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Point-to-Axial Chirality Transfer—A New Probe for "Sensing" the Absolute Configurations of Monoamines

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Supporting Information

ABSTRACT: A host molecule, capable of freely adopting *P* or *M* helicity, is described for molecular recognition and chirality sensing. The host, consisting of a biphenol core, binds chiral amines via hydrogen-bonding interactions. The diastereomeric complex will favor either *P* or *M* helicity as a result of minimizing steric interactions of the guest molecule with the binding cavity of the host, resulting in a detectable exciton-coupled circular dichroic spectrum. A working model is proposed that enables non-empirical prediction of the chirality of the bound amine.

The assignment of stereochemistry is central to the progress of chemistry in any of its sub-disciplines that require the use of molecules for function, whether it is a pharmaceutical agent, synthetic intermediate, new natural product, etc. To this end, there are a number of methods developed to establish the absolute stereochemistry of chiral molecules, however; each have specific strengths and weaknesses that limits the use of a single system as a probe for all molecules. One such method, the exciton coupled circular dichroism (ECCD) protocol, has enjoyed tremendous growth and popularity in recent years.[1] This is mainly because it provides a non-empirical solution to the assignment of helicity based on the observed Cotton effects in CD.

The porphyrin tweezer methodology, a powerful technique for the absolute stereochemical determination of organic molecules, is an example of the application of the ECCD protocol.[2] It also serves as an example of a technique with its own unique limitations. Complexation of a chiral guest with a porphyrin tweezer host leads to induced asymmetry of the host, yielding a CD-observable signature. The induced host helicity, assigned from the observed ECCD of the porphyrins, can be correlated to the absolute stereochemistry of the bound guest molecule. In order to orient the porphyrins in a helical arrangement with respect to each other, the guest molecule needs to contain two sites of attachment (two functional moieties that can bind to the metalated porphyrin). For diamines, diols, amino alcohols, etc., this prerequisite is not an issue.[2,3] For molecules with one site of attachment, however, the requirement for a second site is accomplished only through chemical derivatization, which artificially introduces the second binding site.[4]

A derivatization-free ECCD protocol for molecules with one coordinating group has been a difficult pursuit, with only a few limited examples in the literature. Inoue and co-workers utilized an octaethyl substituted porphyrin tweezer linked by an ethylene group at the porphyrins' *meso* positions, for the absolute stereochemical determination of monoamines.[5] In an elegant twist of their original tripodal system, Anslyn, Canary, and co-workers have reported on chromophoric hosts capable of covalent modification with chiral amines, carboxylic acids and alcohols, resulting in a derivatized host that adopts an ECCD active conformation.[4f,g,k,6] Our approach has been to develop host systems that are predisposed to adopt both *P* or *M* helical structures (helicates). Upon interaction with the chiral compound through coordination with the helicate, the population of either *P* or *M* helicity is enhanced (diastereomeric differentiation) and a unique ECCD should be observed. Inspiration for the host system developed here comes from the work of Ishii et al., having described a 2,2′-biphenol sensor for chiral amino alcohols.[7] In their work, they propose that a hydrogen-bonding network established between the biphenol hydroxyls and the amino alcohol leads to the predominance of one atropisomeric structure.

The use of hydrogen-bonding interactions in forming complexes is commonly found in biphenol systems. In fact, there are a large number of excellent examples of chiral supramolecular complexes formed via H-bonding with biphenols reported in the literature.[8] 2,2′-Biphenol systems are intrinsically chiral and exist in two conformations, *P* and *M*, which differ only by rotation around the central single bond (*atropisomers*). Rotation can be hindered by substituents; however, the unsubstituted system interconverts rapidly at room temperature. In a racemic mixture, the *P* and *M* conformers exist in a 1:1 equilibrating mixture. This equilibrium, however, can be disturbed by the introduction of an external chiral bias, causing one population to be favored over the other as a consequence of its interaction with chiral ligands. A seminal discovery in this area was reported by Mizutani and co-workers, demonstrating preferential axial chirality of biphenols upon H-bonding with chiral diamines, which leads to the formation of an excess of one atropisomer that results in a CD-observable Cotton effect.[8a]

