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State of the art in the development of biomimetic oxidation catalysts

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Abstract

Work during the last decade laid down the basis for biomimetic oxidation catalysis, which has become an established technique. Preliminary work relied on the use of metal complexes of 5,10,15,20-tetrakisphenylporphyrin (TPP), but these proved to be inadequate to perform the catalytic function. Further, derivatives of TPP with suitable and adequately positioned substituents, allowed the preparation of high performance catalysts, in terms of catalytic efficiency and stability, for some selected oxidations under specific reaction conditions and for a diversity of oxygen donors. The first oxidations were achieved using the 'special' oxygen donor iodosylbenzene, but cheaper and generally available oxidants such as sodium hypochlorite or hydrogen peroxide are presently used as the oxidants. Catalysts capable of promoting stereoselective catalysis are reported. Conditions for the efficient use of the catalysts so far reported require particular specificities and the catalytic activity is only shown, in the majority of the reported works, in the presence of selected species to act as axial ligands to the metal ion of the catalyst. Specific porphyrin structures were reported where the addition of a specific axial ligand can be avoided.

Keywords: Porphyrin; Oxidation; Synthesis; Hydrogen peroxide; Hypochlorite; Ligand; Metalloporphyrin; Chiral porphyrins; Epoxidation; Hydroxylation

1. Introduction

For more than a decade much effort has been put into the study and development of an efficient model of systems mimicking the activity of cytochrome P-450. A diversity of metalloporphyrins, mainly iron and manganese, in appropriate systems, proved to be able to catalyse oxidation reactions with monooxygen donors like iodosylbenzene [1–8], sodium hypochlorite [9–17] hydroperoxides [18–21], hydrogen peroxide [22–25], potassium monopersulphate [26,27], peroxyacids [28–31], amine N-oxides [32], magnesium monoperoxyphthalate [33,34], tetra-butyl ammonium periodate [35] or even with oxygen [36–42], usually requiring in this case the presence of a reducing agent ($NaBH_4$, $H_2 + Pt$, ascorbate, Zn) The majority of the studies have been addressed to the oxidation of hydrocarbons [43], oxidation of amines [44–46] and also reactions of olefins with diazoesters [47,48], N-demethylation of secondary aromatic amines [49,50], oxidation of sulfoxides [23] and oxidative chlorination [51].

The purpose of this paper is not to review the field of oxidation reactions catalysed by metalloporphyrins because this has been covered by other authors [43,52–60] [61–63], but we intend

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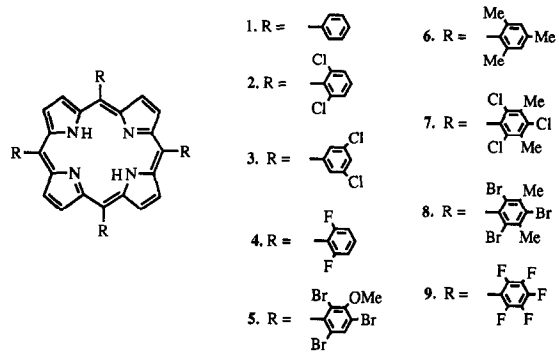
to concentrate on the role of the structure of the porphyrin and of the axial ligand on the stability, selectivity and activity of this type of catalyst.

In the natural cytochrome P-450 systems the porphyrin ligand is protoporphyrin-IX and a thiolate residue of cysteine is the axial ligand [64,65] whereas imidazole of histidine residue is the ligand in haem proteins, such as haemoglobin [66] and cytochrome-*c* peroxidase [67].

In the artificial catalytic processes where metal complexes of 5,10,15,20-tetrakisphenylporphyrin-**1** are the usual porphyrin ligand, the importance of the fifth axial ligand was identified since the original work published by Groves [1] in 1979 and Meunier [68] in 1980, aimed to achieve hydrocarbon oxidation reactions catalysed by metalloporphyrins. These first artificial catalysts had relatively low activity and poor stability. It immediately became clear that TPP-**1**, the macrocycle used in the first artificial catalyst had to be replaced. TPP derivatives, however, remained the selected basic structures in the development of synthetic oxidation catalysts in the extensive work performed in the last decade, which is reported in a large number of publications. Highly significant advances were obtained, but the development of new metalloporphyrins which are both efficient and stable catalysts is still a challenging objective.



Scheme 1.

