Control of Epoxidation Enantioselectivity by Axial Ligation in Manganese Chiroporphyrins with Diastereotopic Faces

Shu-Qing Liu,[a] Jacques Pécaut,[a] and Jean-Claude Marchon*[a]

Keywords: Porphyrins / Enantioselectivity / Ligand effects / Manganese

A manganese(III) chiroporphyrin with alternate pentafluorophenyl and chiral cyclopropyl meso-substituents in the αFαF conformation has been shown by X-ray crystallography to have its chloro axial ligand predominantly on the non-chiral β face. Epoxidation of 1,2-dihydronaphthalene by iodosylbenzene induced by the neat catalyst in dichloromethane solution shows a twofold increase in enantioselectivity relative to the same reaction in the presence of pyridine. These observations suggest that the location of the chloro ligand on the β face can block that face from participating in catalytic epoxidation, and direct the reaction to take place on the chiral α face.

Introduction

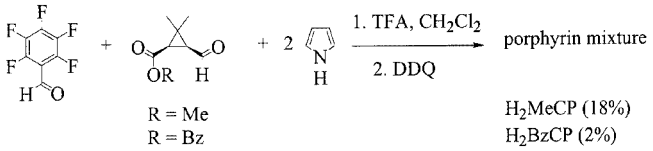
Chiroporphyrins derived from (1*R*)-*cis*-hemicaronaldehydic acid (**1**) display an αβαβ conformation of the chiral *meso*-substituents which make their two faces equivalent.[1] Their manganese(III) complexes such as chloromanganese(III) tetramethylchiroporphyrin [MnCl(TMCP)] (**2**) are mild asymmetric catalysts in olefin epoxidation by iodosylbenzene, with *ee*'s in the range 60−86% for the epoxidation of 1,2-dihydronaphthalene.[2,3] With the aim of improving the reactivity of these catalysts, we have introduced electron-withdrawing pentafluorophenyl substituents in the two opposite *meso* positions.[4] We report here that the resulting chiroporphyrin free bases have a predominant conformation (labelled αFαF) in which two opposite chiral cyclopropyl substituents are located on the same face of the macrocycle (labelled α), leaving the other face (labelled β) devoid of stereogenic groups. The enantioselectivities of 1,2-dihydronaphthalene epoxidation induced by several catalysts of this type have been measured with or without added pyridine, and the results provide new insights into the stereochemistry of the active oxidant.

Results and Discussion

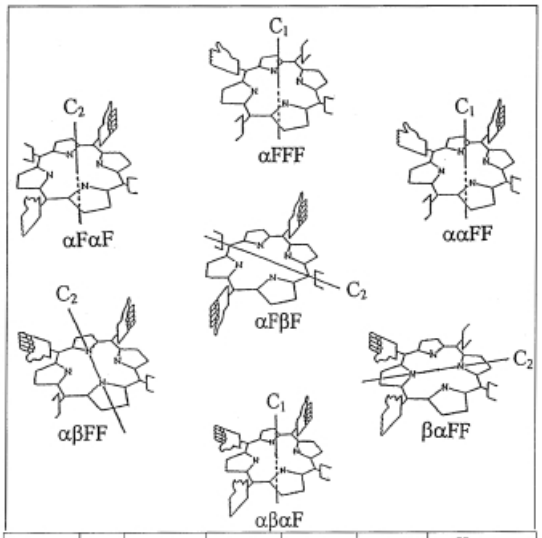
Methyl and benzyl esters were obtained by deprotonation of **1** with sodium hydride followed by nucleophilic attack on methyl iodide or benzyl iodide, respectively.[5] Mixed condensation of either aldehyde ester with pentafluorobenzaldehyde and pyrrole, catalysed by trifluoroacetic acid under standard reaction conditions,[6] afforded a mixture of porphyrins (Scheme 1) from which pure products could be isolated after several consecutive separations on TLC plates. Ten types of chiroporphyrin-free bases with mixed *meso*-substitution are expected in this case, of which seven were obtained in amounts sufficient for characterization by electrospray mass spectrometry and NMR spectroscopy. The stereochemistries of the seven compounds, depicted schematically in Scheme 2, were assigned on the basis of the observed ^{1}H and ^{13}C NMR spectral multiplicities. Among the chiroporphyrins with two pentafluorophenyl groups, those with identical orientations of the chiral substituents (αFαF and ααFF) were predominant for both ester derivatives (respective yields for H_2MeCP: 4% and 4%; respective yields for H_2BzCP: 0.2% and 0.2%). Compounds of the type αβFF and βαFF were obtained in minute amounts among the benzyl ester derivatives, but they could not be separated. The αFβF stereoisomer was obtained in 0.2% yield in the H_2BzCP mixture, but it was not detected in the H_2MeCP mixture. The αβαF chiroporphyrin was obtained in 3% yield among the methyl ester derivatives, but it was not detected among the benzyl ester derivatives. The chloromanganese(III) complexes shown in Figure 1 were obtained by standard metal insertion methods, and pure samples obtained by TLC were characterized by electrospray mass spectrometry and UV/Visible spectroscopy.