Based on the precedence discussed above, we envisioned 3,3′-bisporphyrin-substituted 2,2′-biphenol (**1**, MAPOL), designed to take advantage of the H-bonding ability of the biphenol unit in order to form chiral complexes with monoamine chiral guests. Our strategy in the design of MAPOL was to incorporate tetraphenyl porphyrins at the 3 and 3′ positions such that a bulky chromophoric pocket is created in the vicinity of the diol binding elements (Scheme 1, dashed box on top). As a consequence, we surmised that the semi-enclosed binding cavity would lead to increased stereodifferentiation of the bound chiral guest. Steric

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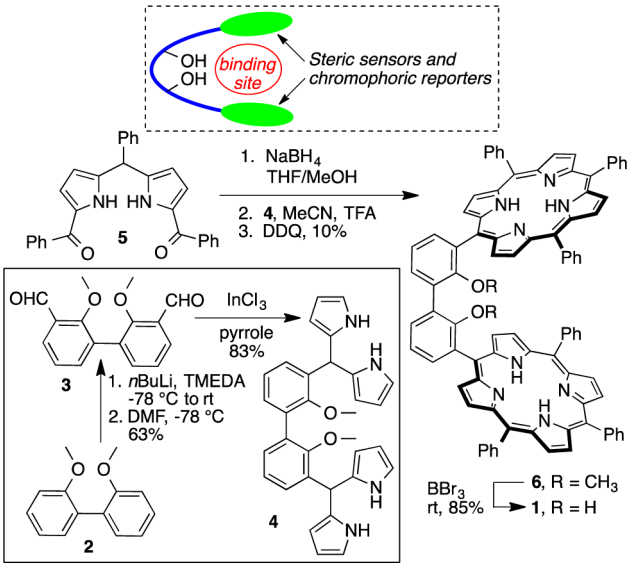
Scheme 1. Synthesis of MAPOL (1)[a]



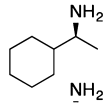
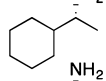
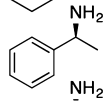
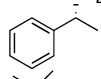
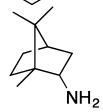
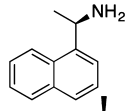
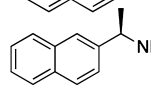
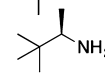
[a]The diol unit provides the binding element, while the porphyrin rings create a binding cavity and function as chromophoric reporters of helicity.

drivers, the description of which will appear below, would favor one of two diastereomeric forms of the complex (either *P* or *M* helicity complexed with the chiral guest). The two porphyrins provide the chromophores necessary for ECCD spectroscopy. Ultimately, the asymmetry from the stereogenic center of the bound guest is transferred to the host as a twist of the biphenol unit via H-bonding interactions. The coupled electric dipole transition moments of the chromophores should result in a predictable ECCD, which can then be related back to the chirality of the bound guest.

MAPOL (**1**) is synthesized as shown in Scheme 1, from commercially available starting materials. Formylation of the *o*-lithiated compound **2** provided the bisaldehyde **3**, which upon condensation with pyrrole leads to **4**.[9] Reduction of dipyrromethane **5**[10] to the corresponding diol, and subsebsequent 2+2 cyclization[11] and DDQ oxidation yields bisporphyrin **6**. Demethylation with BBr_3 provides **1**, which exhibited λ_{max} = 413 nm in hexane (ε = 420 000 M^{-1} cm^{-1}).

Table 1 lists a number of alkyl and aryl chiral amines that were complexed with **1** in hexane at 1:20 host:guest ratio.[12] Gratifyingly, we observe strong ECCD spectra in all cases, centered on the porphyrin Soret band, pointing to the fact that a preferred helicity of the biphenol moiety predominates upon complexation with chiral amines. Inspection of the results in Table 1 reveals a trend: *S* amines yield negative ECCD spectra, while positive ECCD signals are observed for the *R* amines. It should be noted, however, that the Cahn–Ingold–Prelog stereochemical designation does not necessarily follow steric size; thus, the trend above will not hold unless the large substituent at the chiral center is considered as the second priority (the amine being the highest priority). For all compounds in Table 1, the largest substituent is the second priority for stereochemical assignment. As expected enantiomeric pairs produced opposite ECCD spectra (Table 1, entries 1, 2 and 3, 4). More significantly, the system is able to register small differences in size based on their *A* values (see entry 6, methyl *A* = 1.74 vs ethyl *A* = 1.79).