2. Effect of the porphyrin structure on the stability of the catalyst

5,10,15,20-Tetrakisphenylporphyrin, TPP-**1**, was the most easily available porphyrin due to the simplicity of the Rothemund synthesis and the subsequent improvements to this synthetic method [69]. This fact allied with the first catalytic studies with TPP metal complexes, made TPP and its derivatives the metalloporphyrins of choice for oxidation metalloporphyrin catalysis. The preliminary works concerning these oxidation reactions used the iron and manganese complexes of **1** and iodosylbenzene [1] or hypochlorite [68] as single oxygen atom donors, respectively. It was clearly demonstrated the potential of artificial metalloporphyrin oxidation catalysts and also that those metalloporphyrins were only able to oxidise the substrate in the presence of a fifth axial ligand such as imidazole or pyridine. They were poorly efficient catalysts which were easily oxidised in the reaction medium. Those catalysts were called by Meunier [59] 'first generation catalysts'. Studies to overcome the low activity and poor stability of the 'first generation catalysts' led to the discovery that the presence of two chlorine atoms in the 2,6 positions of the *meso* phenyl groups of TPP-**1**, originated catalysts showing far higher activity and stability. However, the required 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin, **2**, was not as easy to synthesize as TPP-**1**, and the interest raised in the synthesis of this and other potentially useful porphyrins (Scheme 1) led to the development of new improvements to the Rothemund synthesis by several different research groups [70–74].

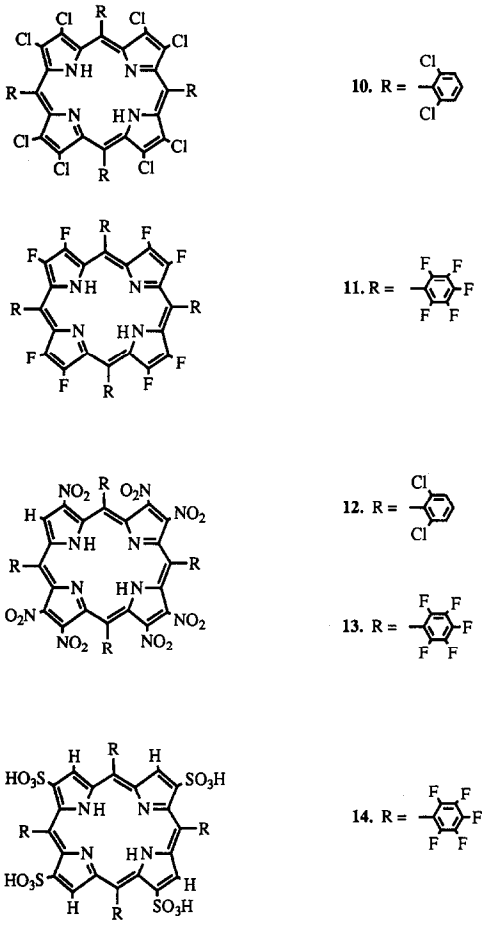
The manganese or iron complex of **2** is able to catalyse the epoxidation of several olefins [75–77] by H_2O_2 or NaOCl [77,78] as oxygen donors. In these oxidations, after complete conversion of the substrate, the residual porphyrin is present in an amount higher than 95%. The beneficial effect of the two chlorine atoms in the phenyl 2,6 positions was demonstrated in further studies [78,79]. Pereira [79] observed

that replacing the chlorine atoms by fluorine as in 5,10,15,20-tetrakis(2,6-difluorophenyl)porphyrin complex Mn-**4**, the epoxidation by H_2O_2 was still efficient but the catalyst showed a very poor stability. Only 15% of residual Mn-**4** was present at the end of the reaction. In this study the substrate/oxidant ratio was 1:3, which is quite unfavourable for the stability of the catalyst compared to that in previously reported studies where the substrate was present in large excess. A comparison of the catalytic activity of Mn-**5** and Mn-**2** under similar conditions shows that Mn-**2** is able to promote 100% conversion of *cis*-cyclooctene in 10 min, whereas Mn-**5** gave only 52% of conversion [80] after 60 min. Other authors have observed that the presence of the two bulky bromine atoms in the 2,6-positions makes the epoxidation reaction very slow [81] and interpreted this as a consequence of a sterically difficult approach between the substrate and the active centre. In a similar reaction performed with a catalyst where electron-withdrawing groups were replaced by bulky and electron donating methyl groups in the 2,6 positions of the phenyl ring, Mn-**6**, Montanari [82] observed that the epoxidation of *cis*-cyclooctene was efficient, but that after one hour 50% of metalloporphyrin had been destroyed.

