Enhanced Selectivity by an 'Open-well Effect' in a Metalloporphyrin-catalysed Oxygenation Reaction

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A selection of aliphatic alkenes, substituted styrenes, and *cis*-stilbene has been epoxidised with aqueous NaOCl, employing two different porphyrins, Mn(TPP)OAc† and Mn(TMP)Cl, as catalysts. Large increases in reaction rate, product selectivity, and stereoselectivity are found with the bulkier TMP ligand. The results are interpreted in terms of an 'open-well effect' around the manganese–oxygen active site.

During the last decade much attention has been devoted to metalloporphyrins as structural examples of metalloenzymes or biological oxygen carriers,[1] thus ensuring a better understanding of the physical properties (structure, magnetism, oxidation state, *etc*...) of enzymes like oxygenases, peroxidases, or catalase. These studies have usually been focused on the ground state or highly stable oxidation states of these various enzymes. Remarkable results have also been obtained with modified porphyrins in modelling the oxygenated form of hemoglobin.[2] More recently, it has been shown that metalloporphyrins are able to mimic catalytic oxygenation reactions, epoxidation and hydroxylation, usually performed in living systems by mono-oxygenases like cytochrome P-450 (for a recent review, see ref. 3). These biomimetic oxygenation reactions with metalloporphyrins instead of the normal oxygen source used by cytochrome P-450 in aerobic conditions, O_2 and NADPH, are performed with one-oxygen donor oxidants such as alkyl hydroperoxides,[4] iodosylbenzene,[5] or periodate,[6] already used with P-450 enzymes in anaerobic conditions.[7]

Recent evidence for a large isotope effect in the demethylation of anisole or the high stereospecificity observed in hydroxylation[8] demonstrated that Groves' system [Fe(TPP)Cl–PhIO] provides a reliable model for cytochrome P-450 oxygenases.

In our laboratory we have shown that sodium hypochlorite is also a convenient source of oxygen atoms for these metalloporphyrin-catalysed oxygenation reactions[9] and that a metal-oxo or 'oxo-like' complex is probably involved in the electrophilic transfer of oxygen to the substrate.[10] As for enzymes, it has been possible to demonstrate the great influence due to an axial ligand *trans* to the metal-co-ordinated oxygen atom in terms of reaction rate and chemo- and stereo-selectivity.[11] For all the enzymes having the same metalloporphyrin, namely iron protoporphyrin IX, as the prosthetic group, the different activities are modulated not only by the axial ligands, but also by the 'cage-effect' due to the three-dimensional shape of the protein around the prosthetic group.

Here we report that a similar 'cage-effect', designated for this synthetic porphyrin the 'open-well effect', is observed in the catalytic epoxidation reaction with the Mn(porphyrin)X–NaOCl system. Such an 'open-well effect' was expected to avoid the dimerization of the catalyst through formation of a μ-oxo bridge.[12]

From preliminary kinetic data[10] we knew that for meso-tetramesitylporphyrin ligand (TMP), steric hindrance is sufficient to avoid self-oxidation of the catalyst by a bimolecular process, but that these steric constraints are removed from the active site, *i.e.* the manganese–oxo bond, to a sufficient degree to leave the necessary space for substrate approach as in a typical enzymatic process.

We should mention here that Groves' publication[13] on hydroxylation of hydrocarbons is a direct illustration of the same concept of the 'open-well effect'. Here data are reported comparing the 'normal' TPP ligand and the 'open-well' TMP ligand in the manganese porphyrin–NaOCl catalytic oxidation and showing the strong influence due to the macrocyclic ligand on reaction rate, product selectivity, and stereoselectivity of this new epoxidation route.

Results and Discussion

Epoxidation of Alkenes.—The results obtained by employing Mn(TPP)OAc or Mn(TMP)Cl as catalysts are listed in Table 1. For most olefins, the reaction time with TMP is half that observed with the 'normal' TPP ligand.

One possible explanation is that the steric hindrance due to the *ortho*-methyl groups on the phenyl substituents (see Figure 2) is sufficient to reduce the possibility of transfer of the electrophilic oxygen atom from one manganese porphyrin to another (bimolecular decomposition process). One should remember that, in the absence of substrate, rapid bleaching of the catalyst occurs, while this decomposition seems to be reduced in the case of TMP.

