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Absolute Configuration for 1,*n*-Glycols: A Nonempirical Approach to Long-Range Stereochemical Determination

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Supporting Information

ABSTRACT: The absolute configurations of 1,*n*-glycols (n = 2−12, 16) bearing two chiral centers were rapidly determined via exciton-coupled circular dichroism (ECCD) using a tris(pentafluorophenyl)porphyrin (TPFP porphyrin) tweezer system in a nonempirical fashion devoid of chemical derivatization. A unique "side-on" approach of the porphyrin tweezer relative to the diol guest molecule is suggested as the mode of complexation.

1,*n*-Glycols are widely present in natural products and as synthetic intermediates, yet the determination of their absolute stereochemistry presents a considerable challenge. NMR analysis[1] and exciton-coupled circular dichroism (ECCD) of dibenzoates[2] or cyclic derivatives[3] of diols are the most common techniques for determining the configurations of 1,2- and 1,3-glycols. Nonetheless, these approaches are not suitable for acyclic long-chain diols separated by more than four carbons. This is due to the flexible nature of the derivatized molecules, which adopt multiple conformations in solution. Moreover, they also lack internuclear coupling in NMR since the asymmetric centers are far apart. With the exception of Molinski's elegant tactic[4] that restricts the orientation of the linear chain to a stretched-out zigzag motif through interactions of the glycol with liposomes, there are no other methods that can interrogate the absolute stereochemistry of two remote centers simultaneously. In the latter system, the ECCD of porphyrin-derivatized 1,*n*-glycols provides a solution for a subset of diols (n = 5, 7, 9). Herein we demonstrate a different approach that utilizes the porphyrin tweezer methodology to address the absolute stereochemical determination of glycols with up to 14 carbons between the two chiral centers.

The porphyrin tweezer methodology has been successfully employed to elucidate the absolute stereochemistry of amines,[5] alcohols,[6] and carboxylic acids.[7] In our efforts to determine the absolute configuration of 1,2-diols, we developed a highly fluorinated zinc porphyrin tweezer, Zn-TPFP-C_5-tz (**A**),[8] that can bind strongly with hydroxyl groups because of the enhanced Lewis acidity of the metal centers (Figure 1). We realized that the success of the fluorinated tweezer was solely due to its ability to limit the number of conformations upon complexation with its chiral guest molecule as a result of its tighter binding profile. **A** was successfully used to determine the absolute stereochemistry of threo and erythro vicinal diols, amino alcohols, and diamines via ECCD.[8] This porphyrin tweezer also demonstrated good binding affinity with epoxidic

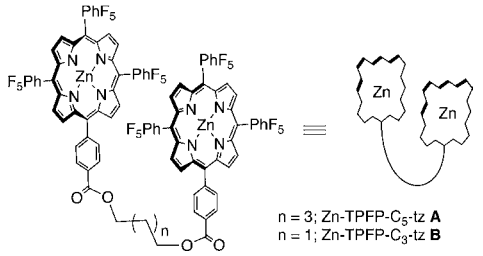

Figure 1. Zinc TPFP porphyrin tweezers **A** and **B**.

O atoms, facilitating the assignment of chiral 2,3-epoxy alcohols with different substitution patterns.[9]

The flexible skeletons of acyclic molecules with remote stereochemistry present a major challenge for ECCD analysis as a result of multiple conformations in solution, which complicates configurational analyses. We envisaged that the strong complexation of **A** with diols would rigidify the supramolecular assembly, reduce the number of conformations, and thus facilitate the stereochemical differentiation at each asymmetric center, leading to predictable ECCD spectra.

Chiral diols **1** and **3**−**13** were synthesized (>95% ee) by known methodologies[10] [see the Supporting Information (SI)], and diol **2** was obtained from Acros. The diols were then subjected to ECCD measurement. As expected, diols **1**−**13** bound well with tweezer **A** in hexane at 0 °C (as evident from UV−vis analysis) to form a 1:1 supramolecular complex (as shown by Job's plot analysis; see the SI), resulting in an intense ECCD curve arising from the porphyrin Soret band. The expected ECCD signs in Table 1 were based on our previous rationalization for 1,2-diols,[8] which can be summarized as follows. Binding interactions invariably occur between the hydroxyl groups at the two stereogenic carbons and the Zn centers of the porphyrins.[11] It is assumed that independent steric differentiation at each asymmetric center proceeds through the binding of the porphyrin moiety opposite the largest substituent on the chiral center, the methyl group in most cases for the compounds in Table 1. As a result, the methyl groups are anti to the bound porphyrin rings and are not involved in the steric differentiation process. The remaining two substituents on the chiral carbon, the H and the alkyl chain, are the steric discriminants that project toward the bulky porphyrin. As such, the porphyrin ring slides toward the smaller H atom and away from the larger alkyl chain, resulting in a helicity that culminates in the predicted ECCD.

