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The rate-determining step in the epoxidation of alkenes by the cytochrome P-450 model manganese(III) porphyrin/hypochlorite

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Abstract. Using low-temperature trapping experiments with 1,1-diphenyl-2-picrylhydrazine monitored by UV/Vis spectroscopy, it is shown that the rate-determining step in the epoxidation of alkenes by hypochlorite, catalysed by manganese(III) porphyrins, involves the formation of the active oxo-manganese species \( [(P)\text{MnO}]^+ \).

Introduction

The discovery, that the cytochrome P-450 mode of oxidation can be mimicked by simple metallo(III) porphyrins \([(P)\text{M}^{III}]^+; \text{M} = \text{Fe, Cr, Mn} \) using "single-oxygen" donors, has founded a new class of epoxidation systems. Typical "single-oxygen" donors are pentafluoroiodosylbenzene \((C_6F_5\text{IO})^+\), hydrogen peroxide \((\text{H}_2\text{O}_2)^2\), tert-butyl hydroperoxide \((\text{t-BuOOH})^3\), \(m\)-chloroperoxybenzoic acid \((\text{mCPBA})^4\), \(\beta\)-cyano-N,N-dimethylaniline N-oxide \((\text{pCNDMANO})^5\), and hypochlorite \((\text{OCl}^-)^6,7\). In general, these systems generate an electrophilic oxo-metal species \([(P)\text{MO}]^+\) which transfers its oxygen atom to an alkene to yield epoxide in a catalytic fashion. On the basis of product distributions, it can be concluded that, for all "single-oxygen" donors, the reaction proceeds via identical oxo-metal species\(^8\). The epoxidation rates depend on the type of "single-oxygen" donor, which suggests that the oxidant is present in or before the rate-determining step (r.d.s.).

In a previous study\(^9\), we established that the transportation of the hypochlorite anion from the aqueous phase to the organic layer is not the rate-limiting step. In the present article, we describe one way of measuring the rate of formation of the active \([(P)\text{MnO}]^+\) species. For mCPBA and pCNDMANO, these rates have been established by trapping the oxo-metal species with 2,4,6-tri-tert-butylphenol (TBPH)\(^0,1,13\) or with 1,1-diphenyl-2-picrylhydrazine\(^#\) (DPPH)\(^1,14\) to yield the stable 2,4,6-tri-tert-butylphenoxyl (TBP\(*\)) or 2,2-diphenyl-1-picrylhydrazyl (DPP\(*\))

\[\text{Cl}^- \rightarrow \text{to revert to (P)MnOCl}.\]

In addition, we showed that the kinetics observed by Collman et al. were caused by a gradual destruction of the employed axial ligand, viz. \(N\)-(4-acetylphenyl)imidazole\(^9\). Since the axial ligand is crucial for a proper functioning of the catalytic system, this destruction leads to an epoxidation rate which decreases with time.

To resolve the present disagreement, we sought an unambiguous way of determining which step is rate-determining. In a previous study\(^6\), we established that the transportation of the hypochlorite anion from the aqueous phase to the organic layer is not the rate-limiting step. In the present article, we describe one way of measuring the rate of formation of the active \([(P)\text{MnO}]^+\) species. For mCPBA and pCNDMANO, these rates have been established by trapping the oxo-metal species with 2,4,6-tri-tert-butylphenol (TBPH)\(^10,11\) or with 1,1-diphenyl-2-picrylhydrazine\(^#\) (DPPH)\(^13,14\) to yield the stable 2,4,6-tri-tert-butylphenoxyl (TBP\(*\)) or 2,2-diphenyl-1-picrylhydrazyl (DPP\(*\))
Scheme 2

radical, respectively, which can be detected spectrophotometrically. H* transfer reactions from DPPH (A and B, see Eqn. 1) are very rapid10,13.

