of the terminal position is remarkable as it is better than that reported for the hydroxylation of heptane by PhIO catalyzed by the very bulky Mn[tetra-(2,4,6-triphenyl)phenylporphyrin].[24] In fact, this regioselectivity in favor of primary C-H bonds is the best one reported so far for alkane functionalisation catalyzed by metalloporphyrins.[23] This result shows that, by a proper choice of the shape of the group to be transfered and of the nature of the porphyrin ring, it should be possible to control the regioselectivity of the functionalisation of substrates catalyzed by metalloporphyrins.
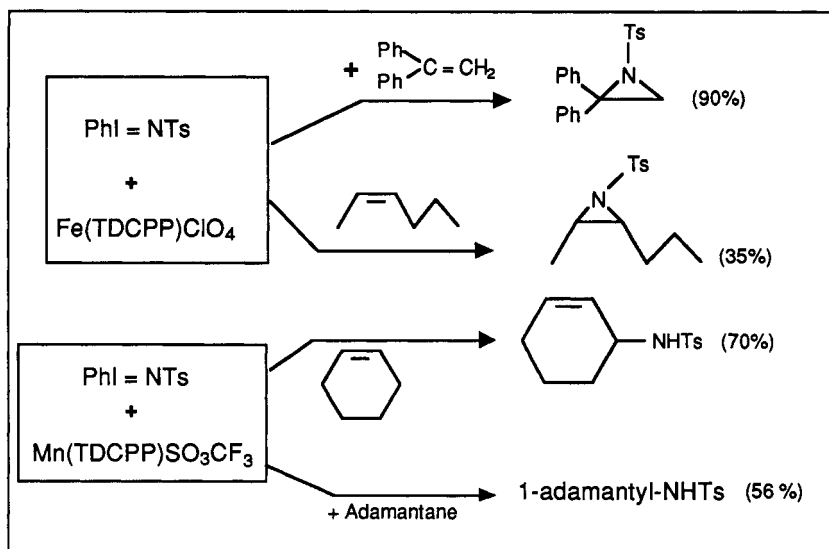
Fig. 5 : Examples of aziridination of alkenes and amination of C-H bonds
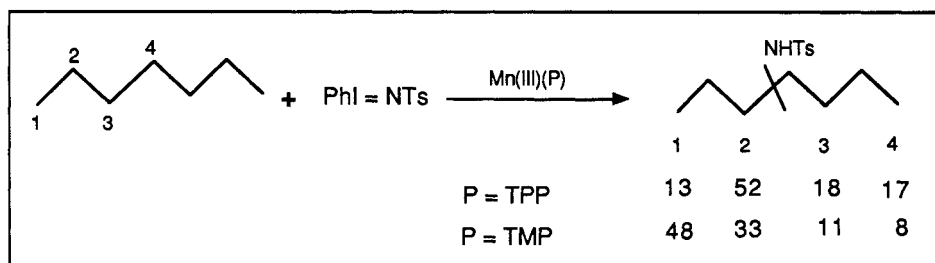by PhINTs catalyzed by metalloporphyrins

Fig. 6 : Regioselectivity of the N-tosylamination of heptane
by PhINTs catalyzed by Mn(III)-porphyrins

III – TOWARDS MORE PRACTICAL CATALYSTS: BIOMIMETIC OXIDATION CATALYSTS SUPPORTED ON INORGANIC MATRICES

The preparation of supported metalloporphyrin catalysts appears as an important step towards efficient biomimetic oxidation systems, for at least two main reasons. First, they should be more practical for preparative applications, the metalloporphyrin being easily recovered at the end of the reactions by simple filtration. Second, the environment of the metalloporphyrin provided by the polymeric support could lead to substrate or product selectivity. The following results illustrate some potential interests of such supported catalysts.