In a study of the stability of Mn-**2**, -**3**, -**6**, -**7** and -**8** where NaOCl was the oxidant in a reaction medium of pH 10.5 and pyridine derivatives were the axial ligands, Montanari [82] observed that after one hour the amount of residual porphyrin was 100, 74, 80, 100 and 100%, respectively. Thus, it was proved that in this system the presence of electronegative bulky groups namely chlorine or bromine atoms in the 2,6 positions has the advantage of conferring high stability to the catalyst. All the preceding results have contributed to establishing the metal complexes of TDCPP-**2** or its derivatives as the best choice of catalyst for epoxidation [77,78]. Following his previously proposed designation of TPP-**1** complexes as first generation catalysts, Meunier [59] designated the metal complexes of TDCPP-**2** as 'second generation catalysts'.

As illustrated in the preceding examples the presence of electron-withdrawing groups in the 2,6-positions has a remarkable effect on the stability of the catalysts. Recently Su [83] has demonstrated that the manganese complex of the water-soluble 5,10,15,20-tetrakis(*N*-methyl-2-pyridyl)porphyrin is able to catalyse electrolytically the allylic oxidation of olefins at pH 5.5 buffer solution, without any destruction of the metalloporphyrin. By contrast the manganese complexes of 5,10,15,20-tetrakis(*N*-methyl-4-pyridyl)porphyrin or 5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin are unstable at pH less than 9.

The effect of the presence of halogen atoms attached to tetrapyrrolic macrocycle to stabilise and activate the metalloporphyrins as catalysts in oxidation reactions prompted several authors to synthesize β-substituted porphyrins [27,84–106] such as those presented in Scheme 2. In several publications it was suggested that the new β-octa-halogenated porphyrins were much more active as catalysts and significantly more resistant to oxidative degradation [84,85,88] than their β-unsubstituted analogous. This was consistent with the expectation that the presence of electronegative substituents should increase significantly the oxidation potential of the porphyrin macrocycle. However, Johnstone [93] observed early that the manganese complex of β-(8Cl)-TDCPP-**10**, was in fact less stable than the corresponding Mn-**2**. The apparently high stability of Mn-**10** firstly claimed was mainly due to the fact that the previously reported experiments were performed in the presence of a large excess of substrate [84]. When the molar ratio H_2O_2/substrate is 3:1, the catalyst Mn-**10** is inactivated and precipitates out of the reaction medium as a black material [93]. This material is still a macrocycle having a Soret band at 448 nm, has one less chlorine atom and an extra oxygen relatively to the original catalyst, and shows a broad carbonyl band in the infrared. Further studies by the same research group [78]



Scheme 2.

compared the chemoselectivity and stability, in epoxidation of olefins, between Mn-**2** and the corresponding Mn-**10**, in NaOCl oxidations performed at pH 10.5. It was shown that the epoxidation catalysed by Mn-**2** was more selective and the catalyst was 98% recovered in the end of the reaction, whereas Mn-**10** was converted into the inactive species with the main absorption peak at 448 nm. Montanari [77] has disclosed similar observations and conclusions.

Electrochemical [107] and theoretical [108–111] studies were performed contributing for a better understanding of the catalytic behaviour of β-perhalogenated metalloporphyrins and to help in the design of new improved catalysts. Recent studies by Ghosh [112–114] using density functional theory (DFT) give a different interpretation of the behaviour of β-octachloro and β-octabromo substituted porphyrins than the one given by the Hartree–Fock [108,109] approach. β-Chlorinated and β-brominated porphyrins are estimated to have first ionisation potentials (IP) which are not much different from those of the corresponding non-β-halogenated compounds in agreement with the electrochemical measurements. In this manner, the DFT results confirm what was suggested by the catalytic studies [77,78]. β-Octachloro or β-octabromo derivatives do not correspond to an appropriate design for high potential porphyrin ligands.

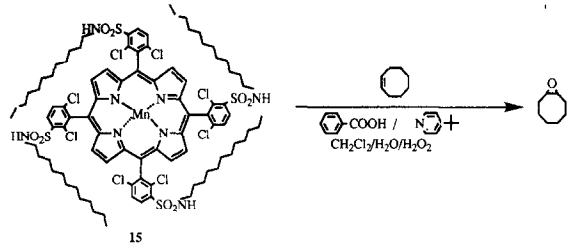
Contrary to brominated or chlorinated porphyrins, β-fluorinated porphyrins are subjected to electronic withdrawing effect without being affected by stereochemical crowding. Through DFT calculations it is estimated that substituting all the 28 peripheral hydrogens by fluorine should increase the IP by 1.65 eV. In a surprisingly unique experimental result reported by Seno [115], it is described that the Fe-**11** complex is a remarkably stable and efficient catalyst for hydrocarbon oxygenation, namely hydroxylation of benzene and epoxidation of *cis*-cyclooctene, when H_2O_2 was used as the oxygen donor. Studies with fluorinated compounds have been scarce, certainly due to difficulties in the synthesis of such compounds. The *meso*-perfluoroalkylporphyrin recently synthesized [116] is a structure incorporating strongly electron withdrawing *meso*-substituents. It was designed to mimic the action of cytochrome P-450.

