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Recognition of mandelate stereoisomers by chiral porphyrin hosts: prediction of stereopreference in guest binding a priori using a simple binding model?

Vijay Nandipati, Karthik Akinapelli, Lakshmi Koya, Stephen D. Starnes *

Department of Chemistry, Texas A&M University-Commerce, Commerce, TX 75429, United States

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ABSTRACT

Rigid porphyrin hosts that mimic the spatial arrangement of mandelate recognition motifs lead to stereoselective receptors and illustrate how subtle structural differences in host design have significant impact on guest recognition. The porphyrin hosts are obtained with minimal synthetic effort from readily available chiral amine precursors and are modular in design. The chiral recognition properties of the porphyrin-based hosts with chiral carboxylate-containing guests and chiral amines are described. UV/vis and ^{1}H NMR spectroscopic results indicate some of these porphyrin hosts undergo an induced fit conformational change upon guest binding.

Introduction

To design selective synthetic hosts for chiral guests one must battle another level of complexity in molecular recognition; in addition to considering a guest's size, geometry, recognition motifs, charge density, ionization state, hydration, etc. one must, of course, take into consideration spatial orientation of the guest features. On one hand, it seems this might make selectively binding chiral species easier than non-chiral species—if the guest does not fit the pocket of a host spatially it might not bind at all. Thus, one developing host for chiral guests has an extra tool at their disposal! On the other hand, having to consider a guest's spatial orientation can present challenges (synthetically and financially) in host design. Additionally, for a guest to be chiral inherently means it will have to be fairly large in size, which means a host's binding cavity will likely have to be as well, which presents additional synthetic challenges.

Chiral recognition is a field in supramolecular chemistry with new applications continually emerging. Recent applications have been illustrated in the kinetic resolution of chiral amines,[1] enantiomeric excess determination,[2] chiral supramolecular assemblies,[3] and catalysis for example a large part of the field of chiral organocatalysis is based on principles of molecular recognition.[4] Investigators have been working in the field of chiral host–guest chemistry for over 20 years; this area of supramolecular chemistry is still in its infancy however, with only a few hundred manuscripts published in the field.[5] There are a few examples of porphyrins that show good selectivities in guest binding, for both chiral and non-chiral guests.[6]

We recently reported an example of a chiral porphyrin (**1**, Fig. 1) which showed modest selectivity in the binding of mandelate stereoisomers.[7] Host **1** is characterized by an introverted functional group (an amide) which projects over the porphyrin surface. The amide N–H group was shown to aid in guest binding presumably through a hydrogen bonding interaction with the mandelate hydroxy group. The amide group is positioned to work cooperatively with the zinc metal center in guest binding. Host **1** was shown to bind S-mandelate preferentially to R-mandelate (selectivity ~2). Figure 1 also depicts the structure for the proposed complex with S-mandelate.

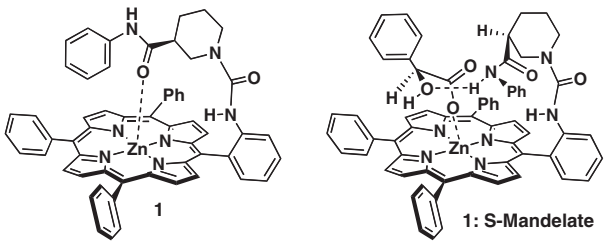

Figure 1. Host **1** and binding model for recognition of S-mandelate.

* Corresponding author. Tel.: +1 903 886 5389; fax: +1 903 468 6020.
E-mail address: stephen.starnes@tamuc.edu (S.D. Starnes).

