Sensing Remote Chirality: Stereochemical Determination of β-, γ-, and δ-Chiral Carboxylic Acids

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Sensing Remote Chirality: Stereochemical Determination of β-, γ-, and δ-Chiral Carboxylic Acids**

*Marina Tanasova, Mercy Anyika, and Babak Borhan**

Abstract: *Determining the absolute stereochemisty of small molecules bearing remote nonfunctionalizable stereocenters is a challenging task. Presented is a solution in which appropriately substituted bis(porphyrin) tweezers are used. Complexation of a suitably derivatized β-, γ-, or δ-chiral carboxylic acid to the tweezer induces a predictable helicity of the bis(porphyrin), which is detected as a bisignate Cotton Effect (ECCD). The sign of the ECCD curve is correlated with the absolute stereochemistry of the substrate based on the derived working mnemonics in a predictable manner.*

Discoveries in enantioselective chemistry have outpaced the growth in methodologies for absolute stereochemical determination of asymmetric molecules. While conventional methods, such as nuclear magnetic resonance (NMR) spectroscopy[1] and exciton coupled circular dichroism (ECCD),[2] allow stereochemical characterization of chiral synthons, they are limited by the position of the stereocenter and are most often applicable to determining the chirality of carboxylic acids, amines, or alcohols bearing stereocenters at the site of functionality. Few reports address the determination of β-chiral carboxylic acids or remote chirality, and among those, the scope of substrates is limited to carboxylic acids which bear either an aromatic moiety[3] or a hydroxy or amino functionality at the stereocenter[4] (the latter functionalities are used as handles for derivatization). Determining the absolute stereochemistry of β-substituted carboxylic acids in the absence of a chromophoric or a derivatizable site or more remote stereocenters remains a challenging task. We present herein a method for the absolute stereochemical determination of β-, γ-, and δ-chiral carboxylic acids by ECCD with the use of bulky porphyrin tweezers.

Complexation of a chiral substrate (guest) with a zinc bis(porphyrin) tweezer (host) yields a conformationally rigid helical system, thus giving rise to exciton coupling (ECCD) between the two chromophores of the tweezer. The sign of the latter ECCD curve, detected as either a positive or a negative signal, reflects the chirality of the bound substrate and enables the direct assignment of the guests' absolute stereochemistry by the use of mnemonics derived for that particular system.[5] The subsequent correlation of the observed ECCD sign with the established geometry of the host–guest complex, which reflects the major ECCD-active conformation of the guest (i.e., mnemonic), enables a direct assignment of the guests' absolute stereochemistry. The ECCD method has enabled the unambiguous absolute stereochemical assignment of a large number of substrates, such as alcohols, amines, diols, epoxides, and carboxylic acids, to name a few.[2f,g,5] We envisioned extending the use of porphyrin tweezers, which have been used successfully with α-substituted functionalities, for sensing remote stereocenters. Nonetheless, the conventional ZnTPP[6] or ZnTPFP tweezers[7] failed to yield observable ECCD spectra when complexed with guest molecules bearing chiral centers remote from the site of coordination with the host metalloporphyrin.

We previously observed that the sensitivity of the tweezer can be modulated by the sterics of the porphyrins[8] and the conformational flexibility of the linker.[6b] Based on the latter studies, and in pursuit of a molecular sensor for determining the absolute stereochemistry of stereogenic centers distal from the sites of binding, we synthesized the sterically demanding zinc 5-(4-carboxyphenyl)-10,50,20-tri-*tert*-butylphenyl porphyrin tweezers, ZnTBP-C_5 (TBP5) and ZnTBP-C_3 (TBP3), which were derived from a pentanediol or propanediol linker, respectively. The 3,5-bis-*tert*-butyl-substituted phenyls of the ZnTBP tweezers (Figure 1) were expected to generate a more sterically sensitive binding cavity and facilitate steric interactions with remote stereocenters within the host–guest complex.

