CHIRALITY 21:374–382 (2009)

Enhancement of Exciton Coupled Circular Dichroism with Sterically Encumbered Bis-Porphyrin Tweezers

MARINA TANASOVA, CHRYSOULA VASILEIOU, OLUWATOYIN O. OLUMOLADE, AND BABAK BORHAN*
Department of Chemistry, Michigan State University, East Lansing, MI

ABSTRACT Porphyrin tweezers have been successfully used as hosts for the absolute stereochemical determination of a variety of chiral compounds. A set of new porphyrin tweezers with substituted aryl groups on the meso position of the porphyrin rings have been synthesized. The modified tweezers are used as hosts for the stereochemical determination of chiral diamines and carrier-derivatized α-chiral carboxylic acids in order to monitor the influence of the various substitutions of the aryl group on the amplitude and sign of the ECCD couplet. *t*-Butyl substitution at the meta positions of the porphyrin's meso phenyl substituents leads to enhanced ECCD amplitudes. *Chirality 21:374–382, 2009.* © 2008 Wiley-Liss, Inc.

KEY WORDS: exciton-coupled circular dichroism; porphyrin tweezers; absolute stereochemical determination; CD amplitude; chiral diamines; chiral carboxylic acids

INTRODUCTION

Exciton-coupled circular dichroism (ECCD)[1,2] has over the years proven to be a reliable tool for the development of nonempirical methods for the absolute stereochemical determination of small organic molecules. Methodology based on ECCD has been successfully applied to a wide variety of compounds including polyols and carbohydrates[3–5], monoamines and monoalcohols,[6,7] diamines and amino acids,[8–11] amino alcohols,[12] hydroxy acids,[13] and vicinal diamines, amino alcohols, and diols.[14] Briefly, the method is based on exciton coupling detected between two or more independently conjugated chromophores oriented in a chiral fashion. The orientation of the chromophores, which is directly governed by the absolute chirality of an asymmetric center, can be detected as either a positive ECCD spectrum arising from the clockwise orientation of the two interacting chromophores, or a negative ECCD spectrum as a result of the counterclockwise orientation of the chromophores. Because the observed sign of the couplet is a direct consequence of the chirality of the substrate, which translates into the helicity of the interacting chromophores, the assignment of chirality is nonempirical.

Chromophores represent a necessary tool for applying the ECCD method and can be introduced through chemical derivatization[3,15–19] or noncovalent binding. The latter mode of binding has been explored through the use of bis-porphyrin "tweezer" systems as a chromophoric host (Fig. 1a).[9,20–22] Incorporation of a metal in the porphyrin core enables the binding of two porphyrins (the host) with a chiral substrate (the guest) that possesses two suitable sites of attachment. This allows for the formation of a porphyrin tweezer—chiral substrate complex (Fig. 1). Complexation leads to a nonequivalent steric environment for the porphyrin closest to the stereocenter. To reduce the steric interactions experienced by the porphyrin closest to the chiral center, the chromophore slides away from the larger group. As depicted in Figure 1b, this leads to a counterclockwise "chiral twist" of the porphyrins relative to each other and is detected as a negative exciton CD couplet. The clockwise orientation of the chromophores in this complex is disfavored due to higher steric interactions between the porphyrin and the larger substituent on the chiral center. Hence, the stereochemistry of the chiral substrate dictates the relative orientation of the porphyrins in the complex through steric interactions between the porphyrin ring and the substituents at the chiral center.

The limitation of the porphyrin tweezer system is the necessity for two coordination sites present within a chiral guest. For molecules with one site of coordination, this limitation is overcome by derivatizing the chiral substrates with small, achiral molecules (carriers) that contain the two necessary sites of attachment. In this manner, the derivatized carrier accomplishes the binding of the chiral guest with the porphyrin tweezer, and if chosen well, should present the chiral center to the porphyrin for steric differentiation. Using this method, the stereochemistry of derivatized chiral monoamines, monoalcohols, and α-chiral carboxlic acids has been determined in a nonempirical fashion according to the sign of the obtained ECCD spectra.[6,7,21,22] An excellent review on the use of CD for absolute stereochemical determination of chiral molecules has

Contract grant sponsor: NSF-CAREER; Contract grant number: CHE-0094131.
*Correspondence to: Babak Borhan, Michigan State University, Department of Chemistry, East Lansing, MI 48824.
E-mail: babak@chemistry.msu.edu
Received for publication 28 December 2007; Accepted 15 April 2008
DOI: 10.1002/chir.20595
Published online 20 June 2008 in Wiley InterScience (www.interscience.wiley.com).

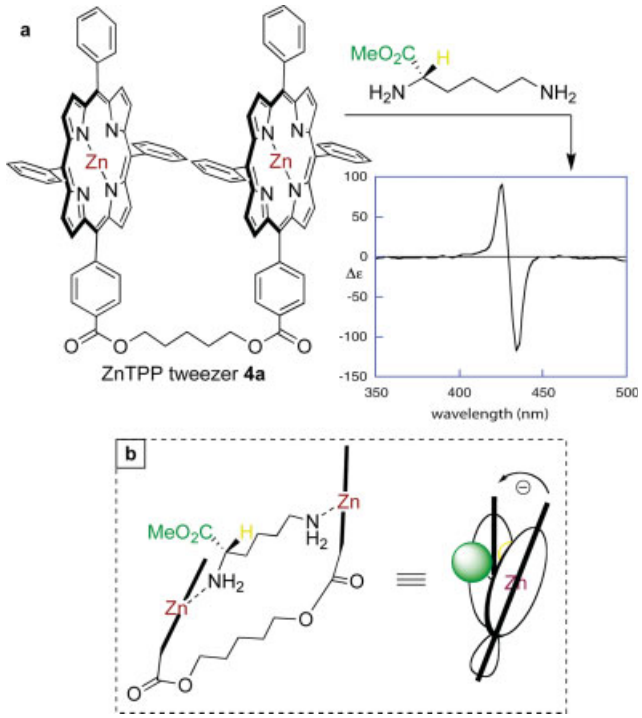


Fig. 1. (**a**) Structure of Zn-TPP tweezer **4a**, which upon binding with (*S*)-lysine methyl ester yields a negative ECCD spectrum; (**b**) proposed binding model of a diamine complexed with **4a** that leads to the observed negative ECCD. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

been recently published and should be consulted for a comprehensive overview.[23]

