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## CYCLOHEXENE EPOXIDATION BY THE MONO-OXYGENASE MODEL (TETRAPHENYLPORPHYRINATO)MANGANESE(III) ACETATE-SODIUM HYPOCHLORITE

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### Summary

Oxidation of cyclohexene by (tetraphenylporphyrinato)manganese(III) acetate (Mn(TPP)OAc) and sodium hypochlorite as oxidant has been studied in a two-phase water-dichloromethane system in the presence of a phase transfer reagent. A kinetic study with this system reveals the following features: (1) the main product of the reaction (yield  $\geq 80\%$ ) is 1,2-epoxycyclohexane; (2) in the presence of excess oxidant the reaction is zero order in cyclohexene; (3) the reaction order in Mn(III) concentration decreases from 1 to  $\approx 0$  with increasing concentration of this catalyst; (4) the reaction order in hypochlorite decreases from 1 to 0 with increasing concentration of this reagent; (5) pyridine and substituted pyridines enhance the reaction rate. A Hammett treatment of the rate data for various substituted pyridines gives a  $\rho$ -value of  $-1.00$ ; (6) anchoring of Mn(TPP)OAc onto poly(vinylpyridine) or a polymer of an isocyanide,  $(R-N=C\langle)_n$ , increases the reaction rate by a factor of 1.5 - 6.0.

Based on these findings and on evidence from the literature, a mechanism for the epoxidation of cyclohexene is proposed. The key intermediate is an oxo-manganese(V) complex, which is formed from Mn(III) and hypochlorite in a pyridine-catalyzed step. The Mn(V) species may react in 2 ways: either with substrate to give epoxide or with Mn(III) to form a  $\mu$ -oxo-manganese(IV) dimer. The latter route is suppressed when the catalyst is anchored to the polymeric support.

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### Introduction

Epoxides are important starting materials in the synthesis of a large number of organic compounds [1]. Nowadays, much effort is being directed towards the development of efficient catalysts that epoxidize olefins under

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mild conditions [2]. Nature has developed the mono-oxygenase enzymes such as cytochrome P-450 which are capable of oxidizing a wide variety of compounds, among others olefins [3]. The active center in these enzymes is an iron(III) porphyrin that catalyzes the NADPH-dependent activation of molecular oxygen. One oxygen atom is incorporated into the substrate, the second is reduced to water.

Recently, interesting model systems have been described [4 - 6], in particular by Groves *et al.* [4] and Hill *et al.* [5], that mimic the enzymatic oxidation of alkanes and olefins. These systems consist of a synthetic metallo(III) porphyrin and a single oxygen donor such as iodosylbenzene. Attention is focussed on the mechanism of the catalytic process and on an elucidation of the intermediate species that are involved. The single oxygen donor systems may provide important information as to which routes should be followed to attain dioxygen activation, a challenging problem that has not yet been solved adequately by chemists.

In the course of our present research [6g, h] we describe a mechanistic study of cyclohexene epoxidation by the mono-oxygenase model (tetraphenylporphyrinato)manganese(III) acetate and sodium hypochlorite as oxidant. This system was discovered by Meunier *et al.* [6c - e] and is of potential practical value as hypochlorite is a relatively cheap oxygen donor.

In mono-oxygenases the metalloporphyrin is surrounded by a globin, which creates site isolation of the active center. In model systems the effect of site isolation on catalytic activity has not yet been studied. In this paper we also deal with this point.

## Results

Epoxidation of cyclohexene by (tetraphenylporphyrinato)manganese(III) acetate (Mn(TPP)OAc), **1a**, and sodium hypochlorite was measured in a two-phase water-dichloromethane system in the presence of a phase-transfer catalyst (PTC). Under standard conditions, *i.e.* pH 13 of the aqueous layer, the main product of the reaction (yield  $\geq 80\%$ ), is 1,2-epoxycyclohexane (Table 1). In the course of the reaction small amounts of 2-cyclohexen-1-one, 2-cyclohexen-1-ol (or 3-cyclohexen-1-ol) and *trans*-2-chlorocyclohexanol are formed. At pHs  $< 9$  the epoxide is partly decomposed to *trans*-1,2-cyclohexanediol while the amount of above-mentioned side products increases.

## Kinetics

Rates were determined by measuring the formation of 1,2-epoxycyclohexane by GLC using toluene as an internal standard. The latter compound was not converted under the reaction conditions employed, as was checked separately. Three different phase-transfer reagents were tested: benzyldimethyltetradecylammonium chloride, dihexadecyldimethylammonium chloride and benzyltriethylammonium chloride (TEBA). Within

TABLE 1  
Oxidation of cyclohexene by different catalytic systems

| Catalyst                           | Conversion of cyclohexene (%) | Yield of epoxide (%)              | Selectivity of epoxide (%) |
|------------------------------------|-------------------------------|-----------------------------------|----------------------------|
| OCl <sup>-</sup> /PTC <sup>a</sup> | 90                            | 18                                | 20                         |
| OCl/PTC/Mn(TPP)OAc <sup>b</sup>    | 100                           | 80                                | 80                         |
| OIPh/Mn(TPP)X <sup>c</sup>         | —                             | 31(4)                             | ≤31 (≤4)                   |
| OIPh/Fe(TPP)Cl                     | —                             | 55 <sup>d</sup> , 48 <sup>e</sup> | ≤55, ≤48                   |

<sup>a</sup>Taken from [9] pH = 8 - 9. Other reaction products are: *trans*-1,2-dichlorohexane (30%), *trans*-2-chlorocyclohexanol (14%), 3-chlorocyclohexene (0.7%), 4-chlorocyclohexene (0.2%), 2-chlorocyclohexanone (0.1%), 3-cyclohexenol (0.1%), 3-cyclohexenone (0.2%).

<sup>b</sup>This work pH = 13. Other reaction products are: 2-cyclohexen-1-one (<1%), 2- (or 3-)cyclohexen-1-ol (<1%), *trans*-2-chlorocyclohexanol (<1%). Addition of pyridine does not affect the product distribution.

<sup>c</sup>From [5d]. Actual catalysts are 2 complexes isolated from the reaction mixture, *i.e.* 8 (X = Cl<sup>-</sup>) and 7 (X = N<sub>3</sub><sup>-</sup>). The data for the latter complex are given in parentheses. Other reaction products are (yields based on iodosylbenzene consumed): 8, 3-chlorocyclohexene (32%), 2-cyclohexen-1-ol (7%), 2-cyclohexen-1-one (1%); 7, 2-azidocyclohexene (41%), 2-cyclohexen-1-ol (<1%), 2-cyclohexen-1-one (<1%).

<sup>d</sup>From [4f]. Yield based on iodosylbenzene consumed. Other reaction product is 2-cyclohexen-1-ol (15%).

<sup>e</sup>From [6f]. Yield based on iodosylbenzene consumed. Other reaction product is 2-cyclohexen-1-ol (13%).

experimental error no difference in activity between these phase-transfer reagents was observed. Therefore, TEBA was chosen for further experiments.

When excess sodium hypochlorite is used, reactions are zero order in cyclohexene up to 90% conversion. The results of varying the Mn(TPP)-OAc concentration at a constant sodium hypochlorite concentration of 0.45 M are given in Table 2. In the concentration range  $0 < [\text{Mn(TPP)X}]^* < 8.26 \times 10^{-3}$  M of the catalyst in the organic phase, the reaction order in catalyst decreases from 1 to  $\approx 0$  with increasing catalyst concentration. A Lineweaver-Burk plot [7] of reciprocal reaction rate *versus* the reciprocal of Mn(TPP)X concentration gives a straight line with slope  $K_m/V_{\max} = 36.5 \pm 0.5$  s and intercept  $1/V_{\max} = (7.5 \pm 0.3) \times 10^3 \text{ M}^{-1} \text{ s}$  (Fig. 1A).

The rate data obtained when varying the sodium hypochlorite concentration at a constant Mn(TPP)OAc concentration of  $3.31 \times 10^{-3}$  M are presented in Table 3. In the concentration range  $0.11 < [\text{NaOCl}] < 0.45$  M in the aqueous phase the reaction order in sodium hypochlorite decreases from 1 to 0 with increasing hypochlorite concentration. The corresponding Lineweaver-Burk plot (Fig. 1B) is linear with slope  $K_m/V_{\max} = (2.0 \pm 0.1) \times 10^3$  s and intercept  $1/V_{\max} = (1.05 \pm 0.05) \times 10^4 \text{ M}^{-1} \text{ s}$ .

\*X = monovalent anion.

TABLE 2

Dependence of rate of cyclohexene epoxidation on concentration of Mn(TPP)X<sup>a</sup>

| [Mn(TPP)X] × 10 <sup>3</sup> <sup>b</sup><br>(M) | <i>v</i> × 10 <sup>5</sup><br>(mol l <sup>-1</sup> s <sup>-1</sup> ) |
|--|--|
| 0.66   | 1.60   |
| 1.80   | 3.46   |
| 2.74   | 4.83   |
| 3.44   | 5.53   |
| 4.13   | 6.13   |
| 4.96   | 6.63   |
| 6.20   | 7.33   |
| 8.26   | 9.16   |

<sup>a</sup>Reaction temperature 25.0 °C; [NaOCl] in aqueous phase 0.45 M, [4-MePy] in organic phase 1.169 M.

<sup>b</sup>Concentration in the organic phase.

