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Graphical abstract

\(m\)-Phthalic diamide-linked zinc bisporphyrinates can not only determine the absolute configuration of monoamines but also distinguish between alkyl and aryl substituents of chiral monoamines.
Discrimination between alkyl and aryl substituents of chiral monoamines by m-phthalic diamide-linked zinc bisporphyrinates

Xianshi Fang, a Zhen Han, a Chenglong Xu, a Xiaohong Li, a Yong Wang, a * and Chuanjiang Hu * a b

m-Phthalic diamide-linked zinc bisporphyrinates have been developed as chirality probes for monoamines. They are capable of determining the absolute configuration of monoamines and distinguishing between alkyl and aryl substituents of chiral monoamines. Our studies suggest steric interactions play critical roles in the molecular recognition process.

Absolute configuration determination is of great importance for chiral molecules since the chirality is crucial in many research fields, such as biological systems, organic synthetic chemistry and pharmacology, etc. Exciton-coupled circular dichroism (ECCD) spectroscopy provides a useful non-empirical method in sensing chirality.1 Based on this method, the sign of the observed CD are determined by the dihedral angles of the transition dipoles of the chromophores, which can be directly related to the absolute configuration of the system being studied.

For monodentate chiral compounds which do not absorb in the UV-vis, it is very difficult to determine their absolute configurations. For monoamines, only a limited systems can differentiate their enantiomers.2-13 Some of them require the monoamines to be derivatized.2-9 For example, Berova, Nakanishi and coworkers have designed a bisporphyrin linked by a pentanediol linker which can assign the absolute configuration of chiral monoamines through their derivatives.2-4 Anslyn and coworkers have recently explored a method to use an in situ amine derivatization and self-assembly process for enantiomeric excess determination of chiral monoamines.9

Since there is only one binding site for monodentate ligands, it is even more difficult to differentiate their enantiomers without chemical derivatization. For nonporphyrin system, several polymers have been reported to be able to assign the absolute configurations of chiral amines.10 So far, only two porphyrin systems have been reported to have such function for monoamines.11-14 One is the ethylene bridged bisporphyrin system developed by Inoue, Borovkov and coworkers, the short linkage causes the steric interactions between the 3,7-ethyl groups of the porphyrin and the substituents of the ligand, resulting in the induced supramolecular chirality.11-13 Another is the biphenol bridged metal-free bisporphyrin system developed by Borhan and coworkers, the hydrogen bonding and steric interactions between the monoamines and the host molecules lead to the stereodifferentiation.14 In those systems, the steric interactions have been suggested to make major contribution to the supramolecular chirality.15 So the bulkiness of substituents of monoamines plays very important roles. For the chiral amines shown in Scheme 1, no matter the substituent R of the chiral carbon is an alkyl or aryl group, it is generally thought that the bulkiness order is R > CH3 > H. So the steric effect led to the same sign of CD for the amines of the same handedness in those systems.

Scheme 1 The Structural Formulas of the Designed m-Phthalic Diamide-Linked Zinc Bisporphyrinates and Used Chiral Monoamines.

But that is not always the case! Our group is focusing on developing a system capable of determining the absolute configuration of monodentate chiral guests. Recently, we have developed a series of amide-linked bisporphyrins.16-19 All these hosts can be used to determine the absolute configuration of amino acid esters, which function as monodentate ligands in the chiral recognition process. For the m-phthalic diamide-linked bisporphyrin
Table 1. Observed CD spectral data of chiral monoamines with hosts in methylene dichloride at 295 K.

<table>
<thead>
<tr>
<th>amine</th>
<th>([Zn_2]^{-1})</th>
<th>([Zn_2]^{-2})</th>
<th>([Zn_3]^{-3})</th>
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<tr>
<td></td>
<td>(\Delta \varepsilon, \lambda \text{ nm})</td>
<td>(\Delta \varepsilon, \lambda \text{ nm})</td>
<td>(\Delta \varepsilon, \lambda \text{ nm})</td>
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<td>+108</td>
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<td>-212, 412</td>
<td>-187, 412</td>
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[a] \(A_{ex} = \Delta \varepsilon_{1} - \Delta \varepsilon_{2}\). This value represents the total amplitude of the experimentally observed CD couplets.

Fig. 1 Circular dichroism spectra (top) and UV-vis spectra (bottom) of a solution of \([Zn_2]^{-1}\) (1.63 \(\times\) 10\(^{-6}\) M) and 1500 equivalents of (A) S-1-phenylethylamine (1S), and (B) S-3-methyl-2-butylamine (5S) in methylene dichloride at 295 K.

