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Absolute Stereochemical Determination of Organic Molecules through Induction of Helicity in Host–Guest Complexes

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Cite This: *Acc. Chem. Res.* 2021, 54, 654–667 Read Online

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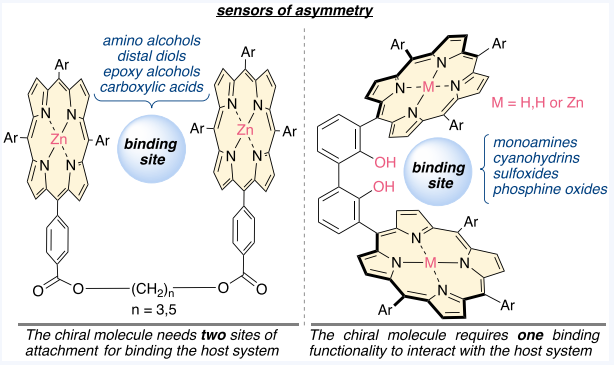
CONSPECTUS: Stereochemistry is a fundamental molecular property with important ramifications for structure, function, and activity of organic molecules. The basic building blocks of living organisms (amino acids and sugars) exhibit a precisely selected set of molecular handedness that has evolved over millions of years. The absolute stereochemistry of these building blocks is manifested in the structure and function of the cell machinery (e.g., enzymes, proteins, etc.), which are essential components of life. In the many chemical subdisciplines, molecular stereochemistry is exceedingly important and is often a strong determinant of structure and function. Besides its biological implications, the centrally important role of stereochemistry in many disciplines of chemistry and related fields has led to tremendous effort and activity, highlighted by the success in stereoselective syntheses of a host of functionalities. In the present climate, it is often the difficulty of assigning absolute stereochemistry as opposed to synthesis, which has become a nontrivial challenge, requiring the attention of the community. There will not be a general solution to this problem, as each system will have its own unique requirements and challenges; however, the need for rapid, routine, and microscale analysis is apparent. This is especially true with parallel and high-throughput arrays for screening conditions and catalysts, generating a large number of samples that require analysis.



In this Account, we summarize our contribution to this field through the development of molecular receptors for sensing molecular asymmetry. These methodologies strive to unambiguously assign the absolute configuration of asymmetric center(s). To accomplish this task, our laboratory has designed a variety of host molecules, bearing various binding elements, to form stable complexes with chiral molecules (guests). During this complexation event, the stereochemistry of a target molecule induces a supramolecular chirality (i.e., helicity) within the host system. The design of the host system is such that the helicity of the host/guest complex can be observed and assigned via Exciton Coupled Circular Dichroism (ECCD), a nonempirical technique for identifying handedness, which is correlated back to the absolute stereochemistry of the bound chiral molecule. Taking advantage of the high sensitivity of chiroptical techniques (in terms of the required amount of sample for analysis) and fast response time, these methodologies offer a microscale, rapid, and nonempirical solution for assignment of absolute stereochemistry.

The first part of this Account describes application of porphyrin tweezers as reporters of chirality for the absolute stereochemical determination of various classes of organic molecules. This methodology is suitable to report the absolute configuration of organic molecules that contain *two* binding elements (nitrogen or oxygen based functionalities). In the second part, host systems that do not require two sites of attachment to form ECCD active complexes will be described. This enables the absolute stereochemical assignment of challenging chiral molecules with functional groups lacking routine techniques for analysis.

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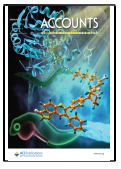
Received: October 3, 2020
Published: January 11, 2021



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Soc. **2012**, *134*, 9026−9029.[2] *With the optimized tweezer, the absolute stereochemistry of remotely spaced diols (as far as 1,16-diols) were determined. A unique "side-on" binding interaction between fluorinated poprhyrin tweezer and 1,n glycols (n ≥ 3) was proposed based on UV−vis, X-ray data, and computational analysis.*

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- Anyika, M.; Gholami, H.; Ashtekar, K. D.; Acho, R.; Borhan, B. Point-to-axial chirality transfer—a new probe for "sensing" the absolute configurations of monoamines. *J. Am. Chem. Soc.* **2014**, *136*, 550−553.[4] *A new bis-porphyrin based host system with a bisphenolic linker was utilized to sense the asymmetry of monoamines without the need for derivatization. Hydrogen bonding of the amine with the host phenol groups yields a diastereomeric complex, in which one of the equlibrating atropisomers (P or M) is favored.*

1. INTRODUCTION

Most biologically active molecules and pharmaceutical agents are stereochemically rich structures. The absolute stereochemistry of a molecule often has a profound impact on its function and interaction, whether it is in the context of biology, synthesis, or even material chemistry. Examples of the latter are levofloxacin, an antibiotic, where the (*S*)-enantiomer binds more efficiently with DNA gyrase than its (*R*)-counterpart,[5] and thalidomide, the "morning sickness" antinausea medicine, where the (*R*)-enantiomer was teratogenic and led to devastating malformities in embryonic development.[6] A reliable and historically relevant method to determine absolute stereochemistry has been to compare the optical properties (i.e., optical rotation) of a compound to that of a known sample. X-ray crystallography can provide an unambiguous assignment of configuration if a high-quality crystal can be obtained.[7,8] Pioneered by Mosher, and with further modifications by other researchers,[9−13] derivatization of a molecule into a diastereomeric pair has offered a fairly practical method for the absolute stereochemical determination of chiral molecules with a site for derivatization (i.e.; hydroxyl or amino group). Limited to specific cases, the derivatization step can be eliminated by using chiral solvating agents.[14,15]

An enabling alternative is to leverage the unique properties of chiroptical techniques and, in particular, circular dichroism (CD) to interrogate absolute stereochemistry.[16] In this approach, the stereochemical identity of a target molecule is translated into a detectable chiroptical response that ultimately leads to its absolute stereochemical determination. Fundamental to this tactic is the diastereomeric interactions of circularly polarized light, both left and right-handed components, with the chiral entities or complexes. This event leads to a characteristic Cotton effect (positive or negative),[16,17] which is the consequence of the molecular helicity of the molecule. Depending on the wavelength, the Cotton effect could be due to the absorption of circularly polarized light by electronic transitions leading to electronic circular dichroism (ECD) or through vibrational transitions leading to vibrational circular dichroism (VCD). Nonetheless, neither of these techniques can be independently utilized to assign the absolute configuration of a stereocenter since the sign of the resultant Cotton effect is empirical in nature. A solution is to compare the experimental results with ECD and VCD spectra obtained through computational methods. As one can expect, the scope of these techniques is limited, and reliable computed ECD[18] and VCD[19,20] spectra are time-consuming and require certain computational expertise.

Within the realm of chiroptical techniques, Exciton Coupled Circular Dichroism (ECCD) provides a nonempirical alternative to the assignment of helicity.[16,17] The fundamentals of the ECCD approach is based on the pioneering work by Nakanishi et al.,[21] illustrating that the through space exciton coupling between two or more helically oriented electric transition dipole moments (*etdm*) of independently conjugated chromophores leads to a bisignate Cotton effect, with a sign that is directly correlated to the helicity of the coupling chromophores.[16,17] Their initial investigations exploited ECCD for the assignment of absolute configuration of conformationally rigid sterols (Figure 1).[21] The alcohol functionalities were derivatized as

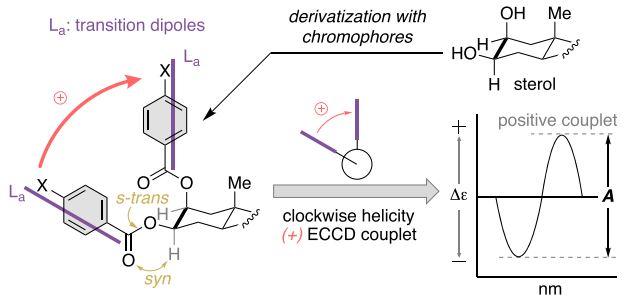

Figure 1. Exciton chirality method, nonempirical determination of absolute configurations.

dibenzoates to introduce the required chromophoric entities. Since either the positive or negative ECCD signal is directly correlated to the *clockwise* or *counterclockwise* arrangement of the chromophores (helicity),[17] respectively, the method unambiguously assigns the absolute configuration of the carbinol centers in a nonempirical fashion. The ECCD method provides an avenue to exploit chiroptical techniques for the absolute stereochemical determination of chiral molecules, in the event they form chiroptically active complexes with chromophoric "molecular receptors." Thus, a general characteristic of such molecular receptors is the presence of two or more chromophores on an achiral skeleton that would be arranged in a unique asymmetric fashion upon complexation with a chiral guest. The helicity of the complex, induced upon binding of the chiral guest, is dictated by the stereocenters in the guest molecule.