The iron and manganese complexes of β-polynitroderivatives, **12** and **13**, recently prepared by Lyons [162] and Mansuy [117] by nitration of the original porphyrin with fuming nitric acid, and by Gonsalves [118] using acetic anhydride/zinc nitrate as the nitration reagent, proved to be able to catalyse the hydroxylation of alkanes and the epoxidation of alkenes without significant destruction of the catalyst. These experimental results confirm the expected high value of the ionisation potential and an efficient

protection of the nitrated porphyrin derivatives against oxidative degradation [114].

An interesting result was obtained with the iron complex of β-sulphonato-5,10,15,20-tetrakis(pentafluorophenyl)porphyrin, **14**, which was obtained via sulphonation of **9** with oleum [119,120]. The iron complex of this porphyrin is able to catalyse the selective oxidation of 1,2-dimethoxyarenes with electron withdrawing groups such as $-COCH_3$ and $-COCHCH_3Ph$ to muconic diesters, and 1,2-dimethoxyarenes with electron donating groups like $-CH_2OH$ and tBu–, to *p*-quinone using magnesium monoperoxyphthalate (MMMP) as oxidant without too significant degradation, even after more than 100 turnovers, Scheme 3.

Chlorosulphonation of both the *meso*-phenyls and of the β-pyrrolic positions of porphyrins proved to be easily performed in a sequential way and opened the possibility to synthesize several macrocycle ligands, namely derivatives of **2** having a diversity of sulphonamide groups [121,122]. The stability of the manganese complexes of these porphyrins to the oxidation reaction conditions was shown to be very sensitive to the size of the side chain of the sulphonamide group [123]. In the case of H_2O_2 epoxidation of *cis*-cyclooctene in a two phase system, and with metalloporphyrins having sulphonamide with linear 12 carbon atom side chains, the stability

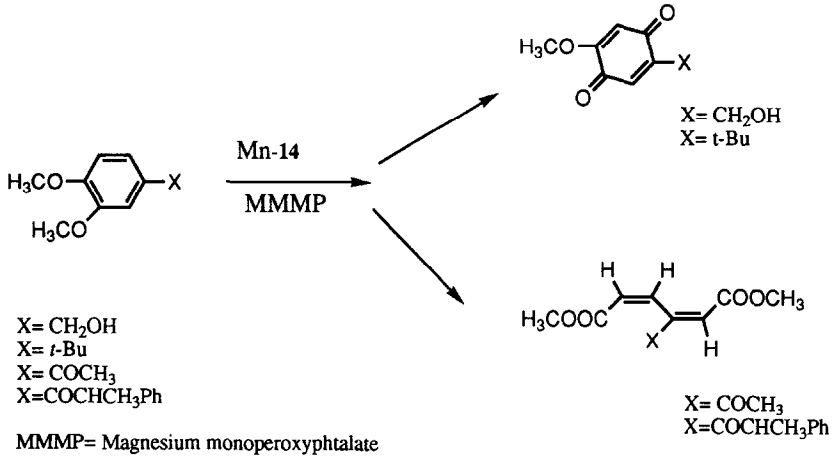


15

Scheme 4.

of the catalyst is high and is likely to be due to a formation of a hydrophobic 'pocket' in which the metalloporphyrin **15** is protected from oxidation, Scheme 4.

An attempted approach to reduce the metalloporphyrin degradation is to immobilise the catalyst by attachment to an organic or inorganic polymer. This strategy can avoid μ-oxo dimer formation and the approach between the active species and the macrocycle of another molecule [124]. More than an advantage to the stability of the catalyst, the attachment to the polymer would easily permit to recover the catalyst from the products at the end of the reaction and allow for its subsequent recycling. Several methods have been employed to attach the catalyst to solids, including ionic [125–128] or covalent binding of the porphyrins to the support [129], intercalation of the porphyrin between the layers or in the pores of a solid matrix [130] and also axial