In addition, the fast epoxidation rate obtained with the TMP ligand indicates that the size of the cage around the manganese–oxo site is still suitable for efficient oxygen transfer to the substrate. Furthermore, the best epoxide selectivity observed in all cases favours steric control of the substrate approach to the manganese–oxo species. With the TMP ligand, most of the chemoselectivities are actually in the range 90—98%. Such high selectivity and conversion for epoxidation of cyclohexene, 1-methylcyclohex-1-ene, *etc.* contribute to make the NaOCl–Mn(TMP)X system a method of practical interest for the epoxidation of non-activated olefins (yields usually obtained with peracids are within 60—80%). The most interesting result is obtained with oct-1-ene. Whereas with the TPP ligand this category of terminal olefins gives very poor yields of the corresponding epoxide, the Mn(TMP)Cl-catalysed reaction leads to a reasonable yield of 68% which corresponds to a turnover rate of 30—35 cycles per hour (calculated on converted olefin, not on initial rate). This result is in the range of molybdenum-catalysed epoxidation of terminal olefins with t-butyl hydroperoxide,[14] where reactions are performed in refluxing 1,2-dichloroethane, b.p. 83 °C, instead of ambient temperature as in our case.

Another striking feature is the outstanding results obtained with norbornene. With TPP, the conversion is never complete

† The following abbreviations are used in this paper: TMP = mesotetramesitylporphyrin dianion, TPP = mesotetraphenylporphyrin dianion, To-TP = mesotetra-(*o*-tolyl)porphyrin dianion, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

Table 1. Manganese porphyrin-catalysed epoxidation of various olefins by NaOCl[a]

Olefin	Catalyst	Time	Conversion	Epoxide Yield (%)	Selectivity
Styrene	Mn(TPP)OAc	30 min	100	80	80
	Mn(TMP)Cl	15 min	100	90	90
Oct-1-ene	Mn(TPP)OAc	4 h	5	1	
	Mn(TMP)Cl	3 h	69	68	>98
Norbornene[b]	Mn(TPP)OAc	30 min[c]	25	25	>98
	Mn(TMP)Cl	30 min	100	>98	>98
Cyclohexene	Mn(TPP)OAc	4 h	85	72	85
	Mn(TMP)Cl	2.5 h	97	97	>98
1-Methylcyclohex-1-ene	Mn(TPP)OAc	4 h	98	70	72
	Mn(TMP)Cl	2 h	98	92	94

[a] Standard reaction conditions: see Experimental section. Conversion, selectivity, and yield correspond to the percentage of consumed olefin *versus* initial olefin amount, of epoxide *versus* converted olefin, and of epoxide *versus* initial olefin amount, respectively. [b] *exo*-2,3-Epoxynorbornane is the only detected epoxide.[9b] [c] After this time, the conversion reaction stops.

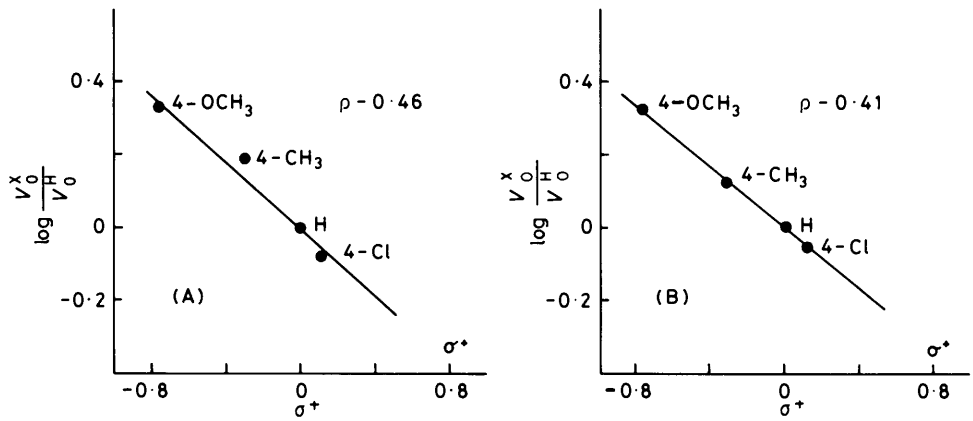

Figure 1. Plot of log (initial rate of substituted styrene to styrene) against σ^+ values of substituents for (A) Mn(TMP)Cl- and (B) Mn(TPP)OAc-catalysed epoxidation with NaOCl

and the epoxide yield is low (25%).* In the case of Mn(TMP)Cl-catalysed reactions, quantitative formation of *exo*-norbornene oxide is obtained.