The X-ray structure of the catalyst [MnCl(αFαF)MeCP] (**3**) was solved, and a stick representation is shown in Figure 2. The porphyrin macrocycle of **3** is less ruffled than that of [MnCl(TMCP)] (**2**),[2] with average out-of-plane displacements of the C_{meso} atoms with respect to the 24-atom mean-planes of 0.43(1) Å for **3** and 0.73(1) Å for **2**, consistent with the absence of steric crowding on the β face of the former. The average $Mn-N_P$ bond length is therefore

[a] Laboratoire de Chimie Inorganique et Biologique (UMR 5046 CEA-CNRS-UJF),
Département de Recherche Fondamentale sur la Matière Condensée, CEA-Grenoble, 38054 Grenoble cedex 9, France
Fax: (internat.) + 33-4/38785497
E-mail: jcmarchon@cea.fr



Scheme 1. Cross-condensation synthesis of the chiroporphyrin mixtures



		H_β pyrr.	^{13}C pyrr.	$^{13}C_\beta$ pyrr.	$^{13}C_{meso}$	H meso substituents
αFFF	C_1	8d	8s	8s	4s	1 type
αFαF	C_2	4d	4s	4s	2s	1 type
ααFF	C_1	8d	8s	8s	4s	2 types
αFβF	C_2	4d	4s	4s	3s	1 type
αβFF	C_2	2s and 2d	4s	4s	2s	1 type
βαFF	C_2	2s and 2d	4s	4s	2s	1 type
αβαF	C_1	8d	8s	8s	4s	3 types

s = singlet; d = doublet

Scheme 2. Symmetry elements and NMR multiplicities of chiroporphyrins with mixed substitution by pentafluorophenyl and chiral cyclopropyl groups; homochiral cyclopropyl substituents are depicted as left hands

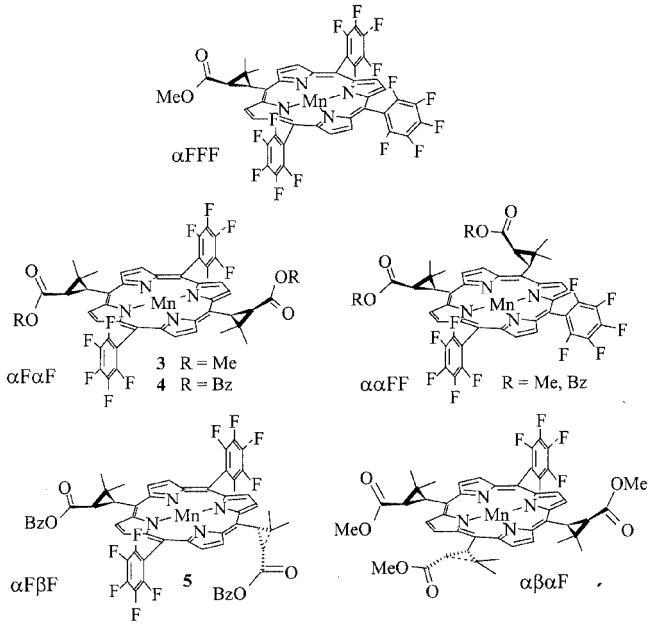


Figure 1. Stereochemistries of the five characterised types of chiroporphyrin catalysts with mixed substitution by pentafluorophenyl and chiral cyclopropyl groups