Modelling studies of the ZnTPP and ZnTBP tweezer complexed with the carrier-derivatized[9] (*R*)-(+)-citronellic acid **1**, a representative substrate bearing a stereocenter at the β-carbon atom, were performed. It is noteworthy that substrate complexation to a bis(porphyrin) tweezer requires two sites of binding, and for carboxylic acids this binding is achieved with the use of a suitable carrier (here 1,4-phenylenediamine). Hence, **1** was modelled in the form represented in Table 1. The tweezer–amide complex was assembled by coordinating the amide carbonyl group and the free amine with the two porphyrins and the steric interactions within the complex were evaluated after geometry optimization (see the Supporting Information for details). The minimized structures revealed the potential for enhanced steric interactions within the ZnTBP tweezer, compared to the ZnTPP tweezer, as a result of the *tert*-butyl substituents which are directed into the binding pocket of the tweezer (Figure 1). A strong

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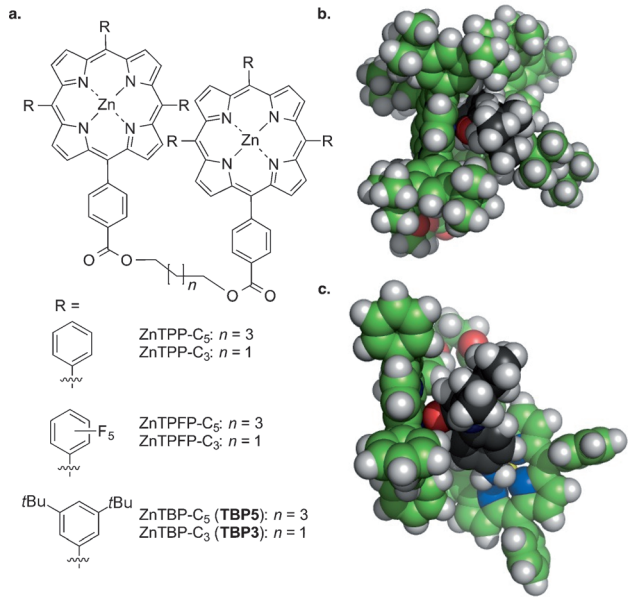
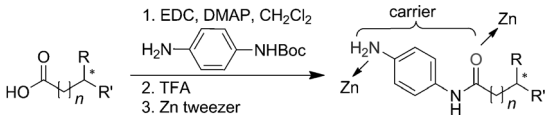


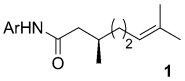
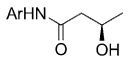
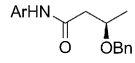
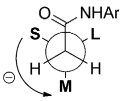
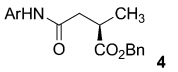
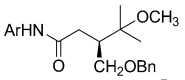
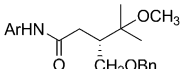
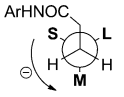
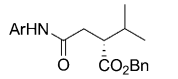
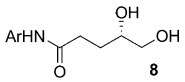
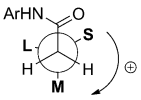
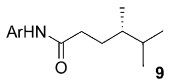
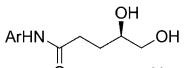
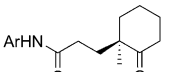
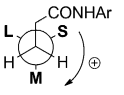
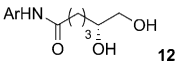
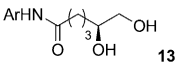
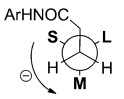
Figure 1. Bis(porphyrin) tweezers: a) Structures of porphyrin tweezer. b) TBP3 tweezer complex with **1**. c) TPP3 tweezer complex with **1** (MMFF, Spartan 14).

negative ECCD spectrum was obtained for **1** with TBP5 and TBP3, and further supports the fact that enhanced steric interactions indeed facilitate sensing of asymmetry within the tweezer–substrate complex (Table 1, entry 1). It should be noted that ECCD is not observed for **1** with the non-bulky ZnTPP tweezer. Encouraged by this result, we synthesized and analyzed a series of β-, γ-, and δ-chiral amides bearing alkyl, alkoxy, and aryl substituents at the asymmetric center and measured ECCD spectra with bulky tweezers.

Our initial focus was to assess the feasibility of using TBP5 and TBP3 for the absolute stereochemical determination of β-chiral carboxylic acids (Table 1). After the required derivatization with the carrier, the resulting chiral amides were complexed with TBP5 and TBP3. The measured K_a values were in the range of $2–3 \times 10^4\,M^{-1}$, and the complexes yielded ECCD spectra with significant magnitudes. The observed ECCD signs with β-chiral amides followed a consistent and predictable trend, with all pseudoidentical substrates yielding the same helicity. We use the term pseudoidentical to describe substrates that have substituents with the same relative size, defining the same handedness, at the asymmetric center (based on their A-values[10]). For instance, the substituents at the chiral center of **3** are as follows: CH_3 is the large group (A-value = 1.74), OBn is the medium group (A-value = 0.9), and H is the small group. The amide **4** bears a CH_3 group (large substituent) and a medium ester moiety (A-value of 1.20). When placed in the same conformation with respect to the carbonyl group, the relative spatial orientation of large/medium/small substituents at the chiral center for **3** and **4** is similar, thus making these two substrates identical with respect to their chirality. When analyzed in this manner, **1–5** constitute one set of pseudoidentical compounds and are expected to induce ECCD of the same sign. Based on the same rationale, **6** and **7** are pseudoidentical to one another,