Previously, we demonstrated the use of ECCD for the determination of the absolute stereochemistry of α-chiral carboxlic acids, where two sites of attachment, provided by 1,4-phenylenediamine (the carrier), allowed complexation of a derviatized chiral carboxylic acid with a host zinc bis-TPP-porphyrin tweezer system (Zn-TPP-tz **4a**).[21] Formation of the complex gave rise to a bisignate CD spectrum, reflecting the relative orientation of the tweezer chromophores, as induced by the absolute stereochemistry of the asymmetric center. A series of ECCD data obtained for various derivatized chiral carboxylic acids allowed us to propose a mnemonic (Fig. 2) that predicts the expected ECCD sign for a given chiral carboxylic acid based on the size of the substituents on the chiral center[21] (it should be noted that Nakanishi and coworkers use a different carrier and thus have arrived at a different mnemonic for derivatized carboxylic acids[22]).

In the course of using Zn-TPP-tz **4a** for the stereodetermination of carrier-derivatized α-chiral carboxylic acids, it was found that the chiral substrates bearing substituents of relatively similar size gave ECCD spectra of low amplitude.[21,22] This result can be explained by the high conformational flexibility of the substrate in the porphyrin tweezer complex due to similar steric interactions between the porphyrin and both substituents at the asymmetric center. Small steric differentiation leads to a small preference of one ECCD active population over the other, and therefore, results in a low amplitude for the spectrum. It is known that, apart from the conformational stability of the chiral substrate, the amplitude of the Cotton effect[2] derives from a combination of factors such as the interchromophoric distances and the dihedral angle of the interacting electric transition dipole moments.[1] The latter observations raise the possibility that additional steric interactions between the substituents of the chiral center and the porphyrin ring in close contact with the chiral center may influence these parameters and improve the amplitudes of the ECCD spectra.

Based on previously published results, increase in the size of the porphyrin surface (tetrabenzoporphyrin was used as the porphyrin monomer to build the tweezer) is not sufficient for the amplification of the ECCD amplitude.[24] Because the crystal structure of zinc tetraphenylporphyrin reveals a perpendicular arrangement of the aromatic rings with respect to the porphyrin plane,[5] it is plausible to assume that the steric differentiation induced in the porphyrin tweezer complexed with a chiral substrate is influenced by the interaction between the phenyl ring on the meso position of the porphyrin ring and the substituents at the asymmetric center. Hence, additional steric interaction introduced by placing substituents on the phenyl ring could lead to greater steric differentiation and thus enhancement of the ECCD amplitudes. Furthermore, additional steric interaction with the asymmetric center can increase the dihedral angle between the chromophores of the tweezer, which can also contribute to increased ECCD amplitude. Finally, we anticipate that increased steric interaction will also confine the conformational flexibility of the chiral guest resulting in a system that can better discriminate between possible ECCD active conformations, which will also serve to enhance the ECCD amplitude. Based on the latter suppositions, we began to investigate the effect of varying the aryl groups at the meso position of the porphyrin rings. In particular, different substituents were introduced at the ortho- and meta positions of the phenyl rings of Zn-TPP-tz **4a**. This article describes the effect of these substitutions on the enhance-

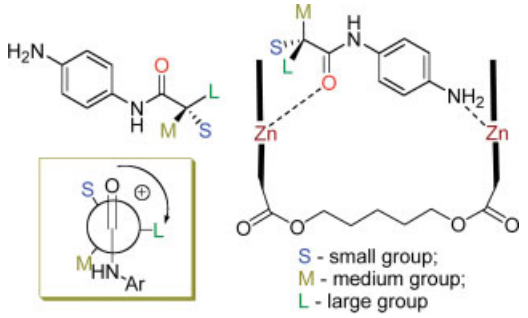
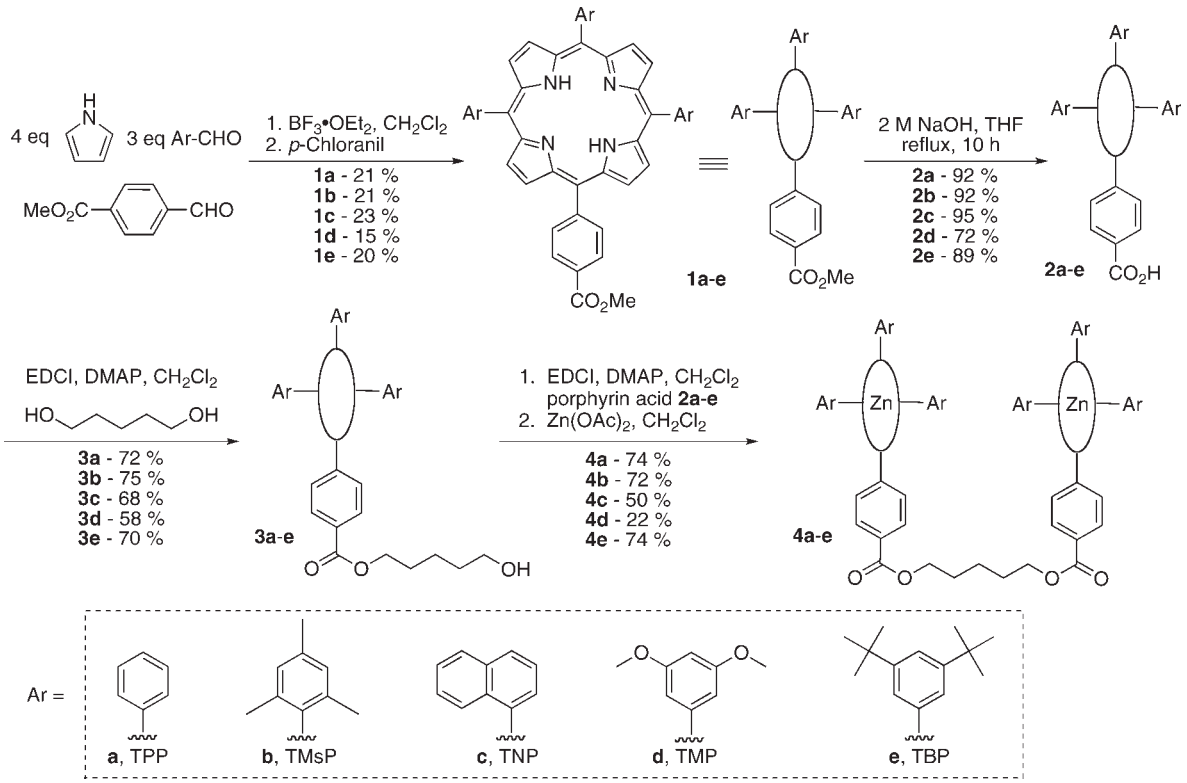


