Electronic Effects on the Stereoselectivity of Epoxidation Reactions Catalysed by Manganese Porphyrins

Enrico Baciocchi,*[a] Tristano Boschi,[†][c] Luigi Cassioli,[a] Carlo Galli,[a] Laurent Jaquinod,[b] Andrea Lapi,*[a] Roberto Paolesse,[c] Kevin M. Smith,[b] and Pietro Tagliatesta*[c]

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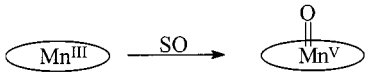
A series of Mn^{III} porphyrins progressively halogenated in the β-pyrrolic positions was employed to catalyse the epoxidation of *cis*-stilbene by iodosylbenzene, and to study the role of the electronic effects on the stereoselectivity of this process. A gradual improvement in the stereoselectivity on increasing the number of β-halogen atoms was observed. The role of steric effects upon the epoxidation was also investigated by placing *ortho*-substituents in the *meso*-phenyl rings, and it was found that steric effects are more important than electronic effects toward the stereoselectivity of this process. These results can be rationalised by proposing a competition between a nonstereoselective electrophilic pathway of addition and a stereospecific pathway of oxygen insertion, the former being disfavoured by electron-withdrawing substituents. Alternatively, the formation of an open intermediate between the Mn^{V} oxene and the substrate could be suggested, where the stereoselectivity ought to be determined by the competition between closure of the epoxide ring and rotation around the C–C bond. In this case, the enhanced stereoselectivity given by our polyhalogenated porphyrins might be attributed to an acceleration of the epoxide ring closure caused by the electron-withdrawing effect of the halogen substituents.

Introduction

Manganese(III) porphyrins have been shown to be efficient catalysts in epoxidation reactions of alkenes[1] in association with a wide variety of oxygen donor species, such as iodosylarenes,[2] hydrogen peroxide,[3] alkylhydroperoxides,[4] peracids,[5] monopersulfates[6] or hypochlorites.[7] The manganese(III) porphyrin is transformed into an oxo-manganese(V) porphyrin [$PMn^{V}=O$], which is believed to be the actual oxidizing species (Equation 1, where SO is the oxygen atom donor).[1]



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A unified mechanism (Scheme 1) for the oxygen transfer from the oxo-metalloporphyrin to the alkenes was proposed by Bruice.[8] It involves the rate-determining formation of a charge transfer complex, which can be converted into the epoxide by a variety of pathways: a one-electron oxidation followed by reaction of the radical cation of the alkene with the reduced form of the manganese-oxo complex (path a), an electrophilic addition leading to a carbocation which then undergoes ring closure (path b), or a concerted oxene insertion (path c). The choice between these three pathways depends upon the structure of the reactants and also upon the oxidation potential of the alkene and of the porphyrin catalyst, the latter being susceptible to modulation by an appropriate choice of substituents connected to the tetrapyrrolic ring or to the *meso* aryl groups.

We have recently been involved in the synthesis of new metalloporphyrins, bearing either *ortho*-dimethoxy substituents in the *meso*-phenyl groups,[9] or halogen atoms in the four β-pyrrolic positions.[10] The idea behind the synthesis of these substituted porphyrins was to build more robust catalysts for the epoxidation of alkenes and the hydroxylation of alkanes. Additionally, we wanted to investigate how the catalytic activity of porphyrins toward the said reactions was influenced by the electronic effect of the halogen substituents in the β-pyrrolic positions.

Herein we report on the influence of electronic effects on the stereoselectivity of the epoxidation reaction catalysed by an extended series of manganese(III) porphyrins, which are substituted in the β-pyrrolic positions by halogen atoms increasing in number from 2 to 8. Since the steric hindrance is kept constant within these series, it should be possible to distinguish electronic from steric effects toward the stereoselectivity of the epoxidation process. This information can be very useful for a better understanding of the mechanism of the epoxidations induced by manganese porphyrins, and particularly of the relative importance of the reaction paths shown in Scheme 1.

