

Biomimetic oxygenations catalyzed by metalloporphyrins and metalloporphyrinoids bearing co-catalytic functions

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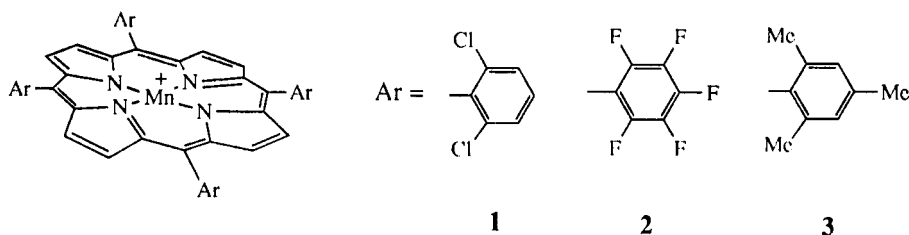
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Abstract - Mn(III)tetraarylporphyrins bearing either a heterocyclic nitrogen base as axial ligand or a carboxylic group, or both, covalently bonded to the porphyrin through a single flexible chain, are efficient biomimetic oxygenation catalysts, specific for the activation of aqueous NaOCl and/or of diluted H₂O₂. Their basic frame is that of the robust tetra(2,6-dichlorophenyl)porphyrin (TDCIPP). Mn(III)-bis porphyrins in which two porphyrin moieties derived from TDCIPP are connected by a rigid spacer have also been synthesized. In the presence of a bidentate lipophilic imidazole ligand they give inclusion complexes with a very high binding constant. They are also very efficient oxygenation catalysts. On the contrary, other metalloporphyrinoids (benzo- and aza-porphyrins, lipophilic phthalocyanines) are very poor and unstable catalysts.

INTRODUCTION

The pursuit of catalytic systems capable of selectively oxidizing hydrocarbons has become of increasing importance in recent years (ref. 1). Among these systems a particular role is played by synthetic metalloporphyrins, capable of mimicking the oxidations mediated by heme-enzymes of the cytochrome P-450 family, at least in terms of reaction types, mechanism and, often, reaction rates (ref. 2). The results obtained so far have stimulated the ambitious project of creating both efficient, and stable, metalloporphyrins capable of becoming competitive catalysts for large scale oxidation processes.

A first step in this direction has been the synthesis of metalloporphyrins (mainly Fe(III) and Mn(III) complexes) resistant enough to oxidation. This has been obtained introducing electron-withdrawing and/or sterically hindering groups in the *o*, *o'*-positions of the aromatic rings of tetraaryl porphyrins. Typical examples are tetra-(2,6-dichlorophenyl), tetra-(pentafluorophenyl) and tetra-mesityl porphyrins **1-3** (ref. 3).



A relevant improvement has been Lindsey's set up of porphyrin synthesis in two subsequent steps, namely cyclocondensation of aromatic aldehydes and pyrrole units to porphyrinogens, followed by oxidative dehydrogenation to porphyrins (ref. 4).

The importance of this variance of the original Rothmund-Adler synthesis (ref. 5) is certified by the spectacular increase of yields that, for the substituted porphyrins mentioned above, moved from values even lower than 1% to more than 30%. A further step has been the synthesis of perhalogenated porphyrins in which also the β -pyrrole positions are substituted by halogens (ref. 6), although in some cases the introduction of halogens in the pyrrole moieties turned out to be deceptive (see later).

All oxidations mediated by synthetic metalloporphyrins are promoted by oxygen donors, somewhat reproducing the short catalytic cycle of cytochrome P-450. A large number of oxygen donors has been used (ref. 2), but we simply focused our attention on sodium hypochlorite and diluted hydrogen peroxide (ref. 7). In both cases the reactions were performed under aqueous-organic two-phase conditions, in the absence of phase-transfer catalysts and at a controlled pH. Both systems require the presence of co-catalysts, namely imidazole or pyridine axial ligands and/or carboxylic acids. Both work under "clean" conditions since the co-products are respectively NaCl and H₂O, an important aspect in the event of large scale application.