A number of groups have engaged in exploring CD active complexes as a means to elucidate the absolute stereochemistry of organic molecules.[22−27] Dynamic covalent interactions (i.e., coordination to metal centers, Schiff base formation, etc.) as well as hydrogen bonding interactions are the most common binding modes to achieve CD active complexes.[22−26] The advantage of these approaches stem from requiring minimal to no chemical manipulation prior to analysis, high sensitivity, and amenability toward high throughput analyses. Indeed, the elegant systems reported from Anslyn, Wolf, and other groups have demonstrated the utilization of CD active complexes for determination

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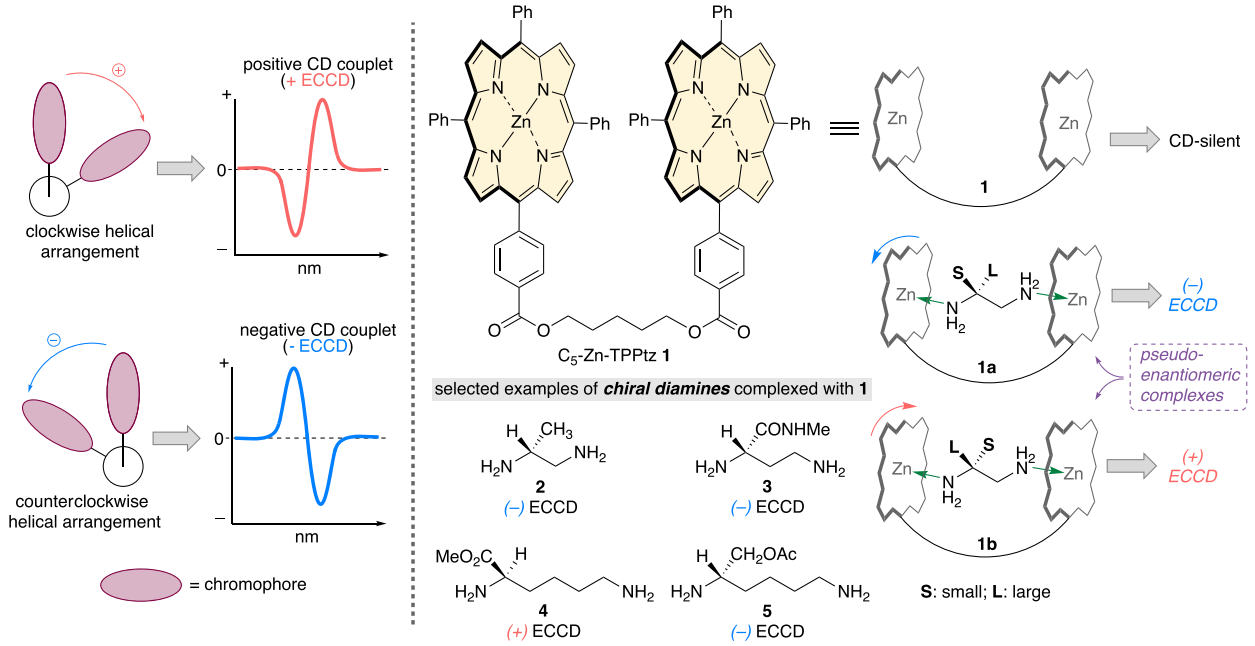
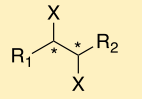
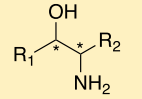
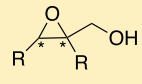
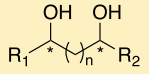
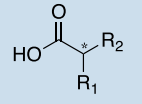
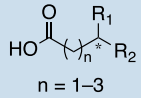
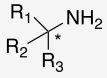
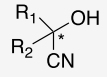
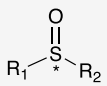
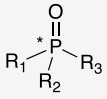


Figure 2. General representation of an ECCD active complex. Utilization of porphyrin tweezer methodology for determination of absolute configuration of chiral diamines.

Chart 1. Summary of Porphyrin-Based Host Systems for the Absolute Stereochemical Determination of Various Functional Groups

Functional Group	Host - Guest ECCD Method
 X = OH or NH_2	○ Host: C_5-Zn-TPFPtz **8** ○ **two sites of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min ○ ***works for both threo and erythro systems***
	○ Host: C_5-Zn-TPFPtz **8** ○ **two sites of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min ○ ***works for both threo and erythro systems***
	○ Host: C_5-Zn-TPFPtz **8** ○ **two sites of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min ○ ***works for both cis and trans systems***
 n = 1-14	○ Host: C_3-Zn-TPFPtz **24** ○ **two sites of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min
	○ Host: C_3-Zn-TPPtz **1** ○ **one site of attachment** ○ **requires derivatization** ○ Required amount: mg ○ Required time: day

Functional Group	Host - Guest ECCD Method
 n = 1–3	○ Host: C_3-Zn-TBPtz **64** ○ **one site of attachment** ○ **requires derivatization** ○ Required amount: mg ○ Required time: day
	○ Host: MAPOL **74** ○ **one site of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min
	○ Host: Zn-MAPOL **82** ○ **two sites of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min ○ ***works for both secondary and tertiary cyanohydrins***
	○ Host: Zn-MAPOL **82** ○ **one site of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min ○ ***works for sulfoxides, sulfinates, sulfinamides***
	○ Host: Zn-MAPOL **82** ○ **one site of attachment** ○ **no derivatization** ○ Required amount: μg ○ Required time: min ○ ***works for phosphine oxides, phosphinates, phosphoramidates, bisphosphine oxides***

of absolute configuration, enantiomeric excess, yield, and composition of a reaction mixture.[28,29]

Our research endeavor finds its origin in the design and utilization of porphyrin tweezers developed by Nakanishi and co-workers (see structure **1**, Figure 2), an achiral molecular host, for the assignment of absolute configuration of amino acids and diamines, using the principles of ECCD.[30] In this approach, two porphyrin subunits, tethered via a flexible alkyl chain, constitute

https://dx.doi.org/10.1021/acs.accounts.0c00650
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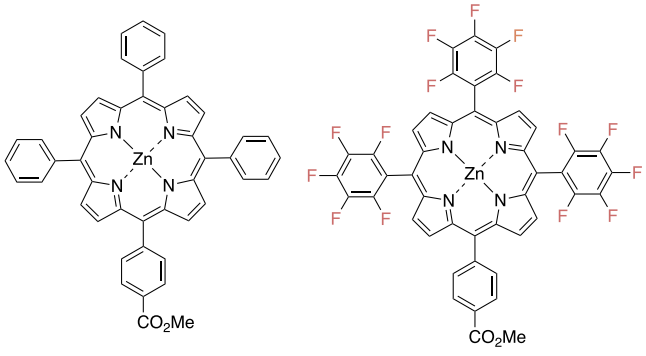
a molecular tweezer that function as a sensor of asymmetry for bound chiral guest molecules.[31−34] Chiral molecules containing two sites of attachment (e.g., *diamines*) form stable complexes with the C_5-Zn-TPPtz **1**,[35] leading to the preponderance of a specific helicity of the porphyrin subunits with respect to each other (**1a** and **1b**, Figure 2). The helicity of the complex is detected as a positive or negative ECCD signal. The key to the absolute stereochemical determination lies in correlating the experimentally observed helical arrangement of the tweezer (either **1a** or **1b**) with the chirality of the bound guest molecule. The adopted helicity of the tweezer system is often in response to the steric demands dictated by the asymmetric carbon center of the bound diamine. The porphyrin closest to the chiral center adopts an orientation to avoid steric repulsion with the larger group (**L**) on the chiral center. This event leads to the preponderance of either the *P* or *M* helical population, and thus, a positive or negative ECCD signal is observed, respectively. This method has been utilized to report the absolute configuration of various chiral diamines. In the following sections, we summarize the evolution of porphyrin-based host systems, utilized for various functional groups over the past 20 years (see Chart 1 for a pictorial summary).

2. DETERMINATION OF ABSOLUTE CONFIGURATION FOR MOLECULES WITH TWO SITES OF COORDINATION

2.1. Absolute Stereochemical Determination of Chiral Diols

The porphyrin tweezer methodology was effective in determining the absolute configuration of chiral molecules containing *two* strongly coordinating groups that bound to the divalent zinc center (diamines).[30] The interaction of the Lewis basic nitrogen atoms with the Lewis acidic divalent zinc atoms of the tweezer was central to the success of this system. Extending this approach to chiral diols or amino alcohols was not trivial. Lower affinity of the oxygen atom as a coordinating functionality led to weak complexation with C_5-Zn-TPPtz **1**, yielding either no ECCD spectra or weak signals. This was demonstrated by measuring the binding affinity of isopropanol with monomeric zinc porphyrin (Zn-TPP monoester **6**), exhibiting a substantially lower affinity as compared to isopropylamine (Figure 3, highlighted box, K_{assoc} of 49 M^{-1} versus 11 400 M^{-1}, respectively).[1] The solution was to increase the binding affinity for oxygen based nucleophiles with the divalent zinc atoms embedded within the porphyrin by using electron deficient porphyrin rings. Predictively, the fluorinated porphyrin analogue (Zn-TPFP monoester **7**) should enhance the Lewis acidity of the divalent zinc center, thus leading to stronger complexation with oxygen-based nucleophiles. Comparison of the HOMO and LUMO energies as well as the charge density on the zinc center in Zn-TPFP monoester **7** with the parent zinc porphyrin Zn-TPP monoester **6** indicated a lower LUMO energy as well as a higher positive charge density on the zinc center (Figure 3). The association constants (K_{assoc}) of isopropylamine and isopropanol complexed with Zn-TPFP monoester **7** showed a much higher affinity toward alcohol as well as amine binding (~40× larger) in comparison to Zn-TPP monoester **6** (Figure 3).[1]