Results and Discussion

The β-halo-substituted Mn^{III} porphyrins employed in this investigation are depicted in Chart 1. Three series were developed: the more extended series has unsubstituted *meso*

[a] Dipartimento di Chimica, Università "La Sapienza", Piazzale A. Moro 5, I-00185 Roma, Italy
Fax: (internat.) + 39-06/490421
E-mail: baciocchi@axcasp.caspur.it
[b] Department of Chemistry, University of California, Davis, CA 95616, USA
[c] Dipartimento di Scienze e Tecnologie Chimiche, Università di Tor Vergata, Via della Ricerca Scientifica, I-00133 Roma, Italy
[†] Deceased

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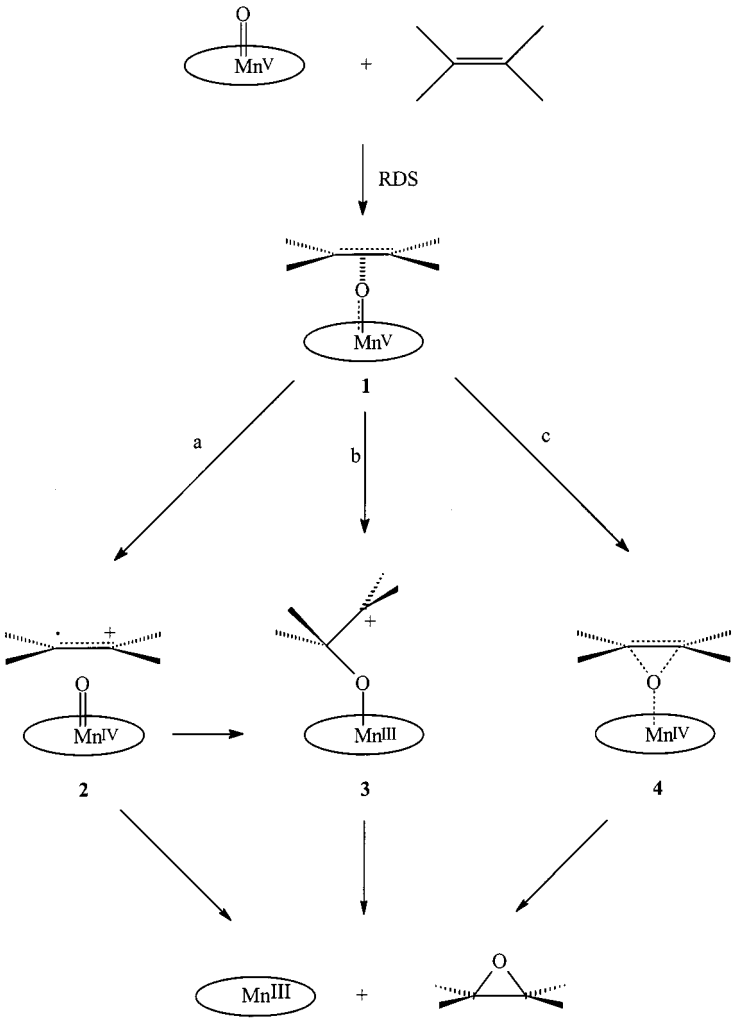
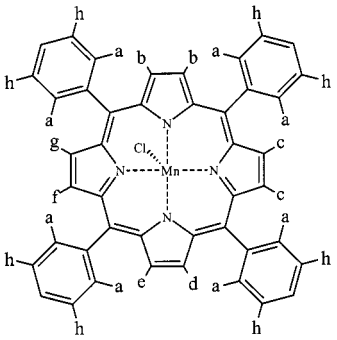


Scheme 1. Unified mechanism for the oxygen transfer from oxo-metalloporphyrins to alkenes[8]

phenyl groups (MnTPPCl) and bears an increasing number, from 2 to 8, of bromo substituents in the β-pyrrolic positions; the second series comprises three members, featuring *ortho*-dimethoxy substitution at the *meso* phenyls (TDMPP) and 0, 4 or 8 chloro atoms in the β-pyrrolic positions. The last series features *ortho*-dichloro substitution at the *meso* phenyls (TDCPP) and 0 or 4 bromo atoms in the β-pyrrolic positions. Even the last shorter series was worth investigating as in a previous paper we reported that the electronic effect of the halogen substituents reaches its maximum effect upon the catalytic activity of the porphyrin with 4 β-halogens.[10] It is also important to stress that all the porphyrins reported in Chart 1 are pure compounds, featuring only those particular halogen atoms in the indicated positions, and are not mixtures of various regioisomers. Besides that, another relevant feature is that the steric hindrance at the *meso* phenyl positions is kept constant within the same series of porphyrins so that, as already mentioned, a clear dissection of electronic effects from steric effects is possible. This is particularly relevant if a decision about the intervening mechanism of epoxidation has to be made with respect to the possible competition of the paths delineated in Scheme 1, where the steric hindrance of the porphyrin ring, as it approaches the substrate, would matter more or less strongly (vide infra).

