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L-Nipecotic Acid-Porphyrin Derivative: A Chiral Host with Introverted Functionality for Chiral Recognition

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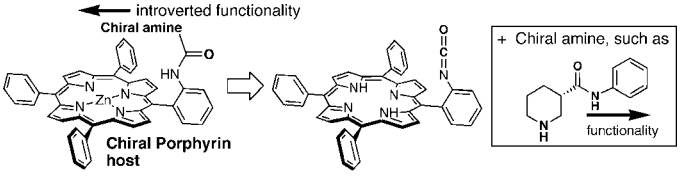
ABSTRACT



The synthesis and chiral recognition properties of a porphyrin host with introverted functionality is reported. The host is a hybrid of tetraphenyl zinc porphyrin and the *N*-phenylamide derivative of (*S*)-nipecotic acid. The chiral recognition properties of the porphyrin host with chiral carboxylate-containing guests is described. UV/vis and ^{1}H NMR spectroscopic results indicate the host shows enantioselectivity for (*S*)-mandelate tetrabutyl ammonium salt.

The first manuscript over anion recognition appeared in the literature in 1968; over the past 44 years, anion recognition has developed into a sophisticated area of research with several thousand manuscripts published in the field.[1] However, a SciFinder search only reveals approximately 200 chiral anion recognition manuscripts.

Several chiral platforms such as binaphthyl derivatives,[2] steroids,[3] and sugars[4] have been utilized for host design. To develop chiral hosts from nonchiral platforms, a useful strategy centers on the utilization of amino acids[5] or chiral amines[6] in the host design. Porphyrins have been utilized for the development of anion receptors,[7] and there are a handful of chiral porphyrin-based receptors reported.[8]

Porphyrins are good scaffolds for synthetic receptors due to their UV/visible and fluorescence spectroscopic properties, their circular dichroism response, and their electrochemical properties. The porphyrin core provides a rigid platform to construct guest recognition pockets by functionalization of β and meso positions; introduction of a metal in the porphyrin provides a guest coordination site.

Aside from host–guest chemistry, chiral porphyrins find applications in other diverse fields. Chiral cobalt(II) and ruthenium(II) porphyrins serve as catalyst for asymmetric epoxidations, cyclopropanations, aminations, aziridinations,

(1) For recent reviews, see: (a) Gale, P. A. *Chem. Commun.* **2011**, *47*, 82. (b) Schmidtchen, F. P. *Chem. Soc. Rev.* **2010**, *39*, 3916. (c) Kubik, S. *Chem. Soc. Rev.* **2010**, *39*, 3648.

(2) For recent examples, see: (a) Yu, S.; DeBerardinis, A. M.; Turlington, M.; Pu, Lin *J. Org. Chem.* **2011**, *76*, 2814. (b) Lu, Q.-S.; Dong, L; Zhang, J.; Li, J.; Jiang, L.; Huang, Y.; Qin, S.; Hu, C.-W.; Yu, X.-Q. *Org. Lett.* **2009**, *11*, 669.

(3) Shinoda, S.; Okazaki, T.; Player, T. N.; Misaki, H.; Hori, K.; Tsukube, H. *J. Org. Chem.* **2005**, *70*, 1835.

(4) (a) Kondo, S.-I.; Kobayashi, Y.; Unno, M. *Tetrahedron Lett.* **2010**, *51*, 2512. (b) Chisholm, C. D.; Wenzel, T. J. *Tetrahedron: Asymmetry* **2011**, *22*, 62.

(5) (a) Lin, W.-C.; Tseng, Y.-P.; Lin, C.-Y.; Yen, Y.-P. *Org. Biomol. Chem.* **2011**, *9*, 5547. (b) Barnard, A.; Dickson, S. J.; Paterson, M. J.; Todd, A. M.; Steed, J. W. *Org. Biomol. Chem.* **2009**, *7*, 1554.