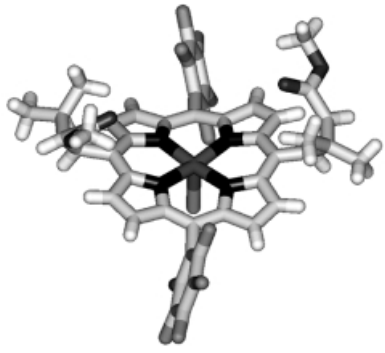


Figure 2. Stick representation of the structure of the major (90%) β-Cl conformer in the crystal lattice of [MnCl(αFαF)MeCP] (**3**), showing the moderate ruffling of the macrocycle; selected bond lengths (Å): [Mn−N_P] average 1.9972(7), Mn−Cl 2.3868(8); Mn is displaced from the porphyrin mean plane towards Cl by 0.14 Å; the C_{meso} atoms are displaced alternatively up [+0.46(1) Å] and down [−0.40(1) Å] with respect to the 24-atom mean plane

longer in **3** [1.9972(7) Å] than in **2** [1.974(2) Å], and the Mn−Cl bond length is also longer [2.3868(8) Å vs. 2.3475(9) Å]. The manganese atom of **3** is slightly displaced from the porphyrin mean plane by 0.14 Å (as compared to 0.44 Å in **2**). There is a small disorder of the chloro ligand of **3**, which is predominantly (ca. 90%) located on the open β face as shown in Figure 2 (β-Cl conformer). The presence of a small amount of α-Cl conformer in the samples of **3** (ca. 10% as indicated by the crystallographic disorder model) was confirmed by TLC on silica gel, which showed a minor, more polar spot very close to the major spot, and inseparable from it. The conformer composition of the chloromanganese(III) complex derived from the analogous benzyl ester derivative {noted [MnCl(αFαF)BzCP] (**4**)} has not been determined.

Asymmetric epoxidation of 1,2-dihydronaphthalene by iodosylbenzene with **3** as catalyst was faster than with the first-generation chiroporphyrin catalysts[3] and gave improved product yields. For example, epoxide yields obtained with **3** under our standard conditions with pyridine co-catalyst reached 96% after only 15 min, as compared to 83% after 60 min for **2** (Table 1). On the other hand, the *ee* lagged below 20% for **3**, as compared to 60% for **2**, indicating that epoxidation takes place at a significant rate on the non-chiral β face of **3**. Bulky bases such as 4-*tert*-butylpyridine, 1-(*tert*-butyldimethylsilyl)imidazole, 1,5-dicyclohexylimidazole, or diazabicyclo[2.2.2]octane had a similar effect to that of pyridine (Table 1). These observations led us to exclude the nitrogen bases and to use the neat chloromanganese(III) complexes **3** and **4** as catalysts. A remarkable improvement of the *ee* (which more than doubled from 18% to 43% for **3**, and from 17% to 35% for **4**) was obtained,

without affecting much the reaction rates and product yields, which remained satisfactory (Table 1).

Table 1. Catalytic asymmetric epoxidation of 1,2-dihydronaphthalene with manganese chiroporphyrins **3**−**5**

Axial ligand[a]	Epoxide yield (%)[b] [c]				*ee* (%, 60 min)[d]
	5 min	15 min	30 min	60 min	
	[MnCl(αFαF)MeCP] (**3**)				
py	62	96	>99	>99	18
bp	48	86	97	>99	17
bsi	80	86	92	95	2
dci	12	61	75	98	5
dabco	33	51	63	67	15
none	73	82	87	88	43
	[MnCl(αFαF)BzCP] (**4**)				
py	33	60	70	80	17
none	79	82	90	96	35
	[MnCl(αFβF)BzCP] (**5**)				
py	48	−	−		17
none	45	75	81	>99	31

