

Porphyrins and Metalloporphyrins: Versatile Circular Dichroic Reporter Groups for Structural Studies

XUEFEI HUANG, KOJI NAKANISHI, AND NINA BEROVA*

Department of Chemistry, Columbia University, New York City, New York

ABSTRACT During the last few years, porphyrins and metalloporphyrins have attracted widespread attention as chromophores for studies in circular dichroism (CD), an indispensable chiroptical tool for monitoring chiral interactions. This review summarizes the multifaceted properties of porphyrins and metalloporphyrins, powerful CD chromophores that are characterized by their intense and red-shifted Soret band, propensity to undergo π – π stacking, facile incorporation of metals, and ease in varying solubility. Such attributes make porphyrins one of the most attractive and sensitive chromophores used in CD studies. They offer possibilities for studying the stereochemistry of chiral porphyrin assemblies, large organic molecules, biopolymers, and compounds available in miniscule quantities. The tendency of porphyrins to undergo π – π stacking and zinc porphyrins to coordinate with amines enable the CD exciton chirality method to be extended to configurational assignments of flexible compounds containing only one stereogenic center. Various artificial porphyrin receptors have been synthesized for the recognition of biologically important chiral guests such as carbohydrates, amino acids, and their derivatives. The induced CD of the host porphyrin Soret band reflects the identity of guests and binding modes of host/guest complexation with high sensitivity. *Chirality* 12:237–255, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: circular dichroism; artificial receptors; molecular recognition; exciton chirality; absolute configuration; fluorescence detected circular dichroism; carbohydrates; amino acids; ceramides; brevetoxin

The study of porphyrins has received increased interest in recent years. Porphyrins have been utilized for the development of artificial receptors for molecular recognition¹ and new chiral catalysts for asymmetric synthesis,^{2–4} for the exploration of the mechanisms of biologically important reactions such as photosynthesis⁵ and P450-catalyzed redox reactions,⁶ and for the study of stereochemistry. In these studies, circular dichroic (CD) spectroscopy has proven to be a critical tool for monitoring chiral interactions. This review is focused on the use of porphyrins as circular dichroic reporter groups.

CD measures the differential absorption of chromophore-containing chiral molecules toward left and right circularly polarized light, where the difference in absorption appears in a CD spectrum around the chromophoric absorption maximum as a peak or a trough (called the Cotton effect, CE). The following attributes of the porphyrins make them powerful, versatile, and multifaceted chromophores for CD studies.

1) *The presence of a red-shifted main absorption band, the Soret band, at ca. 418 nm.* With typical chromophores that absorb below 300 nm, an overlap between the substrate absorbance and that of the introduced chromophore may lead to complications in analysis of CD spec-

tra. It is advantageous, therefore, to use red-shifted chromophores in order to avoid such overlaps.^{7,8} Porphyrins are red-shifted chromophores that fulfill such objectives.

- 2) *Intense extinction coefficients, e.g., ϵ is ca. 440,000 for tetraarylporphyrins.*⁹ Intensities of CEs depend on the extinction coefficient of the chromophore,¹⁰ and hence the intense absorption of porphyrins greatly enhances the sensitivity of CD.
- 3) *Facile modification of substituent groups.* Porphyrins have several distinct functionalization sites, i.e., the meso position, β -position, and inner nitrogens (Fig. 1). The solubility of porphyrin-containing compounds in nonpolar or polar solvents can be modified by varying the porphyrin substituents, while the proper choice of porphyrin and solvent gives rise to intermolecular or intramolecular π – π stacking.
- 4) *Ease of metal incorporation into the porphyrin ring.*¹¹ Metalloporphyrins, such as zinc and magnesium por-

Contract grant sponsor: NIH; Contract grant number: GM 34509, AI 10187; *Correspondence to: Prof. Nina Berova, Department of Chemistry, Columbia University, New York City, NY 10027. E-mail: ndb1@columbia.edu
Received for publication 10 October 1999; Accepted 2 February 2000

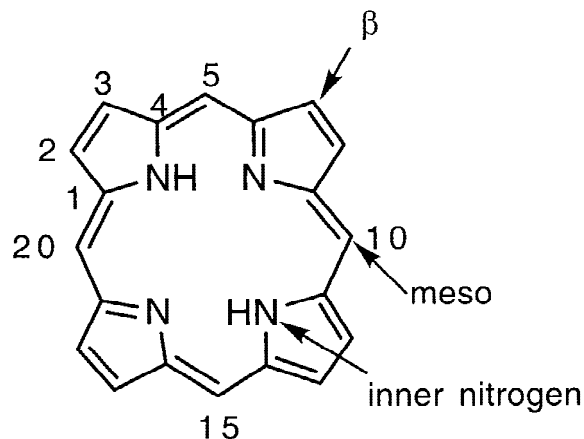


Fig. 1. Structure of the porphyrin core and its functionalization sites.

phyrins, provide extra stereodifferentiation with their Lewis acid sites for binding OH, NH₂, COO⁻, and other functional groups as Lewis bases.

UV-vis SPECTRA OF PORPHYRINS AND METALLOPORPHYRINS

Generally, four absorption bands (Q bands), responsible for the red to purple color, are present in the visible region between 500 to 700 nm ($\epsilon > 10^4$) of the free base porphyrin absorption spectra. A very sharp intense band (B band), also called the Soret band, appears around 400 nm in the near UV region ($\epsilon > 10^5$) (Fig. 2) and is most useful for CD studies. There are also additional bands (N, L, M bands) in the UV, but these are usually quite weak. The Soret band positions are sensitive to substituent groups, e.g., the Soret band of 5,10,15,20-tetraphenylporphyrin is around 419 nm,¹² while that of 2,3,7,8,12,13,17,18-octaethylporphyrin is around 400 nm.¹³ Upon formation of metalloporphyrins, the four Q bands in the visible region collapse into essentially two bands due to their higher D_{4h} symmetry, but the Soret band is barely affected (Fig. 2).

The following discussion on the CD of porphyrins is divided into two sections: 1) CD of monoporphyrins, including induced CD (ICD) due to perturbation of the porphyrin Soret band by chiral substituents or ligands and CD of intrinsically chiral porphyrins; and 2) CD of interacting porphyrins arising from a through-space exciton coupling interaction. The CD originating from the interaction of porphyrins and metalloporphyrins with polypeptides, proteins,^{14–21} and nucleic acids^{21–25} is beyond the scope of this survey.

CD OF MONOPORPHYRINS

Induced CD of Achiral Monoporphyrin Host/Chiral Guest Complexes — Useful Tool for Monitoring Chiral Molecular Recognition and Host–Guest Interactions

Molecular recognition is a fundamental process for a range of chemical and biological phenomena. Metalloporphyrins have been used for the design of artificial chromophoric hosts that selectively bind amino acids,^{26,27} carbohydrates,^{28–31} and diamines.³² In these studies, CD has frequently been utilized to probe the binding modes of

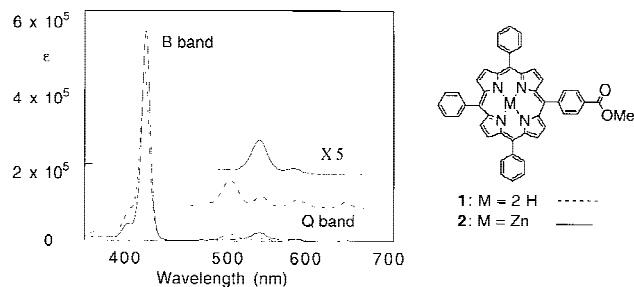


Fig. 2. UV-vis spectra of porphyrin methyl ester **1** and zinc porphyrin methyl ester **2** in CH₂Cl₂.

chiral guests, e.g., amino acid esters and carbohydrates, with the porphyrin host.

Interaction between achiral zinc porphyrin hosts and chiral amino acid derivatives. The design of artificial receptors, including porphyrin receptors capable of recognizing amino acids, has been studied extensively.^{33–37} Ogoshi and coworkers³⁸ synthesized porphyrin host **3**, containing sites for coordination (zinc) and for hydrogen bonding (2-naphthol) (Fig. 3). This host is capable of binding amino acid esters, especially those bearing bulky aliphatic side chains such as Leu-OMe and Val-OMe, through a two-point fixation mechanism, i.e., amine/zinc coordination and ester carbonyl/naphthol hydrogen bonding. L-Amino acid esters consistently induce biphasic CD in the Soret band with negative CEs at longer wavelength and positive CEs at shorter wavelength.²⁸ According to Mizutani et al.³⁸ the split ICD is due to the interaction between the magnetic transition dipole moment of the guest carbonyl group and the electric transition dipole moments of the host Soret band. Molecular orbital calculation of the rotational strength of porphyrin-amino acid ester complexes by the MNDO method indicates that ICD of the complexes is determined by the relative geometry of the carbonyl group and the porphyrin plane.³⁹ The presence of a hydrogen bond donor in the peripheral naphthol moiety is important for the split CD because it presumably fixes the orientation of the ester carbonyl through hydrogen bonding. In the absence of the naphthol moiety or the ester carbonyl, the CD is much weaker and is not split.

For amino acids containing polar sidechains such as dimethyl glutamate and dimethyl aspartate (Asp-OMe), an additional attractive interaction between the porphyrin host and amino acid guests is necessary. A trifunctional zinc porphyrin host **4** was shown to bind Asp-OMe selectivity through a three-point interaction (Fig. 4a).⁴⁰ The ICD of the complex **5** is also of the split type (Fig. 4b) as in the case of the amino acid ester complex with zinc porphyrin host **3**.

Interaction between magnesium porphyrins and amino acid guests. When magnesium mesoporphyrins **6** (MgMP) and magnesium protoporphyrins **7** (MgPP) are mixed with various amino acids they are capable of forming 1:1 and 1:2 complexes (Fig. 5).^{41,42} Magnesium porphyrins complexes with L-histidine, L-proline, L-serine, L-

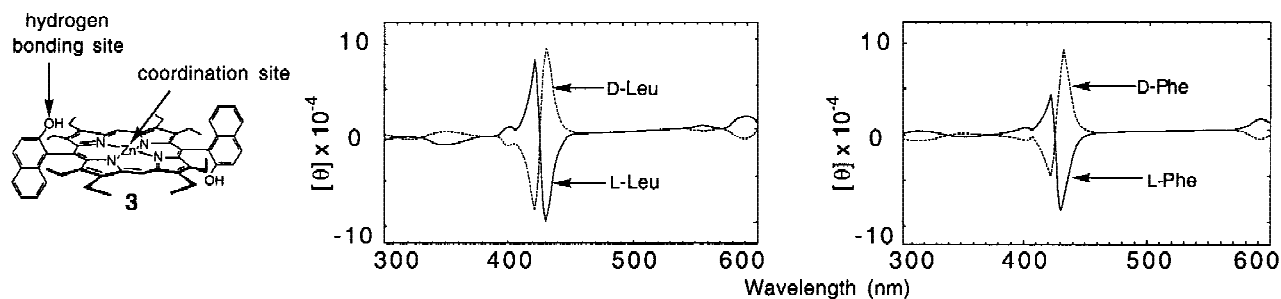


Fig. 3. Two-point fixation of amino acid esters with zinc porphyrin host **3**. (Reproduced from Ref. 38 with permission of the American Chemical Society.)

threonine, and L-tryptophan show large split-type CD, which is most probably due to coupling between the carbonyl magnetic moment of the amino acid and the porphyrin Soret band.³⁸ The fact that no CE is observed with amino acids such as leucine is probably because of the absence of additional localizing effects that restrict the carbonyl movement in the complex. Namely, the hydroxyl groups in L-serine and L-threonine can form hydrogen bonds with the carboxylic acid functions on the porphyrin sidechains, while in the case of L-histidine and L-tryptophan, π - π stacking between the aromatic rings (imidazole or indole) and the porphyrins is considered as a possible localizing factor.

Interaction between gadolinium(III) porphyrin and amino acids. An achiral gadolinium(III) porphyrin **8** was able to extract chiral amino acids from aqueous solution, forming a 1:1 complex (Fig. 6), through bidentate chelation with the carboxylate and amino groups.⁴³ Intense bisignate ICD spectra were observed in the Soret region of the porphyrin with the sign reflecting the absolute configuration of the amino acids. The strong CD of the porphyrin **8**/amino acid complex suggests that the gadolinium(III) porphyrin **8** may serve as a new sensitive chirality probe for unprotected amino acids.