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Host **1** and the hosts described here (Fig. 2) are fairly rigid in structure—they are dynamic due to free rotation around urea O=C–N bonds, but they do not have much conformational space available to themselves due to the preferred planar nature of ureas. With a rigid framework imparted from the porphyrin and urea platform, guest recognition sites are fairly well spatially pre-organized and thus positioned to complement the orientation of a chiral guest's molecular recognition motifs. Due to the rigid nature of these types of hosts, we envisioned that carboxylate-containing guests would in general bind as illustrated in Figure 3, where the guest carboxylate would coordinate the metallo center and hydrogen bond to the porphyrin urea hydrogen, a polar substituent on the guest α-position could hydrogen bond to a polar pyrrolidine or piperidine substituent, and a bulky or aryl group on the guest α-position could interact favorably or unfavorably with the porphyrin π-surface. Thus, there should be at least three points of spatially different interactions between host and guest, which is necessary for chiral recognition. If this binding model is accurate and general for these types of guests, we might be able to predict a priori which enantiomer of a guest will preferentially bind to these hosts.

Since host **1** binds S-mandelate preferentially, will hosts with similar spatial arrangement of a hydrogen bond donating substituent (in the Pro-S position, Fig. 3, such as **4**, **6**, and **8**) also preferentially bind S-mandelate? Will hosts **3**, **5**, and **7**, which have the opposite spatial arrangement of a hydrogen bond donating group (in the Pro-R position), bind R-mandelate preferentially? One would predict so using the binding model in Figures 1 and 3.

Hosts **2**–**8** were prepared by reacting amines **9**–**15** (Fig. 4) with porphyrin isocyanate **17**[8] (Scheme 1 illustrates a representative eg.,—the synthesis of **3**). Amines **9**, **14**, and **15** are commercially available. Amines **10**–**13** were synthesized as illustrated in Scheme 1. The synthesis of each compound was straightforward and proceeded smoothly, but with a couple of interesting observations. First, compounds **19**–**22** (Scheme 1) appear to exist as a mixture of conformational isomers in slow exchange on the NMR timescale. As revealed by ^{13}C NMR (Supporting information), the four pyrrolidine ring carbons appear as two signals each at room temperature which collapse to broad signals at higher temperatures. Compounds **19**–**22** may exist as a mixture of *cis* and *trans* carbamate derivatives similar to proline amide derivatives.[9] Second, during the metallation final step in the synthesis of hosts **3**

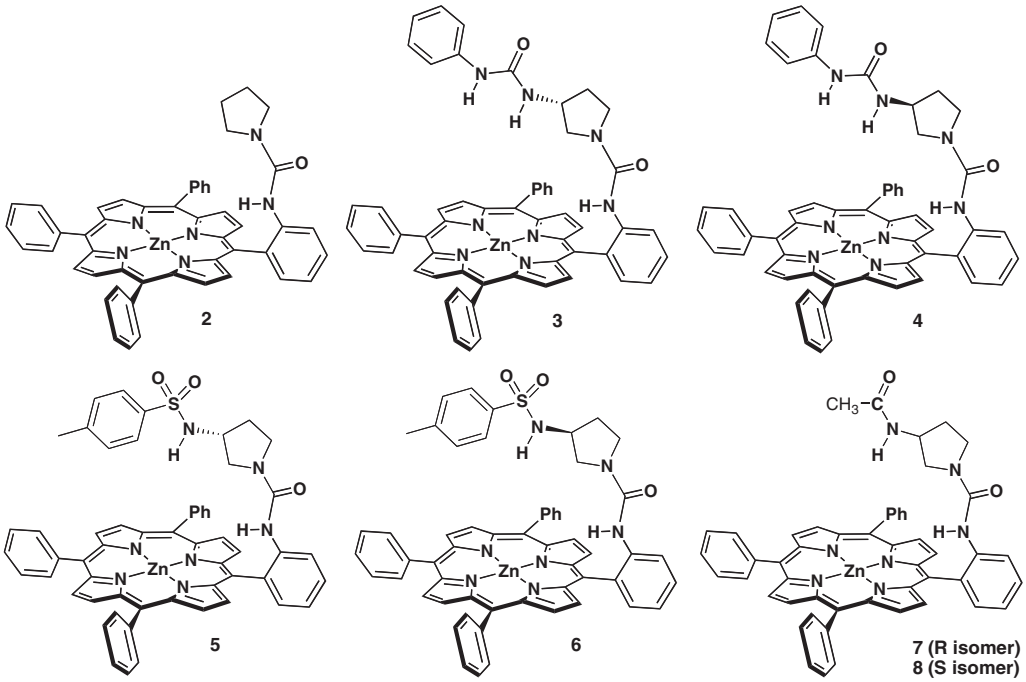


Figure 2. Porphyrin hosts.

