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5,15-Diaryl-β-substituted-porphyrinato-manganese(III) chlorides as probes for structure–activity relationships in porphyrin-based epoxidation catalysts

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ABSTRACT: Manganese complexes of 5,15-diaryl-β-substituted-porphyrins were prepared and their behaviour as oxidation catalysts was studied. The role of the pyrrolic and *meso*-substituents on the activity and selectivity of these catalysts was studied to reveal new structure–activity relationships in these porphyrin-based epoxidation catalysts. The beneficial effect of the halogen atoms at the *meso*-phenyls is still observed with these catalysts but, for the first time, a strong dependence on the selectivity of the epoxide production was found to be dependent on the nature of the non-halogen substituents at the β-pyrrolic positions of the porphyrin. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: 5,15-diaryl-β-substituted-porphyrins; manganese; epoxidation catalysts

INTRODUCTION

The progress made in recent years in the development of biomimetic oxidations of cytochrome P-450 brought significant advances to the knowledge of these reactions and opened the way for a diversity of applications. Reasonably stable active complexes based on simple porphyrin structures were found, allowing the use of various oxygen donors such as hydrogen peroxide [1], hypochlorites [2], oxone [3] and even oxygen [4]. It was established that metalloporphyrin-catalysed oxidations either in natural or synthetic processes usually occur through high-valence oxygenated species, formed by transfer of an oxygen atom to the metalloporphyrin, from a suitable oxygen donor.

The role of bulky or electron-withdrawing substituents in the *meso*-phenyls [5, 6] and the halogenation of the β-pyrrolic positions over the basic skeleton of *meso*-tetraphenylporphyrin (TPP) have been recognised [5–8] and the use of elaborated porphyrin structures [9, 10] has also been studied.

The 5,15-diarylporphyrins are interesting compounds and have been used in many recent studies, namely, as starting units for the synthesis of elaborated porphyrins [11] or as precursors of photodynamic pharmaceuticals [12].

Following our own contributions to this field [13], in this paper we present a study with manganese 5,15-diaryl-β-substituted-porphyrins designed to clarify the role of the substituents, particularly those at the β-pyrrolic positions, on the overall performance of the metalloporphyrin-based oxygenation catalysts.

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EXPERIMENTAL

All reagents were synthesis reagent grade (Aldrich) and all solvents were purified by the usual methods before use. The gas liquid chromatography (GLC) analyses during the epoxidation reactions were carried out on a Hewlett-Packard HP5890 Series II with a Mass Selective Detector 5970, on a HP OV-1 silica column, using nitrogen as carrier gas at a flow rate of 5 ml/min. The injector and the FID detector were at 250 °C and the oven temperature started at 50 °C for 2 minutes and then increased to 200 °C at a rate of 15 °C/min.

In a typical epoxidation experiment, 1 mmol of metalloporphyrin is added to 10 ml of CH_2Cl_2 with 100 mmol of 1-methyl-cyclohexene, 20 mmol of pyridine and 2 mmol of tetrabutylammonium bromide as phase transfer agent. Then 10 ml of sodium hypochlorite 0.6 M are added and the reaction is maintained at room temperature with controlled stirring.

The 5,15-diarylporphyrin free bases were synthesised by the method described by Young and Chang [14] using the appropriate dipyrrilmethanes and benzaldehydes. The products were purified by chromatography, crystallised from CH_2Cl_2/hexane and characterised by mass spectrometry (FAB+), visible spectroscopy and ^{1}H NMR, giving spectroscopic data in full agreement with those expected. The manganese complexes used as catalysts in the epoxidation reactions were prepared and purified using the procedure of Adler *et al.* [15] from the porphyrin free base and manganese(II) chloride in dimethylformamide.

To the best of our knowledge the free base porphyrins **2**, **3**, **5** and **6**, and the corresponding manganese complexes, although made by the method in Ref. [14], are new compounds whose identification data is as follows:

2,2,8,12,18-tetramethyl-3,7,13,17-tetraethyl-5,15-di(2,6-dichloro)phenylporphyrin

Yield 10%, m.p. > 300 °C, FAB: M^+ isotopic cluster at 768.

