react with acrolein. As expected for the series of reactions shown in eq 22, the product ion was m/z 68, corresponding to the incorporation of a deuterium atom. If the product had been I, no deuterium incorporation would be expected.

Other α,β-unsaturated carbonyl compounds react analogously. Addition to methyl vinyl ketone results in loss of acetaldehyde and again the formation of pyrazole anion (eq 24) while crotonaldehyde forms a small amount of methylpyrazole anion with loss of formaldehyde (eq 25).

$$H\bar{C}N_2 + CH_2CHCOCH_3 \rightarrow C_3H_3N_2^- + CH_3CHO \quad (24)$$

$$H\bar{C}N_2 + CH_3CHCHCHO \rightarrow C_4H_5N_2^- + CH_2O \quad (25)$$

Similarly, methacrolein forms methylpyrazole anion and tiglic aldehyde (*trans*-2-methyl-2-butenal) forms a small amount of dimethylpyrazole anion with loss of formaldehyde. For these carbonyl compounds, proton abstraction and addition with loss of N_2 are important, often major, channels. On the other hand, mesityl oxide ($(CH_3)_2CCHCOCH_3$) fails to react with the diazomethyl anion, either because the presence of the two β-methyl groups blocks Michael addition or because there is no acidic proton to abstract from the cyclization product.

As a neutral reagent diazomethane undergoes few gas-phase ionic reactions other than proton abstraction. We did find, however, that it accepts a hydride ion from HNO^-.[24] In theory, addition could occur at either carbon (eq 26a) or at nitrogen (eq 26b). Attack on carbon would form an azomethyl anion, which might be expected to lose nitrogen easily;[26] the product ion formed is quite stable and unreactive and is best formulated as the anion from formaldehyde hydrazone (eq 26b). This is in accord with the usual site of reaction of diazo compounds with reducing agents in solution.[1]

$$CH_2{=}\overset{+}{N}{=}\bar{N} + HNO^- \rightarrow \begin{cases} CH_3{-}N{=}N^- + NO & (26a) \\ CH_2{=}N{-}NH^- + NO & (26b) \end{cases}$$

In summary, we have found that the diazomethyl anion reacts in interesting ways with a number of reagents in the gas phase. An initially exothermic addition reaction can deposit sufficient energy into the product ion to induce loss of nitrogen to form a carbene, which in turn may rearrange, fragment further, or react with a neutral reagent. Michael adducts are also found to cyclize and eliminate aldehydes to form pyrazole anions as well as to lose nitrogen. Diazomethane itself undergoes a proton transfer reaction with most ionic reagents but can be reduced by an appropriate hydride donor.

Acknowledgment. We gratefully acknowledge support of this work by the U.S. Army Research Office (Contract DAAG29-85-K-0046) and the National Science Foundation (Grant CHE-8503505). We also thank Dr. Jonathan Filley for help with some of the experiments.

Registry No. CH_2N_2, 334-88-3; $CHN_2^{\bullet}$, 20813-32-5; CHN_2^-, 100840-43-5; CS_2, 75-15-0; COS, 463-58-1; CO_2, 124-38-9; SO_2, 7446-09-5; CH_3OH, 67-56-1; $CH_2{=}CHCHO$, 78-94-4; $CH_2{=}CHCOCH_3$, 78-94-4; $CH_3CH{=}CHCHO$, 4170-30-3; pyrazole, 288-13-1; methacrolein, 78-85-3; tiglic aldehyde, 497-03-0.

(26) The dissociation of $CH_3N_2^-$ to methide ion and molecular nitrogen is expected to be exothermic as long as the hydride affinity of CH_2N_2 to form $CH_3N_2^-$ is $\leq$70 kcal/mol. Based on known hydride affinities of other molecules, this upper limit appears reasonable.

Investigation on Factors Ruling Catalytic Efficiency and Chemical Stability of Mn(III) Porphyrins in HOCl Olefin Epoxidation: Conditions for Practical Application

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The use of stable Mn(III) porphyrins (P), e.g. **2–4**, and of imidazole or pyridine axial ligands (L), **8–10**, entirely soluble in the organic phase has allowed an extensive investigation of the factors ruling the catalytic activity of porphyrins in the olefin epoxidation carried out at 0 °C under two-phase conditions with ClO^- and/or HOCl as oxidants. We have determined (i) the influence of the pH of the aqueous phase and of the phase-transfer catalyst on the reaction rate and on the Mn(III) porphyrins stability; (ii) the best ligand/porphyrin ratio (L/P) necessary to obtain the fastest conversion of cyclooctene (more reactive substrate) and 1-dodecene (less reactive substrate) to the corresponding epoxides; (iii) the oxidative demolition of the axial ligands **8–10**; (iv) the activity of *N*-oxides **11** and **12** as axial ligands; (v) the possibility to epoxidize reactive olefins with HOCl in the absence of the phase-transfer catalyst and of the axial ligand, buffering the pH of aqueous NaOCl at 10.5. The association constants (K_1, K_2) of imidazole with Mn(III) porphyrins **1** and **2** and of *N*-hexylimidazole (**8**) with **2** have also been evaluated in order to rationalize the effect of ligand/porphyrin ratio on the reaction rate.

Mn(III) tetraarylporphyrins have been used by Tabushi,[1] Meunier,[2] Collman,[3] and others[4,5] as catalysts in olefin epoxidation promoted by NaOCl under phase-transfer conditions.[6] Reaction rates are greatly enhanced when

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heterocyclic bases, usually imidazoles or pyridines, act as axial ligands on the complexed metal.[2c-1,6] Fe(III)tetraaryl porphyrins have also been used as catalysts under these same conditions, but their efficiency is generally lower.[6] Most metalloporphyrins are rapidly bleached by oxidative degradation either with NaOCl[1-6] or with other oxidants.[6,7] Recently we studied[5e] the relative stability of a series of Mn(III) porphyrins in the oxidations carried out with NaOCl: some porphyrins were demolished, but others were perfectly stable under the reaction conditions. Therefore we are now in the position of finally being able to clarify the factors ruling the catalytic activity of metalloporphyrins and to define the conditions for using these highly efficient catalysts in large-scale syntheses. Indeed, none of the porphyrin-catalyzed oxidations reported so far are really suitable for practical application or even to scale-up reactions.[8]

In this paper we report an extensive investigation on HOCl-promoted olefin epoxidations, particularly on (i) the influence of the pH of the aqueous phase, of the phase-transfer catalyst, and of the ligand/porphyrin ratio on the epoxidation rate and porphyrin stability and (ii) the efficiency on the axial ligand as a function of its structure and chemical stability.

Results

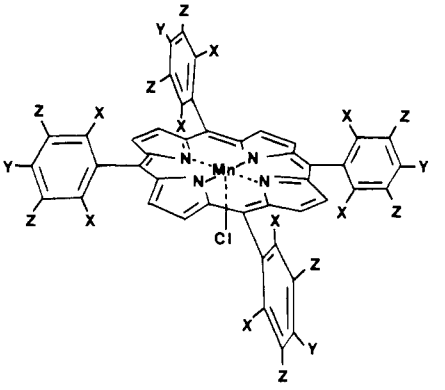
Cyclooctene and 1-dodecene were used as model substrates. The epoxidations were carried out with 0.35 M NaOCl at 0 °C under CH_2Cl_2/H_2O two-phase conditions by using molar ratios Mn(III) porphyrin:olefin:oxidant = 1:200:700, and axial ligand and quaternary onium salt ranging from 0 to 25 and 0 to 5 molar equiv, respectively. Mn(III) porphyrins 1–7 were used as catalysts, although most of the experiments were performed with Mn(T2,6Cl_2PP)Cl **2**. Porphyrins **2–4** proved to be very stable under the reaction conditions. The synthesis of porphyrins **3–5** was recently reported.[5c]

Table I. Molarity of HOCl in the CH_2Cl_2 Solution[a]

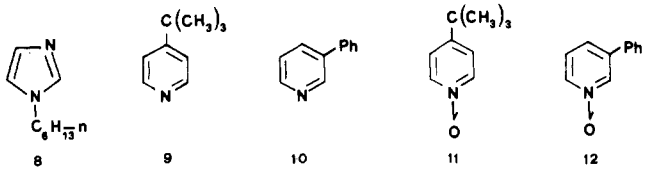
pH	HOCl, M × 10^4	pH	HOCl, M × 10^4
9.5[b]	1.2	11.0[b]	0.28
10.0[b]	0.5	12.7	0.008
10.5[b]	0.35		

[a] After equilibration at 0 °C with 0.35 M aqueous NaOCl under the reaction conditions, but in the absence of substrate and of prophyrin. [b] Buffered with $Na_2B_4O_7$.