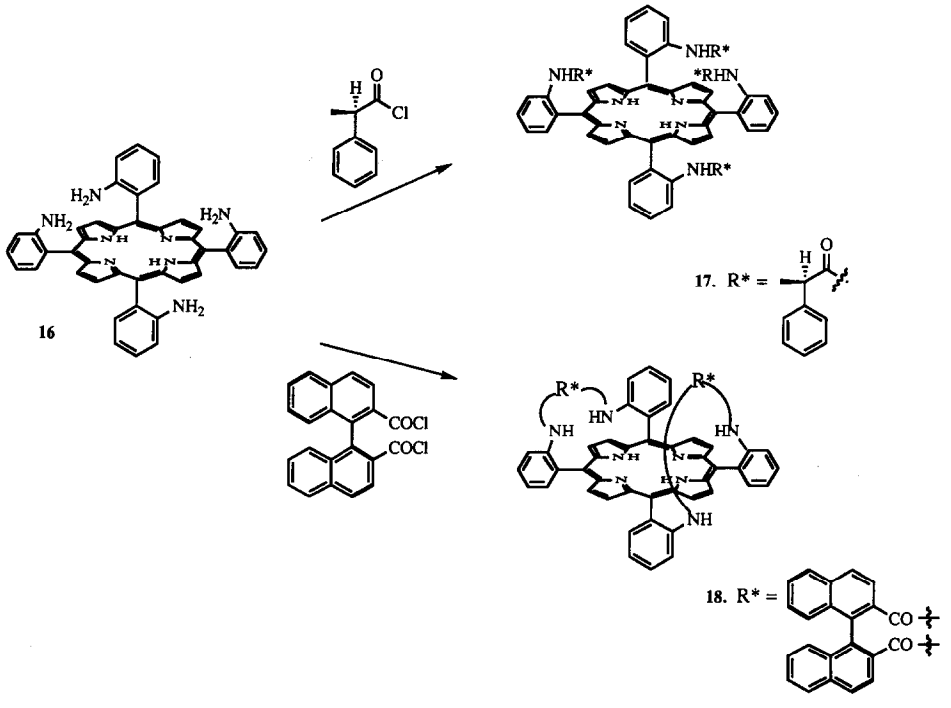
Scheme 3.

ligation through axial ligands which are bonded to the matrix [131].

3. Stereoselectivity induced by the porphyrin structure

The development of asymmetric catalysts capable of generating carbon–oxygen bonds stereoselectively, is of great importance due to the significance of optically active organic compounds. The asymmetric epoxidation of olefins can be performed through the Sharpless reaction where a titanium complex is used. The enantiomeric excesses in this reaction can be higher than 90% but it is limited to functionalized olefins such as allylic alcohols [132–135]. The Sharpless catalyst requires coordination to the functionalized substrate in order to achieve high optical yields. Due to this limitation, methods for the enantioselective epoxidation of unfunctionalized olefins were sought. Chiral salen (metal) complexes were consequently developed and are at the moment the most effective asymmetric catalysts for unfunctionalized olefins [136–138]. Jacobsen reported an ee greater than 80% in the epoxidation of *cis*-disubstituted olefins, in an NaOCl oxidation performed in the presence of chiral manganese of those salen complexes as catalysts. The limitations of this method are optical yields lower than those obtained with other olefin types and that the metallosalens become inactive under the reaction conditions, becoming ineffective in less than 40 turnovers [138].

Metalloporphyrins were likely choices to attempt stereoselective catalytic oxidations with the perspective of being of wider use than those of the preceding examples. Reported work shows that the porphyrin structure not only affects the stability of the catalyst but also its stereoselectivity [139–151]. An appropriate metalloporphyrin able to promote substantial asymmetric induction, poses a higher design demand than those previously discussed for ordinary epoxidation reactions. The inducing chiral moieties



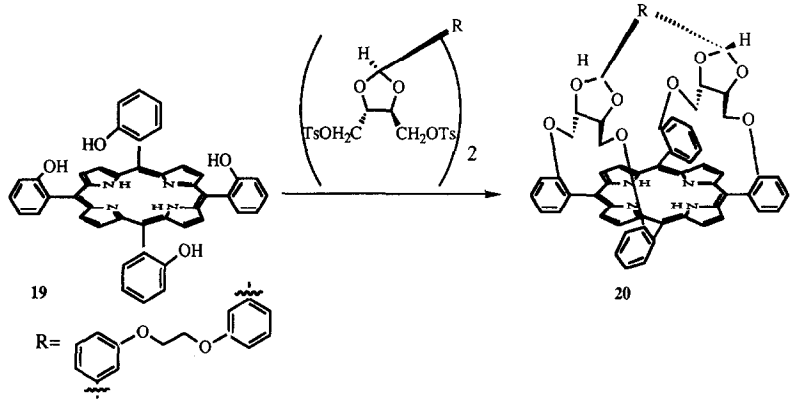
Scheme 5.