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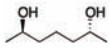
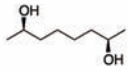
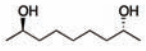
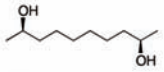
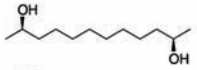
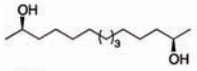
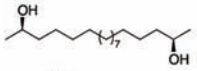
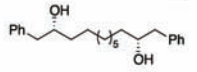
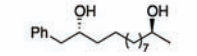
Table 1. ECCD Data for 1,*n*-Glycols in Hexane with Tweezers A and B[a]

	1,n-Glycols	Predicted ECCD	A λ nm, (△ε)	B λ nm, (△ε)
1 2*R*,3*R*		*pos*	425 (+128) 413 (-96) A = +224	425 (+102) 413 (-77) A = +179
2[b] 2*S*,4*S*		*neg*	424 (+81) 413 (-71) A = +152	423 (-36) 412 (+37) A = -73
3 2*R*,5*R*		*pos*	424 (+205) 413 (-163) A = +368	424 (+72) 414 (-66) A = +138
4 2*R*,6*R*		*pos*	424 (+174) 413 (-135) A = +309	423 (+136) 414 (-100) A = +236
5 2*R*,7*R*		*pos*	426 (-70) 418 (+53) A = -123	422 (+322) 415 (-203) A = +525
6 2*R*,8*R*		*pos*	423 (+237) 413 (-199) A = +436	423 (+152) 414 (-142) A = +294
7 2*R*,9*R*		*pos*	426 (+146) 415 (-140) A = +286	426 (+156) 416 (-197) A = +353
8 2*R*,10*R*		*pos*	423 (+172) 414 (-130) A = +302	424 (+400) 415 (-351) A = +751
9 2*R*,11*R*		*pos*	425 (+314) 415 (-177) A = +491	427 (+408) 416 (-326) A = +734
10 2*R*,13*R*		*pos*	430 (-91) 423 (+506) 414 (-171)	424 (+193) 415 (-123) A = +316
11[c] 2*R*,17*R*		*pos*	422 (+28) 415 (-20) A = +58	421 (+33) 414 (-22) A = +55
12 2*R*,11*R*		*neg*	423 (-163) 416 (+143) A = -306	427 (-97) 416 (+117) A = -214
13 2*R*,12*S*		*neg*	422 (-38) 415 (+42) A = -80	423 (-76) 415 (+62) A = -138

[a]A tweezer:substrate ratio of 1:40 and a tweezer concentration of 2.5 mM at 0 °C in hexane were used, unless otherwise indicated. [b]Tweezer:substrate ratio = 1:100. [c]Tweezer:substrate ratio = 1:60 in 5% CH_2Cl_2/hexane at 5 °C.

A general trend could be ascertained, indicating that (*R*,*R*)-diols exhibit positive ECCD spectra upon complexation with tweezer **A** (Table 1). However, several complications were noticed. First, although complex **2**/**A** was expected to give a negative ECCD signal, a positive signal was observed. Second, complicated ECCD curves were obtained for complexes **5**/**A** and **10**/**A**. We also observed a switch in the sign of the ECCD spectrum (from negative to positive) when >20 equiv of diol **5** was added (Figure S1a in the SI). For complex **10**/**A**, three peaks were seen when 5−100 equiv of the diol was added to the tweezer solution (Figure S1b).

These observations suggest the possible presence of multiple competing ECCD-active conformations. although their UV−vis profiles did not reflect this speculation, essentially exhibiting the same features as other diols. Altering the solvent (methylcyclohexane or CH_2Cl_2) or the temperature (room temperature or −10 °C; Figure S3) did not result in any improvement with the problematic diols. At this juncture, we were in need of a more robust supramolecular host for reliable absolute stereochemical determination of long-chain chiral diols.

