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DEFINITIVE EVIDENCE FOR A PROXIMAL EFFECT OF PYRIDINE IN THE NaOCl/Mn(PORPHYRIN)X / PYRIDINE CATALYTIC OXYGENATION SYSTEM

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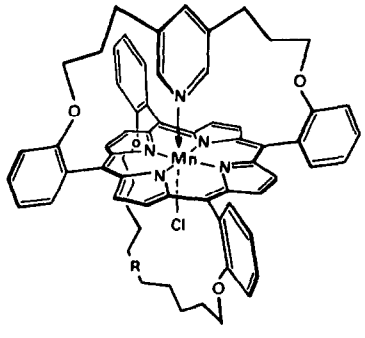
Summary: Using pyridine-attached manganese porphyrins, it has been possible to obtain definitive evidence that pyridine behaves as a proximal ligand in the NaOCl/Mn(porphyrin)X catalytic oxygenation system.

It is well-known in enzymology that axial ligands play a fundamental role in the chemical and biochemical properties of several hemoproteins such as cytochrome P-450, peroxidase, catalase, hemoglobin and myoglobin, all containing an iron-protoporphyrin IX moiety as prosthetic group.[1] For some of them, the nature of the *proximal* group in the fifth position is well established: an imidazole of an histidine residue in the case of hemoglobin and myoglobin,[2] or cytochrome c peroxidase,[3] a phenoxy group from a tyrosine in catalase,[4] and a cysteinato ligand in cytochrome P-450.[5]

For most of these hemoprotein, the nature and the influence of the *distal* ligand are known. The basic nitrogen atom of an histidine is involved in catalase[4] or in myoglobine for the stabilization of the iron-dioxygen complex by hydrogen bonding.[2] In cytochrome c peroxidase, one histidine and one arginine are close to the distal position and a possible distal-assistance by a carboxy group has been invoked by Sligar et al.[6] in the oxygen-oxygen bond cleavage in cytochrome P-450.

Recently, we have been able to modify the chemical properties of a catalytic oxygenation system, NaOCl/Mn(porphyrin)X, by pyridine[7] or by an imidazole derivative[8] (for a recent review on P-450 models, see reference 9). Such ligands greatly enhance the rate of olefin epoxidation, the chemo- and stereo-selectivity of the reaction, which has been attributed to a proximal effect of pyridine or N-substituted imidazole.[10]

In this context, manganese porphyrin complexes 2 and 3 with a pyridine directly bonded *trans* to the manganese-leaving group appear as suitable candidates for confirming the hypothesis



2 R = $-(CH_2)_{12}-$
3 R = $-(CH_2)_4-\text{PP}-(CH_2)_4-$

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of the pyridine coordination *trans* to the active manganese-oxo site. These modified porphyrins have been synthetized by one of us for studies on models of hemoglobin.[14]

In the present work, we wish to report data which provide definitive evidences of the *proximal* effect of pyridine using these modified manganese-porphyrins 2 and 3.

Table 1 describes the modification of the stereoselectivity in the epoxidation of *cis*-stilbene with the NaOCl/Mn(porphyrin)X system. In the case of a "normal" porphyrin such as TPP, we

Table 1. Manganese porphyrin-catalyzed epoxidation of *cis*-stilbene by NaOCl.[a]

Run No.	Pyridine equivalent[b]	Catalyst type	% *cis* epoxide	% *trans* epoxide	Reference
1	none	1	35	65	7b
2	0.03	1	70	30	7b
3	0.16	1	78	22	7b
4	none	2	89	11	c
5	0.03	2	91	9	c
6	0.09	2	92	8	c
7	none	3	89	11	c
8	0.09	3	86	14	c

a Standard reaction conditions: manganese complex (0.0063 mmol), phase transfer agent: benzyldimethyltetradecylammonium chloride (0.0125 mmol), *cis*-stilbene (1.0 mmol), NaOCl (1.8 mmol) in CH_2Cl_2-H_2O (2.5 mL - 5 mL) at 25°C under nitrogen.

b Equivalent of pyridine with respect to the olefin.

c This work.

knew from a previous study that the stereoselectivity is largely increased by the presence of pyridine[7b] (*cis/trans* epoxide ratio equal to 35/65 in the absence of pyridine and to 70/30 with 0.03 equiv. of pyridine, runs 1 and 2). The *cis/trans* epoxide ratio increases also with the pyridine concentration (run 3). With catalysts 2 and 3 (one pyridine per metal atom), the *cis/trans* epoxide ratio is 89/11 in the absence of any extra pyridine (runs 4 and 7). The addition of a small amount of "free" pyridine causes no appreciable modifications of this ratio (runs 5, 6, and 8). Furthermore, the similar stereochemical results obtained with 2 and 3 (runs 4 and 7, or 6 and 8) indicate that the second chain with R = $-(CH_2)_{12}-$ for 2 and R = $-(CH_2)_4-C_6H_4-(CH_2)_4$ for 3 on the opposite side of bonded pyridine does not influence the stereochemistry of *cis*-stilbene epoxidation. But, if "free" pyridine does not affect the *cis/trans* ratio, still we found out that it consistently increased the epoxidation reaction rate. The data are shown in Figure 1, using 2 as catalyst in the absence or in the presence of "free" pyridine compared to epoxidation with Mn(TPP)OAc 1 as catalyst in the absence or in the presence of pyridine. In other words, with Mn(TPP)OAc, the addition of pyridine influences both the stereoselectivity and the reaction rate, whereas with pyridine-attached manganese porphyrins, 2 and 3, the only effect of free pyridine is on the reaction rate.

