Twisting the Porphyrin Ring to Enhance Epoxidation Enantioselectivity

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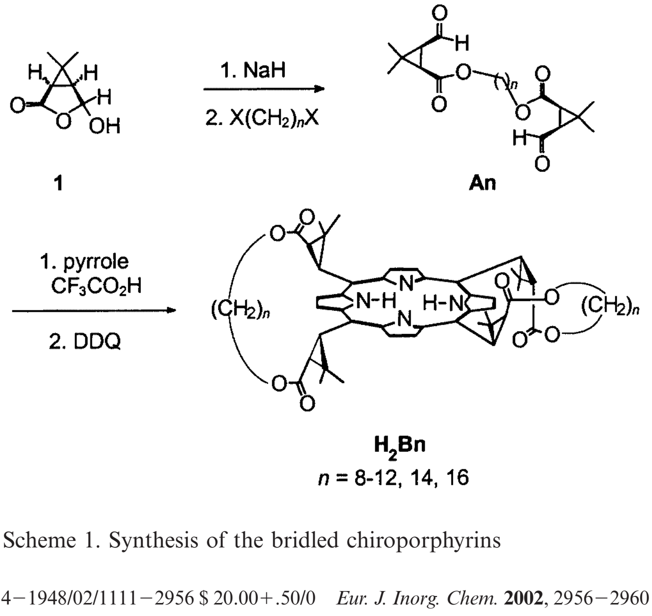
A series of bridled chiroporphyrins has been prepared in which the distortion of the porphyrin ring is controlled solely by the length of the bridles. The influence of ring distortion on the enantioselectivity of catalytic epoxidation by their manganese complexes has been investigated. Twisting the porphyrin ring is found to enhance the enantioselectivity of dihydronaphthalene epoxidation.

Introduction

Despite numerous recent advances in the area of asymmetric catalysis by chiral metal complexes,[1] the specific features (steric, conformational, electronic, etc.) of the chiral ligand that influence the enantiomeric excess (*ee*) are far from being completely understood. Among stereochemical factors, steric exclusion is widely considered a major determinant of asymmetric induction in a host of metal-catalyzed reactions. The influence of conformation is less clear; the impact of the distortion of a nominally planar ligand has been suspected only recently.[2,3] In this report, we examine the influence of porphyrin ring distortion on the enantioselectivity of catalytic epoxidation by manganese chiroporphyrins.

Steric crowding by bulky *meso* substituents is known to result in a ruffling distortion of the porphyrin[4] which influences the spectral and chemical properties of the molecule.[5] The asymmetric epoxidation of dihydronaphthalene by iodosylbenzene induced by ruffled manganese(III) chiroporphyrin complexes was investigated recently in our laboratories: the *ee* of the epoxide product has been found to increase as the porphyrin becomes more ruffled.[6] Since the origin of the ruffled distortion is the congestion induced by the bulky *meso* substituents near the porphyrin ring in an αβαβ conformation, we have not been able to determine whether the asymmetric induction is due to a conformational or a steric effect, or both. In an attempt to resolve these two influences, we have designed a series of chiroporphyrins H_2Bn (Scheme 1) in which the ester functions on adjacent *meso* substituents are linked by a strap of adjustable length (n = 8 to 16 methylene groups). We expected that the ruffling induced by the αβαβ conformation could be restricted by these bridles, and that the resulting distortion could be tuned by the strap length while the substituent volume and electronic effects would remain unchanged. Here we report our investigations of the ruffling of the bridled chiroporphyrin free bases and nickel(II) complexes by ^1H NMR and resonance Raman spectroscopy. We show that the ruffling in solution can indeed be controlled by the bridle length, and that it has a positive influence on the epoxidation enantioselectivity.