Ligands **8–10** were chosen because, differently from most of imidazoles and pyridines used until now,[1-4] they entirely remain in the organic phase, where the reaction occurs.



		X	Y	Z
1	Mn(TPP)Cl	H	H	H
2	Mn(T2,6Cl_2PP)Cl	Cl	H	H
3	Mn(T$Cl_3$$Me_2$PP)Cl	Cl	Cl	Me
4	Mn(T$Br_3$$Me_2$PP)Cl	Br	Br	Me
5	Mn(T3,5Cl_2PP)Cl	H	H	Cl
6	Mn(TF_5PP)Cl	F	F	F
7	Mn(TMP)Cl	Me	Me	H



Influence of pH of the Aqueous Phase and of Phase-Transfer (PT) Catalyst. As we previously reported,[5] epoxidation rates progressively increase by lowering the pH of the aqueous NaOCl solution from 12.7 to 9.5; below this value the concomitant olefin chlorination becomes unacceptably high.

HOCl is a very weak acid (pK_a = 7.54), its anion and the undissociated species coexisting in a wide range of pH. Since it is fairly soluble in polar organic solvents, it is partitioned between the aqueous phase and CH_2Cl_2.[11] Molarities of HOCl in CH_2Cl_2 at 0 °C, the reaction temperature, increase by decreasing the pH (Table I). The amount of HOCl in the organic phase becomes significant below pH 11.0, making the presence of a PT catalyst unnecessary, as previously observed for reactions carried out at 25 °C.[5a] Under these conditions, HOCl is the only oxidant in the reaction medium.

When the pH of the aqueous NaOCl solution is lowered to 9.5 by the addition of 10% aqueous HCl, the ep-

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(8) Olefin epoxidation and alkene hydroxylations catalyzed by metallotetraarylporphyrins, which mimic the oxygenations promoted by cytochrome P-450, have been carried out with a variety of oxidants;[6] from among them alkali hypochlorites,[1-5] hydrogen peroxide,[7f,g,9] potassium hydrogen persulfate (oxone),[10] and molecular oxygen[6b,c] are potentially suitable for large-scale application.

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Table II. Stability of Mn Porphyrins in the Epoxidation of Cyclooctene[a]

entry	porphyrin	pH	L/P	Q^+X^-, %	residual Mn porphyrin,[b] % (min)
1	1	9.5[c]	25	5	24 (5), 9 (10)
2			25	1.2	89 (5), 36 (10), 25 (20)
3		10.5	1	0	57 (10), 40 (20), 28 (40)
4	2[d]	9.5[c]	25	5	100 (120)
5		10.5	1	0	100 (120)
6			0	0	100 (180)
7	5	9.5[c]	25	5	0 (15)
8		10.5	25	0	74 (15)
9			1	0	70 (60), 0 (300) (conv 52%)
10	6	9.5[c]	25	5	41 (5), 16 (10)
11			25	1.2	73 (5), 47 (10)
12		10.5	25	0	47 (10)
13			1	0	73 (10), 64 (20), 51 (40)
14			0	0	70 (300), 40 (420)
15	7	9.5[c]	25	5	91 (10), 62 (30), 56 (45)
16		10.5	25	0	80 (20)
17			1	0	100 (40), 100 (60)
18			0	0	100 (120)

[a] 0 °C, L = *N*-hexylimidazole. [b] Measured after complete conversion of cyclooctene; reaction times are indicated in parentheses. [c] Initial value; nonbuffered solution. [d] Identical behavior for Mn porphyrins 3 and 4.

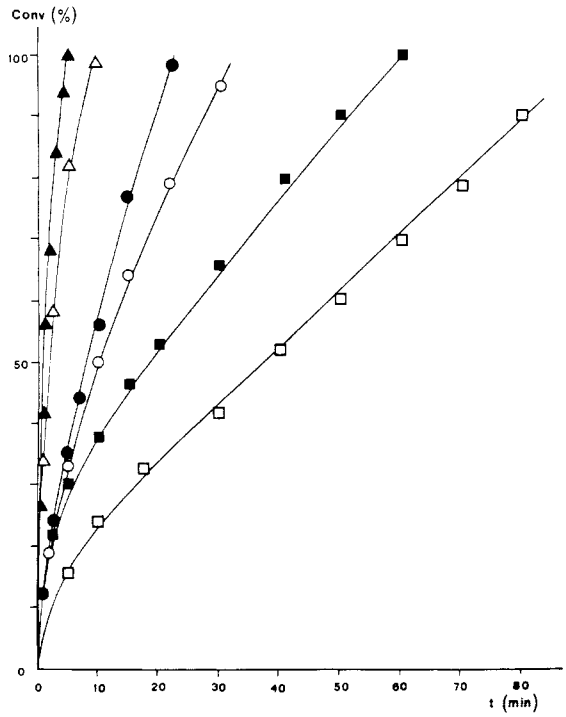


Figure 1. Influence of pH and of phase-transfer catalyst (Q^+X^-) on the epoxidation of cyclooctene catalyzed by Mn(T2,6Cl_2PP)Cl (**2**) and *N*-hexylimidazole (**8**) at 0 °C: pH 9.5 (△, ▲); pH 10.5 (○, ●); pH 9.5, not buffered (□, ■); presence (full symbols), absence (empty symbols) of Q^+X^-. Reagents molar ratio 2:olefin:8:NaOCl (0.35 M):Q^+X^- = 1:200:25:700:0–10.

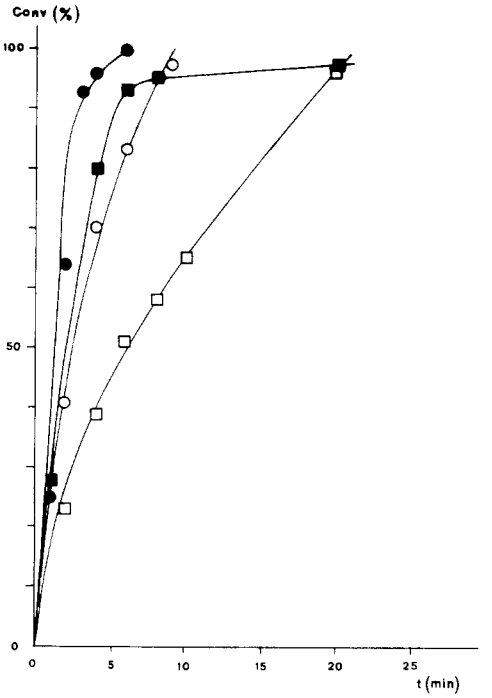


Figure 2. Influence of pH and of phase-transfer catalyst (Q^+X^-) on the epoxidation of 1-dodecene catalyzed by Mn(T2,6Cl_2PP)Cl (**2**) and *N*-hexylimidazole (**8**) at 0 °C: pH 9.5 (○, ●); pH 10.5 (□, ■); presence (full symbols), absence (empty symbols) of Q^+X^-. Reagents molar ratio 2:olefin:8:NaOCl (0.35 M):Q^+X^- = 1:200:25:700:0–10.

oxidation rate is still high at 0 °C and the selectivity good (≥90%), but, as previously observed,[5a] the pH increases to about 11.0 in the course of the reaction; this is most likely related to the chlorination reaction which drives equilibrium (1) toward the right. As a consequence,

$$ClO^- + Cl^- + H_2O \rightleftharpoons Cl_2 + 2OH^- \quad (1)$$

trans-1,2-dichlorocyclooctane is the only side product in the epoxidation of cyclooctene[5a] and is almost exclusively formed in the early stages of the reaction.

When the pH of the aqueous phase is maintained at 9.5 during the reaction, the epoxidation rate is enhanced (Figure 1), but the amount of chlorinated product becomes even more relevant, lowering the epoxide selectivity to 65%. On buffering the pH at 10.5, the epoxide selectivity was ≥95% whereas the reaction rate remained satisfactorily high (Figure 1).

In the case of 1-dodecene, the chlorination reaction is negligible; hence, at pH 9.5 the selectivity and reaction rate are only slightly affected by the absence of the buffer (Figure 2).

The addition of a PT catalyst slightly increases the epoxidation rate but also speeds up the oxidative degradation of porphyrins (Tables II and III).

