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Conformational Preference in Bis(porphyrin) Tweezer Complexes: A Versatile Chirality Sensor for α-Chiral Carboxylic Acids

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Metallated porphyrin tweezers have demonstrated a remarkable ability to function as reporters of absolute stereochemistry for a number of different classes of organic molecules. Flexibility in binding, however, can result in an ensemble of different Exciton Coupled Circular Dichroism (ECCD) active conformations that could lead to variable results. Linker flexibility was found to be a key determinant of binding conformation. Experimental results indicate that a balance between linker flexibility and rigidity could yield an optimum porphyrin tweezer that stabilizes a common conformation for all bound chiral guests. This leads to a more simplified approach to absolute stereochemical determination of asymmetry for small organic molecules. This was demonstrated by the use of a C_3-linked zincated porphyrin tweezer that yields a common conformational preference for a variety of α-chiral carboxylic acids derivatized with a diamine carrier.

Introduction

The need for reliable spectroscopic methods for the absolute stereochemical determination of chirality cannot be overstated. Although, chiroptical spectroscopy such as Circular Dichroism (CD) is inherently sensitive to chirality, it has not enjoyed tremendous use as a method for stereochemical determinations, mainly because the results of CD analysis are empirical. Exciton Coupled Circular Dichroism (ECCD) is a nonempirical spectroscopic method that is based on detecting the through-space exciton interaction between helically orientated independently conjugated chromophores.[1] The porphyrin tweezer methodology pioneered by Nakanishi, Berova, and co-workers in the late 1990s further simplified the use of ECCD as a practical tool for absolute stereochemical assignments.[2] The tweezer, consisting of two zinc porphyrins connected through a flexible linker (Figure 1, a), allows for noncovalent complexation with a chiral molecule provided that the guest molecule has two sites that can coordinate with the two metallated porphyrins. In case the guest molecule has only one site of attachment, a carrier is used to convert it into a molecule with two coordinating sites necessary for porphyrin tweezer complexation (Figure 1, b). Chirality transfer from the guest molecule to the bis-chromophoric host in this complex results in a helical disposition of the two porphyrins, which is detected as a bisignate ECCD curve.[1] The sign of the observed ECCD is directly related to the helicity of the complex and, furthermore, can be correlated to the chirality of the bound substrate, thus providing a nonempirical assignment that is characteristic of ECCD analysis. This has led to the development of a robust and efficient method for the absolute stereochemical determination of diamines, amino alcohols and amino acids,[2b] monoamines and monoalcohols,[2c–f] carboxylic acids[2g,2i] and lactams,[2h,3] as well as chiral 1,2-diols[4] and 2,3-epoxy alcohols.[5] Working mnenonics derived for each case allow for easy correlation of the observed ECCD spectra with the absolute stereochemistry of the chiral substrate. Nonetheless, further simplification and unification of the porphyrin tweezer methodology that would follow a universal mnemonic would make the method more appealing, less of a specialized application, and more amenable for use as a standard analytical tool.

Typically, complexation of a chiral guest molecule with porphyrin tweezers leads to a predominant rotameric configuration such that the porphyrin that is bound closer to the asymmetric center sterically differentiates between two groups that are projected in its direction. This stereodifferentiation leads to a helical arrangement of the two interacting porphyrins, and results in an ECCD signal (Figure 1, c). Stereodifferentiation with porphyrin tweezers is sensitive to the substrate geometry and the type of substituents at the asymmetric center. For instance, a separate mnemonic was needed for the absolute stereochemical determination of α-halogenated carboxylic acids compared to their alkyl analogues (Figure 1, d and e) with the ZnTPP-C_5 tweezer.[3] Analysis of a number of α-chiral alkyl carboxylic acids after their derivatization with the "carrier" 1,4-phenylenediamine (Figure 1, b)[2i] led to a working mnemonic (Figure 1, d) in which the large (*i*Pr) and small (H) groups (relative size of

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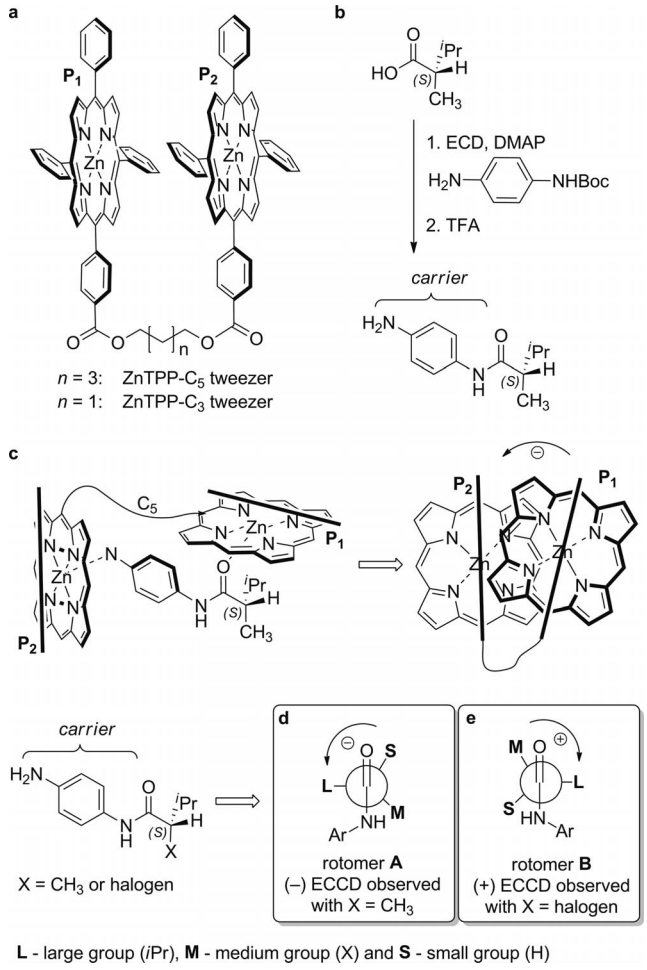


Figure 1. Porphyrin tweezer as a tool for the absolute stereochemical determination of α-chiral alkyl/alkoxy carboxylic acids: (a) structure of porphyrin tweezers; (b) 1,4-phenylenediamine as a carrier providing two coordination sites for complexation with the porphyrin tweezer; (c) substrate–tweezer complexation results in an ECCD active complex; (d) a simplified mnemonic for the absolute stereochemical determination of 1,4-phenylenediamine (NHAr) derivatized α-chiral alkyl/alkoxy carboxylic acids derivatized with the ZnTPP-C_5 tweezer; (e) a simplified mnemonic depicting the major ECCD active conformation for α-chiral halocarboxylic acids derivatized with 1,4-phenylenediamine (NHAr) bound to the ZnTPP-C_5 tweezer. Helicity of the complex and the corresponding ECCD sign is reflected by rotation from the smaller to the larger substituent. The relative sizes of the substituents are based on their *A* values.