The inconsistencies observed with **A** were attributed to its flexible nature, which presumably would allow the host/guest system to search multiple conformations. We had two approaches to "tighten" the complex. The first approach entailed the use of fluorinated porphyrin tweezers, which would increase the binding affinity of the zincated porphyrins with the guest molecules. This was successfully applied for the absolute stereochemical determination of 1,2-diols. In our second approach, we shortened the linker connecting the two porphyrin rings, resulting in a less flexible porphyrin tweezer. We successfully showed that this C_3 porphyrin tweezer is less apt to stabilize multiple conformations.[12] To determine the absolute stereochemical determination of 1,*n*-diols, we envisaged that combining these two features would give a porphyrin tweezer system that is not only capable of strong binding with the diols but also less flexible, leading to stabilization of predominately one bound conformation.

Zn-TPFP-C_3-tz (**B**) was synthesized following procedures similar to those reported previously (λ_{max} = 415 nm, ε = 670 000 cm^{-1} M^{-1} in hexane).[8] Binding of **B** with diols **1**−**13** yielded surprisingly strong ECCD signals, which gratifyingly were consistent in all cases with the predicted signs (Table 1). Complexation of **B** with diols **2**, **5**, and **10** (problematic diols with **A**) produced the expected results across a large range of diol concentrations (5−100 equiv of diol; see Figure S4 for **5** and **10**).

The strongest ECCD amplitude was observed with 40 equiv of diol in most cases, so this was chosen as the optimal amount for use with **B**. Because of the low solubility of diol **11** (which precipitated under the standard conditions), the ECCD analysis was performed in a mixed solvent system (5% CH_2Cl_2 in hexane) at slightly elevated temperature (5 °C) after screening for the optimal conditions. The relatively low CD amplitude of **11** in comparison with other diols (A = +55) is ascribed to competitive binding of CH_2Cl_2 with **B**. We previously postulated the binding of heteroatom-containing solvents with the fluorinated porphyrins due to the highly Lewis acidic nature of the Zn metallocenter (chiral 1,2-diols complexed with **B** are ECCD-silent in coordinating solvents such as CH_2Cl_2, $CHCl_3$, CH_3CN, THF, and Et_2O).[8]

Having at hand a system that can report the absolute stereochemistry of remotely spaced diols, we turned our attention to developing a better understanding of the binding mode for short- and long-chain diols with **B**. Two points are important to note: (1) the C_3 tweezer seemingly can bind a variety of methylene-spaced diols in the same manner, thus leading to consistent results; (2) the C_3 tweezer, with its shortened linker, not only binds well-spaced diols just as well as the C_5 tweezer but also yields stronger ECCD amplitudes in comparison. These two points did not seem to fit the conventional binding mode developed previously for **A**, which assumed that the two porphyrins approach the guest molecule in a "head-on" fashion (Figure 2a). In such a scenario,

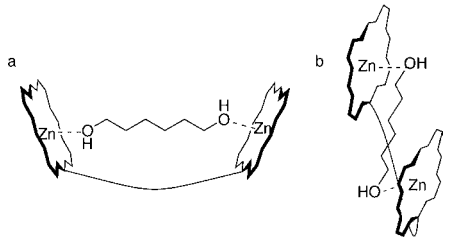


Figure 2. Complexation patterns for 1,*n*-diols with tweezers: (a) head-on; (b) side-on.

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the porphyrins of the tweezer are arranged face-to-face, and binding of longer diols leads to a greater separation of the two aromatic rings. It would be difficult to rationalize why shortening the linker length (as in **B**) would lead to more consistent results, especially with longer-chain diols.

