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Chiral dinaphthylporphyrin with C_2 symmetry: synthesis, resolution, and enantio-discrimination by single-crystal X-ray diffraction analysis

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ABSTRACT

An intrinsic chiral dinaphthylporphyrin with C_2 symmetry, namely [5,15-*trans*-bis(2-hydroxynaphthyl)-10-phenyl-20-(4-hydroxyphenyl)porphyrinato]zinc(II) (**ZnDNP**), has been designed and synthesized. The molecular structure of **ZnDNP** was determined by single crystal X-ray diffraction analysis. Resolution of the racemic mixture was achieved with chiral HPLC technique. In particular, the stereostructures of the enantiomers and the specific interactions between the chiral *meso*-dinaphthylporphyrin with L-Phe-OMe were elucidated in the solid state by single-crystal X-ray diffraction analysis.

Chiral porphyrins are attractive scaffolds for chiral sensing[1,2] and asymmetric catalysis[3] due to their rigid frameworks and unique spectroscopic properties.[4] Generally, chiral porphyrins were obtained by incorporating chiral substituents (extrinsic chirality),[5] or configuring achiral substituents alone a chiral axis of the porphyrin ring (intrinsic chirality).[6] Atropisomerism[7] is one of the typical mechanisms toward intrinsic chiral porphyrins, by which the molecular chirality can generate as a result of hindered rotation about a bond axis in the meso[8] or β[9] position. Because of the facilities for the introduction of hydrogen-bonding donor/acceptor and the flexibility of the dynamic rotation, chiral atropisomeric porphyrins play crucial roles in supramolecular chemistry, such as molecular recognition[8] and ordered molecular assembly.[10]

However, chiral *meso*-dinaphthylporphyrin derivatives remain extremely rare, limited to the couple of examples of Ogoshi and co-workers with octaethylporphyrin skeleton,[8,11] and the stereostructure of this typical class of atropisomeric porphyrin has not been discussed so far. On the other hand, detailed understanding of the supramolecular interactions between a chiral porphyrin host and a chiral guest molecule is informative for the design of porphyrin-based chirality-sensing[12] and asymmetric catalysis[13] systems. Herein we report the synthesis of achiral dinaphthylporphyrin porphyrin derivatives, namely [5,15-*trans*-bis(2-hydroxynaphthyl)-10-phenyl-20-(4-hydroxyphenyl)porphyrinato]zinc(II) (**ZnDNP**). The enantiomers of **ZnDNP** were separated successfully, and their absolute configurations were assigned by a direct method of single-crystal X-ray diffraction analysis. The interactions between the enantiomerically pure dinaphthylporphyrin molecules with L-Phe-OMe were also elucidated in the solid state.

The two enantiomers of **ZnDNP** are shown in Figure 1. 2-Hydroxylnaphthyl groups are introduced to two opposite *meso* positions of the porphyrin core. The large steric hindrance of the

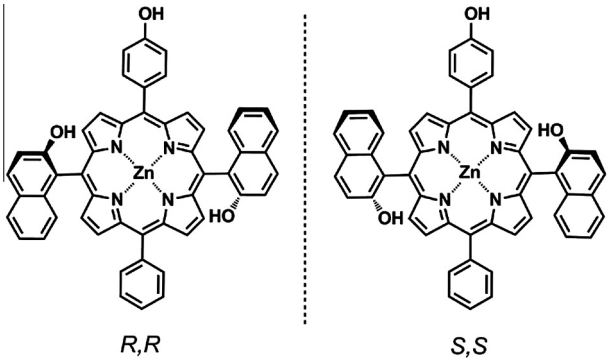

Figure 1. Two enantiomers of **ZnDNP**.

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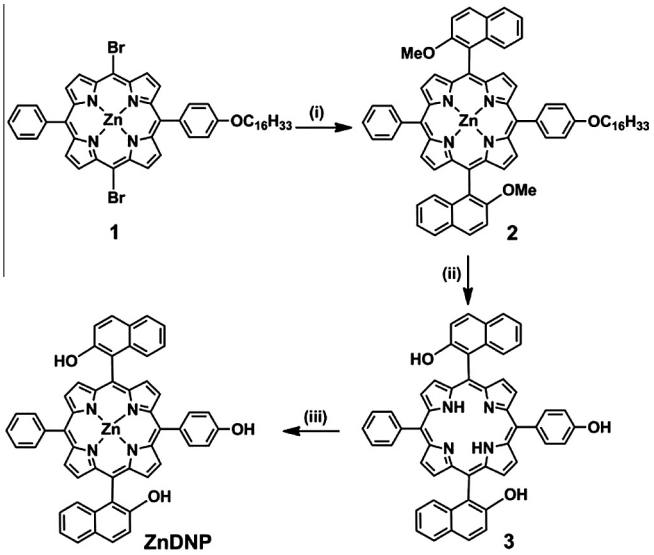

Scheme 1. Synthesis of **ZnDNP**. Reagents and conditions: (i) 2-methoxy-1-naphthylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/toluene; (ii) BBr_3, CH_2Cl_2; (iii) $Zn(OAc)_2$, $CHCl_3$/MeOH.