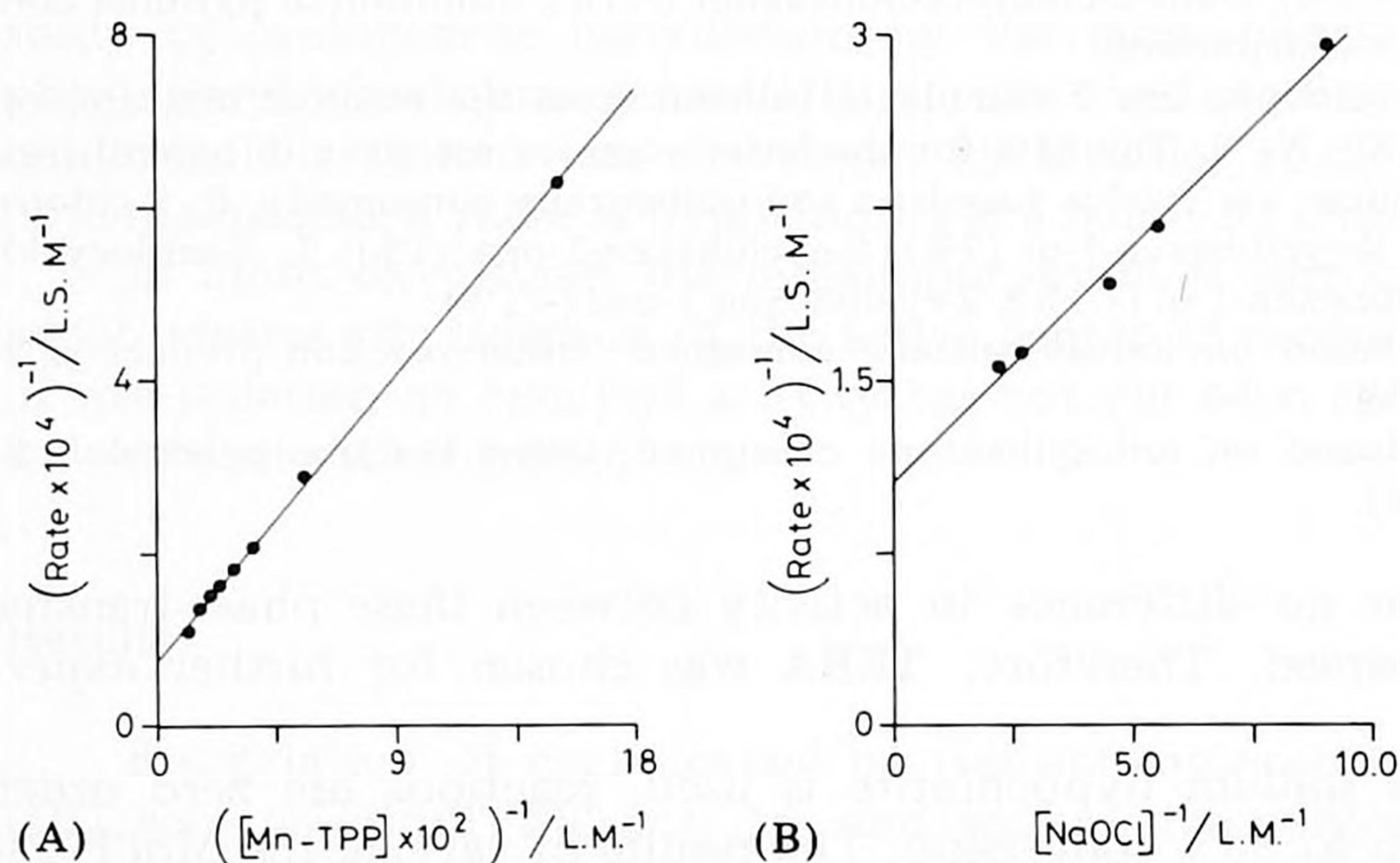


Fig. 1. Lineweaver-Burk plot of reciprocal rate of epoxidation *vs.* the reciprocal of Mn(TPP)X concentration (A); similar plot of reciprocal rate of epoxidation *vs.* the reciprocal of NaOCl concentration (B). For reaction conditions see Tables 2 and 3.

TABLE 3

Dependence of rate of cyclohexene epoxidation on concentration of NaOCl<sup>a</sup>

| [NaOCl] <sup>b</sup><br>(M) | <i>v</i> × 10 <sup>5</sup><br>(mol l <sup>-1</sup> s <sup>-1</sup> ) |
|-----------------------------|--|
| 0.11                        | 3.40   |
| 0.18                        | 4.63   |
| 0.22                        | 5.23   |
| 0.37                        | 6.19   |
| 0.45                        | 6.43   |

<sup>a</sup>Reaction temperature 25.0 °C; [Mn(TPP)X] 2.75 × 10<sup>-3</sup> M, [4-MePy] 1.949 M (both concentrations are in the organic phase).

<sup>b</sup>Concentration in the aqueous phase.

Pyridine and substituted pyridines considerably enhanced the rate of epoxidation, in accordance with similar findings by Meunier *et al.* [6d, k]. The rate-enhancing effect of various substituted pyridines are given in Table 4. As can be seen from this Table, electron-donating substituents at the pyridine ring increase the rate. A Hammett treatment of the rate data gives a good linear correlation and a  $\rho$ -value of  $-1.00 \pm 0.05$  (Fig. 2).

The effect of varying the concentration of 4-methylpyridine at constant NaOCl and Mn(TPP)OAc concentrations of 0.45 and  $3.30 \times 10^{-3}$  M, respectively, is given in Fig. 3. The rate of epoxidation increases with increasing concentration of this additive up to a maximum value at a [4-methylpyridine]/[Mn(TPP)X] ratio of about 650 and subsequently slows down. Pyridine-*N*-oxide gave a small rate-enhancing effect. Imidazole was found to inhibit epoxidation completely.

TABLE 4

Rate of cyclohexene epoxidation in the presence of various substituted pyridines and correlation with Hammett  $\sigma$ -values<sup>a</sup>

| X in XC <sub>5</sub> H <sub>4</sub> N | $\nu \times 10^5$<br>(mol l <sup>-1</sup> s <sup>-1</sup> ) | $\sigma_X^b$ |
|---------------------------------------|---|--------------|
| 3-CH <sub>3</sub>                     | 7.30  | -0.069       |
| 4-CH <sub>3</sub>                     | 8.17  | -0.170       |
| H                                     | 6.50  | 0            |
| 3-Br                                  | 2.55  | 0.391        |
| 3-CN                                  | 1.32  | 0.678        |
| 4-CN                                  | 1.28  | 0.628        |

<sup>a</sup>Reaction temperature 25.0 °C; [XC<sub>5</sub>H<sub>4</sub>N] in the organic phase varies with X. The rates are corrected to a constant [XC<sub>5</sub>H<sub>4</sub>N] value of 1.46 M; [Mn(TPP)X] in organic phase  $3.44 \times 10^{-3}$  M; [NaOCl] in aqueous phase 0.45 M.

<sup>b</sup>See [12].

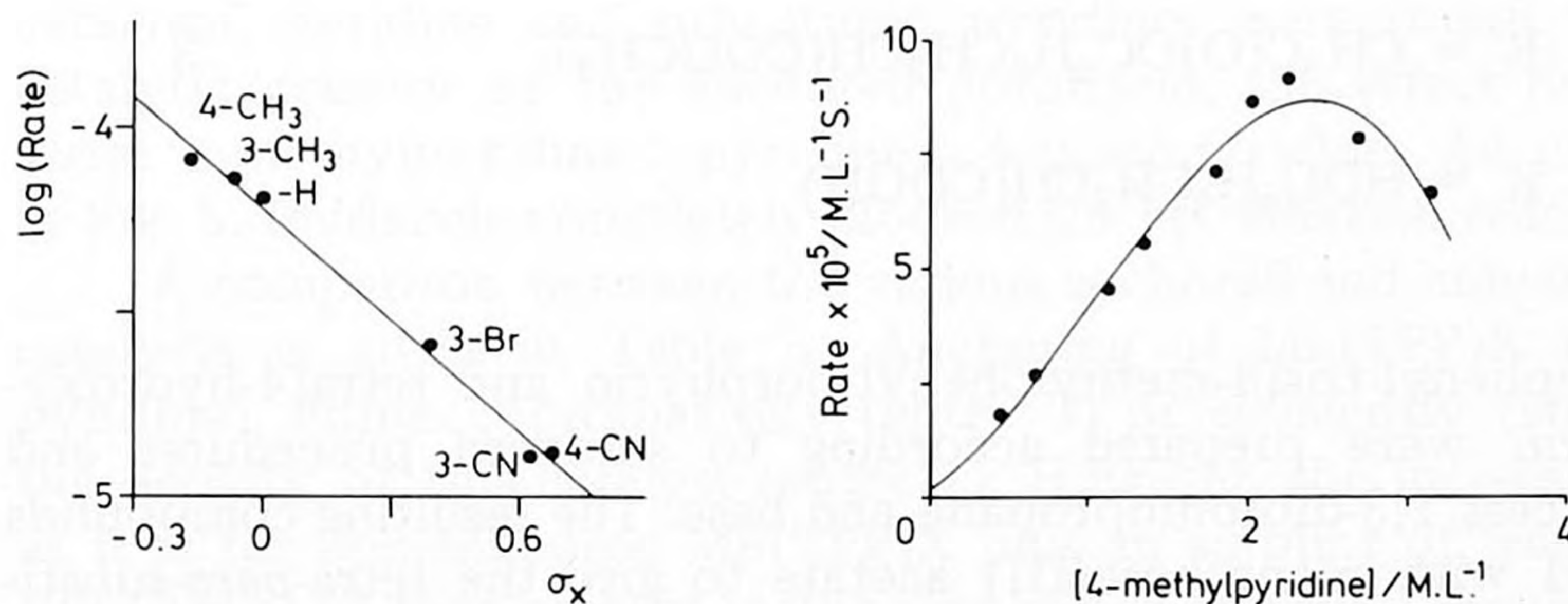


Fig. 2. Logarithm rate of cyclohexene epoxidation in the presence of various substituted pyridines *vs.* Hammett  $\sigma$ -values. For experimental conditions see Table 4.

Fig. 3. Rate of cyclohexene epoxidation as a function of concentration of 4-methylpyridine. Reaction conditions:  $3.4 \times 10^{-3}$  M Mn(TPP)OAc, [NaOCl] in aqueous phase 0.45 M.