Elementary analysis: calculated for $C_{44}H_{42}Cl_4N_4$: C 68.75, H 5.51, N 7.29; found: C 68.9, H 5.6, N 7.4. ^{1}H NMR ($CDCl_3$, TMS): −2.6 (s, 2H), 1.9 (t, 12H), 2.6 (s, 12H), 4.0 (q, 8H), 7.7 (m, 12H), 10.3 (s, 2H). Visible spectra ($CHCl_3$, nm) (rel. % of Soret band): 409 (100), 505 (13), 535 (8), 565 (5), 625 (3). Visible spectra of the manganese complex ($CHCl_3$, nm) (rel. % of Soret band): 475 (100), 570 (18), 605 (5).

3,2,8,12,18-tetramethyl-3,7,13,17-tetraethyl-5,15-di(2,3,4,5,6-pentafluoro)phenylporphyrin

Yield 10%, m.p. >300 °C, FAB: M^+ at 811. Elementary analysis: Calculated for $C_{44}H_{36}F_{10}N_4$: C 65.18, H 4.48, N 6.91; found: C 64.9, H 4.4, N 7.0. ^{1}H NMR ($CDCl_3$, TMS) (δ in ppm, multi., int.): −2.4 (lm, 2H), 1.8 (t, 12H), 2.7 (s, 12H), 4.1 (q, 8H), 10.3 (s, 2H). Visible spectra ($CHCl_3$, nm) (rel. % of Soret band): 402 (100), 505 (11), 540 (8), 575 (5), 625 (4). Visible spectra of the manganese complex ($CHCl_3$, nm) (rel. % of Soret band): 470 (100), 565 (20), 595 (10).

5,2,8,12,18-tetramethyl-3,7,13,17-tetrabenzyl-5,15-di(4-nitro)phenylporphyrin

Yield 15%, m.p. >300 °C, FAB: M^+ at 969. Elementary analysis: calculated for $C_{64}H_{52}N_6O_4$: C 79.32, H 5.41, N 8.37; found: C 79.1, H 5.3, N 8.9. ^{1}H NMR ($CDCl_3$, TMS) (δ in ppm, multi., int.): −3.7 (s, 2H), 3.5 (s, 12H), 5.3 (m, 8H), 7.1 (m, 20H), 7.5 (m, 8H), 10.0 (s, 2H). Visible spectra ($CHCl_3$, nm) (rel. % of Soret band): 400 (100), 500 (16), 530 (11), 560 (6), 620 (4). Visible spectra of the manganese complex ($CHCl_3$, nm) (rel. % of Soret band): 476 (100), 563 (20), 590 (8).

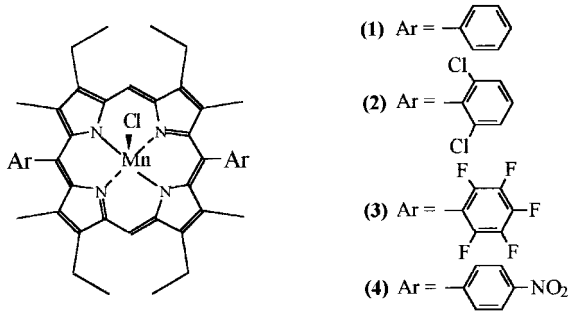
6,2,8,12,18-tetramethyl-3,7,13,17-tetraphenyl-5,15-di(4-nitro)phenylporphyrin

Yield 20%, m.p. >300 °C, FAB: M^+ at 913. Elementary analysis: calculated for $C_{60}H_{44}N_6O_4$: C 78.93, H 4.86, N 9.20; found: C 79.0, H 4.9, N 9.4. ^{1}H NMR ($CDCl_3$, TMS) (δ in ppm, multi., int.): −3.5 (s, 2H), 3.6 (s, 12H), 7.6 (m, 20H), 8.1 (m, 8H), 10.0 (s, 2H). Visible spectra ($CHCl_3$, nm) (rel % of Soret band): 409 (100), 500 (15), 535 (11), 570 (7), 625 (4). Visible spectra of the manganese complex ($CHCl_3$, nm) (rel. % of Soret band): 475 (100), 565 (20), 590 (8).