9-hydrogen atoms and 2-hydroxy groups of the naphthyl rings with the adjacent porphyrin β-hydrogen atoms effectively hinders the free rotation about the naphthyl-*meso* carbon bonds,[14] thus producing two atropisomeric sites. In addition, the 2-hydroxy groups can serve as hydrogen bonding donors and the Zn(II) center as a coordination site[15] for guest molecule binding. In the design of **ZnDNP**, phenyl and 4-hydroxy-phenyl were introduced into the other two opposite *meso*-positions, the different electron-donating capacities and polarities between these two groups are crucial for the chiral discrimination and resolution properties.

The synthesis of **ZnDNP** is shown in Scheme 1. The dibrominated porphyrin **1** was prepared through bromination of a *trans*-AB-porphyrin[16,17] with *N*-bromosuccinimide (NBS), which was isolated and characterized by single-crystal X-ray diffraction analysis (Fig. S1 and Table S1). Then, compound **2** was synthesized through a Suzuki-Miyaura coupling reaction[18] of **1** with 2-methoxy-1-naphthylboronic acid, the *cis*-isomer (*R*,*S*-**2**′) was removed by silicon gel column chromatography and the *trans*-isomer (**2**) was obtained with a yield of 35%. The alkoxy version of the chiral dinaphthylporphyrin zinc(II) complex **2** was hydrolyzed by BBr_3 to convert to the free-base hydroxy version **3**, followed by re-metalation to obtain complex **ZnDNP**. The target compound **ZnDNP** and the intermediates **1**–**3** were characterized by mass, NMR, and electronic absorption spectroscopies in addition to elemental analysis (see the Supporting Information for details).

The molecular structure of racemic **ZnDNP** was determined by X-ray diffraction analyses. Single crystals were obtained by slow diffusion of hexane into a solution of **ZnDNP** in $CHCl_3$/pyridine (100:1 v/v). As shown in Figure 2, **ZnDNP** crystallizes in the monoclinic space group ($P2_1/n$) with two pairs of enantiomeric molecules per unit cell. The Zn center is five-coordinated by four pyrrole nitrogen atoms of porphyrin and one pyridine nitrogen atom, forming the slightly distorted rectangular pyramid coordination geometry. The bond distance of Zn–N(pyridine) (2.128(5) Å) is longer than the mean Zn–N(porphyrin) bond distance (2.076(5) Å), which are similar to the corresponding reported values for other pyridine-Zn-porphyrin systems.[16,19] Because of the axial coordination of pyridine ligand, the Zn center deviates from the N_4 mean plane (by 0.344 Å) and points to the axial pyridine ligand.[20] The two naphthyl ring is almost perpendicular to the N_4 mean plane of porphyrin with a dihedral angle of 86.26° and 87.87°, respectively, as a result of the large steric hindrance effect. In addition, the neighboring molecules of **ZnDNP** are bound together through hydrogen bondings of O(2-hydroxy-1-naphthyl)-HO