substituents is defined by their *A* values)[6] bisect the carbonyl (rotamer **A**). Steric differentiation of these two substituents by the carbonyl-bound porphyrin results in counterclockwise twist between chromophores and a negative ECCD. In contrast, 1,4-phenylenediamine derivatives of α-halogenated carboxylic acids were found to prefer rotamer **B** (Figure 1, e) in which the large (alkyl) and the medium (halogen) substituents are directed towards the carbonyl-coordinated porphyrin, yielding ECCD spectra opposite to those obtained from the corresponding α-alkyl analogues.[3] The nature of this conformational switch was attributed to the C–X-π interaction between the substrate and the porphyrin.[3]

Deviation from the mnemonic has been observed in other classes of organic molecules.[4,5] Although from a structural/chemical viewpoint the observed deviations can be rationalized, a uniform system that is not susceptible to variations is desirable. To this end, a better understanding of factors that influence the observed ECCD signals as a function of porphyrin tweezer structure could aid in the development of a uniform chromophoric host that would reduce conformational variability and stabilize one common ECCD active conformation for a major class of compounds.

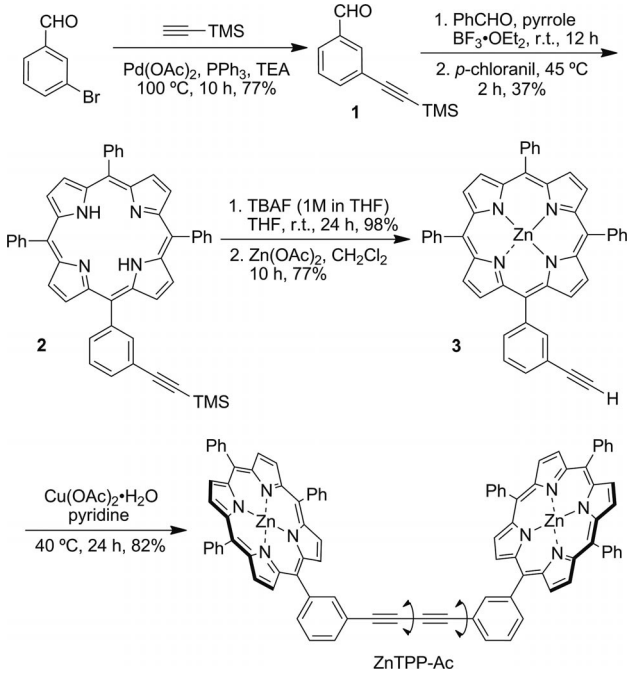
The role of tweezer flexibility, steric encumbrance, and binding affinity in molecular recognition has been studied for various systems.[7] In pursuit of unifying the stereochemical determination of carrier-derivatized α-chiral carboxylic acids with porphyrin tweezers, we evaluated the role of steric changes to the porphyrin ring in an attempt to favor one ECCD-active conformer, however, a unified mode of stereodifferentiation was not observed.[7c] Our observations led us to hypothesized that, in fact, it is the flexibility of the C_5-porphyrin tweezer that leads to an alternative orientation of the bound, derivatized, nonhalogenated analogues in comparison with the α-halocarboxylic acids. The following describes our efforts with less flexible tweezers to address the latter hypothesis.

Results and Discussion

Synthesis of Porphyrin Tweezers and Binding Studies

Two new porphyrin tweezers, altered in linker length and rigidity, were synthesized. In comparison to the pentane linker in the ZnTPP-C_5 tweezer, ZnTPP-C_3 tweezer (Figure 1a, n = 1) is assembled through a shorter propane linker, and the ZnTPP-Ac tweezer is connected through a rigid bis(acetylene) moiety (Scheme 1). Whereas the shorter C_3 linker allows for ZnTPP-C_3 tweezer binding with substrates of different size, the smaller number of sp^3 bonds in the linker can significantly reduce conformational freedom. Moreover, the reduced size of the binding pocket should also restrict the number of coordination modes, thus leading to a predominant conformation of the bound guest molecule. The bis(acetylene) linker in the ZnTPP-Ac tweezer restricts the size of the binding pocket and therefore, is less accommodating to various ligands. Nonetheless, free rotation about the single bonds should enable the tweezer to adopt a preferred helicity upon interaction with a bound chiral guest molecule.

The ZnTPP-C_3 tweezer was synthesized in the same manner previously reported for ZnTPP-C_5.[7c,8] Synthesis of the ZnTPP-Ac tweezer commenced with the Sonogashira coupling of 3-bromobenzaldehyde and (trimethylsilyl)ethyne to deliver 3-[(trimethylsilanyl)ethynyl] benzaldehyde (**1**).[9] Lewis acid catalyzed condensation of aldehyde **1** with pyrrole and benzaldehyde, followed by in situ oxidation with *p*-chloranil yielded 5,10,15-triphenyl-20-(3-trimethylsilanylethynyl-phenyl)porphyrin (**2**).[10] Deprotection of the TMS protecting group with tetrabutylammonium fluoride

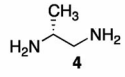
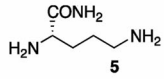
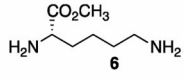


Scheme 1. Synthesis of the ZnTPP-Ac tweezer.

(TBAF) proceeded smoothly, followed by zincation with $Zn(OAc)_2$ to deliver porphyrin **3**. It is noteworthy that zincation of porphyrin **3** was necessary at this stage for the application of the standard Glaser–Hay procedure.[11] Metal-free porphyrin submitted to the coupling underwent copper insertion, preventing the reaction from occurring. The copper-mediated homocoupling of porphyrin **3** afforded the ZnTPP-Ac tweezer in 82% isolated yield.