Mineral supports were selected because of their inertness in strongly oxidizing media. The tetracationic Mn-porphyrin, Mn(TMPyP=tetra-4 N-methylpyridiniumyl porphyrin)Cl5, was found to bind very strongly to silica by adsorption. This binding was strong enough for that stirring of a suspension of the supported Mn-porphyrin in CH_2Cl_2 or CH_3CN, which are usual solvents for oxidations catalyzed by soluble Mn-porphyrins, failed to lead to any release of the porphyrin even after several days.[25] Reaction of cyclooctene with PhIO in CH_2Cl_2 and in the presence of a suspension of the supported Mn-porphyrin catalyst led to an almost quantitative yield of cyclooctene epoxide in less than 1 h at 20°C (Fig.7). More than 100,000 turnovers could be obtained under these conditions without appreciable degradation of the catalyst which could be recovered at the end of the reaction by simple filtration.[25] This supported catalyst was also used to convert 1 g of α-ionone into the corresponding epoxide (cis + trans) (0.8g) and allylic ketone (0.2g) with high yields and under very simple and mild conditions (2h at 20°C, filtration to recover the intact catalyst and a simple column chromatography). It appeared to be of special interest for the hydroxylation of linear alkanes.[25] When compared to homogeneous catalysts like Mn(TPP)Cl, Mn(TMPyP)Cl5 and even Mn(TDCPP)Cl, one of the best known homogeneous catalysts for such reactions, the supported catalyst exhibited two major advantages. First it led to better yields for the oxidation of heptane and much better yields for the oxidation of pentane. Second, it led to much higher alcohol : ketone ratios. Thus, it appeared as a catalyst especially good for the oxidation of relatively short and unreactive alkanes to the corresponding alcohols.

Although the origin of this particular property of the supported Mn-porphyrin remains to be determined, the aforementioned results indicate that the presence of a support may improve the catalytic properties of a metalloporphyrin.
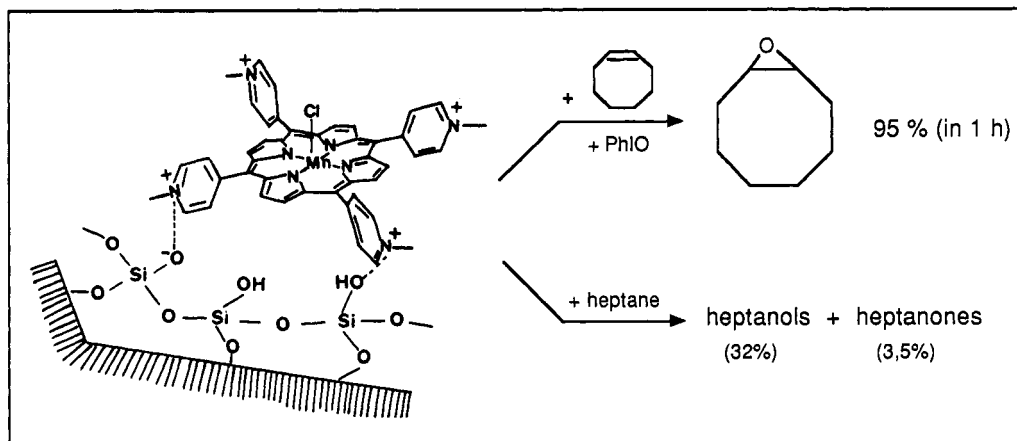
Fig. 7 : Oxidations catalyzed by a tetracationic Mn-porphyrin supported on silica

Biomimetic systems based on robust polyhalogenated Mn- or Fe-porphyrins are now available for efficient epoxidations of alkenes and hydroxylations of alkanes and aromatic rings by H_2O_2 or O_2 itself. They can be used already for preparative oxidations of some subtrates and appear particularly useful for the preparation of oxidized metabolites of drugs or other xenobiotics. Similar catalysts can be used for the aziridination of alkenes or N-tosylamination of alkanes by PhINTs. Particular regioselectivities in favor of ω-oxidation of linear alkanes have been obtained. Finally, more practical catalysts can be prepared by binding the metalloporphyrin on an inert support. Cationic Mn-porphyrins strongly bound to silica have been found to be particularly active for the hydroxylation of linear alkanes thanks to a support effect of unknown origin so far. Such supported metalloporphyrins appear as new powerful catalysts for controlled oxidations in organic chemistry.