Interaction between porphyrin hosts and carbohydrates. A quinoline-containing zinc porphyrin, **9**, was de-

signed to bind carbohydrates through a combination of Lewis acid (zinc) and Lewis base (quinolyl nitrogens) binding sites (Fig. 7).²⁸ The induced CD in the porphyrin Soret band region due to complexation with carbohydrates displayed a characteristic pattern for each sugar. The binding of α -D-octylmannopyranoside (α -Man) with host **9** in CHCl_3 ($K = 15,500 \text{ M}^{-1}$) induced a negative first and positive second bisignate CD curve at room temperature (Fig. 7a). This ICD probably arises from the perturbation of the Soret transition of the porphyrin host by the relatively fixed guest α -Man. α -D-Octylglucopyranoside (α -Glc) showed very weak CEs despite the fact that its binding affinity to host **9** was very similar to that of α -Man (Fig. 7b). Variable temperature CD revealed that while the CD of **9**/ α -Man did not vary much with temperature, the **9**/ α -Glc complex at -60°C did exhibit a bisignate CD curve similar to that of **9**/ α -Man (Fig. 7b). This indicates that while α -Glc fluctuates in the **9**/ α -Glc complex, α -Man is quite rigidly fixed to **9** at room temperature. Namely, the CD of the host **9**-guest complexes sensitively reflected the host/guest interaction modes, particularly the guest orientation and fluctuation in the complex.

Instead of utilizing more traditional hydrogen bonding, Shinkai and coworkers^{44,45} designed porphyrin hosts bearing boronic acids for recognizing carbohydrates through covalent boronate bond formation. It is well known that boronic acids are capable of forming five-membered rings

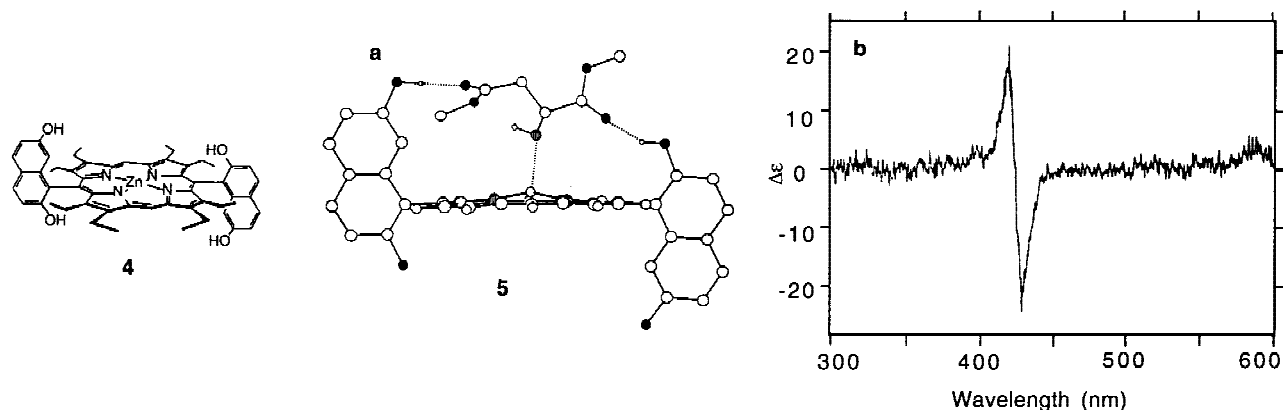


Fig. 4. Structure of the trifunctional zinc porphyrin host **4**. a: Schematic representation of the three-point interaction between host **4** and Asp-OMe. b: ICD of the complex **5** formed between host **4** ($3.9 \times 10^{-6} \text{ M}$) and Asp-OMe ($6.34 \times 10^{-4} \text{ M}$) in CHCl_3 at 25°C . (Reproduced from Ref. 40 with permission of the American Chemical Society.)

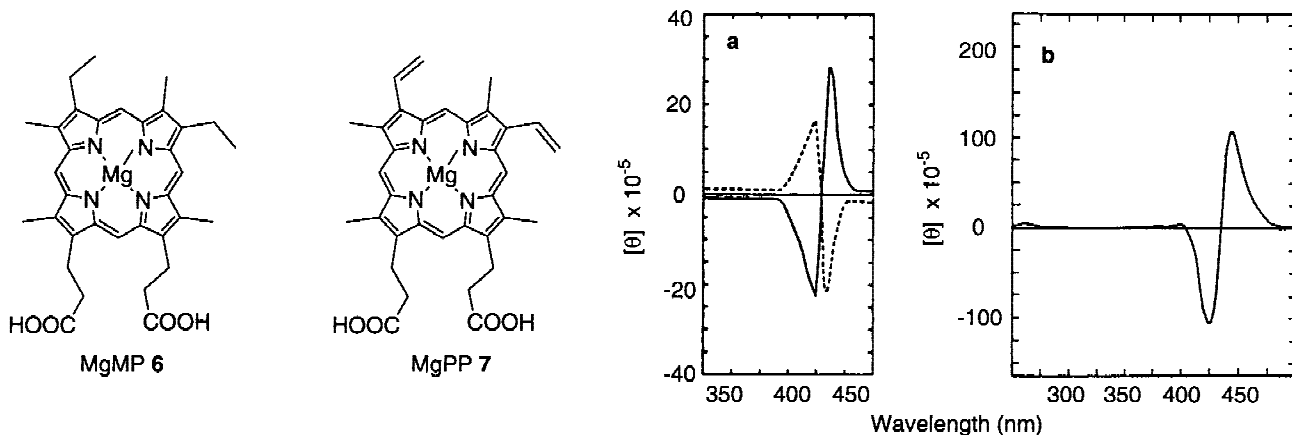


Fig. 5. a: CD of MgMP **6** in 0.1 M L-proline (dashed line) and in 0.1 M D-proline (solid line). b: CD spectrum of MgPP **7** in 0.1 M L-histidine. (Reproduced from Refs. 41 and 42 with permission of Elsevier Science.)

with *cis*-1,2-diols and six-membered rings with 1,3-diols.⁴⁶ A mixture of boronic acid appended zinc porphyrin **10** and 3-pyridyldimethylboronate self-assemble through zinc-nitrogen coordination to create a novel diboronic acid system **11**, which recognizes monosaccharides such as D-fucose, D-arabinose, D-glucose, and D-threitol.³⁰ The type of saccharides capable of binding to the porphyrin diboronic acid complex can be sensitively detected by CD spectra (Fig. 8). The large induced CD in the Soret band region was ascribed to immobilization of the saccharide and pyridine group on the top of the porphyrin macrocyclic ring.³⁰ Utilization of ternary complex formation allows fine-tuning of the boronic acid – boronic acid distance and geometry, important factors for the design of an artificial host for selective binding of specific saccharides.

Zinc porphyrin **12**, with *ortho*-boronic acid on the 5-phenyl group, was shown to bind D-glucose-6-phosphate (G-6-P) through a two-point interaction, i.e., one between the phosphate and zinc and the other between the glucose C1,C2-diol moiety and boronic acid. However, in α -D-glucose-1-phosphate (G-1-P), the distance between the

phosphate and the C4,C6-diol is relatively short. Thus, the phosphate group in G-1-P cannot coordinate with zinc when C4,C6-diol are bound to the boronic acid. The large difference in CD of the mixture of **12** and G-6-P or G-1-P (Fig. 9) allows facile discrimination of these two biologically important glucose derivatives.^{47,48}

Interaction between porphyrin and chiral carboxylic acids. When porphyrins are fully substituted, they become nonplanar due to steric repulsion between neighboring substituents. Aida and coworkers⁴⁹ reported that octaalkyltetraarylporphyrins such as **13** tend to adopt a saddle conformation with the pyrrole nitrogen groups alternately pointing up and down. The saddle-shaped porphyrin **13** with two different aryl groups in the opposite *meso*-positions hence should exist in chiral forms, although they cannot be resolved due to facile saddle-to-saddle macrocyclic inversion. When treated with a chiral acid, all pyrrole nitrogen atoms of porphyrin **13** become fully protonated. The fully protonated porphyrin **13** is capable of forming 1:2 complexes with enantiomerically pure mandelate

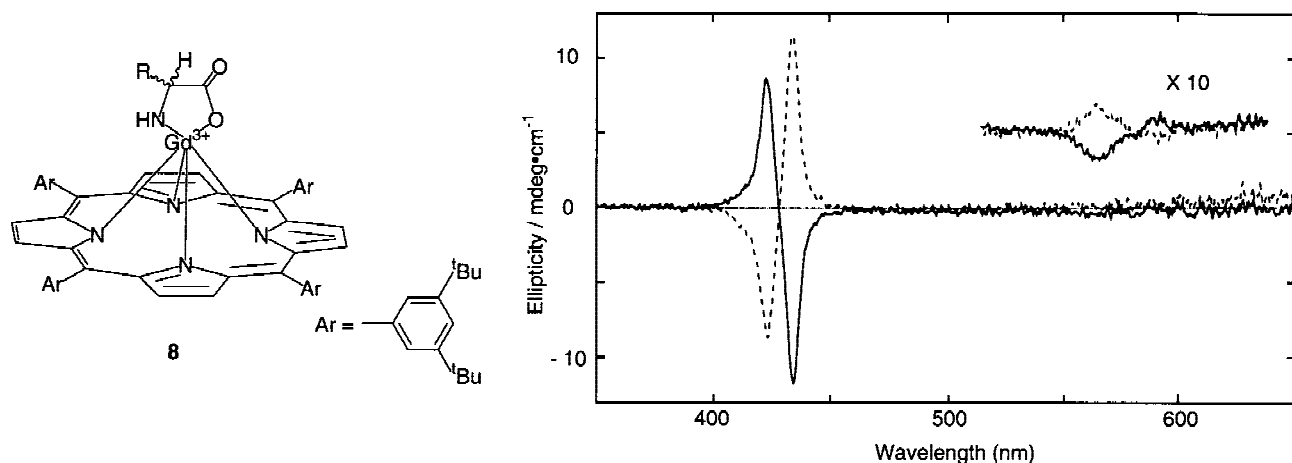


Fig. 6. CD and proposed structure of gadolinium(III) porphyrin **8** complex formed after shaking a solution of porphyrin **8** in CH_2Cl_2 (80 mL, 1.3×10^{-5} M) with an aqueous solution (3.8 mL, 2.7×10^{-4} M) of L-phenylalanine (solid line) and D-phenylalanine (dashed line). (Reproduced from Ref. 43 with permission of Elsevier Science.)

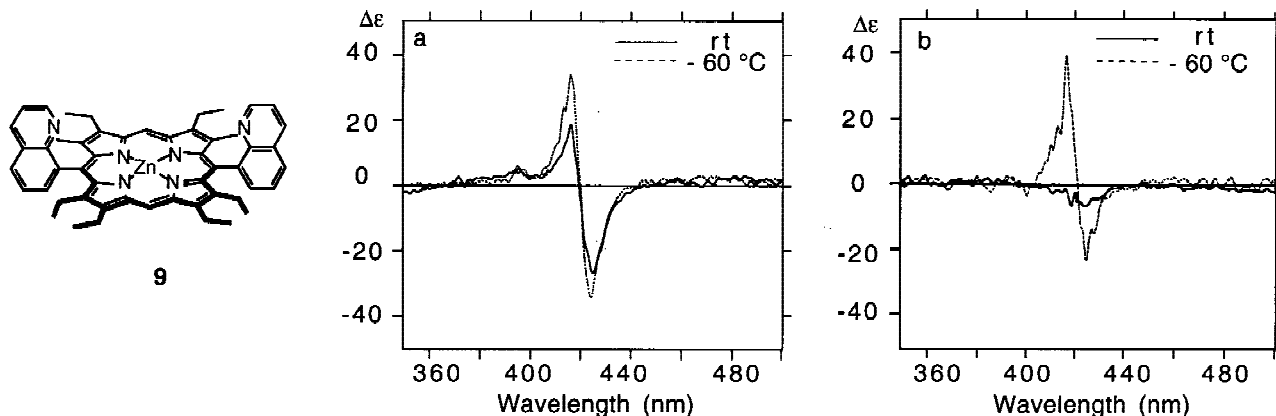


Fig. 7. Structure of a quinoline-bearing zinc porphyrin host **9**. a: CD of the host **9**/ α -Man complex. b: CD of the host **9**/ α -Glc complex at variable temperatures. (Reproduced from Ref. 28 with permission of the American Chemical Society.)

through the ditopic hydrogen bonding of the protonated pyrrole nitrogens with negative-charged carboxylates. A strong bisignate CD in the Soret band region was observed with the sign determined by the mandelic acid configuration (Fig. 10). The enantiomers of other chiral acids such as 2-methylbutanoic acid, 2-hydroxypropanoic acid, camphanic acid, *N*-(benzyloxycarbonyl)-alanine, and 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, can also be distinguished by CD of the complexes formed with porphyrin host **13**. Interestingly, host **13** not only reflects the chirality of the acid, but also memorizes the guest configuration. Namely, the CD of the **13**/*S*-mandelate complex was retained even after (*S*)-mandelic acid was replaced with acetic acid, presumably due to the increased barrier of macrocyclic inversion for the fully protonated porphyrin **13**.

