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Absolute Stereochemical Determination of Chiral Carboxylic Acids

Qifei Yang, Courtney Olmsted, and Babak Borhan*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

borhan@cem.msu.edu

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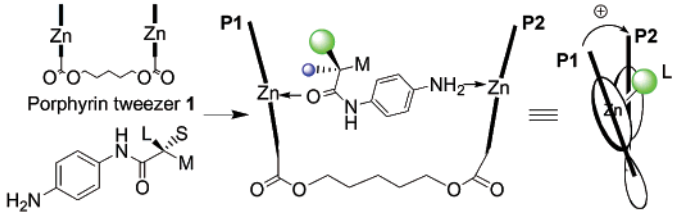
ABSTRACT



Monoamidation of 1,4-diaminobenzene with α-chiral carboxylic acids leads to a carrier strategy for absolute stereochemical determination with bis-zinc porphyrin tweezers by exciton-coupled circular dichroism (ECCD). The helicity induced in the porphyrin tweezers upon complexation with the derivatized carrier originates from the preferred conformation of the $C_{carbonyl}$—C_{chiral} bond. Correct ECCD signs can be predicted by the rotamer that places the large group perpendicular to the carbonyl group with the small group facing the porphyrin.

The exciton-coupled circular dichroism (ECCD) method, a nonempirical approach for absolute stereochemical determinations,[1,2] has been applied to a wide variety of compounds. These include polyols and carbohydrates,[3,4] amines,[5] amino acids, and amino alcohols,[6,7] and hydroxy acids.[8,9] ECCD is observed between two or more chromophoric systems that have no or only negligible molecular orbital overlap and interact through space in a chiral fashion. The relative orientation of the two chromophores in space results in a predicted sign of the couplet; i.e., a clockwise orientation of two interacting chromophores yields a positive couplet and vice versa (Figure 1, insert).[1] Therefore, the challenge lies in orienting two or more chromophoric receptor groups in a chiral fashion as a direct result of the binding of a chiral compound and extrapolating the chirality of the bound compound from the ECCD spectra. Since the observed sign of the couplet is a direct consequence of the relative position of the chromophores, the assignment of chirality is nonempirical.[1]

The general applicability of this approach has been demonstrated by binding of the bis-zinc porphyrin dimer (porphyrin tweezer) **1** with various chiral diamines.[10] The chirality of diamines can be rationally predicted by anticipating favorable steric interactions between the receptor porphyrins and the chiral center in which the bound porphyrin closer to the asymmetric center (**P1**) slides away from the bulky group. This in turn leads to ECCD coupling of the two porphyrins, and the sign of the bisignate reflects the chirality of the bound compound.

However, the porphyrin tweezer method is not directly applicable to chiral compounds with only one site of attachment since the two porphyrin groups cannot be oriented relative to each other. A solution to this problem was recently

(1) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.
(2) Nakanishi, K.; Berova, N. *The Exciton Chirality Method*; VCH Publishers: New York, 1994.
(3) Rele, D.; Zhao, N.; Nakanishi, K.; Berova, N. *Tetrahedron* **1996**, *52*, 2759.
(4) Chang, M.; Meyers, H. V.; Nakanishi, K.; Ojika, M.; Hill, J.; Park, M. H.; Takeda, R.; Vazquez, J. T.; Wiesler, W. T. *Pure Appl. Chem.* **1989**, *61*, 1193.
(5) Skowronek, P.; Gawronski, J. *Tetrahedron Lett.* **2000**, *41*, 2975.
(6) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643.
(7) Zahn, S.; Canary, J. W. *Org. Lett.* **1999**, *1*, 861.
(8) Gimple, O.; Schreier, P.; Humpf, H.-U. *Tetrahedron*: *Asymmetry* **1997**, *8*, 11.
(9) Rickman, B. H.; Matile, S.; Nakanishi, K.; Berova, N. *Tetrahedron* **1998**, *54*, 5041.
(10) Huang, X.; Rickman, B.; Borhan, B.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 6185.