\[
[(P)Mn^{IV}O]^+ + \text{DPPH} \rightarrow [(P)Mn^{IV}OH]^+ + \text{DPP}^* \quad (A)
\]

\[
[(P)Mn^{IV}OH]^+ + \text{DPPH} \rightarrow [(P)Mn^{II}]^+ + \text{H}_2\text{O} + \text{DPP}^* \quad (B)
\]

In experiments with mCPBA or pCNDMANO, an excess oxidant with respect to porphyrin catalyst can be used since these oxidants do not react with DPPH in the absence of porphyrin catalyst. This procedure cannot be followed with hypochlorite, because the "free" hypochlorite ion is an oxidant of TBPh and of DPPH in its own right. Therefore, we had to develop a modified procedure in which no "free" hypochlorite ion occurs in the reaction mixture. In our procedure, we treat \((P)Mn^{III}\) at -50°C with 1 equivalent of triethylbenzylammonium hypochlorite (TEBAOCl) to produce the stable \((P)Mn\text{OCl}\) complex9. This complex decomposes in a slow reaction to \((P)Mn^{II}\) (Eqn. 2).

\[
[(P)Mn^{III}]^+ + \text{OCI}^- \rightarrow (P)Mn\text{OCl} \quad (A)
\]

\[
(P)Mn\text{OCl} \rightleftharpoons [(P)Mn^0] + \text{Cl}^- \quad (B)
\]

To the \((P)Mn\text{OCl}\) solution, DPPH or any other substrate is added and the reaction is monitored conveniently with a spectrophotometer following the build-up of DPP* and \([(P)Mn^{III}]^+\). To prevent dimerization, we used the sterically hindered catalysts (chloro)manganese(III)\(5,10,15,20\)-tetakis(2,4,6-trimethylphenyl)porphyrinate \((Mn(T_{2.4.6}\text{trimMePP})Cl)\) and (chloro)manganese(III)\(5,10,15,20\)-tetakis(2,6-dichlorophenyl)porphyrinate \((Mn(T_{2.6}\text{diClPP})Cl)\).

**Experimental**

**Chemicals and reagents**

All reagents were purchased from Aldrich and were used as received unless otherwise stated. Dichloromethane was dried over CaCl\(_2\), distilled from CaCl\(_2\), and stored under N\(_2\) over 5,10,15,20-tetrakis(2,4,6-trimethylphenyl)porphyrin (H\(_2\)(T\(_{2.4.6}\text{trimMePP})) and 5,10,15,20-tetakis(2,6-dichlorophenyl)porphyrin (H\(_2\)(T\(_{2.6}\text{diClPP})) were synthesized and converted into Mn(T\(_{2.4}\text{trimMePP})Cl and Mn(T\(_{2.6}\text{diClPP})Cl using standard methods15,16.

Mn(T\(_{2.4}\text{trimMePP})Cl: UV/Vis (CH\(_2\)Cl\(_2\), \(\lambda/\text{nm}, [\log(e/\text{dm}^{-3}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1})]: 375 (4.67), 348 (4.60), 370 (4.71), 392 (4.55), 477 (4.97), 578 (4.01), 604 (3.66). Phenylacetaldehyde was purified by a double distillation under N\(_2\). Norbornene was sublimed. Cyclohexene was distilled and passed through a short column of alumina prior to use. TEBAOCl was prepared by dissolving triethylbenzylammonium chloride, TEBA, (0.5 g, 4.4 mmol) in 10 cm\(^3\) of an ice-cold 0.35 mol dm\(^{-3}\) sodium hypochlorite solution (obtained by dilution of a 10% sodium hypochlorite solution (Janssen Chimica)). When all TEBA had dissolved, the water was removed on a rotavap/oil pump combination at 20°C (0.001 mm Hg) to produce a clear white solid consisting of TEBA (X = OC\(_1\), Cl, OH) and inorganic salts. When perfectly dry and stored at 4°C in the absence of light, the compound is stable for several months. Solutions of TEBAOCl were prepared by shaking 75 mg of the solid with 1 cm\(^3\) of CH\(_2\)Cl\(_2\). The supernatant was then used to titrate the \((P)Mn(\text{III})\) solution. The molarity of the TEBAOCl solution, as determined by titration with DPPH, was 6.8 x 10\(^{-4}\) mol dm\(^{-3}\). A fresh TEBAOCl solution was prepared for each experiment.