Effect of the Ligand–Porphyrin Ratio. Only a few papers concerning the structure optimization of the axial ligand and the influence of the ligand–porphyrin ratio (L/P) on the reaction rates can be found in the literature. It has been reported that alkyl-substituted pyridines and 4′-(imidazol-1-yl)acetophenone are more efficient axial ligands than pyridine and methylimidazoles, respective-

Table III. Stability of Mn Porphyrins in the Epoxidation of 1-Dodecene[a]

entry	porphyrin	pH	L/P	Q^+X^-, %	residual Mn porphyrin,[b] % (min)
1	1	9.5[c]	25	5	0 (5)[d] (conv 15%)
2	2	9.5[c]	25	0	80 (60)
3			25	5	60 (60)
4		9.5	25	5	45 (60)
5		10.5	25	5	75 (60)
6	3	9.5[c]	25	0	70 (60)
7		9.5	25	5	62 (60)
8		10.5	10	0	92 (30)[d] (conv 90%)
9	4	9.5[c]	25	5	60 (30)
10		9.5	25	0	60 (60)
11		10.5	10	0	85 (45)[d] (conv 75%)
12			25	0	76 (20)[d] (conv 90%)
13	5	9.5	25	5	0 (16)[d] (conv 32%)
14		10.5	10	0	50 (20), 40 (60)[d] (conv 27%)
15	6	9.5[c]	25	5	38 (60)[d] (conv 73%)
16			25	0	50 (60)[d] (conv 91%)
17		10.5	25	0	60 (60)[d] (conv 92%)
18	7	10.5	10	0	75 (60)[d] (conv 75%)

[a] 0 °C, L = *N*-hexylimidazole. [b] Measured after complete conversion of 1-dodecene, if not stated otherwise; reaction times indicated in parentheses. [c] Initial value; nonbuffered solution. [d] Reaction stopped before complete conversion.

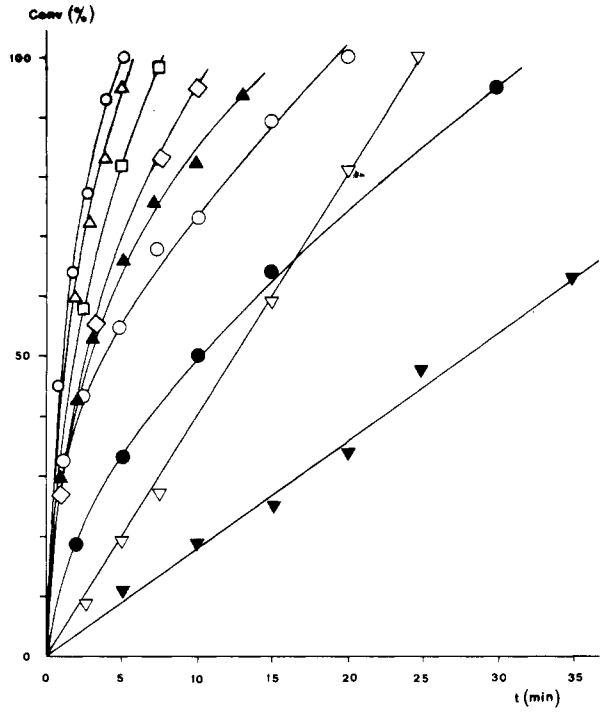


Figure 3. Influence of ligand/porphyrin ratio (L/P) on the epoxidation of cyclooctene catalyzed by Mn(T2,6Cl_2PP)Cl (**2**) and *N*-hexylimidazole (**8**) at 0 °C: pH 9.5 (empty symbols); pH 10.5 (full symbols). L/P: 0 (▽, ▼), 0.5 (○), 1 (△, ▲), 3 (□), 10 (◇), 25 (○, ●). Reagents molar ratio 2:olefin:8:NaOCl (0.35 M) = 1:200:0–25:700.

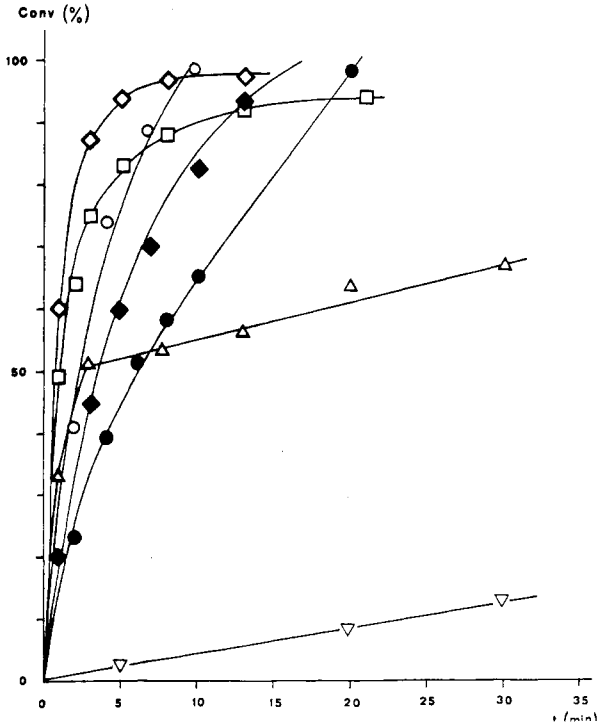


Figure 4. Influence of ligand/porphyrin ratio (L/P) on the epoxidation of 1-dodecene catalyzed by Mn(T2,6Cl_2PP)Cl (**2**) and *N*-hexylimidazole (**8**) at 0 °C: pH 9.5 (empty symbols); pH 10.5 (full symbols). L/P: 0 (▽), 1 (△), 5 (□), 10 (◇, ◆), 25 (○, ●). Reagents molar ratio 2:olefin:8:NaOCl (0.35 M) = 1:200:0–25:700.

ly.[2d,3a] According to different authors optimum L/P's are in the range 15–650.[1-5] This wide range is most likely due to a combination of several factors, such as the chemical instability of the porphyrins and of the axial ligands and the distribution of the ligand between the aqueous and the organic phase.

In order to get a better understanding of these parameters, we used the chemically stable Mn(T2,6Cl_2PP)Cl **2** as catalyst, and *N*-hexylimidazole (**8**), which is totally insoluble in water, as axial ligand.

As is shown in Figure 3, at pH 9.5 epoxidation rates of cyclooctene are greatly enhanced by addition of very small amounts of **8**; the maximum rate is found for L/P = 0.5–1.0, and under these conditions, the reaction is over in 5 min. At pH 10.5 the epoxidation rates are slower, and again a maximum is reached for L/P = 0.5–1.0. In the absence of the axial ligand the rates sharply decrease, and conversions are complete in 25 and 60 min at pH 9.5 and 10.5, respectively.

A very different behavior is observed when 1-dodecene is the substrate (Figure 4). Complete conversion is obtained after 10 min at pH 9.5 with L/P = 25. Below this value, the reaction is initially fast and then suddenly slows down and proceeds at the same rate as is found in the absence of the axial ligand (see below). At pH 10.5, the reaction is over in 20 and 15 min with L/P = 25 and 10, respectively. As observed for cyclooctene, with higher amounts of **8**, longer times are required to reach complete conversion. In the absence of the ligand the reaction is extremely slow.

Without the axial ligand, but in the presence of a PT catalyst, epoxidation is inhibited with both substrates.

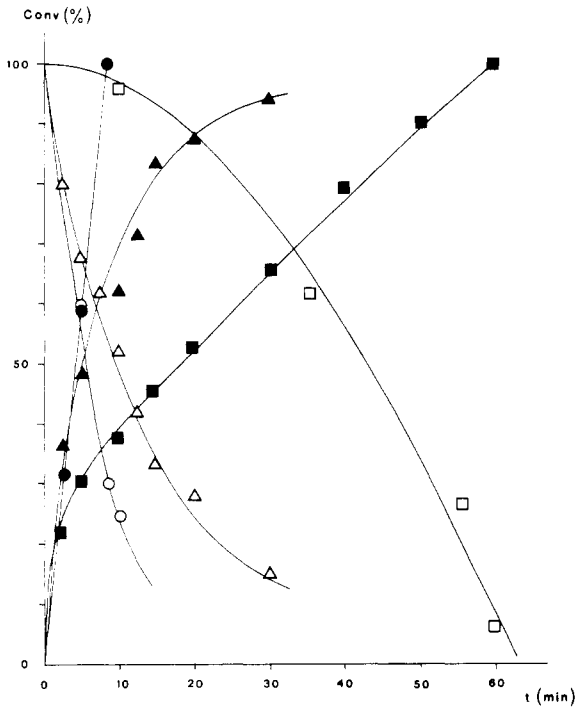


Figure 5. Fate of the axial ligand in the olefin epoxidation catalyzed by Mn(T2,6Cl$_2$PP)Cl (**2**) at 0 °C and pH 9.5: olefin epoxidation (full symbols), ligand demolition (empty symbols); cyclooctene, *N*-hexylimidazole (■, □); 1-dodecene, 4-*tert*-butylpyridine (▲, △); 1-dodecene, 3-phenylpyridine (●, ○). Reagents molar ratio 2:olefin:ligand:NaOCl (0.35 M):Q^+X^- = 1:200:25:700:10.

