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Effect of pH on the epoxidation of alkenes by the cytochrome P-450 model manganese(III) porphyrin/hypochlorite

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Abstract. The epoxidation of alkenes by hypochlorite catalysed by manganese(III) tetraarylporphyrins in a two-phase water/dichloromethane system is accelerated by lowering the pH of the aqueous phase. This effect is explained by a faster formation of the active [(P)MnO] + species from a (P)MnOCl complex for all types of porphyrin catalysts and additionally by a suppression of dimerization phenomena for non-sterically hindered catalysts.

Introduction

Effective epoxidation systems consisting of a metallo(III) porphyrin and a single oxygen donor have recently been developed1-7. Most of the oxidants employed, however, have a high price or a low oxygen content per gram, or are dangerous to handle. Hypochlorite does not suffer from these disadvantages and thus this system may be of practical value. The epoxidation reaction is carried out in a two-phase system: an organic layer (CH2Cl2) in which the catalyst [manganese(III) tetraarylporphyrin], substrate (alkene) and axial ligand (4-picoline) are dissolved and an aqueous phase which contains the hypochlorite1,2. By means of a phase-transfer catalyst (TEBA)8, the hypochlorite anion is transported into the organic phase. Recently, it has been reported that lowering the pH of the aqueous phase from pH 13.0 to 9.5 has a beneficial effect on the epoxidation rate6. This effect was interpreted in terms of an acceleration of the rate-determining break-down of a cyclic metallaoxetane intermediate (1) [Collman’s Michaelis-Menten scheme7] by an unknown mechanism. Since this Michaelis-Menten scheme contrasted with our previously reported scheme (see Scheme 1), in which the formation of the active species [(P)MnO] + (3)9 from a (P)MnOCl (2) complex is the rate-determining step, we decided to reinvestigate the “pH effect”.

Results and discussion

The reaction rates of the epoxidation of cyclohexene by various manganese(III) porphyrin catalysts at different pH values are given in Table I. The reaction is zero in alkene up to 40% conversion, indicating that the alkene is not involved in the rate-determining step2,10. The following features appear from our data: i. For all catalysts, a decrease in pH increases the epoxidation rate. The main increase is from pH 13.5 —► 12.7. ii. The increase in epoxidation rate on going from pH 13.5 to 12.7 is first order in proton for Mn(TPP)X. Catalysts with bulky and/or electronegative substituents [Mn(T2,4,6triMePP)X, Mn(T2,4,6triCIPP)X, Mn(T5,CIPP)X, Mn(TpentaFPP)X] show an order in proton less than one. iii. The selectivity with respect to epoxide formation decreases with decreasing pH.

Table I Rates and selectivities of cyclohexene epoxidation using manganese(III) tetraarylporphyrin catalysts at various pH values of the aqueous phase.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>pH</th>
<th>Rateb</th>
<th>Selectivityc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn(TPP)X</td>
<td>13.5</td>
<td>1.2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>6.1</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>6.4</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>11.0</td>
<td>7.0</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>8.3</td>
<td>82</td>
</tr>
<tr>
<td>Mn(T2,4,6triMePP)X</td>
<td>13.5</td>
<td>0.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>1.9</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>2.9</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>3.1</td>
<td>71</td>
</tr>
<tr>
<td>Mn(T2,4,6triCIPP)X</td>
<td>13.5</td>
<td>0.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>0.6</td>
<td>80</td>
</tr>
<tr>
<td>Mn(T5,CIPP)X</td>
<td>13.5</td>
<td>2.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>4.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>6.4</td>
<td>84</td>
</tr>
<tr>
<td>Mn(TpentaFPP)X</td>
<td>13.5</td>
<td>2.0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>3.0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>4.3</td>
<td>85</td>
</tr>
</tbody>
</table>

a For conditions, see experimental. b Rate x 105/(mol · dm -3 · s -1). c [epoxide formed]/[cyclohexene consumed] x 100%.