Table 1. ECCD Data of Chiral Amines with MAPOL in Hexane[a]

entry	amine		predicted sign	MAPOL λ nm, (Δε)	MAPOL A (A_{corr})[b]
1		**7*S***	neg	418, -237 409, +257	-494 (-556)
2		**7*R***	pos	419, +187 410, -345	+532 (+560)
3		**8*S***	neg	429, -15 420, +46	-61 (-80)
4		**8*R***	pos	427, +36 409, -12	+48 (+81)
5		**9*R***	pos	418, +153 420, -62	+215
6		**10*R***	pos	425, +161 412, -177	+338 (+344)
7		**11*R***	pos	423, +41 414, -26	+67 (+68)
8		**12*R***	pos	422, +147 414, -59	+206
9		**13*S***	neg	428, -30 412, +90	-120
10		**14*R***	pos	429, +62 412, -121	+183

[a]All CD measurements were performed with 1 μM MAPOL in hexane at 0 °C; 20 equiv of amine was used to obtain the data. [b]A_{corr} refers to amplitudes corrected for % ee for samples <99% ee.

The predicted signs in Table 1 are derived from the anticipated H-bonding of the amines to the biphenol unit in a manner that favors one atropisomer as a result of minimizing steric interactions. Although it is generally assumed that the barrier to rotation for biphenols is low, it is difficult to cite an experimental value from the literature. Theoretical considerations suggest a barrier in the range of 8–13 kcal/mol.[8c–e,13] Figure 1 depicts our suggested model for binding to MAPOL with (*S*)-cyclohexyl ethylamine, 7*S*. For both the *P* and *M* helicities of the complex, the large cyclohexyl group is positioned in the least sterically demanding location, while the location of the medium (CH_3) and small (H) groups is dictated by the configuration of the chiral center as illustrated. For the *M*-(*S*) diastereomer **A**, the medium group (CH_3) finds itself in a more sterically tolerable region, while the smallest group (H) occupies the most sterically congested area (pseudo-eclipsed with the large porphyrin substituent). On the other hand, having placed the large cyclohexyl group in the least demanding location, the *P*-(*S*) diastereomer encounters steric repulsion of the medium (CH_3) group with the porphyrin substituent (see complex **B**). This hypothesis was corroborated by our quantum mechanical modeling. The two complexes were evaluated at the B3LYP/6-31G*/SM8 (hexane) level of theory. The *M*-helical MAPOL complexed with the *S*-enantiomer is favored energetically by 1.67 kcal/mol, leading to the observed negative ECCD spectrum (see SI for details).

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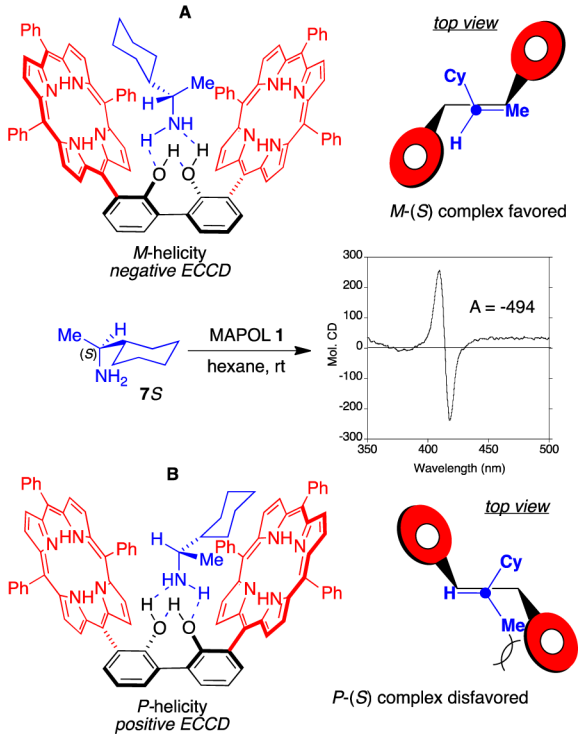

Figure 1. Proposed working model for assigning the absolute stereochemistry of chiral amines. Complexation of (*S*)-cyclohexyl ethyl amine **7***S* with **1** is illustrated with both *M* and *P* helicity of the host molecule. The *P*-(*S*) complex leads to positioning of the medium CH_3 group in a sterically encumbered region as compared to the *M*-(*S*) complex, which places the smallest group (H) in the same comparable location. The experimental result yields a strong negative ECCD spectrum that corroborates the predicted assignment.