(6) (a) Willener, Y.; Joly, K. M.; Moody, C. J.; Tucker, J. H. R. *J. Org. Chem.* **2008**, *73*, 1225. (b) Sahim, O.; Memon, S.; Yilmaz, M. *J. Macromol. Sci., Part A: Pure Appl. Chem.* **2010**, *47*, 20. (c) Durmaz, M.; Yilmaz, M.; Sirit, A. *Org. Biomol. Chem.* **2011**, *9*, 571.

(7) For examples, see: (a) Wienkers, M.; Ramos, J.; Jemal, H.; Cardenas, C.; Wiget, P.; Nelson, A.; Free, S.; Wu, J.; Roach, R.; Vulcan, M.; Waynant, K.; Fort, K.; Vladimirova, A.; Sun, J.; Hunt, S. E.; Rudkevich, D. M.; Starnes, S. D. *Org. Lett.* **2012**, *14*, 1370. (b) Beer, P. D.; Drew, M. G. B.; Jagessar, R. C. *J. Chem. Soc., Dalton Trans.* **1997**, 881. (c) Arungundram, S.; Saunders, C. H.; Starnes, S. D. *Tetrahedron Lett.* **2002**, *43*, 7785. (d) Calderon-Kawasaki, K.; Kularatne, S.; Li, Y. H.; Noll, B. C.; Scheidt, W. R.; Burns, D. H. *J. Org. Chem.* **2007**, *72*, 9081.

(8) For a few examples, see: (a) Mizuno, Y.; Aida, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 5278. (b) Fa, H.-B.; Zhao, L.; Wang, X.-Q.; Yu, J.-H.; Huang, Y.-B.; Yang, M.; Wang, D.-J. *Eur. J. Inorg. Chem.* **2006**, *21*, 4355. (c) Wang, C. Z.; Zhu, Z. A.; Li, Y.; Yun, T. C.; Wen, X.; Fang, M. M.; Chan, W. L.; Chan, A. S. C. *New J. Chem.* **2001**, *25*, 801. (d) Nicolas, I.; Chevance, S.; Maux, P. L.; Simonneaux, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1788.

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Michael reactions, and carbenoid insertion in C–H bonds.[9] Chiral porphyrins are being utilized for the development of novel materials[10] and for chiral discrimination in NMR.[11]

In porphyrin design, the platform is typically functionalized in a convergent fashion at phenyl ortho-meso positions (depicted as **A** and **A′** in Figure 1). Or functionalization is divergent at phenyl meta- or para-meso or beta positions as depicted by **B** and **C**. The design reported here is the attachment of substituents at the phenyl ortho-meso positions with recognition elements directed over the surface of the porphyrin (depicted as **D**). The introverted nature of the recognition element positions it where it can work in tune with the metal center in guest binding. Ogoshi et al. reported an axially chiral porphyrin with recognition elements directed over the porphyrin surface, which showed good selectivity for amino acid ester guests.[12] Figure 1 presents our first example, host **1**, of a chiral porphyrin containing this design consideration. Host **1** contains an amide functionality asymmetrically directed into the interior of the porphyrin pocket positioned to hydrogen bond with guests that simultaneously coordinate the zinc center.

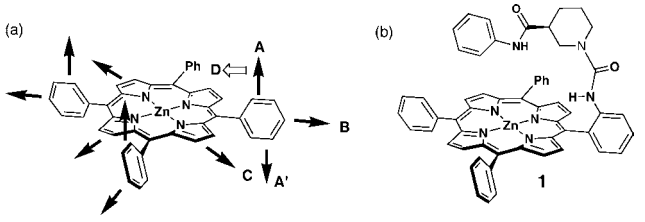


Figure 1. (a) Porphyrin design strategies. (b) Receptor **1**.