[a] Axial ligands: py = pyridine; bp = 4-*tert*-butylpyridine; bsi = 1-(*tert*-butyldimethylsilyl)imidazole; dci = 1,5-dicyclohexylimidazole; dabco = 1,4-diazabicyclo[2.2.2]octane. [b] Reactions conditions: 1.0 μmol of catalyst, 100 μmol of iodosylbenzene, 250 μmol (or none) of axial ligand, and 1.00 mmol of 1,2-dihydronaphthalene in 2 mL of CH_2Cl_2, 1 h. [c] Based upon iodosylbenzene and determined by GC analysis with 20 μL of *n*-tridecane as internal standard. [d] Determined by GC (Cyclodex-B chiral capillary column). The major enantiomer had 1*S*,2*R* absolute configuration in all cases.

The detrimental effect of pyridine on enantioselectivity in this system is unexpected, since in most previous investigations the *ee* increases upon addition of a nitrogen base. A complete understanding of this effect is difficult because the nature of the active catalyst in the presence of pyridine, and that of the active oxidant, have never been established.[7,8] However, our results are consistent with a simple mechanism in which the presence of the chloro ligand on the β face favours the binding of added ligands on the vacant site of the α face. Pyridine binding on the chiral α face would, in turn, direct the formation of the active oxidant on the non-chiral β face, resulting in a poor *ee*, while iodosylbenzene binding on the α face in the absence of pyridine would generate the active oxidant on that same face and induce a good enantioselectivity. A rough calculation based on potential *ee* values of 60% for the α face (similar to that of **2**) and of 0% for the β face, and assuming equal reactivities on both faces, gives an overall *ee* value of about 50% for the mixture of conformers of **3** in a 90:10 β-Cl:α-Cl ratio. The reasonable agreement with the observed *ee* suggests that **2** and the β-Cl conformer of **3** have similar enantioselectivities.

Conclusion

In summary, although several elaborate synthetic routes to A_2B_2 porphyrins are available,[9] cross condensation is an expedient method to obtain the free-base precursors of active chiroporphyrin catalysts for a quick screening of their *ee*'s in a combinatorial sense. The two diastereotopic faces of a chiroporphyrin with mixed *meso*-substitution by pentafluorophenyl and chiral cyclopropyl groups in an αFαF conformation have widely different potential for enantiocontrol. The preference of the chloro ligand of manganese for the β face devoid of stereogenic groups in **3** directs the formation of the active oxo species on the α face and allows enantioselective olefin epoxidation. The electrophilicity of **3** allows the catalytic epoxidation to be carried out without exogenous ligand such as pyridine, which is advantageous since the latter can be a competitive substrate.[7]

Experimental Section

General Remarks: Solvents and chemicals were used without purification unless indicated. Dichloromethane was stabilized by ethanol (ACS for analysis, C_2H_5OH 0.1%). Pyrrole was purified by filtration through alumina before use. The methyl and benzyl esters of **1** (biocartol esters) were prepared according to previously published procedures.[1] Thin-layer chromatography was performed using Merck precoated silica plates 60F-254. Silica gel (230−400 mesh) and alumina (neutral, act. I) were used for column chromatography.

Spectroscopy: UV/Visible spectra were recorded on a Perkin−Elmer Lambda 9 instrument. Nuclear magnetic resonance spectra were obtained with Bruker AC 200, or Varian Avance 400 and 500 instruments. Spectra are tabulated in the following order: chemical shift (δ values), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet), number of protons, assignment [CH_{aro} (aromatic proton or carbon), $C_{aro\text{-}F}$ (pentafluorophenyl carbon), H_β (β pyrrolic protons of chiroporphyrins), C_α and C_β (α and β pyrrolic carbon of chiroporphyrins), C_{meso} (meso carbon of chiroporphyrins)]. The δ values of the C atoms connected to F atoms are not reported in the ^{13}C NMR spectra for some porphyrins because of high coupling constants.[10] Mass spectra were determined in the electrospray mode on a Finnigan MATLCQ instrument.