Fate and Structure of the Axial Ligand. One of the reasons that complicate the understanding of the influence of the ligand/porphyrin ratio on the olefin epoxidation is the concomitant oxidation of the axial ligand. Indeed, both *N*-hexylimidazole (**8**) and pyridines **9** and **10** are oxidized along with the olefin; this reaction is particularly fast when almost all the substrate has been consumed. A few significant examples with the olefin:ligand:porphyrin **2** ratio = 200:25:1 are reported in Figure 5. When equimolecular amounts of ligand **8** and cyclooctene were used, the ligand was 50% oxidized at 95% olefin conversion (45 min); the residual ligand was entirely oxidized in a further 15 min. In the absence of olefin, ligands **8**, **9**, and **10** were completely oxidized at 0 °C and pH 9.5 in 30, 60, and 90 min, respectively.

Pyridines **9** and **10** afforded the corresponding *N*-oxides **11** and **12**, which were isolated in high yields. From *N*-hexylimidazole (**8**) an unresolvable mixture of products was obtained.[12]

The behavior of *N*-hexylimidazole (**8**), 4-*tert*-butylpyridine (**9**), 3-phenylpyridine (**10**), and of *N*-oxides **11** and **12** as axial ligands in the oxidation of cyclooctene is almost identical. For instance, at pH 10.5, 0 °C, and L/P = 1, with porphyrin **2** the reaction was over in 14–18 min, whatever the ligand (Figures 3 and 6). In the oxidation of 1-dodecene, L/P = 10, imidazole **8** is the best ligand (Figures 4 and 6). Surprisingly, in the oxidation of this olefin, 3-phenylpyridine *N*-oxide (**12**) is more effective than the corresponding pyridine **10** (Figure 6). The same result was found when the porphyrin/substrate ratio was 10 times lower (2:ligand:1-dodecene = 1:10:2000), since 60%

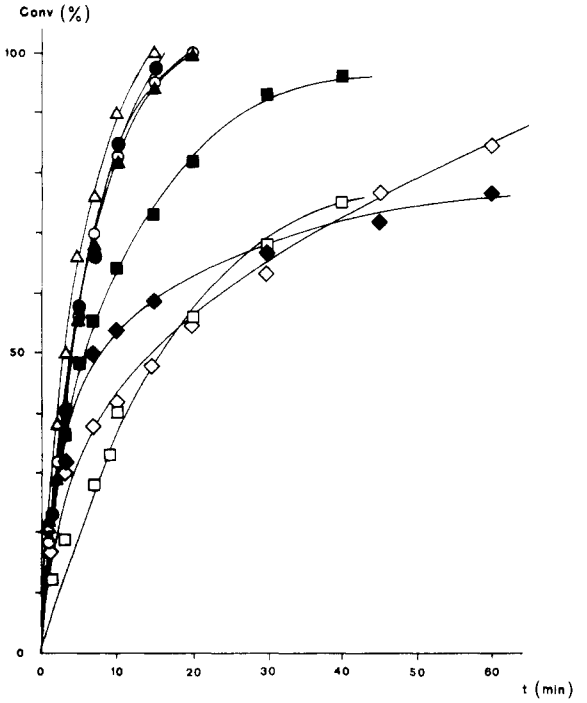


Figure 6. Influence of pyridines **9**, **10** (empty symbols) and of the corresponding *N*-oxides **11**, **12** (full symbols) in the olefin epoxidations catalyzed by Mn(T2,6Cl$_2$PP)Cl (**2**) at 0 °C, pH 10.5, L/P = 1 and 10 in the epoxidation of cyclooctene (first symbol) and of 1-dodecene (second symbol), respectively: 4-*tert*-butylpyridine (**9**) (△, ◇), 3-phenylpyridine (**10**) (○, □), 4-*tert*-butylpyridine *N*-oxide (**11**) (▲, ◆), 3-phenylpyridine *N*-oxide (**12**) (●, ■). Reagents molar ratio 2:olefin:ligand:NaOCl (0.35 M) = 1:200:1–10:700.

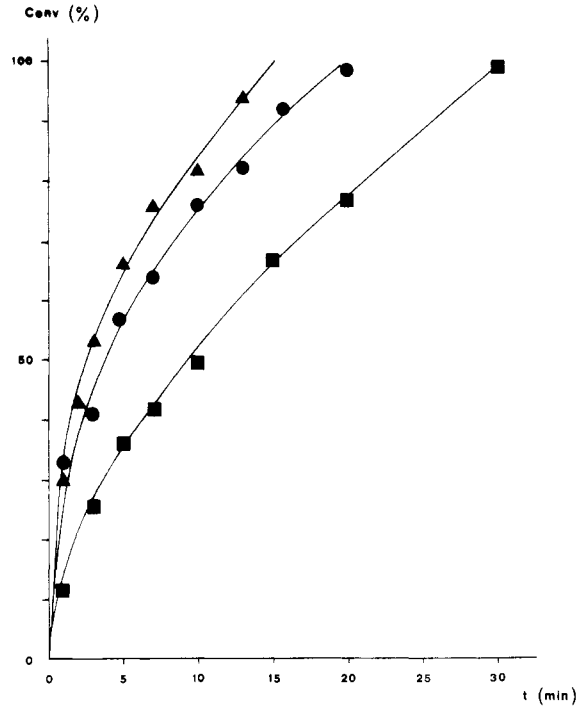


Figure 7. Epoxidation of cyclooctene catalyzed by Mn(T2,6Cl$_2$PP)Cl (**2**) (▲), Mn(TCl$_3$Me$_2$PP)Cl (**3**) (●), Mn(TBr$_3$Me$_2$PP)Cl (**4**) (■), at 0 °C and pH 10.5. Reagent molar ratio Mn porphyrin:olefin:8:NaOCl (0.35 M) = 1:200:1:700.

and 80% conversions (1200 and 1600 turnovers) were obtained after 285 min at pH 10.5 and 0 °C, with **10** and **12**, respectively. In the oxidation of 1-dodecene, where L/P = 10 is required, the difference in efficiency of **11** and **12** is mainly due to their partitioning between H_2O and

(12) It is known that imidazole *N*-oxides cannot be prepared by direct oxidation of the heterocyclic ring.[13]

(13) (a) Botvinnik, M. M.; Porkofev, N. A. *J. Gen. Chem. USSR* **1937**, *7*, 1621. (b) Lettau, H. *Z. Chem.* **1970**, *10*, 211. (c) Grimmett, M. R. *Adv. Heteroc. Chem.* **1970**, *12*, 103.

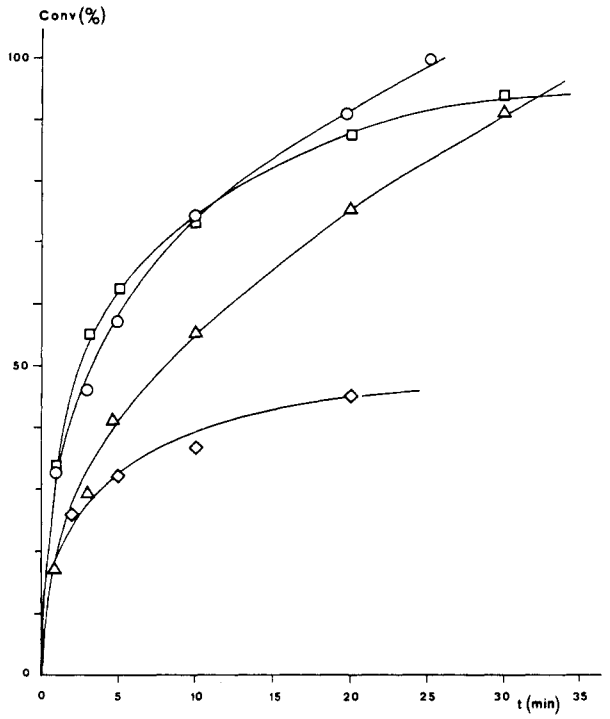


Figure 8. Epoxidation of cyclooctene catalyzed by Mn(TPP)Cl (1) (○), Mn(T3,5Cl$_2$PP)Cl (5) (◇), Mn(TF$_5$PP)Cl (6) (□), and Mn(TMP)Cl (7) (△), at 0 °C and pH 10.5. Reagents molar ratio Mn porphyrin:olefin:8:NaOCl (0.35 M) = 1:200:1:700.