Binding of the three tweezers with diamines was investigated by UV/Vis analysis of the porphyrin's Soret band (λ_{max} of ZnTPP-C_5, ZnTPP-C_3, and ZnTPP-Ac are 418, 419, and 418 nm, respectively). Binding of an amine, such as isobutylamine, to a zincated porphyrin resulted in a 10–12 nm redshift. In contrast, binding of a short chain diamine, such as a 1,2-diaminoethane, resulted in a significantly reduced redshift (typically 3–4 nm). The latter is the result of two competing effects.[2a] The anticipated amine coordination should result in a much larger redshift, however, this is counterbalanced by the close proximity of the two porphyrin planes, which results in a blueshift. As expected, the use of tweezers with longer chain 1,n-diamines, which separate the rings by a larger distance, led to larger redshifts. This dependence of the Soret band shift on the distance between the binding sites of the guest molecule is indicative of a 1:1 complex between the porphyrin tweezer and the guest molecule.[2a,2c,12] For the three tweezers in question, equimolar diamine concentrations induced a redshift of the Soret band (λ_{max}), the magnitude of which ($\Delta\lambda$) increased from approximately 3 to 8.5 nm with increased length of the bound diamine, suggesting formation of a 1:1 tweezer–diamine complex (Table 1). Moreover, the change in the absorption maxima observed for the C_3-tweezer closely matches that seen with the C_5-linked ZnTPP tweezer, suggesting a similarity in the distance of the chromophores in each tweezer system. There are, however, some differences in the ability to form a host–guest complex with the ZnTPP-Ac tweezer. Namely, the rigid bis(acetylene) linker of ZnTPP-Ac tweezer does not allow stoichiometric complexation of short 1,2- and 1,3-diamines and results in a 1:2 tweezer–diamine complex with $\Delta\lambda$ = 10 nm (Table 1).

Table 1. UV/Vis redshift of tweezer absorption upon formation of a 1:1 tweezer–diamine complex[a] and ECCD of chiral diamines.[b]

	ZnTPP-C_5	ZnTPP-C_3	ZnTPP-Ac
$NH_2(CH_2)_nNH_2$[c]	$\Delta\lambda$, nm ($\Delta\lambda = \lambda_{complex} - \lambda_{tweezer}$)[a]		
$n = 2$	3.0	3.2	10[a]
$n = 3$	3.9	3.8	10[a]
$n = 4$	6.0	6.1	4.7
$n = 5$	6.7	6.5	5.3
$n = 6$	6.9	6.8	6.1
$n = 7$	7.2	7.1	6.8
$n = 8$	8.2	8.3	7.4
$n = 9$	8.6	8.5	7.9
Isobutylamine	10.0	10.0	9.7
A, ECCD of 1:1 tweezer-diamine complexes[d]			
 **4**	–160	–275	n.d.[e]
 **5**	–36	–156	–22
 **6**	–392	–400	–78

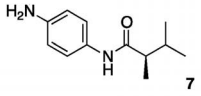
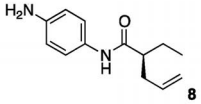
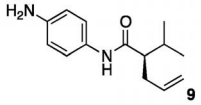
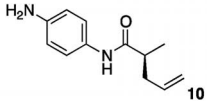
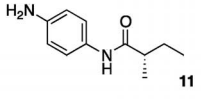
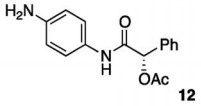
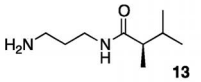
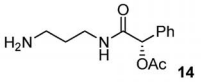
[a] $\Delta\lambda$ was obtained with 1 μM porphyrin tweezer in dichloromethane upon titration with 1 mM solution of amine at 1:1.2 tweezer/diamine ratio (100% complexation). [b] 10 mM solutions of diamine in dichloromethane were used for measurements. [c] ECCD obtained with 1 μM porphyrin tweezer in hexane and reported at 1:20 tweezer/substrate ratio (ca. 20% tweezer–amide complex). [d] Redshift resulting from formation of 1:2 tweezer/diamine complex. [e] Not detected.

Chiral diamines **4**–**6** were then used to investigate the mode of stereodifferentiation with the new tweezers. Restricted to form 1:1 complexes with short substrates, the ZnTPP-Ac tweezer is ECCD silent with (*R*)-1,2-diaminopropane (**4**). Nonetheless, an increase in the length of the diamine, such as those in chiral 1,4- and 1,5-systems (substrates **5** and **6**, Table 1), gave rise to prominent negative bisignate CDs. In comparison to the other two, the ZnTPP-Ac tweezer leads to smaller redshift of the Soret band and also to smaller ECCD amplitudes. The ZnTPP-C_3 tweezer closely mimics the ZnTPP-C_5 tweezer in both UV/Vis and ECCD measurements with diamines, yielding ECCD of high amplitude. Importantly, all three tweezers show analogous ECCD patterns with chiral diamines, suggesting that binding and stereodifferentiation remains the same with this class of chiral molecules.

Use of ZnTPP-C_3 and ZnTPP-Ac Tweezers in the Stereochemical Determination of Carrier-Derivatized α-Chiral Carboxylic Acids

For CD measurements, a dilute (1 μM) solution of porphyrin tweezer in methylcyclohexane was titrated with chiral amides. The ECCD data summarized in Table 2 indicate that both ZnTPP-Ac and ZnTPP-C_3 tweezers are effective in sensing chirality. As expected, diminished ECCD amplitudes were observed with the rigid ZnTPP-Ac tweezer. Interestingly, despite a large difference in linker geometry and rigidity, the ZnTPP-C_5 tweezer and the ZnTPP-Ac tweezer exhibit similar ECCD, namely, both yield the same sign of the bisignate curve.

Table 2. ECCD of carrier-derivatized chiral α-alkyl/alkoxy carboxylic acids.[a]

Substrate[b]	A[c]		
	ZnTPP-C_5	ZnTPP-C_3	ZnTPP-Ac
 **7**	+98	–132	+45
 **8**	+54	–149	+26
 **9**	+87	–175	+26
 **10**	–23	+90	–12
 **11**	–41	+67	–16
 **12**	–37	+127	–22
 **13**	–133	–138	–60
 **14**	–89	–137	–41

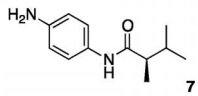
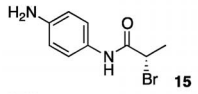
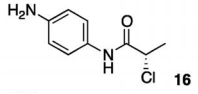
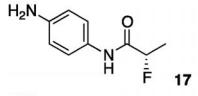
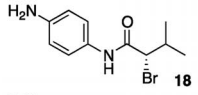
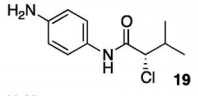
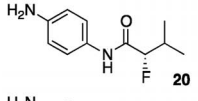
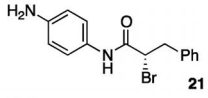
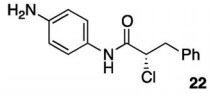
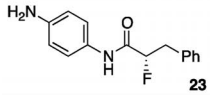
[a] Methylcyclohexane was used as the solvent for ECCD measurements. [b] 10 mM solutions of amides in dichloromethane were used for all ECCD measurements. [c] 1 μM tweezer concentration was used for all measurements; ECCD data was collected at 0 °C and reported at 1:20 tweezer/substrate ratio (ca. 20% tweezer–amide complex).