Fig. 2. Stereochemical determination of α-chiral carboxylic acids with 1,4-phenylenediamine as a carrier. Depicted is the postulated binding of the guest with the zinc porphyrin host. The absolute stereochemistry of α-chiral carboxylic acids can be determined with the mnemonic shown earlier. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



Scheme 1. Synthesis of porphyrin tweezers **4a–4e.**

ment of ECCD amplitudes with different diamines and carrier-derivatized carboxylic acids.

MATERIALS AND METHODS

The solvents used for CD measurements (hexane and methylcyclohexane) were purchased from Aldrich and were of spectra grade. Anhydrous CH_2CI_2 was obtained after drying over CaH_2 and consequent distillation. The stock solutions of porphyrin tweezers and chiral substrates were prepared in flame-dried glassware. Column chromatography was performed using SiliCycle silica gel (230-400 mesh). ^{1}H NMR spectra were obtained using a Varian Inova 300 or 500 MHz instrument and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (J) in Hertz (Hz). UV–Vis spectra were recorded on a PerkinElmer Lambda 40 spectrophotometer and are reported as λ_{max} [nm]. CD spectra were recorded on a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low temperature studies. The CD spectra were measured in millidegrees, normalized for the concentration of the porphyrin to $\Delta\varepsilon/\lambda$ [nm] units and are reported as λ [nm] ($\Delta\varepsilon_{max}$ [1 mol^{-1} cm^{-1}]). All the CD spectra were taken with 1 μM solution of porphyrin tweezer in hexanes (for chiral diamines) or methylcyclohexane (for carboxylic acids) using a 10-mm UV-quartz cell at 0°C and are reported at 20 equiv of the chiral substrate. Porphyrin tweezers **4a–4e** were synthesized according to Scheme 1, following the procedures described below.[9]

General Procedure for the Synthesis of 5-(4-Methylcarboxyphenyl)-10,15,20-Triarylporphyrins 1a–1e

Pyrrole (4 equiv), aryl aldehyde (3 equiv), and 4-methylcarboxybenzaldehyde (EDCI, 1 equiv) were dissolved in dichloromethane or chloroform (0.01 M solution) and stirred under nitrogen for 30 min. To initiate the condensation reaction $BF_3{\cdot}OEt_2$ (0.3 equiv) was added, and the reaction was stirred for 4-16 h. *p*-Chloranil (2 equiv) was then added to the reaction mixture in one portion, and the solution was stirred for an additional 2 h. After completion of oxidation (monitored by TLC), the solvent was removed under reduced pressure, and the crude product (mixture of porphyrins) was submitted to column chromatography to purify porphyrin monoesters **1a–1e**.

General Procedure for the Hydrolysis of 5-(4-Methylcarboxyphenyl)-10,15, 20-Triarylporphyrins 2a–2e

Porphyrin methyl esters **1a–1e** (0.3–0.5 mmol) were dissolved in THF (30 ml), and 2 M NaOH (20 ml) was added. The solution was refluxed for 16 h and cooled to room temperature, acidified with 10% HCI (observed change of purple color to green) to pH = 1, and the THF was removed under reduced pressure. The remaining aqueous phase was extracted with dichloromethane (6 × 100 ml). The organic extracts were combined, washed with water (3 × 100 ml, color changed back to purple), and dried with anhydrous Na_2SO_4. The solvent was

removed under reduced pressure, and the resulting purple solid was precipitated with hexane from the dichloromethane solution to afford pure 5-(4-carboxyphenyl)-10,15,20-triarylporphyrins **2a–2e**. The residue was filtered out, and the crystals were washed with hexane and dried.

General Conditions for Coupling of 5-(4-Carboxyphenyl)-10,15,20-Triarylporphyrin with 1,5-Pentanediol (3a–3e)

Porphyrin acid (1 equiv), EDCl(1.4 equiv), 4-dimethylaminopyridine (DMAP, 1.4 equiv), and 1,5-pentanediol (3 equiv) were added in a round-bottomed flask and dissolved in dry CH_2Cl_2 (50 ml per 0.2 mmol of porphyrin acid). The solution was allowed to stir for 12–14 h at room temperature under nitrogen atmosphere, after which was directly loaded onto a silica column and purified by column chromatography (eluted with 10% EtOAc in CH_2Cl_2).

Synthesis of Tweezers 4a–4e

The free alcohol in derivatized porphyrins **3a–3e** (1.5 equiv) was subjected to a second round of coupling with the corresponding porphyrin acids **1a–1e** (1 equiv) with EDCI (1.2 equiv) and DMAP (1.2 equiv) in dry CH_2Cl_2 to yield the symmetric bis-porphyrin tweezers. The crude product was purified by silica column chromatography (CH_2Cl_2) to afford the porphyrin tweezers. Metal insertion was accomplished by dissolving purified porphyrin tweezers in dry dichloromethane, adding 4 equiv of $Zn(OAc)_2$, and stirring the solution overnight. Compounds were purified by silica column chromatography (CH_2Cl_2) to afford pure Zn-porphyrin tweezers **4a–4e**.

Computational studies

The models of the tweezer-diamine complexes depicted in Figures 3 and 4 were obtained as a result of direct minimization using Molecular Mechanics, force field MMFF94, Spartan v.5.1.3. A random arrangement of the porphyrins, located at a distance more that 6 Å away from the ligand, was used as the input structure. Input structures with the porphyrins located at different positions relative to the bound diamine resulted in similar final models. The lower energy conformations are shown in the figures. Because the models shown are not the products of an extensive conformational search, they only act as a pictorial representation of the complexes, rather than true energy minimized structures.