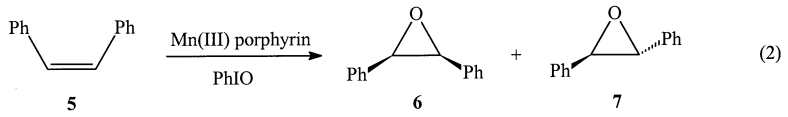
The epoxidation reactions were carried with *cis*-stilbene as the substrate, in aerobic conditions at 25°C in dichloromethane, with iodosylbenzene (PhIO) as the oxygen atom donor (Equation 2). No supplemetary axial ligands were added in view of the fact that they can influence the stereoselectivity of the epoxidations induced by manganese porphyrins, thereby masking the substituent effects. In all cases *cis*-stilbene oxide and *trans*-stilbene oxide were the only products formed. No carbonyl compounds were detected. Product yields and *cis*/*trans* epoxide ratios are reported in Table 1.

Inspection of Table 1 shows a regular increase in the stereoselectivity for an increase in the number of halogen atoms in the macrocycle β-positions. Within the family of the simple tetraphenylporphyrins (entries 1−7) the *cis*/*trans* epoxide ratio ranges from 0.6 for the nonhalogenated porphyrin (entry 1) to 8.0 when all the eight β-positions are substituted with bromine atoms (entry 7). For the *meso* 2,6-dimethoxyphenyl porphyrins (TDMPP) the *cis*/*trans* ratio



Porphyrin	a	b	c	d	e	f	g	h
MnTPPCl	H	H	H	H	H	H	H	H
$MnTPPBr_2Cl$	H	Br	H	H	H	H	H	H
$MnTPPBr_3Cl$	H	Br	H	Br	H	H	H	H
$MnTPPBr_4Cl$	H	Br	H	Br	Br	H	H	H
$MnTPPBr_6Cl$	H	Br	Br	Br	Br	H	H	H
$MnTPPBr_7Cl$	H	Br	Br	Br	Br	Br	H	H
$MnTPPBr_8Cl$	H	Br	Br	Br	Br	Br	Br	H
MnTDMPPCl	OCH_3	H	H	H	H	H	H	H
$MnTDMCl_8PPCl_4Cl$	OCH_3	Cl	H	Cl	Cl	H	H	Cl
$MnTDMCl_8PPCl_8Cl$	OCH_3	Cl	Cl	Cl	Cl	Cl	Cl	Cl
MnTDCPPCl	Cl	H	H	H	H	H	H	H
$MnTDCPPBr_4Cl$	Cl	Br	H	Br	Br	H	H	H

Chart 1. Mn^{III} porphyrins employed in this work



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approaches 20, when eight chloro atoms substitute the β-positions of the catalyst (entry 10), while it soars to the remarkable value of 61 for the *meso* 2,6-dichlorophenyl porphyrin (TDCPP) substituted by four β-bromo atoms (entries 11−12). The increase in stereoselectivity appears remarkably regular, as a good linear correlation is observed between the logarithm of the *cis*/*trans* epoxide ratio and the sum of Hammet's σ_p of the substituents in β-positions (Figure 1), for both the MnTPPCl ($r^2 = 0.95$, $\rho = 0.58$) and the MnTDMPPCl ($r^2 = 0.99$, $\rho = 0.30$) series. Thus, in view of the constant steric effects, it appears firmly established that the presence of electron-withdrawing substituents significantly enhances the stereoselectivity of the epoxidation.