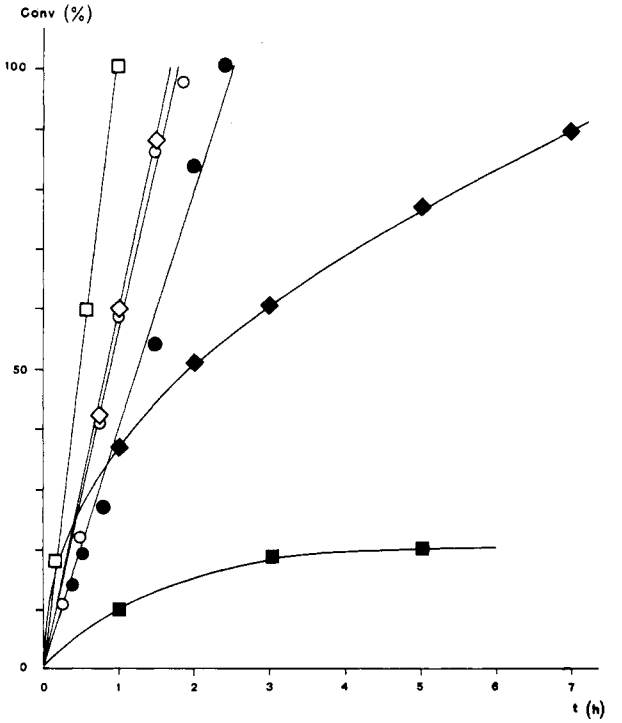


Figure 9. Epoxidation of cyclooctene catalyzed by Mn porphyrins (2) (□), 3 (●), 4 (○), 5 (■), 6 (◆), and 7 (◇) at 0 °C and pH 10.5, in the absence of axial ligand. Reagents molar ratio Mn porphyrin:olefin:NaOCl (0.35 M) = 1:200:700.

CH_2Cl_2 (45:55 and 0:100, respectively).

Comparison of Catalytic Activity of Mn Porphyrins 1–7. Catalytic activity of Mn porphyrins 1–7 has been compared under the optimized conditions set up for porphyrin 2 in the oxidation of cyclooctene and 1-dodecene. At pH 10.5, 0 °C, L/P = 1, and with porphyrins 2–4 as catalysts, cyclooctene was oxidized in 15–30 min (Figure 7); porphyrins were still unchanged at the end of the reactions (Table II). Under these same conditions and using porphyrins 1 and 6, reactions were over in 30–35 min (Figure 8), but degradation was observed (40% and 64% after 20 min, 28% and 51% after 40 min, of residual porphyrins 1 and 6, respectively) (Table II). Porphyrin 5 was totally destroyed within few minutes when a quaternary salt was used; in the absence of the latter it is relatively more stable but the reaction stops at <50% conversion due to the complete degradation of the ligand. Porphyrin 7 is stable under the reaction conditions but catalyses a fast oxidation of cyclooctene until 60% conversion (5 min), and then the reaction becomes very slow and is complete in 1 h (Figure 8 and Table II). The last part of the reaction proceeds at the same rate as is found in the absence of the axial ligand.

In the absence of ligand, catalysts 2–4 and 7 allow complete conversion of cyclooctene in 1–2 h, the catalysts still being unchanged at the end of reaction (Table II and Figure 9). Complete conversion was also obtained with 6 in about 8 h, but the catalyst undergoes partial demolition (70% and 40% of residual porphyrin after 5 and 7 h, respectively). Porphyrins 1 and 5 do not catalyze cyclooctene epoxidation in the absence of the axial ligand and are completely bleached in 4–5 h.

In epoxidation of 1-dodecene carried out at pH 10.5, 0 °C, and L/P = 10, all reactions stopped before reaching the end (Figure 10). Complete conversion was achieved only with porphyrin 2 (Figure 4). By increasing the amount of the axial ligand (L/P = 25) also 3 and 4 completed the reaction (Figure 10). Once again this behavior

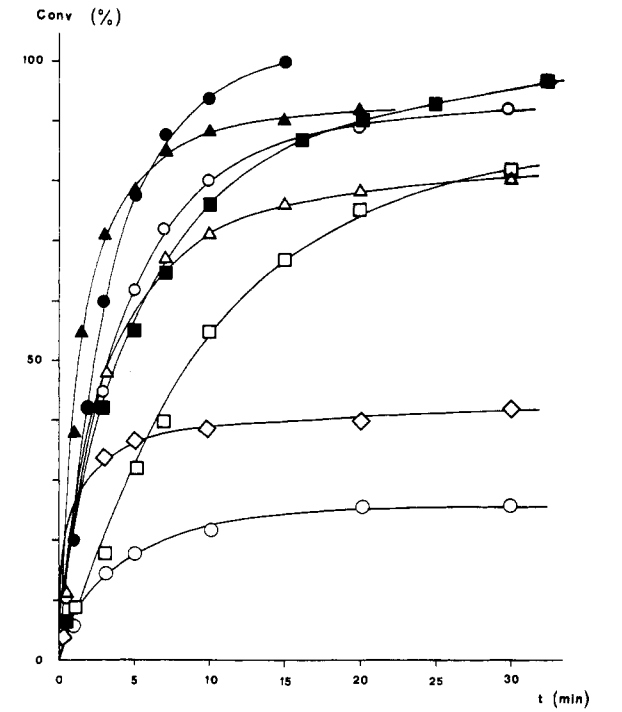


Figure 10. Epoxidation of 1-dodecene catalyzed by Mn porphyrins 3 (o, ●), 4 (□, ■), 5 (○), 6 (△, ▲), and 7 (◇) at 0 °C and pH 10.5: L/P = 10 (empty symbols), L/P = 25 (full symbols). Reagents molar ratio Mn porphyrins:olefin:8:NaOCl (0.35 M) = 1:200:10–25:700.

is due to the competitive demolition of the axial ligand and to a partial or total degradation of the porphyrins; 100% conversion is reached with the most stable porphyrins 2–4 only when enough ligand survives. In the presence of 1-dodecene, a poorly reactive substrate, the excess of axial ligand also catalyses a slow demolition of porphyrins 2–4, which however does not exceed 20–25% and stops when

all the ligand has been oxidized.[14]

Discussion

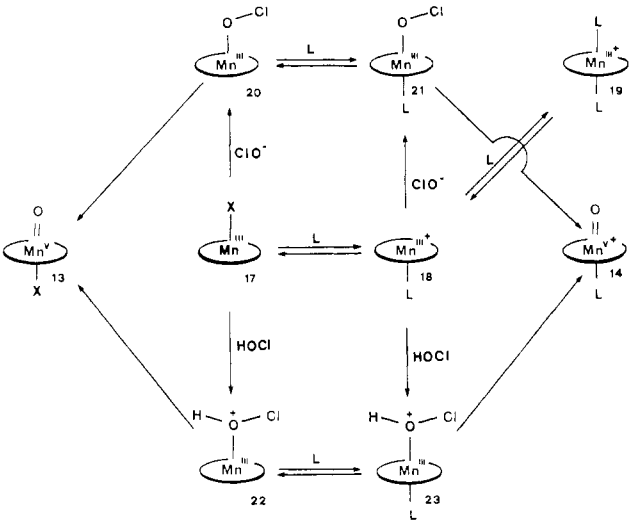
In the NaOCl-promoted epoxidations reactivity and chemical stability of porphyrins **1–7** depend on a complicated combination of several factors: the porphyrin and olefin structure, pH of the aqueous NaOCl solution, presence of a quaternary onium salt as phase-transfer catalyst, lipophilicity of the axial ligand, ligand–porphyrin ratio, etc.

It has already been published that the resistance of metallotetraarylporphyrins toward oxidative degradation is strongly increased by the presence of bulky and/or electronegative substituents in the aryl rings;[7e] however, it is only recently that the relative importance of these two parameters has been investigated.[5b,c,15] A strong degree of uncertainty derives from the fact that *the stability of metalloporphyrins has often been studied by using a large excess of substrate with respect to the oxidant*, i.e. under conditions that are particularly "harmless" to the porphyrin and do not allow a clear cut evaluation of the real stability of the latter.

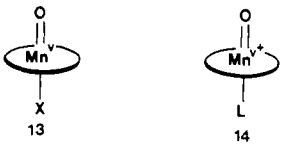
In the NaOCl epoxidations carried out at pH 9.5 under two-phase conditions, only Mn porphyrins **2–4** combining the presence of electron-withdrawing substituents with the steric protection of the metal center are stable toward oxidative degradation.[5b,c] They are particularly suitable catalysts in the oxidation of poorly reactive substrates such as α-olefins.