At pH 13.5, the reaction order in Mn(TPP)X decreases from one to zero with increasing catalyst concentration (0–2.5 × 10 -3 mol · dm -3)10,11. Under the same conditions, Mn(T2,4,6triMePP)X exhibits a linear first-order behaviour over the entire concentration range. This decrease in order was explained by an increased dimerization (5) and catalyst destruction at higher Mn(TPP)X concentrations10. These processes do not take place with the sterically hindered Mn(T2,4,6triMePP)X catalyst. Remarkably, at pH ≤ 12.7, both Mn(TPP)X and Mn(T2,4,6triMePP)X show a first-order behaviour over the range 0–2.5 × 10 -3 mol · dm -3 (see Fig. 1). This points to the absence of dimerization phenomena at lower pH.
Previously\textsuperscript{12}, we have shown that dimerization can be prevented by trapping the \([(P)MnO]^{+}\) species (3) with carbonyl compounds to form a carbonyl oxide, which in turn acts as a powerful epoxidation reagent\textsuperscript{13}. The absence of any rate-enhancing effect of cyclopentanone at pH 10 for Mn(TPP)X (epoxidation rate without cyclopentanone $8.3 \times 10^{-5}$ mol $\cdot$ dm$^{-3}$$ \cdot$ s$^{-1}$, with cyclopentanone $8.4 \times 10^{-5}$ mol $\cdot$ dm$^{-3}$$ \cdot$ s$^{-1}$) supports the conclusion that dimerization is absent under these conditions\textsuperscript{14}. 

cis-Stilbene has been used as a probe for the stereoselectivity of the epoxidation reaction\textsuperscript{10,15}. The ratio of its possible reaction products, cis- and trans-stilbene epoxide, reflects the outcome of the competition between direct ring closure (cis-epoxide) and C–C bond rotation followed by ring closure (trans-epoxide). Any alteration in the reactivity of the oxo species (and so of the oxygen atom in complex 4) or of the break-down of the oxo-species-substrate complex 1 would, therefore, be expected to have an effect on the cis/trans ratio. In the absence of 4-picoline\textsuperscript{16}, no change in the cis/trans ratio is observed on lowering the pH (cis/trans ratio at pH 13.5 is 60:40, cis/trans ratio at pH 10.0 is 62:38). Therefore, a change in mechanism as well as a faster decomposition of the oxo-species-substrate complex (as suggested by Montanari \textit{et al.})\textsuperscript{4} may be excluded.