On the other hand, CD data obtained with the ZnTPP-C_3 tweezer exhibited a number of important differences. The observed ECCDs for amides **7**–**12** bound to ZnTPP-C_3 are opposite to that observed with ZnTPP-C_5 or ZnTPP-Ac tweezers. Namely, a two-carbon shortening of the linker (from C_5 to C_3) leads to the stabilization of an entirely new conformation, which leads to a change in the sign of the ECCD spectra. Interestingly, α-chiral carboxylic acids derivatized with 1,3-diaminopropane (Nakanishi's carrier),[2g] which exhibited opposite ECCDs for the same chiral carboxylic acids derivatized with 1,4-phenylenediamine with ZnTPP-C_5 tweezer, yield the same ECCD with ZnTPP-C_3 (cf. **7** and **8** with **12** and **14**, Table 2). Thus, it appears that, unlike the other two tweezers, ZnTPP-C_3 stabilizes one common ECCD active conformation with α-alkyl amides, and that this conformation is tolerant of changes to the carrier geometry and flexibility. It is also noteworthy that, at the same concentrations and the same tweezer/substrate ratios, the ZnTPP-C_3 tweezer yields ECCD spectra of significantly enhanced magnitude, most probably indicating the presence of a larger population of the ECCD active conformation, considering that the binding affinities for both C_5 and C_3 tweezers are similar.

In contrast to the ZnTPP-C_5 tweezer, with which the sign of the ECCD couplet switches with α-halocarboxylic acids, the ECCD observed with the ZnTPP-C_3 tweezer remains consistent and yields the same sense of helicity whether it is bound to halogenated or nonhalogenated carrier-derivatized α-chiral carboxylic acids. This is clearly shown in Table 3, in which the ZnTPP-C_3 tweezer yields positive ECCD spectra for substrates **15**–**23** and a negative ECCD with substrate **7**. Note that **7** is a pseudoenantiomer of substrates **15**–**23**. Similar to their nonhalogenated counterparts, the ZnTPP-C_3 tweezer exhibits larger ECCD amplitudes in most cases in comparison to its C_5 analogue. The reduced flexibility of the ZnTPP-C_3 tweezer, in contrast to the C_5 tweezer, leads to the stabilization of a single common geometry for the derivatized α-chiral carboxylic acids, presumably with the orientation depicted in Figure 1, e. With a few exceptions that lead to unexpected ECCDs, the ZnTPP-Ac tweezer follows the same trends observed with the ZnTPP-C_5 tweezer. Clearly, the strained nature of the ZnTPP-Ac tweezer leads to unpredictable geometries that highlight a balance necessary between flexibility and rigidity.

Tweezer–substrate binding affinity and binding geometry are the key components contributing to the magnitude of ECCD and stabilization of the ECCD active conformation. To investigate any correlation between binding affinity and changes in the sign and magnitude of ECCD spectra, K_a for complexation of each tweezer with α-chiral amides **7** and **8** was measured in methylcyclohexane by performing standard UV/Vis titration experiments. A redshift in the porphyrin's Soret band (from 417 to 420 nm) accompanies the binding event, which can be used to easily measure binding constants through a nonlinear least square regression analysis (see Table S1 in the Supporting Information).[13] The data indicates similar binding affinities for complexation of ZnTPP-C_5 and ZnTPP-C_3 tweezers with amides **7** and **8**, whereas diminished affinities were obtained for the more rigid ZnTPP-Ac tweezer. Similarity in binding affinity of the C_3 and C_5 linked porphyrin tweezers argues against binding as a factor affecting the change in sign and

Table 3. ECCD of carrier-derivatized chiral α-halo carboxylic acids.[a]

Substrate[b]	A[c]		
	ZnTPP-C_5	ZnTPP-C_3	ZnTPP-Ac
 **7**	+98	–132	+45
 **15**	+296	+210	+61
 **16**	+63	+288	+65
 **17**	+65	+80	complex CD
 **18**	+194	+586	+51
 **19**	+214	+349	+37
 **20**	+207	+290	-42
 **21**	+90	+383	-72
 **22**	+41	+313	+56
 **23**	+50	+222	complex CD

[a] Methylcyclohexane was used as the solvent for ECCD measurements. [b] 10 mM solutions of amides in dichloromethane were used for all ECCD measurements. [c] 1 μM tweezer concentration was used for all measurements; ECCD data were collected at 0 °C and reported at 1:20 tweezer/substrate ratio (ca. 20% tweezer–amide complex).

magnitude of ECCD observed between the ZnTPP-C_3 and ZnTPP-C_5 tweezers. Nonetheless, one can postulate that the difference in flexibility of the two tweezers affects the conformational preference of bound chiral amide within the complex.

NMR Analysis of Conformational Preference in the ZnTPP-C_3 Tweezer Complex

To confirm the conformational change postulated for the ZnTPP-C_3 tweezer and to identify the ECCD active conformation within the tweezer–amide complex, we performed NMR studies of ZnTPP-C_5 and ZnTPP-C_3 tweezers with amide **8**. The strong diamagnetic anisotropy of the porphyrin ring[14] has been used successfully to dissect and interrogate the predominant conformation adopted by substrates that are complexed to a metalated porphyrin ring.[2e,2f,15] In the complex of ZnTPP-C_3 the shielding of the chiral center is expected primarily from the carbonyl coordinated porphyrin $\mathbf{P_1}$ (Figure 2, a), whereas the amine-coordinated porphyrin $\mathbf{P_2}$ affects primarily the protons of the carrier.[16] The porphyrin-induced anisotropic shift in the spectrum of the tweezer-bound substrate can be correlated with the position of the substituents relative to the porphyrin plane and the center of the shielding cone. This information can then be mapped to reveal the ECCD-active conformation.

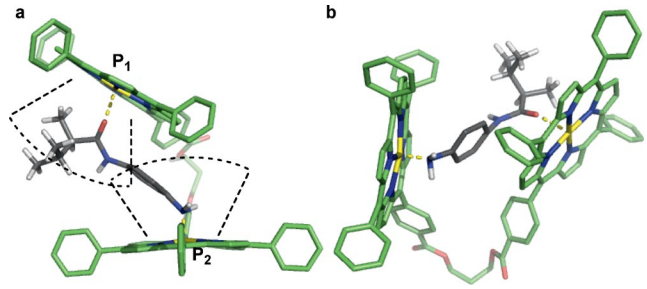


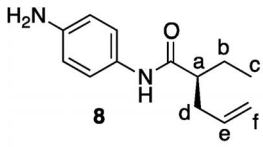
Figure 2. ZnTPP-C_3 tweezer complex with amide **7**: (a) top view, showing the putative effect of shielding cones of the two porphyrins on the bound amide; (b) side view, showing the major ECCD active conformations of amide **7** [Conformational search, Monte Carlo force field, Merck Molecular Force Field (MMFFs), Spartan V. 1.5.3].