REFERENCES

1   P.R. Ortiz de Montellano "Cytochrome P-450 : structure, mechanism and biochemistry", Plenum Press, New York (1986).
2   B. Meunier, Bull. Soc. Chim. Fr., **4**, 578 (1986).
3   T.J. McMurry, J.T. Groves "Cytochrome P-450 : structure, mechanism and biochemistry" (P.R. Ortiz de Montellano, ed.) p.1, Plenum Press, New York. (1986).
4   T.C. Bruice, Ann. NY Acad. Sci. **471**, 83, (1987).
5   D. Mansuy, Pure Appl. Chem. **59**, 759 (1987).
6   D. Mansuy , P. Battioni, "Frontiers of biotransformation" (K. Ruckpaul et H. Rein, ed.) p. 66 Akademie-Verlag, Berlin (1989).
7   D. Mansuy, P. Battioni, J.P. Battioni, Eur. J. Biochem. **184**, 267 (1989).
8   J.T. Groves, T.E. Nemo, R.S. Meyers, J. Am. Chem. Soc. **101**, 1032 (1979).
9   P.S. Traylor, D. Dolphin, T.G. Traylor, J. Chem. Soc., Chem. Commun. 279 (1984).
10   T.G. Traylor, J.C. Masters, T. Nakano, B.E. Dunlap, J. Am. Chem. Soc. **107**, 5537 (1985).
11   T.G. Traylor, S. Tshuchiya, Inorg. Chem. **26**, 1338 (1987).
12   D. Mansuy, J.F. Bartoli, M. Momenteau, Tetrahedron Lett. **23**, 2781 (1982).
13   P. Battioni, J.P. Renaud, J.F. Bartoli, M. Reina-Artiles, M. Fort, D. Mansuy, J. Am. Chem. Soc. **110**, 8462 (1988).
14   J.P. Renaud, P. Battioni, J.F. Bartoli, D. Mansuy, J. Chem. Soc., Chem. Commun. 888(1985).
15   P. Battioni, J.P. Renaud, J.F. Bartoli, D. Mansuy, J. Chem. Soc., Chem. Commun. 341 (1986).
16   I. Tabushi, Coord. Chem. Rev. **86**, 1 (1988).
17   P. Battioni, J.F. Bartoli, P. Leduc, M. Fontecave, D. Mansuy, J. Chem. Soc., Chem. Commun. 791 (1987).
18   R. Breslow, S.H. Gellman, J. Chem. Soc.,Chem. Commun. 1400, (1982).
19   R. Breslow, S.H. Gellman, J. Am. Chem. Soc. **105**, 6728 (1983).
20   D. Mansuy, J.P. Mahy, A. Duréault, G. Bedi, P. Battioni, J. Chem. Soc., Chem. Commun. 1161 (1984).
21   J.P. Mahy, G. Bedi, P. Battioni, D. Mansuy, J. Chem. Soc. Perkin Trans II, 1517 (1988).
22   J.P. Mahy, G. Bedi, P. Battioni, D. Mansuy, Tetrahedron Lett. **29**, 1927 (1988).
23   J.P. Mahy, G. Bedi, P. Battioni, D. Mansuy, New J. Chem. **13**, 651 (1989).
24   B.R. Cook, T.J. Reinert, K. Suslick, J. Am. Chem. Soc. **108**, 7281 (1986).
25   P. Battioni, J.P. Lallier, L. Barloy, D. Mansuy, J. Chem. Soc. Chem. Commun. 1149 (1989).