At pH 13.5, the colour of the reaction mixture is brown ($\lambda_{\text{max}}$ 422 nm), indicative of a high-valent manganese(IV or V) species\textsuperscript{17}. Since our kinetic measurements have shown that the formation of the \([(P)MnO]^{+}\) species is the rate-determining step\textsuperscript{2,10}, this species will only be present in very low concentrations. An accumulation of the dimer \([(P)Mn^{IV}O-Mn^{IV}(P)]^{2+}\) (5) may also be excluded since a similar colour of reaction mixture is observed in the case of Mn(T$_{2,4,6}$triMePP)X which cannot dimerize. Elsewhere\textsuperscript{10,18} we have presented evidence to show that the brown colour is the result of a build-up of a \((P)MnOCl\) species (2) which decomposes in a rate-determining step to the active \((P)MnO\)\textsuperscript{+} species (3). This step is rate-determining, partly because, in order to form the \([(P)MnO]^{+}\) species, the \((P)MnOCl\) complex has to expel a chloride anion which is rather poorly solvated in the apolar CH$_2$Cl$_2$ phase (see Scheme 2). At a lower pH, the \([(P)MnO]^{+}\) species will be formed more rapidly by expulsion of a neutral HCl molecule from a protonated \([(P)MnHOCl]^{+}\) species. Low-temperature trapping experiments with DPPH (according to the method described in ref. 18) support this view. Addition of a HCl containing DPPH solution in CH$_2$Cl$_2$ to a \((P)MnOCl\) solution results in a faster formation of DPP* [For Mn(T$_{2,4,6}$triMePP)X we found $v(DPP^*)$ $68.5 \times 10^{-9}$ mol $\cdot$ dm$^{-3}$$ \cdot$ s$^{-1}$ in the presence of 4-picoline and $v(DPP^*)$ $150 \times 10^{-9}$ mol $\cdot$ dm$^{-3}$$ \cdot$ s$^{-1}$ in the presence of 4-picoline and HCl]. This indicates a faster formation of \([(P)MnO]^{+}\) from \([(P)MnHOCl]^{+}\). The latter species can be formed by coordination of HOCI to the Mn(P)X or by protonation of the \((P)MnOCl\) complex. If the former possibility were true, a phase-transfer catalyst would no longer be required at low pH since the neutral HOCI species does not require a phase-transfer catalyst to cross the phase boundary. The latter possibility is most likely since, even at pH 10.0, a phase-transfer catalyst is needed. Since the acid acts catalytically, only a small amount is required. This explains the sharp increase in epoxidation rate upon a moderate change in pH. Actually, the formation of \([(P)MnO]^{+}\) is accelerated to such an extent that no large accumulation of
(P)MnOCl takes place, resulting in a less brown, but greener, reaction mixture \( \lambda_{\text{max}} 476 \text{nm} \) [Mn\(^{11}\)(P)X]\(^{16}\). The epoxidation rate can be increased somewhat further by working at pH < 12.7. However, under these conditions, the selectivity with respect to epoxide formation is markedly lowered. A GC/MS analysis showed the formation of 3-chlorocyclohexene, trans-1,2-dichlorocyclohexane, 2-chloro-5-cyclohexen-1-ol and 2-chloro-5-cyclohexen-1-one. These products are derived from non-catalytic reactions involving halohydrin and ClO\(^-\) routes\(^{20,21}\). The rather modest change in rate observed upon lowering the pH below 12.7 indicates that, under these conditions, the formation of the active [(P)MnO\(^+\)] from [(P)MnHOCl\(^+\)] remains the rate-determining step, i.e. its formation cannot be further accelerated by adding more protons.

Addition of methanol increases the polarity of the organic phase, leading to a more rapid formation of the [(P)MnO\(^+\)] species (at pH 13.5) because of a better solvation of the chloride anion\(^{10,22}\). At pH 10.0, methanol also increases the epoxidation rate since HCl is more soluble in a polar organic phase (epoxidation rate without methanol 8.3 \( \times 10^{-5} \) mol \( \cdot \) dm\(^{-3}\) \( \cdot \) s\(^{-1}\), with methanol 15.0 \( \times 10^{-5} \) mol \( \cdot \) dm\(^{-3}\) \( \cdot \) s\(^{-1}\)). The similar behaviour of the system at pHs 13.5 and 10.0 supports the view that, on lowering the pH, there is no major change in mechanism, i.e. although the formation of the [(P)MnO\(^+\)] is accelerated, it still remains the rate-determining step.

The absence of dimerization phenomena at lower pH as indicated by the lack of an accelerating effect of cyclopentanone and the observed first order in Mn(TPP)X may be explained in the following way. In our original scheme (see Scheme 1), \( \mu \)-oxo dimer formation, followed by destruction, is the result of a reaction between [(P)MnO\(^+\)] and [(P)Mn\(^{11}\)]\(^+\) (2). We now propose that, in addition, the \( \mu \)-oxo dimer may also be formed by a reaction between the (P)MnOCl complex and [(P)Mn\(^{11}\)]\(^+\). Since, at pH 13.5, the concentration of (P)MnOCl is high, the dimerization reaction via (P)MnOCl may be very important at this pH. At lower pH, the (P)MnOCl concentration is reduced and consequently the dimerization reaction via this route.