The epoxidation of olefins catalysed by manganese porphyrins is generally endowed with a low stereoselectivity, unless there are substituents in the *ortho*-position of the *meso*-phenyl rings,[2b,7c] or neutral axial ligands, such as pyridine or imidazole,[7b,7c,11] are added to the solution. A number of interpretations have been offered to account for such a complex situation. Thus, the generally low stereoselectivity of the epoxidation catalysed by Mn^{III} porphyrins may be attributed to the formation of an open intermediate such as **3**, where rotation along the C−C bond is possible before closure of the epoxide ring.[12] On this basis, the effect of *ortho*-substituents would be that of hindering such a rotation.[2b,7c] Alternatively *ortho* substituents may favour the concerted (stereoselective) oxygen insertion by preventing the interaction of the alkene with the π-electron system of the porphyrin. This interaction would stabilise the development of the positive charge on the alkene and promote a nonstereoselective electrophilic mechanism involving the

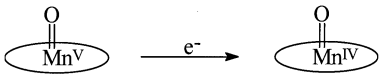
Table 1. Product yields in the epoxidation of *cis*-stilbene with PhIO catalysed by three series of increasingly halogenated Mn^{III} porphyrins

Entry[a]	Porphyrin	*cis*-epoxide yield (%)[b]	*trans*-epoxide yield (%)[b]	*cis*/*trans*[c]
1	MnTPP	22	39	0.6
2	$MnTPPBr_2$	33	40	0.8
3	$MnTPPBr_3$	48	25	1.9
4	$MnTPPBr_4$	49	20	2.5
5	$MnTPPBr_6$	57	16	3.7
6	$MnTPPBr_7$	57	14	4.1
7	$MnTPPBr_8$	12	1.6	8.0
8	MnTDMPP	9.0	1.9	4.7
9	$MnTDMCl_8PPCl_4$	50	5.7	8.8
10	$MnTDMCl_8PPCl_8$	52	3.1	17
11	MnTDCPP	76	3.3	23
12	$MnTDCPPBr_4$	78	1.3	61

[a] Reactions were carried out in dichloromethane at 25°C with a molar ratio Substrate/Oxidant/Porphyrin = 50:5:1. – [b] Yields are referred to the oxidant; errors, based on duplicated experiments, are ± 5%. – [c] *cis*/*trans* epoxide molar ratio.

formation of a carbocationic intermediate.[8a] However, according to more recent suggestions, the low stereoselectivity might also arise from a contamination of the Mn^V-oxo complex by a nonstereoselective oxo-manganese(IV) species (i.e. $PMn^{IV}=O$)[8][13] and any beneficial effect from axial ligands would be that of preventing the conversion of $PMn^V=O$ to $PMn^{IV}=O$.[13b]

Against this background we can now try to rationalise the observed regular enhancement of the stereoselectivity on increasing the number of electron-withdrawing (EWG) substituents at the pyrrolyl β-positions. Certainly, it seems very difficult to attribute some share of this role to the presence of a nonstereoselective $PMn^{IV}=O$ contaminant, unless we suggest that the amount of $PMn^{IV}=O$ regularly decreases on increasing the number of β-halogens atoms. This appears unlikely as $PMn^{IV}=O$ should be formed by a one-electron reduction of the $PMn^V=O$ species (Equation 3),[13] and therefore its formation should be made easier the greater the number of EWG halogens, as they accordingly raise the reduction potential of the porphyrin.[14] Therefore, the amount of the nonstereoselective $PMn^{IV}=O$ complex should increase along the series, and the stereoselectivity decrease, which is contrary to what is actually observed.



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Another strong indication against a significant role for $PMn^{IV}=O$ is the absence of any detectable amount of carbonyl compounds in the reaction mixture, which would be expected from the reaction of this species under aerobic conditions.[8b,10b] It should be noted here that, in the presence of an olefin substrate, the Mn^V oxene reacts directly to give the epoxide, rather than undergoing a preliminary reduction to the Mn^{IV}-oxo porphyrin.[15] A more reasonable explanation would be that the stereochemistry of the process is determined by a competition between the rate of a stereoselective (concerted) oxygen insertion and a nonstereoselective electrophilic attack of the oxygen to the alkene, to give a carbocationic intermediate (Scheme 1). As already mentioned, the competition between these two pathways may depend upon the strength of the interaction of the alkene with the π-electron system of the porphyrin, which favours the non stereoselective path b.[8a] The presence of EWG substituents may reduce the electron density of the π-system of porphyrins, and make the carbocation pathway less favoured than the concerted insertion. Thus, increasing the number of electron-withdrawing substituents on the pyrrole rings ought to increasingly disfavour the formation of the carbocation, and the concerted stereoselective pathway should progressively predominate.[16] Consistent with this view is the reduced sensitivity of the *ortho*-dimethoxy-substituted MnTDMPPCl porphyrin to the electronic effects of the β-halogen substituents, relative to the simple MnTPPCl, which is evident from the above-reported ρ values. The bulky *ortho*-methoxy groups may hinder the interaction between the alkene and the π-electron system of the porphyrin, thus lowering the effect of the β-substituents.