Table 1: Stereochemical analysis of β-δ-chiral alkyl and alkoxy amides.[a]



Substrate	TBP5 λ [nm] (Δε)	TBP3 λ [nm] (Δε)	Conformation/ ECCD Sign
 **1**	431 (−104) 422 (+80) A = −184	430 (−82) 421 (+78) A = −160	
 **2**	431 (−57) 422 (+53) A = −110	429 (−52) 422 (+48) A = −100	
 **3**	430 (−120) 421 (+102) A = −222	429 (−57) 421 (+44) A = −101	
 **4**	431 (−120) 421 (+115) A = −235	429 (−123) 421 (+94) A = −217	
 **5**	430 (−37) 421 (+35) A = −72	429 (−212) 420 (+183) A = −395	
 **6**	431 (+214) 421 (−120) A = +334	429 (+240) 421 (−192) A = +432	
 **7**	432 (+163) 421 (−133) A = +296	429 (+145) 421 (−100) A = +245	
 **8**	430 (+61) 422 (−45) A = +107	430 (−42) 421 (+33) A = −75	
 **9**	430 (+105) 423 (−87) A = +192	430 (−118) 423 (+101) A = −209	
 **10**	430 (−58) 422 (+40) A = −98	429 (+43) 421 (−27) A = +70	
 **11**	430 (−17) 425 (+10) A = −27	429 (+32) 421 (−30) A = +62	
 **12**	435 (+35) 422 (−26) A = +61	430 (+42) 420 (−47) A = +89	
 **13**	435 (−43) 422 (+33) A = −76	430 (−49) 420 (+53) A = −102	

[a] ECCD obtained in methylcyclohexane at 0 °C with 1 μM porphyrin tweezer and 20 equiv of chiral substrate. The total amplitude of the ECCD spectrum is reported as a sum of $|\Delta\varepsilon|$. The (+) or (−) sign of the ECCD corresponds to the sign of the CD at higher wavelength. Ar = *p*-aminophenyl, A = total amplitude.

but pseudoenantiomeric to **1–5**. Therefore, tweezer complexes with **1–5** versus **6** and **7** are expected to yield ECCD spectra of opposite sign. Indeed, as can be seen from Table 1, **1–5** induced a negative ECCD, while a positive ECCD was observed for **6** and **7**. Moreover, complexes of TBP5 and

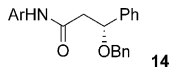
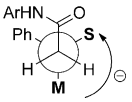
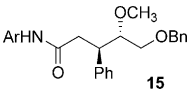
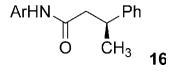
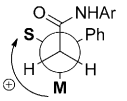
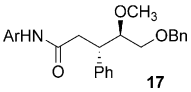
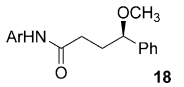
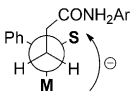
TBP3 were of the same helicity, thus yielding ECCD spectra of the same sign.

The next task was to extend the analysis to alkyl and alkoxy γ- and δ-substituted amides. Gratifyingly, despite the remote positioning of the chiral center from the carbonyl-bound porphyrin, all complexes produced strong ECCD signals, with a consistent trend where pseudoidentical substrates such as **8** and **9** produced an ECCD of the same sign, while the pseudoenantiomeric substrate **10** yielded an ECCD of the opposite sign (Table 1). Interestingly, the presence of a free hydroxy group in **8** and **10** did not interfere with the binding conformation, thus suggesting tolerance of the method to potential coordinating or hydrogen-bonding moieties. It is noteworthy that differentiation is also effective with a quaternary stereocenter. Thus, the substrate **11**, bearing a tetrasubstituted chiral carbon atom, induced ECCD of the same sign as its pseudoidentical analogue **10**. The two enantiomeric δ-chiral amides **12** and **13** (Table 1) induced ECCD spectra showing opposite helicity. Although we have tested a limited number of δ-chiral substrates, the amplitude of the observed ECCD indicates a significant sensitivity of TBP5 and TBP3, even with such remotely positioned stereocenters.