**Equipment**

Kinetic measurements were carried out on a Perkin Elmer 555 spectrophotometer fitted with a home-built low-temperature device thermostatted at -50°C. A Varian Model 3700 gaschromatograph (5% Carbowax 20M on Chromosorb W, 2.50 m x 2 mm) connected to a Shimadzu C-R3A model integrator was used to quantify the amount of epoxide formed.

**Methods**

All low-temperature experiments were carried out under N\(_2\). A 1-cm quartz cell filled with a solution of Mn(T\(_{2.4}\text{trimMePP})Cl or Mn(T\(_{2.6}\text{diClPP})Cl in CH\(_2\)Cl\(_2\) (3 cm\(^3\), 2.25 x 10\(^{-5}\) mol dm\(^{-3}\)) was placed in the low-temperature device and allowed to cool to -50°C. Thereafter, TEBAOCl, dissolved in CH\(_2\)Cl\(_2\), was syringed in until the Mn(III) peak at 478 nm had decreased to \(\approx 5\%\) of its original height (ca. 0.1 cm\(^3\) were required). After further equilibrat-
ing for 15 min, 0.1 cm$^3$ of CH$_2$Cl$_2$ containing DPPH (7 × 10$^{-3}$ mol dm$^{-3}$) were added and optionally 4-picoline (4-methylpyridine) (0.2 mol dm$^{-3}$), methanol (0.5 cm$^3$) or phenylacetaldehyde (0.1 mol dm$^{-3}$). The progress of the reaction was followed by monitoring the change in absorbance at 478 nm ([P(Mn(III)]$^+$, log(e/dm$^{-1}$ · mol$^{-1}$ · cm$^{-1}$) = 5.08 in the absence of 4-picoline and log(e/dm$^{-1}$ · mol$^{-1}$ · cm$^{-1}$) = 4.89 in its presence) and at 520 nm in the absence of 4-picoline (DPP*, log(e/dm$^{-1}$ · mol$^{-1}$ · cm$^{-1}$) = 4.38) or at 530 nm [DPP*, log(e/dm$^{-1}$ · mol$^{-1}$ · cm$^{-1}$) = 4.39] when 4-picoline is present. Initial rates were determined from pseudo-zero-order plots of the data obtained during the first minute.

### Results and Discussion

The addition of TEOACl to Mn(T$_{2,4,6}$triMePP)Cl in CH$_2$Cl$_2$ at −50°C instantaneously causes the colour of the solution to turn from green to brown, which is illustrated by the spectral transformations shown in Fig. 1. This species has the structure Mn(T$_{2,4,6}$TMePP)OCl (2a)$^9$. The spectrum of 2a includes new bands at 422 nm [log(e/dm$^{-1}$ · mol$^{-1}$ · cm$^{-1}$) = 5.06] and 520 nm [log(e/dm$^{-1}$ · mol$^{-1}$ · cm$^{-1}$) = 4.23]. At −50°C, 2a is stable for several hours. Similar results were obtained using Mn(T$_{2,4,6}$diClPP)Cl in which case Mn(T$_{2,6}$,diCIPP)OCl (2b) is formed. Addition of DPPH to a preformed solution of 2a at −50°C causes a decrease in the absorption bands of 2a (most prominently the 422 nm band) accompanied by a simultaneous increase in absorbance at 478 nm (formation of [(P)Mn(III)]$^+$) and 530 nm (formation of DPP$^*$). A typical trace of DPP$^*$ appearance, as monitored at 530 nm, is shown in Fig. 2. Rate data obtained for the reaction of DPPH with 2a and 2b are presented in Table I$^7$. It should be noted that the ratio of rates for DPP$^*$ and [(P)Mn(III)]$^+$ formation is close to the theoretical value of two.