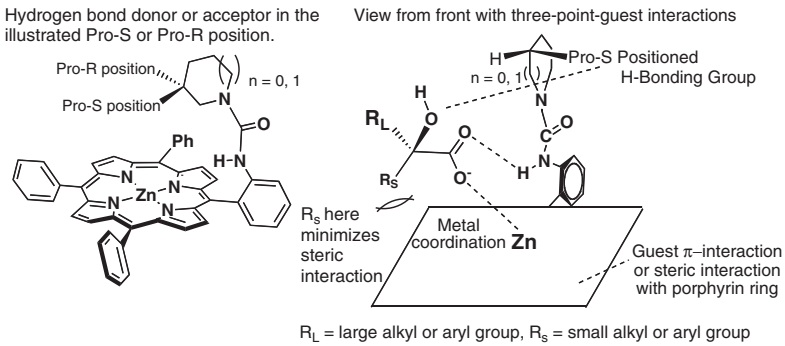


Figure 3. Proposed binding model of hosts with α-hydroxy guests.

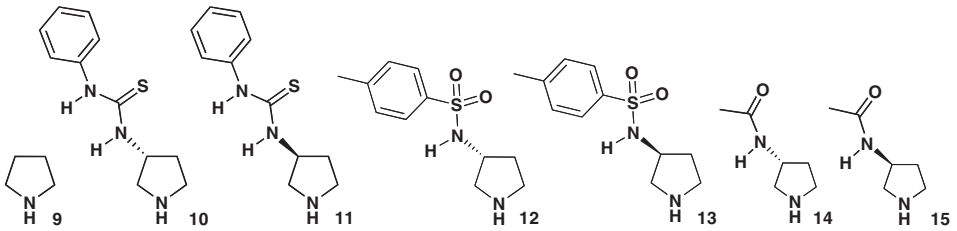
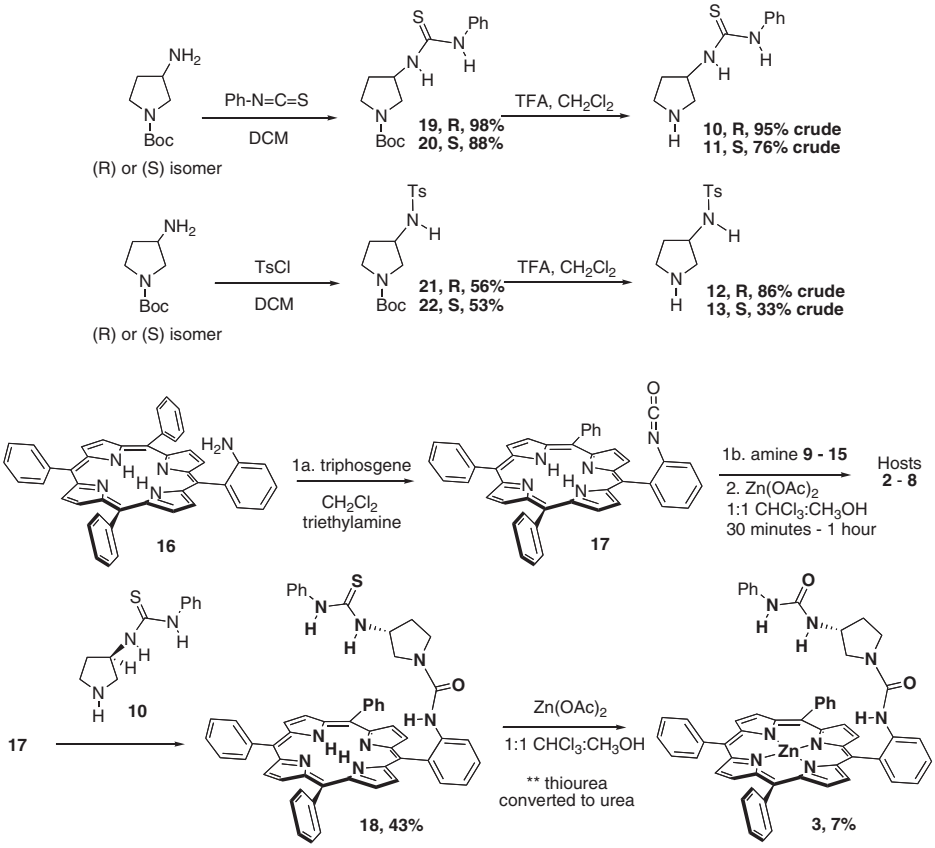