### Anchoring

Site isolation of the Mn(TPP)X catalyst was achieved by anchoring this compound onto a polymeric support. Two types of support were used: a commercial poly(4-vinylpyridine-co-styrene) and a polymer of an isocyanide, (R-N=C<)<sub>n</sub> (3). Poly(4-vinylpyridine) has a relatively flexible backbone, whereas poly(isocyanide) 3 has a rigid helical main chain with 4 repeating units per helical turn (Fig. 4) [8]. The side chains of the latter polymer protrude into solution and, therefore, are easily accessible to reagents.

Polymer 3 was prepared from L-tyrosine (Scheme 1). The carboxylic acid function of the latter compound was esterified and its α-amino function converted into a formamide group. After protection of the phenolic -OH group by an acetyl function, the formamide was dehydrated to give the isocyanide. The latter compound was polymerized with nickel chloride to yield protected 3. The molecular weight of this polymer amounted to  $\bar{M}_v$  25 000, which corresponds to 100 repeating units. After deprotection, 3 was obtained in 51% overall yield from L-tyrosine.

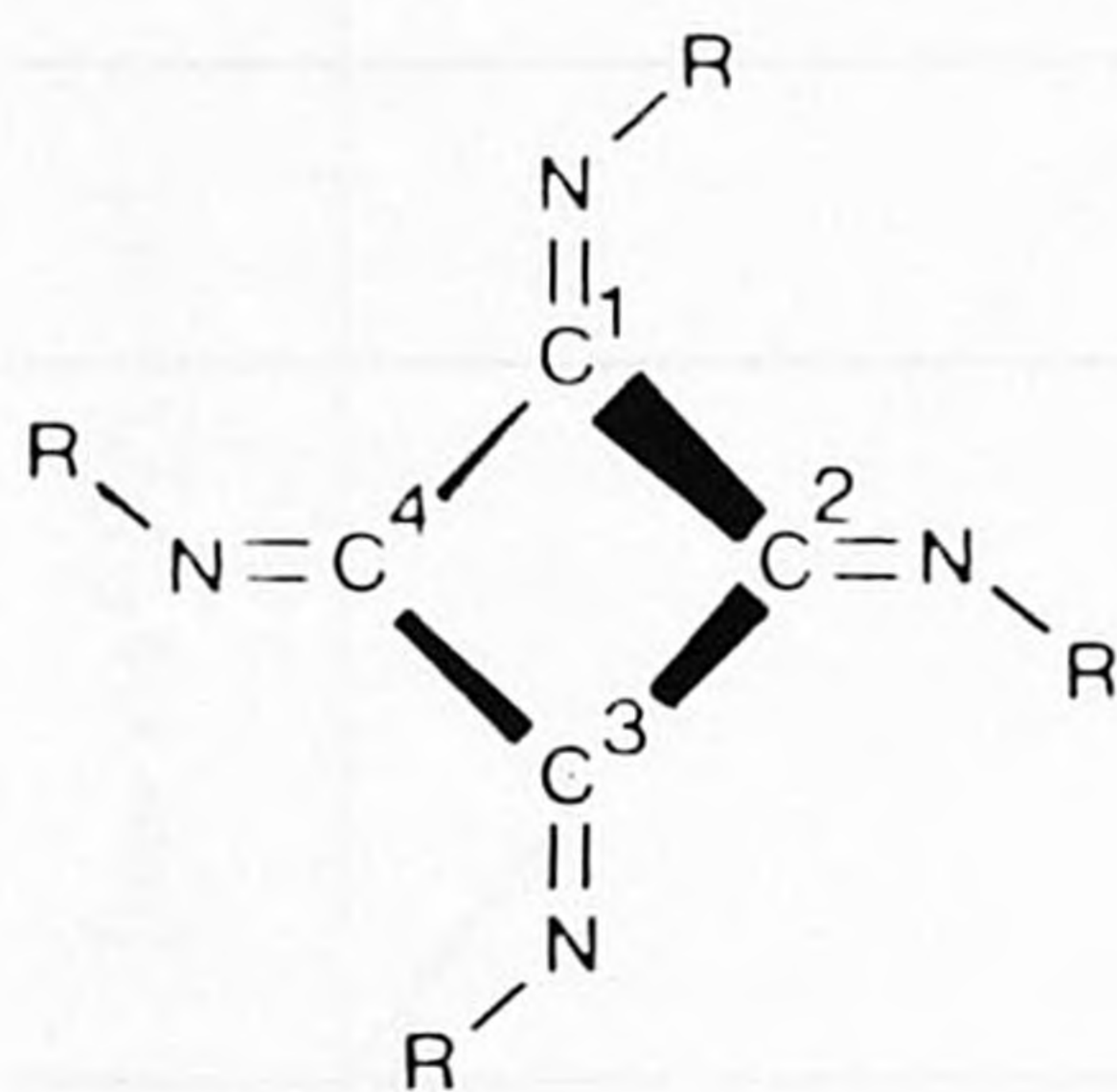
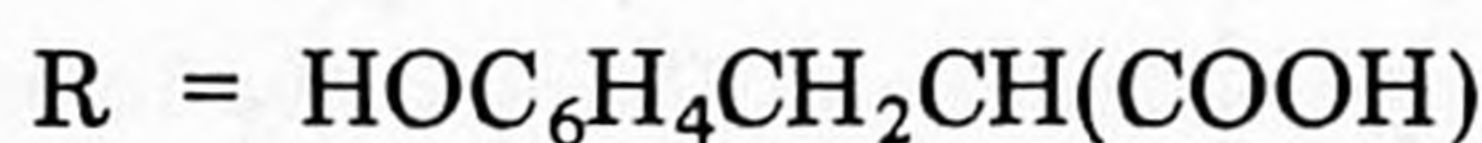
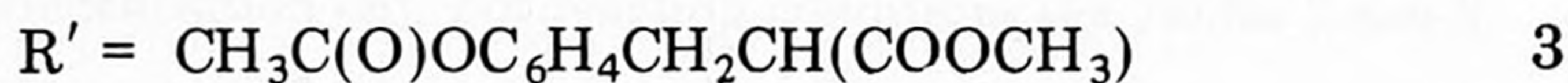
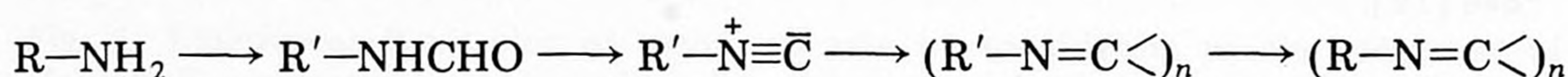


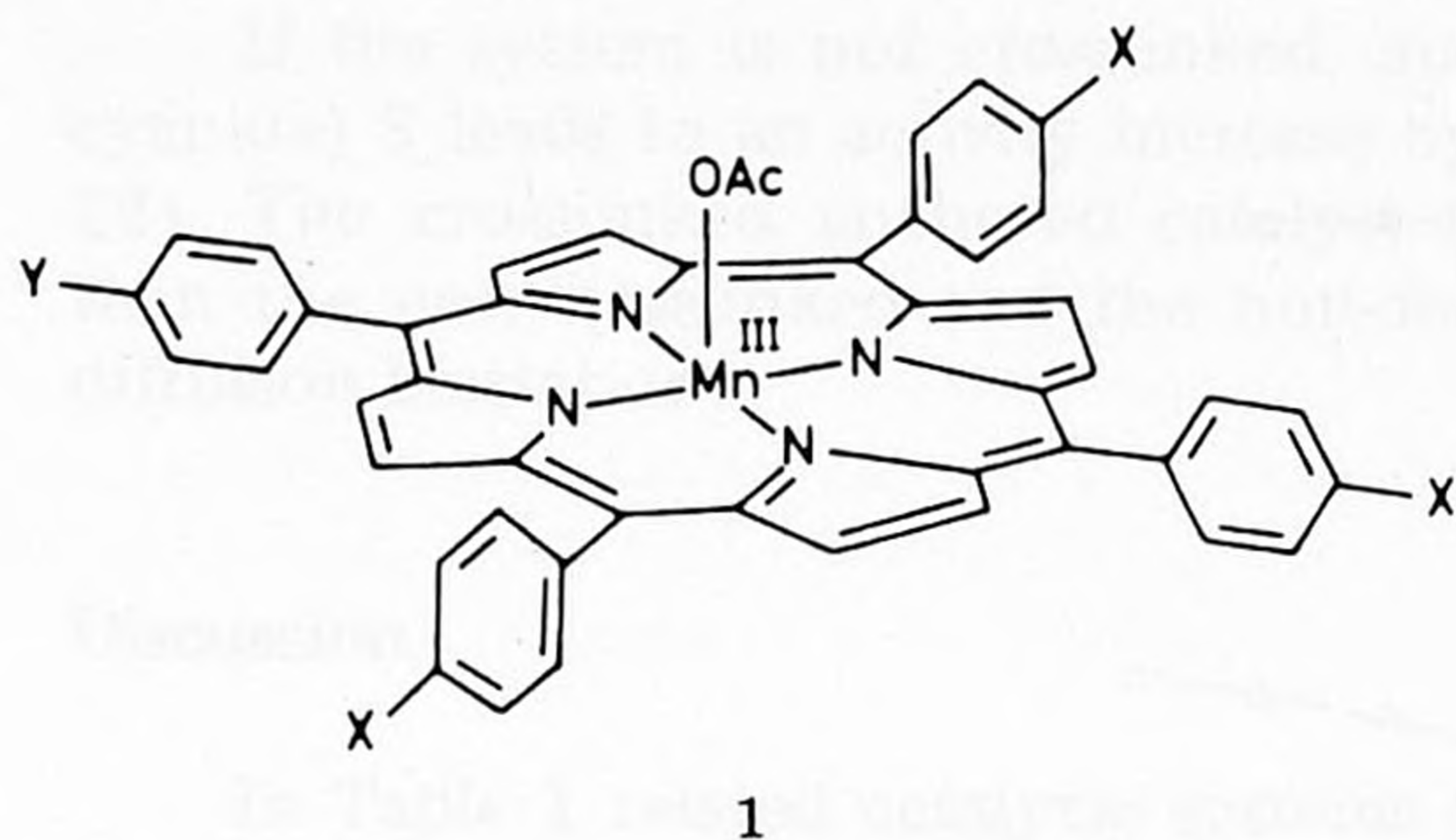
Fig. 4. Projection of a polymer of an isocyanide along its helical axis. Repeating unit C<sup>5</sup> is behind C<sup>1</sup>, C<sup>6</sup> behind C<sup>2</sup>, etc.