Based on the latter understanding, C_5-Zn-TPFPtz **8** was prepared and complexed with chiral diols in hexane, leading to consistent ECCD signals (Figure 4). The choice of solvent for ECCD analysis is critical. It is of utmost importance that the solvent does not compete or interfere with the complexation of the chiral guest molecule with the zincated porphyrin host system. We have found that nonpolar solvents such as hexane and methylcyclohexane satisfy the latter requirement, while keeping the components of the analysis soluble. It should be



	E_{LUMO} eV	$E_{LUMO} - E_{HOMO}$ eV	Mulliken charge of Zn^{2+}	electrostatic charge of Zn^{2+}	K_{assoc} (*i*PrOH) M^{-1}	K_{assoc} (*i*PrNH$_2$) M^{-1}
6	−2.211	3.891	0.942	1.337	49±2	11400±950
7	−2.818	3.284	0.961	1.387	2170±140	473000±8700

Figure 3. Electronic manipulation of porphyrin tweezers.

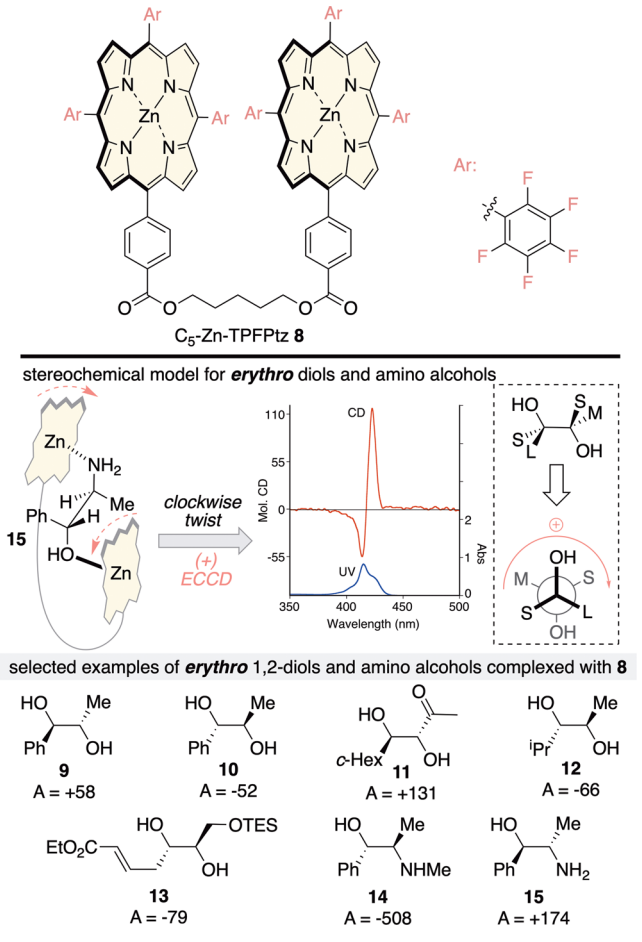


Figure 4. *erythro*-1,2-Diols and amino alcohols complexed with tweezer **8**. Typically, 1 μM porphyrin tweezer was bound with 100 equiv of diol in hexane at 0 °C. For amino alcohols such as **14** and **15**, 5 equiv of substrate was utilized.

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noted that, in the case of *erythro* and *threo* diols and 1,2-amino alcohols, the porphyrin bound to each stereogenic functionality governs the induced helicity of the bound porphyrins. In analogy to the mnemonic described for C_5-Zn-TPPtz **1** with chiral diamines (Figure 2), the sterics projected from the chiral centers of the guest molecules determine the respective arrangements of the bound porphyrins. As illustrated in Figure 4 for *erythro* compounds (for instance **15**), the two coordinating sites prefer the *anti* arrangement to alleviate steric repulsion of the substituents on vicinal stereocenters. Furthermore, the porphyrin rings coordinate to the binding sites (oxygen or nitrogen atoms) *anti* to the largest group on the chiral center (phenyl and methyl groups). The porphyrin rings would further adopt a twist toward the small group (hydrogen), which in the illustrated case leads to a clockwise twist, and thus a positive ECCD signal. The stereochemical model for *erythro* diols can be further simplified in the form of a Newman projection (Figure 4, dashed box). It should be noted that, prior to this work, absolute stereochemical determination of *erythro* diols via the dibenzoate methodology[1] was not possible since the high population rotamer places the benzoates *anti* to each other. This is an ECCD silent conformation.

The use of the fluorinated tweezer C_5-Zn-TPFPtz **8** was easily extended to *threo* diols (Figure 5).[1] In these compounds, the

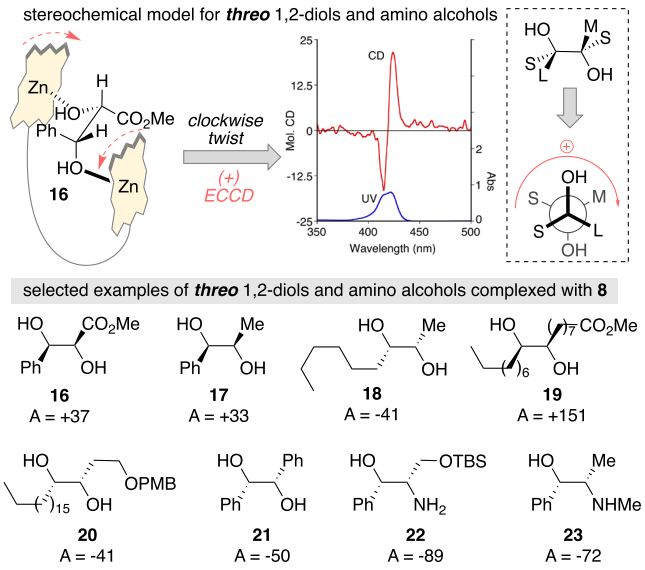

Figure 5. *threo*-1,2-Diols and amino alcohols complexed with tweezer **8**. Typically, 1 μM porphyrin tweezer was bound with 40 equiv of diol in methylcyclohexane at 0 °C. For amino alcohols such as **22** and **23**, 5 equiv of substrate was utilized.

preferred conformation is such that the large groups on adjacent chiral centers adopt an *anti*-orientation, thus placing the binding elements in a *gauche* conformation. The binding paradigm and stereo differentiation scenario is analogous to that described above for *erythro* compounds.

2.2. Absolute Stereochemical Determination of Distal Diols

Having demonstrated the utility of the C_5-Zn-TPFPtz **8** (optimized for weakly coordinating functionalities), we next examined if the methodology could be extended to molecules with coordinating group separated by more than two atoms.[2] The distance between the two binding sites, and the increased flexibility of the system could result in multiple energetically close conformations, leading to potential issues requiring attention. When a set of chiral 1,*n*-diols ($n \geq 3$) were complexed with C_5-Zn-TPFPtz **8**, inconsistent ECCD signals were observed. This was attributed to the increased flexibility of the complex, resulting in multiple unanticipated conformations. These discrepancies were resolved by switching to a more rigid porphyrin tweezer that reduced the flexibility of the overall complex when bound with 1,*n*-diols (Figure 6). Tweezer C_3-Zn-

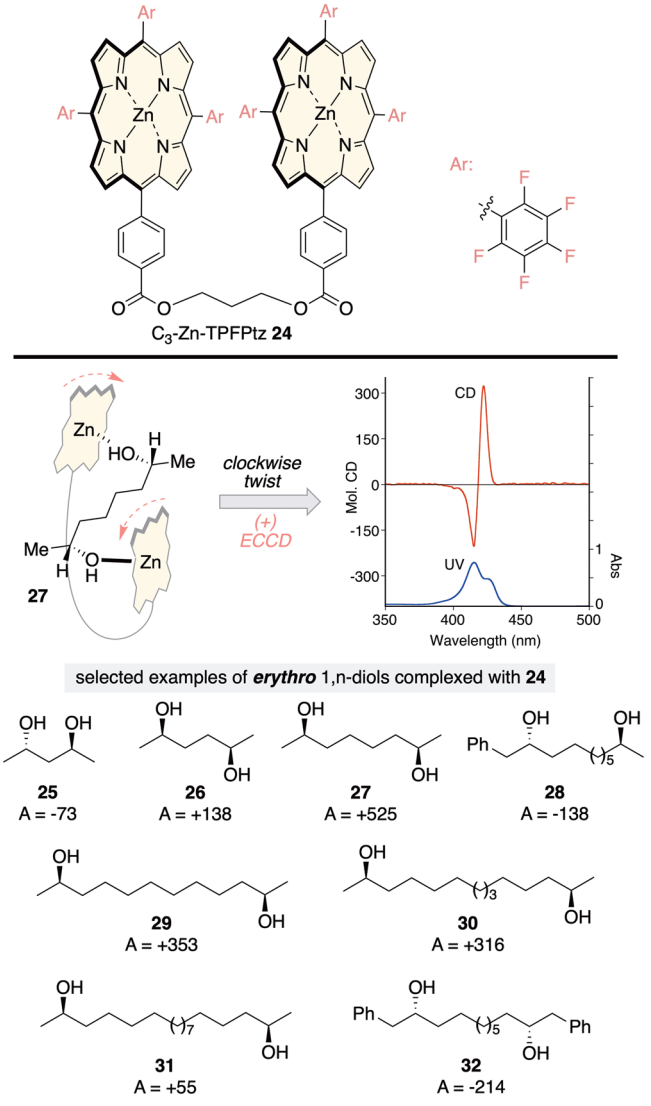

Figure 6. Distal diols complexed with tweezer **24**. Typically, 2.5 μM porphyrin tweezer was bound with 40 equiv of diol in hexane at 0 °C.