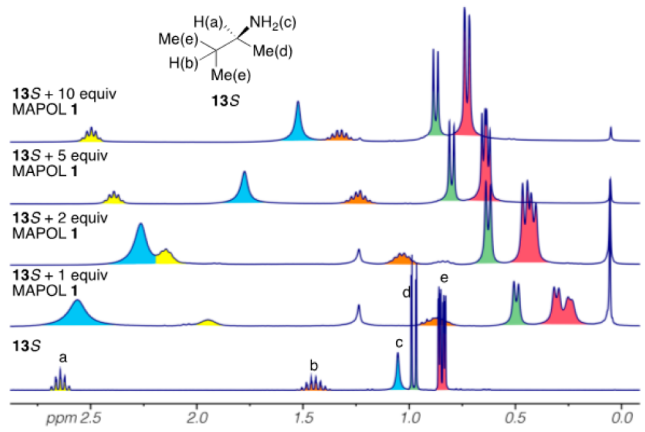

Figure 2. Stacked NMR spectra of amine **13***S* and various equivalents of **1**. The amine resonances have been color coded, illustrating the initial upfield shift as the result of the anisotropic shielding effect of the porphyrin rings (1 equiv spectrum). The protons of the biphenol hydroxyl groups without addition of amine are observed at ~6.06 ppm (not shown). The amine and hydroxyl protons coalesce at ~2.55 ppm (1 equiv of **1**).

At the onset of our investigations, a 1:1 complex stoichiometry for binding of amines **7***S* and **13***S* with **1** was established by Job's continuous plot analysis (Figures S1−S5). A battery of NMR experiments followed to better delineate the interactions between **1** and the complexed amines. Because of the large π system, nuclei that fall within the boundary of porphyrin rings experience a large diamagnetic anisotropy, leading to upfield shift of resonance. Figure 2 depicts a stack of NMR spectra collected at different amine **13***S*:MAPOL equivalents. All non-exchangeable amine protons undergo a significant upfield shift, implying that they lie within the shielding cone of the porphyrin rings. Increasing equivalents of amine leads to averaged signals due to rapid exchange in the NMR time scale and approaches the original chemical shifts for the unbound amine resonances. The phenolic and amine protons coalesce at ~2.5 ppm (1 equiv spectrum), suggesting a rapid and indistinguishable identity, which agrees well with the binding motif suggested in Figure 1. Note, the latter coalescence of the amine and phenolic protons results in the apparent downfield shift of H_c. Increased equivalence of the amine leads to the upfield shift of the exchangeable protons, approaching the original chemical shift of the free amine protons (~1.1 ppm). The porphyrin's pyrrolic protons do not undergo a significant change in the NMR (steady at ~ −3 ppm), indicating that the chiral amines do not H-bond to the central nitrogen atoms of the porphyrin rings (see SI for full spectra).

Further evidence to eliminate the role of the porphyrins in H-bonding with the amines came from ^{1}H NMR titrations of **13***S* with tetraphenyl porphyrin (A4-TPP). As depicted in Figure S7, no significant change in both the appearance, as well as the chemical shift of either the amine or the porphyrin resonances are detected, suggesting little to no interaction between the two parties. More proof for the proposed H-bonding between the phenolic moiety of **1** and the amine functionality was obtained from CD analysis of the bismethoxy analog **6**. Addition of amine **7***S* to a solution of **6** under identical conditions as described for **1** did not lead to any observable CD signal. Additionally, this is supported by the lack of any observable UV−vis changes upon addition of the amine to host compound **6** (complexation of amines with MAPOL **1** does lead to changes in the UV−vis spectra). These observations support the proposed of complex formation by H-bonding interactions between the biphenol unit and the amine.

In summary, we demonstrate the utility of a new bis-porphyrin-biphenol host (MAPOL, **1**), capable of H-bonding with chiral monoamines, for the prompt determination of absolute configuration. The H-bonding to the biphenol moiety yields a diastereomeric mixture that originates from the atropisomerization of the host molecule. Preference for either axial chirality is dictated through minimizing steric interactions of the guest molecule with the bulky porphyrin substituents that comprise the "binding cavity". This leads to an overpopulation of either *P* or *M* helicity, which can be easily detected as an ECCD signal. Relating the sign of the CD couplet to the absolute stereochemistry of the bound amine follows a predictable mnemonic. This method requires only microgram amounts of substrate and produces the necessary ECCD spectra in matter of minutes. We are presently exploring the extension of this methodology to secondary amines, alcohols, and other functional groups.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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