What strikes the eye, is the “burst”, i.e. the almost instantaneous formation of DPP$^*$, occurring at t = 0 upon addition of DPPH. At first glance, this would suggest the presence of “free” hypochlorite ions in solution as a consequence of the following equilibrium (see Eqn. 3).

\[
\text{(P)MnOCl} + X^- \rightleftharpoons \text{(P)Mn(III)X} + \text{OCI}^-
\]  

However, several facts mitigate against the presence of “free” hypochlorite ions.

**i.** Exactly equal amounts (1 equivalent) of TEOACl solution are required for Mn(T$_{2,4,6}$triMePP)Cl and Mn(T$_{2,6}$diCIPP)Cl in order to convert them into 2a and 2b, respectively, disfavouring equilibrium (3), since this would depend on the kind of porphyrin ligand.

**ii.** Species 2a can be isolated as a brown solid$^{18}$. After several washings with ice-cold water to remove any “free” hypochlorite salt, solid 2a showed, when added to CH$_2$Cl$_2$ at −50°C, a similar [DPP$^*$] versus time profile (including the burst) as the in situ prepared complex 2a.

**iii.** When norbornene was added to 2a instead of DPPH, a similar burst and reaction rate [monitored by the appearance of [(P)Mn(III)$^+$] were obtained as with DPPH. In the case of norbornene, the formation of 90% of the theoretical amount of epoxide was established. This implies that the [(P)MnO]$^+$ species must have been involved, since the “free” hypochlorite ion is not an epoxidizing agent under these conditions.

Since the presence of a “free” hypochlorite ion may be excluded, the burst in DPP$^*$ formation must be due to the presence of a certain amount of free [(P)MnO]$^+$. Apparent, an equilibrium exists between [(P)MnO]$^+$ and (P)MnOCI$^{19}$ (Eqn. 4) before DPPH is added. This equilibrium affords a straightforward explanation of the results of Table I. The height of the burst is directly correlated to the amount of [(P)MnO]$^+$ present under equilibrium conditions. The large burst observed for 2a relative to 2b is the result of the facilitated cleavage of the O−Cl bond due to the presence of twelve electron donating CH$_3$ groups on the phenyl rings of the catalyst. The eight electron-withdrawing Cl groups of Mn(T$_{2,4,6}$diCIPP)Cl decrease the tendency of the O−Cl bond to break$^{20}$ as is reflected by the relatively low burst for complex 2b.

\[
\text{(P)MnOCI} \rightleftharpoons [(P)MnO]^+ + \text{Cl}^-
\]  

The addition of 4-picoline to the two-phase system increases the epoxidation rate$^{7,9,21}$. We attributed this effect to an easier cleavage of the O−Cl bond because of electron donation by 4-picoline$^{7,9}$. As a result, the rate of formation of [(P)MnO]$^+$ is increased. The experiments in which

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![Fig. 1. Spectral changes observed upon addition of TEOACl to a solution of Mn(T$_{2,4,6}$triMePP)Cl (1) in CH$_2$Cl$_2$ at −50°C to produce Mn(T$_{2,4,6}$triMePP)OCl (2a) (conditions: see experimental).](image1)