TPFPtz **24** with a shorter alkyl linker (C_3) was complexed with chiral diols shown in Figure 6 to provide ECCD signals in full agreement with the predicted helicities. Key for the success of this approach was to assume a unified binding interaction between 1,*n*-diols with various lengths (1,3 to 1,16) and C_3-Zn-TPFPtz **24**. Although it seems counterintuitive that a shorter linker is required to achieve consistent binding with diols that have up to 14 methylene spacer units, the picture that emerged was that the shorter linker forced what we referred to as the "side-on" binding for all diols. This interaction scenario was arrived at on the basis of UV−vis data, computational modeling studies, and X-ray analysis of long chain diols. As opposed to the "head-on" binding that would require an increase in the interchromophoric distance between the porphyrin rings with

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increased spacing of the diols, the "side-on" binding model predicts the porphyrins will slide in a hinge-like fashion to accommodate small and large diols. In this manner, the interchromophoric distance would not change as much, as the porphyrins slide away from each other in a face-to-face manner. Evidence for this came from similar binding constants for diols of various length, as well as the observed minimal changes in the UV−vis spectrum of the short vs long diols complexed with C_3-Zn-TPFPtz **24**. Interchromophoric distance between two porphyrins results in predictable shifts in the Soret band[36] and thus can be used as a "molecular ruler."[37] Therefore, in support of the "side on" binding model, the negligible change in the absorption band upon binding a 1,6 vs a 1,12-diol indicated little change to the interchromophoric distance between the planes of the porphyrin rings.

2.3. Absolute Stereochemical Determination of Epoxy Alcohols

Having successfully used the fluorinated porphyrin tweezers for complexation with alcohols, we turned our attention to the absolute stereochemical determination of a historically challenging class of compounds, the epoxy alcohols.[38] The readily accessible chiral epoxy alcohols are incredibly versatile and highly useful as one of the most important members of the chiral pool. Determination of their absolute configuration, however, is primarily based on analogy or chemical manipulation by converting them into known molecules.[39−42] The association constant of C_5-Zn-TPFPtz **8** bound to epoxy alcohols was slightly lower than that of diols (K_{assoc} of **35** with **8** is 2.88×10^4 M^{-1} versus 1.5×10^5 M^{-1} for a typical diol).[38] Nonetheless, the concurrent coordination of the primary alcohol and the epoxide oxygen atom to the zinc centers was sufficient to drive the complex formation, and to generate ECCD active complexes (Figure 7). A mnemonic was proposed to correlate the observed ECCD signal to the absolute stereochemistry of the bound epoxy alcohol. In the proposed mnemonic, the coordination of the primary alcohol and epoxide oxygen atom (from the less sterically hindered face of epoxide ring) to the zinc atoms was considered as the main binding interaction. In a typical substrate, where the order of bulkiness of substituents is as follows: $R_1 > R_2 \geq R_3$, the porphyrin attached to the epoxide oxygen atom would slide away from the larger group (R_1) and slide toward the smaller group (R_2). This arrangement would force the porphyrin attached to the hydroxyl group to slide toward the R_3 substituent to avoid steric clash between two porphyrin rings. For the stereochemistry depicted in Figure 7, the two porphyrins would adopt a counter clockwise twist, thus leading to a negative ECCD signal. This mnemonic was successfully utilized to determine the absolute stereochemistry for a number of differentially substituted chiral epoxy alcohols. The methodology described above requires the epoxy alcohol functionality (dual binding) and thus fails for monoepoxides that have no other coordinating group. Elegant contributions from Trapp, Kreckel, and co-workers,[43] Takanami et al.,[44] and Jiang et al.[45] address the absolute stereochemical determination of monoepoxides.

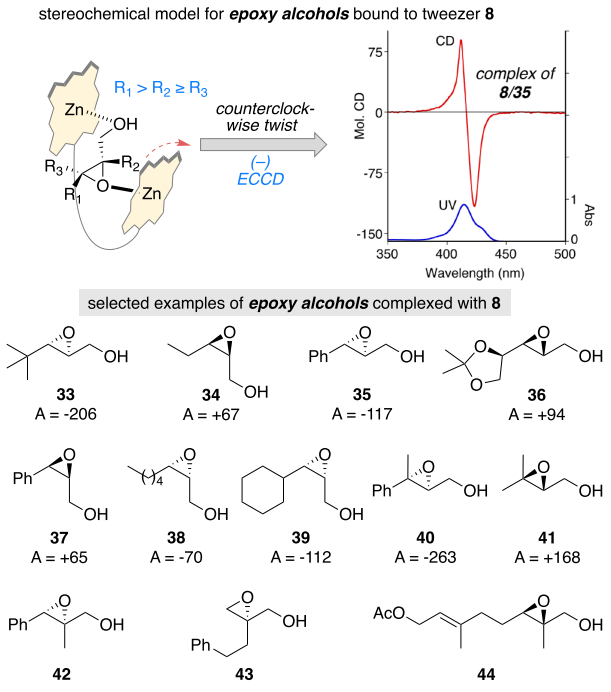

Figure 7. Epoxy alcohols complexed with tweezer **8**. Typically, 2 μM porphyrin tweezer was bound with 40 equiv of epoxy alcohol in hexane at 0 °C.

3. DETERMINATION OF ABSOLUTE CONFIGURATION FOR MOLECULES WITH A SINGLE SITE OF COORDINATION WITH DERIVATIZATION

3.1. Absolute Stereochemical Determination of α-Chiral Carboxylic Acids

As highlighted thus far, the tweezer methodology was confined to chiral molecules with *two* sites of attachment. This methodology was amended to sense the absolute configuration of chiral molecules with *one* site of attachment through a derivatization step prior to complexation with porphyrin tweezers. The strategy entailed the use of a "carrier," which was installed on the chiral molecule to provide an additional binding site for complexation with the chromophoric tweezers.[46] The constrains for a suitable carrier were set as follows: (a) It should bear an appropriate functionality for derivatization; (b) it should have functional groups, preferably nitrogen based motifs, for strong coordination to the zincated porphyrins; (c) a desirable carrier would have a rigid framework, so that it will not contribute to conformations that could complicate prediction of geometry; (d) a carrier should be achiral since the asymmetry of the unknown molecule should be the only element that dictates the helicity of the bound porphyrin tweezer.

Nakanishi, Berova, and co-workers used the carrier-based strategy for the absolute stereochemical determination of chiral monoamines and monoalcohols.[47,48] We used an analogous approach for the absolute stereochemical determination of α-chiral carboxylic acids. Our initial carrier developed for this purpose was the amino pyridine **45** (Figure 8), which quickly demonstrated the need for rigidified carriers as the results were inconsistent, leading to unpredictable ECCD spectra.