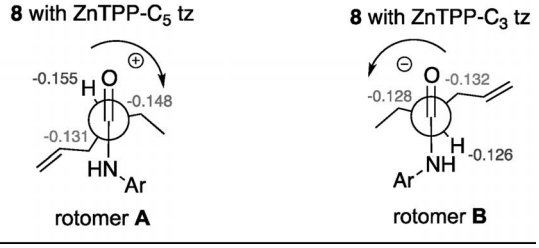
Table 4 lists the changes in chemical shift ($\Delta\delta = \delta_{complex} - \delta_{free}$, $\Delta\delta$ in ppm) for α-chiral amide **8** bound with ZnTPP-C_5 and ZnTPP-C_3 tweezers. A more negative $\Delta\delta$ value indicates greater shielding of the proton, and can result from its closer proximity to the center of the porphyrin ring and/or closer distance to the plane of the ring. Because interrogation of the distance of different protons to the plane of the ring is the key factor for probing the rotameric orientation of the bound guest molecule, it is imperative to compare protons that have similar distances to the stereocenter.

Considering the structure of amide **8**, the chemical shift dependence of the protons on the asymmetric center is directly correlated with the rotamer that is adopted. For example, when H_a and the ethyl group (H_b protons) bisect the carbonyl, they would be positioned closer to the porphyrin ring that is coordinated to the carbonyl oxygen. Thus, H_a and H_b would experience a greater degree of shielding compared with the protons of the allyl group (H_d) that would be situated *anti* to the carbonyl group. Table 4 lists the change in chemical shift for each proton upon coordination with the porphyrin tweezer.

As expected, the methylene protons in amide **8** are diastereotopic, and, therefore, only one of the two would be closest to the porphyrin, resulting in a larger chemical shift change. Proton H_a of amide **8** bound to ZnTPP-C_5 experiences the largest change in chemical shift, thus suggesting its closer proximity to the plane of the porphyrin ring. Proton H_{b1} in comparison to H_{d1} is shielded to a larger extent, which would therefore also suggest that the larger ethyl group is closer to the plane of the porphyrin ring than the allyl group.[17] The latter observations lead to a rotameric

Table 4. ^{1}H NMR shift observed upon complexation of alkyl amides with ZnTPP-C_5 and ZnTPP-C_3 tweezers.[a]

H	$\Delta\delta = \delta_{complex} - \delta_{free}$, ppm[b]	
		
	ZnTPP-C_5	ZnTPP-C_3
a	**–0.155**	**–0.126**
b1	**–0.148**	**–0.128**
b2	–0.069	–0.052
c	–0.074	–0.067
d1	**–0.131**	**–0.132**
d2	–0.093	–0.085
e	–0.095	–0.089
f1	–0.068	–0.063
f2	–0.035	–0.024



[a] ^{1}H NMR spectra taken in $CDCl_3$ at 1:10 tweezer/substrate, total tweezer concentration: 10 μM. [b] Data represents the average NMR shift in the proton spectrum of chiral amides upon complexation to the tweezer.

picture that has H_a and the ethyl group bisecting the carbonyl functionality, and, as a result, the medium sized allyl substituent *syn* to the amide nitrogen. In fact, this confirms the previously suggested mnemonic (rotamer **A**, Table 4, further proof of mnemonic in Figure 1, d) proposed for binding of 1,4-phenylenediamine derivatized α-chiral carboxylic acids with the ZnTPP-C_5 tweezer.[18]

Complexation of amide **8** with the ZnTPP-C_3 tweezer leads to a different pattern of chemical shift changes. In contrast to the ZnTPP-C_5 tweezer in which H_a was shielded the most, here H_a exhibits the least shielding in comparison to H_{b1} and H_{d1}. This suggests that H_a is oriented *syn* to the amide nitrogen and *anti* to the carbonyl that is coordinated to one of the porphyrin rings. Note that H_a is closer to the center of the porphyrin axis, and thus will be shielded more than H_{b1} and H_{d1} if all three protons were equidistant to the plane of the porphyrin ring. Protons H_{b1} and H_{d1} experience similar shielding effects, which suggests that they are positioned in similar environments relative to the plane of the porphyrin. This would mean that both the ethyl and allyl groups bisect the carbonyl and present themselves to the porphyrin for steric differentiation. This is opposite to the mnemonic developed for the ZnTPP-C_5 tweezer, in which the large and small groups bisect the carbonyl. The conformation suggested for amide **8** bound to the ZnTPP-C_3 tweezer is the same as that observed with the 1,3-diaminopropane-derivatized α-chiral alkyl carboxylic acids and is also the same for α-halocarboxylic acids derivatized with the 1,4-phenylenediamine carrier.[3] The NMR experiments provide further proof that rotamer **B** (Table 4, same as mnemonic in Figure 1, e) is operational when the ZnTPP-C_3 tweezer is utilized.[19]

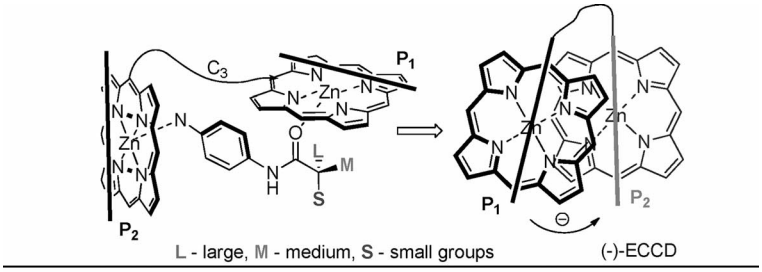
General Mnemonic for the Absolute Stereochemical Determination of α-Chiral Alkyl, Alkoxy, and Aryl Halo Carboxylic Acids

