Biomimetic Models of Cytochrome P-450. A Doubly Tailed Manganese(III)–Tetraaryl Porphyrin; an Extremely Efficient Catalyst for Hydrocarbon Oxygenations promoted by 30% H_2O_2

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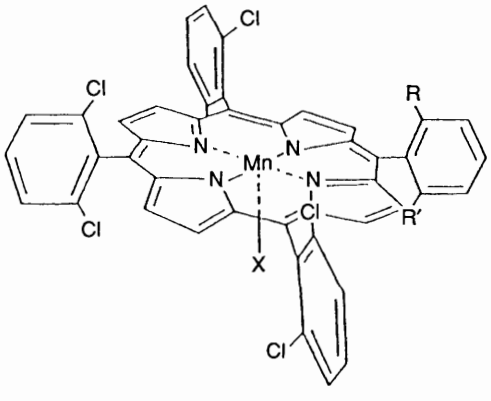
Mn^{III}–porphyrin **1**, bearing an imidazole axial ligand and a carboxylic group juxtaposed on opposite sides of the porphyrin plane, is an extremely efficient catalyst for the activation of 30% H_2O_2 in hydrocarbon oxygenations carried out in CH_2Cl_2–H_2O; initial rates at 1 min up to 500 turnovers min^{-1} at 0 °C in the epoxidation of cyclooctene are obtained.

Oxygenation reactions of saturated and unsaturated hydrocarbons, catalysed by metallo-porphyrins mimicking monooxygenase enzymes such as cytochrome P-450, are of current interest.[1] An ideal model for cytochrome P-450 would hold the axial ligand anchored to the porphyrin so as to obtain the same proximity effect of the thiolate group in the natural enzyme. A huge number of highly structured porphyrins have been synthesized, mainly to give information on the mechanism of natural oxygenation processes,[2] but very few of them have been used as catalysts for preparative purposes.[3] It is expected that these porphyrins should also be highly efficient catalysts and highly stable molecules, two qualities which are combined with difficulty.

We have recently found that 30% H_2O_2 can be activated under very mild conditions (0 °C, pH 4.5–5.0), working in CH_2Cl_2–H_2O in the presence of three components: a chemically robust Mn^{III}–tetraaryl porphyrin (P), a lipophilic heterocyclic base as axial ligand (L), and a lipophilic carboxylic acid (A), in L : P = 0.5–2 and A : P = 1–8 molar ratios, respectively.[4]

We have now synthesized Mn^{III}–porphyrin **1** in which the axial ligand and the carboxylic acid are both covalently linked