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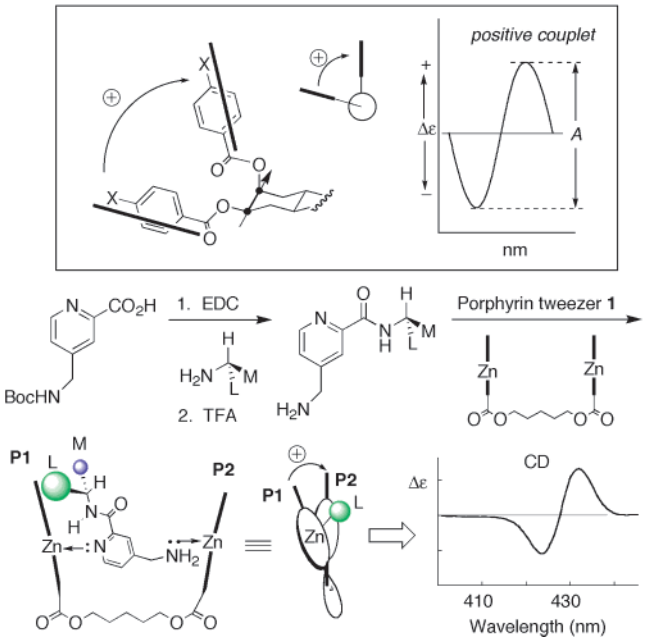
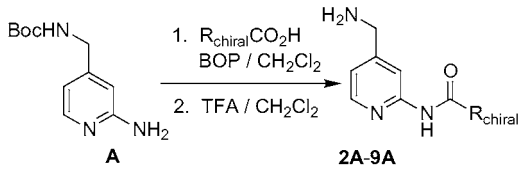


Figure 1. Insert: Through−space interaction of two independently conjugated chromophores results in an ECCD spectrum, the sign of which depends on the orientation of the two interacting electric transition dipole moments. The absolute stereochemistry of chiral amines can be investigated by carrier-based porphyrin tweezer methodology.

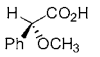
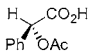
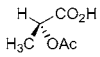
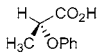
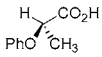
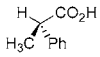
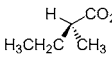
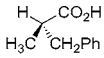
published by Nakanishi, Berova, and co-workers, where monoamines with one site of attachment were derivatized to a carrier that would provide the necessary two binding sites for the porphyrin tweezer.[11] This is illustrated in Figure 1,[11] where derivatization of a chiral amine through the carboxylate functionality of the carrier led to the formation of a conjugate that yielded the observed ECCD spectra upon binding with **1**. This technique has proved to be successful for the absolute stereochemical determination of amines and alcohols in a nonempirical fashion.[11,12] Herein, we have applied the porphyrin tweezer method using carriers derivatized with α-chiral carboxylic acids.

To be effective, the carrier needs to possess the following characteristics. (1) It should have a functional group that could be used for attaching the chiral compounds. For example, an amine would serve well in cases where a chiral carboxylic acid is to be analyzed. (2) The derivatized carrier should be able to bind with porphyrin tweezer **1**[13] or a comparable host to form a 1:1 macrocyclic complex. (3) The derivatized carriers should be reasonably rigid because flexible structures would give multiple conformations leading to weak or even complex CD spectra. (4) The carriers should be achiral since chiral compounds coupled with chiral carriers would yield diastereomers, which would complicate interpretation of the resulting CD spectra. With these limitations in mind, carrier **A** (Table 1) was synthesized as our first target.[13] Derivatization of chiral acids with carrier **A** was uneventful and followed standard amide formation methodology with BOP in CH_2Cl_2.[14]

Table 1. CD Predictions and Amplitudes of Carrier **A**-Derivatized Chiral Carboxylic Acids Bound to Porphyrin Tweezer **1**



A **2A-9A**

chiral acid	predict	Δε	A
 **2** (*S*)	**2A** neg	Not observed	---
 **3** (*S*)	**3A** neg	432 (-35) 424 (+46)	-81
 **4** (*S*)	**4A** neg	431 (-28) 423 (+29)	-57
 **5** (*S*)	**5A** neg	429 (+70) 421 (-54)	+124
 **6** (*R*)	**6A** pos	429 (-58) 420 (+60)	-118
 **7** (*R*)	**7A** pos	427 (-15) 417 (+14)	-29
 **8** (*S*)	**8A** neg	430 (-33) 422 (+39)	-72
 **9** (*R*)	**9A** neg	430 (-6) 422 (+15)	-21