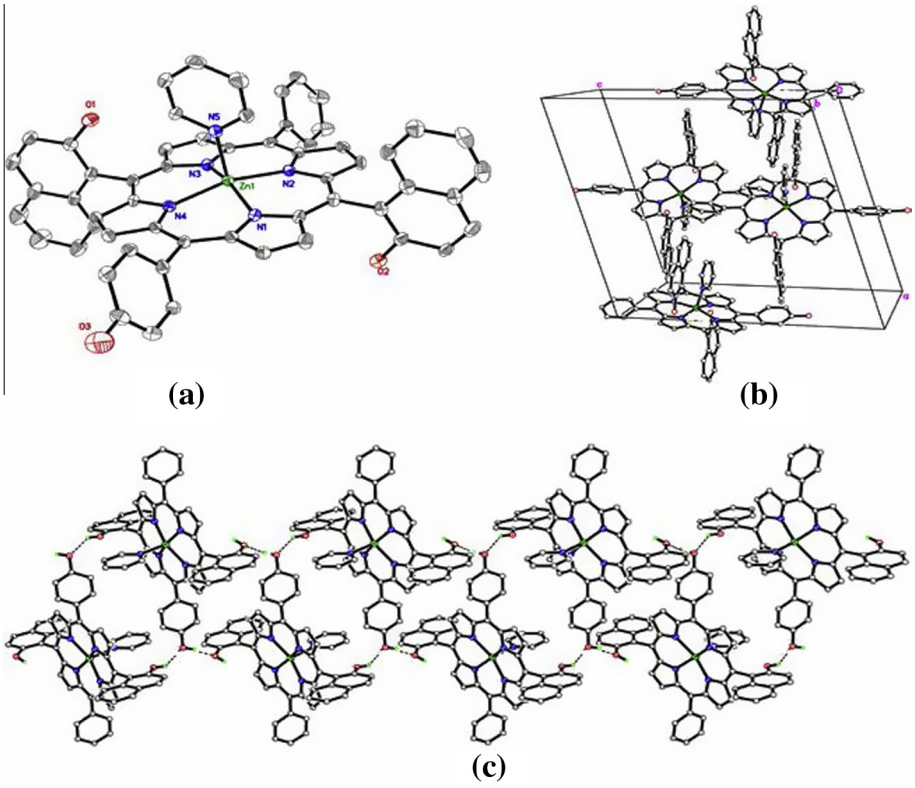

Figure 2. (a) X-ray crystal molecular structure of complex **ZnDNP** showing the 30% probability thermal ellipsoids for all non-hydrogen atoms. (b) Unit cell of complex **ZnDNP**. (c) 1D supramolecular chain structure. Hydrogen atoms are omitted for clarity except for those of hydroxyl groups in (c).

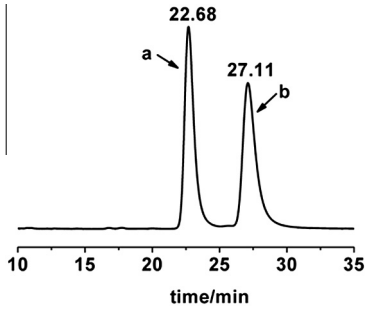

Figure 3. Chromatogram of **ZnDNP** monitored by a UV detector at 425 nm (ChiralPak IC, i.d. 10 × 250 mm, Daicel Co.; 25 °C; isopropanol/CH_2Cl_2/hexane (1:50:50, v/v/v); isocratic flow rate: 2 mL/min).

(4-hydroxy-phenyl) and O(4-hydroxy-phenyl)-HO(2-hydroxy-1-naphthyl), with distances of 1.820(9) and 1.977(9) Å, respectively, forming one-dimensional (1D) supramolecular single-chain structure. Here, the hydroxyl of the naphthyl, as well as that of the phenyl, serves both as hydrogen bonding donor and acceptor. The above observations imply that the porphyrin **ZnDNP** can be a chiral receptor with multiple intermolecular interactions of coordination and hydrogen bonding.

By using a chiral HPLC method, the complex **ZnDNP** has been separated into two fractions with a 1:1 ratio as shown in Figure 3. The two fractions with retention times of 22.68 and 27.11 min are denoted as **a** and **b**, respectively, both show very weak circular dichroism (CD) signals which is in accordance with previous observations for similar systems,[8,16] whereas **a** and **b** fractions possess identical electronic absorptions and NMR spectra, indicating the successful resolution of enantiomers.

To examine the supramolecular binding capability of the pure enantiomers, association constants between host **a** and a pair of amino acid esters (L- and D-Phe-OMe) were determined by UV–vis spectrophotometric titrations, Figures 4 and S2 (Supporting Information). Upon adding L- and D-Phe-OMe to host **a** gradually, the Soret absorption maxima underwent bathochromic shift from 425 to 435 nm, due to the formation of supramolecular complexes **a**·L-Phe-OMe and **a**·D-Phe-OMe, respectively. A sharp isosbestic point appears at 430 nm for each titration, which verifies the 1:1 stoichiometry of host to guest and allows for determining the association constants (K_{assoc}) by applying a nonlinear curve-fitting method.[21] The K_{assoc} are evaluated as high as 1.9×10^4 and $2.7 \times 10^4\ M^{-1}$ for **a**·L-Phe-OMe and **a**·D-Phe-OMe respectively (errors estimated as ±5%), resulting very weak enantioselectivity of 1.4 ($K_{assoc(\mathbf{a}\cdot D\text{-Phe-OMe})}/K_{assoc(\mathbf{a}\cdot L\text{-Phe-OMe})}$).

In order to assign the absolute configuration, we have tried to prepare single crystals from the pure enantiomers **a** and **b**, however, it was unsuccessful because of the poor crystallinity.