RESULTS AND DISCUSSION

In a systematic fashion, the meso phenyl groups of the porphyrin tweezers were substituted with sterically demanding groups in order to probe their effect on steric differentiation upon complexation with a chiral substrate. The readout for increased steric influence would be enhanced amplitude of the ECCD spectrum when compared with the same complex formed with Zn-TPP-tz **4a**. The first tweezer was synthesized with 2,4,6-trimethyl substitution of the meso phenyl groups yielding zinc bis-5-(4-carboxyphenyl)-10,15,20-tri-mesitylporphyrin tweezer **4b** (Zn-TMsP-tz) according to Scheme 1. The UV absorption of Zn-TMsP-tz **4b** in methylcyclohexane was detected at 418 nm with an extinction coefficient of 630,000 M^{-1} cm^{-1}, which is comparable to λ_{max} = 417 nm and ε = 650,000 M^{-1} cm^{-1} of the previously reported zinc bis-5(4-carboxyphenyl)-10,15,20-triphenylporphyrin tweezer **4a** (Zn-TTP-tz). The symmetry of methyl substitutions on the phenyl rings in Zn-TMsP-tz **4b** ensures that one set of methyl groups on each phenyl ring would always point into the cavity of the tweezer upon complexation with the chiral guest. This could obviously hinder the approach of the guest molecule to the metallo-porphyrin and, therefore, affect the formation of porphyrin tweezer-substrate complex. Qualitative examination of the effect of the newly introduced bulk onto the complexation process can be obtained from titrating 1 μM solution of porphyrin tweezer with 1,*n*-diamines of different length. It is well known that coordination of an amine group with the metalloporphyrin induces a red shift of the Soret band.[8] Moreover, it has been established that complexation of Zn-TPP-tz **4a** with diamines of different length results in the formation of a 1:1 complex, with the Soret band of the new species red shifted to values that depend on the separation of the two interacting porphyrin planes, namely, closer interacting porphyrin rings red shift to a lesser degree as opposed to porphyrin rings that are well separated.[8] This phenomenon is explained as a result of two counteracting effects: binding of the amine to the metalloporphyrin that leads to ~12 nm red shift, and blue shift of the absorption as a result of bringing the two porphyrin planes close to each other. Similar studies with the new porphyrin tweezers, after comparison with the known data obtained with Zn-TPP-tz **4a** should provide qualitative information with regards to their binding characteristics. For example, the amount of diamine necessary to fully complex the porphyrin tweezers will provide a measure for steric encumbrances due to the newly introduced aryl groups. Analysis of the extent of red shifting could yield qualitative information with regards to the separation of the two porphyrin planes complexed with the diamine as a result of substitution on the phenyl rings.

Table 1 presents a comparative UV–vis study of porphyrin tweezer-diamine complexes for Zn-TPP-tz (**4a**) and Zn-TMsP-tz (**4b**). A set of 1,*n*-diamines of different length was used for the complexation with the porphyrin tweezer. As can be seen from Table 1 (entry 1), binding of 1,2-ethanediamine with Zn-TMsP-tz **4b** results in a similar red shift when compared with the shift obtained with Zn-TPP-tz **4a**. However, unlike Zn-TPP-tz **4a**, which required an equimolar ratio of diamine, full complexation of Zn-TMsP-tz **4b** was detected after 30 equiv of 1,2-ethanediamine. On the other hand, binding of Zn-TMsP-tz **4b** with 1,3-diaminopropane required only 1 equiv of substrate for complete complexation, also leading to a similar red shift as that observed for Zn-TPP-tz **4a** (Table 1, entry 2, 4.3 nm shift for **4b**, 3.9 nm shift for **4a**). Complexation of all diamines of a larger size with Zn-TMsP-tz **4b** (Table 1, entries 3–8) also yielded similar red shifting when compared with Zn-TPP-tz **4a**, suggesting similar binding behavior with the two tweezers.

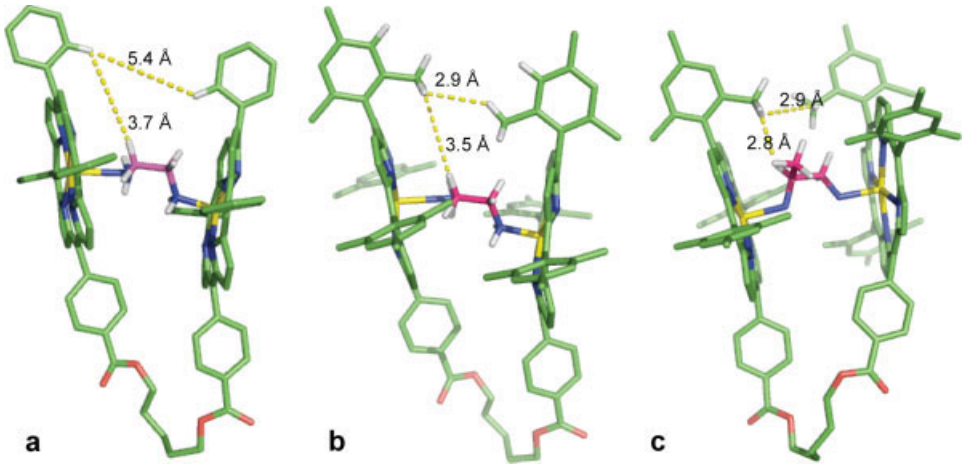


Fig. 3. (**a**) Zn-TPP-tz **4a** bound with 1,2-ethanediamine, (**b**) Zn-TMsP-tz **4b** bound with 1,2-ethanediamine, (**c**) Zn-TMsP-tz **4b** bound with (*S*)-2,3-diaminopropane, (molecular mechanics, force field MFF94, Spartan v.5.1.3). The models indicate steric interaction between the ortho methyl substituents on the phenyl groups and close proximity of the ortho methyls to the asymmetric center. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

A general understanding of the observed results can be gained from molecular modeling of the porphyrin tweezer-diamine complex. Figure 3a and 3b depicts the models of Zn-TMsP and Zn-TPP tweezers complexed with 1,2-ethanediamine, respectively. Binding of the small diamine with Zn-TMsP-tz **4b** is hindered by the steric interaction between the two methyl groups, which can explain the need for 30 equiv of the diamine for full complexation. The interaction between the two methyl groups on the opposing porphyrin rings is diminished with the lengthening of the substrate, thus leading to the similar red shift behavior observed for both Zn-TMsP-tz **4b** and Zn-TPP-tz **4a** with diamines that are well separated.