Alternatively, we have postulated a "side-on" approach in which the diols are stretched out in their most energetically stable, zigzag conformation and the porphyrins of the tweezer approach the hydroxyls from the side (Figure 2b). In this manner, the linker behaves as a hinge that allows the porphyrins to slide across each other. Shorter diols lead to a smaller angle and larger stretched out diols to a larger angle between the coupling porphyrins. Interestingly, the strength of the ECCD coupling depends on the angle of the coupling electric-dipole transition moments, which for vicinal 1,2-diols it approaches a maximum at 70°.[13] While this dependence has not been previously demonstrated for the systems studied here, one could postulate that an angle dependence for 1,*n*-glycols bound to the porphyrin tweezer could also affect the ECCD amplitude. The side-on approach could well explain why larger separated hydroxyl groups lead to larger ECCD amplitudes (see Table 1), as they would lead to a larger angle between the coupling porphyrin rings (it should be noted that the binding constants for diols of different lengths are similar: K_a = 3200 M^{-1} for **5** and 3750 M^{-1} for **10**; see Figure S5). More importantly, the interchromophoric distance predicted by the side-on approach would not change greatly for longer diols. This is suggested by the small observed difference in λ_{max} for binding short versus long diols (1.3 nm for 1,6-diol **5** vs 3 nm for 1,12-diol **10**). The correlation of λ_{max} with the porphyrin interchromophoric distance is the result of two opposing effects.[8] The binding of electron donors such as hydroxyl groups with the Zn^{2+} causes a bathochromic shift. Conversely, the closer proximity of the two chromophores as a result of the coordination of the guest molecule leads to a hypsochromic shift. Therefore, the magnitude of the bathochromic shift is dependent on the nature of the coordinating element and how close the two porphyrin rings are to each other.[14]

Modeling of **5** (a 1,6-diol) binding with **B** in a side-on approach leads to a 6 Å separation of the two porphyrin rings, whereas modeling of **10** (a 1,12-diol) gave a separation of only 7 Å. This is in contrast to the head-on approach, which would clearly separate the porphyrin rings much more with the longer diols (~7 Å for **5** vs 16 Å for **10**). The similar red shifts for short and long chiral diols in UV–vis titrations of **B** in hexane (see the SI) suggest that the interchromophoric distance does not change to a large extent, providing further proof for the proposed side-on binding of **B** with 1,*n*-diols.

A more detailed analysis of the side-on approach necessitates a difference in the binding conformations with the host porphyrin tweezers for diols separated by even or odd numbers of methylenes. For diols with an even number of intervening carbons (even-*n* diols), the most stable trans, all-staggered conformation (energy-minimized structure; Figure 3 top) has the terminal methyl groups pointing in opposite directions. Since the porphyrins approach the hydroxyl groups opposite the methyl substituents at the chiral centers, in the most stable zigzag conformation, the porphyrins approach the hydroxyls from opposite sides of the chain in the side-on approach. The crystal structure of diol **10** (Figure 3 bottom) shows the same orientation of the hydroxyl groups as postulated above for the bound system. Considering our previously developed mnemonic for steric differentiation described above, we can easily

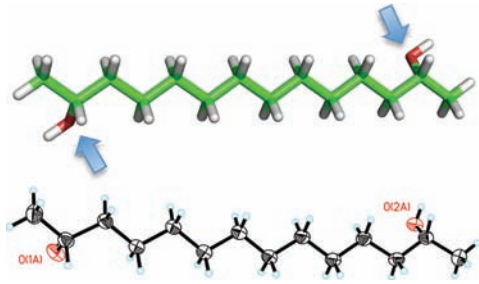

Figure 3. (top) Energy-minimized trans, all-staggered conformation of **10** and (bottom) its corresponding crystal structure. The arrows denote the putative approach of the porphyrins anti to the methyl substituents at the two chiral centers; thus, the porphyrins approach the diol from opposite faces of the molecule.

rationalize the observed helicity of the bound complexes. For even-*n* (*R*,*R*)-diols, **P1** would rotate counterclockwise toward the smaller H atom and away from the larger alkyl chain, and similarly, **P2** would rotate clockwise to minimize the steric repulsion with the bulky alkyl chain (Figure 4). Overall, a

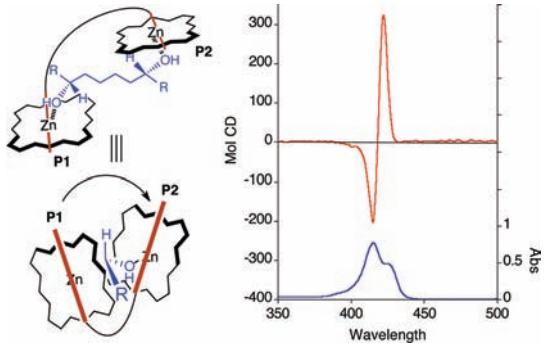

Figure 4. Proposed side-on binding of tweezer **B** with even-*n* diols. **P1** and **P2** approach the hydroxyls anti to the methyl groups and sterically differentiate between the smaller H and the larger alkyl chain, leading to the observed helicity. As anticipated, a positive ECCD was obtained for complexation of diol **5** with **B**.