Common intermediates in the synthesis of porphyrin hosts are porphyrin isocyanates **2**[13] and **3**[14] (Figure 2). We are working to bring a variety of commercially available chiral amines to bear on recognition by coupling them with isocyanates **2** and **3**, as illustrated by the synthesis of host **1** (Scheme 1); Collman reported the condensation of alanine with **2** to create a chiral porphyrin; the amines we are working with are pyrrolidine and piperidine derivatives, which contain a higher degree of preorganization and ring substituents bearing recognition elements directed over the porphyrin surface. The synthesis started with the conversion of commercially available Boc-protected L-nipecotic acid (**4**) to its *N*-phenylamide derivative **5** (68% yield). The Boc-protecting group was removed with trifluoroacetic acid to give **6** in 80% yield. The porphyrin synthesis utilized the known mononitroporphyrin.[14] Reduction of the mononitro compound with tin(II) chloride gave **7**, which was converted to isocyanate **3** by reaction with triphosgene.[13a] Condensation of **3** in situ with **6** gave the metal free version of host **1**. Metalation was accomplished in the usual manner through reflux in 1:1 chloroform/methanol containing zinc(II) acetate.

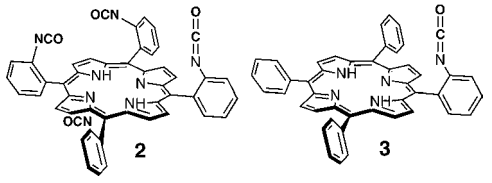


Figure 2. Porphyrin isocyanates.

Scheme 2 illustrates the types of interactions we anticipated guests to have with **1**. The amide is available for hydrogen bonding interactions with guests. Lewis basic guests can coordinate to the zinc center. Aromatic guests may benefit from $\pi-\pi$ interactions with the porphyrin surface, or the porphyrin surface may pose a steric hindrance to guest binding. These interactions represent 3–4 points of interaction between host and guest, which could result in stereoselective guest binding. Because of the free rotation around N—C=O urea bonds, host **1** lacks an element of preorganization (Scheme 2). We envisioned the preferred rotomer of host **1** to be that with the hydrogen bond accepting or donating group rotated into the cavity for participation in guest binding.

The binding of host **1** with chiral guests was examined through UV/vis titrations of a solution of the porphyrin receptor in CH_2Cl_2 ($\sim 1 \times 10^{-6}$ M) with CH_2Cl_2 solutions of the tetrabutylammonium salts of the anions. Titration of **1** with anion guests gave sharp isosbestic points for all anions studied. As representative examples, Figure 3 shows titration of **1** with (*S*)- and (*R*)-mandelate salts. Binding constants of host **1** with each guest was determined by nonlinear regression analysis of the binding isotherms. Binding constants of host **1** with guests are shown in Table 1, which also shows the binding selectivities observed.

As Table 1 shows, host **1** did not show selectivity between *N*-acetylalanine stereoisomers. Modest selectivity was observed between *N*-acetylphenylalanine and *N*-acetyltryptophan stereoisomers (ratio of binding constants between L and D isomers was ~1.5). Better selectivity was observed between (*S*)- and (*R*)-mandelate isomers. Host **1**

(9) For a few examples, see: (a) Fantauzzi, S.; Gallo, E.; Rose, E.; Raoul, N.; Caselli, A.; Issa, S.; Ragaini, F.; Cenini, S. *Organometallics* **2008**, 6143. (b) Cui, X.; Xu, X.; Lu, H.; Zhu, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 3304. (c) Thu, H.-Y.; Tong, G. S.-M.; Huang, J.-S.; Chan, S. L.-F.; Deng, Q.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2008**, *47*, 9747. (d) Proline modified porphyrin: Boitrel, B.; Baveux-Chambenoit, V.; Richard, P. *Helv. Chim. Acta* **2004**, *87*, 2447.

(10) (a) Hizume, Y.; Tashiro, K.; Charvet, R.; Yamamoto, Y.; Saeki, A.; Seki, S.; Aida, T. *J. Am. Chem. Soc.* **2010**, *132*, 6628. (b) Helmich, F.; Lee, C. C.; Schenning, A. P. H. J.; Meijer, E. W. *J. Am. Chem. Soc.* **2010**, *132*, 16753.

(11) Ema, T.; Ura, N.; Eguchi, K.; Ise, Y.; Sakai, T. *Chem. Commun.* **2011**, *47*, 6090.