1 R = —$O(CH_2)_6$—N⟨imidazole⟩

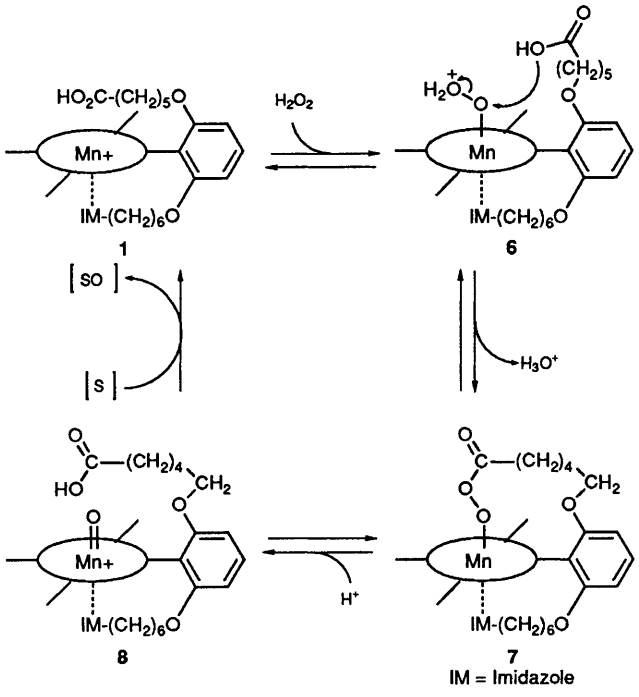
R′ = —$O(CH_2)_5$—CO_2H

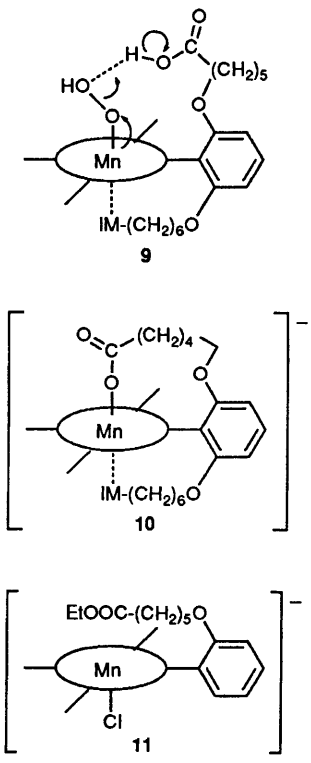
2 R = R′ = OCH_3

3 R = R′ = Cl

4 R = —$O(CH_2)_6$—N⟨imidazole⟩ R′ = Cl

5 R = —$O(CH_2)_n$—CO_2H (n = 5), R′ = Cl





to the porphyrin ring.† Porphyrin **1** is an extremely efficient catalyst for oxygenation reactions promoted by 30% H_2O_2 and does not require the presence of external co-catalytic species.

In designing the synthesis of **1** the following factors were considered: (*i*) the porphyrin structure is as far as possible similar to that of the chemically robust $Mn^{III}T(2,6\text{-}Cl_2PP)Cl$ **3** (T = tetra); (*ii*) the axial ligand and the carboxylic group are each linked to the porphyrin by flexible spacing chains;‡ (*iii*) linkages in positions 2 and 6 of the same phenyl ring ensure that, along with an improved synthetic simplicity, the axial ligand and the carboxylic group are juxtaposed on opposite sides of the porphyrin ring plane.

In the presence of 0.1 mol% of **1** and of 2 mol equiv. of 30% H_2O_2 buffered at pH 5.0, cyclooctene was epoxidized in 3 min at 0 °C under CH_2Cl_2–H_2O two-phase conditions, at initial rate (1 min) of 500 turnovers min^{-1} (Fig. 1), with 100% conversion and selectivity. Other alkenes, such as α-methyl styrene, *p*-chlorostyrene, α-pinene and camphene were similarly oxidized at initial rates (1 min) of 200–270 turnovers min^{-1}, with overall 700–1000 turnover numbers. With less reactive substrates, *e.g.* in the epoxidation of dodec-1-ene and in the oxygenation of cyclooctane to cyclooctanol–cyclooctanone, reactions stop after 250–350 turnovers, but initial rates are still very high (130–170 turnovers min^{-1} at 0 °C).

The catalytic efficiency of **1** is better evaluated by comparison with that of $Mn^{III}T(2,6\text{-}Cl_2PP)Cl$ **3** and Mn^{III}–porphyrins **4** and **5**. Porphyrins **4** and **5** are similar to **1**, but have only one tail connecting the imidazole and the carboxylic group, respectively. In the case of **3** molar ratios were

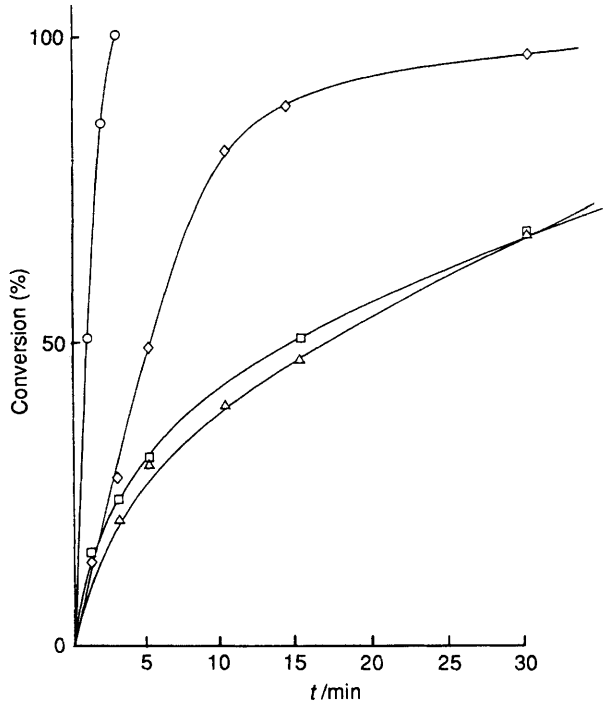


Fig. 1 Cyclooctene epoxidation catalysed by Mn^{III}–porphyrins **1** (○), **3** (□), **4** (△) and **5** (◇), at 0 °C and S : P = 1000