Epoxidation of 4-*Substituted Styrenes.*—The great increase of the epoxide selectivity may be *a priori* interpreted in terms of steric control by the ligand of olefin approach to the active site, *i.e.* manganese–oxo, or of modified electronic properties of the metal–oxygen bond. In order to distinguish between these two effects, we made a comparative study on the epoxidation rate of 4-substituted styrenes with Mn(TMP)Cl and Mn(TPP)OAc. Electron-donating substituents enhance the rate of epoxidation. A Hammett treatment of the data, calculated from initial rates for a series of *para*-substituted styrenes (see Figure 1), gives a good linear correlation against σ^+ with ρ −0.46 and −0.41 for the Mn(TMP)Cl- and Mn(TPP)OAc-catalysed epoxidation, respectively. The negative value of ρ and the better correlation obtained with σ^+ than with σ strongly support the electrophilic character of the co-ordinated oxygen atom. Lindsay Smith has reported[15] a Hammett ρ value of −0.93 for the epoxidation of the same 4-substituted styrenes with PhIO–Fe(TPP)Cl, and a value of −1.30 for epoxidation with peracids.[16] These results are in favour of the development of a positive charge on the α-carbon atom of the styrene in the transition state.[17] In the absence of complementary kinetic data, *e.g.* isotopic effects, the lower ρ values obtained with NaOCl–Mn may be due to the radical character of oxygen atom transfer or to the position of the transition state closer to the reactants.

However, one can notice that the ρ value is nearly the same for TMP and TPP ligands indicating that the modification of the macrocyclic periphery by *ortho*-substituents does not affect the electronic state of the manganese–oxygen bond.

Epoxidation of cis-*Stilbene.*—Two factors influence the epoxidation rate and product selectivity of this reaction, the presence of a neutral ligand such as pyridine and the substitution pattern of the porphyrin ring as shown in Table 2. As already pointed out,[18] the presence of a small amount of pyridine is able to change the ratio between the *cis* and *trans* epoxides both with Mn(TPP)Cl–NaOCl (runs 1 and 3) and with Mn(TPP)Cl–PhIO (runs 5 and 8). We have previously provided evidences that this modification of stereoselectivity is related to the co-ordination of pyridine on manganese during the catalytic cycle.[11d,18]

However, in the present case, the product selectivity is mainly modified by steric hindrance of the porphyrin periphery. Groves *et al.*[5b] have already observed that changing Mn(TPP)Cl for Mn(To-TP)Cl as catalyst, in the Mn(porphyrin)X–PhIO system, reverses the *cis* : *trans* epoxide ratio (runs 5 and 6). In this context, the Mn(TMP)Cl-catalysed oxidation yields 90% of

* Yields above 40% are obtained by increasing the amount of catalyst (see ref. 9*b*). At present, we have no explanation why the conversion stops between 30 and 60 min.

Table 2. *cis*:*trans* ratio in the epoxidation of a *cis*-stilbene catalysed by Mn(porphyrin)X with different sources of oxygen[a]

Run	Pyridine[b]	Oxidant	Catalyst	% *cis*	% *trans*	Time[c]	Ref.
1	None	NaOCl	Mn(TPP)Cl	35	65	7	18
2	None	NaOCl	Mn(TMP)Cl	98	2	5	*d*
3	0.03 equiv.	NaOCl	Mn(TPP)Cl	70	30	3	18
4	0.03 equiv.	NaOCl	Mn(TMP)Cl	98	2	2	*d*
5	None	PhIO	Mn(TPP)Cl	38	62	*e*	5*b*
6	None	PhIO	Mn(To-TP)Cl	74	26	*e*	5*b*
7	None	PhIO	Mn(TMP)Cl	90	10	5	*d*
8	0.15 equiv.	PhIO	Mn(TPP)Cl	57	43	5	18
9	0.03 equiv.	PhIO	Mn(TMP)Cl	97	3	5	*d*

[a] All reactions are performed in standard conditions (see Experimental section). [b] Pyridine equivalents with respect to the equivalents of substrate. [c] Time refers to conversion >80%. [d] This work. [e] Unknown.