Figure 4. Amines utilized in the synthesis of **2**–**8**.



Scheme 1. General scheme for the synthesis of hosts **2**–**8**.

and **4**, the thiourea was converted to a urea. This became apparent from high-definition mass spectral analysis of chromatographic fractions. The only fraction with mass near the correct mass had a mass 16 units off (see Supporting information). We believe zinc(II) acetate with trace water catalyzed the conversion of the thiourea to a urea—a hydrogen sulfide smell was apparent during the reaction. More work is needed to confirm if zinc(II) acetate was the culprit leading to the conversion. To the best of our knowledge, this would be the first example of zinc(II) catalyzed conversion of a thiourea to a urea. Zinc sulfide nanoparticles have been prepared from the hydrolysis of thiourea[10] and bismuth(III) nitrate has recently been demonstrated to catalyze the conversion of thioureas and thioamides to their oxygen analogs.[11] The normally high yielding metallation step used to prepare **3** and **4** proceeded in only 7% and 5% yield, respectively,—the low yield is probably due to side product formation from the thiourea reaction.

The chiral recognition properties of hosts **2**–**8** were examined by UV/vis and ^{1}H NMR titration experiments. UV/vis titrations were conducted in dichloromethane and ^{1}H NMR titration experiments were conducted in $CDCl_3$. Figure 5 shows representative UV/vis titration spectra. Anion guests were prepared as their tetrabutylammonium salts for solubility in dichloromethane and $CDCl_3$. Table 1 lists the binding constants of hosts **2**–**8** with a variety of anion guests as well as two chiral amines (L-nicotine and (*R*,*S*)-ephedrine).

Host **2** generally showed binding constants with carboxylate-containing guests of ~1000–5000 M^{-1}. Hosts **3**–**6** binding constants are 2–3 orders of magnitude larger, which we attribute to the strong hydrogen bonding ability of ureas and sulfonamides, which are commonly utilized in the design of anion hosts.[12] To our surprise, hosts **5** and **6** did not show selectivity for any pair of enantiomer guests. Hosts **3** and **4**, however, did show modest selectivity for mandelate stereoisomers (ratio of binding constants ~3). Host **4** binds S-mandelate with a binding constant of 470,000 M^{-1} and R-mandelate with a binding constant of 150,000 M^{-1}. The enantiomer of **4**, host **3**, showed opposite enantioselectivity. Host **3** preferentially binds R-mandelate over S-mandelate with a selectivity ~3. If the binding model that we proposed for host **1** (Fig. 1) and the general binding model for these types of hosts (Fig. 3) is reasonable, then the observed selectivities