3 : L : A : S : H_2O_2 = 1 : 1 : 1 : 1000 : 2000. With catalysts **4** and **5** the same molar ratios were used, but L and A, respectively, were absent (S = cyclooctene, L = *N*-hexylimidazole, A = benzoic acid). As can be seen from Fig. 1, all reactions are considerably slower than those carried out with **1**. With poorly reactive substrates, the difference in the catalytic efficiency between **1** and the other three porphyrins is again very high in the initial stage; then all reactions slow down and stop, mainly for the oxidative demolition of the axial ligand (external or

† Condensation of 2,6-dimethoxybenzaldehyde, 2,6-dichlorobenzaldehyde and pyrrole in 1:3:4 molar ratio under the general conditions of Lindsey porphyrin synthesis[5] afforded 5(2,6-dimethoxyphenyl)-10,15,20-tris(2,6-dichlorophenyl) porphyrin **2** in 9.4% yield. Demethylation with BBr_3, condensation with ethyl 6-bromohexanoate and then with *N*-(6-bromohexyl)imidazole, followed by complexation with $Mn(OAc)_2$ and alkaline hydrolysis of the ester afforded **1** in 9.7% overall yield from **2**; visible spectrum (CH_2Cl_2) λ_{max} 380, 477 and 574 nm (ε 36.0, 64.1 and 9.5 dm^3 $mmol^{-1}$ cm^{-1}); MS–FAB$^+$ for $C_{59}H_{46}Cl_6N_6O_4Mn^+$ *m/z* 1169 cluster (100%).

‡ Connections of the chains through amido groups in *o*,*o*′-positions of a phenyl ring in a tetraaryl porphyrin are much less stable than oxygen bridges, and are easily demolished under oxidative conditions.[6]

covalently bonded to the porphyrin).§ In the case of **4** and **5** no reaction occurs if A or L, respectively, are absent. The same is observed for **3** without either of the two co-catalysts.

The mechanism that we tentatively propose for the H_2O_2 activation by **1** *via* **6**, **7** and **8** is reported in Scheme 1. It is similar to that suggested for the H_2O_2 oxygenations with porphyrin **3** in the presence of external axial ligand and carboxylic acid.[4]¶

The much higher reactivity of porphyrin **1** compared with that of porphyrins **3–5** strongly indicates that both imidazole coordination and nucleophilic attack by the carboxylic group on the Mn–H_2O_2 complex should occur in an intramolecular way.‖ Furthermore, in **1** the face is defined of the porphyrin ring in which the metal oxene is produced. This property could be important in the design of porphyrins bearing a suitably placed chiral residue, as catalysts for enantioselective oxygenations.

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§ With S:P = 200 epoxidation of cyclooctene catalysed by **3–5** is completed in 10–13 min at 0 °C, before the demolition of the porphyrin and/or of the axial ligand. However, it must be pointed out that the UV–VIS spectra of porphyrins **1** and **3–5** remain substantially unchanged at the end of reactions, thus indicating that the porphyrin skeleton is not involved in the deactivation.

¶ A referee has suggested that the co-catalytic effect of the carboxylic group could be explained through a proton-transfer mechanism, which assists heterolysis of the O–O bond, as indicated in **9**.

‖ On the basis of FAB^- analysis the structure of porphyrin **1** was detected as anion **10** of the internal salt. Similar behaviour was observed for **5**, whereas the ethyl ester of **5** showed Cl^- as counterion as indicated in **11**. By changing the number of CH_2 groups in the tail of porphyrin **5** (*n* in the 3–7 range), no appreciable variation of catalytic activity could be observed.

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