Hypochlorous acid, one of the most powerful oxidants known,[11] is particularly suitable for assessing the chemical stability of porphyrins. By lowering the pH of the aqueous phase to 9.5–10.5, significant amounts of HOCl are partitioned in the organic phase (Table I). The addition of a quaternary onium salt increases the amount of oxidant in the latter by extracting ClO^- from the aqueous phase.[19] Under these conditions, the anion ClO^- associated to the quaternary cation Q^+ is extremely reactive both as oxidant and nucleophile.[22] In agreement with this the stability of porphyrins strongly decreases by increasing the amount of the quaternary salt (Table II).

Scheme I



In the epoxidations catalyzed by Fe(III) and Mn(III) porphyrins, it was suggested that the reaction intermediate is a high valent oxomanganese complex **13**, expressed formally in a +5 oxidation state.[3e,6,23] When a pyridine or an imidazole is coordinated to **13**, the corresponding oxo complex **14** becomes so reactive that it is capable of catalyzing the self-destruction of Mn porphyrins, including the most robust compounds such as **2–4**.



Indeed the stability of all the investigated porphyrins diminishes in the presence of the axial ligand and is inversely related to the amount of this latter (Tables II and III). The effect is particularly evident with α-olefins, which require high L/P values. In the presence of bulky and electron-withdrawing substituents in the ortho positions of the phenyl rings, the noncoordinated oxo complex **13** can still oxidize the olefin without self-destruction. In the absence of the ligand, not only Mn porphyrins **2–4**, but also **7**, are perfectly stable (Figure 9 and Table II).[28]

(14) Previously we reported[5c] that porphyrins **2–4** are perfectly stable during the oxidation of 1-dodecene carried out with an excess of axial ligand (L/P = 10–25). This conclusion relied upon the invariance of the intensity of the Soret band (in the range 477.5–480 nm depending on the Mn(III) porphyrin) for at least 120 min after the end of the reaction. Now we find that with L/P = 25 the absorbance is 20–25% lower than that in the absence of the ligand (situation at the end of the reaction), without appreciable shift of λ_{max}. As a consequence, the partial demolition of porphyrin balances the expected increase of absorbance.

(15) A few qualitative scales of stability under certain conditions have been proposed.[2g,10,16] Mn- and Fe-(T2,6Cl$_2$PP)Cl are constantly described as exceptionally robust porphyrins,[7e,h] but the metal complexes of other porphyrins are also reported as a very stable, among them tetrakis(pentafluorophenyl)porphyrin,[2g,3d,7c,10b] tetramesitylporphyrin,[2f,10b] tetrakis-(2,4,6-triphenylphenyl)porphyrin,[16] tetrakis(3,5-di-*tert*-butyl-2-nitrophenyl)porphyrins,[4i] and those deriving from the perchlorination and perbromination of **2** at the pyrrolic rings.[17] Obviously, the stability also depends on the nature of the oxidant,[7e,18] and an isolated report can be found[3a] on the influence of the axial ligand.

(16) Cook, B. R.; Reissert, T. J.; Suslick, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7281.

(17) Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338.

(18) Traylor, T. G.; Xu, F. *J. Am. Chem. Soc.* **1987**, *109*, 6201.

(19) It has been reported by Sasson[20] that the amount of ClO^- transferred into the organic phase (CH_2Cl_2) by a lipophilic quaternary cation is maximum at pH 9–11 (50–90%); the hypochlorite is complexed to undissociated hypochlorous acid by hydrogen bonding. Bruice has recently published that with aqueous LiOCl at pH 10.5, about 0.1 equiv of ClO^- per equivalent of quaternary onium cation are transferred into the organic phase.[21] This is probably due to the competition between ClO^- and the large amounts of Cl^- present in the aqueous phase, as counterions extracted by the lipophilic cation.[22]

(20) (a) Abramovici, S.; Neumann, R.; Sasson, Y. *J. Mol. Catal.* **1985**, *29*, 291. (b) *Ibid.* **1985**, *29*, 299.

(21) Lee, R. W.; Nakagaki, P. C.; Balasubramanian, P. N.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 641.

(22) (a) Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* **1982**, *101*, 147. (b) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 2nd ed.; Verlag Chemie: Weinheim, 1983. (c) Lee, G. A.; Freedman, H. H. *Isr. J. Chem.* **1985**, *26*, 229.

(23) No assignment of the electronic configuration of the active species is intended; indeed other formulations cannot be ruled out.[24] In the case of the oxidizing system Mn(III) porphyrin/NaOCl the active species has been isolated and characterized by visible spectroscopy, magnetic measurements, cyclic voltammetry, and EXAFS.[25] A structure in which oxygen is inserted into the metal–nitrogen bond has been alternatively proposed for Fe(III) porphyrins and theoretical calculations have predicted that it may be significantly more stable than the oxo complexes.[26] However such a species has only been recently prepared and characterized, and it has been shown that it is chemically distinct from the formally expressed isomeric oxo complex.[27]

(24) (a) Meunier, B. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 314. (b) Van der Made, A. W.; Drenth, W.; Nolte, R. J. M. *Ibid.* **1987**, *106*, 330. (c) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3812. (d) Czernuszewicz, R. S.; Su, Y. O.; Stern, M. K.; Macor, K. A.; Kin, D.; Groves, T. G.; Spiro, T. G. *J. Am. Chem. Soc.* **1988**, *110*, 4158.

(25) (a) Bortolini, O.; Meunier, B. *J. Chem. Soc., Chem. Commun.* **1983**, 1364. (b) Bortolini, O.; Ricci, M.; Meunier, B.; Friant, P.; Ascone, I.; Goulon, J. *Nouv. J. Chim.* **1986**, *10*, 39.

(26) (a) Balch, A. L.; Chan, Y. W.; Olmstead, M.; Renner, M. W. *J. Am. Chem. Soc.* **1985**, *107*, 2393. (b) Jørgensen, K. A. *Acta Chem. Scand.* **1986**, *B-40*, 512. (c) *J. Am. Chem. Soc.* **1987**, *109*, 698.

(27) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7836.

Both the quaternary salt and the axial ligand play an intriguing role in the epoxidations, which can be accelerated, slowed down, or even inhibited by them. We can speculate that this is due to the equilibrium between Mn porphyrin **17** and its mono- and bisligated species **18** and **19**, and to the different reactivities of **17–19** in the presence of HOCl and of the ion pair Q^+ClO^- (Scheme I).[31]

At pH 12.7, when ClO^- associated to the quaternary onium cation is the only oxidizing species in the organic phase, only **18** via **21** can afford the active oxo complex **14**, the driving force being the electron donation to the metal by the coordinated nitrogen base. Under these conditions, but in the absence of the axial ligand, no appreciable reaction occurs; this means that the possible formation of **13** from **17**, via the hypothetic species **20**, must be an extremely slow process.

At pH 9.5–10.5 and in the absence of the quaternary onium salt, HOCl is now the oxidizing species. In this case the reaction proceeds also in the absence of the axial ligand. The driving force should be the positive charge on the oxygen in the possible intermediate **22**, to give **13** from **17**.[32] Since epoxidation is inhibited by the phase-transfer catalyst, formation of **22** should be prevented by the competitive reaction of the more nucleophilic ClO^- with **17**. At pH 9.5–10.5, formation of **14** from **18** via **23** is also favored by the electron donation from the axial ligand, in agreement with experimental results (Figure 3).

It has recently been reported by Bruice[33] that in the epoxidations promoted by *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide and catalyzed by Mn porphyrin **2** in the presence of imidazole (IMH) as axial ligand, the maximum reaction rate corresponds to the maximum concentration at the equilibrium of the monocoordinated species (Por)Mn(IMH)Cl; this occurs at a $L/P \simeq 18$.