OXIDATIONS PROMOTED BY HOCl/ClO⁻

In the NaOCl aqueous solutions the nature of the actual species essentially depends on the pH: at 12-13, which is the pH of a standard concentration of commercial NaOCl, the prevailing species is ClO⁻; lowering the pH, a progressive increase of HOCl (pK_a 7.54) is observed. Oxidations catalyzed by Mn(III) (TPP)Cl in the presence of aqueous NaOCl and a phase-transfer catalyst at pH 12.5 were first described by Tabushi (ref. 8). Meunier improved the catalytic system introducing a pyridine or imidazole base as axial ligand, thus noticeably increasing both catalytic activity and chemo- and stereoselectivity of the reaction (ref. 9). We found (ref. 10) that buffering the pH of the aqueous phase at 9.5-10.5 and using lipophilic axial ligands, a further noticeable increase of both reaction rate and selectivity is obtained. Under these conditions the oxidizing species is HOCl, which is soluble in part in the organic phase (CH₂Cl₂), so that the addition of a phase-transfer catalyst is no longer necessary. Furthermore, in the epoxidation of electron-rich alkenes even the presence of an axial ligand may not be necessary (ref. 11), thus leading to a noticeable simplification of the catalytic system. In particular, side reactions concerning quaternary salt and axial ligand oxidations are avoided.

Whenever required, the axial ligand must be lipophilic, since the reaction entirely occurs in the organic phase. On the contrary, the imidazole and pyridine bases used by most authors are largely soluble in water, and therefore in part removed from their role of axial ligand. Finally, in the equilibria of mono- and bis-complexation of the axial ligand to the metalloporphyrin, the mono-coordinated species (P)L only is catalytically active and capable of coordinating the oxidant in the second axial position; the non-coordinated species (P) and the bis-coordinated species (P)L₂ are not very active and completely inactive, respectively. Measuring the K₁ and K₂ coordination constants, the optimum initial ligand concentration can be

established which maximizes the (P)L concentration at the equilibrium. When the oxidation rates are fast enough to minimize the competing oxidative demolition of the axial ligand, nearly equimolecular amounts of porphyrin and ligand generally ensure the maximum (P)L concentration, therefore the maximum reaction rate.

The reactions are usually carried out at 0°C with an excess of oxidant with respect to the substrate. Under these conditions, with porphyrin/substrate ratios in the range 1:100-1000, reactions are completed in a few minutes with high selectivity. The experimental data agree with Michaelis-Menten saturation kinetics. With electron-rich alkenes, in the absence of axial ligand, up to 30,000-100,000 catalytic cycles have been obtained. With electron-poor alkenes, such as 1-alkenes, no more than 200 cycles could be reached.

OXIDATIONS PROMOTED BY 30% H₂O₂

Reactions promoted by 30% H₂O₂ also occur under aqueous-organic two-phase conditions, possibly at 0°C. It was found that these reactions require Mn(III)-porphyrins particularly resistant to the oxidants, such as Mn(III)-(TDCIPP)Cl **1** (ref. 12), but also require the contemporary presence of a lipophilic axial ligand, e.g. N-hexylimidazole, and of a lipophilic carboxylic acid, e.g. benzoic acid, both in molar amounts equal or slightly higher than those of the porphyrin (ref. 13).

The mechanism proposed for these reactions is reported in Fig. 1. In this case also the reactions follow Michaelis-Menten saturation kinetics. To the best of our knowledge, our conditions for the activation of hydrogen peroxide are by far the mildest among those reported in the literature (ref. 12, 14, 15). Also cycloalkanes (giving a mixture of alcohols and ketones) and 1-alkenes can be oxidized. Reaction rates are very high (100 turnovers/min or more), but overall turnovers, although the highest reported so far for H₂O₂ promoted oxidations, do not exceed 1000.