Having shown that the binding of Zn-TMsP-tz **4b** with various diamines mimics closely what has been observed with Zn-TPP-tz **4a**, we next investigated the effect of the added steric bulk on the amplitude of the ECCD spectra upon complexation with a number of different chiral guests. As can be seen from Table 2 (entries 1-3), both Zn-TPP-tz **4a** and Zn-TMsP-tz **4b** gave ECCD signals that exhibit the same helicity with diamines **5–7**.[9] This implies that complexation proceeds through the same mode of binding and results in analogous conformations for both chromophoric systems. Interestingly, the ECCD amplitude of (*R*)-1,2-diaminopropane (**5**) complexed with Zn-TMsP-tz **4b** was enhanced three fold.

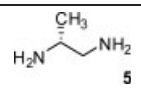
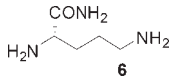
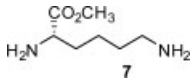
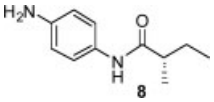
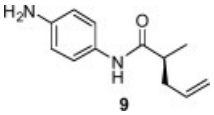
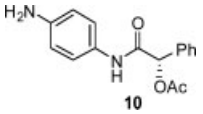
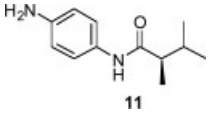
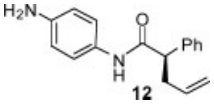
The source of this can be rationalized by examining the models depicted on Figure 3. The distance between the ortho hydrogen of the phenyl group on Zn-TPP-tz **4a** and the methyl substituent of the asymmetric carbon is estimated at 3.7 Å. Placement of the methyl group at the ortho position shortens the distance to 2.8 Å, hence increasing the steric differentiation as a result of larger interaction between the two groups (Fig. 3c). Along with that, a significant interaction introduced into the complex formed by tweezer **4b** is detected between two methyl substituents of the opposite porphyrins that are located at a distance of 2.9 Å (Figure 3b). Considering that the interchromophoric distance in both tweezer complexes is similar (based on the results obtained earlier, see Table 1), relaxation of the complex might occur through the increase of the dihedral angle between the chromophores, which contributes to the increase in the amplitude of the ECCD signal. It is also possible that the cofacially complexed porphyrins adopt a more twisted arrangement to avoid steric interaction. This would increase the dihedral angle between the excitonically coupled chromophores within the complex and thus contribute to the observed enhancement of the ECCD amplitude. Although an increase in amplitude is also observed for (*S*)-ornithine methyl amide **6**, a decrease in amplitude is registered for (*S*)-lysine methyl ester **7**. Significant drop in amplitude was also observed upon complexation of Zn-TMsP-tz **4b** with the carrier derivatized α-chiral carboxylic acids (Table 2, entries 4–8). In particular (*S*)-methylbutyric acid **8** and (*S*)-2-ethyl-4-pentenoic acid **9** represent cases in which similar size of substituents (A_{values}: CH_3 = 1.74, C_2H_5 = 1.79, $CH_2CH{=}CH_2$ = 1.68)[25] induce a small helical preference when complexed with Zn-TPP-tz **4a**. Complexed with Zn-TMsP-tz **4b**, com-

TABLE 1. UV red-shift of tweezers upon titration with diamines in dichloromethane ($\Delta\lambda = \lambda_{complex} - \lambda_{tweezer}$)[a]

Entry	$NH_2CH_2(CH_2)_nNH_2$	Tweezers, Δλ (nm) **4a**	**4b**
1	$n = 1$	3.0	3.0[b]
2	$n = 2$	3.9	4.3
3	$n = 3$	4.3	5.7
4	$n = 4$	6.7	6.2
5	$n = 5$	6.9	6.3
6	$n = 6$	7.2	7.6
7	$n = 7$	8.2	7.9
8	$n = 8$	8.6	8.1

[a]One micromolar tweezer was used for all measurements; data obtained at 1:1 tweezer/substrate ratio.
[b]Data obtained at 30 equivalents of diamine.

TABLE 2. Stereochemical determination of diamines[a] and carrier-derivatized α-chiral carboxylic acids[b] with 4a and 4b[c]

		Tweezer[d]			
		4a		**4b**	
Entry	Substrate	λ, nm (Δε)	*A*	λ, nm(Δε)	*A*
1	 **5**	426 (−82) 416 (58) 428 (−20)	−160	432 (−310) 418 (262) 432 (−30)	−572
	 **6**				
2	 **7**	418 (16) 429 (−260)	−36	419 (43) 431 (−60)	−73
3	 **8**	419 (132) 428 (−23)	−392	416 (52)	−112
4	 **9**	421 (+18) 429 (+21)	−22	—	n/o[e]
5	 **10**	420 (−21) 429 (−16)	+42	— 432 (−8)	n/o[e]
6	 **11**	420 (21) 425 (31)	−37	414 (11) 431 (18)	−19
7	 **12**	418 (−20) 428 (−75)	+98	414 (−9) 431 (−51)	+27
8		421 (60)	−135	414 (44)	−95

[a]Hexane was used as the solvent for ECCD measurements.
[b]Methylcyclohexane was used as the solvent for ECCD measurements.
[c]One micromolar tweezer concentration was used for all measurements.
[d]Tweezer/substrate ratio—1:20.
[e]n/o indicates that ECCD was not observed.

pounds **8** and **9** did not lead to CD active bands. And while the other carrier-derivatized substrates **10–12** did lead to observable ECCD spectra upon complexation with Zn-TMsP-tz **4b**, the ECCD amplitudes were significantly lower than the same compounds complexed with Zn-TPP-tz **4a**.* Parallel UV–vis titration of the tweezers with carrier-derivatized carboxylic acids **8–12** revealed a significantly lower-binding affinity with Zn-TMsP-tz **4b** (1.85×10^3 M^{-1} measured for **12** in methylcyclohexane) when compared with Zn-TPP-tz **4a** (2.94×10^4 M^{-1} measured for **12** in methylcyclohexane). Therefore, it appears that the functionalization of the porphyrins at ortho-position of the phenyl rings somewhat hinders the binding of chiral substrates to the tweezer and is not a globally applicable solution for improvement of ECCD amplitudes.†