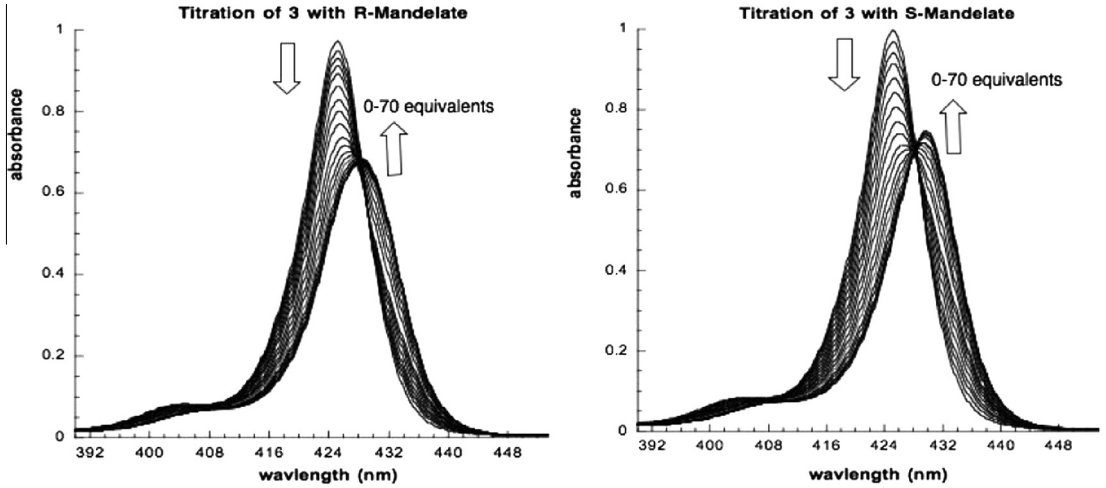


Figure 5. UV/Vis titration spectra of **3** with mandelate isomers.

Table 1
Association constants (K, M^{-1}) for receptors **2**–**8** with guests and selectivity of receptors **3** and **4** with guests[a]

Guest	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Selectivity ratio of K (**3**/**4**)
Acetate	2000	100,000	97,000	123,000	133,000	—	—	1.0
N-Ac-glycine	4100	292,000	296,000	300,000	245,000	—	—	1.0
R-Mandelate	2000	460,000	150,000	58,000	54,000	19,000	14,000	3.0
S-Mandelate	1900	152,000	470,000	66,000	63,000	20,000	16,000	0.32
N-Ac-D-alanine	1400	331,000	328,000	180,000	200,000	—	—	1.0
N-Ac-L-alanine	1600	299,000	326,000	163,000	175,000	—	—	0.91
N-Ac-D-Ph-alanine	2700	299,000	273,000	137,000	175,000	—	—	1.1
N-Ac-L-Ph-alanine	2900	304,000	291,000	177,000	130,000	—	—	1.0
N-Ac-D-Ph-glycine	5100	171,000	176,000	131,000	140,000	—	—	0.97
N-Ac-L-Ph-glycine	5000	184,000	157,000	123,000	128,000	—	—	1.2
S-Ibuprofen	4200	312,000	302,000	154,000	149,000	—	—	1.0
Naproxen	3200	173,000	144,000	104,000	105,000	—	—	1.2
L-Nicotine	18,000	6500	5000	34,000	21,000	—	—	1.3
RS-Ephedrine	1100	1060	1070	2700	2200	—	—	1.0

[a] Anions as their tetrabutylammonium salts for solubility in dichloromethane. Error ± 10%.