CD of Intrinsically Chiral Monoporphyrins

Porphyrins can become intrinsically chiral due to the presence of chiral substituent groups, restricted rotation leading to atropisomerism,⁵⁰ asymmetric disposition of a

strap,²⁷ or methylation of the inner nitrogen.^{51–53} Chiral porphyrins can be utilized in enantioselective recognition of chiral guests²⁷ and asymmetric catalysis.^{2–4,6} In some cases CD has been the primary tool used for enantiomeric differentiation of chiral porphyrin hosts. Strapped chiral *N*-methylated zinc porphyrin **14** was synthesized and resolved by HPLC by Inoue and coworkers²⁷ to achieve enantioselective binding of amino acids. The antipodes of **14** showed large mirror image CD in the Soret band region arising from perturbation by the strap (Fig. 11). Employment of resolved **14** as a chiral receptor led to high enantioselectivity (up to 23:1) in the binding of carboxylate anions of enantiomeric amino acids with protected nitrogen groups. However, the CD profile of the complexes formed between receptor **14** and enantiomerically pure amino acids turned out to be almost identical to the CD of the uncomplexed receptor **14**, indicating that CD of the complexes is largely determined by the stereochemistry of the chiral host. Hydrogen bonding interaction between the receptor and substrates was shown to be crucial for host/guest recognition by IR and NMR studies.

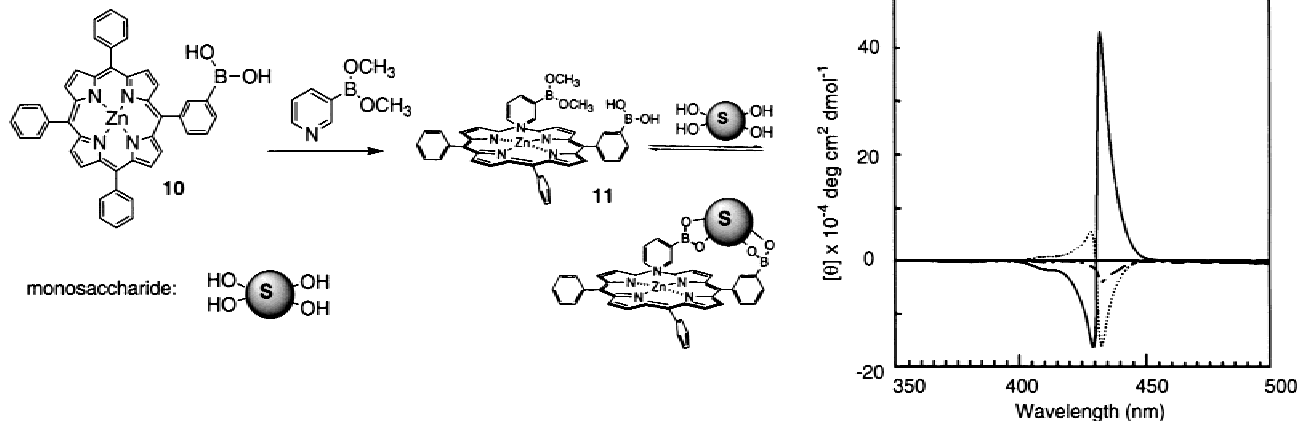


Fig. 8. Structure of the boronic acid appended zinc porphyrin **10** and CD spectra obtained after extraction of solid *D*-fucose (solid line), *D*-arabinose (dotted line), and *D*-threitol (dashed line) into a solution of **10** ($7.4 \times 10^{-6} \text{ M}^{-1}$) and 3-pyridyl-dimethyl-boronate ($2.1 \times 10^{-3} \text{ M}^{-1}$) in CH_2Cl_2 . (Reproduced from Ref. 30 with permission of the Chemical Society of Japan.)

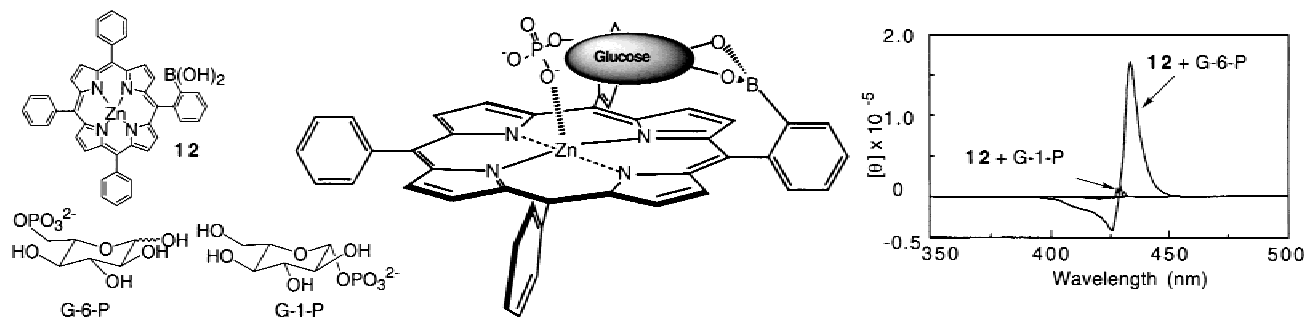


Fig. 9. Structure of boronic acid-bearing zinc porphyrin **12** (2.68×10^{-3} M) in the presence of G-6-P (2.68×10^{-3} M) or G-1-P (2.68×10^{-3} M) in DMSO. (Reproduced from Ref. 48 with permission of Elsevier Science.)

CD OF INTERACTING PORPHYRINS

When two or more chromophores are chirally oriented and close to one another in space, their excited states couple and become nondegenerate, a situation known as exciton coupling. This coupling of excited states gives rise to a characteristic intense bisignate CD (CD couplet). The intensity of this couplet is dependent on the UV ϵ value and the distance between interacting chromophores, while the sign is dictated by the projection angle between the effective electric transition moments. If the chiral twist between the transition moments is clockwise or "positive," the first CE at longer wavelength is positive and the second CE at shorter wavelength is negative. Such coupled CD is defined as a positive couplet, and vice versa.^{54,55} The measurement of the exciton couplet represents a sensitive microscale approach for determining the absolute sense of twist between electric transition moments of interacting chromophores and allows for nonempirical assignments of absolute configurations, provided there is no conformational ambiguity. The configurational analysis based on CD exciton coupling, known also as the exciton chirality method, has been applied to absolute configurational assignments of a wide variety of compounds, including polyols,⁵⁶ carbohydrates,^{57,58} quinuclidine,⁵⁹ hydroxy acids,^{60–62} etc.^{54,55} In the following section we discuss the utility of porphyrin exciton coupled CD for absolute configurational assignments as well as for studying the geometry of chiral porphyrin assemblies.

Utility of Porphyrins in Absolute Configurational Assignment

Effective electric transition moments of porphyrins and zinc porphyrins. Since the direction of the chromophoric electric transition moment is crucial in the exciton chirality CD method, this should be established first before applying the chromophore for CD analysis. The UV-visible bands (B band and Q bands) of porphyrins are ascribed to the in-plane π - π^* transitions, which can be rationalized by the four-orbital model, i.e., the spectra are related to the properties of the two highest occupied and two lowest unoccupied π orbitals.^{63–65} Because of the higher intensity of the Soret band compared to the Q bands, the former is usually used in CD studies. The Soret band consists of two perpendicularly polarized transitions, B_x and B_y (Fig. 12), with the electric transition moment B_x in the NH-NH direction and B_y in the N-N direction. In the free-base form of porphyrins, due to their lower D_{2h} symmetry, these transitions are not exactly degenerate. However, there is no sizable splitting or intensity difference observed experimentally in the two components of the Soret band. The near degeneracy and approximate equivalence of B_x and B_y enables one to use linear combinations such as B_x' and B_y' to represent the two transition moments of the porphyrins (Fig. 12). Recently, we carried out systematic studies on 5-(4-carboxyphenyl)-10,15,20-triphenyl porphyrin **15** as a CD chromophore.^{66,67} Although there appears to be no strict theoretical data regarding the direction of polariza-

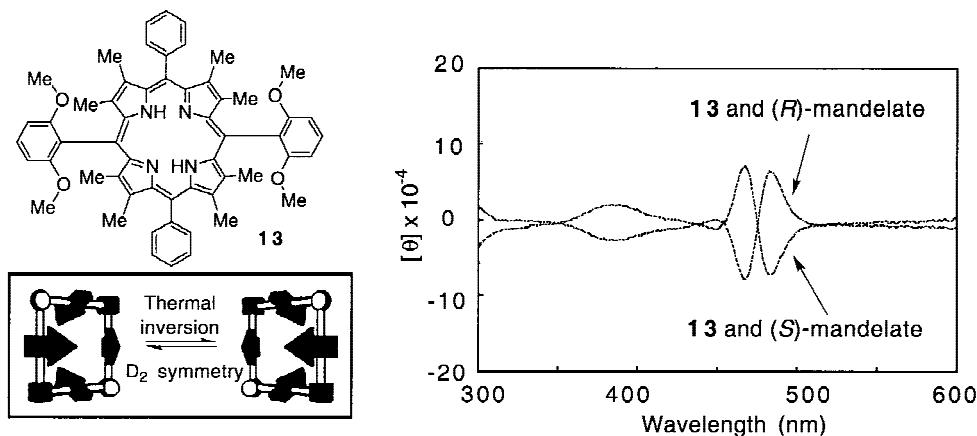


Fig. 10. Structure of porphyrin **13** and CD spectra of the diastereomeric mandelate/**13** complexes in dichloroethane. (Reproduced from Ref. 49 with permission of the American Chemical Society.)

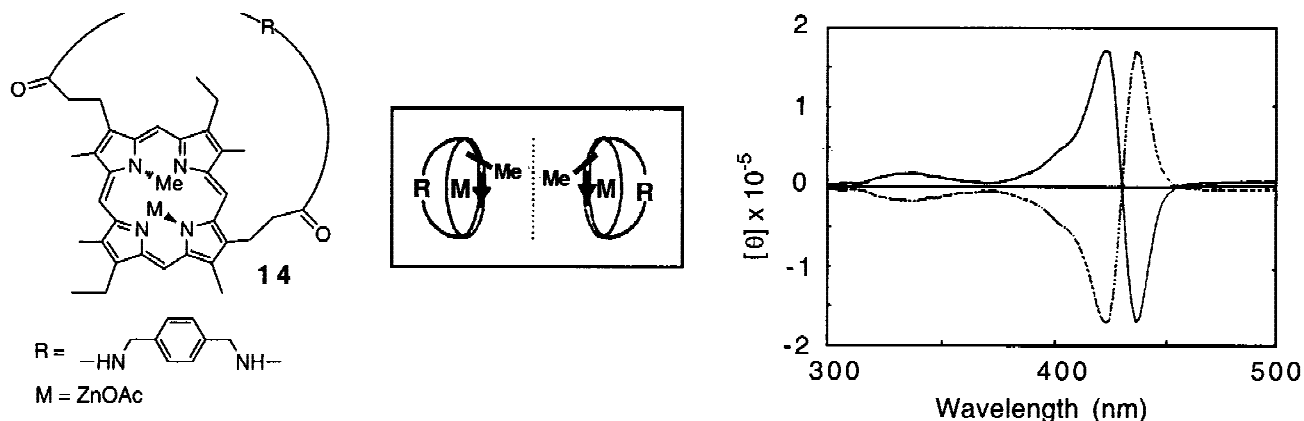


Fig. 11. Structure and CD of the enantiomeric chiral porphyrin hosts **14** in CHCl_3 (40 μM). (Reproduced from Ref. 27 with permission of the American Chemical Society.)