Scheme 1. Synthesis of the bridled chiroporphyrins

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Results and Discussion

The bridled chiroporphyrins H_2B9-16 were obtained in 3−12% yield following the procedure outlined in Scheme 1, which we designed earlier for the synthesis of H_2B8 from biocartol **1**.[7] In contrast to H_2B8, which is obtained as the αααα isomer,[7] the αβαβ conformation of the free bases with longer bridles (H_2B9-16) is apparent from their D_2-symmetric ^1H NMR spectra, with a pair of singlets for the β-pyrrolic protons and a single signal for each group of *meso* protons. The resonances of the methylene protons of H_2B9-16 appear near $\delta = 1.6-1.8$ ppm, indicating that the two straps are directed away from the ring current and connect adjacent substituents on opposite faces of the porphyrin. Metal insertion gave the nickel complexes NiB8−16 as pure αβαβ conformers, and the manganese complexes MnClB8−16 as a mixtures of αβαβ and αααα conformers, which were separated by TLC on silica gel and identified by X-ray crystallography. The more abundant isomer was assigned the αβαβ conformation, and the more polar, less abundant one was assigned the αααα conformation. Single crystals were obtained by slow diffusion of *n*-hexane into a chloroform solution of MnClB10. The determination of the X-ray structure showed that the asymmetric unit contains one αβαβ-MnClB10 complex and two very similar, but crystallographically distinct, αααα-MnClB10 complexes, and it confirmed the assignments made on the basis of the relative polarities observed in TLC. Views of the X-ray structures of the two conformers are illustrated in Figure 1. Notable features of these structures are the ruffled porphyrin conformation of the αβαβ conformer and the two straps connecting adjacent *meso* substituents on opposite faces, and the slightly domed porphyrin conformation of the αααα conformer and the two straps connecting adjacent *meso* substituents on the same face. Also noteworthy is the variable conformation of the four ester moieties, which have their carbonyl group inwardly directed in the αβαβ isomer and outwardly directed in the αααα isomer.

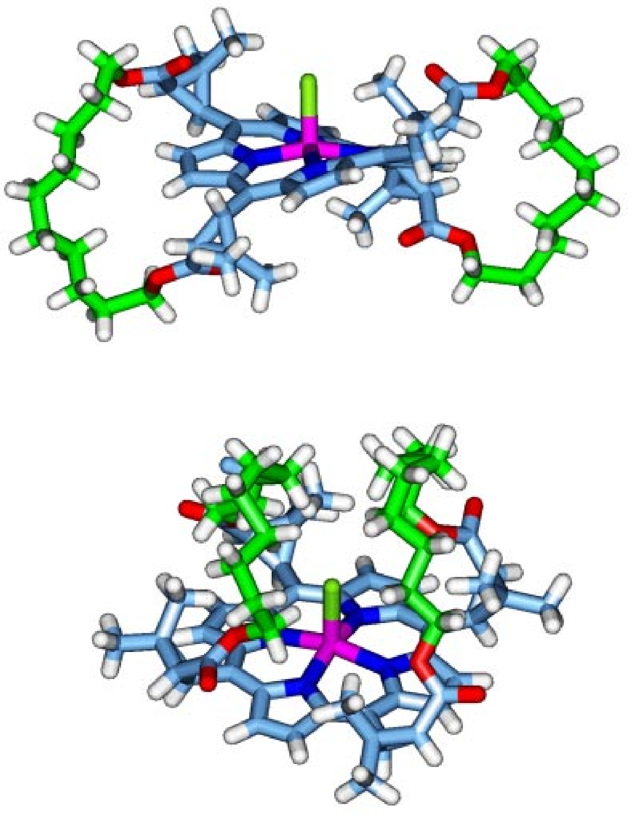

Figure 1. X-ray structures of the bridled manganese(III) complex MnClB10; (top) stick representation of the αβαβ-MnClB10 molecule showing the ruffled porphyrin conformation and the two straps connecting adjacent *meso* substituents on opposite faces; selected bond lengths (Å): Mn(1)−N(1) 1.983(8); Mn(1)−N(2) 1.987(8); Mn(1)−N(3) 1.968(8); Mn(1)−N(4) 1.993(8); Mn(1)−Cl(1) 2.371(3); (bottom) stick representation of one of the two αααα-MnClB10 molecules showing the slightly domed porphyrin conformation and the two straps connecting adjacent *meso* substituents on the same face; selected bond lengths (Å): Mn(2)−N(11) 2.024(9); Mn(2)−N(12) 2.053(8); Mn(2)−N(13) 2.033(8); Mn(2)−N(14) 2.057(8); Mn(2)−Cl(2) 2.365(3). Mn(3)−N(21) 2.019(8); Mn(3)−N(22) 2.014(8); Mn(3)−N(23) 2.018(8); Mn(3)−N(24) 2.037(9); Mn(3)−Cl(3) 2.360(3)