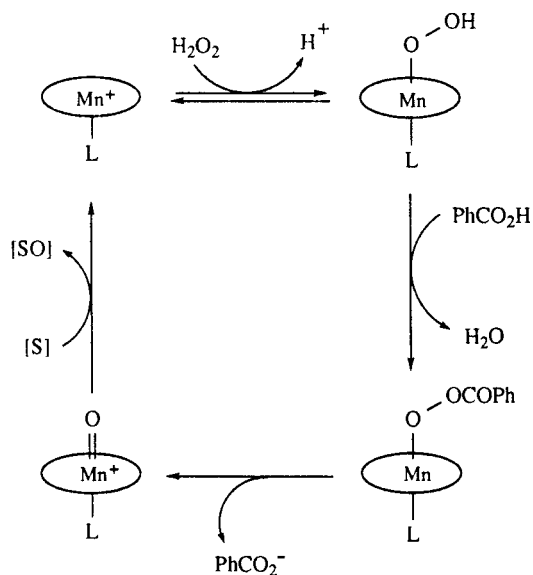


Fig. 1. Catalytic cycle of oxidation catalyzed by Mn(III)-tetraaryl-porphyrins and promoted by 30% H₂O₂ in the presence of N-hexylimidazole (L) and benzoic acid.

OXIDATIONS CATALYZED BY PERHALOGENATED PORPHYRINS AND PORPHINOIDS

In the attempt to realize metalloporphyrins more resistant to demolitive oxidation, perhalogenated porphyrins were synthesized, bearing halogens (F, Cl, Br) either in the phenyl rings and in β -pyrrole positions (ref. 6). However, in most cases these porphyrins were used in the presence of a large excess of substrate with respect to the oxidant, namely under conditions of particular protection of the catalyst. The same porphyrins were re-examined in the presence of an excess of oxidant with respect to the substrate, and compared, under these more realistic conditions, with the most stable porphyrins already known, e.g. **1**. It was found, at least with oxidants such as PhIO , HOCl/ClO^- and 30% H_2O_2 , that the introduction of halogens in the β -pyrrole positions decreases, instead of increasing, the resistance to the oxidants (ref. 16). An exception is octabromo-tetramesitylporphyrin (ref. 17), about as stable and active as tetramesitylporphyrin **2**, but again less stable than Mn-**1**. The perfluorinated porphyrins, which allowed the direct hydroxylation of benzene (ref. 18) and of inert alkanes, like propane and iso-butane (ref. 19), seem to be the only perhalogenated catalysts particularly active.

Discouraging results were obtained with Mn(III) complexes of porphinooids like tetrabenzotetraaryl porphyrins **4**, in which isoindole moieties replace the pyrrole moieties of porphyrins, octaphenyl phthalocyanines **5** and lipophilic phthalocyanines **6**. It is interesting to observe that phthalocyanine complexes, which are extremely stable to light and to chemical agents under the form of insoluble pigments (e.g. copper-phthalocyanine), become very fragile if they are made soluble in organic solvents by alkyl substituents as in **6**. Indeed the macroring is flat, without any protection against the oxidants. The introduction of eight phenyl rings perpendicular to the phthalocyanine plane, as in **5**, slightly improves the stability and catalytic performance, but a maximum of 4 and 20 catalytic turnovers are obtained with HOCl and H_2O_2 , respectively (ref. 20).

STRUCTURED PORPHYRINS

Structurally complex porphyrins have been reported by several authors (ref. 21), mainly to reproduce heme-similar systems capable of coordinating dioxygen. Some models have nitrogen bases covalently linked to the porphyrin ring in order to better control the axial coordination of the metal. For example, metalloporphyrins in which the axial ligand is bound to a bridge connecting two opposite phenyl rings of a tetra-arylporphyrin turned out to be efficient catalysts in alkene epoxidations (ref. 22).

However, a contradiction should be stressed. The increase of catalytic activity obtainable in structured porphyrins is hardly consistent with the chemical robustness of these same porphyrins. Indeed, the instability towards the oxidants used as oxygen donors increases with the increase of molecular complexity.

