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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?

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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.

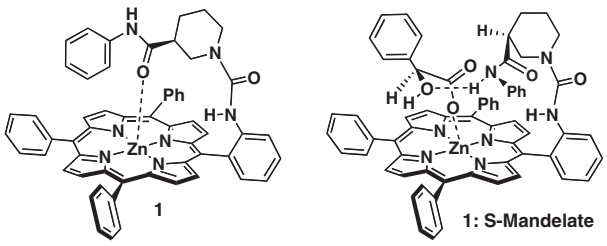

Figure 1. Host **1** and binding model for recognition of S-mandelate.

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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**

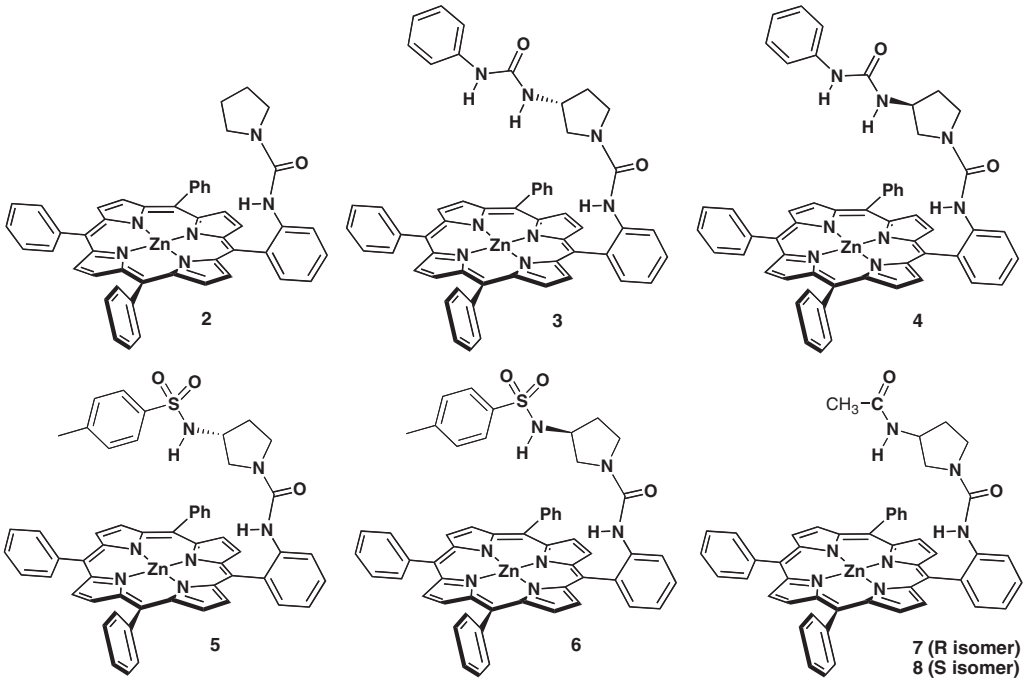

Figure 2. Porphyrin hosts.

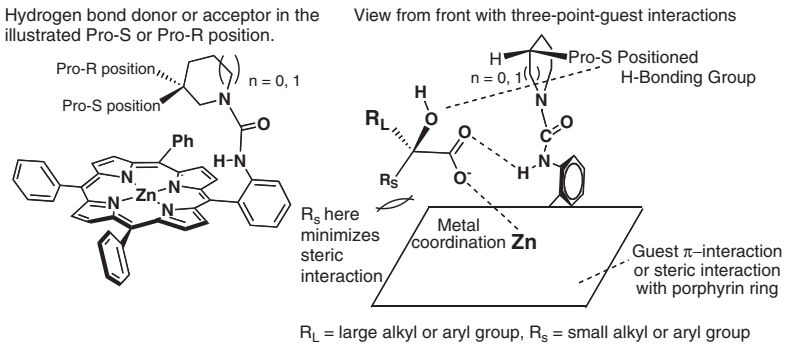

Figure 3. Proposed binding model of hosts with α-hydroxy guests.