tion of the Soret band in **15**, the direction of the effective transition moment of **15** was assigned experimentally as follows. A comparison of the CD of a series of bisporphyrin derivatives with those of the corresponding bis(dimethylaminobenzoate) (dmaBz) esters revealed that in all cases the bis dmaBz and bisporphyrin derivatives exhibited exciton coupled CD of the same sign (examples are shown in Fig. 13 **16b/16e**, **17b/17e**, **19b/19c**).^{66–68} It is well established that the effective electric transition moment of dimethylaminobenzoate runs along the longitudinal C4/C1 axis of the benzene ring.^{54,55} In light of this evidence, the effective electric transition moment of **15** was assigned to be in the direction of C5/C15 (B_x') of the porphyrin ring, as shown in Figure 12.^{66,67}

In symmetrically substituted metalloporphyrins with D_{4h} symmetry, such as zinc porphyrins, the B_x and B_y transitions are degenerate and have almost identical intensities. It was found that the exciton coupled CD spectra of bis (zinc porphyrin) derivatives showed identical signs with those of the corresponding bis (free base porphyrin) compounds (Fig. 13, **16b/16c**, **17b/17c**).⁶⁹ For this reason, the effective electric transition moment of the 5-(4-carboxyphenyl)-10,15,20-triphenyl zinc porphyrin was also assigned to be in the C5/C15 direction, as in the case of

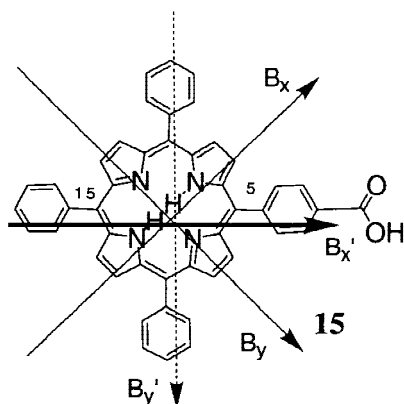


Fig. 12. The directions of B_x , B_y of Soret band and the effective transition moment B_x' (in bold) of porphyrin acid **15**.

free base porphyrin **15** (Fig. 12). Moreover, addition of methanol or amines to the porphyrin derivatives does not change the sign of the exciton CD couplets (Fig. 13, **16b/16d**, **17b/17d**, **18b/18c**).⁷⁰ It follows that the effective transition moments of the zinc porphyrins bearing alcoholic or amino axial ligands are along the C5/C15 axis as well.

Sensitivity enhancement of CD with tetraarylporphyrins. The strong absorbance of porphyrins (ϵ ~440,000 and 550,000 for 5-(4-methylcarboxy-phenyl)-10,15,20-triphenylporphyrin and its corresponding zinc analog, respectively) greatly enhances the CD sensitivity.^{9,71} Namely, there is a 10-fold amplitude enhancement over dmaBz, one of the most commonly used chromophores (Fig. 13, **16b/16e**, **17b/17e**). Thus, the tetraarylporphyrins readily allow reliable CD measurements at the low-micromolar level (Fig. 14a), a huge advantage when only a very limited sample amount is available. We recently demonstrated that the sensitivity of CD can further be enhanced by about 100-fold in fluorescence-detected CD (FD CD).⁷² This observation was confirmed with strong absorbing zinc porphyrins. The amplitude of the FD CD of bis (zinc porphyrin) steroid derivative **16c** was similar to that of the CD at a relatively high concentration ($c = 1.0 \times 10^{-6}$ M) (Fig. 14a). However, at lower concentrations the sensitivity of FD CD, despite the relative low quantum yield of the zinc porphyrin (~0.12), was higher; a solution of **16c** gave an FD CD with satisfactory signal/noise ratio even at $c = 10^{-10}$ M (Fig. 14b), i.e., a 100-fold sensitivity enhancement over conventional CD (Fig. 14c).

Porphyrins exhibited exciton coupling over large distances when placed at terminal 17,17'-positions of dimeric steroids connected at 3,3' (**19b**), or in the brevetoxin B (BTX-B) derivative (**20b**) shown in Figure 13. The interchromophoric distance in BTX-B is 50 Å; this is believed to be the largest interchromophoric distance where exciton-coupled CD has been observed. Calculations by Woody⁷³ using polarizability theory predicted the possibility of porphyrin/porphyrin interactions in mammalian hemoglobin and myoglobin when the hemes are separated by 25–40 Å. These results indicate that the porphyrins are promising

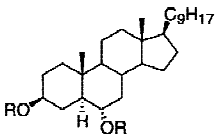
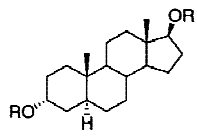
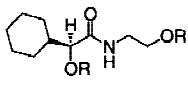
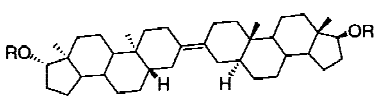
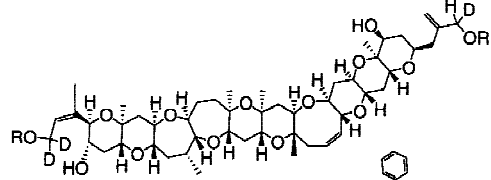
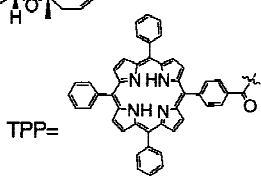
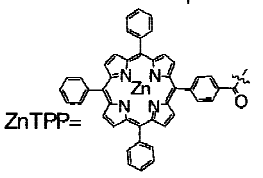
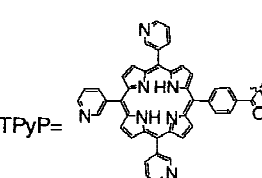
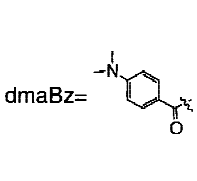
Compounds	Solvents	1st λ ($\Delta\epsilon$)	2nd λ ($\Delta\epsilon$)	A	
	16a: R = H	CH ₂ Cl ₂	----	----	
	16b: R = TPP	CH ₂ Cl ₂	422 (+342)	414 (-226)	+568
	16c: R = ZnTPP	CH ₂ Cl ₂	425 (+523)	415 (-426)	+949
	16d: R = ZnTPP	CH ₃ OH	426 (+495)	418 (-419)	+914
	16e: R = dmaBz	20% dioxane /EtOH	319 (+59)	294 (-30)	+89
	17a: R = H	CH ₂ Cl ₂	----	----	
	17b: R = TPP	CH ₂ Cl ₂	423 (+122)	414 (-71)	+193
	17c: R = ZnTPP	CH ₂ Cl ₂	424 (+153)	416 (-117)	+271
	17d: R = ZnTPP	CH ₃ OH	426 (+172)	418 (-130)	+302
	17e: R = dmaBz	20% dioxane /EtOH	316 (+17)	289 (-4)	+21
	18a: R = H		----	----	
	18b: R = TPP	CH ₂ Cl ₂	422 (+82)	414 (-56)	+138
	18c: R = ZnTPP	1% <i>i</i> PrNH ₂ /CH ₂ Cl ₂	434 (+86)	424 (-71)	+157
	19a: R = H		----	----	
	19b: R = TPP	CH ₂ Cl ₂	423 (+23)	414 (-9)	+32
	19c: R = dmaBz	CH ₂ Cl ₂	311 (+2)	----	----
	20a: R = H		----	----	
	20b: R = TPyP	H ₂ O pH = 4	425 (-16)	403 (+5)	- 21
					
					
					
					

Fig. 13. Comparison between the CD of porphyrin and dmaBz chromophoric derivatives. The CD amplitude or A-value denotes the difference in $\Delta\epsilon$ values between the CD extrema (CEs) of the split CD. The sign of the A-value is represented by the sign of the CE at longer wavelengths.

chromophores for extending the exciton chirality CD method to unexplored areas such as conformational analyses of large molecules and biopolymers. However, in compounds with a short distance between the chromophore attachment sites (<2 Å), precautions are needed since the bulky porphyrin chromophores may lead to significant conformational changes. For example, in the case of *trans*-(1*R*, 2*R*)-cyclohexanediol bisporphyrin, the lowest-energy conformation obtained by conformational search has the two porphyrins in diaxial orientations. The observed temperature dependence in ¹H NMR corroborated this conclusion.⁶⁷

Absolute configurational assignment of single stereogenic center with two attachment sites: stereoselective intramolecular porphyrin π - π stacking. The determination of absolute configurations of rigid molecules with fixed conformations by the exciton chirality CD method is straightforward and unambiguous. However, when applying this method to flexible acyclic compounds, accurate conformational analysis is often indispensable.^{56,59,74,75} One useful approach for the absolute configurational analysis of acyclic compounds is to restrict the conformational

flexibility in a stereocontrolled manner. This has been demonstrated by utilizing the π - π stacking properties of porphyrins^{76,77} to determine the absolute configurations of compounds containing a single stereogenic center *CX-YSL, where X is -OH or -NH₂, Y is an acyclic chain with terminal -OH or -NH₂, and S (small) and L (large) represent two sterically distinct groups.^{70,78} In L-lysine bisporphyrin **21** (Fig. 15), the two amino groups of X (NH₂) and Y (CH₂CH₂CH₂CH₂NH₂) moieties are derivatized by 5-(carboxyphenyl)-10,15,20-triphenylporphyrin **15**. It is known that porphyrins tend to undergo π - π stacking in which stable porphyrin dimers are observed in solution and in crystal structures.^{76,77,79,80} Porphyrins dimerize with a lateral shift of about 1–8 Å with an overlap between their π -electron rich periphery and electron-deficient “positive holes” in the central cavity.⁷⁶ The flexibility of the hydrocarbon chain in **21** enables the two porphyrins to undergo stereoselective intramolecular π , π -stacking in hexane in a way that the terminal porphyrin preferably approaches the chiral center from the less-hindered side carrying the hydrogen (S group) (**I**, Fig. 15). Thus, in the case of L-lysine the preferred counterclockwise arrangement between the

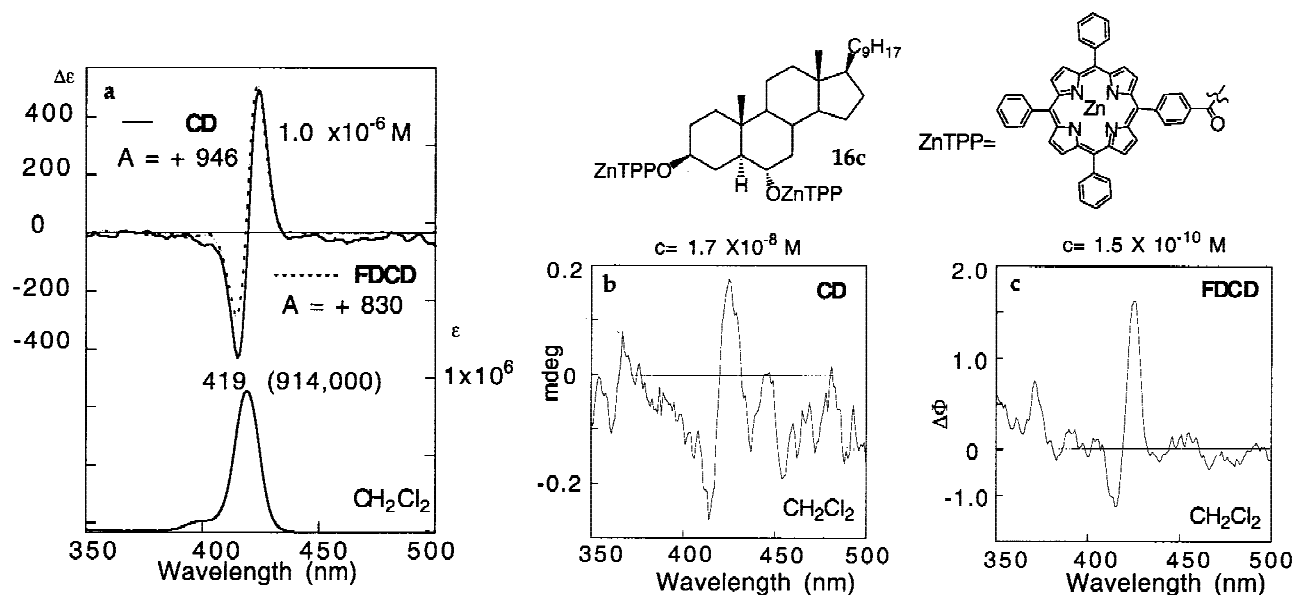


Fig. 14. a: CD and FDCD of bisporphyrin steroid derivative **16c** in CH_2Cl_2 at relative high concentration ($c = 1.0 \times 10^{-6}$ M). b: CD of **16c** in CH_2Cl_2 ($c = 1.5 \times 10^{-8}$ M). c: FDCD of **16c** in CH_2Cl_2 ($c = 1.7 \times 10^{-10}$ M).