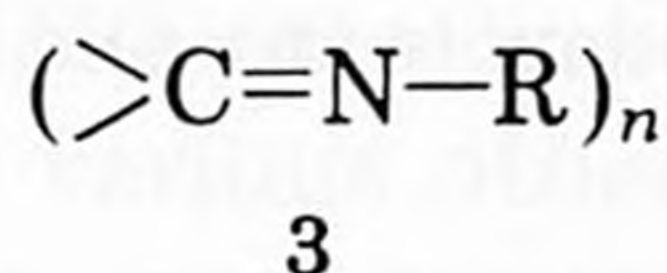
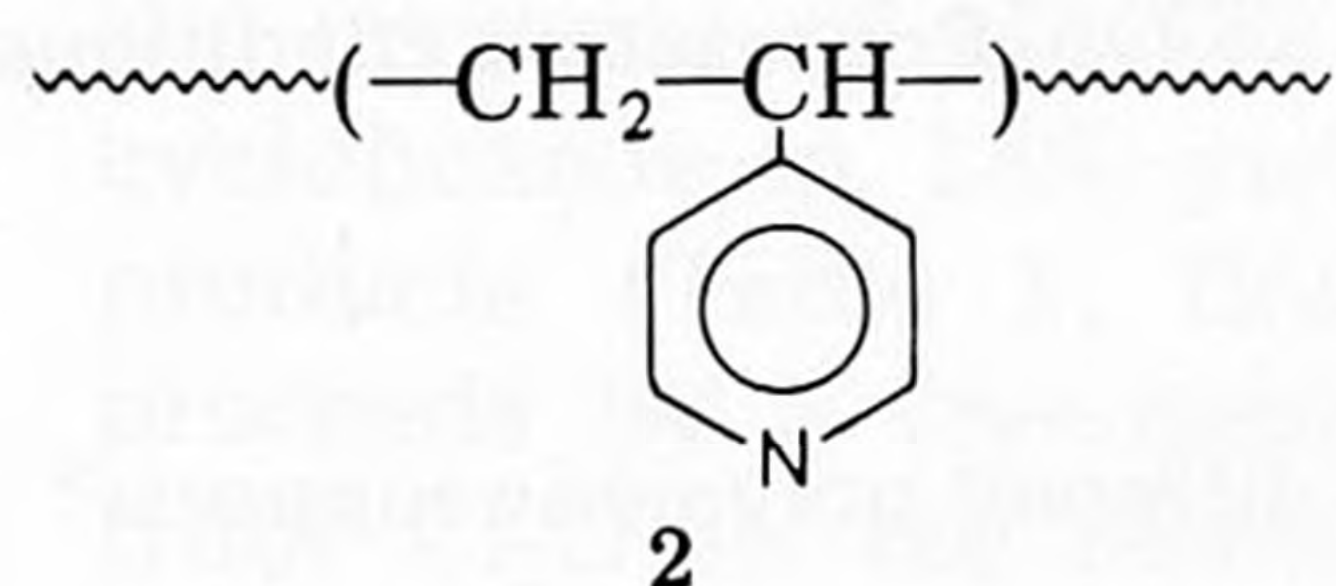
Scheme 1.

4-Hydroxyphenyl-tris(4-methylphenyl)porphyrin and tetra(4-hydroxyphenyl)porphyrin were prepared according to standard procedures and reacted with excess 1,3-dibromopropane and base. The resulting compounds were metallated with manganese(III) acetate to give the tetra-*para*-substituted phenylporphyrinatomanganese(II) acetates 1c and 1d.

Porphyrin 1c was coupled to poly(4-vinylpyridine) by means of a quaternarization reaction in toluene-methanol. The product polymer 2c contained 30.0 wt.% of bound 1c. This is equivalent to an average of 0.06 molecule of catalyst per polymer repeating unit. Compounds 1c and 1d



- a, X = Y = H  
 b, X = Y = CH<sub>3</sub>  
 c, X = CH<sub>3</sub>, Y = O(CH<sub>2</sub>)<sub>3</sub>Br or O(CH<sub>2</sub>)<sub>3</sub>— (after coupling)  
 d, X = Y = O(CH<sub>2</sub>)Br or O(CH<sub>2</sub>)<sub>3</sub>— (after coupling)



3c, d is 1c, d covalently anchored to 3

2c is 1c covalently anchored to 2

were coupled to polymer 3 in DMF in the presence of base. After removal of free porphyrin the coupled products 3c and 3d contained 5 and 1.5 wt.% of bound porphyrin, respectively. This corresponds to an average of 1.0 and 0.5 molecule of catalyst per polymer chain, respectively. Compound 3d is assumed to have a crosslinked structure, whereas 3c is not.

The catalytic activity of the anchored catalysts 2c, 3c and 3d in the epoxidation of cyclohexene was tested in a triphase system under conditions essentially the same as described above. Just as with the non-anchored catalysts, pyridine and substituted pyridines were found to increase the catalytic activity of the anchored porphyrin, the effect decreasing in the series 4-methylpyridine > pyridine > 4-cyanopyridine. An example is given in Fig. 5. Imidazole completely blocked the epoxidation reaction.

A comparison between the various anchored and non-anchored Mn(III) catalysts is given in Table 5. Anchoring of Mn(TPP)X to poly(4-vinylpyridine), either coordinatively (entry 3) or covalently (entry 4) increases the activity of this catalyst (entry 1). However, the increase is not as large as it is for non-anchored Mn(TPP)X plus an amount of free pyridine molecules equal to that present in the side chains of poly(4-vinylpyridine) (entry 2). Apparently, the capability of the pyridine side chains to coordinate to Mn(III) is restricted. In the presence of a large excess of added free pyridine, the anchored catalysts are more active than the non-anchored one under the same conditions (entries 5 - 7).



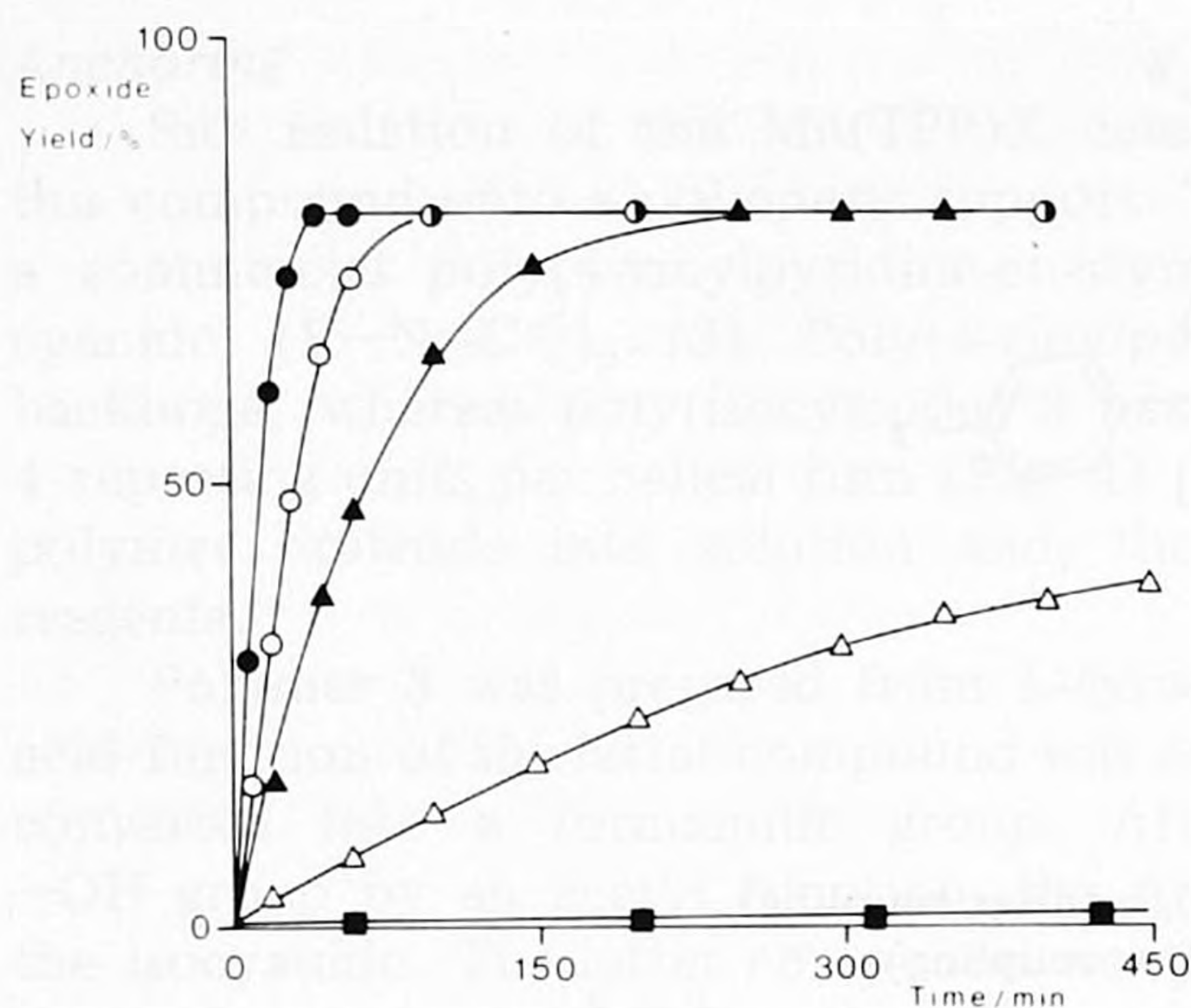


Fig. 5. Cyclohexene epoxidation by **3c** in the presence of 4-methylpyridine (●), pyridine (○), 4-cyanopyridine (▲), imidazole (■), and without additive (△). For reaction conditions see Table 5, footnote a, B.