A simple evolution to a more rigidified carrier led to the use of 1,4-diamino benzene **46** for facile derivatization with chiral carboxylic acids. The resultant amides complexed with C_5-Zn-TPPtz **1** generated ECCD signals consistent with the asymmetry of the guest molecule. Computational modeling of amides obtained with **46** indicated a dominant conformational preference in which the large group on the chiral center resides perpendicular to the amide nitrogen. In this arrangement, the small group is pointed toward the porphyrin plane and the

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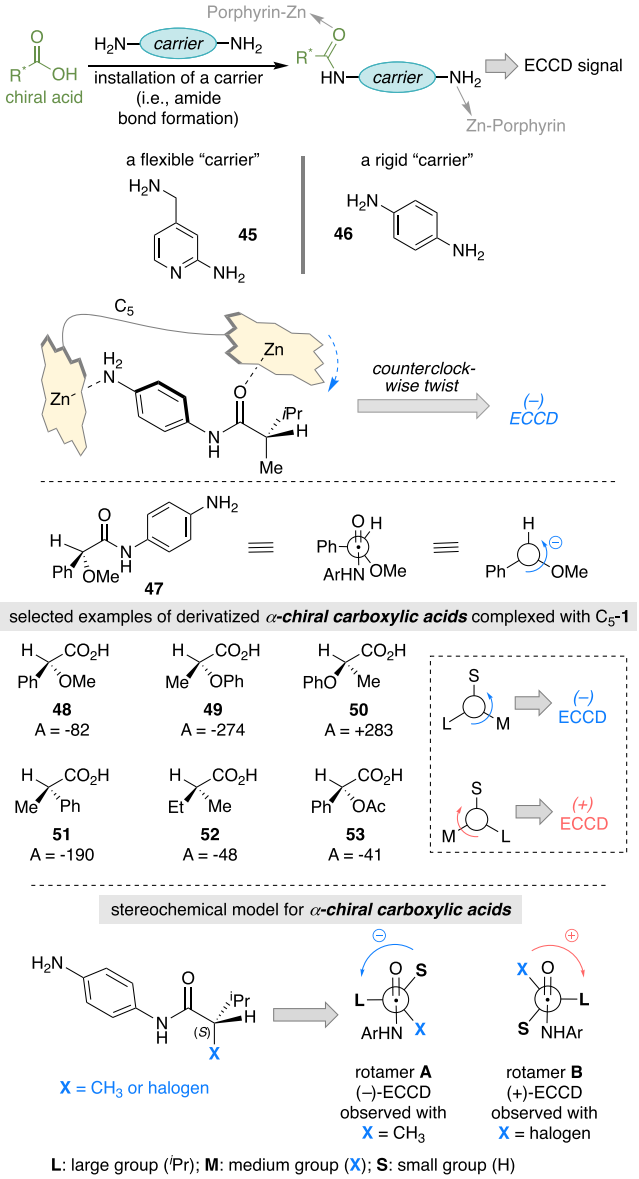

Figure 8. Sensing asymmetry of α-chiral carboxylic acids; Development of a *carrier*. Typically, 1 μM porphyrin tweezer was bound with 40 equiv of carrier derivatized chiral carboxylic acid in methylcyclohexane at 0 °C.

medium group is staggered with respect to the amide proton (Figure 8). The relative size of substituents (based on their A-strain values) dictates the arrangement of the bound porphyrins. As such, the porphyrin bound to the amide nitrogen (closer proximity to the chiral center), would prefer to slide away from the larger substituent to alleviate steric repulsion. A simplified mnemonic derived from this analysis was developed and utilized to correlate the sign of the observed ECCD signals to the absolute configuration of the bound derivatized carboxylic acids (Figure 8, dashed box).[46]

Extension of this methodology to chiral α-halo carboxylic acids led to a peculiar observation.[49] The mnemonic developed above did not explain the observed ECCD signals (Figure 8). A thorough analysis of the results showed that a different rotamer is preferred for the bound derivatized α-halo carboxylic acids. As illustrated in Figure 8, rotamer **A** is preferred for nonhalogenated carboxylic acids; however, rotamer **B** dominates for α-halo carboxylic acids. This switch in conformational preference was attributed to a possible halogen–π interaction with the porphyrin system. We realized that, among various tweezers, C_3-Zn-TPPtz **1** produced ECCD signals that were correlated to the identity of the asymmetric center, irrespective of the nature of the substituents on the α-carbon (Figure 9).[50] This

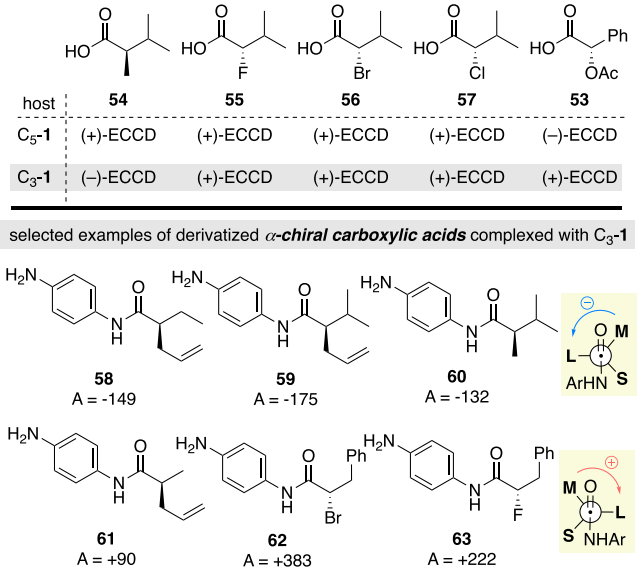

Figure 9. In pursuit of a unified host for sensing the absolute configuration of α-chiral carboxylic acids. Typically, 1 μM porphyrin tweezer was bound with 20 equiv of carrier derivatized chiral carboxylic acid in methylcyclohexane at 0 °C.

observation once again highlighted the importance of a more rigidified host system (via a short linker) that limits the number of possible rotamers, leading to a consistent readout of chirality. With this optimized tweezer in hand, a set of chiral carboxylic acids, including α-halogenated examples, were derivatized with **46** to yield their corresponding amides (Figure 9). Gratifyingly a unified working model was obtained to report the absolute configuration of chiral carboxylic acids based on the size of the substituents on the asymmetric center.

3.2. Determination of Absolute Configuration of Remote Stereocenters on Chiral Carboxylic Acids

Most of the methodologies developed for stereochemical determination require the binding element(s) reside on the stereocenter. Applying the same strategy to detect the absolute stereochemistry of chiral centers remote from the point of attachment is often fruitless. This piqued our interest to investigate the ability of the tweezer system to sense the absolute configuration on remote stereocenters in carboxylic acid (i.e., β-, γ-, and δ-chiral carboxylic acids).[3] Quickly we realized that this challenge requires an altered host system with "tentacles" that can reach further from the point of attachment with the zincated porphyrins. This idea led to C_5-Zn-TBPtz **64**, with 3,5-di-*tert*-butyl phenyl groups on the *meso* positions of the porphyrin rings, which was able to sense the asymmetry on remote stereocenters (Figure 10). We further rigidified the system using the shorter C_3 linker (C_3-Zn-TBPtz **64**) to deliver consistent ECCD data upon complexation with derivatized chiral carboxylic acids bearing remote stereocenters. The stereochemical model for each class is illustrated in the dashed boxes in Figure 10. Of note, the presence of heteroatoms on the remote stereocenter (hydroxyl for instance) did not interfere with the binding

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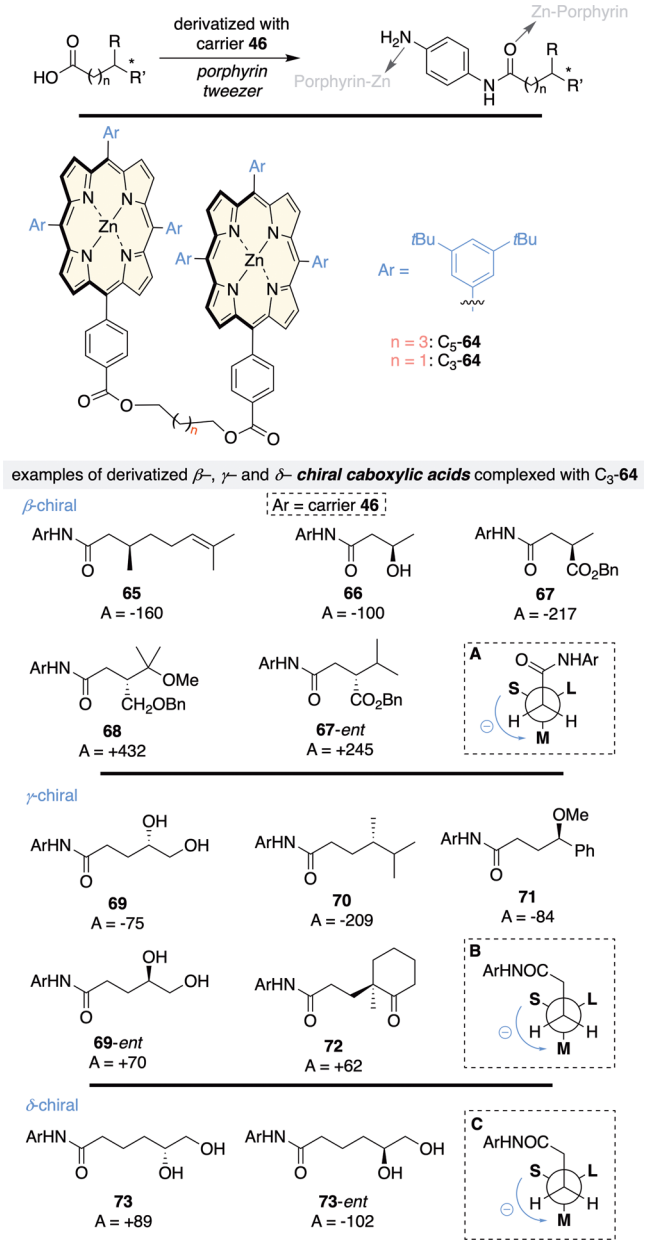

Figure 10. Sensing the absolute configuration of carboxylic acids bearing remote stereocenters. Typically, 1 μM porphyrin tweezer was bound with 20 equiv of carrier derivatized chiral carboxylic acid in methylcyclohexane at 0 °C.

since the porphyrins used were not fluorinated, and thus were not capable of strong binding to hydroxyl groups. This highlights the ability to tune the electronics of metalloporphyrins to selectively bind desired functional groups.

