

## Recognition of Chirality and Residual Groups of Amino Acid Esters using New Trifunctional Chiral Porphyrins with $C_2$ Symmetry

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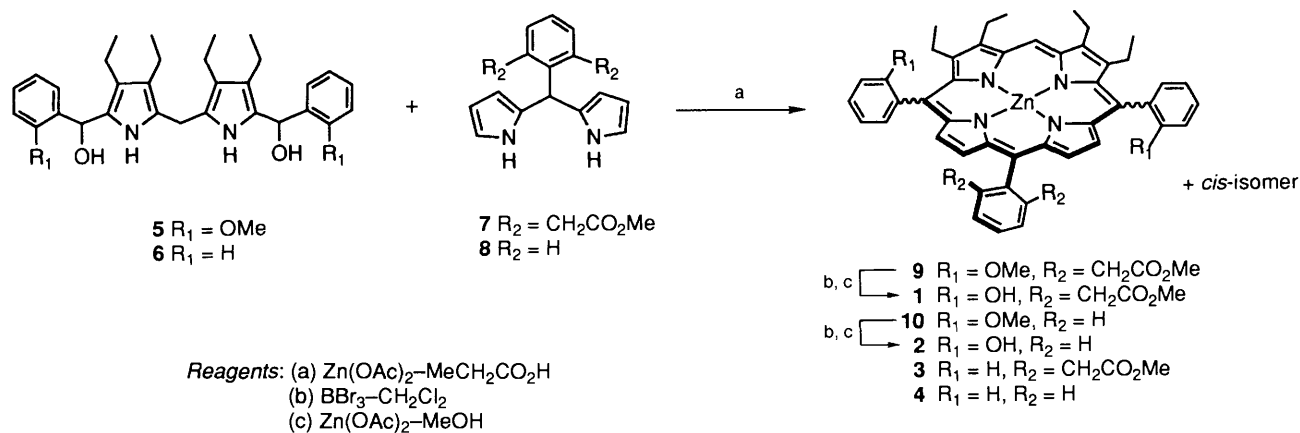
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An intrinsic chiral recognition host, [*trans*-5,15-bis(2-hydroxyphenyl)-10-(2,6-bis(methoxycarbonylmethyl)phenyl)-2,3,17,18-tetraethylporphyrinato]zinc(II) **1**, is synthesized and found to show an enantioselectivity of *ca.* 2 : 1 for L- and *o*-amino acid esters having non-polar residues, whereas it shows a reversed enantioselectivity of *ca.* 1 : 2 for L- and *o*-Ser-OBzl.

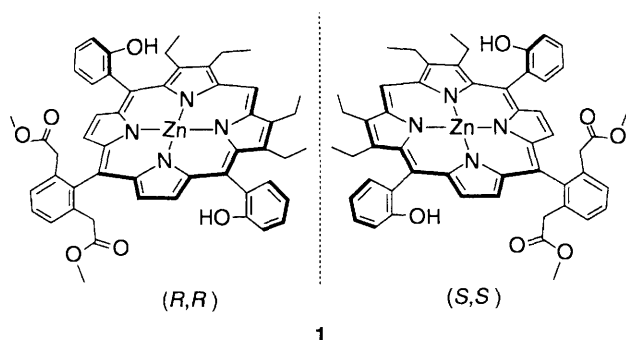
Chiral selectivity and substrate selectivity toward biologically important molecules are of current interest in the area of supramolecular chemistry.<sup>1</sup> Synthetic feasibility and disposition of recognition groups in a complementary fashion should be simultaneously achieved to realize such selectivities. Investigation of well designed host-guest complexation will allow us to make separative determinations of the interaction energies between each recognition group,<sup>2</sup> which in turn would be of help in designing improved host-guest systems. In this paper we describe the design, synthesis and binding features of a trifunctional chiral porphyrin with  $C_2$  symmetry.

The chiral porphyrin **1** was synthesized by the pyrrole-methanol method.<sup>3</sup> Two dipyrromethane units, **5** and **7**, with

recognition groups OH and CO<sub>2</sub>Me, were cyclized in propionic acid<sup>4</sup> in the presence of zinc acetate at 95 °C, giving a mixture of the *trans*- and *cis*-isomer **9** in 9–17% yield without forming other regioisomers (Scheme 1). Cleavage of the methyl group and chromatographic separation from the *cis*-isomer afforded **1**. The *trans*-isomer **1** was resolved into two enantiomers (**1a** and **1b**) by high-performance liquid chromatography (HPLC) on a chiral column. This pyrrole-methanol method is advantageous over the conventional cyclization of pyrroles and aldehydes for the preparation of porphyrins with  $C_2$  symmetry owing to its regioselectivity of the cyclization step. Reference porphyrins **2–4** were also prepared similarly to evaluate the interaction energies caused



Scheme 1



by each recognition group.<sup>†</sup> In host **1**, three recognition groups (Zn, OH and  $\text{CO}_2\text{Me}$ ) were fixed to a rigid skeleton in a convergent fashion, forming a chiral recognition pocket. In the  $^1\text{H}$  NMR spectra, the protons of *o*-hydroxyphenyl groups in host **1** appeared at almost the same chemical shift as that observed for those of host **2**. This fact and the following binding experiments indicated that the intramolecular hydrogen bonding did not take place between the OH group and the  $\text{CO}_2\text{Me}$  group in host **1**.