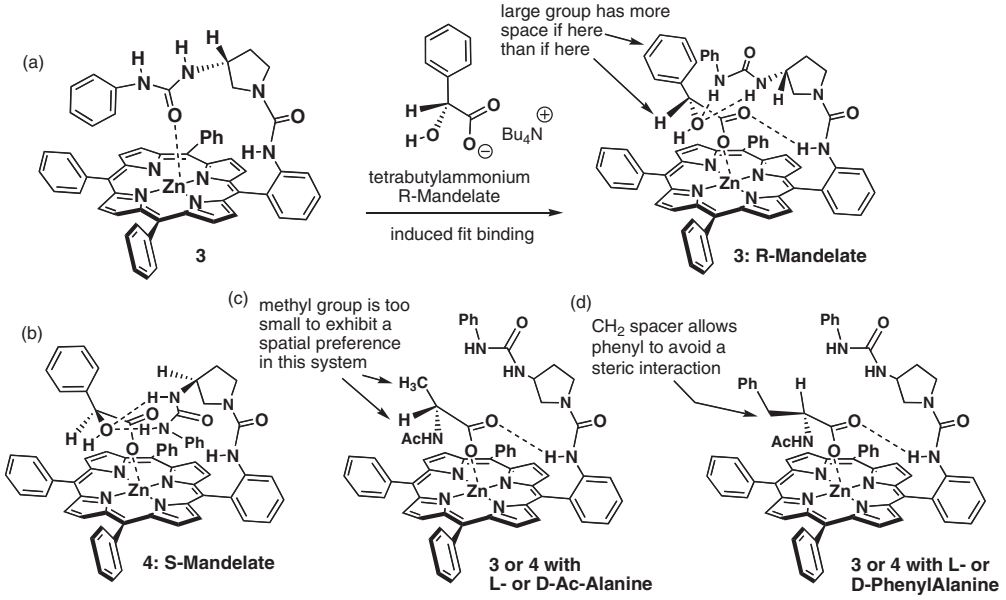


Figure 6. Proposed host/guest complexes of **3** and **4**.

of hosts **3** and **4** are exactly what one would predict a priori. Host **3**, with a hydrogen bond donating group in the Pro-R position of the pyrrolidine ring binds (R)-mandelate preferentially. Host **4**, with a hydrogen bond donating group in the Pro-S position of the pyrrolidine ring binds (S)-mandelate preferentially, similar to the molecular recognition stereopreferences of **1**, which has a hydrogen bonding group in the Pro-S position and also showed a preference for S-mandelate.

Figure 6 depicts the proposed binding model for **3** and **4** with mandelate isomers. Similar to host **1** and other porphyrins that we have recently reported on,[13] we believe hosts **3**, **4**, **7**, and **8** exist in a conformation which has the zinc internally coordinated by the