TABLE 5

Epoxidation of cyclohexene by Mn(TPP)OAc anchored to different polymeric supports<sup>a</sup>

| Entry | Catalytic system                        | $v \times 10^5$ <sup>b</sup><br>(mol l <sup>-1</sup> s <sup>-1</sup> ) | Relative rate |
|-------|---|--|---------------|
| A     |   |  |               |
| 1     | 1a - d                                  | 0.206 <sup>c</sup>   | 1             |
| 2     | 1b + Pic (17 equiv)                     | 1.35   | 6.6           |
| 3     | 1b + PVP (17 equiv) <sup>d</sup>        | 0.87   | 4.2           |
| 4     | 2c <sup>d</sup>                         | 0.72   | 3.5           |
| 5     | 1b + Pic (260 equiv)                    | 3.90   | 18.9          |
| 6     | 2c + Pic (243 equiv) <sup>d</sup>       | 6.47   | 31.4          |
| 7     | 1b + PVP + Pic (243 equiv) <sup>d</sup> | 4.98   | 24.2          |
| B     |   |  |               |
| 8     | 1b + Pic (500 equiv)                    | 6.60   | 1             |
| 9     | 3c + Pic (500 equiv) <sup>e</sup>       | 21.1   | 3.2           |
| 10    | 3d + Pic (500 equiv) <sup>e</sup>       | 2.20   | 0.3           |
| C     |   |  |               |
| 11    | 1b + Pic (750 equiv)                    | 2.21   | 1             |
| 12    | 3c + Pic (750 equiv) <sup>e</sup>       | 13.3   | 6.0           |

<sup>a</sup>Abbreviations used are: PVP = poly(4-vinylpyridine), Pic = 4-methylpyridine; reaction conditions: A, 0.00275 mmol Mn(III) catalyst (either polymer-attached or free), [NaOCl] in aqueous phase 0.32 M; B, 0.0025 mmol Mn(III) catalyst, [NaOCl] in aqueous phase 0.35 M; C, 0.00051 mmol Mn(III) catalyst, [NaOCl] in aqueous phase 0.45 M; reaction temperature 25.0 °C; solvent mixture: 0.5 ml CH<sub>2</sub>Cl<sub>2</sub>, 2 ml aqueous solution containing TEBA (5 mM); in B 1.0 ml of CH<sub>2</sub>Cl<sub>2</sub> was used.

<sup>b</sup>Rate of epoxide formation in organic phase.

<sup>c</sup>Rates are the same within 5%.

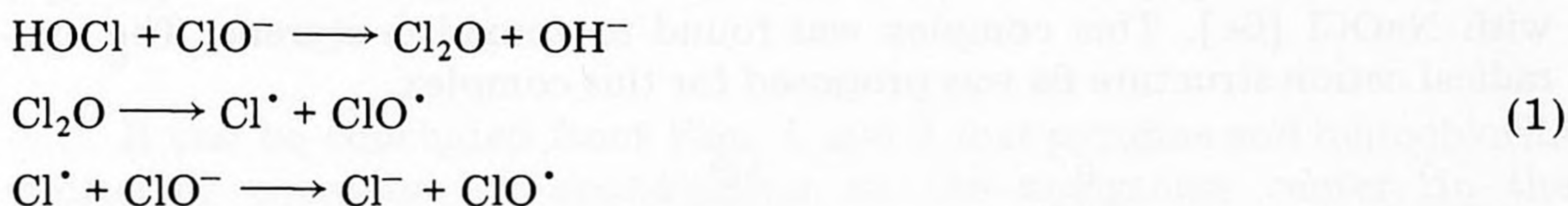
<sup>d</sup>17 Equiv of polymer repeating pyridine units; PVP is partly dissolved in the solvent mixture.

<sup>e</sup>3c and 3d are insoluble in the solvent mixture.

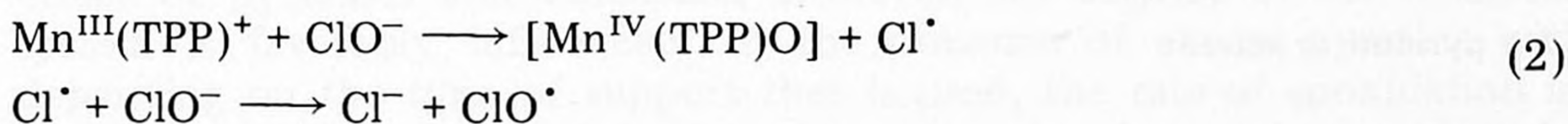
If the system is not crosslinked, anchoring of Mn(TPP)X to poly(isocyanide) **3** leads to an activity increase by a factor of 3 - 6 (entries 8, 9, 11, 12). The crosslinked anchored catalyst (entry 10) shows a lower activity than the non-crosslinked and the non-anchored ones, probably because of diffusion limitation.

## Discussion

In Table 1 related catalytic systems that oxidize cyclohexene are compared from the literature. As can be seen from this Table, the Mn(TPP)-OAc/NaOCl two-phase system gives the highest yield of epoxide and displays the highest selectivity. Of special interest is a comparison with the recent work of Fonouni *et al.* [9] who studied oxidation of hydrocarbons, among others cyclohexene, by the same system we used, however without the presence of Mn(TPP)OAc. Cyclohexene was converted into 1,2-epoxycyclohexane in 18% yield and into various other oxidated and chlorinated products (Table 1, first entry). It was proposed that the epoxidation proceeds by a free-radical mechanism involving the ClO<sup>•</sup> radical formed from Cl<sub>2</sub>O in the reaction mixture at pH 8 - 9 (eqn. 1). At pHs >9, the reaction slowed down due to the fact that significant amounts of HOCl are no longer present to generate Cl<sub>2</sub>O.

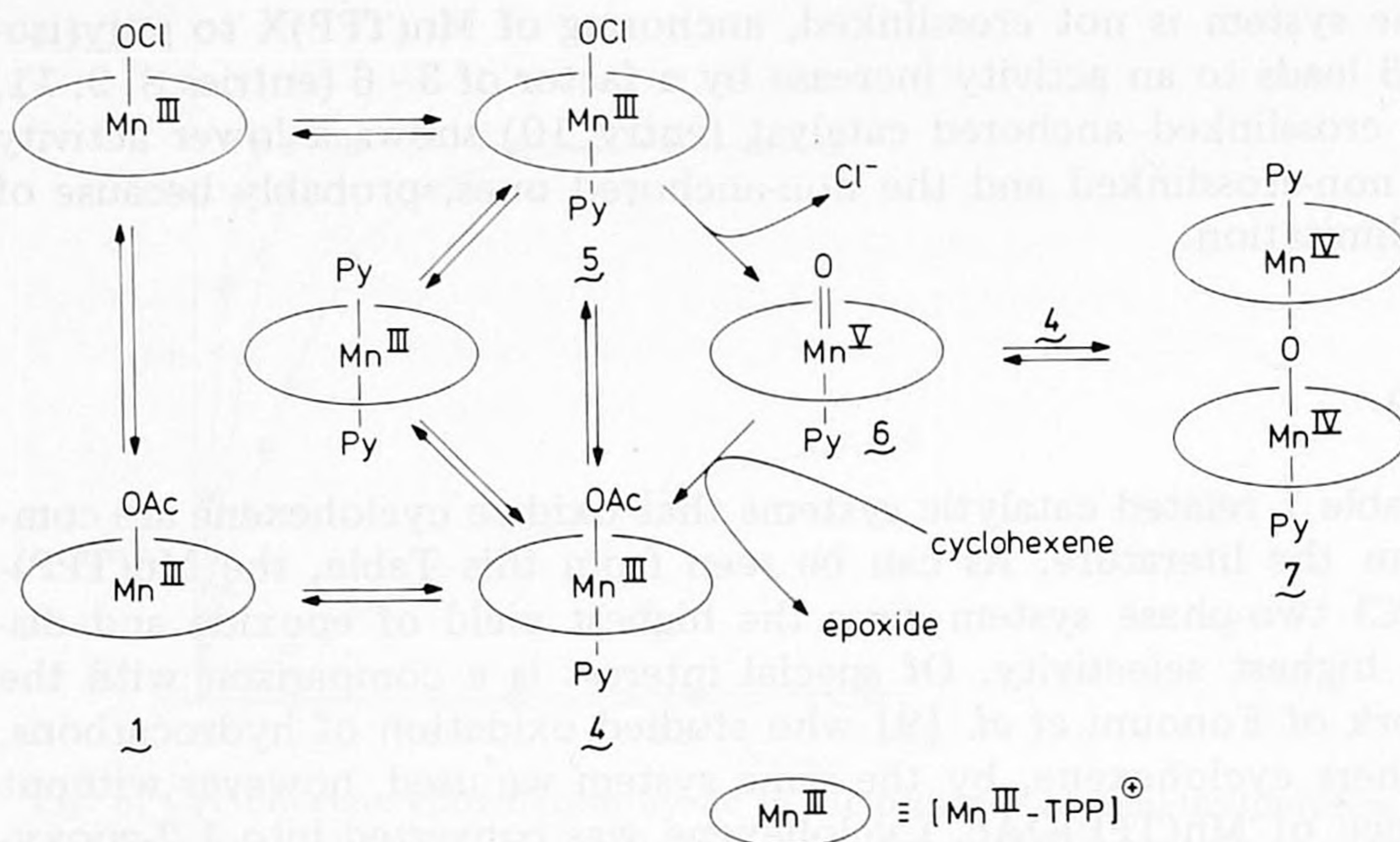


Under our reaction conditions, *i.e.* pH 13 of the aqueous layer, the formation of ClO<sup>•</sup> radicals according to eqn. 1 is less likely. However, it is possible that these species are generated in a Mn-catalyzed reaction, *e.g.* as in eqn. 2.