The binding constants of a series of amino acid esters (Ala-OMe, Val-OMe, Leu-OMe, Ile-OMe, Leu-OBzl, Ser-OBzl) to hosts **1a**, **2**–**4** were determined in chloroform at  $15^\circ\text{C}$  by UV-VIS titration and listed in Table 1. In the case of Val-OMe, Leu-OMe, Ile-OMe and Leu-OBzl, host **1a** showed an enantioselectivity of *ca.* 2:1 in respect to L- and D-amino acid esters.<sup>‡</sup> The binding constants of Ala-OMe were smaller and a similar trend was observed for the binding to [5,15-bis(2-hydroxy-1-naphthyl)-2,3,7,8,12,13,17,18-octaethylporphyrinato]zinc.<sup>2</sup> On the other hand, the binding features of Ser-OBzl to hosts **1**–**4** were completely different.<sup>§</sup>

<sup>†</sup> All the hosts were characterized by  $^1\text{H}$  NMR, FAB mass spectra, and UV-VIS spectra, confirming the expected structure. Host **1** was resolved into two enantiomers by use of HPLC with a chiral column. The first eluted fraction **1a** was used throughout the binding experiments.

<sup>‡</sup> The other enantiomer **1b** showed reversed enantioselectivity of *ca.* 1:2 in respect to L- and D-Leu-OMe.

<sup>§</sup> Owing to the poor solubility of Ser-OMe in chloroform, Ser-OBzl was used.

Table 1 Binding constants (*K*) of amino acid esters to zinc porphyrins<sup>a</sup>

	<i>K</i> /dm <sup>3</sup> mol <sup>-1</sup>			
	<b>1a</b>	<b>2</b>	<b>3</b>	<b>4</b>
L-Ile-OMe	6780	13 700	780	1420
D-Ile-OMe	2420			
L-Leu-OMe	6160	13 300	680	1130
D-Leu-OMe	2460			
L-Val-OMe	6130	12 600	650	1240
D-Val-OMe	2440			
L-Ala-OMe	1590	3460	720	740
D-Ala-OMe	1420			
L-Leu-OBzl	3450	10 100	560	1060
D-Leu-OBzl	1540			
L-Ser-OBzl	1340	2400	920	480
D-Ser-OBzl	2840			

<sup>a</sup> At  $15^\circ\text{C}$  in chloroform; standard deviations were within 4%.

It is noteworthy that the enantioselectivity of host **1a** was reversed, showing a preference for the D-isomer.

A high binding ability of host **2** compared with host **4** can be ascribed to the hydrogen bond between the host OH group and the guest C=O group  $\{-0.9$  to *ca.*  $-1.4$  kcal mol<sup>-1</sup>, (1 cal = 4.184 J), calculated from  $-RT \ln [K(2)/K(4)]\}$ . This hydrogen bonding was observed for all the amino acid esters and has been well characterized in similar systems.<sup>2</sup> The  $\text{CO}_2\text{Me}$  group of host **1a** served three different functions depending on the residual group and chirality of the guest. It acted as a minor steric repulsive site for L-isomer of the guests  $\{+0.4$  to *ca.*  $+0.5$  kcal mol<sup>-1</sup>, calculated from  $-RT \ln [K(1a,L)/K(2)]\}$ , as a major steric repulsive site for D-isomer of apolar amino acid esters  $\{+0.9$  to *ca.*  $+1.0$  kcal mol<sup>-1</sup> except Ala-OMe ( $+0.5$  kcal mol<sup>-1</sup> for Ala-OMe) calculated from  $-RT \ln [K(1a,D)/K(2)]\}$ , and as an attractive site for D-Ser-OBzl  $\{-0.1$  kcal mol<sup>-1</sup>, calculated from  $-RT \ln [K(1a,D)/K(2)]\}$ . If the steric repulsion energy between **1a** and D-Ser-OBzl can be assumed to be comparable with that observed between **1a** and D-Ala-OMe or D-Val-OMe, then the attractive interaction between the host  $\text{CO}_2\text{Me}$  group and the Ser residue would be *ca.*  $-0.6$  to  $-1.0$  kcal mol<sup>-1</sup>, which may be attributed to the hydrogen bond between them.

We suggest that two-point fixation of the guest by zinc and the host OH group will determine the direction of the residual group of the amino acid esters. The observed selectivities suggest that the residual group be directed toward the host  $\text{CO}_2\text{Me}$  group in D-guest-**1a** complexes, but directed away

from the host CO<sub>2</sub>Me in L-guest-**1a** complexes. This work has demonstrated that recognition of chirality and residual groups of amino acid esters is accomplished by the cooperative action of three recognition groups.

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