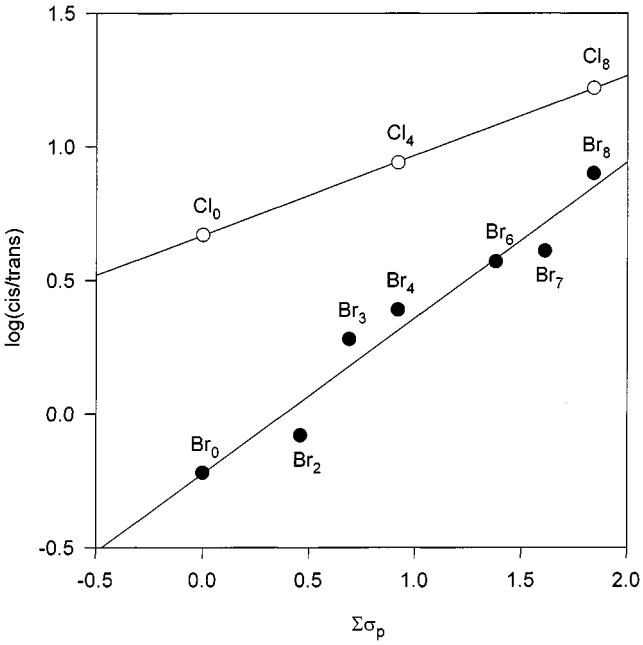

Figure 1. Correlation diagram of the logarithm of the *cis*/*trans* epoxides ratio vs. the sum of Hammett's σ_p for the epoxidation of *cis*-stilbene catalysed by a series of progressively β-halogenated MnTPPCl (filled circles) and MnTDMPPCl (open circles)

Alternatively, one might assume that the epoxidation proceeds mainly by the electrophilic attack of the oxygen to the alkene to give the carbocation intermediate (Scheme 1, path b), and that the *cis*/*trans* stereoselectivity is determined by the competition of two processes: the rotation around the alkene C–C bond and the epoxide ring closure.[17] The observed regular increase in stereoselectivity upon increasing the number of β electron-withdrawing substituents might be explained by assuming that this electronic effect gradually speeds up the ring-closure, while the rate of the C–C bond rotation should reasonably remain unaffected throughout the same series of porphyrins. Accordingly, the *cis*/*trans*

epoxide ratio should become larger, as it is, in fact, observed.

Finally the data in Table 1 also clearly confirm that the effect upon the epoxidation stereoselectivity of substituents at the *ortho*-positions of the *meso*-phenyl rings is mainly of steric origin. Accordingly, both MnTDMPPCl (*ortho*-methoxy phenyl substituents) and MnTDCPPCl (*ortho*-chloro phenyl substituents) exhibit a higher stereoselectivity than MnTPPCl (no *ortho*-substituents in the phenyl rings), in spite of the fact that methoxy and chloro exert opposite electronic effects.[18] However, the stereoselectivity of MnTDCPPCl is greater than that of MnTDMPPCl, which is probably due to the superposition of steric and electronic effects, since chlorine is an electron-withdrawing group.

Experimental Section

General: Dry CH_2Cl_2 was obtained by refluxing and distilling over P_2O_5. 1,2-Dichloroethane and 1,2-dibromoethane were dried over anhydrous K_2CO_3. Methanol (HPLC grade) was purchased from Carlo Erba. *cis*-Stilbene was purchased from Aldrich and used as received. *cis*-Stilbene oxide and *trans*-stilbene oxide were purchased from Fluka. Iodosylbenzene was prepared by basic hydrolysis of iodosylbenzene diacetate as previously reported,[19] stored at −20°C and titrated every 3 months. NMR spectra were performed on a Bruker AM 400. HPLC analysis were performed on a HP-1050 equipped with a LC-18-DB column and connected to a HP-1047 UV/Vis detector. UV/Vis spectra were performed on a HP-8453 diode array spectrophotometer. FAB mass spectra were performed with a multiple quadrupole instrument (VG Quattro); samples were bombarded with a 8−10 kV caesium beam from a caesium gun anode.