(12) Kuroda, Y.; Kato, Y.; Higashioji, T.; Hasegawa, J.-y.; Kawanami, S.; Takahashi, M.; Shiraishi, N.; Tanabe, K.; Ogoshi, H. *J. Am. Chem. Soc.* **1995**, *117*, 10950.

(13) (a) Collman, J. P.; Wang, Z.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 2424. (b) Lee, J.-D.; Kim, Y.-H.; Hong, J.-I. *J. Org. Chem.* **2010**, *75*, 7588.

(14) Landrum, J. T.; Grimmett, D.; Haller, K. J.; Scheidt, R.; Reed, C. A. *J. Am. Chem. Soc.* **1981**, *103*, 2641.

Scheme 1. Synthesis of Host **1**

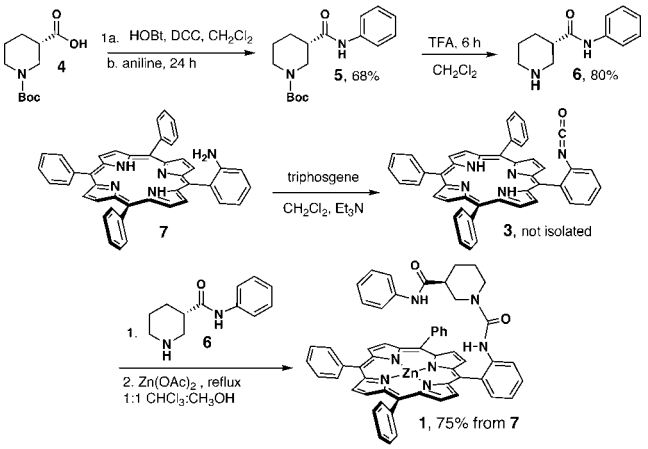


Table 1. Association Constants (K, M^{-1}) and Selectivity of Receptor with Chiral Anions[a]

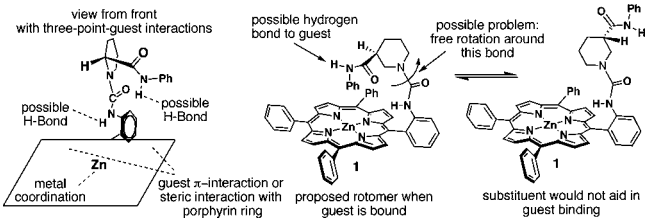
	binding constants (M^{-1})		selectivity with **1**	
	Zn TPP[b]	**1**	L/D (*S*/*R*)	D/L (*R*/*S*)
N-Ac-D-Ala	1200	17 400		1.0
N-Ac-L-Ala	1400	18 100	1.0	
N-Ac-D-Phe	1600	20 800		0.7
N-Ac-L-Phe	1400	30 200	1.5	
N-Ac-D-Tryp	1100	50 200		1.4
N-Ac-L-Tryp	1200	37 100	0.7	
R-Mandelate	2400	14 500		0.5
S-Mandelate	2500	30 300	2.1	

[a] Anions as their tetrabutylammonium salts for solubility in dichloromethane. [b] ZnTPP = zinc tetraphenylporphyrin. Error ± 10%.

binds (*S*)-mandelate with a binding constant approximately double that of (*R*)-mandelate. Although the selectivities observed here are modest, they are comparable to many known receptors recently reported in the literature. Furthermore, we believe part of the novelty of the work is the ease of synthesis of these types of receptors; because of the commercial availibility of numerous chiral amines, it will require little synthetic work to produce variations of host **1** to try and improve on these selectivities and in turn learn more about the requirements for chiral guest recognition.