clockwise (positive) helicity of **P1** relative to **P2** and a positive ECCD spectrum would be observed.[15] It should be noted that the steric differentiation depends on the sizes of the substituents at the chiral center and not necessarily the Cahn–Ingold–Prelog priority. For example, (*R*,*R*)-**12** leading to a negative ECCD couplet also follows these rules. The change in priority (Me vs benzyl) leads to the assignment of substrate **12** as 2*R*,11*R*, while its pseudoenantiomer **9** is also assigned as 2*R*,11*R*. Nonetheless, one would expect substrates **9** and **12** to yield opposite ECCD spectra given the sizes of the substituents on the chiral center, as indeed they do.

For odd-*n* diols, the most stable trans, all-staggered conformation (Figure 5a) would lead to a steric clash of bulky **P1** and **P2**, since they would approach the diol from the same face (the methyl groups at the end of the chain are syn to each other). Alternatively, the second most stable trans, all-staggered conformation, which results from a 60° rotation about the C–C bond, disposes the methyl groups anti to each other and thus would accommodate the side-on binding of **P1** and **P2** (Figure 5b). Interestingly, both of these staggered conformations postulated for odd-*n* diols are observed in the crystal structure of diol **8** (Figure 5). Stereochemical differ-

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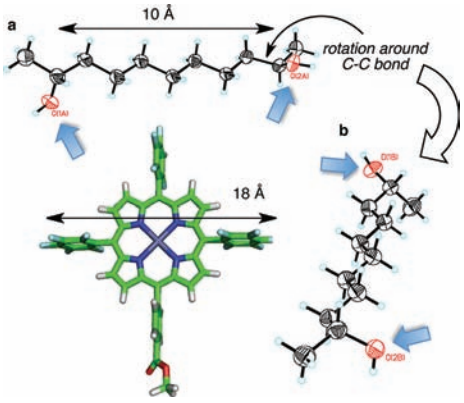

Figure 5. (a) Crystal structure of diol **8**, which is in agreement with the lowest-energy-minimized all-staggered conformation for odd-*n* diols. The arrows denote the putative approach of the porphyrin rings anti to the methyl groups. The large size of the porphyrin rings precludes the approach of both metalloporphyrins from the same face of the diol. (b) Present in the crystal structure is a second energetically close-lying conformation, suggesting that a C−C bond rotation could lead to the desired arrangement enabling the approach of the metalloporphyrins from opposite sides of the molecule.

entiation as described above for even-*n* diols leads to the observed ECCD of the odd-*n* diols.

The latter suppositions were further substantiated by conformational searches using molecular mechanics, which showed a clear preference for positive helicity for the *R,R* supramolecular assembly among the low-energy conformers examined (see the SI). Conformational searches also favored the slipped cofacial geometry of the porphyrin tweezer (see Figures S17−S20 and further discussion in the SI). Although we favor the side-on approach for binding with **B**, we cannot preclude the possibility of head-on binding for smaller diols that could be accommodated with the short C3 linker.

In conclusion, we have established a new supramolecular host system that is capable of binding a variety of 1,*n*-diols in a predictable manner and leads to reliable interrogation of absolute stereochemistry. We postulate that the tweezer host system can provide consistent results for a host of different diol lengths by its tendency to bind in a side-on fashion. This, we believe, is a result of having limited the porphyrin tweezer's conformational freedom through two distinct pathways. First, tight binding as a result of the enhanced Lewis acidity of the metallocenter (fluorinated porphyrins) leads to a much-improved binding affinity for the bound diol. Second, shortening the linker between the porphyrins leads to less conformational flexibility of the complex. The combination of these factors leads to a consistent binding motif that enables predictable assignment of chirality. Further application of this method to complex diol molecules has revealed promising results and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and modeling procedures and results and crystallographic data (CIF). 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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