\([Zn_2]^{-1}\) (Scheme 1), the structure suggests such porphyrin adopts syn-configuration, which provides a possible binding cavity for the absolute configuration determination of chiral monoamines. In this paper, a series of chiral monoamines have been tested (Scheme 1). The CD spectra did show strong signals in the Soret band region. But to our surprise, when the substituent (R) is an aryl group, the signs of their CD signals are opposite to those when R is an alkyl group! To the best of our knowledge, this new host system is the first system which can not only determine the absolute configuration of chiral monoamines but also distinguish those two different types of chiral monoamines. What cause the difference between the alkyl and the aryl substituents? We report further investigations on the possible mechanism in the molecular recognition process.

In this study, \([Zn_2]^{-1}\), \([Zn_2]^{-2}\) and \([Zn_3]^{-3}\) were used as hosts. Hosts and enantiopure amines were mixed in methylene dichloride, and the corresponding CD spectra were measured. The spectra showed strong signals with typical bisignate Cotton effects in the Soret band region. The amplitude of CD signals is up to 680 cm\(^{-1}\).mol\(^{-1}\). The spectra for S-1-phenylethylamine (1S) and S-3-methyl-2-butylamine (5S) are displayed in Fig. 1, and others are shown in the supporting information.

Inspection of these results in Table 1 reveals the following trend: 1) For a pair of enantiomers of chiral amines, the CD spectra showed similar shapes and intensities but opposite signs. 2) More importantly, the signs of CD for the chiral amines of the same handedness with R as an aryl group are just opposite to those with R as an alkyl group. For example, for 1S-1-phenylethylamine, the longer-wavelength peak of the Soret band was negative and the shorter-wavelength peak was positive. While for S-3-methyl-2-butylamine, the corresponding spectrum showed the opposite sign.

In order to understand the structural information in the chiral recognition process, we tried to grow crystals of the host-guest complexes. Unfortunately, we did not obtain single crystals suitable for X-ray crystallography. Instead, we got single crystals for the host compounds. \([Zn_2]^{-1}\) was reported previously.\(^{16}\) Now, we also obtained the single crystals of \([Zn_3]^{-3}\). For bisporphyrin 2, we obtained the structure of its copper complex instead of zinc complex.

The structure of \([Cu_2]^{-2}\) was solved in the space group \(I4_1\). Its ORTEP diagram and packing diagrams are provided in supporting information (Figs. S21-S23). Its structure resembles that of \([Zn_2]^{-1}\).\(^{17}\) Instead of zinc, the central metal is copper. Different from \([Zn_2]^{-1}\) and \([Cu_2]^{-2}\), for the crystal of \([Zn_3]^{-3}\), the space group is \(C_{1h}\), achiral. One asymmetric unit contains two zinc bisporphyrinate units.

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Among them, three zinc atoms, Zn(1), Zn(3) and Zn(4), are five-coordinate. While Zn(2) is four-coordinate (Fig. 2). Two zinc bisporphyrinates are connected with each other by the Zn(3)–O(502) bond. There are also coordination bonds between Zn(1) and O(601A), Zn(4) and O(501B), O(501) and Zn(4C), O(601) and Zn(1D), which lead to two dimensional coordination layers along ab plane as shown in Figure S24. In these structures, two porphyrin subunits form a twist with torsional angle (C(m3)–C(m1)–C(m1A)–C(m3A)) of 52.33° for [Zn2–I], 53.93° for [Cu2–2], 53.30° and 42.05° for [Zn2–I]. In all the cases, two porphyrin subunits adopt syn-configuration. The metal to metal distance is 10.66, 10.32, 11.23 or 10.56 Å, which makes the intraporphyrin cavity suitable for the accommodation of axial ligands, such as amines.

When excess ligands (L) were mixed with the hosts, there are three possible binding modes as shown in Fig. 3: “inside-outside” mode a, “inside-inside” b and “outside-outside” mode c. For the “outside-outside” binding mode c, the coordination environment around the ligand is similar to that for [Zn(TPP)]. So we did comparison experiments by measuring the CD spectra of the mixture of [Zn(TPP)] and chiral amines. No observable signals were obtained (Fig. S19). It suggests the “outside-outside” mode c is less likely to contribute to the CD. Similar cases have been reported by Borovkov et al. 11,12,20

In order to get some insight on the chiral recognition process, we did further investigation by DFT calculations on the mode a and b. We chose [Zn2–I] as the host, and 1S, 5S as the guests. Firstly, we performed DFT calculations on the free host [Zn2–I]. Then we did calculations on the corresponding complexes formed between [Zn2–I] and guest 1S or 5S.