Syntheses of the Porphyrins: The *meso*-tetraphenylporphyrin β-brominated bases, $H_2(TPPBr_x)$, (x = 3, 4, 7, 8) were synthesised according to literature procedures.[20] $H_2(TDMPP)$, $H_2(TDMCl_8PPCl_8)$ and $H_2(TDCPP)$ were synthesised as reported in the literature.[21−23] $H_2(TPPBr_2)$ was prepared by bromination of $H_2(2\text{-}NO_2TPP)$ followed by denitration and rearomatisation of the chlorin. $H_2(TPPBr_6)$ was prepared by perbromination of $Cu^{II}(2\text{-}NO_2TPP)$ followed by denitration. Both $H_2(TPPBr_2)$ and $H_2(TPPBr_6)$ have been characterised by X-ray crystallography. Details of the synthesis of $(TPPBr_2)H_2$ and $(TPPBr_6)H_2$ are given elsewhere.[24]

H_2(TDMPPCl$_{12}$): $H_2(TDMPP)$ (200 mg, 0.23 mmol) was dissolved in dry 1,2-dichloroethane (100 mL) and *N*-chlorosuccinimide (436 mg, 3.22 mmol) was added to the solution, which was then refluxed for 4 h in air, while being protected from moisture with a $CaCl_2$ valve. The reaction was continuously monitored on silica gel TLC plates, eluting with $CHCl_3$, and checked by FAB-MS. The solvent was evaporated under vacuum and the residue was purified twice on a silica gel column by elution with $CHCl_3$. The fraction containing the desired porphyrins was evaporated and the residue was recrystallised from $CHCl_3$/hexane (1:3), giving 124 mg of product (42% yield). UV/Vis ($CHCl_3$): λ_{max} = 428, 523, 596, 651. − ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.8 (s, 4 H, β-H pyrrole), 7.83 (s, 4 H, *p*-phenyl), 3.2 (s, 24 H, OCH_3). − FAB-MS: *m*/*z* = 1266 $[M - 2H]^+$. − $C_{52}H_{34}Cl_{12}N_4O_8$ (1268): C 49.25, H 2.70, N 4.42; found: C 49.29, H 2.60, N 4.47.

H_2(TDCPPBr$_4$): $H_2(TDCPP)$ (200 mg, 0.22 mmol) was dissolved in dry 1,2-dibromoethane (100 mL) and *N*-bromosuccinimide (480 mg, 2.64 mmol) was added to the solution, which was then maintained at 90°C for 24 h in air, while being protected from moisture with a $CaCl_2$ valve. The reaction was continuously monitored using silica gel TLC plates, eluting with $CHCl_3$, and checked by FAB-MS. The solvent was evaporated under vacuum and the residue was purified twice on a silica gel column by elution with $CHCl_3$.The fraction containing the desired porphyrins was evaporated and the residue recrystallised from $CHCl_3$/hexane (1:3), giving 107 mg of product (39% yield). UV/Vis ($CHCl_3$): λ_{max} = 428, 523, 600, 656. − ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.7 (s, 4 H β-H pyrrole), (m, 8 H, phenyl), 7.65−7.83 (m, 12 H, phenyl). − FAB-MS: *m*/*z* = 1206 $[M]^+$. − $C_{44}H_{18}Br_4Cl_8N_4$ (1206): C 43.83, H 1.50, N 4.65; found C 43.79, H 1.44, N 4.97.

Manganese(III) Derivatives: The manganese derivatives of $H_2(TPPBr_x)$, (x = 1−8), $H_2(TDMPP)$, $H_2(TDCPP)$, $H_2(TDMCl_8PPCl_4)$ and $H_2(TDCPPBr_4)$ were synthesised following a method described in the literature.[25] In a typical synthesis the free porphyrin base (100 mg) was dissolved in degassed DMF (50 mL) and $MnCl_2{\cdot}4H_2O$ (100 mg) was added under nitrogen. The solution was refluxed for 4 h under nitrogen and the solvent evaporated under vacuum. The residue was taken up in $CHCl_3$, washed with water, and then dried over NaCl. The solvent was evaporated and the residue purified by column chromatography on silica gel eluting with $CHCl_3$ to isolate the starting free base and then with $CHCl_3/CH_3OH$ (97:3). The fraction containing the metal complex was evaporated and the residue crystallised from a $CHCl_3$/hexane (1:3) solvent mixture. Yields were between 60 and 70%. The UV and FAB-mass spectra and the elemental analysis of the new compounds are reported in Table 2, Table 3 and Table 4, respectively.