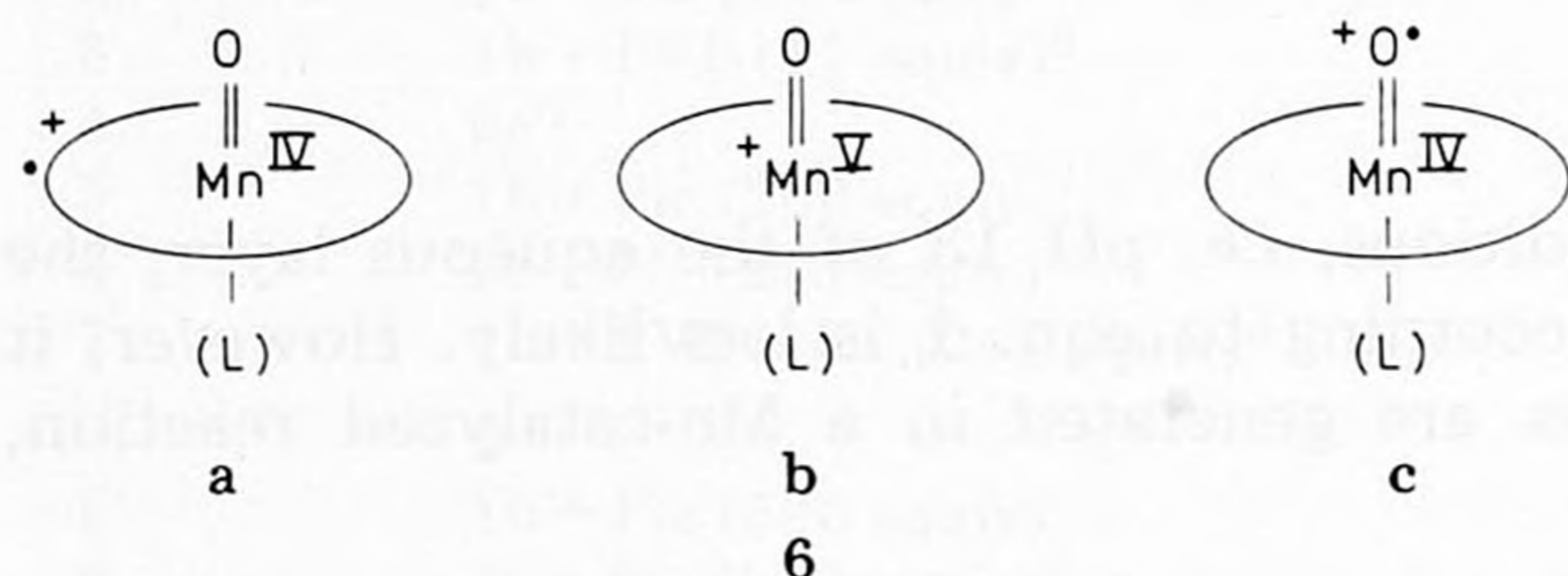
Inspection of Table 1 (footnotes a and b) reveals that the product distributions from the reaction of cyclohexene with ClO<sup>-</sup>/PTC and with ClO<sup>-</sup>/PTC/Mn(TPP)OAc-TPP are completely different. Thus a ClO<sup>•</sup> radical is probably not operative in our system.

A possible route to 1,2-epoxycyclohexane is via an intermediate chlorinated species such as the chlorohydrin. Carvalho and Meunier have recently shown that such a route is not followed in the ClO<sup>-</sup>/Mn(TPP)OAc system [10]. On the basis of our experiments we propose a mechanism as outlined in Scheme 2. The key intermediate is a high-valent manganese complex. There is evidence from the literature which supports the presence of such a



Scheme 2.

complex. Carnieri *et al.* have performed an electrochemical and spectroscopic study which reveals that Mn(III) porphyrins are oxidized by hypochlorite to Mn(IV) and subsequently to Mn(V) porphyrins [11]. Bortolini and Meunier have very recently isolated the complex  $[\text{Mn}(\text{TMP})\text{O}]\text{Cl}$  (TMP = tetramesitylporphyrinato dianion) from the reaction of  $\text{Mn}(\text{TMP})\text{Cl}$  with  $\text{NaOCl}$  [6e]. This complex was found to epoxidize styrene. The oxo-radical cation structure 6a was proposed for this complex.

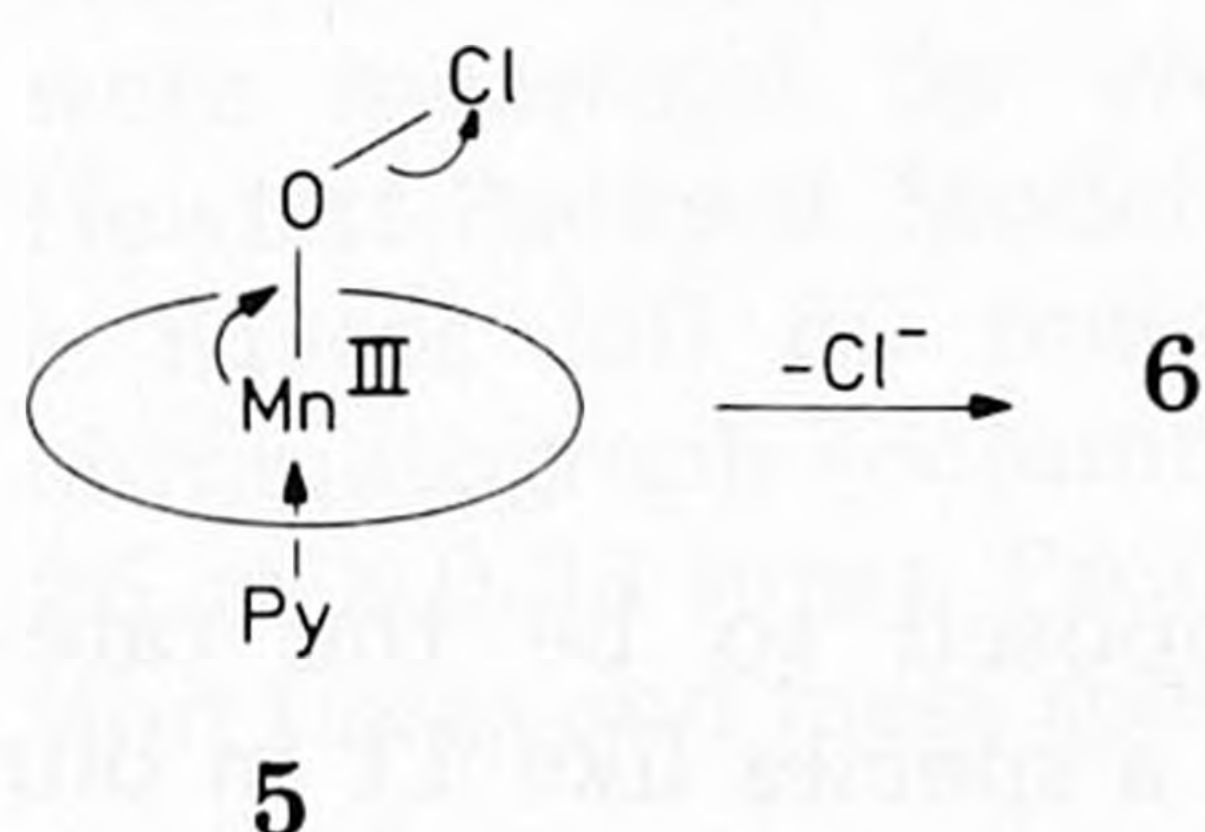


L = pyridine or solvent

Groves *et al.* obtained a similar complex (6) when  $\text{Mn}(\text{TPP})\text{Cl}$  was oxidized with excess iodosylbenzene and when  $\text{Mn}(\text{TMP})\text{Cl}$  was treated with *m*-chloroperoxybenzoic acid and base [4c, g]. The compound was able to epoxidize cyclooctene and was reduced by iodide to manganese(III) via an intermediate manganese(IV) species. On the other hand, Hill *et al.* have isolated the dimeric  $\mu$ -oxo-manganese(IV) porphyrin complexes  $\{[\text{Mn}^{\text{IV}}(\text{TPP})]_2\text{O}\}\text{X}_2$  ( $\text{X} = \text{N}_3^-$ ,  $\text{OCN}^-$ ), 7, and  $\{[\text{Mn}^{\text{IV}}(\text{TPP})\text{OIPh}]_2\text{O}\}\text{X}_2$  ( $\text{X} = \text{Cl}^-$ ,  $\text{Br}^-$ ), 8, from reaction of  $\text{Mn}^{\text{III}}(\text{TPP})\text{X}$  with iodosylbenzene [5c, e]. Oxidation of cyclohexene by 7- $\text{N}_3$  and 8-Cl yielded 1,2-epoxycyclohexane in 4 and 32% yields, respectively, and various other oxidated products (Table 1). This product distribution is appreciably different from the distribution

obtained with our catalytic system, suggesting that in our case the dimeric complex **7** is not the active catalyst. This conclusion is supported by the kinetic data which reveal an order in  $\text{Mn}(\text{TPP})\text{OAc} \leq 1$ , which is too low if **7** were the active species, except when **7** first dissociates into two monomeric species. The possibility of a monomeric  $\text{Mn}(\text{IV})$  complex being the active catalyst cannot be ruled out yet. However, in view of the results obtained by Meunier and Groves (*vide supra*) we believe that the oxo-manganese(V) complex **6**, which has the canonical forms **6a** - **c**, is the most likely candidate.