We tried to tackle this problem in several ways. We first chose a model (porphyrins **7** and **8**) in which the axial ligand is covalently bonded to the porphyrin ring by a single flexible chain (ref. 23). In **7** and **8** the high coordinating capability of the heterocyclic base is further increased by a loss of conformational and rotational entropy lower than that found with external ligands, the result being a lower free energy of coordination. The formation of a penta-coordinated species is entropically favoured with respect to the

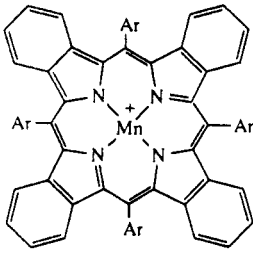
hexacoordinated species, even when $K_1 \ll K_2$ as for Fe(III)-complexes. Mn(III)-porphyrins **7,8** turned out to be very efficient catalysts, but the absence of electron-withdrawing and/or sterically hindering substituents in the aryls leads to a complete bleaching of the porphyrins by HOCl after 200 catalytic cycles.

The use of a porphyrin structure similar to that of octachloroporphyrin **1** led to models **9-11**, whose catalytic activity is equal to or higher than that of **1** (ref. 24). No external axial ligand is required for **9**, only benzoic acid must be added in the H_2O_2 promoted reactions. In model **10** a carboxylic group is linked through a flexible chain, in this case an external axial ligand being required. Finally, model **11** contains both the axial ligand and the carboxylic group covalently linked through two different chains on opposite sides of the porphyrin plane. This porphyrin is a particularly efficient catalyst in the H_2O_2 promoted oxidations, and does not require the presence of any external co-catalyst. With molar ratio **11**: substrate = 1:1000, alkenes and cycloalkanes are oxygenated at initial rates up to 500 turnovers/min at 0°C. Unfortunately, catalytic activity is over in a very short time, so that after only a few minutes at 0°C, the total turnover number does not exceed 1200.

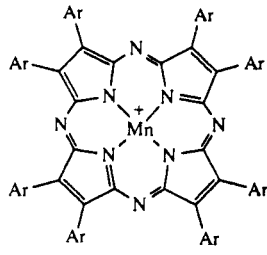
The main reason for this deactivation appears to be the demolitive oxidation of the axial ligand. Notwithstanding the highly favoured intramolecular coordination of the ligand in **9** and **11**, non-coordinated conformers exist at the equilibrium. We found that as long as the heterocyclic base is coordinated to the metal, it is sufficiently resistant to the oxidant, but it is more easily oxidized when it is free. Furthermore, both rates of oxidative demolition of the porphyrin and of the axial ligand, which are the concomitant causes of the end of catalytic activity, are directly linked to the porphyrin activity. With porphyrins having a low catalytic activity, the side reactions of oxidative demolition of the porphyrin and of the ligand become negligible. In spite of widespread opinion, the addition of further ligand after it has been demolished is substantially ineffective, the porphyrin apparently being poisoned by the destroyed ligand via an unknown mechanism.

The synthesis of bis-metalloporphyrins **12** and **13** has been an attempt at solving the problem of the presence of non-coordinated axial ligand at the equilibrium in solution (ref. 25). It was demonstrated by Tabushi (ref. 26) that dimeric metalloporphyrins connected through a single spacer, in the presence of a suitable bidentate heterocyclic base (L-L), preferentially form complexes in which the ligand is coordinated within the cavity determined by a face to face conformation of the porphyrin ring. The very high value of the binding constant ($K_D \sim 10^8 M^{-1}$) ensures an extremely low concentration of the free L-L at the equilibrium. Furthermore, the access of the oxidizing species to the coordinated ligand inside the cavity is sterically prevented.

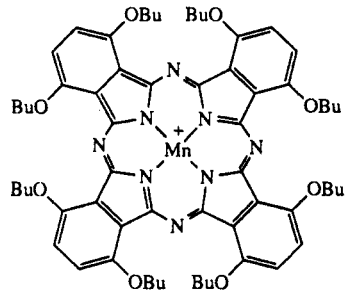
In the bis-Mn(III)-porphyrins **12** and **13** the two porphyrin units are those of the chemically robust octachloroporphyrin **1** and the rigid spacer is derived from *m*-xylene or from *m*-terphenyl. Lipophilic bis-imidazole **14** turned out to be a particularly suitable bidentate ligand. Bis-Mn(III)-porphyrins **12, 13** and ligand **14** give rise to inclusion complexes whose formation is supported by UV-Vis titrations and, in the gas phase, by MS-FAB⁺ spectra. UV-Vis titration is difficult to interpret, and does not allow the direct measurement of K_D . However, a noticeable difference exists between the behaviour observed by adding the bidentate base **14** to the porphyrin and that observed with the mono-dentate base, N-hexylimidazole. In the former case the Soret absorption band associated to the non-axially coordinated Mn(III)-porphyrin almost