Due to the asymmetric arrangement, the host molecules exist as two enantiomers, conformers I and II as shown in Fig. S31. When guests are coordinated with the hosts, both conformers I and II could form the corresponding complexes. The calculations suggest the “inside-inside” mode b is energetically unfavorable (Figs. S32–33), which could be due to the steric repulsions between guest molecules. So mode a should be the major contributor to the CD.

In mode a, the coordination of 1S to [Zn2–I] leads to the complexes, Conformer 1S or Conformer 1S as shown in Fig. 4. The calculations suggest that the Conformer 1S is more energetically favourable (1.16 kJ/mol lower) than the Conformer 1S. In their optimized structures, a noteworthy difference is the orientation of the substituent R. The R group is facing the linking phenyl ring in the Conformer 1S, while it is away from the linking phenyl ring in the Conformer 1S. Such orientation may cause less steric repulsion for the Conformer 1S and hence, lower its energy. Therefore, the Conformer 1S should be the major contributor to the CD spectra. In the Conformer 1S, the two porphyrin subunits adopt an anticlockwise twist.
exciton chirality method, such a twist will lead to negative Cotton effect. While for SS guest, for the same reason, the Conformer I-SS is more energetically favourable (5.85 kJ/mol lower) than the Conformer II-SS, which leads a clockwise twist and positive Cotton effect (Fig. S34). These are consistent with our experimental results.

Fig. 5 DFT B3LYP/6-31G* optimized structures of the complexes. (A) Conformer I-1S and (B) Conformer I-5S. For clarity, the outside binding ligand, some phenyl rings at meso-positions and most hydrogen atoms are omitted.

But why do 1S and SS lead to different twists? One notable difference between alkyl and aryl groups is their geometries. An aryl group has planar geometry, while an alkyl does not. If we compare a phenyl with a methyl group, along the direction perpendicular to the phenyl ring, the size of phenyl is similar to one carbon atom, while for the methyl, such size should be similar to a CH group. So along certain orientation, the methyl could be more bulky than the phenyl group! But for other alkyl groups, nonplanar geometry makes them more bulky than the methyl group. The above difference could be the key leading to different signs of CD signals. On the other hand, our linker is larger and more rigid than that in the ethylene bridged bisporphyrin. When the monoamine is coordinated to zinc, the intraporphyrin cavity is large enough to accommodate the ligand. That could cause steric interactions between the monoamine and the uncoordinated porphyrin subunit in the syn-configuration. The above explanation is also confirmed by our DFT calculations. As shown in Fig. 5, besides the steric repulsions between the linking phenyl and R, there are also repulsions between the substituents and the top porphyrin plane. When S-1-phenylethylamine (1S) is used, both the phenyl group and the methyl group are facing the top porphyrin subunit. The phenyl plane (Fig. 5A) is near parallel to the top porphyrin to avoid the repulsion, while the nonplanar methyl group causes more repulsion, which lead to the anticlockwise twist. The parallelised orientation also causes weak π-π interactions between the phenyl ring of 1S and the porphyrin plane (the corresponding centroid to centroid distance is 4.48 Å), which could also have contribution to the stabilization of the host-guest structure. For S-3-methyl 2-butylamine, the competition come from the isopropyl group and the methyl group, both have nonplanar geometry. The isopropyl is more bulky, and it causes more repulsions than the methyl, and leads to the clockwise twist. We also notice that CD magnitudes vary for different monoamine guests or bisporphyrin hosts. But there is no clear pattern between the bulkiness of the substituents and CD magnitudes. One possible reason is that the above mentioned two types of steric interactions make the system more complicated, no simply correlation can be established.

Conclusions

To conclude, we have developed an m-phthalic diamide-linked bisporphyrin system which can not only function as chirality probes for chiral monoamines but also distinguish between aryl and alkyl substituents of monoamines. Our studies suggest the steric interactions between host and guest molecules are the keys to lead to different CD. These bisporphyrins are potential chirality probes for other monodentate chiral molecules, such as monooalcohols. Related investigations are still ongoing.

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Notes and references