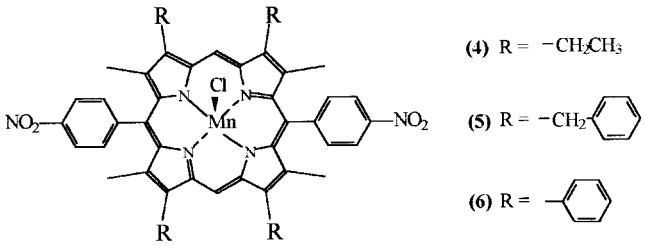
RESULTS AND DISCUSSION

Although the 5,15-diarylporphyrins may, at first, seem not to be very robust catalysts due to the two *meso* unprotected positions, which make them more susceptible to macrocycle oxidative decomposition, our recent study [13] with the manganese complex of etioporphyrin II, proving that this is a very active catalyst during the few minutes it stands oxidative conditions of the medium, led us to exploit the possibility that the 5,15-diaryl-β-substituted-porphyrins could in some way conjugate the high activity of the *meso* free metalloporphyrins, e.g. cytochrome P-450, and the resistance of the *meso*-phenyl-substituted porphyrins, e.g. TPP.

However, the primary reason for the selection of the 5,15-diarylporphyrins as catalysts relies on the fact that they could be prepared through MacDonald-type synthesis



Scheme 1.



Scheme 2.

from a diversity of dipyrromethanes. Thus, we had a choice of a larger structural variability than with the TPP derivatives of the first and second generation usually used as porphyrin-based oxidation catalysts. This allowed us to prepare and study for the first time macrocycles with series of alkyl, benzyl and phenyl substituents on the β-pyrrolic positions. The effect of these substituents on the β-pyrrolic positions was almost unknown since the only β-pyrrolic macrocycles used as oxidation catalysts were the β-halogenated derivatives of the TPP family and our manganese-etioporphyrin and manganese-octaphenylporphyrin [13].

The structural diversity of the β-substituents was important enough to be exploited even if we would not get very stable catalysts. As it happened, in the case of the etioporphyrin and octaphenylporphyrin, some new structure–activity relationships could be detected in less stable catalysts and could help to clarify the effect of the substituents of the porphyrin core on these catalysts.

The study was divided in two parts. The basic structural pattern of the 5,15-diaryl-β-substituted-porphyrinato manganese(III) selected corresponds to porphyrins shown in Schemes 1 and 2. In Scheme 1, the aryl groups bear substituents of different size and electron-donating characteristics, corresponding therefore to the type of structure of catalysts more widely studied; while the porphyrins in Scheme 2 have a diversity of substituents in the β-pyrrolic positions, selected in order to build a series of structures of different size and rigidity around the porphin macrocycle.

To test the catalytic characteristics of these metalloporphyrins our choice was a well-established system for the epoxidation of 1-methyl-cyclohexene, where aqueous sodium hypochlorite is used as oxidant in a two-phase system with a phase transfer agent as reported by De Carvalho and Meunier [16]. The epoxide was the main product. With all the catalysts 3-methyl-2-ene-cyclohexanol and 3-methyl-2-ene-cyclohexanone were also identified as secondary oxidation products using GC/MS.

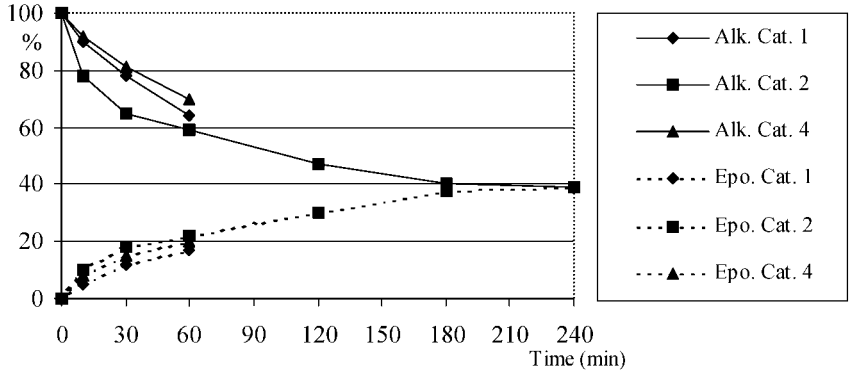


Fig. 1. Substrate and product evolution in the epoxidation of 1-methyl-cyclohexene with catalysts **1, 2** and **4**, until total catalyst degradation. (1 mmol of metalloporphyrin, 100 mmol of 1-methyl-cyclohexene, 20 mmol of pyridine and 2 mmol of tetrabutylammonium bromide, 10 ml of NaOCl 0.6 M.).