High-frequency Raman lines in the region 1340−1640 cm^{-1} have been shown to be especially sensitive to the ruffling mode of deformation of nickel(II) porphyrins.[5] In the resonance Raman spectra of the bridled nickel(II) complexes NiB8−16 (Figure 2), all of the high-frequency marker lines show a similar frequency dependence on bridle length. The correlation between frequency and the number of methylene groups in a bridle is depicted in Figure 3 for ν_2. At first ($8 \leq n \leq 12$), lengthening the bridle induces a decrease of the line frequency, indicating increased ruffling of the ring as we expected. Apparently the constraints imposed by the bridles, which prevent adjacent *meso* substituents on opposite faces from moving away from each other, are gradually relaxed as the number of methylene groups increases, thus allowing the porphyrin to reach a more distorted conformation until a maximum is attained for $n = 12$. Further lengthening of the bridles beyond $n = 12$ unex-

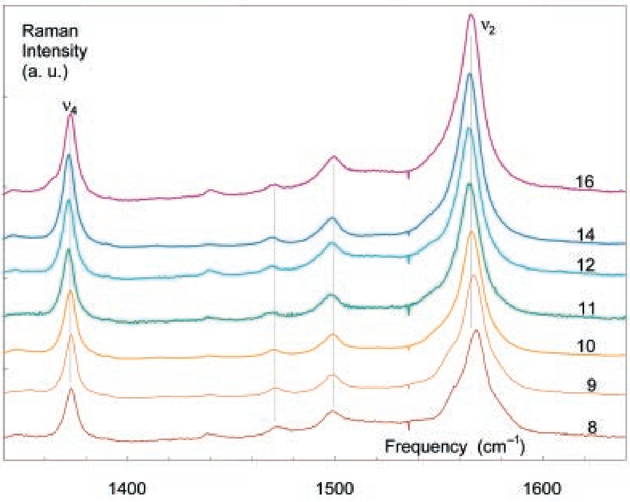

Figure 2. High-frequency region of the resonance Raman spectra for the bridled nickel(II) complexes NiB8−16 obtained at 407.6 nm laser excitation in carbon disulfide; the number on each spectrum refers to the number of methylene groups in a bridle of the complex

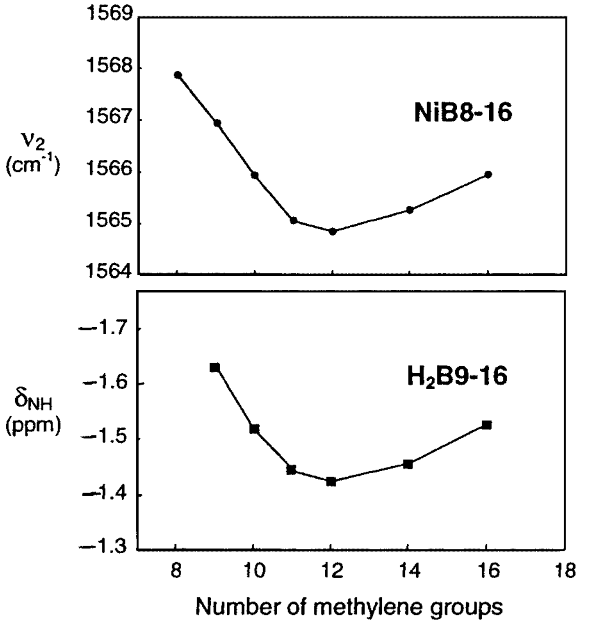

Figure 3. Dependence of the frequency of the structure-sensitive line ν_2 for the nickel(II) complexes αβαβ-NiB8−16 (upper trace), and of the chemical shift of central protons δ_{NH} for the free base chiroporphyrins αβαβ-H_2B9−16 (lower trace) on the number of methylene groups in a bridle

pectedly induces a small decrease in the ruffling, as evidenced by the small increase in the marker line frequencies.