4. DETERMINATION OF ABSOLUTE CONFIGURATION FOR MOLECULES WITH ONE SITE OF ATTACHMENT WITHOUT DERIVATIZATION

4.1. Absolute Stereochemical Assignment of Chiral Monoamines

What has been described thus far are methodologies that can be applied to molecules with *two* sites of attachment for bidentate coordination with the two zincated porphyrin rings of the tweezers. For compounds such as diols, amino alcohols, diamines, etc. the latter binding regime is achieved directly. Molecules with *one* site of attachment, however, require a prefunctionalization step that installs an extra coordination site for binding to the tweezers. A significant improvement would entail the formation of an ECCD active complex with chiral molecules that possessed *one* coordination/binding element without the need for derivatizations or other prefunctionalization steps. We have described various mechanisms utilized to rigidify and thus heighten the sensitivity of the tweezer host for steric interaction as well as to produce complexes with limited conformational flexibility that led to increased reliability for sensing chirality. Based on Inoue et al.'s work on the determination of the absolute configuration of chiral monoamines,[51] we envisioned that further rigidification of the host skeletal system would be necessary such that a monodentate binder could exert its influence and force a preferred helicity of the host system. Further inspiration came from the elegant work of Feringa and co-workers, where they had utilized the biphenol core to induce atropisomerism through hydrogen bonding interaction.[52−54] In lieu of having a rigid linker, we envisaged the interaction of the biphenol core via hydrogen bonding with the chiral guest molecule would result in the induction of a preferred helicity.

The latter thoughts led to the bis-porphyrin substituted biphenol **74** (named as MAPOL) illustrated in Figure 11.[4]

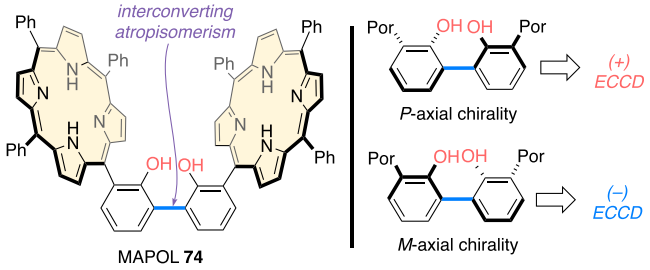

Figure 11. Structural features of a new class of molecular receptor, MAPOL **74**.

Biphenol's relatively low barrier to rotation enables the system to equally populate *P* and *M* helicities at room temperature.[52,53] Additionally, the anticipated intramolecular hydrogen binding of the 2,2′-hydroxyl groups favors a *syn* arrangement of the porphyrins, i.e., having the porphyrin rings on the same side as opposed to having them rotate away (*anti*) to each other. This is critical, since in the *anti*-arrangement the porphyrins do not interact to yield a reliable ECCD spectrum. This arrangement of the porphyrin units reveals *P* and *M* helices with equal populations in the absence of a chiral guest. We speculated that the racemic *P*/*M* population can be perturbed to favor one helicity as a result of a monodentate interaction of the guest molecule with the host system. In effect, binding of a chiral molecule to the MAPOL **74** host would result in a diastereomeric mixture (nondegenerate energy), which can interconvert to favor one helicity. Although initially the design was to utilize the hydrogen bonding interaction of the biphenol core with the guest molecule as the driver to form the host/guest complexation, the ability to exploit other binding handles, such as the porphyrin rings, was not dismissed.

As a proof of concept, chiral monoamines were complexed with MAPOL **74**, noting that MAPOL **74** lacks the zincated center, and thus the only mode of interaction would be through hydrogen binding with the biphenol hydroxyl groups (Figure 12).[4] NMR analysis of MAPOL **74** in the presence of different

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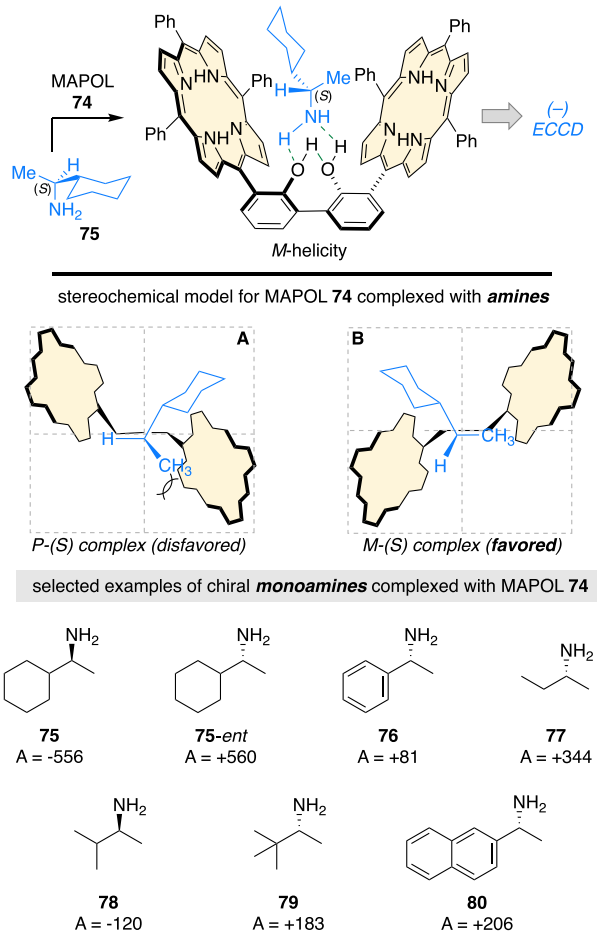

Figure 12. Hydrogen bonding enabled complexation of chiral monoamines with MAPOL **74**. Typically, 1 μM MAPOL was bound with 20 equiv of chiral amine in hexane at 0 °C.

molar ratios of amine **75** led to substantial changes in the chemical shift of the guest protons, indicative of binding of the amine to **74**. The degree of change in chemical shift was used to obtain the binding constant as well as the stoichiometry of the complex (1:1). Illustrated in Figure 12, we surmised the hydrogen bonding of the amine with the 2,2′-biphenol hydroxyl groups would orient the chiral molecule such that the substituents on the asymmetric center are positioned between the porphyrin rings on a 3-fold rotamer (looking through the C−N bond). The free rotation about the C−N bond enables the molecule to adopt an energetically preferred rotamer. As such, the most demanding steric element (cyclohexyl group in the illustration, Figure 12) would occupy the most open quadrant between the two porphyrins. This arrangement would dictate the position of the medium and small groups relative to the steric sensors (the porphyrin rings), thus forcing interactions that are energetically different for the *P* and *M* helicity. As shown for monoamine **75**, placing of the cyclohexyl in the open quadrant leads to arrangement **A** for the *P*-helical MAPOL **74** and arrangement **B** for the *M*-helicity. The methyl group (medium size substituent) is forced to reside in the filled quadrant in **A**, while the smaller hydrogen atom occupies the filled quadrant in **B**. With these considerations, one would expect the *M* helicity is the energetically favored diastereomer, and thus would have a higher population in solution, leading to the anticipated negative ECCD signal. Indeed, this was observed experimentally. This analysis was extended to various chiral monoamines, a few of which are illustrated in Figure 12. It bears mention that hydrogen bonding is the sole interaction that results in the complex formation event, while the porphyrin rings act solely as readouts of helicity. This is in contrast to the tweezers described above, where the porphyrin rings were responsible for not only binding interactions with the chiral guests, but also functioned as reporters of chirality.

4.2. Absolute Stereochemical Assignment of Chiral Cyanohydrins

Having demonstrated proof-of-principle for the MAPOL system with chiral monoamines, we sought to extend the utility of this method to other, rather challenging chiral substrates that lack a direct method for their absolute stereochemical determination. The chemically versatile chiral cyanohydrins belong to the latter group.[55] Absolute stereochemical determination of this class of molecules was based on modified Mosher methods.[11,56,57] We envisioned that MAPOL **74** could provide a solution via hydrogen binding of the core biphenol moiety with the hydroxyl group, leading to the formation of an ECCD active complex.

Cyanohydrin **81** was complexed with MAPOL **74** under conditions that were employed for chiral monoamines. To our disappointment an ECCD signal was not observed. This was attributed to a weak hydrogen bonding interaction between MAPOL **74** and the hydroxyl group of cyanohydrin **81**. In order to improve the binding interaction, MAPOL **74** was zincated to potentially achieve a dual binding scenario. As discussed above, the porphyrin rings in MAPOL **74** were originally chosen only because of their chromophoric value and were not intended for complexation with chiral molecules. Nonetheless, their zincation could provide a second coordination site that along with the hydrogen bonding could entropically aide complexation. In fact, addition of **81** to Zn-MAPOL **82** resulted in a strong ECCD signal (Figure 13). Indeed, both coordination to the divalent zinc atom and hydrogen bonding with the biphenol core were crucial. This was demonstrated by the diminishing ECCD signal as a result of the addition of binding competitors (acetonitrile as competitive inhibitor of Zn^{2+} complexation and methanol as a hydrogen binding competitor). With these results in hand, a binding mnemonic was proposed to correlate the sign of the ECCD signals to the stereochemical identity of the bound cyanohydrins. In analogy with chiral monoamines, the hydroxyl group hydrogen bonds with the biphenol moiety of the host system. The nitrile group coordinates with the metal center. These arrangements force the projection of the two remaining substituents on the chiral center toward the unbound porphyrin ring (Figure 13). Rotamer **A**, in which the larger tolyl group is positioned in the open quadrant, is predictably favored as compared to rotamer **B**. The latter scenario would yield a positive ECCD signal for the proposed complex, which is indeed observed experimentally (Figure 13).