$$(Por)MnX + L \overset{K_1}{\rightleftharpoons} (Por)Mn(L)X \quad (2)$$

$$(Por)Mn(L)X + L \overset{K_2}{\rightleftharpoons} (Por)Mn(L)_2X \quad (3)$$

$$(Por)MnX + 2L \overset{\beta_2}{\rightleftharpoons} (Por)Mn(L)_2X \quad (4)$$

$$\beta_2 = K_1K_2 \quad (5)$$

In the oxidation of cyclooctene with NaOCl at pH 9.5, **2** as catalyst and *N*-hexylimidazole (**8**) as axial ligand, we observed a maximum rate for $L/P = 0.5$. Measuring[33–35] K_1 and β_2 in CH_2Cl_2 at 25 °C for the equilibria reported in eq 2–5, we found for Mn(TPP)Cl **1**, $K_1 = 58 \pm 2\ M^{-1}$, $\beta_2 = (10.7 \pm 0.11) \times 10^3\ M^{-2}$, and $K_1 = 182 \pm 15\ M^{-1}$, $\beta_2 = (59.2 \pm 0.82) \times 10^3\ M^{-2}$, when *N*-hexylimidazole (**8**) and imidazole were the axial ligands, respectively; the latter K_1 and β_2 values are in good agreement with those reported by Bruice.[36,37] In the case of Mn(T2,6Cl_2PP)Cl **2** and of **8**, K_1 and β_2 were $(1.18 \pm 0.2) \times 10^3\ M^{-1}$ and $(8.91 \pm 0.25) \times 10^6\ M^{-2}$, corresponding to a K_2/K_1 ratio of about 6.5. The maximum concentration at 25 °C of the monoligated species can be calculated from eq 6 (PL = monocoordinated porphyrin; L = ligand, P_0 = Mn porphyrin employed), obtained from equilibria 2–5. It occurs at L/P

$$[PL] = \frac{K_1[L][P_0]}{1 + K_1[L] + \beta_2[L]^2} \quad (6)$$

= 0.3, a value in very good agreement with the observation of a maximum rate for L/P = 0.5 at 0 °C. This result shows that **18** is by far the most reactive species among the nonligated, mono- and bisligated Mn porphyrins **17–19**.[39]

The oxygen transfer from the oxomanganese complex to the olefin is still the object of much debate. Collman and Meunier have proposed the reversible formation of a metallaoxetane **15**,[2e,3c] formally derived from a 2 + 2 cycloaddition,[41] whereas a ring-opened intermediate **16** has alternatively been proposed, deriving from an electron

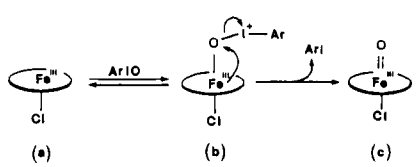
(28) As has been found for Fe(III) porphyrins,[29] it might be possible that the slow demolition of **2–4** observed in the epoxidation of 1-dodecene is due to the N-alkylation of the Mn porphyrin (suicide inhibition by the substrate).[6b,30] Although this event cannot be totally excluded it seems indeed less probable, since it was not possible to identify any species having properties comparable with those[28] of Fe(III) *N*-alkyl porphyrins.

(29) (a) Mansuy, D.; Devocelle, L.; Artaud, I.; Battioni, J.-P. *Nouv. J. Chem.* **1985**, *9*, 711. (b) Mashiko, T.; Dolphin, D.; Nakano, T.; Traylor, T. G. *J. Am. Chem. Soc.* **1985**, *107*, 3735. (c) Collman, J. P.; Hampton, P. L.; Brauman, J. C. *Ibid.* **1986**, *108*, 7861. (d) Traylor, T. G.; Nakano, T.; Miksztal, A. R.; Dunlap, B. E. *Ibid.* **1987**, *109*, 3625. (e) Artaud, I.; Devocelle, L.; Gregoire, N.; Battioni, J.-P.; Mansuy, D. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 336. (f) Artaud, I.; Devocelle L.; Battioni, J.-P.; Girault, J.-P.; Mansuy, D. *J. Am. Chem. Soc.* **1987**, *109*, 3782.

(30) (a) Ortiz de Montellano, P. R.; Correia, M. A. *Ann. Rev. Pharmacol. Toxicol.* **1983**, *3*, 481.

(31) This is only a formal representation and does not reflect the real coordination of the Mn species.

(32) We can observe the analogy with other oxidations catalyzed by metalloporphyrins, for example those promoted by iodosyl and pentafluoroiosodyl benzene, in which step b → c is very fast and does not require any axial ligand, the driving force being the positive charge on the iodine atom in b.[3d]



(33) Wong, W.-H.; Ostovic, D.; Bruice, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 3428.

(34) Walker, F. A.; Lo, M.-W.; Ree, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 5552.

(35) (a) Byers, W.; Cossham, J. A.; Edwards, J. O.; Gordon, A. T.; Jones, J. G.; Kenny, E. T. P.; Mahmood, A.; McKnight, J.; Sweigart, D. A.; Tondreau, G. A.; Wright, T. *Inorg. Chem.* **1986**, *25*, 4767. (b) Brewer, C. T.; Brewer, G. A. *Inorg. Chem.* **1987**, *26*, 3420. (c) Momenteau, M.; Scheidt, W. R.; Eigenbrot, C. W.; Reed, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 1207.

(36) Yuan, L.-C.; Bruice, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 1643.

(37) In the case of Mn(III) porphyrins, it has been reported[38] that when X is a tightly binding counterion (such as Cl^-, Br^-, or N_3^-), equilibrium constants K_1 and K_2 are comparable, independently of their absolute values;[38] only if the counterion is a poorly binding ligand (such as ClO_4^-), K_1 may be 15–18 times higher[21] than K_2. The behavior of Mn(III) porphyrins is in contrast with that of Fe(III) porphyrins in which generally only the overall stability constants β_2 is observed being $K_2 \gg K_1$.[34] Accordingly, it has also been observed that pyridine or imidazole bases inhibit catalytic activity of Fe(III)(TPP)Cl in the presence of NaOCl,[2h,3a,4i] the equilibrium concentration of the catalytically active monocoordinated species being too low to be detected.

(38) (a) Kelly, S. L.; Kadish, K. M. *Inorg. Chem.* **1982**, *21*, 3631. (b) Collman, J. P.; Brauman, J. I.; Fitzgerald, J. P.; Hampton, P. D.; Naruta, Y.; Michida, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 47.

(39) This result is quite interesting, even though Walker's analytical method,[34] followed by us, has been questioned[38b,40] due to the unwarranted assumption that the absorption coefficients of the mono- and bisligated species are the same at the wavelength chosen for analysis. A detailed investigation on this subject is under way. As observed by a referee, this calculation does not take into account of the loss of ligand, via oxidation, during the reaction. This loss is evidenced by the nonlinearity of the epoxide formation (Figures 3, 4, 7, 10); the effect is particularly dramatic for the less reactive α-olefins, where the disappearance of the ligand suddenly slows down the reaction (Figure 4). A linear conversion is regularly observed in the absence of axial base (Figures 3, 4, 9). We do not know in detail the reaction of bisligated porphyrin with NaOCl, but we know that in the presence of an excess ligand, when the bisligated species is practically the only one at the equilibrium (see supplementary material), the catalytic activity of the Mn porphyrins dramatically slows down.

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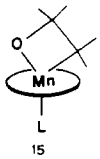
transfer from the alkene, followed by radical collapse to give a carbocation.[4i,43]



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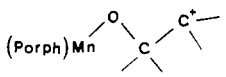

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Whatever the intermediate species involved, its equilibrium formation strongly depends on the electronic density of the olefin; actually, cyclooctene is more easily oxidized than 1-dodecene. The latter always requires the presence of an axial ligand (L/P = 10–25) in order to get complete conversion.

Cyclooctene is readily oxidized at a very low L/P, and complete conversion can be reached even in the absence of the ligand, provided that the phase-transfer catalyst is also absent. Taking into account that both the axial ligand and the quaternary onium salt accelerate the porphyrin degradation, we found that using Mn porphyrin **2** as catalyst at pH 10.5 and 25 °C, more than 60.000 turnovers were reached in 21 h, with 80% selectivity. These are conditions of choice for the scale up of the reaction.

A last comment concerns the formation of *N*-oxides **11** and **12** from pyridines **9** and **10** under the reaction conditions and their activity as axial ligands. Oxidation of pyridines (included 4-*tert*-butylpyridine) to the corresponding *N*-oxides, when used as axial ligands on Mn porphyrins in the olefin epoxidation promoted by $NaHSO_5$, has been recently reported.[21] Aliphatic *N*-oxides can transfer the oxygen atom to olefins and to alkanes in the presence of Fe(III) or Mn(III) porphyrins[44] and of imidazoles as axial ligands, whereas pyridine *N*-oxides are inert under these conditions.[2d] Stable 2:1 complexes between *N*-oxides and $Mn(TPP)ClO_4$ have been isolated,[45] and it has been reported[2e] that pyridine *N*-oxide behaves as a fairly efficient axial ligand in the olefin epoxidation promoted by NaOCl and Mn(TPP)Cl under phase-transfer conditions. The efficiency of **11** and **12** as axial ligands is quite striking since it opens up the prospect of synthesizing more stable axial ligands particularly suitable for α-olefins epoxidations.