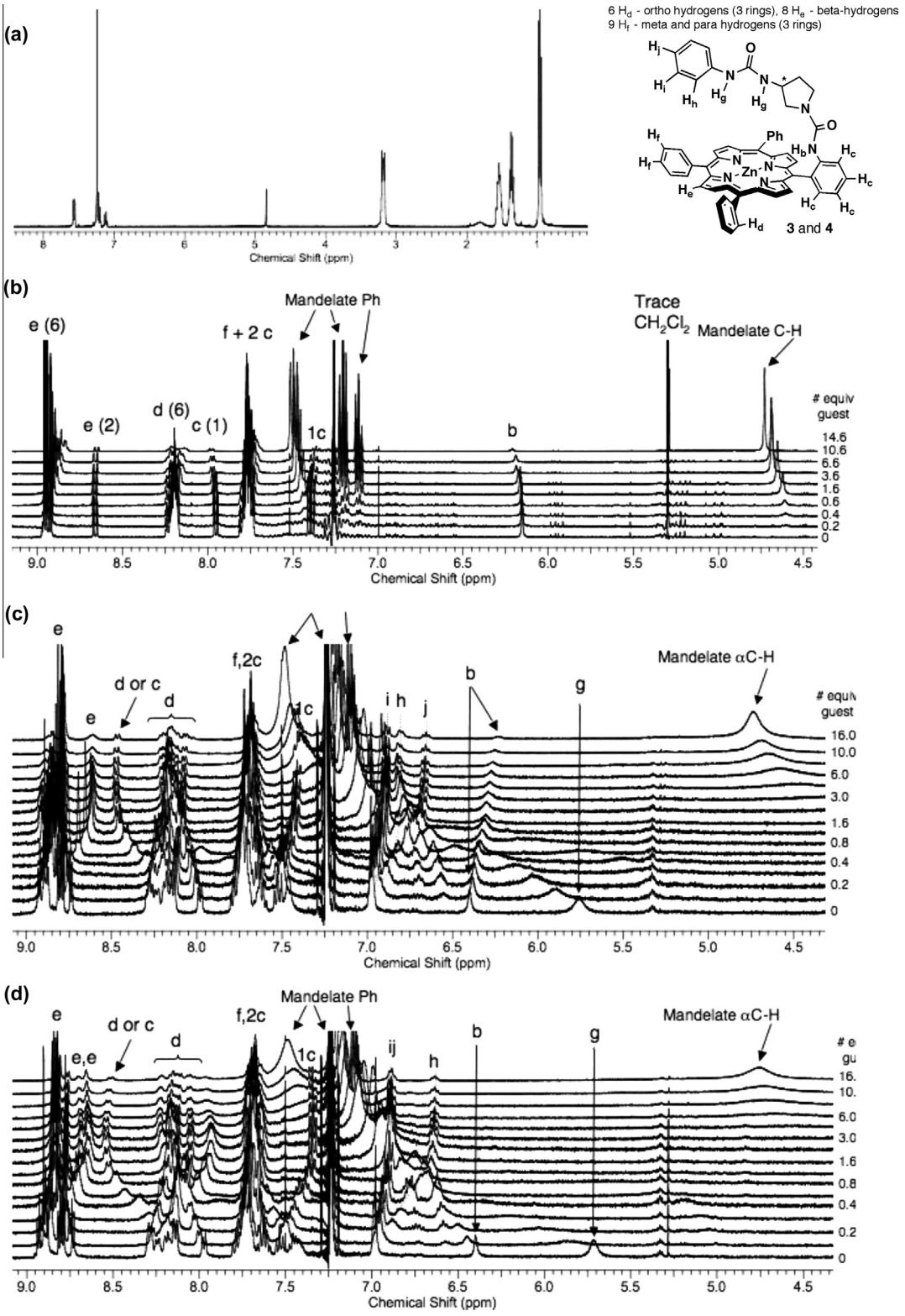


Figure 7. (a) R-mandelate NBu_4 in $CDCl_3$. (b) **2** Titration with S-mandelate, (c) **3** titration with S-mandelate, (d) **3** titration with R-mandelate.

carbonyl of the urea or amide pyrrolidine substituent. λ_{max} for hosts **2**, **5**, and **6** is 420 nm, whereas that of **3**, **4**, **7**, and **8** is 425 nm (host **1** λ_{max} is 424 nm). Thus, we believe the red shift in λ_{max} for hosts **3**, **4**, **7**, and **8** (and **1**) compared to **2**, **5**, and **6** is attributed to this intramolecular zinc coordination which is not exhibited in hosts **2**, **5**, and **6**.

Upon guest binding, the λ_{max} for host's **2**–**8** complexes are typically 429–431 nm. Thus, there seems to be a general trend whereby these types of porphyrin hosts which have introverted functional groups exist in a conformation with the metallo center intramolecularly complexed if this interaction is not sterically precluded (which it may be in **5** and **6**, or the sulfonamide group may be a poor ligand for zinc). Other porphyrin examples with this feature have been reported[14] (this is a general phenomena in porphyrin-based metallo proteins as well). This represents another example of conformationally induced guest binding.[15]

We believe hosts **3** and **4** bind mandelate through carboxylate coordination to zinc and a hydrogen bond interaction between the urea and the hydroxy group. Host **3** may bind R-mandelate with greater affinity than S-mandelate because the R-isomer fits the porphyrin binding cavity better. If R-mandelate binds in the manner depicted in Figure 6, the phenyl group would not experience a steric interaction. If S-mandelate binds in a similar fashion however, the phenyl group could experience a steric interaction with the porphyrin surface. To avoid a steric interaction, we believe S-mandelate binds to **3** in a different, un-defined conformation. A ^{1}H NMR titration of **3** with R- and S-mandelate supports this (Fig. 7).