Figure 4 illustrates the proposed binding and structure for host **1**–mandelate anion complexes. In the absence of guest, we believe the amide of host **1** is coordinated to the zinc center. This is supported by UV/vis spectroscopic studies. For model compound zinc tetraphenylporphyrin (ZnTPP), λ_{max} = 419 nm. For host **1**, λ_{max} = 424 nm. Other zinc-porphyrin hosts that we have reported show λ_{max} between 424 and 429 nm, which was attributed to urea and sulfonamide coordination to the metallocenter[7a]. Guest coordination to host **1** resulted in a red shift of the porphyrin Soret band; host–guest complexes typically had a λ_{max} of 430–431 nm. Zn-TPP complexes with anions typically show λ_{max} = 429–432 nm. The longer λ_{max} for **1** compared to ZnTPP suggests that **1** exists in a conformation where the zinc center is coordinated to the amide. As further evidence, host **1** shows signals further upfield in its ^{1}H NMR spectrum than metal free host **1**; two proton signals of the *N*-phenyl group are shifted upfield ~0.6 ppm compared to nonmetalated **1**, and several of the piperidine signals are shifted upfield ~0.5–1 ppm in **1** compared to nonmetallated **1** (Supporting Information), which would be expected because of anisotropic shileding if these protons reside closer to the porphyrin surface because of amide–zinc coordination. Furthermore, the ^{1}H NMR spectrum of host **1** shows signals for the *N*-phenyl substituent at 5.5 and 6.4 ppm, which is upfield of the *N*-phenyl group signals of compound **5** (7.0, 7.2, and 7.5 ppm, Supporting Information). These UV/vis and ^{1}H NMR spectroscopic results lead us to believe that anion binding to **1** is an example of complexation-induced organization of the host upon anion binding. This has been observed in other anion hosts[15] and in the dynamics of porphyrin-based receptors[16] and enzymes.[17]

Scheme 2. Possible Binding Interactions of Host **1** with Guests and Proposed Host Conformations



To verify the stoichiometry of binding, Job plots for the binding of host **1** with guests were obtained (see the Supporting Information for a Job plot of **1** with (*S*)-mandelate). The Job plot of **1** with guests shows a maximum at a 1:1 molar ratio of host to guest, which indicates the binding is 1:1.

We believe host **1** binds (*S*)-mandelate through carboxylate coordination to the zinc center, a hydrogen bond interaction between the amide N–H and mandelate hydroxyl group, and a hydrogen bond interaction between the urea-NH and the guest carboxylate group (Figure 4).[18] ^{1}H NMR titration results (vide infra) support this. Binding constants (Table 1) support this as well; host **1** binds these guests an order of magnitude stronger than ZnTPP, which lacks hydrogen bonding capabilities. Host **1** may bind

(15) (a) Swinburne, A. N.; Paterson, M. J.; Beeby, A.; Steed, J. W. *Chem.—Eur. J.* **2010**, 2714. (b) Beeren, S. R.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2011**, *133*, 3804. (c) Beeren, S. R.; Sanders, J. K. M. *Chem. Sci.* **2011**, *2*, 1560.

(16) Weiss, J. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *40*, 1.

(17) Schneider, S.; Sharp, K. H.; Barker, P. D.; Paoli, M. *J. Biol. Chem.* **2006**, *281*, 32606.

(18) Le Gac, S; Najjari, B.; Fusaro, L.; Roisnel, T.; Dorcet, V.; Luhmer, M.; Furet, E.; Halet, J.-F.; Boitrel, B. *Chem. Commun.* **2012**, 3724.

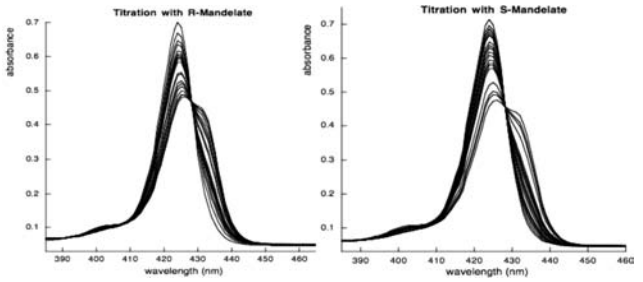


Figure 3. UV/vis titration spectra of **1** with mandelate isomers.