![Fig. 2. DPP$^*$ formation versus time upon addition of DPPH to a preformed solution of 2a in CH$_2$Cl$_2$ at −50°C, monitored spectrophotometrically at 530 nm (conditions: see experimental). The small peak indicated by the arrow is caused by the closure of the cell compartment.](image2)
4-picoline and DPPH are added simultaneously to 2a and 2b at low temperature, as summarized in Table I, support this view. Burst kinetics are also observed in the presence of 4-picoline. This is to be expected since 4-picoline is added after equilibration. The observed acceleration due to 4-picoline in the case of 2a (≈6 times) agrees reasonably well with the value previously reported by us for the two-phase epoxidation system with Mn(T246triMePP)Cl as catalyst (8 times)\(^3\). From \(\Delta H^*\) and \(\Delta S^*\) values, determined\(^2\) for Mn(T246triMePP)Cl in the two-phase system using cyclohexene as a substrate, the rate of epoxidation at \(-50^\circ C\) may be calculated. This rate amounts to \((5 \pm 5) \times 10^{-4} \text{ mol} \cdot \text{dm}^{-3} \cdot \text{s}^{-1} \cdot (\text{mol catalyst})^{-1}\) and is of the same order of magnitude as the rate measured for the reaction with DPPH (see Table I, \(v([\text{(P)Mn}]) + [\text{catalyst}]\)), viz. \(14.5 \times 10^{-4} \text{ mol} \cdot \text{dm}^{-3} \cdot \text{s}^{-1} \cdot (\text{mol catalyst})^{-1}\).

These experiments make it quite acceptable that reaction with DPPH and epoxidation in the two-phase system have an identical r.d.s., i.e. the formation of \([\text{(P)MnO}]^+\) from the hypochlorite complex 2.

We previously reported\(^9\) that, in the two-phase system, methanol increases the epoxidation rate by a factor of 1.5. This increase was ascribed to a better solvation of the chloride anion, pulling Eqn. 2 (B) more to the right\(^9\). Addition of methanol at low temperature also gives a faster DPP\(^*\) formation (1.3 times) (Table I). Methanol is not oxidized since DPP\(^*\) is produced in the theoretical amount.

In conclusion, our measurements indicate that the rate-determining step in the epoxidation of alkenes by hypochlorite catalysed by Mn(T246triMePP)Cl at \(-50^\circ C\). We used standard states of reactants at 1 mol \(\cdot\) dm\(^{-3}\). States A, B, C, and D represent: Mn(T246triMePP)Cl + OCl\(^-\) + S, (T246triMePP)MnOCl + Cl\(^-\) + S, [(T246triMePP)MnO]\(^+\) + 2 Cl\(^-\) + S, Mn(T246triMePP)Cl + Cl\(^-\) + SO, respectively. The values of \(\Delta G^*\) for B → C and C → D have been calculated from the values of \(K_{equilibrium}\) (Eqn. 4) and \(K_{observed} \times \frac{v((\text{P})\text{Mn}^{ll})^+)}{v([\text{catalyst}])}\) under the assumption that, in the case of DPPH, the return reaction of \((\text{T246triMePP})\text{MnO}^+\) with Cl\(^-\) (Eqn. 4) may be neglected. From the \(K_m\) value (9.36 \(\times\) 10\(^{-2}\))\(^9\) of the equilibrium depicted in equation 5, the energy difference between states A and B was determined. The heights of the ground states are reported relative to A.

\[
\text{Mn}(\text{P})\text{Cl} + \text{OCl}^- \rightleftharpoons \text{Mn}(\text{P})\text{OCl} + \text{Cl}^- \tag{5}
\]

The energy content of D has been set below that of A as befits an exergonic reaction. Since the reaction of B → C is rate determining under normal conditions, the energy barriers for A → B and C → D have been set below that of B → C.