Typical Procedure For the Synthesis of Free Base Porphyrins: A 2.5 L commercial brown bottle filled with CH_2Cl_2 (containing 0.1% ethanol), equipped with a gas inlet, and shielded from ambient light by aluminium foil, was purged with argon for one hour. The flask was then charged with 6.4 mmol of biocartol methyl or benzyl ester, 6.4 mmol of pentafluorobenzaldehyde, and 15.4 mmol (1.2 equiv. relative to total aldehyde) of pyrrole under argon, followed 10 minutes later by the addition of 15.4 mmol (1.2 equiv.) of TFA. The resulting mixture was stirred at room temperature under gentle argon flow for 3 days. After this time, 12.8 mmol (1 equiv.) of DDQ was added to the reaction mixture which was stirred at room temperature for 4 hours. The solvents were then evaporated to dryness. The residue was chromatographed on alumina (neutral, act. I), eluting with CH_2Cl_2 containing 2% methanol under UV/Visible spectroscopic control, to afford a mixture of porphyrins. Pure compounds were obtained by preparative chromatography on successive TLC plates.

Selected Spectroscopic Data for H_2(αFαF)MeCP: ES-MS: *m*/*z* = 895.2 (calcd. 895.8 for [MH^+]). UV/Vis (CH_2Cl_2): λ_{max} = 421 nm, 519, 551, 595, 652. ^1H NMR (400 MHz, $CDCl_3$): δ = −2.26 (br, 1 H, NH), 0.99 (s, 6 H, CH_3i), 1.95 (s, 6 H, CH_3e), 2.85 [d, 2 H,

CH−C(O)], 3.13 (s, 6 H, OCH_3), 4.96 [d, 2 H, C*H*−CH−C(O)O], 8.64, 8.71, 9.31, 9.52 (4d, 8 H, H_β) ppm. ^{13}C NMR (Zn^{II} complex, 200 MHz, $CDCl_3$): δ = 18.6 (CH_3), 27.9 (C^{IV}), 29.2 (CH_3), 33.7 (CH), 38.8 (CH), 51.1 (OCH_3), 101.9, 113.7 (C_{meso}), 129.4, 129.5, 130.1, 132.0 (C_β), 133.5−144.8 (m and br, $C_{aro\text{-}F}$), 148.0, 148.1, 151.8, 152.5 (C_α), 171.2 [C(O)] ppm.

Selected Spectroscopic Data for H_2(αFβF)BzCP: ES-MS: *m*/*z* = 1047.3 (calcd. 1047.9 for [MH^+]). UV/Vis (CH_2Cl_2): λ_{max} = 422 nm, 520, 550, 594, 654. ^1H NMR (400 MHz, $CDCl_3$): δ = −2.35 (br, NH), 1.05 (s, 6 H, CH_3i), 1.96 (s, 6 H, CH_3e), 2.93 [d, 2 H, CH−C(O)], 4.38, 4.61 (2d, 4 H, OCH_2), 4.88 [d, 2 H, C*H*−CH−C(O)O], 6.65−6.85 (m, 10 H, CH_{aro}), 8.42, 8.65, 9.23, 9.42 (4d, 8 H, H_β) ppm. ^{13}C NMR (Zn^{II} complex, 400 MHz, $CDCl_3$): δ = 19.0 (CH_3), 28.3 (C^{IV}), 29.5 (CH_3), 33.9 (CH), 39.4 (CH), 66.2 (OCH_2), 101.4, 101.9, 113.5 (C_{meso}), 128.1, 128.5, 128.9 (CH_{aro}), 129.6, 130.0, 130.3, 131.9 (C_β), 136.4 (C^{IV}_{aro}), 147.8, 148.3, 152.2, 152.9 (C_α), 170.9 [C(O)] ppm.