Initially, a simplistic model based on a molecular modeling conformational search (Monte Carlo)[13] of the chiral carboxylic acid conjugated carrier **A** was used to predict the anticipated sign of the ECCD spectra. Our expected ECCD were dictated by placing the medium group syn to the amide hydrogen, which in turn would give rise to a preferred helicity of the bound porphyrin tweezer as a result of avoiding steric interactions with the large group. However, early on we had to abandon this method of analysis since the predictions did not match the observed ECCD spectra (see Table 1, conjugates **2A**, **5A**, **6A**, and **7A**), most probably because we had not incorporated the binding of the porphyrin to the pyridine nitrogen atom into our modeling. Ligation of the zinc tetraphenylporphyrin (Zn-TPP) to carrier **A** conjugates and conformational analyses suggested a flaw in the design of carrier **A**. To a large degree, this was attributed to the rotation of the $C_{aryl}-N_{amide}$ bond upon binding of the porphyrin moiety since the coplanar amide-phenyl arrangement was not maintained due to steric crowding (Figure 2).[13]

(11) Huang, X.; Borhan, B.; Rickman, B. H.; Nakanishi, K.; Berova, N. *Eur. J. Chem.* **2000**, *6*, 216.
(12) Kurtan, T.; Nesnas, N.; Li, Y. Q.; Huang, X. F.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2001**, *123*, 5962.
(13) See Supporting Information.
(14) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676.

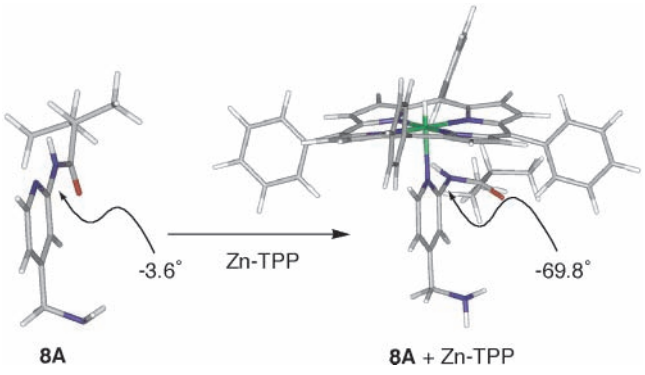


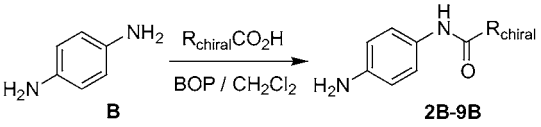
Figure 2. Binding of the Zn porphyrin to carrier **A** conjugates forces the rotation of the $C_{aryl}-N_{amide}$ bond, causing the nearly coplanar amide to become staggered with respect to the aromatic ring.

It became apparent that a more rigid carrier could limit the number of possible conformations upon binding to the zinc porphyrin.

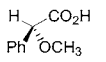
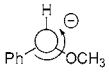
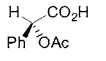
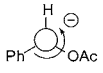
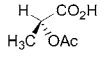
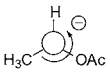
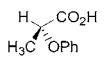
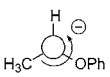
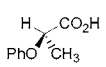
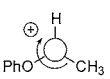
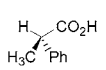
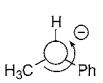
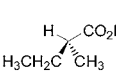
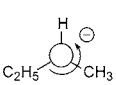
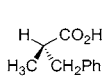
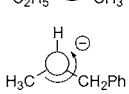
Carrier **B** (Table 2) was proposed as an alternate in order to alleviate the problems associated with carrier **A**. Mono-amidation of 1,4-diaminobenzene (carrier **B**) with chiral carboxylic acids and BOP was facile and led to the isolation of the conjugates in 70−92% yield. It was expected that the binding of the porphyrin tweezer to conjugates of carrier **B** would not be as strong as carrier **A**, since the zinc porphyrin would have to bind to the amide carbonyl oxygen. However, binding in this manner would bring the porphyrin moiety closer to the chiral center. Also, the $C_{aryl}-N_{amide}$ bond rotation would not be consequential in this system. The induced helicity within the porphyrin tweezer would thus be governed by the rotation of the $C_{carbonyl}-C_{chiral}$ bond.