effective porphyrin transition moments would give rise to a negative exciton split CD band. The other possibility with the terminal porphyrin stacking from the methoxycarbonyl side (L group) (**II**, Fig. 15) would be sterically less favorable. The predicted negative CD couplet agreed with the experimentally observed negative couplet ($A = -184$ in hexane) (Fig. 15). The presence of intramolecular π, π stacking between the two porphyrins is supported by the split patterns of the ^1H NMR aromatic signals (Fig. 15), the chemical shifts of which do not vary with concentration.^{70,78} This approach has been applied successfully in absolute configurational assignments of amino alcohols, diols, and α -hydroxy acids following a one-step derivatization with ethanolamine.^{70,78}

Nanogram-scale absolute configurational assignment of ceramides. The absolute configuration of amphiphilic ceramides carrying a 1,3-diol moiety can be determined by intramolecular porphyrin π - π stacking of their bis (zinc porphyrin) derivatives. Absolute configurational assignments of ceramides, biologically important sphingolipid metabolites,⁸¹ present a challenging stereochemical problem because of the acylated amino group at stereogenic center C-2 and the flexible acyclic 1,3-diol moiety. Their limited availability has further hindered configurational analysis. However, the assignment has recently been achieved at the nanogram scale by CD analysis of zinc porphyrin ceramides without hydrolysis of the amide function. This approach is exemplified with *D*-erythro-C18-bisZnTPP-ceramide **22** and *L*-threo-C18-bisZnTPP-ceramide **23** in Figure 16.⁹

Absolute configuration at C-3. The *D*-ceramide derivative **22** with 3*R* configuration yields a negative CD couplet, while *L*-ceramide derivative **23** with 3*S* configuration exhibits a positive CD couplet. The correlation between the sign of the CD couplet and the C-3 stereochemistry can be

accounted for by the stereoselective intramolecular π, π stacking of the two zinc porphyrins.^{78,79}

Erythro/threo stereochemistry at C-2/C-3. The CD amplitude of *erythro* derivatives **22** is two-fold that of *threo* derivative **23**. The *erythro/threo* differentiation can be further supported by addition of various acyclic α, ω -diamines, $\text{H}_2\text{N}(\text{CH}_2)_n\text{NH}_2$ ($n = 2$ –12) which form 1:1 intramolecular macrocyclic complexes with bis (zinc porphyrin) ceramides **22** and **23**. In this case, the through space interactions between the two intramolecularly bridged Zn-porphyrins, instead of the original π, π stacking, lead to changes in intensities and signs of the CD couplets.⁹ Of the various diamines tested, 1,3-diaminopropane had the most pronounced effects on CD. While the signs of CD couplets of *erythro* derivative **22** do not change, the CD amplitude is greatly reduced (Fig. 16a). In contrast, in the case of *threo* derivatives, addition of the 1,3-diaminopropane induces sign inversion and doubling of CD amplitude (Fig. 16b). Although their nature remains to be clarified, the unexpected diamine-induced changes^{82–84} in the intensity and sign of exciton coupled CD should be of great practical utility for nanogram-scale stereochemical analyses of ceramides isolated from cell lines and tissues.

Zinc porphyrin tweezers in host/guest complexation: absolute configurational assignment of single stereogenic centers with two sites of attachment without porphyrin derivatization. As mentioned above, porphyrins can be employed for absolute configurational assignments by the exciton chirality method after derivatization of the compound with 5-(carboxyphenyl)-10,15,20-triphenylporphyrin **15**. However, since the reported yield for preparation of the porphyrin acid **15** is quite low, $\sim 8\%$,⁶⁷ it would be highly desirable if the absolute configuration could be assigned without attaching porphyrin chromophores to the chiral compounds of interest. One possibility to achieve

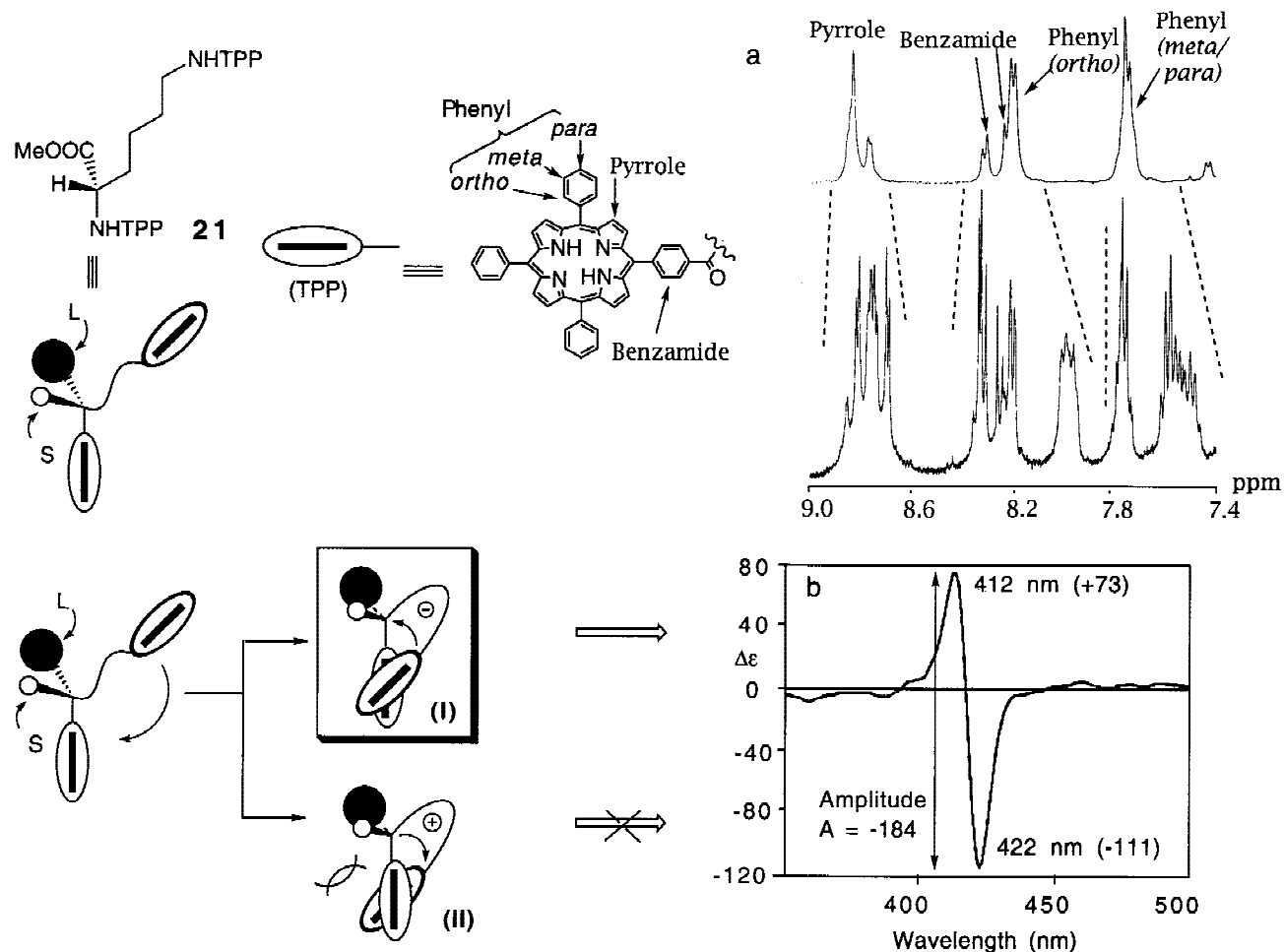


Fig. 15. Bisporphyrin L-lysine derivative **21** in sterically favored (I) and unfavorable (II) intramolecular π - π -stacked conformations. **a:** The aromatic signals of the ^1H NMR of **21** in CDCl_3 (lower spectrum) are split compared to those of the monoporphyrin L-lysine derivative, indicating the presence of intramolecular π - π stacking. **b:** The CD spectrum of **21** in hexane. The observed negative CD couplet agrees with the energetically favored conformation I of **21**.

this is to utilize the complexation of chiral guests to achiral porphyrin hosts, which can be recovered after spectroscopic measurements. This approach is based on the idea that the chirality of the guest will be reflected by the CD of the host/guest complexes, in which the two porphyrins, depending on the host configuration, will preferably adopt a specific twist that is sterically more favored.

The zinc porphyrin host **24**, a pentanediol-linked bis zinc porphyrin molecule or "porphyrin tweezer," is capable of binding various chiral acyclic α,ω -diamines to form 1:1 macrocyclic host/guest complexes.⁸⁵ Binding of the α,ω -diamine to porphyrin tweezer **24** leads to a unique twisted arrangement of the effective electric transition moments of the two zinc porphyrins to yield a coupled CD. The absolute sense of this twist can be correlated with the sign of the CD and hence with the configuration of the diamine as follows (Fig. 17). When (*R*)-1,2-diaminopropane **25** and porphyrin tweezer **24** form a complex, the substrate is sandwiched between the two porphyrin planes P-1 and P-2. This would lead to either conformer **I** where the larger group (L) projects out and the smaller group (S) is clamped between P-1/P-2, or conformer **II** where the situ-

ation is reversed. For steric reasons, conformer **I** associated with a negative CD couplet should be energetically favored, and this is indeed observed experimentally (Fig. 17), λ_{ext} 435 nm ($\Delta\epsilon$ -93) and 421 nm ($\Delta\epsilon$ +76), *A* -169.

The tweezer approach is a very sensitive method for absolute configurational assignment of α,ω -diamines, requiring only microgram quantities of the guest diamine. It bypasses the need for chromophoric derivatizations of the chiral compound of interest, thus greatly simplifying the overall protocol. This method can also be extended to other classes of compounds containing only one amino group, e.g., amino acids and amino alcohols. In such cases, the carboxyl and hydroxyl groups are derivatized with ethylene diamine and glycine, respectively, to yield diamines.⁸⁵

Zinc porphyrin tweezers in host/guest complexation: absolute configurational assignment of single stereogenic centers with single site of attachment. For compounds containing only one site of attachment, such as monoamines, the exciton chirality method is not directly applicable due to the lack of two sites for connecting the inter-

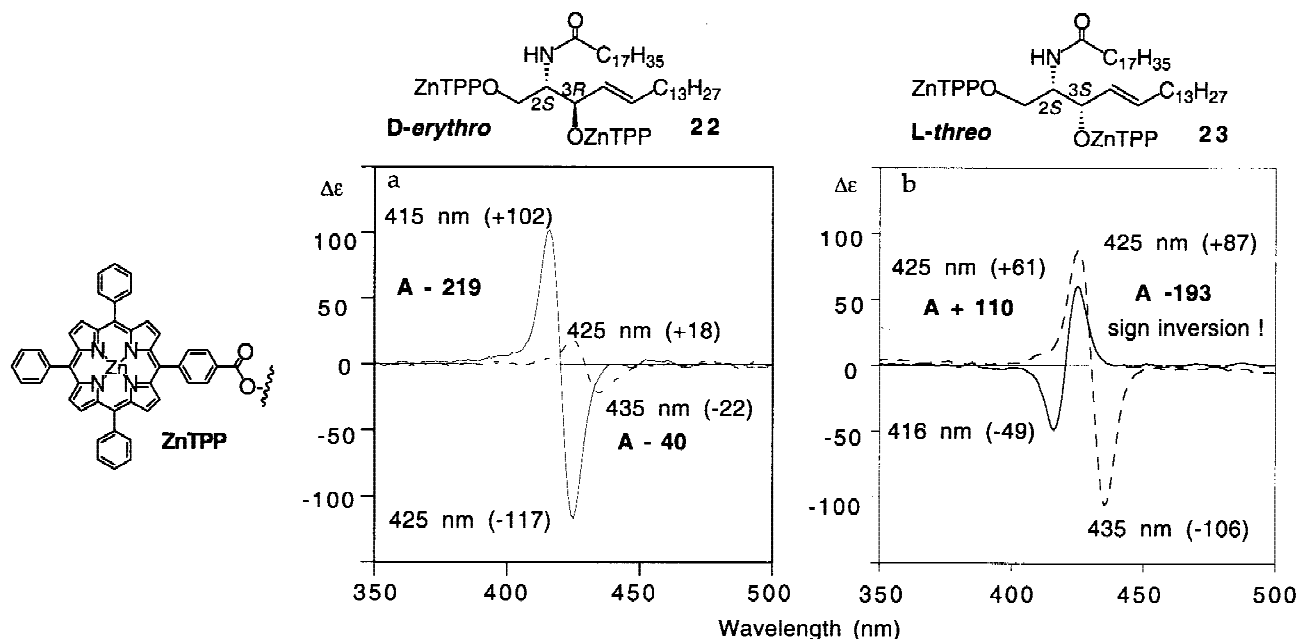


Fig. 16. CD of (a) *D-erythro*- and (b) *L-threo*-ceramide derivatives **22** (1 μM) and **23** (1 μM) (solid line) and in presence of 1,3-diaminopropane (20 μM) (dashed line) in CH_2Cl_2 .