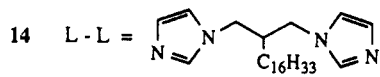
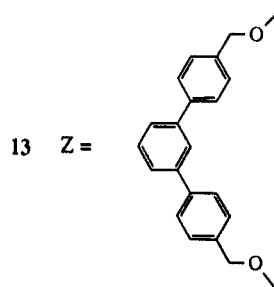
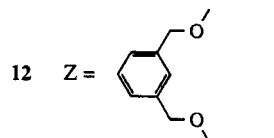
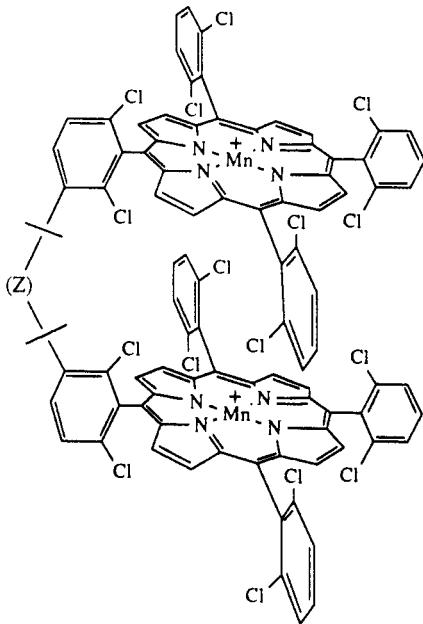
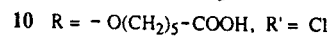
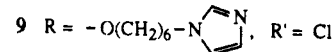
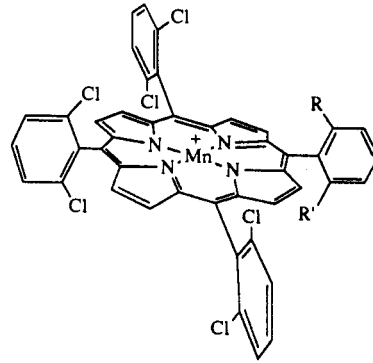
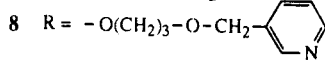
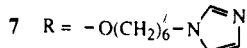
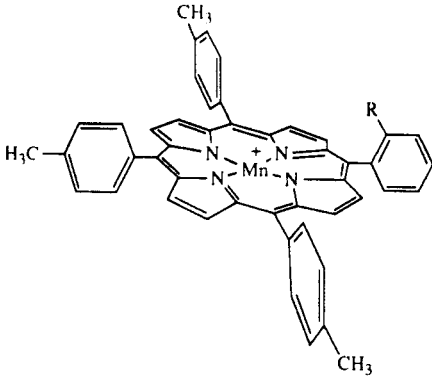
4



5



6



entirely disappears by addition of 1 molar equivalent of **14**. In the second case the disappearance of the Soret band is more gradual, and is complete only by the addition of 100 molar equivalents of ligand. In the gas phase monomeric porphyrins, like Mn(III)-porphyrin **1**, and N-methylimidazole almost exclusively give rise to the mono-axially coordinated species Mn(P)L, even when a large excess of ligand is present in the matrix. Similar experiments carried out on Mn(III) **12** and **13** show that mono- and bis-adducts are present in the gas phase, thus indicating the independent behaviour of the two porphyrin rings. On the contrary, in the presence of the bidentate ligand **14**, only a mono-adduct is formed with **12** and **13**. No bis-adduct is observed, even adding a huge excess of N-methylimidazole jointly with **14**. However, the catalytic activity of **12** and **13** in the presence of **14** is somewhat disappointing, since it is only twice that of the single porphyrin **1**, and the overall turnovers are almost the same.

The achievement of a chemically robust porphyrin capable of realizing a large number of catalytic cycles, at least with traditional oxygen donors, is therefore still an open question.

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