Table 2. UV characterisation of the new compounds (in $CHCl_3$)

Compound	λ (nm)		
$[MnTPPBr_2]^+Cl^-$	377	482	624
$[MnTPPBr_3]^+Cl^-$	378	487	593
$[MnTPPBr_4]^+Cl^-$	380	477	580
$[MnTPPBr_6]^+Cl^-$	389	501	652
$[MnTPPBr_7]^+Cl^-$	384	499	654
$[MnTPPBr_8]^+Cl^-$	420	501	660
$[MnTDMCl_8PPCl_4]^+Cl^-$	426	498	646
$[MnTDCPPBr_4]^+Cl^-$	380	475	576

Table 3. The FAB-Mass spectra of the new compounds

Compound	calculated	found
$[MnTPPBr_2]^+$	825.4	827
$[MnTPPBr_3]^+$	904.3	904
$[MnTPPBr_4]^+$	983.2	985
$[MnTPPBr_6]^+$	1141.0	1142
$[MnTPPBr_7]^+$	1219.9	1220
$[MnTPPBr_8]^+$	1298.8	1297
$[MnTDMCl_8PPCl_4]^+$	1321.2	1322
$[MnTDCPPBr_4]^+$	1258.8	1260

The manganese derivative of $H_2(TDMCl_8PPCl_8)$ was obtained using a method reported by us,[22] and modified as follows: the porphyrin base (100 mg) was dissolved in degassed propionic acid (50 mL) and then $MnCl_2{\cdot}4H_2O$ (100 mg) was added under nitrogen. The solution was refluxed for 4 h and then the solvent was evaporated under vacuum. The residue was taken up in $CHCl_3$, washed with 10% $NaHCO_3$ solution, water and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel with $CHCl_3$ to elute the starting

Table 4. Elemental analysis of the new compounds (calcd./found)

Compound	C	H	N
$[MnTPPBr_2]^+Cl^-$	61.39/61.08	3.04/3.20	6.51/6.67
$[MnTPPBr_3]^+Cl^-$	56.23/55.99	2.68/2.55	5.96/6.08
$[MnTPPBr_4]^+Cl^-$	51.88/51.66	2.37/2.30	5.50/5.40
$[MnTPPBr_6]^+Cl^-$	44.92/45.10	1.88/1.92	4.76/4.55
$[MnTPPBr_7]^+Cl^-$	42.10/42.22	1.69/1.77	4.46/4.59
$[MnTPPBr_8]^+Cl^-$	39.61/39.94	1.51/1.60	4.20/4.12
$[MnTDMCl_8PPCl_4]^+Cl^-$	46.04/45.87	2.38/2.44	4.13/4.15
$[MnTDCPPBr_4]^+Cl^-$	40.83/42.12	1.25/1.33	4.33/4.29

free base and then with $CHCl_3/CH_3OH$ (97:3). The fraction containing the metal complex was evaporated and the residue was recrystallised from a $CHCl_3$/hexane (1:3) solvent mixture (yield 75%).

Oxidation of *cis*-Stilbene with PhIO: The reactions were carried out in a thermostated bath at 25°C. PhIO (4.4 mg, 20 mmol) was added to a stirred solution of the metalloporphyrin (4 mmol) and *cis*-stilbene (37.2 mL, 200 mmol) in dry CH_2Cl_2 (1 mL) in a 5 mL Schlenk tube. The mixture was stirred for 5 min at room temperature; the internal standard (0.250 mL, 0.1 M acetophenone in methanol) was then added, followed by the addition of sodium metabisulfite (2 mL, 5×10^{-2} M) in order to quench the residual oxidant. The solvent was removed under an argon stream, the residue diluted in 12 mL of methanol/water (70:30), and then analysed by HPLC on an LC-18-DB column with methanol/water (70:30) as eluent. Yields were determined using a calibration curve of response factors vs. peak area. Product characterisation was performed by comparison with authentic specimens using HPLC and ^1H NMR spectroscopic analysis.

Acknowledgments

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