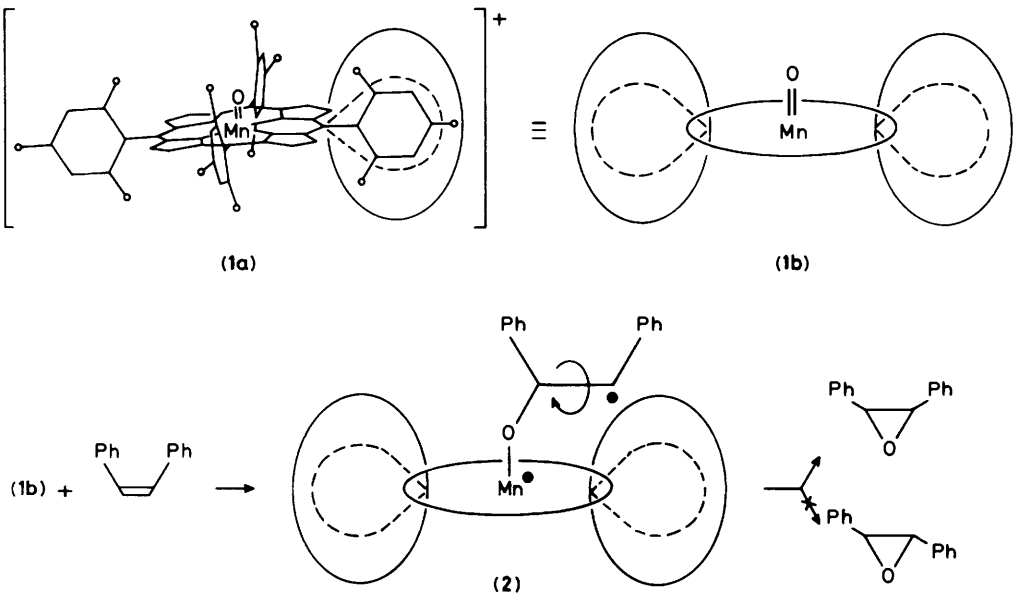

Figure 2. Schematic representation of: (**1a**) high-valent manganese–oxo species formed in the presence of the oxidant; (**1b**) the different steric hindrance around the active oxygen passing from TPP (– – –) to TMP (——) ligands; (**2**) the intermediate biradical adduct

cis-epoxide (run 7) but, quite surprisingly, a nearly quantitative yield (98%) of *cis*-epoxide is obtained by employing the Mn(TMP)Cl–NaOCl oxidizing system in the absence of pyridine (run 2).

These results are consistent with a mechanism (see Figure 2) in which the restricted dimension of the 'open well' around the manganese–oxo or 'oxo-like' species[10] strongly influences the possibility of rotation around the carbon–carbon bond of the intermediate biradical adduct formed, as previously proposed by Groves.[5b]

Finally, the presence of pyridine is effective not only on the selectivity but also on the epoxidation rate which is considerably enhanced (runs 1 and 3, 2 and 4) as already noted for the oxidation of other olefins.[18]

Conclusions.—The results described indicate that the biomimetic epoxidation system Mn(porphyrin)X–NaOCl is strongly influenced by: (i) the nature of the axial ligand *trans* to the active metal–oxo species and (ii) the 'open-well effect' due to the steric hindrance of modified porphyrins. As in enzymes, both effects contribute to modulate the rate and the selectivity of this catalytic reaction.

Work is in progress to demonstrate similar effects in hydroxylation of hydrocarbons with the same system.