should be close to the centre of the macrocycle where the oxidation occurs, but not too close, to avoid that they themselves become potential substrates of the hydroxylation [151]. In fact, the close proximity of the chiral substituents to the metal might induce intramolecular oxidation of these substituents which would alter or destroy the catalyst. Some of the chiral porphyrins described in the literature [139,140] were prepared by the reaction of an acid chloride, having a chiral centre close to the chlorocarbonyl function, with a 5,10,15,20-tetrakis(2-aminophenyl)porphyrin, **16**, Scheme 5. This was an attractive approach because the connection is through a stable C–N bond of the amide group, the atropisomers being so stable to rotation at room temperature that they can be isolated. Groves [139] obtained an ee of 31% in the epoxidation of styrene catalysed by the iron complex of **17**. The author [139–141] used the same strategy to prepare a porphyrin where a binaphthyl group was attached to the porphyrin core. This was expected to be a useful appendage creating a relatively large and rigid chiral cavity around the metal centre. With an iron complex of **18**, the iodosylbenzene epoxidation of styrene originated styrene epoxide with an ee of 48%. However, on attempting to use the same catalyst in a second experiment, the ee lowered dramatically showing that the catalyst was affected during the reaction [139].

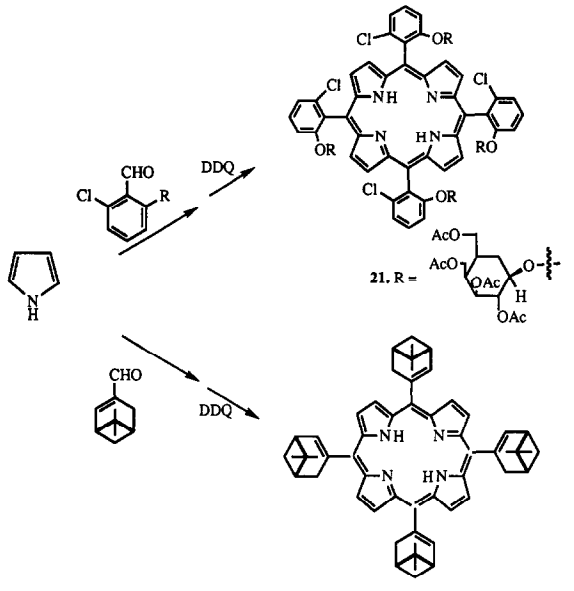
In order to obtain a more rigid chiral environment for the metal centre, Mansuy [145] described the synthesis of 'basket-handle' porphyrins having a rigid amino acid chain above and behind the macrocycle. The iron complexes of these porphyrins catalyse the iodosylbenzene epoxidation of *p*-chlorostyrene giving values of ee similar to those described above.

Using a different strategy, Collman [147,151] promoted the condensation of 5,10,15,20-tetrakis(2-hydroxyphenyl)porphyrin, **19**, with a ketal-protected ditosylthreitol, Scheme 6, obtaining 3 different atropisomers. Using the manganese complex of the out–out bridged chiral porphyrin isomer, **20**, Scheme 6, in which two threitol straps attached to the porphyrin are connected by a bridge which spans the centre of the macrocycle. Collman was able to obtain, under the same reaction conditions, an ee of 58%, evidence of the beneficial effect of pulling the chiral centre closer to the active centre.

Recently, Marchon [152] and Momenteau [148] selected the Lindsey [71] conditions for porphyrin synthesis to synthesize directly chiral porphyrins through the condensation of pyrrole with (1*R*)-myrtenal, or 2-glucosyl-6-chlorobenzaldehyde, Scheme 7. When the porphyrin has a glucosyl substituent linked to one of the *ortho* positions of the *meso*-phenyl and an electron withdrawing chlorine atom in the other *ortho* position, **21**, the stability of the catalyst is sig-



Scheme 6.



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Scheme 7.

nificantly increased. This was the first chiral catalyst which was able to catalyse the epoxidation of 4-chlorostyrene by H_2O_2 capable of 58 turnovers and giving an ee of 22%.

All the research efforts and results so far reported in order to achieve metalloporphyrins catalysed chiral epoxidations have tremendous limitations if they are intended to be applied in large scale reactions. Oxidants other than iodosylbenzene give poor epoxidation yields and provide low enantioselectivity.

4. The role of the axial ligand on the catalytic activity of metalloporphyrins

Distinctive structural features of cytochrome P-450 are the singular thiolate coordination to heme and also the hydrophobicity near the active site. The importance of the specific axial coordination and environment of cytochrome P-450 is emphasised by the fact that, between biological systems, it is the only heme enzyme able to hydroxylate alkanes [65]. In several studies using synthetic metalloporphyrins as biomimetic catalysts for hydrocarbon oxidation reactions, the authors observed the primary importance of the fifth axial ligand in both the relative rate and selectivity of the oxidation reactions [9,153].