Host **1** did not show any selectivity for other chiral guests that we studied, just as is observed here for **3** and **4**. This begs the questions: why is there no selectivity for other guests such as *N*-acetylalanine and *N*-acetylphenylalanine stereoisomers? And why do not hosts **5** and **6** show any stereoselectivity in guest binding, even with mandelate stereoisomers? Since **5** and **6** did not show selectivity in binding mandelate isomers, we predicted hosts **7** and **8** would not either. As Table 1 shows, hosts **7** and **8** show no selectivity in binding mandelate isomers; we expect no selectivity for **7** and **8** with other guests of Table 1 and thus they have not been studied with other guests at this point. We believe the other chiral guests examined show no stereopreference in guest binding because either the alkyl group on the α-position is too small to have a spatial preference in these complexes (such as in *N*-acetylalanine) or as in the case of *N*-acetylphenylalanine isomers, the CH_2 spacer of the α-side chain allows the phenyl ring the ability to avoid a steric interaction with the porphyrin surface (Fig. 6 illustrates this tentative explanation for the lack of stereoselectivity with other guests.). Thus, if the amino acid derivatives form complexes similar to mandelate with hosts **3** and **4** such that the carboxylate coordinates zinc and the *N*-acyl group hydrogen bonds to the host, it is not surprising that *N*-acetylalanine stereoisomers show no selectivity in binding since the methyl group does not have much greater steric demands than a hydrogen. For phenylalanine, although the benzyl side chain is relatively large, the guest could adopt a conformation in which the CH_2 group is directed at the porphyrin surface rather than the phenyl group, which would minimize steric interactions and hence eliminate selectivity in binding.

Of course, the host/amino acid complexes could exhibit an entirely different conformation than those of α-hydroxycarboxylate guests (mandelate) which would be reasonable if the *N*-acyl group of amino acids does not match the hydrogen bonding motifs of the host. Lastly, hosts **5**–**8** may show no selectivity with these guests because the sulfonamide or amide substituents may not be optimally positioned to interact with a guest that simultaneously complexes zinc—the urea substituent of hosts **3** and **4** has an N–H group 2 atoms further from the pyrrolidine ring that may be better positioned to hydrogen bond with a guest than the N–H of the amide or sulfonamide substituents of hosts **5**–**8**. Small changes in structure can have huge effects on molecular recognition, particularly in rigid systems—one atom's diameter, the direction of an amide bond, etc. can make all the difference in the stability of a host–guest complex.[16]

Figure 7 shows the ^{1}H NMR titration of **2** with S-mandelate. Proton H_b shifts downfield with increasing concentration of S-mandelate, but the shift is only apparent when large amounts of guest are added (~5 equiv addition at a time), which implies weak binding of S-mandelate to **2**, which is in line with the results of Table 1. Thus, the urea proton of **2** seems to contribute little to binding of guests by itself.

For the titration of **3** with R-mandelate, the signals for the urea protons (labeled b and g) rapidly move downfield with small increments of guest addition, which suggest the binding constant is large compared to that of **2** with mandelate. The rapid change in chemical shift of H_b suggests a cooperative interaction between H_b, H_g and the metallo center in guest binding. The urea phenyl proton signals (labeled h–j) are initially ~7 ppm but move upfield and two sets of protons become non-chemical shift equivalent in the process. When **3** is titrated with S-mandelate, the signal for urea H_b moves upfield! The signal for the urea phenyl protons also moves upfield and splits into three sets of non-chemical shift equivalent protons. This suggests that **3** forms conformationally different complexes with R- and S-mandelate.

In summary, we have developed a class of easy-to-synthesize and modular chiral porphyrin-based hosts that are unique because recognition motifs are directed over the porphyrin surface in a well-defined fashion where they work in tune with the metal center for cooperative guest binding. Preliminary results suggest that we can predict a priori which stereoisomer of mandelate stereoisomers will bind these hosts. Future work will be conducted to determine if these hosts might in general stereoselectively bind other chiral α-hydroxy carboxylate compounds. We are working to improve on the chiral selectivity. Others working in this field have noted the importance of geometrical confinement of the guest to achieve good enantioselectivity in chiral recognition.[17] Variations of these types of porphyrins with optimally positioned recognition motifs are in the works.

Acknowledgments

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Supplementary data

Supplementary data (HD mass spectral data for hosts **2**–**8**. ^{1}H NMR and ^{13}C NMR spectra of compounds (room temperature and 45 °C)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.046.

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