4.3. Determination of Absolute Configuration of Chiral Sulfoxides

Research on chiral sulfoxides is a vibrant field as evident by the number of pharmaceuticals that bear the functional group. Yet, their absolute stereochemical determination has posed a challenge, especially with chiroptical techniques. The most useful technique is a modified Mosher analysis, requiring an initial oxidation of the sulfoxide to generate an iminosulfanone, and subsequent derivatization as an MPA-amide.[58] Additionally, limited applications of ECD and VCD via exploiting the S−O bond as a "chromophore" and its interaction with an aryl group in selected examples have been reported as alternative methods

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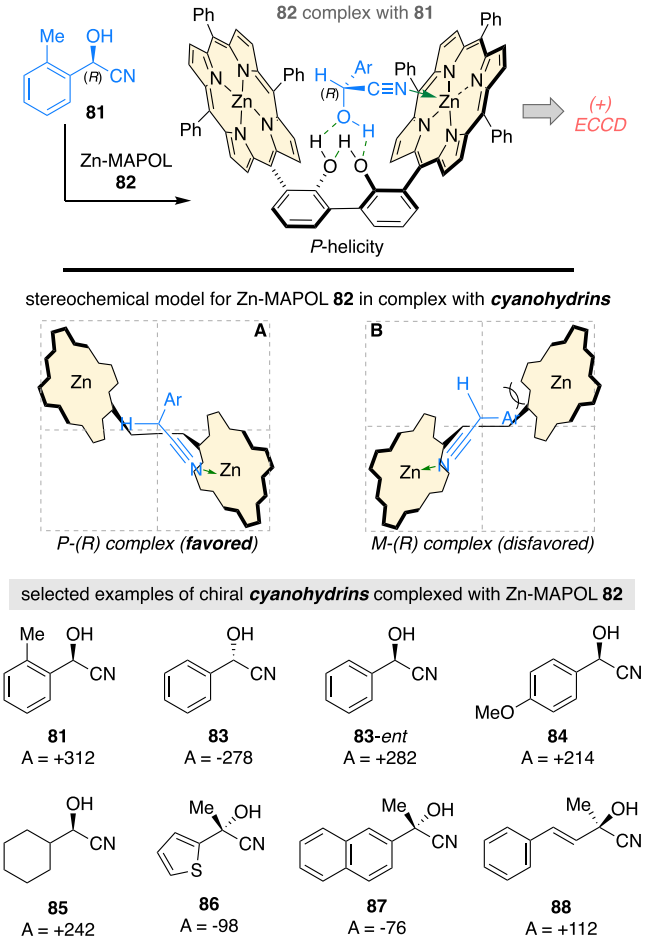

Figure 13. Sensing the absolute configuration of chiral cyanohydrins using Zn-MAPOL **82**. Typically, 1 μM (for 2° cyanohydrins) or 2 μM (for 3° cyanohydrins) Zn-MAPOL was bound with 50 equiv of cyanohydrin in hexane at 0 °C.

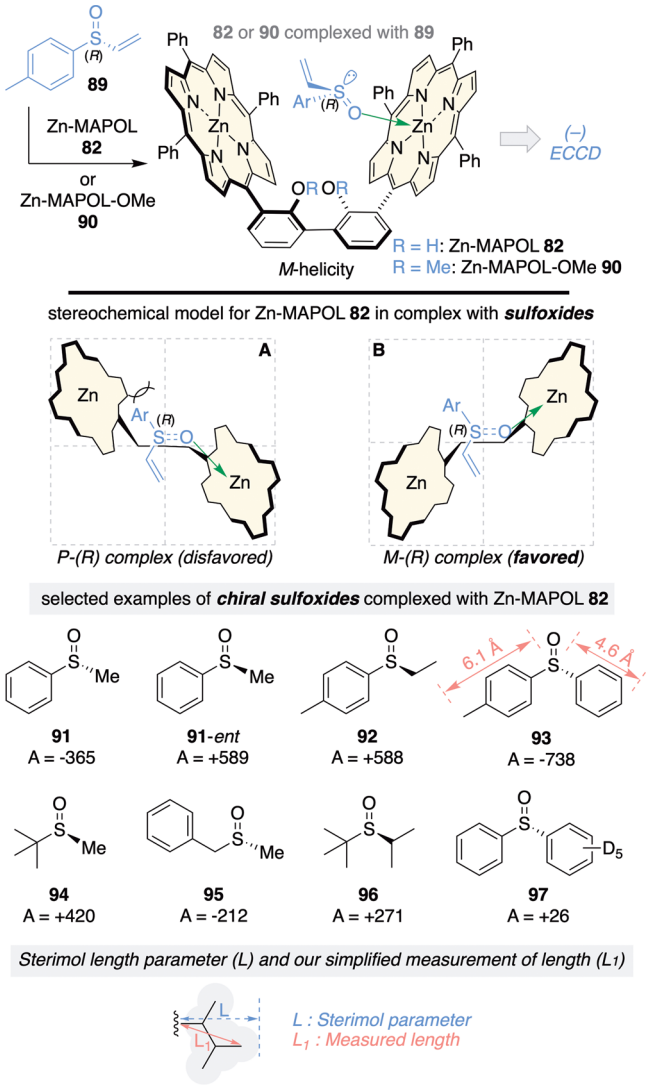

Figure 14. Sensing the absolute configuration of chiral sulfoxides using Zn-MAPOL **82**. Typically, 1 μM Zn-MAPOL was bound with 50 equiv of chiral sulfoxide in hexane at 0 °C.

for assignment of absolute configuration.[59,60] With the successful utilization of Zn-MAPOL **82** for cyanohydrins, we mused on its ability to bind sulfoxides, leading to a simple, efficient, and rapid methodology for stereochemical readout.[61] Complexation of **89** with Zn-MAPOL **82** led to the production of a strong ECCD signal (Figure 14). As with previous functional groups, a diverse set of chiral sulfoxides, bearing aliphatic and aromatic substituents as well as heteroatoms, succumbed to successful analysis. Stemming from the strong binding affinity of sulfoxides with Zn-MAPOL **82** (i.e., K_{assoc} = 14 500 M^{-1} for the **82**/**81** complex), strong ECCD signals were obtained with low detection limits and high sensitivities (<1 μg of sample per analysis).

The presence of the divalent zinc atom was crucial for the success of the method. Further confirmation of this was obtained from the ECCD active complex formed between Zn-MAPOL-OMe **90** (not competent to form hydrogen binds with sulfoxides), yielding the same helicity, albeit with diminished intensity as compared with Zn-MAPOL **82**. The proposed mnemonic featured coordination of the oxygen atom of sulfoxide **89** with the metallocenter, while orienting the lone pair of the sulfur atom pointed toward the bound porphyrin (Figure 14). This arrangement would project the remaining alkyl/aryl substituents toward the second porphyrin. Given the projected orientation of the substituents on **89** toward the porphyrin ring not bound to the sulfoxide (larger *p*-tolyl vs smaller vinyl group), the *M* complex is more stable than the *P*, leading to a negative ECCD signal. This agrees with the experimental results (Figure 14).

A critical factor for all methods discussed thus far is the ability to correlate the relative size of the substituents on a chiral center, which is presumably the driver for the helicity of the host system, to the observed CD signal. We have mainly relied on A-strain values[62] as a thermodynamic parameter to rank the substituents based on their relative size. Nonetheless, this analysis failed for chiral sulfoxides, and rather it became evident that the length of the substituents dictates size. Length as a steric parameter is described in the sterimol analysis, which considers "bulkiness" of a substituent in terms of its length (L1) and its width (B1 and B5).[63] In analogy, for sulfoxides we utilized the measured length of the substituents on chiral sulfoxides from the sulfur atom to the furthest heavy atom as a general steric parameter to differentiate the relative size of the substituents on the sulfur stereocenter. A representative example of such measurements is shown for the substituents on chiral sulfoxide **93** (Figure 14). Thus, reexamining the observed ECCD with **93**, the *p*-tolyl substituents is substantially "*longer*" than the phenyl group (6.1

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Å vs 4.8 Å) and as projected toward the unbound porphyrin, dictates steric differentiation to yield the observed signal. Since the alkyl/aryl substituents on a chiral sulfur project toward the unbound porphyrin (10−12 Å away), a longer substituent could have a more profound steric effect than a shorter and/or bulkier group. Indeed, this analysis stood true for all the sulfoxides that were analyzed.