Part A: The Effect of the Substituents on the *meso*-phenyls

The series of 5,15-di(aryl)porphyrinato manganese(III) **1**, **2** and **4** showed very different catalytic activity. Catalysts **1** and **4** originated overall low substrate conversions, between 30 and 35%, and very similar conversion curves for substrate depletion and epoxide formation (less than 20%) as shown in Fig. 1. On the other hand, the chlorinated catalyst **2** lead to 60% substrate consumption and generated 40% epoxide production.

These results were expected and confirm the beneficial protection brought about by the presence of the chlorine atoms at the *meso*-phenyl groups, explaining the different behaviour of catalyst **2** and catalysts **1** and **4**. However, it is apparent from Fig. 1 that the better performance of catalyst **2** is not due to a higher reactivity but just to a better resistance to the oxidative reaction conditions, as in the first 60 min the curves for epoxide production and alkene consumption are quite similar. To clarify that point we followed the epoxidation reactions by visible spectroscopy.

The stability of the catalyst was checked during the course of each experiment by visible spectroscopy following the intensity of the Soret band. In all three catalysts, a gradual loss of intensity of that band was observed simultaneously with the progress of the epoxidation. With catalysts **1, 2** and **4**, the epoxide production stops when the Soret band vanishes and the solution becomes colourless. In this case, the Soret band vanishes without the appearance of any new bands in the ultraviolet or visible regions, pointing to a degradation of the porphyrin macrocycle and not to its inactivation by any other process.

Data in Fig. 2 confirms the beneficial protection of the large chlorine atoms at the *meso*-phenyl groups of catalyst **2** and explains its better performance comparatively to catalysts **1** and **4**, as result of a better resistance to the oxidative reaction medium.

The behaviour of catalyst **3**, manganese 2,8,12,18-tetraethyl-3,7,13,17-tetramethyl-5,15-di(2,3,4,5,6-pentafluoro)phenylporphyrinato chloride, proved to be singular. This catalyst is robust, leading the reaction to completion before significant degradation had occurred, as we can see in Fig. 3. Using NaOCl (0.6 M) as oxidant we found it convenient to split the amount of oxidant and add a second solution of NaOCl after 4 h instead of using more concentrated hypochlorite or the full amount at once, to minimise the degradation of the catalyst. With more

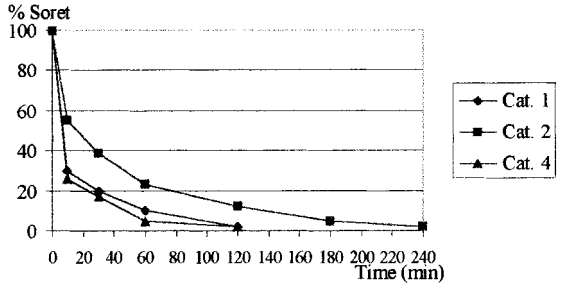


Fig. 2. Time variation of the Soret band of the catalysts **1, 2** and **4**.

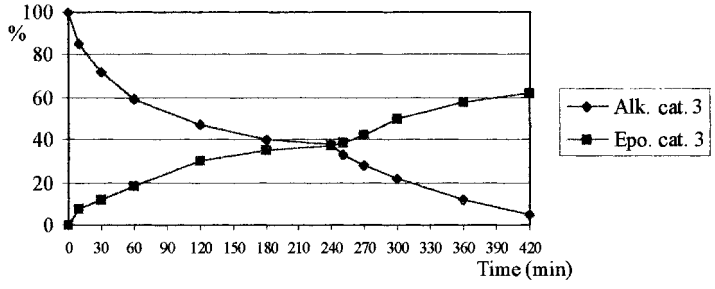


Fig. 3. Substrate and product evolution in the epoxidation of 1-methyl-cyclohexene with catalysts **3**. (1 mmol of metalloporphyrin, 100 mmol of 1-methyl-cyclohexene, 20 mmol of pyridine and 2 mmol of tetrabutylammonium bromide, 20 ml of NaOCl 0.6 M.).

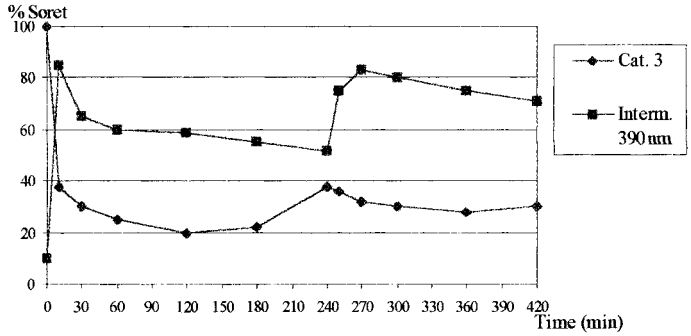


Fig. 4. Time variation of the Soret band of catalyst **3**.