An entirely similar biphasic behavior has been detected for the free bases H_2B9−16 by ^{1}H NMR spectroscopy (Figure 3), using the chemical shift δ_{NH} of the central protons as a probe of the ring current; the latter is directly related to the nonplanar distortion of the porphyrin. The similar trends found for the free bases and their nickel(II) complexes is a strong indication that in these intrinsically ruffled compounds the amount of distortion of the porphyrin ring arises mainly from the restraints imposed by the bridles, and that it is not strongly influenced by the size of the metal center. Molecular dynamics simulations also give average structures for NiB8−16 that indicate a dependence of the magnitude of ruffling similar to that shown in Figure 3.[10]

We surmise that long straps ($n \geq 12$) have sufficient flexibility to allow other conformational states of the ester group to be populated, for example by rotation of their oxo and alkoxy substituents. Conformations in which the carbonyl group is either inwardly or outwardly directed, as seen in Figure 1, have been observed earlier in the X-ray structure of the nickel chiroporphyrin derived from the bornyl ester of **1**.[6] In a chiroporphyrin with long bridles, a change from an outwardly to an inwardly directed carbonyl group would result in an effective shortening of the strap, and therefore to a less-distorted porphyrin ring.[10] In agreement with this proposed mechanism, the conformational flexibility of the 16-methylene chains of H_2B16 is apparent from the presence of a single signal at $\delta = 3.62$ ppm for the two diastereotopic protons of the methyleneoxy groups, which are in fast exchange on the NMR time scale. In contrast, the shorter-chain congeners are more conformationally rigid, as indicated by the anisochronicity of the two diastereotopic protons of the methyleneoxy groups, which give two broad signals. It is also possible that additional flexibility in the straps introduces new ways in which the straps can influence the out-of-plane macrocycle distortion

Table 1. Yields, enantiomeric excesses, and enantiomeric compositions obtained in the asymmetric epoxidation of 1,2-dihydronaphthalene by iodosylbenzene induced by catalysts MnClB8−16[a]

Number of methylene groups in bridle	Yield[b] (%)		*ee*[c] (%)		Enantiomeric composition (%)	
8	64	average 62	46	average 44(2)	73	average 72(1)
	61		45		73	
	62		42		71	
9	61	average 63	54	average 51(3)	77	average 76(1)
	65		47		74	
	64		52		76	
10	57	average 58	65	average 63(4)	83	average 82(1)
	61		66		83	
	56		59		80	
11	51	average 54	59	average 61(2)	79	average 80(1)
	55		62		81	
	56		62		81	
12	63	average 60	62	average 61(2)	81	average 80(1)
	58		59		79	
	60		63		81	
14	51	average 48	51	average 53(3)	76	average 77(1)
	46		54		77	
	47		53		77	
16	48	average 47	69	average 64(5)	85	average 82(2)
	45		62		81	
	49		60		80	

[a] Reaction conditions: catalyst/substrate/PhIO 1:1000:100 μmol at room temperature in 2 mL CH_2Cl_2. [b] Yield relative to PhIO. [c] Measured by GC on a Cyclodex-B chiral column.

through nonbonding interactions or additional degrees of freedom at the meso substituents.

Each catalyst of the series αβαβ-MnClB8−16 was carefully purified by TLC on silica gel. The yields and *ee*'s obtained in the catalytic epoxidation of 1,2-dihydronaphthalene by iodosylbenzene are collected in Table 1. Figure 4 shows a plot of the enantiomer composition (ec) of the major 1*S*,2*R* epoxide versus the ν_2 frequency of NiB8−16. The observed correlation suggests that similar distortions of the ring are obtained irrespective of the core metal (Ni or Mn). It also indicates that the enantioselectivity induced by the manganese catalysts increases as the ruffling of the porphyrin increases, i.e. that twisting the porphyrin ring is beneficial to the asymmetric induction.