TPP = *meso*-tetraphenylporphyrin dianion ligand.

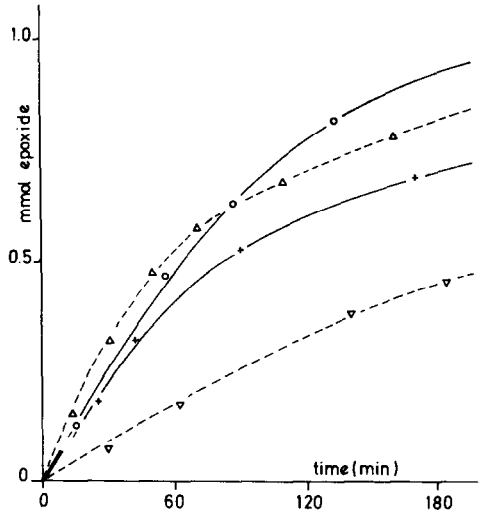

Fig. 1. Epoxidation of cis-stilbene with NaOCl catalyzed by Mn(TPP)OAc in the absence of pyridine (▽), in the presence of 0.16 equivalent of pyridine (0), and epoxidation catalyzed by 2 in the absence (+), and in the presence of 0.09 equivalent (Δ) of pyridine.

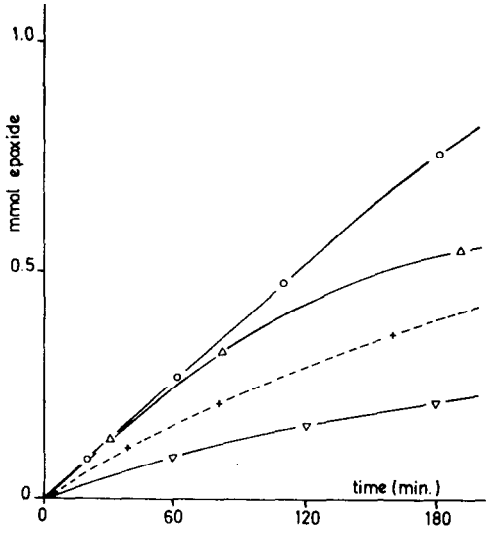

Fig. 2. Epoxidation of cyclohexene catalyzed by Mn(TPP)OAc in the absence (▽) and in the presence of 0.16 equivalent (o) of pyridine, or catalyzed by 2 in the absence (+) and in the presence of 0.09 equivalent (Δ) of pyridine.

We found a similar trend with substrates other than *cis*-stilbene and Figure 2 summarizes the data for cyclohexene epoxidation in terms of reaction rate. The addition of pyridine in the reaction catalyzed by 2 enhances the epoxidation rate. However, 2 alone, without extra pyridine, is a better catalyst than Mn(TPP)OAc without pyridine, confirming also in this case the role of pyridine as proximal ligand.

These experimental results can be explained by a possible double role of neutral ligands in these catalyzed reactions: (i) a coordination *trans* to the manganese-oxygen active species in a *proximal effect* and (ii) a *distal effect* which stabilizes the manganese-oxo moiety and assists the oxygen transfer from manganese to the substrate. This proposal is in line with the distal role of the nitrogen ligand in hemoglobin and myoglobin, which has been previously pointed out, and with more recent data[15] on peroxidase catalysis where essential features of the enzyme activity are an acid-base catalysis by a distal histidine and a charge stabilization by an arginine residue. During the work on the possible distal effect of pyridine in the NaOCl/Mn(porphyrin)X system, Taylor et al. also obtained experimental evidences of distal effect of a carboxylate group in model compounds of peroxidases.[16]

However, in the present case, the distal effect cannot be considered as clearly demonstrated. As a matter of fact, ^{1}H n.m.r. with the iron analog of 2 indicates that only 85% of the molecules in the iron porphyrin complex exist as penta-coordinated species.[17] So, a similar phenomenon should be considered in the case of the manganese complex, suggesting that the effect of added pyridine on 2 or 3 might be partly due to the proximal coordination of extra pyridine. We are currently working on the design of new pyridine-linked manganese porphyrins with complete coordination of the hanging pyridine. With such manganese-porphyrins, it will be possible to discuss further a possible distal effect of added pyridine.

As a conclusion, the main influence of neutral ligands on the NaOCl/Mn(porphyrin)X oxygen-

ation system can be attributed to a proximal effect. As we previously described a cage-effect with the porphyrin macrocycle in catalytic reactions,[18] we may now mimic, with such a model of cytochrome P-450, the two major keys for the control of reactivity and selectivity in hemo-enzymes, i.e. the cage-effect of the protein structure and the proximal effect of the ligand *trans* to the active site.

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10 The pyridine coordination has been proposed according to data obtained in the catalytic reaction with various substituted pyridines.[7] We should remember that the visible spectrum of manganese porphyrins shows no significant change if increasing quantities of pyridine or other neutral ligands are added to the solution of the manganese complex.[11] In agreement with data previously reported,[12] all attempts to determine the nature of the adduct(s) formed by addition of p-methylpyridine to a solution of Mn(TPP)X using ^{1}H n.m.r. techniques were unconclusive. This problem has been solved by ^{13}C and ^{2}H n.m.r. studies[13] while this work was in progress.

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