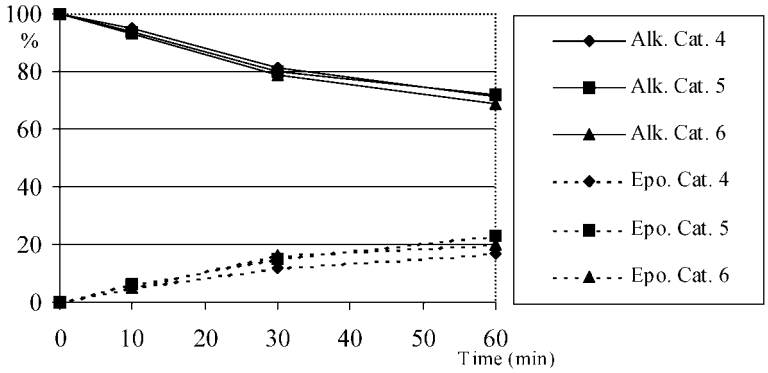


Fig. 5. Substrate and product evolution in the epoxidation of 1-methyl-cyclohexene with catalysts **4, 5** and **6**, until full catalyst degradation. (1 mmol of metalloporphyrin, 100 mmol of 1-methyl-cyclohexene, 20 mmol of pyridine and 2 mmol of tetrabutylammonium bromide, 10 ml of NaOCl 0.6 M.).

concentrated hypochlorite the degradation may reach 15% of the starting porphyrin after 8 h. Even so this result provides evidence that catalyst **3** is far more robust than the other structures studied in this work, performing far better than the chlorinated porphyrin **2**.

Also, the difference with respect to the other catalysts is dramatic as shown by visible spectroscopy (Fig. 4). In this case, the appearance of a new 'Soret-like' band at 390 nm is observed. This band increases rapidly at the expense of the 402 nm Soret. The new band is likely to correspond to an oxidised form of the catalyst, which in this case has a concentration and lifetime long enough to be detected as the epoxidation progresses.

As referred, the initial amount of hypochlorite is clearly not enough to promote the oxidation of the manganese porphyrin and the original Soret band recovers while the Soret at 390 nm vanishes and the epoxidation slows down after 180 min. If an extra amount of NaOCl is added after 240 min the 390 nm intermediate is restored, giving evidence of almost no degradation of catalyst **3**.

These results emphasise the importance of the presence of electronegative substituents in the *meso*-phenyls producing very robust and active catalysts from macrocycles which would, otherwise, be very unstable.

Part B. The Effect of the β-Pyrrolic Substituents

The task was followed using the study of manganese porphyrins having different substituents in the β-pyrrolic positions, as shown in Scheme 2. These compounds have different degrees of mobility, stereo constraint and electronic conjugation to the porphyrin macrocycle.

As shown in Fig. 5, the pair of 5,15-di(4-nitrophenyl)porphyrinato manganese(III) **5** and **6** showed catalytic activity, small resistance to the reaction conditions and overall low substrate conversions, very similar and typical of the unprotected porphyrin-based catalysts reported, like catalyst **4**.

The spectroscopic behaviour corresponds in all cases to catalysts with poor resistance to the oxidative conditions of the epoxidation, as shown in Fig. 6. The epoxide production stops when the Soret band vanishes and the solution becomes colourless. In these reactions the disappearance of the Soret band is not associated with the appearance of any new bands, corresponding to the degradation of the porphyrin macrocycle and not inactivation by any other process.

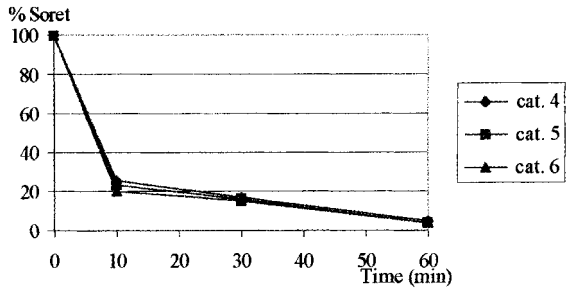


Fig. 6. Time variation of the Soret band of catalysts **4, 5** and **6**.