While both TBP5 and TBP3 tweezers effectively sense β-, γ-, and δ-stereocenters, there appears to be a discrepancy in the sign of the ECCD induced by γ-chiral amides when complexes to TBP5 versus TBP3. We have previously observed behavioral shifts with alterations in linker length and flexibility, and attributed them to the greater flexibility of C_5- versus C_3-linked porphyrin tweezers.[6b,11] Unlike TBP5, the complexes of TBP3 with all amides (**1**–**13**) follow the same mode of stereodifferentiation regardless of the position of the chiral center. Namely, the pseudoidentical substrates **2**, **8**, and **13**, representative of β-, γ-, and δ-chiral amides, respectively, induce a negative ECCD, while the pseudoidentical **7** and **12** yield a positive ECCD. As a result, the TBP3 tweezer was chosen as the optimal metalloporphyrin host for all of our studies.

ZnTBP tweezers are also effective sensors for β- and γ-chiral amides bearing an aromatic group at the asymmetric center (Table 2). Similar to β-chiral alkyl and alkoxy amides, the pseudoidentical aryl amides **14** and **15** (Ph: A-value 2.8, large group) induce a negative ECCD signal with both TBP5 and TBP3 tweezers, while their pseudoenantiomeric analogues **16** and **17** induce an opposite, positive ECCD signal. It is also noteworthy that stereodifferentiation is effective for cases where substrates bear two stereocenters (**15** and **17**). Despite the asymmetric center at C4, stereodifferentiation by the tweezer is based on the closest C3 stereocenter. Complexation of bulky tweezers with γ-substituted aryl amides also induces strong ECCD signals (see **18**; Table 2). Nonetheless, ECCD spectra obtained with aryl-substituted amides are opposite in sign with respect to their alkyl analogues. Thus, the pseudoenantiomeric amides **1** and **14** induce ECCD spectra of the same sign, while the pseudoidentical amides **1** and **16** induce ECCD signals of the opposite sign. The inversion in the ECCD signals observed for amides bearing an aryl group has been documented previously.[8,9] Aryl-group-directed change in conformational preference was also

Table 2: Stereochemical analysis of β- and γ-chiral aryl amides with TBP5 and TBP3.[a]

Substrate	TBP5 λ [nm] (Δε)	TBP3 λ [nm] (Δε)	Conformation/ ECCD Sign
 **14**	435 (−40) 425 (+44) A = −84	429 (−59) 420 (+61) A = −120	
 **15**	436 (−58) 426 (+65) A = −123	430 (−40) 421 (+45) A = −85	
 **16**	430 (+230) 421 (−140) A = +370	431 (+162) 421 (−100) A = +262	
 **17**	435 (+58) 424 (−53) A = +111	429 (+58) 421 (−40) A = +98	
 **18**	435 (+25) 422 (−27) A = +52	430 (−41) 420 (+43) A = −84	

[a] ECCD obtained in methylcyclohexane at 0 °C with 1 μM porphyrin tweezer and 20 equiv of chiral substrate. The total amplitude of the ECCD spectrum is reported as a sum of $|\Delta\varepsilon|$. The (+) or (−) sign of the ECCD corresponds to the sign of the CD at higher wavelength. Ar = *p*-aminophenyl, A = total amplitude.

detected in nanoassemblies, where complexation of β-δ chiral aryl versus alkyl carboxylic acids with gold nanoparticles led to complexes of different geometries, probably as a result of the secondary interaction between metal nanoparticles and closely situated aryl substituents.[12] With respect to the β-, γ-, and δ-chiral amides analyzed herein, the conformational change appears to be induced by the secondary interaction with the N-Ar carrier, since no change in the ECCD sign between pseudoidentical alkyl- and aryl-substituted substrates was observed when 1,3-diaminopropane was used as the carrier in studies with α-chiral acids.[13]

With the empirical observations in hand, we focused on understanding the mode of stereodifferentiation with the goal of generating a working mnenonic. To derive the correlation between the observed ECCD and chirality of amides tested in this study, we performed conformational analyses of amides and evaluated the contribution of the lowest-energy conformer (LEC), and conformers within 2 kcal mol^{-1} of the LEC, to the observed ECCD (see the Supporting Information for details). The LEC of the β-chiral amides **1** and **7** has the small group pseudo-*syn* to the carbonyl group (Figure 2 a and b). The medium group occupies the position perpendicular to the carbonyl group, thus effectively hindering one side of the molecule. Upon complexation of the tweezer with the LEC, **P1** would be expected to approach the amide carbonyl group from the least hindered side (side opposite to the medium group, Figure 2 a). Binding of **P2** to the amine group opposite **P1** completes the complex. For **1** such binding would yield a complex of negative helicity, thus matching the observed (−)-ECCD. The other four conformers of **1**, lying within 2 kcal mol^{-1} of the LEC, represent rotational isomers around the C3–C4 bond and also predict a (−)-ECCD (see the