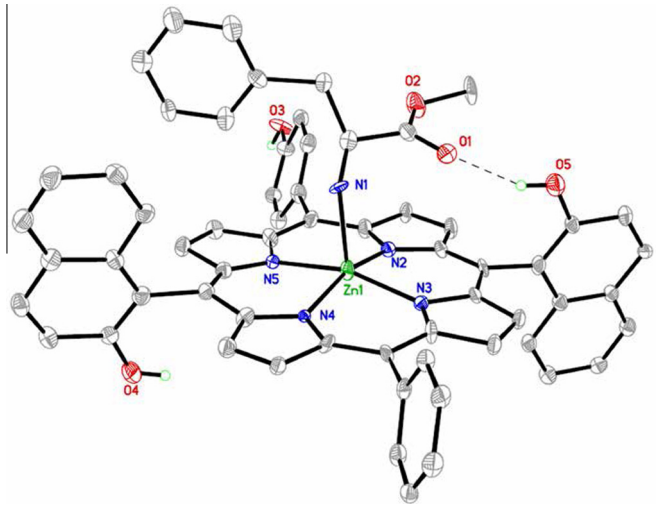

Figure 5. X-ray crystal structure of complex *S*,*S*-**ZnDNP**·L-Phe-OMe. The thermal ellipsoids are scaled to be the 30% probability level. Hydrogen atoms are omitted for clarity except for those of hydroxyl groups.

Fortunately, after the formation of host-guest complex, suitable crystals of **b**·L-Phe-OMe for X-ray analysis were obtained by slow diffusion of hexane into a chloroform solution of **b** and L-Phe-OMe in a 1:1 ratio. The absolute structure of **b**·L-Phe-OMe was acquired by the single crystal X-ray analysis results (Fig. 5 and Table S1 in the Supporting Information), in which the **b** fraction possesses *S*,*S*-configuration, with a convincing absolute structure parameter of 0.02 (3).[22] Hence, the **a** fraction should possess *R*,*R*-configuration.

The specific supramolecular interactions between *S*,*S*-**ZnDNP** and L-Phe-OMe have also been presented by the single-crystal X-ray diffraction analysis results. As shown in Figure 5, L-Phe-OMe binds *S*,*S*-**ZnDNP** by Zn—NH_2 coordination (2.196 (11) Å) and OH—O=C hydrogen bonding (2.024(17) Å) interactions. The complex *S*,*S*-**ZnDNP**·L-Phe-OMe crystallizes in the monoclinic system in a chiral space group (*P*1) with one molecule per unit cell. The Zn(II) ion is also five-coordinated, forming slightly distorted rectangular pyramid coordination geometry. The Zn center deviates from the N_4 mean plane (by 0.306 Å) and points to the L-Phe-OMe side. The bond distance of Zn–N(Phe) (2.196(11) Å) in *S*,*S*-**ZnDNP**·L-Phe-OMe is longer than that of Zn–N(Py) (2.128(5) Å) in **ZnDNP**·Py, indicating a weakened coordination interaction in the former.

In summary, an intrinsic chiral dinaphthylporphyrin **ZnDNP** has been designed and prepared. The single crystal structure of the racemic mixture of **ZnDNP** was obtained. The resolution for compound **ZnDNP** was achieved by the chiral HPLC technique. The absolute configurations of the pure enantiomers were assigned

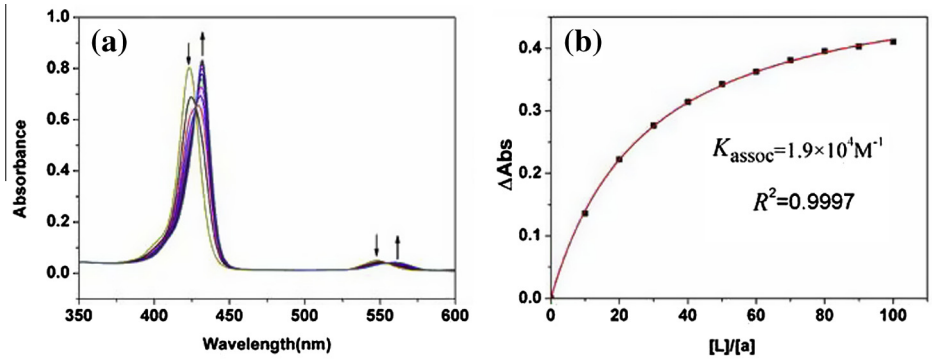

Figure 4. (a) Spectral change upon titration of **a** with L-Phe-OMe in $CHCl_3$ at 25 °C. (b) Changes in ΔAbs at 425 nm for evaluating K_{assoc}. [**a**] = 2.0×10^{-6} M; [**L**]/[**a**] = 0–100.

by single-crystal X-ray diffraction analysis. The specific supramolecular interactions between the enantiomerically pure dinaphthylporphyrin *S*,*S*-**ZnDNP** with L-Phe-OMe were elucidated in the solid state.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.067.

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