Modeling studies with tweezer complexes containing meta substitution of the phenyl groups suggested the possibility of increased interaction between the phenyl groups of the tweezer and the substituents on the complexed chi-

*The sign of ECCD for substrate **12** deviates from the mnemonic, considering that an aromatic interaction between the phenyl substituent of the asymmetric center and porphyrin leads to the inversion of the ECCD sign as was described in reference 21.
†CD measurements of chiral substrates with porphyrin tweezers **4a-4d** were carried out at host-guest ratio of 1:20. Increasing the concentration of the guest beyond to 20 equiv (up to 50 equiv) led to decreased ECCD amplitudes, most probably as a result of breaking up the 1:1 tweezer-chiral guest complex. In most cases, increasing the equiv of guest added beyond 50 equiv led to complete disappearence of the ECCD signal.

ral center, without the undesired weakening of binding affinity due to increased interchromophoric steric interactions. Consequently, the following three porphyrins were synthesized: zinc bis-5-(4-carboxyphenyl)-10,15,20-tri-1-naphthyl porphyrin (**4c**, Zn-TNP-tz, λ_{max} = 421 nm, ε = 623,800 M^{-1} cm^{-1}), bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenyl porphyrin (**4d**, Zn-TMP-tz, λ_{max} = 419 nm, ε = 1,150,000 M^{-1} cm^{-1}), and bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-di-*t*-butylphenyl porphyrin (**4e**, Zn-TBP-tz, λ_{max} = 419 nm, ε = 630,800 M^{-1} cm^{-1}).

The binding study (UV–vis) of the three new tweezers **4c–4e** performed with a set of 1,*n*-diamines is summarized in Table 3. It is noteworthy that all new tweezers resulted in complete complexation after addition of 1 equiv of the diamines, including 1,2-diaminoethane with the bulky Zn-TBP-tz **4e**, suggesting similar binding as compared to Zn-TPP-tz **4a**. The red shift induced upon the complexation of tweezers **4c–4e** with diamines of various length closely follows the trend observed with Zn-TPP-tz **4a**, suggesting that the interchromophoric distance is not altered greatly.

The utility of porphyrin tweezers **4c–4e** was evaluated with chiral diamines **5–7** and carrier-derivatized chiral carboxylic acids **8–12** (Table 4). Zn-TNP-tz **4c** yielded variable results, in one case producing the opposite ECCD than what was anticipated (entry 7). Although the ECCD amplitude was enhanced in some cases (entries 6 and 8), with most of the substrates examined the Zn-TNP-tz **4c** produced amplitudes that were significantly lower than those observed with Zn-TPP-tz **4a**. In retrospect, it is not surprising that Zn-TNP-tz **4c** is not an efficient tweezer, because the naphthyl group can rotate away from the interior of the complexed tweezer/chiral substrate system, and thus not participate in steric differentiation. Tweezers **4d** and **4e** are symmetrically substituted on both meta positions, and thus either rotomer of the meso-phenyl group would place the aryl substituent within the interior of the complexed system. As listed in Table 4, binding of Zn-TMP-tz **4d** with diamines **5–7**, and carrier-derivatized chiral carboxylic acids **8–12**, does seem to support the latter supposition. For a number of cases (entries 1, 6–8) a significant increase in the ECCD amplitude is observed. Most striking is the effect of the meta-substituted methoxy groups in the steric differentiation of substituents of the carrier-derivatized chiral carboxylic acids **10–12**, for which up to a 9-fold increase in the amplitude is observed. Nevertheless, for the most challenging substrates, compounds **8** and **9**, in which the steric difference between the substituents on the chiral center is small, Zn-TMP-tz **4d** does not provide a significant enhancement of the amplitude.

Favorable changes observed in the ECCD amplitude with meta substitution of the meso phenyl groups as demonstrated by Zn-TMP-tz **4d** validated the idea of gaining better steric differentiation by substituting the meso position. Thus, to further enhance the steric differentiation of the substituents on the chiral center of the bound guest molecules, the meta substitutions were enlarged using *t*-butyl groups. Table 4 lists the ECCD data generated upon complexation of diamines **5–7** and carrier-derivatized chiral carboxylic acids **8–12** with Zn-TBP-tz **4e**. Gratifyingly,

TABLE 3. UV–vis red-shift of tweezers upon titration with diamines in dichloromethane ($\Delta\lambda = \lambda_{complex} - \lambda_{tweezer}$)[a]

		Tweezer, $\Delta\lambda$ (nm)			
Entry	$NH_2CH_2(CH_2)_nNH_2$	**4a**	**4c**	**4d**	**4e**
1	n=1	3.0	3.5	2.1	3.5
2	n=2	3.9	3.7	4.5	4.3
3	n=3	6.0	5.7	5.9	5.7
4	n=4	6.7	6.7	6.5	6.5
5	n=5	6.9	6.9	6.9	6.7
6	n=6	7.2	7.2	7.3	7.2
7	n=7	8.2	8.2	8.1	8.0
8	n=8	8.6	8.6	8.1	8.4

[a]One micromolar tweezer was used for all measurements; data obtained at 1:1 tweezer/substrate ratio.

Zn-TBP-tz **4e** bound to all of the chiral substrates, leading to strong ECCD spectra. In all cases, the anticipated sign of the bisignate curve is attained, and with the exception of one case (entry 3), the ECCD amplitudes were enhanced to a great degree. The challenging substrates **8** and **9** exhibited a two fold increase in amplitude, signifying a better discrimination of the substituents by the sterically demanding *t*-butyl groups. The largest change was observed upon complexation of compound **12** with Zn-TBP-tz **4e**, which led to >17-fold enhancement of the ECCD amplitude when compared with Zn-TPP-tz **4a**.