Our kinetic experiments suggest that oxo-manganese(V) complex **6** is formed from manganese(III) complex **5**. In this reaction a chloride ion is expelled. The observed rate-enhancing effect of pyridine and substituted pyridines on this reaction (Fig. 2) indicates that electron donation by these molecules facilitates the chloride dissociation. Step  $5 \rightarrow 6$  may be the rate-determining step of the catalytic cycle. The observed zero-order dependency in cyclohexene and the effect of pyridines are in line with such an assignment.

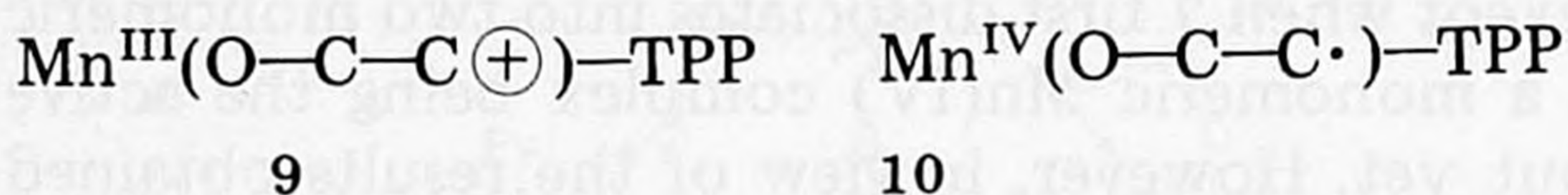


It can be concluded from Figs. 1 and 3 that pyridine and hypochlorite molecules compete for coordination to the manganese center. In the presence of a high concentration of pyridine or when the stronger ligand imidazole is present, both coordination sites at manganese are blocked and epoxidation is prevented.

Anchoring to a polymeric support does not affect the main properties of  $\text{Mn}(\text{TPP})\text{X}$ , as can be concluded from the product distribution and the effect of pyridines and imidazole. However, the activity of the catalytic system is favorably influenced. In the presence of excess pyridine and depending on the type of support that is used, the rate of epoxidation is increased by a factor of 1.5 - 6.0. This rate enhancement is considerable if we take into account that the anchored catalyst is insoluble in the reaction medium and thus less accessible than the non-anchored one. We believe that anchoring prevents the formation of manganese(IV)- $\mu$ -oxo-dimers, e.g. **7** from **6** and **4**. These dimers probably are inactive or less active epoxidation catalysts (*vide supra*).

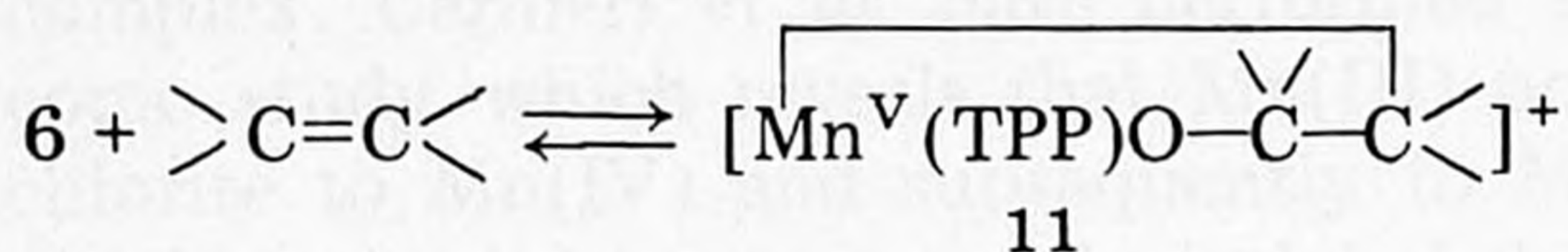
One possible reaction path for complex **6** is dimerization. The other one is reaction with the substrate. Addition of **6** to the double bond of cyclohexene may proceed via either a concerted or a stepwise process [13]. The latter process is the most likely, as it has been demonstrated that loss of stereochemistry occurs at the double bond [4c, 6d]. This phenomenon

can be understood if the addition intermediate, *e.g.* carbocation **9** or radical **10**, is sufficiently long-lived to allow rotation before collapsing to product [4c].



Recently, it has been reported that pyridine not only increases the rate of epoxidation by Mn(TPP)X, but also the stereoselectivity [6d, l]. Thus, in the presence of an excess of this ligand, stereochemistry is retained. This phenomenon has not yet been explained. We believe, and have presented evidence elsewhere [14], that pyridine increases the steric interactions in the addition intermediate **9** or **10** by pulling the manganese atom from its original domed position outside the porphyrin ring into the plane of this ring. This means that the carbocation or radical species is no longer free to rotate and thus is forced to retain its original conformation.

In a very recent paper by Collman *et al.* [6j] it was suggested that epoxidation of olefins by Mn(TPP)Cl and LiOCl proceeds via an intermediate metallaoxetane, **11**.



The decomposition of this intermediate was proposed to be the rate-determining step of the reaction. The presence of a species like **11** in our system cannot yet be excluded. However, if it is present, it should be in equilibrium with open structures such as **9** or **10**. Our results and those found in the literature [6j] may not necessarily be contradictory, but can be interpreted to mean that the rate-determining step of the catalytic cycle depends on the reaction conditions employed. To further illustrate this point, we recently found that upon adding methanol to our reaction mixtures the rate of epoxidation is increased and the reaction order in cyclohexene is changed from zero to one [19]. These observations indicate, with regard to the rate-determining step, that to make a definite conclusion more experimental data will be needed.

It is tempting to compare the role of pyridine in our model system to that of the thiolate anion in the active site of cytochrome P-450. It has been postulated that this thiolate ion facilitates the ultimate cleavage of the oxygen-oxygen bond of molecular oxygen, by serving as an electron donor system through the iron [3]. We ascribe a similar function to pyridine in our system, *i.e.* promotion of the cleavage of the oxygen-chlorine bond of an OCl<sup>-</sup> ion that is coordinated to the manganese center.

The work presented here and that of other groups suggests that by applying principles known from nature (site isolation, effect of additional ligands) the activity and selectivity of the epoxidation catalyst can be regulated. Work along these lines, in particular towards the activation of molecular oxygen, is currently in progress.

## Experimental section

### General methods

Infrared (IR) spectra were recorded on Perkin-Elmer 297 and 283 spectrophotometers. UV/VIS spectra were obtained on a Perkin-Elmer 200 spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded on Varian EM 390, Varian XL 100 and Bruker WP 200 instruments. Chemical shifts ( $\delta$ ) are given in ppm from internal tetramethylsilane. Abbreviations used are: b = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet;  $\beta$ -pyrrole is used to indicate the 2,3,7,8,12,13,17,18-porphyrin protons. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands. Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Solution viscosity data were obtained with a Cannon Ubbelohde viscometer. Gas chromatography was done on a Varian model 3700 instrument equipped with flame ionization detector. The column used for analyses was Carbowax 20 M on Chromosorb W-HP. Peak areas were measured by electronic integration using a Varian CDS 111 or Hewlett-Packard Model 3390 A integrator. Mass spectra were obtained on a Kratos MS 80 mass spectrometer coupled to a Carlo Erba 4160 gas chromatograph (column 3% OV 101, 200 cm  $\times$  2 mm, or a capillary column, 25 m  $\times$  0.33 mm). Products were identified by comparing their GLC retention times and mass spectra with those of authentic samples.

### Materials

Unless otherwise noted, commercial materials were used as received. Cyclohexene was distilled under  $\text{N}_2$  and passed over alumina immediately before use. Pyridines were distilled and stored over molecular sieve 4A. 4-Cyanopyridine was recrystallized twice from chloroform/hexane. Pyrrole was distilled prior to use. Poly(4-vinylpyridine-co-styrene) was obtained from Aldrich. Its styrene content amounted to 10%.

### Porphyrins

5,10,15,20-tetraphenylporphyrin and 5,10,15,20-tetra(4-methylphenyl)porphyrin were synthesized and purified according to literature procedures [15].

### 5-[4-(3-Bromopropoxy)phenyl]-10,15,20-tris(4-methylphenyl)porphyrin [15b, c]

4-Methylbenzaldehyde, 4-hydroxybenzaldehyde and pyrrole were successively dissolved in propionic acid to concentrations of 0.224, 0.076 and 0.3 M, respectively. The mixture was refluxed for 1 h. After cooling and filtration the resulting solid was chromatographed (column: Merck silica gel, Brockmann activity III, eluent  $\text{CHCl}_3$ ). The band having  $R_f$  0.25 was sliced out and extracted with  $\text{CHCl}_3$  to give purple crystals of 5(4-hydroxyphenyl)-10,15,20-tris(4-methylphenyl)porphyrin (yield 6%):  $^1\text{H}$  NMR ( $\text{CD-}$