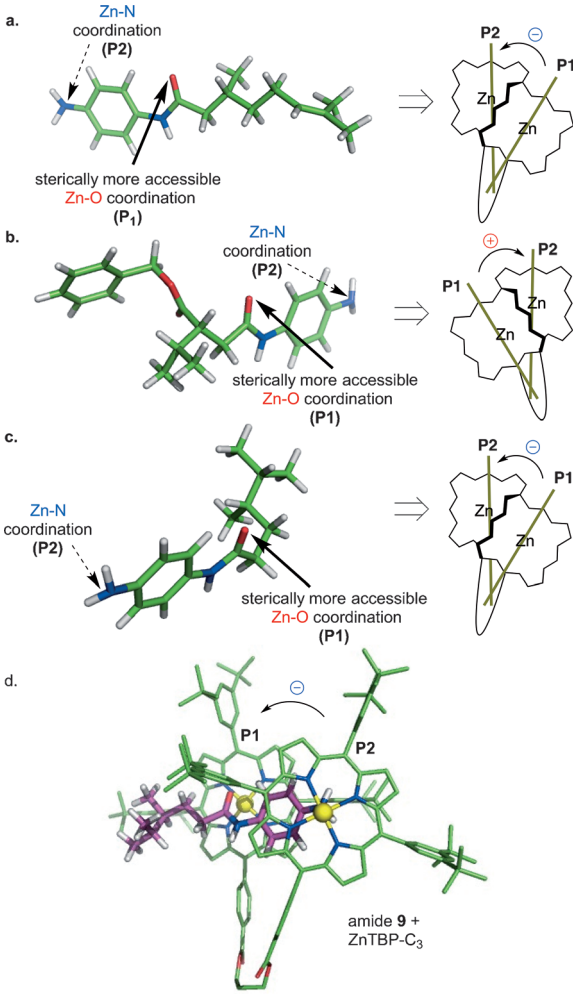


Figure 2. The lowest-energy ECCD-active conformer of a) **1**; b) **7**, and c) **9**. d) Complexation of a low-energy conformer to the tweezer yields a chiral complex with helical orientation of porphyrins corresponding to the observed ECCD sign (molecular modeling with Spartan14, Graphical data visualization by PyMol).

Supporting Information). Other conformational isomers representing rotations around the C2–C3 and C1–C2 bonds are of higher energy and are unlikely to contribute to the ECCD-active population. Likewise, for **7**, we found two rotational isomers which were within 2 kcal mol^{-1} of the LEC, all of which predicted the observed (+)-ECCD.

While the conformational search predicts major ECCD contributors for β-chiral amides, identifying ECCD-active conformers for γ- or δ-chiral amides is complicated by the larger number of conformers which are within 2 kcal mol^{-1} of the LEC. Nonetheless, binding of the lowest-energy conformer identified for the γ-chiral amide **9** bound to TBP3, with **P1** binding the C=O from the most accessible direction, yields a complex of negative helicity, which corresponds to the observed ECCD data (Figure 2c and d). Overall, the consistency in stereodifferentiation of β-, γ-, and δ-amides by the TBP3 tweezer leads to a simplified analysis of the results. For alkyl and alkoxy chiral carboxylic acids, the correlation can be made by viewing the substrate in an extended Newman projection, thus placing the small group *syn* to the carbonyl group, and noting the rotation from the small group (S), through the medium (M), towards the large group (L) (S→M→L, sizes assigned based on A-values; see mnemonics in Tables 1 and 2). If the designated rotation is clockwise, a positive ECCD would be expected, and vice versa. As a result of the π–π interaction, the mnemonic for β- and γ-aryl-substituted carboxylic acids derivatized with 1,4-phenylenediamine is reversed. This working mnemonic can be easily utilized to translate the observed ECCD data into the stereochemistry of the bound guest.

In conclusion, determination of remote stereocenters by using ECCD is now possible with the use of a bulky chromophoric host, TBP3 tweezer. The system is amenable for substrates bearing alkyl and aryl groups at the chiral center, as well as alkoxy, hydroxy, oxo, or carboxyl functionalities.

Keywords: chirality · circular dichroism · host–guest systems · stereochemistry · zinc

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