Conclusion

The availability of chemically stable Mn(III) tetraarylporphyrins, like **2–4**, and the use of imidazole **8** or pyridines **9–10** as axial ligands, which are entirely soluble in the organic phase, allowed us to optimize NaOCl olefin epoxidations carried out under aqueous–organic two-phase conditions. The axial ligand has to be used in different amounts, L/P = 0.5–1.0 and 10–25 for reactive (cyclooctene) and fairly reactive (1-dodecene) olefins, respectively. It greatly enhances the reaction rates, but it is oxidized together with the olefin. Buffering to 10.5 the pH of the aqueous phase, the amount of HOCl in the organic phase becomes significant, and the epoxidation of electron-rich olefins also proceeds in the absence of both the axial ligand and the phase-transfer catalyst. These are the best conditions for the chemical stability of the porphyrin, which can even reach several thousands of turnovers without being demolished, with complete olefin conversion and very high selectivity. In our opinion the latter are the sole conditions that can be effectively transferred on large-scale syntheses.

Experimental Section

^1H NMR spectra were recorded on Bruker WP80SY and Varian XL300 spectrometers in $CDCl_3$ as solvent. UV–vis spectra were obtained with a Varian Cary 219 and Philips PU8720 spectrophotometers. GC analyses were performed on a Varian Model 3700 gas chromatograph flame ionization instrument (20 × 0.125 in. OV-101-5% on CHP 100–125 mesh column), with VISTA CDS 401 Varian chromatography data system. The free base porphyrins, H_2-(TPP),[46] H_2-(T2,6Cl_2PP),[47] H_2-(T$Cl_3$$Me_2$PP),[5c] H_2-(T$Br_3$$Me_2$PP),[5c] H_2-(T3,5Cl_2PP),[5c] H_2-(TF_5PP),[47] and H_2-(TMP)[47,48] were prepared following reported procedures. Mn complexes **1–7** were obtained according to the procedure of Adler.[49] *N*-Hexylimidazole (**8**),[5a] 4-*tert*-butylpyridine *N*-oxide (**11**),[50] and 3-phenylpyridine *N*-oxide (**12**),[51] were prepared as described; 4-*tert*-butylpyridine (**9**), 3-phenylpyridine (**10**), and imidazole were commercially available and were purified before use. Melting points are uncorrected.

4-*tert*-Butylpyridine *N*-Oxide (11). 4-*tert*-Butylpyridine (**9**) (270.4 mg, 2 mmol) in 20 mL of CH_2Cl_2 was treated for 2 h, under vigorous stirring, with 20 mL of buffered aqueous NaOCl (0.34 M, pH 10.5) in the presence of 5×10^{-3} mmol of Mn-(T2,6Cl_2PP)Cl. The reaction progress was monitored by TLC ($CHCl_3$:MeOH = 98:2). At the end of the reaction the phases were separated, and the crude material was purified by column chromatography (silica gel $CHCl_3$:MeOH = 98:2) to give 274 mg (91%) of **11**: mp 102–103 °C in sealed tube (lit.[50] mp 103–104 °C); ^1H NMR ($CDCl_3$) δ 1.3 (s, 9 H), 7.2 (d, 2 H), 8.1 (d, 2 H).

3-Phenylpyridine *N*-Oxide (12). 3-Phenylpyridine (**10**) (315 mg, 2 mmol) was oxidized under the conditions described above. Column chromatography afforded 230 mg (65%) of **12**: mp 115–116 °C in sealed tube (lit.[51] mp 119 °C); ^1H NMR ($CDCl_3$) δ 7.2–7.4 (m, 7 H), 8.2 (d, 1 H), 8.4 (b s, 1 H).

General Procedure of Olefin Epoxidation. Oxidations were carried out in a 20-mL flask equipped with a Teflon-lined screw cap and magnetic stirrer, thermostatted at 0 ± 0.2 °C with circulating ethanol by a Colora Misstechnick GMBH Lorch/Wurtt. cryostat. Stirring speed was maintained at 1300 ± 50 rpm. The flask was charged with (a) 1 mL of CH_2Cl_2 solution containing 0.5 mmol of substrate, 0.25 mmol of decane as internal standard, and 0.025 mmol of trioctyl methyl ammonium chloride (Aliquat 336), when used; (b) 1 mL of 0.0025 M CH_2Cl_2 solution of Mn porphyrin; (c) 5 mL of aqueous 0.35 M NaOCl, whose pH was buffered at the desired value in the range 9.5–10.5 by addition of 0.1 g of $Na_2B_4O_7$ in 10 mL of NaOCl (slight pH corrections were made by the addition of few drops of 10% NaOH or 10% HCl solutions). The required amount of ligand was added via microsyringe (10–50 μL of a CH_2Cl_2 solution in the range 2.5×10^{-1} to 1.25 M concentration). The mixture was stirred, and samples taken at different times were analyzed by GC.

Stability of Mn Porphyrins 1–7. In the epoxidation experiments a 25-μL sample of the organic phase was withdrawn before the addition of the ligand[14] and diluted in 10 mL of CH_2Cl_2

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(zero time); 25-μL samples were withdrawn at different times and diluted in 10 mL of CH_2Cl_2. Mn porphyrin decomposition was followed by UV–vis spectroscopy in the 350–700-nm range, measuring the percentage decrease of the absorbance at the λ_{max} referred to the sample taken at zero time. Results are reported in Tables II and III.

Titration of HOCl Extracted in CH_2Cl_2. In a 100-mL round-bottomed flask, equipped with a magnetic stirrer, were poured 32 mL of CH_2Cl_2 and 40 mL of aqueous NaOCl (0.35 M) buffered at the desired pH. The mixture was vigorously stirred at 0 °C for 30 min; 30 mL of the CH_2Cl_2 solution were carefully separated and stirred for 10 min with an excess of acidic KI solution and titrated with 0.001 N aqueous $Na_2S_2O_3$. Results are reported in Table I.

Determination of Association Constants (K_1, β_2). The K_1 and β_2 values were determined as reported by Walker et al.[34] following the absorbance change of 1.0×10^{-5} M CH_2Cl_2 solution of Mn(TPP)Cl **1** and of Mn(T2,6Cl_2PP)Cl **2** at 477.6 and 477.9 nm, respectively, upon addition of the ligand CH_2Cl_2 solution. The concentration ranges of the latter were 2.10×10^{-4} to 3.15×10^{-2}, 4.02×10^{-4} to 5.25×10^{-2}, and 4.93×10^{-6} to 1.48×10^{-3} M for 1-IMH, 1-8, and 2-8, respectively. Titrations were recorded at 25 ± 0.2 °C under aerobic conditions.

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Registry No. 1, 32195-55-4; 1·imidazole, 79969-69-0; 2, 91463-17-1; 2·imidazole, 118920-72-2; 2·8, 118920-73-3; 3, 118920-69-7; 4, 118920-70-0; 5, 118920-71-1; 6, 79968-43-7; 7, 85939-49-7; 8, 33529-01-0; 9, 3978-81-2; 10, 1008-88-4; 11, 23569-17-7; 12, 1131-48-2; cyclooctene, 931-88-4; 1-dodecene, 112-41-4; hypochlorous acid, 7790-92-3.

Supplementary Material Available: Visible spectrum changes by addition of increasing amounts of ligand 8 to a CH_2Cl_2 of Mn porphyrin 2; mole percent plot of monoligated Mn porphyrin 2 at varying ligand 8 concentration; plots of log $(A - A_0/A_\infty - A)$ vs log [L] of K_1 and β_2 calculation for Mn porphyrins 1 and 2 when *N*-hexylimidazole is the axial ligand (6 pages). Ordering information is given on any current masthead page.

Synthesis of 4-Substituted Prolines as Conformationally Constrained Amino Acid Analogues

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Anionic substitution of *N*-(9-(9-phenylfluorenyl))-protected glutamic acid esters proceeds without loss of optical integrity to give 4-substituted glutamic acid derivatives. The 4-methyl, propyl, cyanomethyl, and phenyl analogues have thus been prepared. Primarily by conversion to the corresponding 5-hydroxypentanoic acids and intramolecular nitrogen alkylation, 4-substituted prolines are obtained in an efficient and chirospecific manner. Because of the restricted side-chain mobility, these 4-substituted prolines behave as conformationally constrained amino acid analogues.

Introduction

Substituted prolines have elicited a wide range of interest. Several alkylated prolines are rare naturally occurring amino acids,[1] they are constituent amino acids in antibiotics,[2] and recently they have gained interest in the development of novel angiotensin converting enzyme inhibitors.[3] Proline itself plays a significant role in the biochemistry of proteins, inducing strong preference for secondary structural motifs (kinks in α-helices and reverse turns).[4] This property has marked effects, for instance, in collagen biosynthesis[5] and in protein folding,[6] and has also been implicated in certain peptide hormone recognition events.[7] Conformationally constrained peptides are emerging as useful tools in developing peptide-derived pharmaceutic agents.[8] Substituted prolines provide a new

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