4.4. Determination of Absolute Configuration of Chiral Phosphine Oxides

Asymmetric phosphorus oxide containing molecules are a privileged functionality found in a wide range of applications and as a superior pharmacophore in drug development.[64] We aimed to utilize the widely recognized coordination of the phosphorus oxide functionality with Lewis acidic metals to achieve CD active complexes. Gratifyingly, complexation of a variety of phosphorus oxide molecules with Zn-MAPOL **82** did not disappoint and resulted in strong and interpretable ECCD signals (Figure 15).[65] Based on the data obtained for binding of various asymmetric phosphorus oxide substrates with Zn-MAPOL **82**, a mnemonic is proposed as depicted in Figure 15. The coordination of the polar P−O bond to the zinc center places the substrates in the cavity of the host Zn-MAPOL **82**. Out of the three substituents on the chiral phosphorus(V) center, the smallest group (methyl group based on A-strain value) points toward the bound porphyrin. This arrangement projects the remaining groups (medium and large, *n*-propyl and phenyl, respectively) toward the unbound porphyrin ring. Thus, in complex **98**/**82** the *M*-helicity is favored as a result of placing the large group (phenyl) in the open quadrant. On the other hand, the *P*-helical complex is predictably disfavored as the large group is oriented in a sterically more demanding region (the occupied quadrant). A similar analogy can be applied to other chiral phosphorus oxides presented in Figure 15.

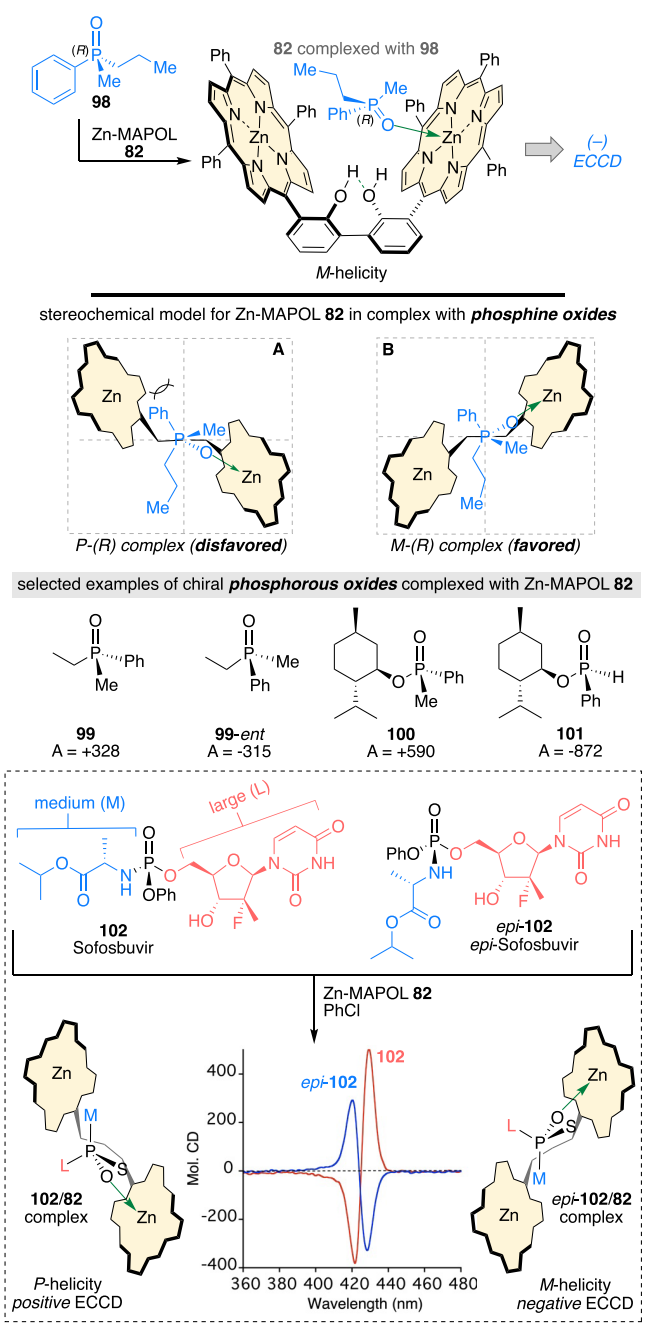

Figure 15. Sensing the absolute configuration of P-chiral phosphorus oxides using Zn-MAPOL **82**. Typically, 1 μM Zn-MAPOL was bound with 5 equiv of chiral phosphorus oxide analyte in hexane at 0 °C.

The generality of this system was demonstrated with the analysis of Sofosbuvir **102**, a commercial antiviral agent, widely used for the treatment of hepatitis C virus.[65,66] The phosphorus oxide moiety in Sofosbuvir **102** is embedded in a complex setting. The host Zn-MAPOL **82** was able to detect the asymmetry of the P-stereogenic center in the presence of other chiral centers and heteroatoms. Furthermore, *epi*-Sofosbuvir, epimeric only at the P-stereocenter, resulted in a opposite signal that confirmed the selectivity of the host system for the phosphorus center in this complex structure. The high binding affinity of the phosphorus oxide moiety with metalloporphyrin (i.e., K_{assoc} of **98** complexed with Zn-MAPOL **82** measured ~2.7 × 10^5 M^{-1} in hexane), as compared to the binding affinity of the zincated porphyrin with oxygen and nitrogen based coordinating groups in Sofosbuvir **102**, was deemed as the key element for selective recognition of the phosphorus asymmetry. Application of the mnemonic proposed for phosphorus oxides binding with Zn-MAPOL **82** predicts a positive ECCD for Sofosbuvir **102**, assuming the large and medium groups as indicated in Figure 15. Conversely, the *M*-helicity is predicted and observed for *epi*-**102**/**82** complex.

5. SUMMARY

We have summarized our methodologies for the assignment of absolute configuration of various classes of organic compounds during the past 20 years. With various stereoelectronic modifications of our initial prototype tweezer, sensing of more complex and challenging functional groups has become practical. With electronically activated zinc porphyrins, we were able to engage oxygen-based coordination with the host. Steric modifications of the porphyrin tweezers enabled sensing of stereocenters located far away from the coordinating site. Although derivatization with "carriers" was an initial solution for some functionalities with a single site of attachment, design of MAPOL and its analogues revolutionized our strategy for challenging subgroup of molecular families. This enabled the absolute stereochemical determination of molecules such as cyanohydrins, sulfoxides, and phosphorus oxides.

https://dx.doi.org/10.1021/acs.accounts.0c00650
Acc. Chem. Res. 2021, 54, 654−667

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†H.G. and D.C. contributed equally. The manuscript was written through contributions of all authors.

Funding

We thank the NSF (CHE-1213759) for continued support of this project.

Notes

The authors declare no competing financial interest.

Biographies

Hadi Gholami received his doctoral degree from Michigan State University under the guidance of Prof. Babak Brohan. His doctoral studies consist of development of techniques for assignment of absolute configuration of chiral molecules, and total synthesis of natural products. He has carried out his postdoctoral studies at Stanford University in the lab of Prof. Barry M. Trost, working on the development of an asymmetric palladium catalyzed fluoroalkylation/trifluoromethylation, and total synthesis of Piericidin A and Kadcoccinic acid A. He is currently a scientist at Janssen Pharmaceuticals.

Debarshi Chakraborty received his B.S. from Ramakrishna Mission Vidyamandira and M.S. from IIT Kanpur, India in Chemistry. Currently, he is a PhD student in Professor Babak Borhan's group at Michigan State University. His research focuses on the design, synthesis, and application of porphyrin based host systems to determine the absolute stereochemistry of chiral molecules and in asymmetric catalysis.

Jun Zhang was born in China and received his B.S. in Chemistry at the Nanjing Normal University. He then moved to Michigan State University, where he worked with Professor Babak Borhan on absolute stereochemistry determination, organic methodology development, and cyanine dye chemistry. After obtaining his Ph.D. in 2018, he joined Promega Corporation and is currently a Process Development Scientist.

Babak Borhan grew up in Iran and then moved to the United States for higher education. He received his B.S. in Biochemistry from University of California, Davis. He remained there to earn his Ph.D. in Chemistry under the guidance of Professor Mark Kurth and Professor Bruce Hammock focusing on the mechanistic studies of hydrolytic enzymes. After receiving his PhD, he moved to Columbia University to work with Professor Koji Nakanishi where he studied the photochemical processes in rhodopsin. Starting his independent career in 1998, currently he is a Professor at Michigan State University.

ACKNOWLEDGMENTS

We are grateful to the past and present group members (Dr. Qifei Yang, Dr. Chrysoula Vasileiou, Dr. Courtney Olmsted, Dr. Marina Tanasova, Dr. Xiaoyong Li, Dr. Mercy Anyika, Dr. Carmin Burrell, and Dr. Saeedeh Torabi Kohlbouni) for their dedication and contributions that was summarized in this account. We also thank Mr. Behrad Masoudi for his help in preparing this manuscript.

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