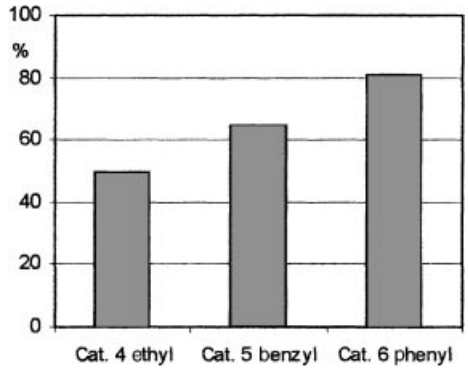


Fig. 7. Selectivity of epoxide formation over the other oxygenated products for catalysts **4, 5** and **6**.

Although they are similar in terms of stability and activity, catalysts **4, 5** and **6** show significant differences in their selectivity for epoxide production as shown in Fig. 7. Catalyst **4**, having ethyl substituents, shows a very low selectivity for epoxide (50%), pointing to a radical mechanism of oxygen transfer typical of the *meso* free etioporphyrin. However, when the ethyl substituent in the structure of the catalyst was replaced by benzyl and phenyl, the selectivity for epoxide formation increases up to 65% and 80% as in catalysts **5** and **6**. This value, typical of the most selective metalloporphyrin catalysts with the four substituted *meso*-positions, points to a concerted mechanism involving (porphyrin)Mn=O species in the epoxidation reaction with catalysts **5** and **6**.

The selectivity in the epoxide production is related to the mechanism of oxygenation of the substrate and depends on the nature of the oxidant [17]. In this study the observed selectivity, with the same oxidising agent, shows that small changes in the nature of the side chains of the β-pyrrolic positions of the macrocycle have an important influence on the selectivity of the catalyst. The nature of the catalytic oxygen transfer is modulated by them.

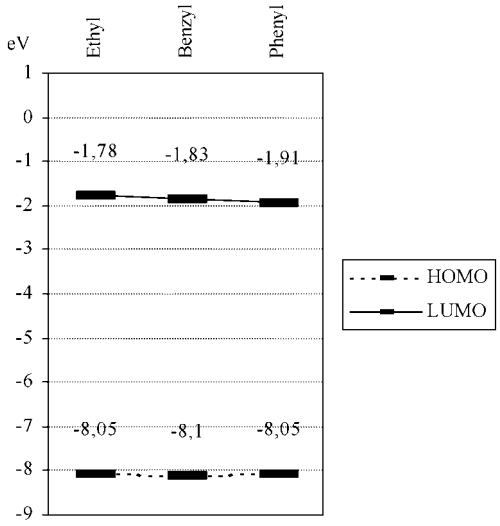


Fig. 8. HOMO and LUMO values (eV) for the porphyrins **4, 5** and **6**. Values from Hyperchem v.3 using the semi-empirical AM1 with a Polak–Ribiere algorithm. Final gradient of 0.01 Kcal $Å^{-1}$ mol^{-1}.

As the values for the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), determined by some semi-empirical calculations, are very similar (Fig. 8), the basis of the observed increase in the selectivity is likely to be due to stereochemical control of the approach of the substrate to the macrocycle due to the large pyrrolic substituents like phenyl and benzyl.

CONCLUSION

In general, manganese porphyrins having only two *meso*-substituents have, as expected, poor stability to catalytic oxidation conditions. A notable exception is the fluorinated manganese porphyrin **3**. The observed stability and consequent catalyst activity of this manganese porphyrin **3** may be compared to that of catalysts having all four *meso*-positions substituted. This observation points to the significance of electronic factors on the *meso*-positions ruling the overall performance of the metalloporphyrin catalysts. The influence is important enough to make the difference for porphyrin **3**.

Another important observation of this study is the role of the non-halogen substituents at the β-pyrrolic positions of the macrocycle. While having no significant protecting capacity they dramatically influence the selectivity of the catalysts.

Taking into account the overall results described, we may conclude that studies to improve the catalytic efficiency of metalloporphyrins must concentrate not only on the structural variation of the *meso*-phenyl groups of porphyrins, as is usually done, but also on the nature of the side chains on the β-positions of the macrocycle periphery, in order to obtain epoxidation catalysts with higher resistance and higher selectivity.

Pyrrole and porphyrin synthetic studies are under way in the same catalyst to conjugate the favourable characteristics of the fluoro group and the β-substituents.

Acknowledgement

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