Figure 4 illustrates an energy-minimized molecular model of Zn-TBP-tz **4e** complexed with diamine **5**. Although speculative in nature, we believe that this model along with the data in Table 4 could suggest a rationale for the increased amplitudes observed with Zn-TBP-tz **4e**. Our working hypothesis was that increased bulk at the meta position would lead to greater steric differentiation of

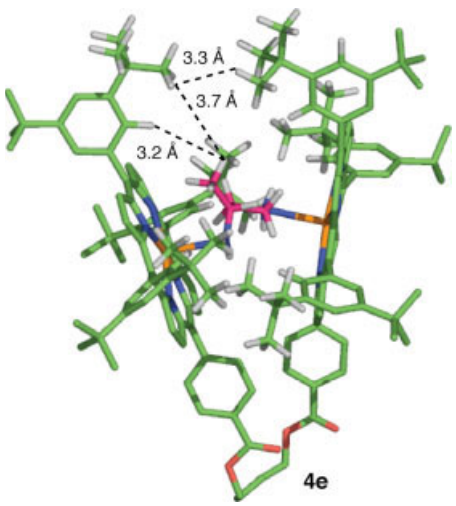
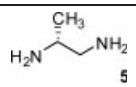
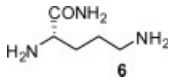
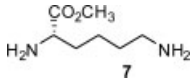
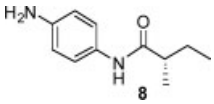
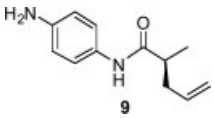
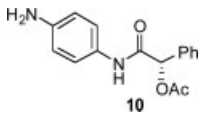
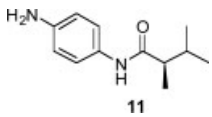
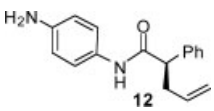


Fig. 4. Zn-TBP tweezer **4e** with (*S*)-2,3-diaminopropane (molecular mechanics, minimized structure, force field MMFF94, Spartan v.5.1.3). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 4. Stereochemical determination of diamines[a] and carrier-derivatized α-chiral carboxylic acids[b] with 4a and 4c-4e[c]

		Tweezer[d]							
		4a		**4c**		**4d**		**4e**	
Entry	Substrate	λ, nm (Δε)	*A*	λ, nm (Δε)	*A*	λ, nm (Δε)	*A*	λ, nm (Δε)	*A*
1	 **5**	426 (−82) 416 (+58)	−160	434 (−28) 419 (+32)	−60	432 (−117) 425 (+94)	−211	433 (−150) 418 (+140)	−290
2	 **6**	428 (−20) 418 (+16)	−36	434 (−18) 419 (+17)	−35	433 (−16) 417 (+6)	−22	433 (−85) 414 (+77)	−162
3	 **7**	429 (−260) 419 (+132)	−392	433 (−157) 423 (+141)	−198	430 (−39) 421 (+59)	−98	430 (−194) 422 (+178)	−372
4	 **8**	428 (−23) 421 (+18)	−22	431 (−10) 420 (+18)	−28	432 (−10) 421 (+12)	−24	430 (−47) 422 (+49)	−96
5	 **9**	429 (+21) 420 (−21)	+42	432 (+27) 424 (−11)	+38	430 (+17) 420 (−11)	+28	430 (+38) 422 (−43)	+81
6	 **10**	429 (−16) 420 (+21)	−37	430 (−94) 420 (+73)	−167	428 (−111) 418 (113)	−224	430 (−30) 418 (+43)	−73
7	 **11**	425 (+31) 418 (−20)	+98	432 (−40) 424 (+43)	−83	431 (+171) 422 (−137)	+308	430 (+268) 422 (−158)	+426
8	 **12**	428 (−75) 421 (+60)	−135	432 (−192) 424 (+141)	−333	432 (−504) 422 (+594)	−1098	430 (−1204) 422 (+1163)	−2367

[a]Hexane was used as the solvent for ECCD measurements.
[b]Methylcyclohexane was used as the solvent for ECCD measurements.
[c]One micromolar tweezer concentration was used for all measurements.
[d]Tweezer/substrate ratio—1:20.

substituents on the chiral center. Along with that, the large bulk of the *t*-butyl group would lead to a larger interchromophoric twist as the two porphyrins are brought closer to each other (as a function of complexation), thus enhancing the ECCD amplitude. Supporting data for this can be surmised from comparing the changes in amplitude observed for diamines **5–7**. Binding of both diamines **5** and **6** with Zn-TBP-tz **4e** leads to large changes in amplitude when compared with Zn-TPP-tz **4a**. This could be due to the close proximity of the two porphyrin rings that can lead to a more twisted conformation in order to avoid steric clash of the meta substituted *t*-butyl groups. On the other hand, complexation of diamine **7** does not lead to an enhancement of the amplitude, although when compared with diamine **6**, the size of the substituents on the chiral center in both cases is similar. What is different is the separation of the two complexed porphyrins; diamine **7** is longer than diamine **6**, thus the complexed porphyrins are held further apart when complexed with diamine **7**, and consequently, the *t*-butyl groups are not as effective in dictating a larger interchromophoric twist. This results in similar amplitude for both Zn-TBP-tz **4e** and Zn-TPP-tz **4a** when bound to diamine **7**. Further support for the latter argument is based on the binding constant calculated for complexation of **12** with Zn-TBP-tz **4e** (1.27×10^4 M^{-1} in methylcyclohexane), which is similar to the binding con-

stant of **12** with Zn-TPP-tz **4a** (2.94×10^4 M^{-1}). As discussed earlier, the ortho methyl-substituted Zn-TMsP-tz **4b** had >10-fold lower binding constant, leading to weak ECCD signals. Meta substitution with the larger *t*-butyl group in Zn-TBP-tz **4e** does not unfavorably affect the binding constant, but does lead to a great enhancement of the ECCD amplitude. As such, it seems likely that the meta substituents of the porphyrin tweezers do not directly interact with the bound chiral guest (as evident by the binding constant), but, in fact, induce a greater interchromophoric twist as the porphyrin planes are brought closer to each other as a consequence of the complexation event.