acting chromophores. This has been a drawback of the exciton chirality method. For this class of compounds, the tweezer method is also not directly applicable due to the lack of two coordinating sites for the tweezer. To overcome this problem, an auxiliary bidentate carrier moiety, such as 4-*N*-Boc-aminomethyl 2-pyridine carboxylic acid **26**, has been designed (Fig. 18).⁸⁶ Derivatization of a monoamine

with bidentate carrier **26** generates a chiral carrier/amine conjugate **27** that possesses two coordination sites to bind to the tweezer. Steric and electronic factors operating in conjugate **27** lead to a lowest-energy conformation where the amide carbonyl is coplanar with the pyridine ring, the oxygen of the carbonyl is *anti* to the pyridine nitrogen, and the methine hydrogen at the chiral center is *syn* to the

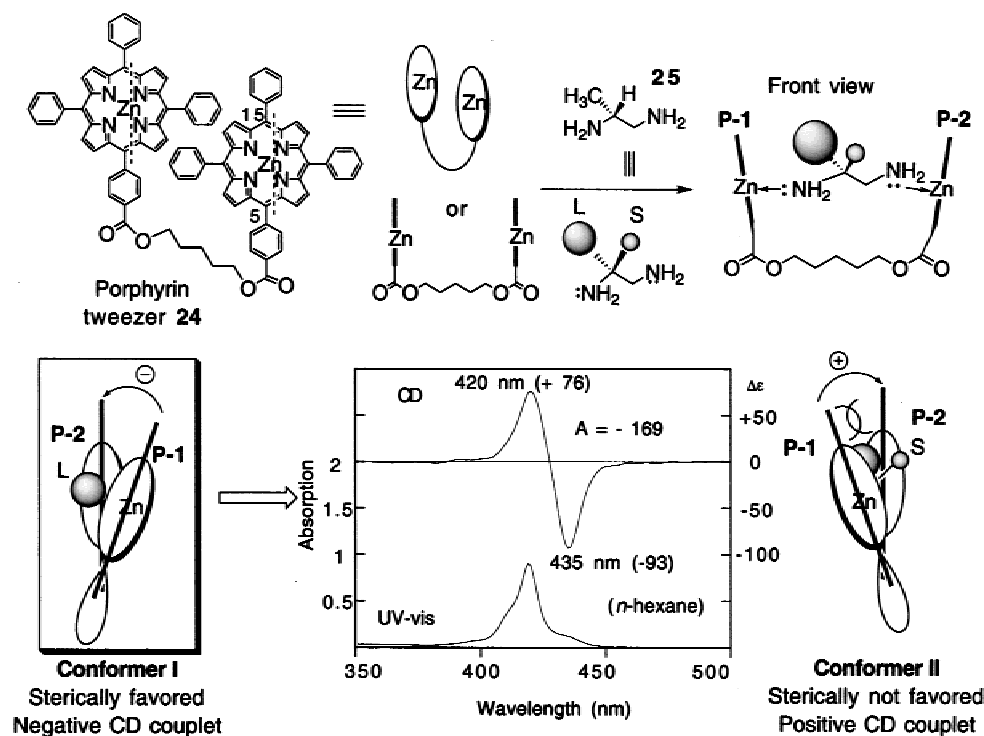


Fig. 17. Adduct formed between porphyrin tweezer **24** and (*R*)-1,2-diamino-propane **25**. The complex of **24** with **25** can adopt two conformations: (I) with the L group projecting out of the sandwich, and (II) with the S group projecting out of the sandwich. The negative sign of the couplet is in agreement with the energetically favored conformer I. The effective transition moment of the zinc porphyrin is in the 5-15 direction, as shown by the dashed line.

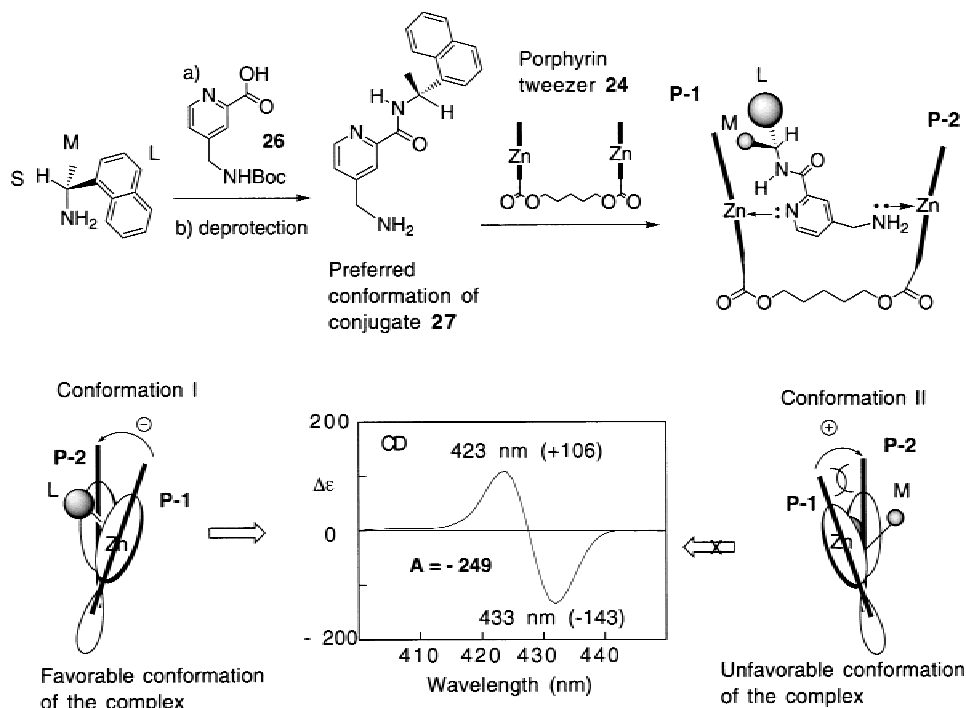


Fig. 18. Conformation and CD spectrum of the complex formed by porphyrin tweezer **24** and conjugate **27** in MCH.

carbonyl oxygen (Fig. 18). Accordingly, the two nonhydrogen substituents (assigned M and L, according to their size) at the chiral center would be oriented on the two opposite sides of the pyridine plane. In the complex formed from (*R*)-1-naphthylethylamine conjugate **27** and porphyrin tweezer **24**, as with (*R*)-1,2-diamino-propane **25** (Fig. 17), the complex with the methyl group clamped between the two porphyrins P-1 and P-2 and the larger naphthyl group pointing outward is sterically favored. This leads to a counterclockwise twist arrangement between the transition moments of the two zinc porphyrins, and hence a negative CD couplet (Fig. 18). This method was shown to be applicable to a wide variety of chiral compounds containing a primary amino group at the chiral center, e.g., aliphatic amines, aromatic amines, amino acid esters, amino sugars, and cyclic amino alcohols.⁸⁶

Porphyrin Assemblies Studied by Intramolecular Exciton-Coupled CD

Synthetic chiral porphyrin assemblies have attracted considerable attention as models for naturally occurring supramolecular arrays of porphyrin derivatives such as the photosynthetic complex (the essential pair), the light-harvesting complex, and cytochrome *c* oxidase. Recent model studies have demonstrated that the distance and orientation between the porphyrins are significant factors in the electron (or energy) transfer efficiencies and in the catalytic activities. The high sensitivity of CD to both distance and orientation between chromophores in chiral porphyrin assemblies makes it an important tool for investigating such supramolecular arrays. Ema et al.⁸⁷ synthesized an optically active porphyrin dimer **28** (Fig. 19). Although the UV-vis spectrum of **28** was almost identical with that of the monoporphyrin, the presence of electronic

interactions between the two porphyrins was clearly evident from the bisignate Soret CD band arising from exciton coupling between the two porphyrins (Fig. 19a). To further adjust the angle and distance between the two porphyrins, chiral cyclophane-linked porphyrin dimer **29a** was prepared.⁸⁴ Conformational analysis showed that in the lowest energy conformation of dimer **29a**, the two

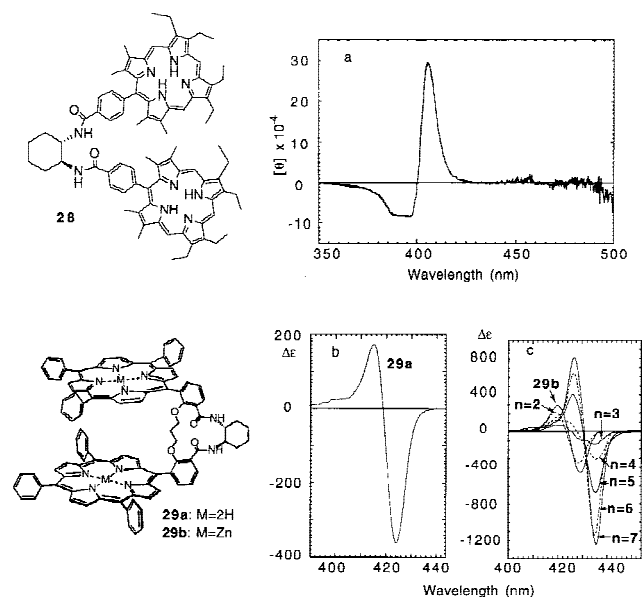


Fig. 19. Structure and (a) CD spectrum of the chiral porphyrin dimer **28** in CHCl_3 . Structure and (b) CD spectrum of the chiral cyclophane-bearing diporphyrin **29a** in CH_2Cl_2 . c: CD spectra of **29b** and in the presence of diamines **30a-f** ($\text{NH}_2(\text{CH}_2)_n\text{NH}_2$, $n = 2-7$) in CH_2Cl_2 . (Reproduced from Refs. 84 and 87 with permission of the Chemical Society of Japan and Elsevier Science.)

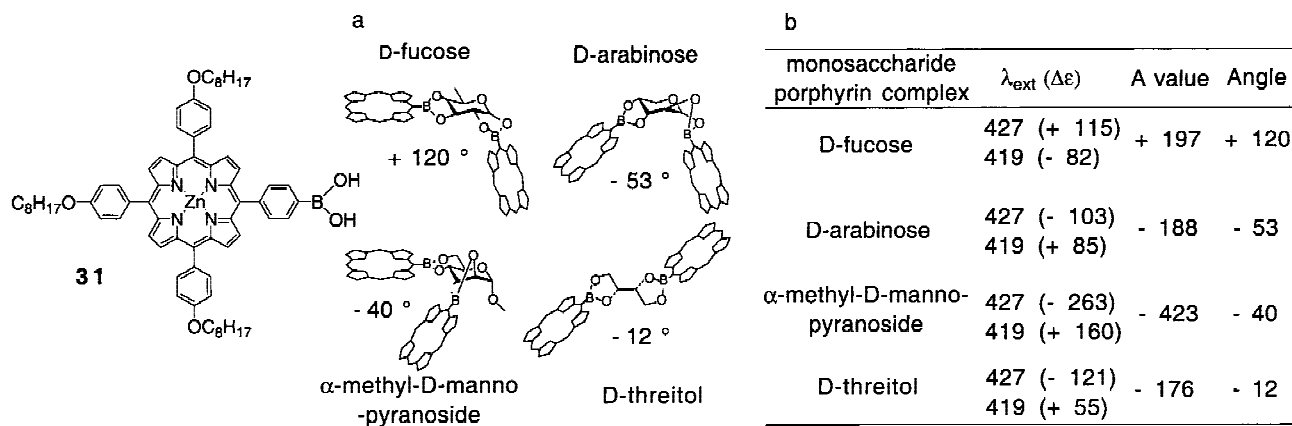


Fig. 20. Correlation between the sign of the exciton coupled CD and the angles between the two porphyrins in the monosaccharide/porphyrin **31** complexes. **a:** The calculated angles between the two porphyrins in the monosaccharide/porphyrin complexes. **b:** CD data of the monosaccharide/porphyrin **31** conjugates. (Reproduced from Ref. 95 with permission of the Royal Society of Chemistry.)