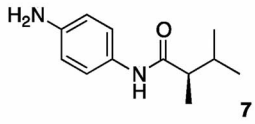
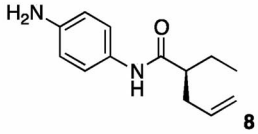
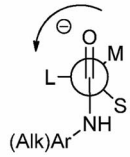
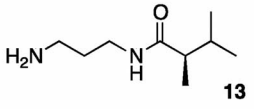
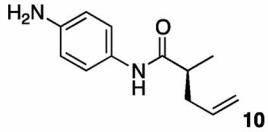
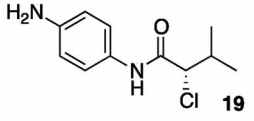
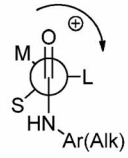
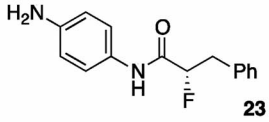
Because chiral induction in porphyrin tweezer complexes occur as a result of steric differentiation of the substituents at the chiral center, the net helicity of the complex reflected by the observed ECCD spectrum can be correlated with the absolute chirality of the bound substrate. As is depicted in Table 5, differentiation between the large and the medium groups at the stereocenter of the amide yields chiral induction with the porphyrin tweezer. Correlation of the observed ECCD sign with the chirality of the substrate is possible by viewing the chiral substrate in its Newman projection.[2f,2g,2i] Viewing from the carbonyl, the counterclockwise arrangement of the small (S), the medium (M), and the large (L) group would lead to a negative helicity and thus a negative ECCD spectrum. In this manner, α-alkyl amides **7**, **8**, and **13** (Table 5), with a counterclockwise S→M→L disposition lead to the observed negative ECCD. Similarly, amides **10**, **19**, and **23** exhibit positive ECCD with the ZnTPP-C_3 tweezer (Table 5) for which the relative arrangement of S→M→L is clockwise.

Conclusions

Conformational freedom of metalated porphyrin tweezer systems is necessary for the chiral guest bound complex to adopt a unique helical orientation. Nonetheless, the predominance of one unique conformation is desired so that a reliable method for absolute stereochemical determination of molecules can be established with confidence. We have demonstrated that neither too little nor too much conformational freedom for a porphyrin tweezer is ideal, and, in fact, a well-balanced compromise between flexibility and rigidity is required. This was demonstrated for α-chiral carboxylic acids, for which the ZnTPP-C_5 tweezer yields different ECCD signs depending on the carrier used. Furthermore, ZnTPP-C_5 stabilizes two different ECCD active conformations for α-halogenated versus nonhalogenated chiral carboxylic acids, again resulting in opposite helicities. ZnTPP-Ac, having a rigidified bis-acetylenic linker, also leads to variability in chiral sensing, presumably because it is too rigid to accommodate a variety of chiral ligands. However, the ZnTPP-C_3 tweezer, containing smaller de-

Table 5. Mnemonic for the stereochemical assignment of carrier-derivatized chiral α-alkyl/alkoxy carboxylic acids.[a]



Representative Substrates[b]	ZnTPP-C_3 tweezer		
	ECCD sign predicted	ECCD sign observed	Working mnemonic[b]
 **7**	neg	neg	
 **8**	neg	neg	
 **13**	neg	neg	
 **10**	pos	pos	
 **19**	pos	pos	
 **23**	pos	pos	

[a] ECCD measurements carried out in methylcyclohexane with 1 μM tweezer at 0 °C. [b] L: large group, M: medium group, S: small group. Relative sizes of substituents are based on the corresponding *A* values.

grees of freedom than ZnTPP-C_5, exhibits a common mode of stereodifferentiation with all 1,4-phenylenediamine-derivatized α-chiral carboxylic acids, regardless the type of substituent at the chiral center.

We have established that, in complexes with the ZnTPP-C_3 tweezer, the chiral carboxylic acid adopts a conformation in which the small group is oriented *syn* to the amide, and the large and the medium groups bisect the carbonyl (Figure 1, e and Figure 2, b). The steric interaction between the carbonyl-coordinated porphyrin with these two substituents governs the resulting helicity of the complex, leading to a predictable ECCD signal. The ZnTPP-C_3 tweezer appears to be a reliable stereochemical tool for the absolute stereochemical determination of derivatized α-chiral carboxylic acids of a broad spectrum due to its ability to adopt a single ECCD active conformer.

Experimental Section

General: The solvents used for CD measurements (hexane and methylcyclohexane) were purchased from Aldrich and were of spectra grade. Anhydrous CH_2Cl_2 was obtained after distillation from CaH_2. The stock solutions of porphyrin tweezers and chiral substrates were prepared in dichloromethane. Column chromatog-

raphy was performed using SiliCycle silica gel (230–400 mesh). ^{1}H NMR spectra were obtained with a Varian Inova 300 MHz 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 with a Perkin–Elmer Lambda 40 spectrophotometer and are reported as λ_{max} [nm]. CD spectra were recorded with a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low temperature studies. The CD spectra were measured as molecular eliplicity (millidegrees), and normalized for the concentration of the porphyrin to yield Molecular CD [$M^{-1}cm^{-1}$]. All the CD spectra were recorded with 1 μM solution of porphyrin tweezer in hexanes (for chiral diamines) or methylcyclohexane (for carrier derivatized carboxylic acids) using a 10 mm UV quartz cell at 0 °C and are reported at 20 equiv. of the chiral substrate. ZnTPP-C_5 and ZnTPP-C_3 were obtained following previously published procedures.[7c] ZnTPP-Ac was synthesized according to Scheme 1, following the procedures described below.

3-[2-(Trimethylsilanyl)ethynyl]benzaldehyde (1): (Trimethylsilyl)-acetylene (3.8 g, 38.7 mmol, 1.8 equiv.), 3-bromobenzaldehyde (4.0 g, 21.6 mmol, 1 equiv.), $Pd(OAc)_2$ (56 mg, 0.25 mmol, 0.01 equiv.), triphenylphosphane (112 mg, 0.43 mmol, 0.02 equiv.), and anhydrous deoxygenated triethylamine (21 mL) were combined in a round-bottomed flask and brought to quick reflux under argon by placing the flask in an oil bath preheated to 100 °C. The solution was heated to reflux for 10 h and cooled to room temperature. The reaction mixture was filtered and the filtrate was extracted with saturated $NaHCO_3$ (2 × 15 mL) and CH_2Cl_2 (2 × 20 mL). The organic layers were combined and the solvent was removed under reduced pressure to give the crude aldehyde as a brown oil. The oil was purified by column chromatography (silica gel; EtOAc/hexanes, 5%) to give 3-(1-trimethylsilylethyne)benzaldehyde (3.34 g, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.07 (s, 9 H), 7.72 (d, J = 7.4 Hz, 1 H), 7.81 (d, J = 7.4 Hz, 1 H), 7.97 (dd, J_1 = 1.6, J_2 = 1.2 Hz, 1 H), 9.87 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 3.4, 98.9, 103.2, 124.4, 128.6, 128.9, 133.2, 136.3, 136.8, 191.6 ppm. MS (DCI): m/z = 202.2 [$C_{12}H_{14}OSi$].