Prior to investigating carrier **B** by modeling, binding of the porphyrin tweezer **1** with carrier **B** conjugates was investigated by NMR and IR. Although it was expected that zinc porphyrins would bind to the carbonyl oxygen,[16] the possibility of binding to the amide nitrogen would drastically change the course of our studies.

Table 2. CD Predictions and Amplitudes of Carrier **B**-Derivatived Chiral Carboxylic Acids Bound to Porphyrin Tweezer **1**



B **2B-9B**

chiral acid		predict	mnemonic	Δε	A
	**2** (*S*)	**2B** neg		427 (-39) 420 (+43)	-82
	**3** (*S*)	**3B** neg		432 (-19) 419 (+22)	-41
	**4** (*S*)	**4B** neg		431 (-50) 420 (+38)	-88
	**5** (*S*)	**5B** neg		429 (-158) 420 (+116)	-274
	**6** (*R*)	**6B** pos		429 (+200) 420 (-83)	+283
	**7** (*R*)	**7B** neg		430 (-105) 420 (+85)	-190
	**8** (*S*)	**8B** neg		430 (-22) 420 (+26)	-48
	**9** (*R*)	**9B** neg		433 (-26) 421 (+28)	-54

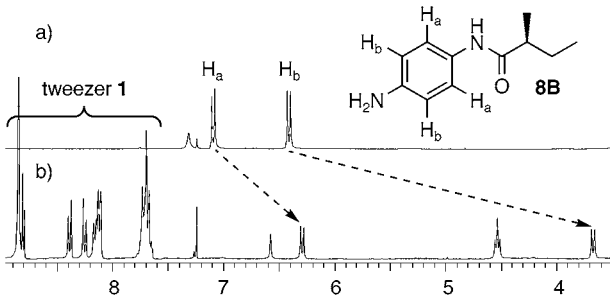


Figure 3. (a) ^{1}H NMR of **8B**. (b) ^{1}H NMR of **8B** with tweezer **1** (1 equiv). The larger upfield shift of H_b signifies its closer proximity to the porphyrin ring.

Figure 3 depicts the NMR of **8B** with and without binding to porphyrin tweezer **1**. The upfield shift of the carrier protons is expected due to the anisotropic shielding by the porphyrin rings. However, the aryl protons H_a are upfield shifted by 0.62 ppm, while H_b shifts by 2.48 ppm. The larger upfield shift of H_b indicates their closer proximity to the bound porphyrin as compared to H_a. We would have expected a larger upfield shift for H_a if the porphyrin was bound to the amide nitrogen. The major change in the IR upon complexation of **7B** with tweezer **1** was a large increase in the intensity of the amide II band. This is also attributed to the binding of the zinc porphyrin to the carbonyl oxygen, which results in a larger C−N amide double-bond character and thus an increased intensity in the NH deformation.

Modeling of the carrier **B** conjugates bound to Zn-TPP resulted in a more uniform set of structures as compared to carrier **A**.[13] In all the structures studied, the rotation of the $C_{carbonyl}-C_{chiral}$ bond is such that the large group is almost perpendicular to the carbonyl with the small group pointed toward the porphyrin plane and the medium group staggered with respect to the amide proton (Figure 4). We would therefore expect the porphyrin to slide in the direction of the small group. The relative size of the substituents is based

(15) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994.
(16) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 385.