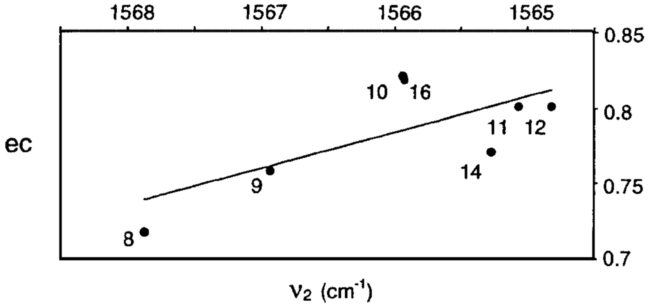

Figure 4. Plot of the enantiomer composition (ec) of the major 1*S*,2*R* epoxide obtained in the asymmetric epoxidation of 1,2-dihydronaphthalene by iodosylbenzene induced by catalysts αβαβ-MnClB8−16 as a function of the frequency of the structure-sensitive line ν_2 of NiB8−16; the number of methylene groups *n* in each bridle is indicated for each data point

The subtle effect by which a conformation change can influence the enantioselectivity of a catalyst is intriguing. We speculate that this influence may be mediated by several factors, either steric or electronic in origin. For example, a folding, or twisting, of the porphyrin ring would put more bulk near the metal center, or induce more asymmetry of charge distribution in the reactive species, respectively. Coming back to the chiroporphyrin catalysts of the first generation,[6] which were the starting point of this investigation, we can now conclude that the extent of their asymmetric induction is the result of several effects. The favorable steric influences of the ester or amide substituents in their various possible conformations are corroborated by the resulting propitious effect of porphyrin ruffling. This finding reveals a novel facet of the origins of stereoinduction in asymmetric catalysis, and it may have implications in catalyst design.

Conclusion

In summary, bridled chiroporphyrins provide the unprecedented possibility of controlling the distortion of the porphyrin ring without substantially modifying the steric and electronic influences of the macrocycle substituents. The dependence of the ruffling on the bridle length shows two opposite trends. Like the structure-sensitive Raman frequencies of the nickel complexes, the ^{1}H NMR chemical shift of the central protons of the free bases is a very sensitive probe of the ruffled distortion of the porphyrin ring in solution. Our finding that this distortion has a positive influence on stereoinduction may open new possibilities for the design or improvement of asymmetric catalysts.

Experimental Section

General Spectroscopic Information: All compounds were characterized by electrospray mass spectrometry (Finnigan MAT LCQ), UV/Vis (Perkin−Elmer Lambda 9), and NMR spectroscopy. The purity of all products was ascertained by TLC, UV/Visible and NMR spectroscopy; elemental analytical data were not obtained due to the generally low yields. ^{1}H NMR spectra of $CDCl_3$ solutions of the compounds (ca. 3 mg in 0.5 mL) were recorded at room temperature on a Bruker AC200 or a Varian Avance 400 NMR spectrometer. Parameters for acquiring proton spectra were the following: 200 MHz, 16 scans, spectral window 4 kHz, 16 K data points; 400 MHz, 8 scans, spectral window 8 kHz, 58.5 K data points. Chemical shifts were measured relative to $CHCl_3$ and they are referenced to tetramethylsilane. Resonance Raman spectra were obtained as reported in a an earlier publication.[8]

Catalytic epoxidations were carried out according to standard procedures.[6,9] Measurements of enantiomeric compositions were carried out at least in triplicate by chiral chromatography on a Cyclodex-B column with a Fisons GC 9000 system.

Synthesis of a Bridle An: A typical procedure is described below for A10. NaH (1.13 g, 28 mmol) was added in small portions to a dry THF (30 mL) solution of biocartol **1** (4 g, 28 mmol) under argon at 10 °C. The mixture was then stirred for 30 min at room temperature and 2.76 mL of 1,10-diiodododecane (7 mmol) in dry DMF (120 mL) was added. After stirring for 24 h under argon at room temperature, diethyl ether was added and the organic layer was washed and dried over Na_2SO_4. The solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography with dichloromethane/methanol (97:3) as eluent to afford A10 as a colorless oil (2.96 g, >99% relative to diiodododecane). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.73$ (d, $J = 6.3$ Hz, 2 H, CHO), 4.09 (dt, $J = 6.8$, $J = 1$ Hz, 4 H, OCH_2), 2.10 (d, $J = 8.8$ Hz, 2 H, CH−C(O)O), 1.82 (dd, $J = 6.3$, $J = 8.8$ Hz, 2 H, C*H*−CHO), 1.62 (m, 4 H, O−CH_2−CH_2), 1.54 (s, 6 H, CH_3), 1.28 (b, 12 H, CH_2), 1.25 (s, 6 H, CH_3).