10,15,20-Triphenyl-5-{3-[2-(trimethylsilanyl)ethynyl]phenyl}-porphyrin (2): Aldehyde **1** (200 mg, 1 mmol, 1 equiv.), pyrrole (260 mg, 4 mmol, 4 equiv.), and benzaldehyde (318 mg, 3 mmol, 3 equiv.) were combined in a flask with CH_2Cl_2 (150 mL) and the solution was purged with N_2 for 15 min. $BF_3{\cdot}OEt_2$ (50 μL, 0.4 mmol, 0.1 equiv.) was added, the reaction vessel was shielded from light, and the reaction mixture was stirred at room temperature overnight. *p*-Chloranil (980 mg, 4 mmol, 4 equiv.) was then added in one portion and the flask was placed in a preheated oil bath at 45 °C. The solution was heated to reflux for 2 h, then cooled to room temperature and the solvent volume was reduced under reduced pressure. The reaction mixture was submitted to flash chromatography (silica gel; CH_2Cl_2/hexane, 50%) affording a mixture of porphyrins. A second round of purification by column chromatography (silica gel; CH_2Cl_2/hexane, 5%) gave **2** (256 mg, 37%). MS (DCI): m/z = 710.7 [$C_{49}H_{38}N_4Si$]. IR (film): $\tilde{\nu}$ = 3292, 3055, 2961, 1597, 1523, 1487, 1441, 1338, 1205, 1070, 1001, 996, 908, 798, 752, 731, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –2.7 (s, 2 H), 0.92 (s, 9 H), 7.8 (m, 9 H), 7.9 (dd, J_1 = 1.8, J_2 = 1.0 Hz, 2 H), 8.2 (m, 7 H), 8.4 (s, 1 H), 8.9 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 2.3, 53.6, 85.6, 116.2, 121.9, 122.7, 126.5, 127.5, 127.9, 129.2, 129.7, 130.3, 130.9, 132.4, 134.6, 142.7, 150.2 ppm.

5-(3-Ethynylphenyl)-10,15,20-triphenylporphyrinatozinc (3): To a solution of **2** (88.5 mg, 0.14 mmol, 1 equiv.) in anhydrous THF (5 mL) was added tetrabutylammonium fluoride (1 M in THF, 0.4 mL, 0.4 mmol, 3 equiv.) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then partitioned between water (10 mL) and CH_2Cl_2 (20 mL), the organic layer was separated, dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. After column chromatography purification (silica gel; CH_2Cl_2/hexane, 10%), 5-(3-ethynylphenyl)-10,15,20-triphenylporphyrin (77 mg, 98%) was obtained. MS (DCI): calcd. for $C_{46}H_{30}N_4$ 638.5 $[M]^+$; found 639.4 $[M + H]^+$, 319.2 $[M]^{+2}$. IR (film): $\tilde{\nu}$ = 3374, 3076, 2967, 2926, 2956, 2161, 1686, 1653, 1558, 1541, 1340, 1250, 1001, 796 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –2.8 (s, 2 H), 3.2 (s, 1 H), 7.8 (m, 9 H), 7.9 (dd, J_1 = 1.8, J_2 = 1.0 Hz, 2 H), 8.2 (m, 7 H), 8.4 (s, 1 H), 8.9 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 83.9, 101,119.3, 120.8, 126.4, 128.2, 131.2, 131.8, 131.9, 134.6, 135.6, 137.7, 140.5, 143.2, 150.1 ppm.

5-(3-Ethynylphenyl)-10,15,20-triphenylporphyrin (18 mg, 0.028 mmol, 1 equiv.) was then zincated with $Zn(OAc)_2{\cdot}2H_2O$ (93 mg, 0.42 mmol, 15 equiv.) in CH_2Cl_2 (10 mL) at room temperature overnight. The color of the solution changed from dark-purple to reddish-purple during the course of the reaction. The reaction mixture was purified by column chromatography (silica gel, CH_2Cl_2) and the purple band was collected. The solvent was removed under reduced pressure to yield zincated porphyrin **3** as a purple solid (16.6 mg, 77%). MS (DCI): calcd. for $C_{46}H_{28}N_4Zn$ 700.1 $[M]^+$; found 701.8 $[M + H]^+$, 350.0 $[M]^{+2}$. IR (film): $\tilde{\nu}$ = 2973, 2929, 2866, 2165, 1682, 1606, 1558, 1340, 1250, 1003, 843, 798, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.2 (s, 1 H), 7.8 (m, 9 H), 7.9 (dd, J_1 = 1.6, J_2 = 1.2 Hz, 2 H), 8.2 (m, 7 H), 8.4 (s, 1 H), 8.9 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 74.8, 78.1, 104.1, 110.5, 115.2, 115.4, 120.7, 121.6, 122.6, 124.5, 124.7, 126.5, 127.9, 128.3, 128.8, 132.3, 132.8, 134.3, 134.6, 135.2, 140.0, 142.3, 142.5, 148.2, 149.9 ppm.

Bis[5-(3-ethynylphenyl)-10,15,20-triphenylporphyrinatozinc] (ZnTPP-Ac Tweezer): Porphyrinatozinc complex **3** (90 mg, 0.14 mmol, 1 equiv.) was combined with $Cu(OAc)_2{\cdot}H_2O$ (235 mg, 1.17 mmol, 8.4 equiv.) and pyridine (12 mL). The solution was stirred at 40 °C under an oxygen atmosphere for 24 h, during which the color of the reaction mixture changed from purple to blue-green. The reaction mixture was then cooled to room temperature and extracted with H_2O (10 mL) and $NaHCO_3$ (20 mL) until the aqueous layer was clear. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude purple-blue film, which was purified by flash chromatography (silica gel; hexane) to yield the ZnTPP-Ac tweezer (79 mg, 82%). MS (FAB+): calcd. for $C_{92}H_{54}N_8Zn_2$ 1402.28; found 1424.2 $[M + Na]^+$. IR (film): $\tilde{\nu}$ = 2983, 2916, 2883, 1684, 1587, 1476, 1361, 1250, 1003, 798 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.7 (m, 18 H), 7.95 (dd, J_1 = 1.8, J_2 = 1.1 Hz, 4 H), 8.2 (m, 14 H), 8.4 (s, 2 H), 8.9 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 72.8, 76.7, 102.9, 110.1, 114.9, 115.0, 119.1, 119.6, 120.1, 123.0, 124.1, 124.3, 125.7, 127.0, 127.3, 127.9, 134.3, 134.8, 136.4, 136.9, 137.2, 140.0, 141.9, 142.1, 146.7, 150.3 ppm.