porphyrins adopt a unique offset geometry, which has also been observed in naturally occurring chlorophyll assemblies.^{88,89} The presence of an extra ether linker between the two porphyrins led to greatly enhanced CD signals, presumably due to decreased conformational flexibility (Fig. 19b). The addition of a series of α,ω -diamines ($\text{NH}_2(\text{CH}_2)_n\text{NH}_2$ **30a-f** $n = 2-7$) to the bis (zinc porphyrin) **29b** further fixes the conformation by forming an intramolecular bridge between the two zinc porphyrins through zinc-amine coordination. The CD of complexes **29b/30a-f** all showed bisignate CD with varying intensities in the Soret region, depending on the chain length of the diamine guests (Fig. 19b). These results indicate that both the distance and the orientation between the two porphyrin chromophores are tuned by the cooperative coordination of diamines. This in turn can be useful for the study of photochemical properties of a series of conformationally isomeric bisporphyrins representing specific spatial arrangements. Other similar chiral porphyrin assemblies include 2,5-piperazinedione-bridged porphyrin dimers,⁹⁰ a tartrate-linked bisporphyrin,⁹¹ chiral amino acid-bridged zinc porphyrin dimers,^{82,92} U-shaped and twisted porphyrin trimers,⁹³ and chiral tetraporphyrin macrocycles formed via coordination to Pt(II) and Pd(II) bisphosphine complexes.⁹⁴

A monoboronic acid containing porphyrin **31** has been shown to form 2:1 conjugates with various sugars.⁹⁵ The sign of the exciton-coupled CD can be correlated with the angle between the two porphyrins in the complex depending on the absolute configuration of the monosaccharide (Fig. 20). The structural diversity of sugars allows for interporphyrin angle and distance fine-tuning, which in turn may be useful for investigating the photochemical properties of dimeric porphyrins.

Porphyrin Assemblies Studied by Intermolecular Exciton-Coupled CD

Porphyrin derivatives of brevetoxin. Brevetoxins (BTX), involved in "red tide" as well as fish poisoning, are known to bind to cell membranes and membrane proteins and to interact specifically with neuronal sodium channels.

More recently, studies with ²³Na-NMR have demonstrated that BTX also induces specific sodium ion movements across lipid bilayers through transmembrane BTX self-assemblies.⁹⁶ In order to demonstrate the structure of the transmembrane assemblies of BTX, CD studies utilizing BTX porphyrin analogs **32** and **34** were performed.⁹⁷

The CD of the bisporphyrin BTXs TPP-BTX-TPP **32** and monoporphyrin BTX-TPP **34** in methanol show no distinct Cotton effects above 300 nm, i.e., the porphyrin chromophores are neither coupled intramolecularly nor intermolecularly due to the linear extended conformation and lack of aggregation in nonaqueous solvents. Titration of hydrophobic TPP-BTX-TPP **32** in methanol with water results in an intense conservative (similar intensities of positive/negative CEs) negative couplet, the intensity becoming maximal in 1:1 methanol/water (Fig. 21a), namely, TPP-BTX-TPP self-assembly **33** is formed. The 418 nm isochroic point indicates that self-organization **32** \rightarrow **33** is a single-step reaction. The CD amplitude remained unchanged upon dilution of a 2.0 μM solution of **33** in MeOH/water 3:1 to 0.4 μM , the limit of accurate detectability, i.e., critical micellar concentration (cmc) is <0.4 μM . Similar titration with water of monoporphyrin BTX **34** in methanol yields a different self-assembly **35** (Fig. 21c). Compared to bisporphyrin BTX assembly **33** (Fig. 21a), the bisignate CD of self-assembly **35** (Fig. 21c) is of opposite sign and weaker. The CD of **35**, which could be due to antiparallel dimers of monoporphyrin **34**, increases with addition of water, and levels off after 50% water. Upon dilution of a 2.8 μM solution in 3:1 MeOH/water, the CD amplitudes remain constant down to 1.7 μM , after which it decreases significantly, showing the cmc to be around this concentration.

In order to study the self-assembly structures of BTX porphyrin conjugates **32** and **34** inside lipid bilayers, TPP-BTX-TPP **32** and BTX-TPP **34** were incorporated into vesicles. The vesicles containing **32** also yielded a strong negative CD couplet centered at 421 nm with $A = -78$, similar to the negative CD couplet (419 nm, $A = -157$) exhibited by TPP-BTX-TPP self-assembly **33** in polar solvents (Fig. 21a). It follows that bischromophoric TPP-BTX-TPP **32**

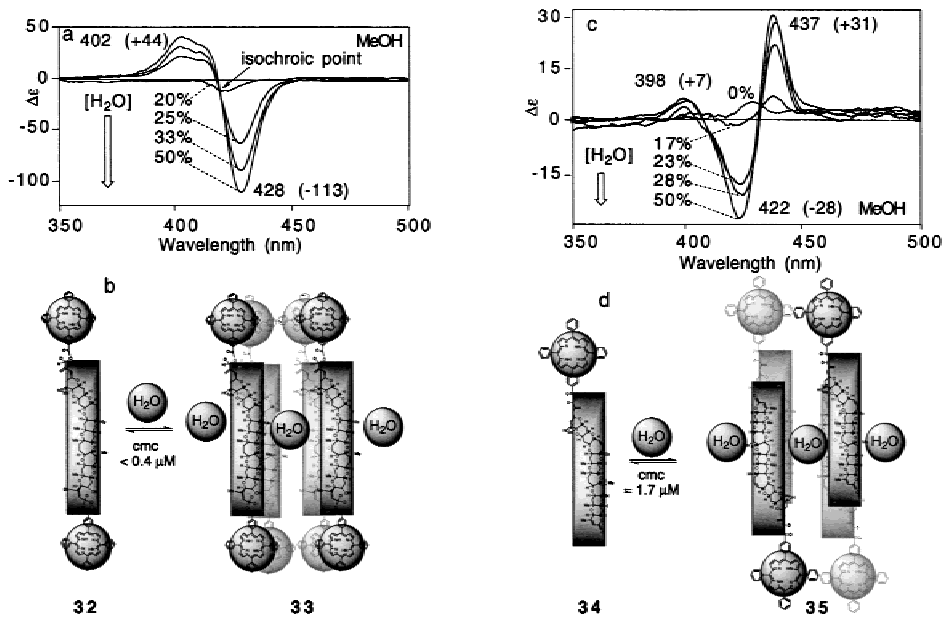


Fig. 21. Self-assemblies of porphyrin-BTX conjugates. **a:** CD spectra change upon titration of a methanolic solution of TPP-BTX-TPP **32** with water. **b:** The self-assembly process showing the proposed cylindrical supramolecule **33** containing six BTX molecules in antiparallel orientation (front two molecules not shown). **c:** Titration of a methanolic solution of BTX-TPP **34** with water. **d:** Model of self-assembly of **34** leading to supramolecule **35**.

self-assembles in lipid bilayers in a manner similar to that in polar solvents (Fig. 21b, structure **33**). In vesicles incorporating BTX-TPP **34**, the porphyrins are randomly immersed in the lipid phase close to the chiral lipid surface, giving rise to a broad negative CD. Upon addition of HCl to the solution, porphyrins in **34** become protonated, as shown by the characteristic red-shifted Soret band (from 418–436 nm). The protonated porphyrins in **34**, which are hydrophilic and do not associate with lipid bilayers, rearrange in space to give rise to a clear bisignate CD couplet similar in sign and shape to that of self-assembly **35** (Fig. 21c), again with red-shifted CEs. Thus, the structure of membrane-bound monochromophoric BTX **34** can also be represented by cyclic self-assembly **35** with antiparallel oriented BTX.

Therefore, the CD studies of BTX-linked porphyrins in aqueous solution and in the presence of vesicles led to the conclusion that the structure of the active BTX-B complex in lipid bilayers is a cyclic, transmembrane supramolecule consisting of antiparallel-aligned BTX molecules. It follows that when the sodium channel opening mechanism of BTXs is discussed, ordered aggregation of BTX also needs to be considered.

Porphyrin derivatives of philanthotoxin. Philanthotoxin (PhTX), a neurotoxin isolated from the venoms of the Egyptian wasp *Philanthus triangulum*, (Fig. 22, structure **36**, right half of dotted line, with a 4-3-3 arrangement of polyamine chain instead of the 3-4-3 shown; the numerals denote the number of methylenes between nitrogen atoms), is an antagonist of the nicotinic acetylcholine and glutamate receptors (nAChR, GluR). Over 150 analogs have been made for studies of 3D structure-activity relations (SAR) of ligand/receptor interactions.⁹⁸

PhTX derivatives with “BIG head” porphyrins were prepared to study the mode of entry of PhTX into the funnel-shaped nAChR, e.g., Figure 22, mode “BIG head-up.” However, in buffer a negative “conservative couplet” appeared around 430 nm, $A = -6.1$, showing that the split CD is due to intermolecular helical stacking **37** with negative chirality. The more soluble Zn complex of the trispyridine porphyrin analog **38** exhibited a bisignate CD, $A = +5.9$, the sign inversion indicating that zinc induced stacking with chirality opposite to that of **37**.⁹⁹ These PhTX porphyrin analogs can be used for studies of interactions between PhTX and nAChR by CD.

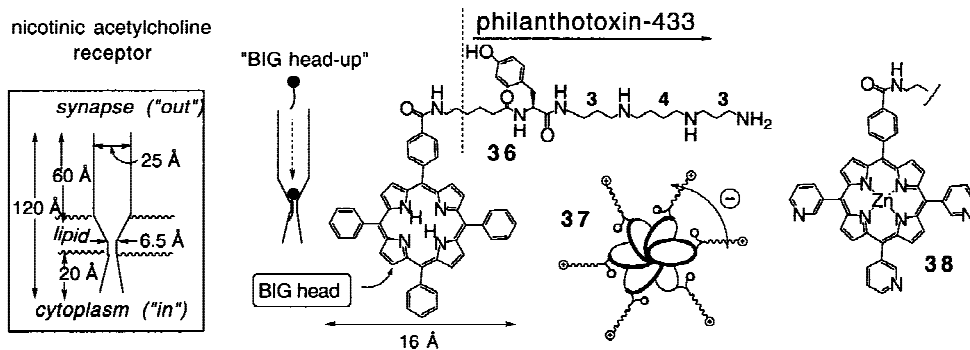


Fig. 22. The nicotinic acetylcholine receptor and porphyrin derivatives of philanthotoxin.

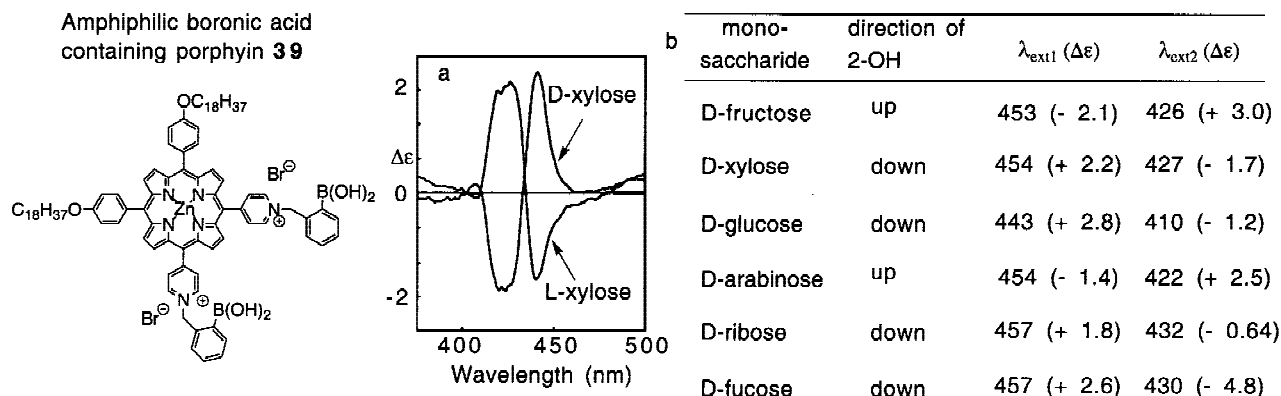


Fig. 23. CD of the amphiphilic boronic acid containing porphyrin **39** complexed with various carbohydrates at pH 10 in 0.10 M carbonate buffer. **a:** Mirror image CD of **39** complexed with D- and L-xylose. **b:** Correlation between the sign of CD and the direction of C2-OH. (Reproduced from Ref. 100 with permission of the Royal Society of Chemistry.)