A species having a lone pair of electrons which is present in the reaction medium can play the role of axial ligand and is generally represented as L. The axial ligand coordinates to the metal of the metalloporphyrin on the axial positions [154] giving place to both mono and bis-ligated species according to equilibrium (1) and (2).

$$M(P) + L \rightleftharpoons M(P)L \quad (1)$$

$$M(P)L + L \rightleftharpoons M(P)L_2 \quad (2)$$

The generation of a high valence metal oxo-species, the active form of the catalyst, usually puts particular demands on the characteristics of the axial ligand. Too strong a ligand favors the bis-ligated form, which attenuates the interaction between the oxygen donor and the metalloporphyrin, an interaction which is easier with the mono-ligated species. The presence of a specific axial ligand is required with the majority of the metalloporphyrins which have been described as oxidation catalysts. This ligand must be able to stabilise the high valence metal oxo species without making it so stable that it can not transfer the oxygen to the substrate.

The axial ligand in the natural cytochrome P-450 was replaced by pyridine in Meunier's [68] first studies of the catalytic activity of Mn-**1** in the biomimetic oxidations with NaOCl as oxygen donor. Mansuy [22] used imidazole as axial ligand of Mn-**2** in his studies of H_2O_2 catalysed oxidations. Later, in the collaborative work of the Coimbra and Liverpool research groups [76] it was shown that when used in the oxidation of alkenes, the latter system is highly limited due to the destructive oxidation of imidazole. It was proved that the better yields and higher reaction rates could only be obtained with the 1:10 ratio of porphyrin/imidazole. Increasing the proportion of imidazole to 1:20 or

1:60 decreases the rate of the reaction and the overall yield of epoxide [76]. This is probably due to the formation of the inactive species $M(P)L_2$. Since imidazole is a very good ligand to facilitate the heterolytic cleavage of the ligated H_2O_2, it can simultaneously play the role of the base which is required to be present, but the oxidation of this ligand during the reaction eliminates any possibility to apply these conditions to an industrial scale process.

The search for alternative axial ligands, to largely overcome the limitations imposed by the oxidative decomposition of imidazole, led the authors [76] to find that amine *N*-oxides, which are formed when alkyl amines are used as an alternative to imidazole, can themselves be used as relatively efficient axial ligands. To catalyse epoxidations of alkenes by Mn-**2** with H_2O_2, tetrabutylammonium hydroxide can conveniently be used as the required stable base and amine *N*-oxide as the stable ligand. The same authors observed that using the preceding oxidizing system, an inorganic base such as sodium acetate or sodium carbonate can promote the epoxidation of *cis*-cyclooctene giving a 91% yield of epoxide without requiring the addition of any other specific ligand. Recently Mansuy [155] extended these studies using several ammonium salts as co-catalysts for Mn-**2**. This author observed that tetrabutylammonium acetate was clearly the best co-catalyst capable of promoting the epoxidation of *cis*-cyclooctene with just one equivalent of H_2O_2 in 2 h, whereas in the presence of imidazole the epoxidation requires the presence of 2 equiv. of oxidant. The new system is also able to catalyse the hydroxylation of alkanes.

Gonsalves and Pereira [78] studied the influence of the donating capacity of the axial ligand on the efficiency of the catalyst. The effect of pyridine, 4-methylpyridine or 2,4,6-trimethylpyridine on the epoxidation of styrene with NaOCl catalysed by Mn-**2** was studied and the reaction rates of 0.5 h, 0.3 h, and 3 h, respectively, were observed. It was concluded that 2,4,6-trimethylpyridine is less efficient because it is so sterically protected that its presence, in practice, is equivalent to the absence of any specific axial ligand.

When using a biphasic system for NaOCl oxidations, Montanari [77] found that it is not necessary to add any specific axial ligand, but in his reported reaction conditions, the pH of the aqueous phase is adjusted to 10.5 by addition of $NaHCO_3$ to the solution. As mentioned above, it was previously reported that metalloporphyrin catalysed oxidations can be performed in the presence of carbonate without requiring the addition of any other specific ligand [76].

Montanari [156,157] developed new catalytic conditions for H_2O_2 oxidations using the two-phase system H_2O_2/CH_2Cl_2 in the presence of *N*-hexylimidazole as axial ligand and also of benzoic acid. It was shown that the presence of the lipophilic carboxylic acid significantly increases the reaction rate. The role of benzoic acid is still a matter of discussion.