Supporting Information (see footnote on the first page of this article): Synthetic procedures and characterization data for all compounds, binding constant determination, ECCD data obtained for chiral amides with sterically encumbered porphyrin tweezers, and molecular modeling data.

Acknowledgments

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[1] a) N. Harada, K. Nakanishi, *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*, University Science Books: Mill Valley, California, **1983**; b) K. Nakanishi, N. Berova, R. W. Woody, *Circular Dichroism, Principles and Application*, New York, **1994**.

[2] a) X. F. Huang, B. Borhan, N. Berova, K. Nakanishi, *J. Indian Chem. Soc.* **1998**, *75*, 725–728; b) X. F. Huang, B. H. Rickman, B. Borhan, N. Berova, K. Nakanishi, *J. Am. Chem. Soc.* **1998**, *120*, 6185–6186; c) X. F. Huang, B. Borhan, B. H. Rickman, K. Nakanishi, N. Berova, *Chem. Eur. J.* **2000**, *6*, 216–224; d) T. Kurtan, N. Nesnas, F. E. Koehn, Y. Q. Li, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2001**, *123*, 5974–5982; e) T. Kurtan, N. Nesnas, Y. Q. Li, X. F. Huang, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2001**, *123*, 5962–5973; f) X. F. Huang, N. Fujioka, G. Pescitelli, F. E. Koehn, R. T. Williamson, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2002**, *124*, 10320–10335; g) G. Proni, G. Pescitelli, X. F. Huang, N. Q. Quraishi, K. Nakanishi, N. Berova, *Chem. Commun.* **2002**, 1590–1591; h) Y. Chen, A. G. Petrovic, M. Roje, G. Pescitelli, M. M. Kayser, Y. Yang, N. Berova, G. Proni, *Chirality* **2010**, *22*, 140–152; i) Q. Yang, C. Olmsted, B. Borhan, *Org. Lett.* **2002**, *4*, 3423–3426.

[3] M. Tanasova, Q. F. Yang, C. C. Olmsted, C. Vasileiou, X. Y. Li, M. Anyika, B. Borhan, *Eur. J. Org. Chem.* **2009**, 4242–4253.

[4] X. Y. Li, M. Tanasova, C. Vasileiou, B. Borhan, *J. Am. Chem. Soc.* **2008**, *130*, 1885–1893.

[5] X. Y. Li, B. Borhan, *J. Am. Chem. Soc.* **2008**, *130*, 16126–16127.

[6] E. L. Eilei, S. H. Willen, L. N. Mander, in: *Stereochemistry of Organic Compounds*, New York, **1994**.

[7] a) T. Mizutani, K. Wada, S. Kitagawa, *J. Org. Chem.* **2000**, *65*, 6097–6106; b) A. Petitjean, J. Leblond, *ChemPhysChem* **2011**, *12*, 1043–1051; c) M. Tanasova, C. Vasileiou, O. O. Olumolade, B. Borhan, *Chirality* **2009**, *21*, 374–382; d) A. W. Kleij, S. J. Wezenberg, G. Salassa, E. C. Escudero-Adan, J. Benet-Buchholz, *Angew. Chem. Int. Ed.* **2011**, *50*, 713–716.

[8] S. Matile, N. Berova, K. Nakanishi, S. Novkova, I. Philipova, B. Blagoev, *J. Am. Chem. Soc.* **1995**, *117*, 7021–7022.

[9] C. Frixa, M. F. Mahon, A. S. Thompson, M. D. Threadgill, *Org. Biomol. Chem.* **2003**, *1*, 306–317.

[10] J. S. Lindsey, S. Prathapan, T. E. Johnson, R. W. Wagner, *Tetrahedron* **1994**, *50*, 8941–8968.

[11] W. B. Austin, N. Bilow, W. J. Kelleghan, K. S. Y. Lau, *J. Org. Chem.* **1981**, *46*, 2280–2286.

[12] H. Onouchi, T. Miyagawa, K. Morino, E. Yashima, *Angew. Chem.* **2006**, *118*, 2441; *Angew. Chem. Int. Ed.* **2006**, *45*, 2381–2384.

[13] Y. Shoji, K. Tashiro, T. Aida, *J. Am. Chem. Soc.* **2006**, *128*, 10690–10691.

[14] M. R. Maurya, L. K. Woo, *J. Organomet. Chem.* **2005**, *690*, 4978–4981.

[15] a) G. Proni, G. Pescitelli, X. Huang, K. Nakanishi, N. Berova, *J. Am. Chem. Soc.* **2003**, *125*, 12914–12927; b) V. V. Borovkov, J. M. Lintuluoto, Y. Inoue, *J. Am. Chem. Soc.* **2001**, *123*, 2979–2989.

[16] See the Supporting Information for specific details.

[17] A. V. Udal'tsov, L. A. Kazarin, A. A. Sweshnikov, *J. Mol. Struct.* **2001**, *562*, 227–239.

[18] Q. Yang, C. Olmsted, B. Borhan, *Org. Lett.* **2002**, *4*, 3423–3426.

[19] To further explore the preferred rotational conformation of amide **8** bound to both ZnTPP-C_3 and ZnTPP-C_5 tweezers, NOESY spectra of the complexes were investigated. Presumably, due to rapid exchange of the bound and unbound amide **8** with the tweezers, an averaged spectrum for each were obtained, thus no conclusive NOE results could be obtained to determine the conformation based on proximity of substituents.

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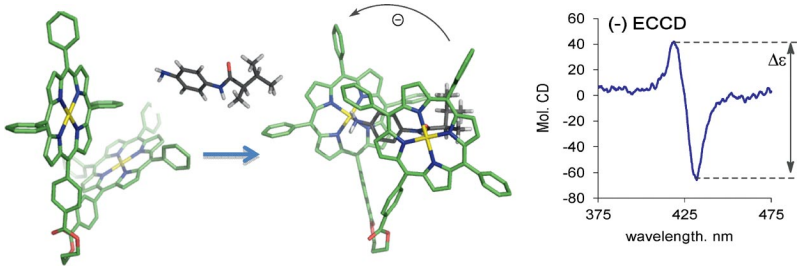

Metallated porphyrin tweezer systems are used as reporters of absolute stereochemistry. They bind to chiral guest molecules and adopt a specific helical arrangement that is observable via exciton coupled circular dichoroism. Conformational flexibility of the linker that joins the two porphyrins of a tweezer stabilizes a common conformation, as shown for a variety of α-chiral carboxylic acids.

Keywords: Stereochemistry / Chirality / Sensors / Helical structures / Host-guest systems / Porphyrinoids