Porphyrin derivatives of carbohydrates. Boronic-acid-appended porphyrin **39** is capable of forming ordered aggregates in aqueous solution in the presence of carbohydrates.^{31,100} The orientation of the aggregates, as indicated by their CD spectra, is governed by the absolute configuration of the sugar. For example, all aggregates between porphyrin **39**, containing the amphiphilic diboronic acid and sugars with the 2-hydroxyl pointing up relative to the furanose or pyranose ring, exhibit positive CD couplets and vice versa (Fig. 23b). This is a novel method for controlling the aggregate morphology⁷⁶ that can be monitored by CD.

Bisporphyrin Hosts in Recognition of Amino Acid Esters, Diamines, and Monosaccharides

Crossley et al.¹⁰¹ synthesized and resolved^{102,103} bisporphyrin Tröger's base analog **40** that binds strongly with α,ω -diamines. The configurations of the two resolved enantiomers have been assigned from their CD, i.e., (-)-**40** showed a very intense negative exciton couplet in the Soret band region, indicating that the two porphyrins form a left-handed screw (Fig. 24). It was found that the chiral Tröger's base analog (+)-**40** is capable of recognizing L-histidine ester in 86% enantioselectivity. The well-defined

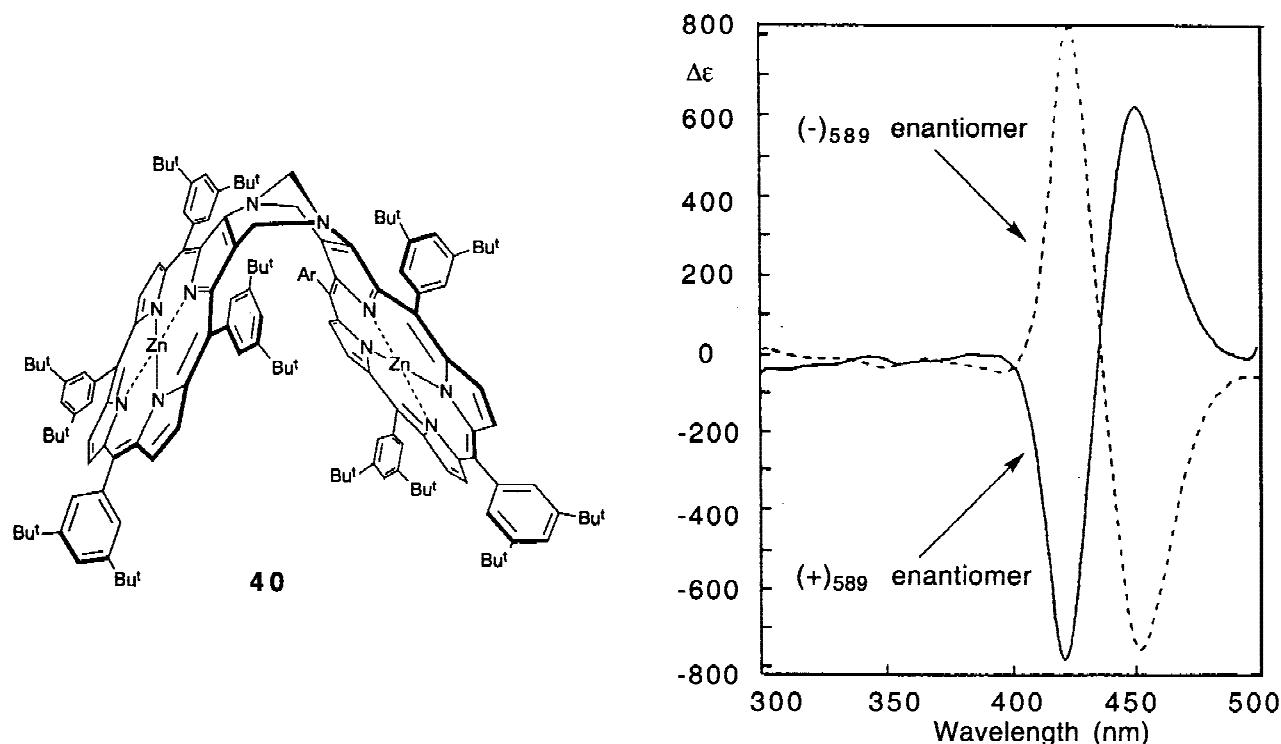


Fig. 24. Structure and CD of the bisporphyrin Tröger's base analog **40**. (Reproduced from Ref. 102 with permission of the Royal Society of Chemistry.)

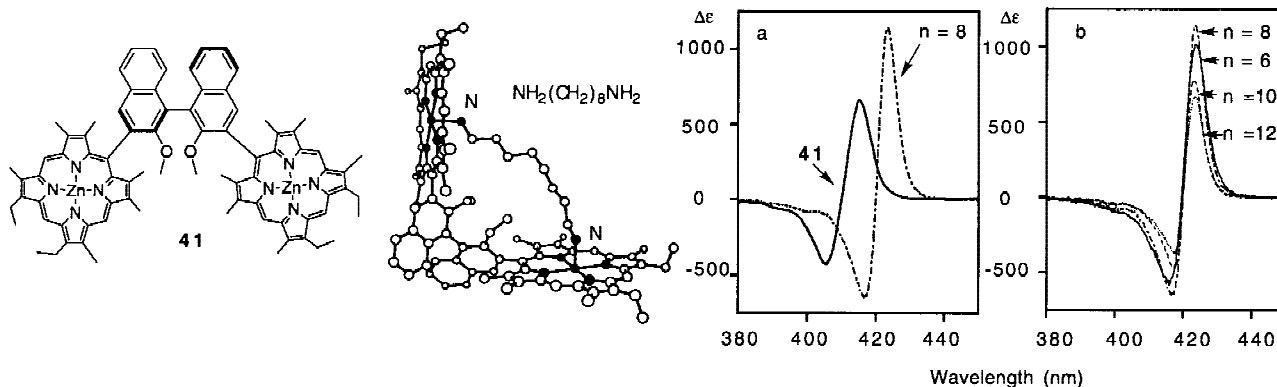


Fig. 25. Structure of chiral porphyrin dimer **41** and the **41**/1,8-diaminooctane complex. **a:** CD of **41** and **41**/1,8-diaminooctane complex. **b:** CD of **41** complexed with α,ω-diamines of various lengths. (Reproduced from Ref. 83 with permission of the Elsevier Science.)

chiral cleft between the two porphyrins in Tröger's base analog **40** is an attractive feature for developing new chiral catalysts.

Ogoshi and coworkers⁸³ prepared the chiral binaphthyl linked zinc porphyrin dimer **41** that exhibited a strong bisignate CD arising from exciton coupling between the two porphyrins (Fig. 25a). The relatively rigid chiral zinc porphyrin dimer **41** showed significantly higher affinity toward long α,ω-diamines H₂N(CH₂)_nNH₂ (n > 5), i.e., $K_a = 9.4 \times 10^5 \text{ M}^{-1}$ (n = 6), $2.1 \times 10^6 \text{ M}^{-1}$ (n = 8) and $5.5 \times 10^5 \text{ M}^{-1}$ (n = 12) as compared to short analogs $K_a = 4.7 \times 10^3 \text{ M}^{-1}$ (n = 2) and $6.6 \times 10^3 \text{ M}^{-1}$ (n = 3). It was found that only diamines with n > 5 could form intramolecular bridges between the two zinc porphyrins through ditopic interaction. The CD spectra exhibited amplitudes clearly dependent on the distance between the two amino groups (Fig. 25b). Thus, CD spectra can reveal subtle structural features such as distance and angles in bisporphyrin **41**/amine complexes.

Porphyrin tweezer **42**, consisting of a bis iron(III) porphyrin linked by a μ,oxo bridge, was found to be highly sensitive and selective as a host for glucose and galactose.²⁹ Although porphyrin host **42** has eight boronic acid

moieties, it only forms 1:1 complexes with the monosaccharides as demonstrated by Job plots. The Soret bands of the two iron(III) porphyrins in tweezer **42** complexes with glucose or galactose gave rise to an intense CD (Fig. 26), which led to the detection of the two monosaccharides even at concentrations around 10⁻⁵ M. The CE signs seemed to be governed by the 4-OH configuration of the saccharides; namely, D-glucose gave a CD similar in shape, but opposite in sign to that of D-galactose. The sole difference between the two sugars is the 4-OH configuration. The large association constants ($K_a = 1.5 \times 10^5 \text{ M}^{-1}$ for glucose and $2.4 \times 10^4 \text{ M}^{-1}$ for galactose) obtained with tweezer **42** are about one to two orders of magnitude greater than those reported previously in water.^{44,45} These results suggest that tweezer **42** could be useful as a sensitive sugar-sensor and a model for designing sugar transporters across cell membranes.

CONCLUDING REMARKS

In recent years, chiroptical spectroscopy, in particular CD, has played an increasingly central role in structural studies. This is due to the better understanding of the role played by stereochemical factors in molecular properties

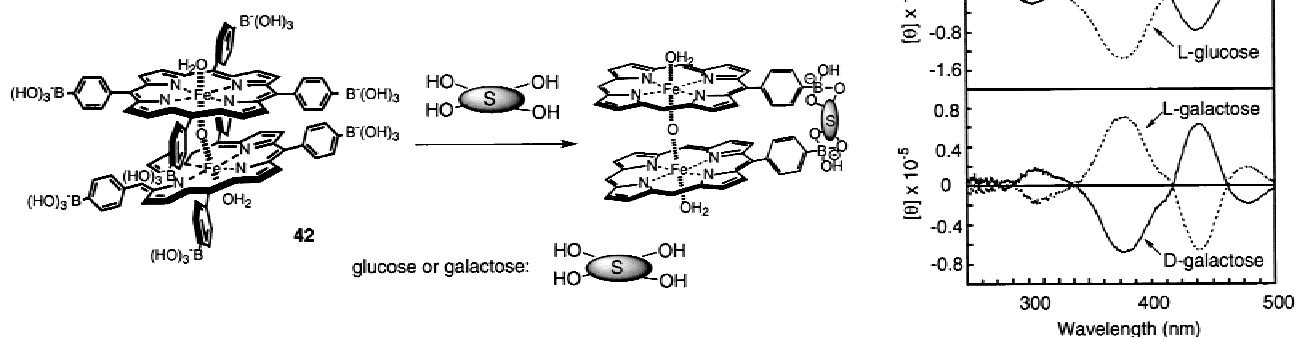


Fig. 26. Structure of sugar tweezer **42** and the CD spectra of tweezer **42** complexed with glucose and galactose. (Reproduced from Ref. 29 with permission of the American Chemical Society.)

and ligand/receptor interactions. Advances in CD are greatly supported by the progress in computational and theoretical studies, as well as by advancements in instrumentation. CD studies of complex molecules incorporating various porphyrins and metalloporphyrins are also seeing rapid progress because of the appealing attributes that make the porphyrin system a unique reporter group for a variety of purposes. Porphyrins have intense red-shifted Soret bands, can complex with metals, and can undergo inter- or intramolecular π - π stacking. All of these properties contribute to make porphyrins highly sensitive CD chromophores. The CD studies described in this review demonstrate the facile introduction and utility of porphyrins and metalloporphyrins as sensitive artificial receptors for recognition of chiral guests such as carbohydrates, amino acids, and their derivatives. The CD of the Soret band of the porphyrin host sensitively reflects the identity of the guests and the binding modes of host/guest complexation. The propensity of porphyrins to undergo π - π stacking and zinc porphyrin coordination with amines enable the exciton chirality CD method to be extended to configurational assignments in more challenging cases, such as compounds that are flexible and those containing only single stereogenic centers. Future studies are necessary to explore the potential of utilizing porphyrins and metalloporphyrins, especially intrinsically chiral porphyrins, as artificial receptors. We hope that the examples presented in this review will stimulate the further application of CD spectroscopy in order to take full advantage of this unique spectroscopic tool in revealing molecular chirality and to extend the use of porphyrins as outstanding CD reporter groups.

ACKNOWLEDGMENTS

The authors thank Drs. S. Matile, B.H. Rickman, and H. Jiang for providing some unpublished results and Dr. C.A. Parish for helpful suggestions during preparation of the manuscript.

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