In summary, we report the comparison of five different porphyrin tweezers as ECCD reporters for diamines and carrier-derivatized chiral carboxylic acids. The tweezers were modified by the placement of substituents at the ortho and meta positions of the phenyl groups attached to the porphyrin meso sites. The ECCD data suggest that ortho substituents are not well tolerated, however, meta substituents do lead to enhanced ECCD amplitudes. In particular, Zn-TBP-tz **4e**, with *t*-butyl groups on the meta positions is an effective tweezer with enhanced ECCD amplitudes for most systems tested. It is believed that the enhancement in the ECCD amplitude is a result of increased interchromophoric twist induced by the steric clash of *t*-butyl groups on opposing porphyrin rings as they are brought close to each other via complexation with a chiral guest molecule.

LITERATURE CITED

1. Harada N, Nakanishi K. Circular dichroic spectroscopy: exciton coupling in organic stereochemistry In: Books US, editor; 1983, University Science Books, Sausalito, CA.
2. Nakanishi KBN, Woody RW. Circular dichroism, principles and application. New-York: VCH; 1994.
3. Wiesler WT, Nakanishi K. Relative and absolute configurational assignments of acyclic polyols by circular-dichroism. I. Rationale for a simple procedure based on the exciton chirality method. J Am Chem Soc 1989;111:9205–9213.
4. Rele D, Zhao N, Nakanishi K, Berova N. Acyclic 1,2-/1,3-mixed pentols. Synthesis and general trends in bichromophoric exciton coupled circular dichroic spectra. Tetrahedron 1996;52:2759–2776.
5. Chang M, Meyers HV, Nakanishi K, Ojika M, Hill J, Park MH, Takeda R, Vazquez JT, Wiesler WT. Microscale structure determination of oligosaccharides by the exciton chirality method. Pure Appl Chem 1989;61:1193–1200.
6. Skowronek P, Gawronski J. A simple circular dichroism method for the determination of the absolute configuration of allylic amines. Tetrahedron Lett 2000;41:2975–2977.
7. Kurtan T, Nesnas N, Li YQ, Huang XF, Nakanishi K, Berova N. Chiral recognition by CD-sensitive dimeric zinc porphyrin host. I. Chiroptical protocol for absolute configurational assignments of monoalcohols and primary monoamines. J Am Chem Soc 2001;123:5962–5973.
8. Huang XF, Borhan B, Berova N, Nakanishi K. UV–vis spectral changes in the binding of acyclic diamines with a zinc porphyrin tweezer. J Indian Chem Soc 1998;75:725–728.
9. Huang XF, Rickman BH, Borhan B, Berova N, Nakanishi K. Zinc porphyrin tweezer in host-guest complexation: Determination of absolute configurations of diamines, amino acids, and amino alcohols by circular dichroism. J Am Chem Soc 1998;120:6185–6186.
10. Shirota O, Nakanishi K, Berova N. Phytosphingosines—a facile synthesis and spectroscopic protocol for configurational assignment. Tetrahedron 1999;55:13643–13658.
11. Hayashi T, Aya T, Nonoguchi M, Mizutani T, Hisaeda Y, Kitagawi S, Ogoshi H. Chiral recognition and chiral sensing using zinc porphyrin dimers. Tetrahedron 2002;58:2803–2811.
12. Zahn S, Canary JW. Absolute configurations of *N*,*N*-dialkyl alpha-amino acids and β-amino alcohols from exciton-coupled circular dichroism spectra of Cu(II) complexes. Org Lett 1999;1:861–864.
13. Gimple O, Schreier P, Humpf HU. A new exciton-coupled circular dichroism method for assigning the absolute configuration in acyclic alpha- and beta-hydroxy carboxylic acids. Tetrahedron-Asymmetry 1997;8:11–14.
14. Li X, Tanasova M, Vasileiou C, Borhan B. Fluorinated porphyrin tweezer: a powerful reporter of absolute configurations for erythro- and threo- diols, amino alcohols and diamines. J Am Chem Soc 2008;130:1885–1893.
15. Hoch U, Humpf HU, Schreier P, SahaMoller CR, Adam W. Configurational assignment of optically active hydroperoxy homoallylic alcohols and the corresponding diols by circular dichroism and multidimensional gas chromatography. Chirality 1997;9:69–74.
16. Lo LC, Chen JY, Yang CT, Gu DS. CD exciton chirality method for determination of the absolute configuration of β-hydroxy-α-amino acid derivatives. Chirality 2001;13:266–271.
17. Matile S, Berova N, Nakanishi K, Fleischhauer J, Woody RW. Structural studies by exciton coupled circular dichroism over a large distance: Porphyrin derivatives of steroids, dimeric steroids, and brevetoxin B. J Am Chem Soc 1996;118:5198–5206.
18. Jiang H, Huang XF, Nakanishi K, Berova N. Nanogram scale absolute configurational assignment of ceramides by circular dichroism. Tetrahedron Lett 1999;40:7645–7649.
19. Snatzke G. Circular-dichroism and absolute conformation—application of qualitative MO theory to chiroptical phenomena. Angew Chem-Int Ed Engl 1979;18:363–377.
20. Proni G, Pescitelli G, Huang XF, Nakanishi K, Berova N. Magnesium tetraarylporphyrin tweezer: a CD-sensitive host for absolute configurational assignments of alpha-chiral carboxylic acids. J Am Chem Soc 2003;125:12914–12927.
21. Yang Q, Olmsted C, Borhan B. Absolute stereochemical determination of chiral carboxylic acids. Org Lett 2002;4:3423–3426.
22. Proni G, Pescitelli G, Huang XF, Quraishi NQ, Nakanishi K, Berova N. Configurational assignment of alpha-chiral carboxylic acids by complexation to dimeric Zn-porphyrin: host-guest structure, chiral recognition and circular dichroism. Chem Commun 2002:1590–1591.
23. Berova N, Di Bari L, Pescitelli G. Application of electronic circular dichroism in configurational and conformational analysis of organic compounds. Chem Soc Rev 2007;36:914–931.
24. Giraud-Roux M, Proni G, Nakanishi K, Berova N. Syntheses and spectroscopic properties of methylbenzoate derivatives of tetrabenzoporphyrin, application to circular dichroism studies. Heterocycles 2003; 61:417–432.
25. Eliel EL, Wilen SH. stereochemistry of organic compounds. New York: Wiley; 1994.