(*R*)-mandelate less favorably because of a steric interaction between the phenyl group of mandelate and the porphyrin ring. We are currently studying these complexes computationally to obtain a more thorough understanding of the host–guest interactions.

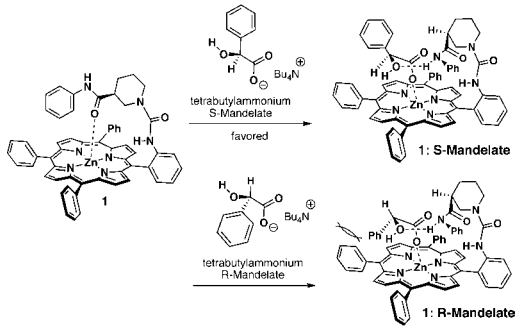


Figure 4. Proposed complexation-induced organization and binding of mandelate guests.

^{1}H NMR titration studies also indicate that host **1** binds (*S*)-mandelate more strongly than (*R*)-mandelate (Figures 5 and 6). For the titration with (*R*)-mandelate, the signal for hydrogen-b (Figure 5) shifts from 6.35 to 6.85 ppm after the addition of 5 equiv of guest. For (*S*)-mandelate, however, the signal for hydrogen-b shifts from 6.35 to 6.85 after the addition of 2.5 equiv of guest. This signal is no longer observable after 5 equiv of guest; the signal shifts further downfield where it overlaps with the mandelate phenyl signals. The larger and more rapid change in the chemical shift of H_b in the (*S*)-mandelate titration compared to the (*R*)-mandelate titration is indicative of a stronger hydrogen bond interaction between **1** and (*S*)-mandelate.

In summary, chiral porphyrin hosts with introverted recognition elements are readily available using the approach described here. We are working to synthesize the enantiomer of host **1** and other chiral porphyrin derivatives. Using this approach, it should be possible to develop more selective hosts for anions and other chiral species such as amines, which form strong coordinative bonds to metalloporphyrins. Hopefully this research will impact other fields, such as the design of porphyrin-based chiral catalysts and chiral materials as well.

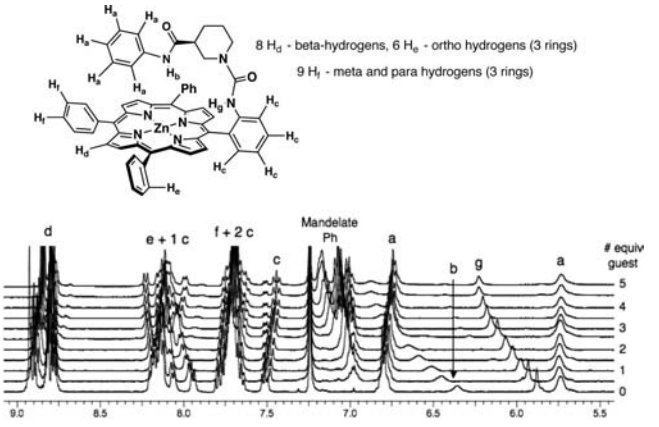


Figure 5. ^{1}H NMR titration of host **1** with (*R*)-mandelate (0.5 equiv additions).

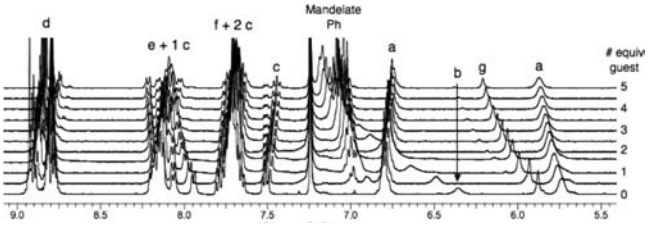


Figure 6. ^{1}H NMR titration of host **1** with (*S*)-mandelate (0.5 equiv additions).

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Supporting Information Available. Synthetic details, HD mass spectral data for host **1**, ^{1}H NMR spectra for **1** at room temperature and 45 °C, ^{1}H and ^{13}C NMR spectra for **5**, and Job plot of host **1** with (*S*)-mandelate. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.