Synthesis of a Bridled Chiroporphyrin H_2Bn: A typical procedure is described below for H_2B10. A degassed dichloromethane (1.9 L) solution containing A10 (3.54 g, 8.4 mmol), 1.4 mL (20 mmol) of pyrrole and 1.55 mL (20 mmol) of TFA was stirred at room temperature under argon for 6 days. The reaction mixture was diluted to 5.7 L by adding 3.8 L of dichloromethane and then oxidized with DDQ (3.8 g, 16.6 mmol). After stirring for 4 h, the solvent was removed under reduced pressure. The residue was chromatographed on an alumina column eluting with dichloromethane/methanol (98:2), then on silica gel plates eluting with the same solvent mixture. The porphyrin H_2B10 was obtained as a purple solid (530 mg, 12%). MS (ES): *m/z* = 1035.7 [MH^+]. UV/Vis (CH_2Cl_2): λ_{max} = 429 nm (Soret), 530, 565, 607, 662. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.12$ and 9.08 (2s, 8 H, Hβ), 4.80 (d, $J = 8.8$ Hz, 4 H, H^2), 4.0 (m, 4 H, OCH_2), 3.55 (m, 4 H, OCH_2), 2.74 (d, $J = 8.8$ Hz, 4 H, H^1), 1.93 (s, 12 H, CH$_3$), 1.82 and 1.69 (2b, 32 H, CH$_2$), 0.79 (s, 12 H, CH$_3$), −1.52 (b, 2 H, NH) ppm. ^{13}C NMR (200 MHz, CDCl$_3$): δ = 169.8 (C=O), 153.0 (Cα), 149.3 (Cα), 131.3 (Cβ), 127.3 (Cβ), 111.0 (*meso* C^{IV}), 64.3 (OCH$_2$), 38.4 (CH^2), 32.9 (CH^1), 29.7 (Me), 29.2 (CH$_2$), 28.9 (CH$_2$), 28.6 (CH$_2$), 27.7 (C^{IV}), 27.3 (CH$_2$), 17.9 (Me) ppm.

MnClBn: A typical procedure is described below for MnClB10. A saturated $MnCl_2 \cdot 4H_2O$ solution (20 mL) in ethanol was added to a solution H$_2$B10 (20 mg, 19.3 µmol) in 10 mL of chloroform. The mixture was stirred under reflux for 72 h. The solvent was removed under reduced pressure and the residue was purified twice by TLC on silica eluting with dichloromethane/methanol (92:8). The resulting product (20.5 mg, 95%) gave a single spot in TLC on silica. MS (ES): m/z = 1087.5 [M$^+$ − Cl]. UV/Vis (CH$_2$Cl$_2$): λ_{max} = 383, 402, 486, 596, 638 nm.

X-ray Crystallographic Study: Dark green single crystals were obtained by slow diffusion of *n*-hexane into a chloroform solution of the complex. Data collection was carried out on a Bruker AXS Smart CCD area-detector diffractometer. The structure was solved by direct methods using the SHELX-TL software package. Crystal data for MnClB10: $3C_{64}H_{80}N_4O_8MnCl \cdot CHCl_3$, M = 3490.50, trigonal, space group $P3_2$, a = 27.3710(8), b = 27.3710(8), c = 23.2007(9) (Å), γ = 120°, V = 15052.6(9) Å^3, T = 193(2) K, Z = 3, μ(Mo-K_α) = 0.329 mm^{-1}, 63323 reflections, 42452 independent reflections (R_{int} = 0.0820) which were used in all calculations. The final R was 0.0965, the final $wR(F^2)$ was 0.2263 [$I > 2\sigma(I)$].

CCDC-156317 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].

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