Additionally, the dimer concentration is also suppressed by an effect noted by Spreer et al.\(^{23}\). They observed that the reversal of the \( \mu \)-oxo dimer, obtained by treating the then soluble Mn(T4MePyP)X with hypochlorite, to Mn\(^{11}\)(P)X and [(P)MnO\(^+\)] was greatly accelerated at lower pH. As a consequence, less catalyst is tied up in the catalytically less active dimer state.

Dimerization is only important in the case of a non-sterically hindered catalyst such as Mn(TPP)X\(^{10}\). All other catalysts employed in this study are classified as sterically hindered catalysts and show no dimerization phenomena\(^{10}\). This explains the drastic increase in epoxidation rate upon lowering the pH for Mn(TPP)X compared to the other catalysts studied. With Mn(TPP)X, the rate of formation of the active species is increased and, additionally, the rate retarding dimer formation is suppressed. For the sterically hindered catalysts, only a more rapid formation of the [(P)MnO\(^+\)] species is observed.

Conclusions

On the basis of these results, we conclude that the observations concerning the effect of lowering the pH of the aqueous phase are accounted for by our previously proposed reaction scheme.

Experimental

Epoxidation reactions were carried out as described previously\(^2,10\) with the following concentrations: [Mn(P)X] \( 2.5 \times 10^{-3} \) mol \( \cdot \) dm\(^{-3}\), [TEBA] \( 5 \times 10^{-3} \) mol \( \cdot \) dm\(^{-3}\), [cyclohexene] 0.626 mol \( \cdot \) dm\(^{-3}\), [4-picoline] 1.3 mol \( \cdot \) dm\(^{-3}\) in CH\(_2\)Cl\(_2\) (volume organic phase 630 \( \mu \)l), aqueous NaOCl (Janssen Chimica 2 cm\(^2\), 0.4 mol \( \cdot \) dm\(^{-3}\), pH 10.0–13.5). The pH was measured using a high-pH stable pH electrode (Ingold U 455-S7) and adjusted by adding 1 mol \( \cdot \) dm\(^{-3}\) aqueous HCl. Hypochlorite solutions of pH < 13 were freshly prepared for each experiment. Reaction temperature 5.0 ± 0.2°C. Carbonyl compound experiments: [cyclopentanone] 0.179 mol \( \cdot \) dm\(^{-3}\). cis/trans ratios were determined by NMR spec-
troscopy according to ref. 15. Methanol effect: MeOH/CH₂Cl₂ = 1:4 v/v. Trapping experiments were performed according to ref. 18. H₃(T₂₆triMePP), H₂(T₂₆diClPP) and H₂(TpentaFPP) were synthesized according to ref. 24 with 2.5 mol dm⁻³ (instead of 0.5 mol dm⁻³) BF₃ etherate complex as a catalyst. 'HNMR and UV/Vis spectra were as previously reported.

References

8. Abbreviations: 4-Picoline = 4-methylpyridine, DPPH = 1,1-diphenyl-2-picrylhydrazine, DPP⁺ = 2,2-diphenyl-1-picryl-hydrazyl radical, L = axial ligand (4-picoline), Mn(P)X = manganes(III) porphyrinato chloride, T₂₆triMePP = 5,10,15,20-tetramesitylporphyrin, TEBA = triethylbenzyl-ammonium chloride. TpentaFPP = 5,10,15,20-tetrakis(penta-fluorophenyl)porphyrin, TPP = 5,10,15,20-tetraphenylporphyrin.
15. Carbonyl oxides are stable at these pH values.
17. Since, in the presence of 4-picoline, the reaction is highly stereospecific (cis/trans ratio 95/5) because of steric effects (see A. W. van der Made and R. J. M. Nolte, J. Mol. Catal. 26, 333 (1984)), measurements were made in the absence of 4-picoline.
20. The Mn–OCI bond does not have an ionic character as, for example, does the MnIII–Cl bond. This is deduced from its UV/VIS spectrum which shows λmax at 422 nm in contrast to all known ionic MnIII porphyrin complexes which have λmax at ≤ 476 nm. Ab initio calculations on the (P)MnOCI complex are in progress.