Experimental

Materials.—All olefins, except *cis*-stilbene and norbornene, were passed through short alumina columns to remove traces of peroxides. Norbornene was purified by sublimation. All other chemicals were used as received. Commercial sodium hypochlorite (*ca.* 0.35N; Prolabo) was used. The epoxides, employed as authentic samples, were prepared from the corresponding alkenes with 3-chloroperbenzoic acid by standard procedures.[19] Iodosylbenzene was prepared following the method of Sharefkin *et al.*[20]

Mesotetramesitylporphyrin $TMPH_2$.—The porphyrin was prepared by condensation of freshly distilled pyrrole and mesitaldehyde, according to the method of Badger *et al.*[21] The zinc complex was demetallated by shaking a toluene solution with concentrated HCl. Column chromatography of the crude product, oxidation with DDQ[22] (2,3-dichloro-5,6-dicyanobenzoquinone), and subsequent dry-column chromatography[23] on neutral alumina (CH_2Cl_2 as eluant) gave $TMPH_2$ (3%).

Mesotetramesitylporphyrinatomanganese Chloride, Mn(TMP)Cl.—The procedure is based on the method published by Adler[24] and partially modified by Basolo *et al.*[25] The chlorin-free porphyrin $TMPH_2$ (500 mg) was dissolved in

refluxing DMF (250 ml). Upon dissolution, $Mn(OAc)_2 \cdot 4H_2O$ (260 mg) was added in two portions over 30—40 min. Thin-layer chromatography indicated no $TMPH_2$ at this point (analytical Merck TLC silica gel 60; CH_2Cl_2 as developer). The mixture was cooled and poured into a flask containing a solution of ice-cold saturated sodium chloride. The green precipitate was filtered out and washed with water several times. The solid was air-dried, dissolved in MeOH (*ca.* 350 ml), and filtered. The resulting solution was poured into ice-cold 6M aqueous HCl solution (350 ml). The green precipitate was filtered out again, washed with water, and air-dried overnight. The product was purified by dry-column chromatography[23] (CH_2Cl_2 as eluant) and crystallized from hexane–dichloromethane to give lustrous green crystals (80%), $\lambda_{max.}(CH_2Cl_2)$ 374 (ε 43 000 dm^3 mol^{-1} cm^{-1}), 400 (35 000), 448sh (9 000), 478 (95 000), 532 (4 000), 587 (7 550), and 620 nm (7 950) (Found: C, 76.7; H, 6.0; N, 7.5. $C_{56}H_{52}ClMnN_4$ requires C, 77.2; H, 6.0; N, 6.4%).

Instrumentation.—Gas-chromatographic analyses were performed on an Intersmat instrument, model IGC 120 DFL, fitted with a Chromopack CPWAX 51 capillary column and equipped with flame ionization detector. Peak areas were measured by electronic integration using an Intersmat ICR 1B integrator. ^1H N.m.r. spectra were recorded on a Perkin-Elmer R12 or on a Bruker WH90 instrument, in Fourier transform mode. Visible spectra were measured on a Cary 14 or on a Beckman 35 spectrometer.

Epoxidation Procedure.—All kinetic experiments were performed as follows: aqueous NaOCl (1.75 mmol; 5 ml) was added to a vigorously stirred solution of Mn(TPP)OAc or Mn(TMP)Cl (0.006 25 mmol), benzyldimethyltetradecylammonium chloride (0.0125 mmol), pyridine (0.13 mmol), and substrate (1.0 mmol) in dichloromethane (2.5 ml), under nitrogen at room temperature. The reaction was periodically monitored by g.c., adding a small amount of the organic phase (0.1 ml) to a known quantity of external standard.

Oxidation with iodosylbenzene was carried out according to the following procedure: iodosylbenzene (1.25 mmol) was added to a stirred solution containing Mn(TMP)Cl (0.006 25 mmol), benzyldimethyltetradecylammonium chloride (0.0125 mmol), and substrate (1.0 mmol) in CH_2Cl_2 (2.5 ml). When all the iodosylbenzene was consumed, the catalyst was removed by passing the reaction mixture through a Florisil column ($CHCl_3$ as eluant). The eluted products were concentrated and analysed by n.m.r. spectroscopy, δ_H ($CDCl_3$; Me_4Si) 4.3 (2 H, s, *cis*-stilbene oxide) and 3.9 (2 H, s, *trans*-stilbene oxide). The reaction products were identified by comparison with authentic samples (for recent analytical data, see ref. 15), and response factors were calculated using standard solutions.

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