More recently it was demonstrated [158] that using a significantly higher concentration of benzoic acid than that used by Montanari, not only increases the reaction rate, but can also provide for the stabilisation of the catalyst. For example, Mn-**1**, is only stable under oxidation reaction conditions in the presence of a high concentration of benzoic acid (1 metalloporphyrin:20 benzoic acid). Although stabilised, this particular metalloporphyrin does not show significant catalytic activity under such conditions. On the contrary, porphyrins like Mn-**15** are simultaneously protected from decomposition and activated as catalyst.

Attempted approaches to attach directly a residue of pyridine, imidazole [159,160] or even thiolate [161] to the metalloporphyrin, have not shown any advantage, compared to the use of free ligands. The catalytic efficiency is highly dependent on the size of the chain to which the axial ligand is bonded. Only in the case where the chain has enough carbon atoms to locate the axial ligand at the convenient distance, is the catalytic performance similar to that obtained

with external ligands. Since the synthesis of these catalysts is more expensive and their stability lower than that of the normal catalysts due to direct auto-oxidation of the axial ligand bonded to the side chain [154], there is little to gain in synthesizing such catalysts.

In a single reported case, where a thiolate residue was directly attached to the metalloporphyrin, was the ligand claimed to originate higher efficiency promoting increased catalytic activity and higher stability of the catalyst. The reaction studied was the hydroxylation of alkanes by peroxyphenylacetic acid and the author [161] observed an increased donor character of the ligands in the order chloride anion < imidazole < thiolate. The thiolate was the best ligand to increase the rate of the heterolytic scission of the O–O bond.

So far a unique highly efficient catalyst was described which is able to promote the epoxidation of alkenes and the hydroxylation of alkanes without requiring the addition of any axial ligand. Mansuy [117] attributes the activity of the catalyst to the presence of the strong electron withdrawing groups in the β-positions of iron β-polynitrated porphyrin, **12**, but further work is required to better clarify the role of the nitro groups.

Work by Collman [151] showed that the axial ligand can play a decisive role in the chemioselectivity and enantioselectivity of the products. In the epoxidation reaction of 4-chlorostyrene with iodosylbenzene catalysed by the Mn-**20** it was shown that with imidazole or pyridine as axial ligands the ee was zero, whereas with larger ligands like chlorotrimazole or 1,5-dicyclohexylimidazole the ee were 69 and 70%, respectively.

5. Conclusion

Attempts to demonstrate the possibility of mimicking the biological oxidation using simple metalloporphyrins as catalysts relied, for a start, on the use of metal complexes of the somewhat improbably adequate structure of TPP. However, although little efficient and poorly stable, MnTPP in the presence of pyridine proved to be a catalyst for epoxidation with the specific oxygen donor iodosylbenzene. At present, metalloporphyrins showing catalytic activity for a range of oxygen donors, including the easily available and low-cost sodium hypochlorite, hydrogen peroxide and even molecular oxygen, were reported. To allow for efficient catalysis and stable catalysts, specific derivatives of TPP were designed and reaction medium conditions were established. Fairly efficient and stable catalysts are the iron and manganese complexes of TDCPP which are now readily available as a consequence of improvements to the Rothemund synthesis stimulated by the interest in biomimetic catalytic studies. Derivatives of TDCPP available through intensive studies on the peripheral reactivity of porphyrins, have given rise to the best performing catalysts presently known. These give the highest oxidation rates and yields obtained up to now in biomimetic oxidation catalysis, and have the highest stability resulting high turnovers. Catalysts were developed which, while showing a high efficiency and stability, do not need the presence of any specific axial ligand.

Despite all the relevant *progress* achieved in biomimetic catalysis during the last ten years, further efforts are required to find the right catalysts and conditions for higher versatility and efficiency for preparative and large scale application purposes, and to increase the type of oxidations allowing for high regio-, chemio-, and stereoselectivity.

TPP derivatives were the basis for the preparation of the most successful catalysts reported up to now, taking advantage of the present ready availability of such macrocycles and the good catalytic performance of the catalysts which were designed. A broader view in the approaches to the design of the macrocycle structure is worthwhile, and can well be fruitful as to the as yet unattained objectives. Higher efficiency in terms of consumed oxidant, favor-

able use of hydrogen peroxide or more preferentially oxygen, higher turnovers of the catalyst and its adaptability to an easy removal from the reaction medium are still far away and thus require continued efforts in the so far highly successful studies of biomimetic catalysis. We are confident that we will see new designs and better catalysts in the years to come.

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