Selected Spectroscopic Data for H_2(αβαF)MeCP: ES-MS: *m*/*z* = 855.3 (calcd. 855.9 for [MH^+]). UV/Vis (CH_2Cl_2): λ_{max} = 425 nm, 524, 563, 603, 654. ^1H NMR (400 MHz, $CDCl_3$): δ = −1.85 (br, NH), 0.90, 0.95, 1.00 (3s, 9 H, CH_3i), 1.97, 2.00, 2.01 (3s, 9 H, CH_3e), 2.86, 2.88, 2.94 [3d, 3 H, CH−C(O)], 3.15, 3.18, 3.19 (3s, 9 H, OCH_3), 4.88, 4.94, 4.96 [3d, 3 H, C*H*−CH−C(O)O], 8.57−9.42 (m, 8 H, H_β) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 18.6 (CH_3), 27.8, 28.1, 28.3 (C^{IV}), 29.2 (CH_3), 33.6 (CH), 38.3, 38.4, 38.6 (CH), 51.4 (OCH_3), 99.8, 111.7, 112.1, 112.3 (C_{meso}), 127.7, 128.2, 128.6, 129.0, 129.3, 131.0, 131.4, 132.0 (C_β), 136.8 (br), 136.6 (br), 138.9 (br), 140.7 (br), 142.4 (br), 143.2 (br, $C_{aro\text{-}F}$), 147.5−150.9 (C_α), 171.0, 171.1, 171.3 [C(O)] ppm.

X-ray Crystallographic Study: Crystal data for **3**: $MnCl(C_{46}H_{30}O_4N_4F_{10})\cdot CHCl_3\cdot 0.5\,CH_2Cl_2\cdot 1.41H_2O$, M = 1170.44, monoclinic space group $P2_1$, a = 13.1971(7), b = 15.3994(8), c = 14.5274(8) Å, β = 115.8040(10)°, V = 2658.0(2) Å^3, T = 223(2) K, Z = 2, μ(Mo-K_α) = 0.583 mm^{-1}, 11678 reflections (R_{int} = 0.0202) which were used in all calculations. The final R was 0.0510, the final $wR(F^2)$ was 0.1258 [$I > 2\sigma(I)$].

CCDC-171628 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This work was supported in part by a grant from the Ministère de la Recherche (postdoctoral fellowship to S.-Q. L.), for which we express our thanks.

[1] C. Pérollier, M. Mazzanti, J.-P. Simonato, F. Launay, R. Ramasseul, J.-C. Marchon, *Eur. J. Org. Chem.* **2000**, 583−589.
[2] For the X-ray structure of chloromanganese(III) tetramethylchiroporphyrin [MnCl(TMCP)] (**2**), see: J. P. Simonato, J. Pécaut, W. R. Scheidt, J. C. Marchon, *Chem. Commun.* **1999**, 989−990.
[3] M. Veyrat, O. Maury, F. Faverjon, D. E. Over, R. Ramasseul, J. C. Marchon, I. Turowska-Tyrk, W. R. Scheidt, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 220−223; C. Pérollier, J. Pécaut, R. Ramasseul, J. C. Marchon, *Inorg. Chem.* **1999**, *38*, 3758−3759.
[4] A similar approach has been described recently: E. Rose, M. Soleilhavoup, L. Christ-Tommasino, G. Moreau, J. P. Collman, M. Quelquejeu, A. Straumanis, *J. Org. Chem.* **1998**, *63*, 2042−2044.
[5] P. E. Pfeffer, L. S. Silbert, *J. Org. Chem.* **1976**, *41*, 1373−1379.
[6] J. S. Lindsey, in *The Porphyrin Handbook* (Eds.: K. M. Kadish, K. Smith, R. Guilard), Academic Press, San Diego, CA, and Burlington, MA, **1999**, vol. 1, chapter 2.
[7] B. Meunier, *Chem. Rev.* **1992**, *92*, 1411−1456.
[8] J. P. Collman, A. S. Chien, T. A. Eberspacher, J. I. Brauman, *J. Am. Chem. Soc.* **2000**, *122*, 11098−11100.
[9] K. M. Smith, in *The Porphyrin Handbook* (Eds.: K. M. Kadish, K. Smith, R. Guilard), Academic Press, San Diego, CA, and Burlington, MA, **1999**, vol. 1, chapter 1.
[10] H. A. Wagenknecht, C. Claude, W. D. Woggon, *Helv. Chim. Acta* **1998**, *81*, 1506−1520.

Received December 21, 2001
[I01526]