### Acknowledgements

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### Table I. Kinetic data for complexes 2a and 2b.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Burst (%)(b,c)</th>
<th>(v(DPP^*))(d,e)</th>
<th>(v([\text{(P)Mn}^{ll}]^+))(d,e)</th>
<th>(v(DPP^*)/v([\text{(P)Mn}^{ll}]^+))</th>
</tr>
</thead>
<tbody>
<tr>
<td>without 4-picoline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>26</td>
<td>10.9 (\times) 10(^{-9})</td>
<td>5.7 (\times) 10(^{-9})</td>
<td>1.93</td>
</tr>
<tr>
<td>2b</td>
<td>8</td>
<td>1.2 (\times) 10(^{-9})</td>
<td>0.6 (\times) 10(^{-9})</td>
<td>1.85</td>
</tr>
<tr>
<td>with 4-picoline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>26</td>
<td>68.5 (\times) 10(^{-9})</td>
<td>32.6 (\times) 10(^{-9})</td>
<td>2.10</td>
</tr>
<tr>
<td>2b</td>
<td>8</td>
<td>25.9 (\times) 10(^{-9})</td>
<td>13.3 (\times) 10(^{-9})</td>
<td>1.95</td>
</tr>
<tr>
<td>with methanol and 4-picoline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>26</td>
<td>88.0 (\times) 10(^{-9})</td>
<td>42.2 (\times) 10(^{-9})</td>
<td>2.08</td>
</tr>
</tbody>
</table>

\(a\) Conditions, see experimental. \(b\) Initially formed amount of DPP\(^*\) or \([\text{(P)Mn}^{ll}]^+\) \(\times 100\%\). \(c\) Longer equilibration times did not alter these figures. \(d\) Rate/(mol \cdot dm\(^{-3}\) \cdot s\(^{-1}\)) (after the burst). \(e\) Error = 10\%.
The active species is often formulated as a high-valent metal complex, e.g. \([\text{P}Mn^\text{IV} = \text{O}]^+\) or \([\text{P}M^\text{V} = \text{O}]^+\). This representation, although correct with respect to the number of oxidizing equivalents present in the complex, implicates formal O\(^{-}\) anion. \(\text{Ab initio}\) calculations, however, show almost no charge on the oxygen atom (\(-0.09\) electron). (D. H. W. den Boer, J. H. van Lenthe and A. W. van der Made, Recl. Trav. Chim. Pays-Bas 107, 256 (1988)). We therefore favour the \([\text{P}Mn\text{O}]^+\) representation; see also D. T. Sawyer, Comm. Inorg. Chem. 6, 103 (1987). Thus, the active species is better described as an oxene–metal (O) rather than an oxo–metal (O\(^{2-}\)) complex. However, since the latter name is well established in the literature, it will be used throughout this article.


Increasing the DPPH concentration did not alter the observed rate. This shows that, although DPPH is employed in only a 10-fold excess based on Mn(T\(_2\)MePP)Cl, this excess is sufficient to trap all \([\text{P}Mn\text{O}]^+\) and render the reaction zero-order in substrate.

See also O. Bortolini, M. Ricci, B. Meunier, P. Friant, I. Ascone and J. Goulon, Nouv. J. Chim. 10, 39 (1986), although the species described therein is not explicitly identified as \([\text{P}Mn\text{OCl}]\).

The possibility that 1 equivalent of DPPH reacts quickly with \([\text{P}Mn\text{O}]^+\) and a second equivalent much more slowly with \([\text{P}Mn\text{OH}]^+\) is unlikely as in that case the burst should correspond to 50% of the total amount of DPPH produced. Moreover, other kinetic studies have shown that both reactions (A) and (B) of Eqn. 1 are very rapid.

This result explains the somewhat confusing observation that Mn(T\(_2\)diClPP)Cl is a very ineffective catalyst under normal two-phase conditions, although it meets all requirements for a good catalyst (sterically hindered and electropositively substituted). With hypochlorite as oxidant, these favourable properties are outweighed by the fact that the O−Cl bond can be broken only with difficulty. For other oxidants, e.g. C\(_6\)F\(_5\)IO, H\(_2\)O or pCNDMANO, the disfavouring effect of Cl substituents on the formation of the \([\text{P}Mn\text{O}]^+\) species is less severe, since a neutral molecule, i.e. C\(_6\)F\(_4\)I, H\(_2\)O or pCNDMA, has to be split off. As a result, Mn(T\(_2\)diClPP)Cl is a very good catalyst with these oxidants.


A. W. van der Made, M. J. P. van Gerwen and C. B. Hansen, unpublished results.