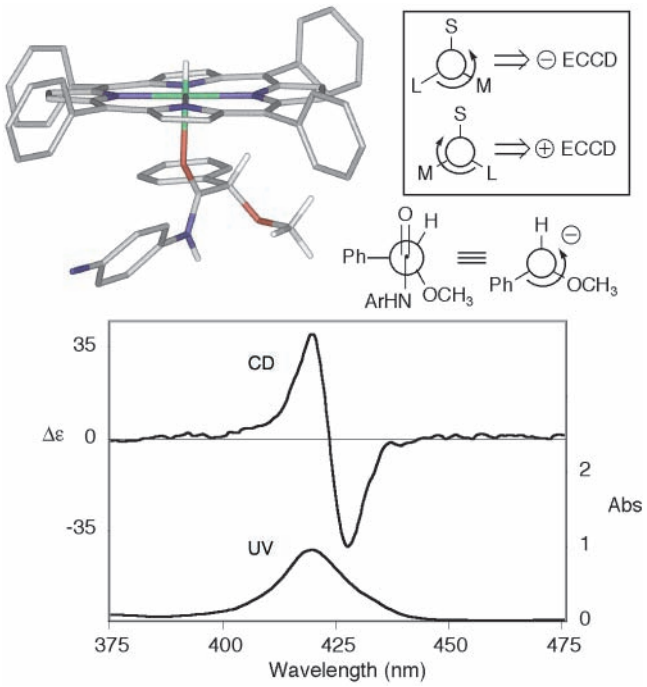


Figure 4. Minimized structure of Zn-TPP bound to **2B** (most of the hydrogen atoms deleted for clarity) in which the chiral center has adopted a conformation to minimize steric strain. In all cases, the large group is nearly perpendicular to the amide carbonyl with the small group pointing toward the porphyrin. UV of **2B** bound to **1** exhibits the Soret band at 419 nm; the CD of the same has a strong negative ECCD couplet. Insert: Clockwise orientation of the large, medium, and small groups based on A values (viewed with the carboxylate in front) leads to a positive ECCD spectrum with carrier **B**-derivatized chiral carboxylic acids, and vice versa.

on the A values for each.[15] The placement of oxygen-containing substituents (invariably the medium group in our group of compounds) was more syn with respect to the amide hydrogen, thus facilitating H-bonding. This arrangement leads to the large and small groups bisecting the carbonyl oxygen and once again dictates the helicity of the bound porphyrin.

Table 2 lists the predicted and observed ECCD for compounds **2B**−**9B**. Gratifyingly, the sign of the observed ECCD signals matches the predicted values based on the mnemonic presented above (Figure 4, insert). Compounds **5B** and **6B** are enantiomers exhibiting opposite ECCD spectra. If one considers that phenyl is larger than methyl group, then the results obtained for **7B** do not fit the prediction, and in fact a positive ECCD would be expected. However, we believe that possible hydrogen bonding between the phenyl and the amide proton, as suggested by others for similar systems,[12,17−19] effectively places the phenyl group syn to the amide hydrogen, thus yielding the observed ECCD. This causes the phenyl group to behave as the medium group when **7B** is bound to tweezer **1**.

The chemical shift of the amide proton for carrier **B** conjugates provides further evidence for the syn-like arrangement of the phenyl and the amide hydrogen. The chemical shift for **8B** with ethyl and methyl substituents is at 7.3 ppm and can be considered as the benchmark for the amide proton that does not interact with the groups at the chiral center. The chemical shift for **2B**−**6B**, which contain an oxygen substituent, ranges from 7.7 to 8.4 ppm and could be indicative of H-bonding between the oxygen and the amide hydrogen. The chemical shift for the amide proton of **7B** resonates at 6.9 ppm. The upfield shift arises from the shielding of the amide proton by the phenyl group.

Another possibility is that consideration of A values for analysis of **7B** is not valid due to other intramolecular forces, namely, stacking interactions. Our modeling of **7B** bound to Zn-TPP suggests that the phenyl group adopts an arrangement parallel to the porphyrin. The probable stacking interaction of the phenyl group could be responsible for the tilting of the porphyrin toward it, thus causing it to behave as a small substituent that results in the observed ECCD.

In conclusion, we have utilized a carrier strategy to investigate the chirality of asymmetric carboxylic acids. Carrier **A**, which is analogous to the carrier utilized for chiral amines previously,[11] did not yield predictable ECCD spectra, most probably due to the unpredictable single-bond rotamers between the porphyrin binding site and the chiral center. However, carrier **B**, with a closer porphyrin binding site with respect to the chiral center, produced consistent ECCD spectra, which can be rationalized and predicted by molecular modeling. Studies with alternate carriers are ongoing.

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Supporting Information Available: Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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