Cl<sub>3</sub>)  $\delta$  8.85 (s, 8H,  $\beta$ -pyrrole), 8.10 (d,  $J = 7.6$  Hz, 6H; 2,6H of 4-MePh), 8.05 (d,  $J = 9.0$  Hz, 2H; 2,6H of 4-HOPh), 7.54 (d,  $J = 7.5$  Hz, 6H; 3,5H of 4-MePh), 7.10 (d,  $J = 9.02$  Hz, 2H, 3,5H of 4-HOPh), 2.70 (s, 9H, CH<sub>3</sub>), -3.12 (s, b, 2H, NH); VIS (CHCl<sub>3</sub>)  $\lambda_{\max}$  418 nm (log  $\epsilon$  5.39), 516 (4.20), 553 (4.01), 590 (3.76), 645 (3.80). The above-mentioned compound (1.0 g, 1.49 mmol) and 1,3-dibromopropane (4.0 g, 19.8 mmol) were dissolved in DMF (30 ml) and stirred with anhydrous K<sub>2</sub>CO<sub>3</sub> for 24 h. The reaction mixture was poured into a mixture of water (170 ml) and MeOH (30 ml). The precipitated porphyrin was filtered off and dried under vacuum. After purification by column chromatography (silica; eluent MeOH, subsequently CHCl<sub>3</sub>/MeOH, 10:1 v/v,  $R_f$  0.9) the title compound (1.1 g, 1.38 mmol, 92%) was obtained as a purple solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.93 (s, 8H,  $\beta$ -pyrrole), 8.14 (d,  $J = 7.7$  Hz, 6H; 2,6H of 4-MePh), 8.10 (d,  $J = 8.8$  Hz, 2H; 2,6H of 4-HOPh), 7.56 (d,  $J = 7.7$  Hz, 6H; 3,5H of 4-MePh), 7.17 (d,  $J = 8.40$  Hz, 2H; 3,5H of 4-HOPh), 4.20 (t,  $J = 5.5$  Hz, 2H, OCH<sub>2</sub>), 3.72 (t,  $J = 6.2$  Hz, 2H, CH<sub>2</sub>Br), 2.77 (s, 9H, CH<sub>3</sub>), 2.40 (m, 2H, CH<sub>2</sub>), -2.65 (s, b, 2H, NH); VIS (CHCl<sub>3</sub>)  $\lambda_{\max}$  418 nm (log  $\epsilon$  5.37), 516 (4.17), 553 (3.93), 590 (3.66), 645 (3.68).

#### *5,10,15,20-Tetra(4-(3-bromopropoxy)phenyl)porphyrin*

This compound was synthesized from the corresponding 5,10,15,20-tetra(4-hydrophenyl)porphyrin [15b] and excess of 1,3-dibromopropane as described above. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.90 (s, 8H,  $\beta$ -pyrrole), 8.10 (d, 8H; 2,6H of Ph), 7.25 (d, 8H; 3,5H of Ph), 4.32 (t, 8H, OCH<sub>2</sub>), 3.73 (t, 8H, CH<sub>2</sub>Br), 2.43 (m, 8H, CH<sub>2</sub>), -2.70 (s, b, 2H, NH); VIS (CHCl<sub>3</sub>)  $\lambda_{\max}$  422 nm, 488, 518, 555, 593, 650.

Metallation of the above-mentioned porphyrins to give complexes 1a - d was performed with manganese(II) acetate in acetic acid or DMF as described in the literature [15d].

#### *N-Formyl-O-acetyl-L-tyrosine methyl ester*

L-Tyrosine was esterified with methanol and dry HCl gas according to a standard procedure [16], and subsequently reacted with formic acid, sodium formate and acetic anhydride [17] to give the *N,O*-diformylated product. The *O*-formyl group was selectively removed by heating in aqueous methanol (1:1 v/v) at 65 °C for 10 h [18]. The resulting compound was acetylated with excess acetic anhydride and a catalytic amount of pyridine [18]. The title compound was obtained as white crystals; yield 63% from L-tyrosine;  $[\alpha]_D^{20}$  (c 0.74, acetone) 30.4°; <sup>1</sup>H NMR (CH<sub>3</sub>COCD<sub>3</sub>)  $\delta$  8.15 (s, 1H, CHO), 7.15 (m, 4H, ArH), 4.78 (m, 1H, CH), 3.69 (s, 3H, OCH<sub>3</sub>), 3.1 (d, 2H, CH<sub>2</sub>), 2.23 (s, 3H, CH<sub>3</sub>).

#### *1-Methoxycarbonyl-2-(4-acetylphenyl)ethyl isocyanide*

To a solution of the preceding formamide (6 g, 23 mmol) and triethylamine (5.65 g, 56 mmol) in dichloromethane (25 ml) was added dropwise at 0 °C phosphorus oxychloride (3.25 g, 23 mmol). The mixture was

stirred at room temperature for 1 h. Aqueous  $\text{Na}_2\text{CO}_3$  (25 ml, 18% solution) was added, and the organic layer was separated, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under vacuum. The product was purified by column chromatography (silica gel, eluent chloroform-methanol 10:1 v/v): yield 5.3 g (95%) of pure isocyanide; IR (neat) 2150 (NC)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.16 (m, 4H, ArH), 4.41 (t, 1H, CH), 3.80 (s, 2H,  $\text{OCH}_3$ ), 3.15 (d, 2H,  $\text{CH}_2$ ), 2.27 (s, 3H,  $\text{CH}_3$ );  $M^+ m/e$  247.

#### *Poly[1-carboxy-2-(4-hydroxyphenyl)ethyliminomethylene] (3)*

The preceding isocyanide (4.50 g, 18 mmol) was polymerized with  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.020 g, 0.5 mol%) in methanol (10 ml) at ambient temperature. After 2 days the solvent was evaporated under vacuum. The residue was dissolved in a small amount of acetone and added dropwise to an excess of vigorously stirred water. The precipitated brown polymer was collected by filtration, washed with water and dried at reduced pressure at 40 °C over KOH: yield 4.3 g (95%) of protected 3;  $[\eta] = 0.064 \text{ dl g}^{-1}$  (toluene, (30.00 °C)); according to a reported Mark-Houwink equation [18] this value corresponds to  $\bar{M}_v$  24 000 (100 polymer repeating units); IR (KBr) 1760 (CO), 1620 (CN)  $\text{cm}^{-1}$ ;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  168.94 ( $\text{CH}_3\text{-CO}$ ), 167 - 175 and 161 - 167 ( $2 \times b$ ,  $\text{CH}_3\text{OCO}$  and  $\text{N=C}$ ), 149.14, 133.3, 129.30, 121.42 (ArC), 50.5 - 53.5 (b, CH and  $\text{CH}_3\text{O}$ ), 37.0 - 40.5 (b,  $\text{CH}_2$ ), 20.84 ( $\text{CH}_3\text{CO}$ ). On exposure to air the polymer slowly takes up oxygen (0.5 equiv per repeating unit) [18]: analysis calculated for  $\text{C}_{13}\text{H}_{13}\text{NO}_{4.5}$ : C, H, N and O.

The preceding polymer was deprotected at its phenolic OH and carboxylic acid functions by stirring with 0.5 M NaOH at 40 °C for 3 days. After acidifying with concentrated aqueous HCl to pH 4, methanol was added. The solid which precipitated was collected by filtration and dried under vacuum to yield 90% of brown polymer; IR (KBr) 3600 - 2300 (OH, COOH), 1740 (COOH), 1610 (CN).

#### *Anchoring*

Complex 1c was covalently anchored to poly(4-vinylpyridine), 2, in the following way. A solution of 2 (1.0 g, 9.52 mmol repeating units) and 1c (0.350 g, 0.386 mmol) in toluene-methanol (4:1 v/v, 50 ml) was refluxed for 48 h. The solvent was removed under vacuum and the product was subjected twice to GPC (Sephadex LH-60, eluent MeOH) in order to remove non-anchored 1c. Yield 0.8 g of 2c. According to elemental analysis and UV/VIS spectroscopy, 2c contained 0.059 mol of 1c per g of polymer.

Anchoring of 1c to 2 by means of a coordinative bond was achieved by simply mixing the appropriate amounts of the components (Table 5) in dichloromethane and stirring for 30 min.

Complex 1c was anchored to poly(isocyanide) 3 as follows. A solution of 3 (100 mg,  $\sim 0.5$  mmol of reactive OH) and 1c (50 mg, 0.055 mmol) in DMF (3 ml) was stirred with anhydrous  $\text{K}_2\text{CO}_3$  (300 mg) at 40 °C for 1 week. The solvent was removed under vacuum and the product was shaken



with water (50 ml) for 20 h. The residual free porphyrin was removed by repeated extraction with boiling chloroform to yield 97 mg of **3c**. According to UV/VIS spectroscopy, **3c** contained 0.050 g (0.055 mmol) of **1c** per g of polymer.

Anchoring of **1d** to **3** was performed as described for **1c** by using a porphyrin-to-polymer repeating unit ratio of 1:25. According to UV/VIS spectroscopy, the product (**3d**) contained 0.015 g (0.017 mmol) of **1d** per g of polymer.

### *Kinetic measurements*

Rates of epoxidation of cyclohexene were measured in vessels thermostatted at 25.0 °C. In a typical experiment the following components were mixed: cyclohexene (0.375 mmol), toluene (internal standard, 0.125 mmol), Mn(TPP)OAc (either polymer-attached or free,  $1.72 \times 10^{-3}$  mmol), pyridine (1.01 mmol) and TEBA ( $5 \times 10^{-3}$  mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml). To this solution an aqueous solution of NaOCl (0.45 M, 2 ml) was added. The mixture was stirred magnetically at a constant rate. From time to time samples (1 μl) were taken which were analyzed by GLC (Carbowax 20 M, 70 - 180 °C at 20 °C min<sup>-1</sup>).

The distributions of pyridine and the substituted pyridines over the organic and aqueous layers under the reaction conditions employed were estimated as follows. Pyridine (80 μl) was dissolved in dichloromethane (0.5 ml) and vortexed with 2.0 ml of aqueous NaOCl (0.45 M) for 2 min. The layers were separated by centrifugation for 2 min. From both the organic and aqueous layers, 5 - 40 μl aliquots were taken which were diluted to 25 ml with EtOH. Subsequently, the absorbance was measured at λ = 250 - 275 nm. From the absorbances the fraction of pyridine in the organic layer, α, was calculated: (X in XC<sub>5</sub>H<sub>4</sub>N, α): 3-CH<sub>3</sub>, 0.88; 4-CH<sub>3</sub>, 0.89; H, 0.74; 3-Br, 0.87; 3-CN, 0.77; 4-CN, 0.76.

### **Acknowledgement**

We thank Prof. W. Drenth for the many stimulating discussions.

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