# Polyfunctionalized macrocycles demonstrate enantioselective and ditopic binding properties†

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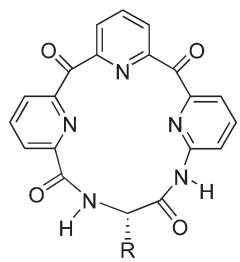
**A pair of enantioselective, ditopic macrocycles is described; the receptors bind chiral ammonium cations in a manner that depends on the stereochemistry of the cation as well as the nature of its counter anion.**

The design of enantioselective artificial receptors continues to be of great interest in supramolecular chemistry.[1] In addition to helping understand enantioselective recognition processes in biological systems, investigations of these artificial receptors raise the opportunity of developing molecular devices for resolution,[2] chiral sensing,[3] membrane transportation,[4] and enzyme mimicking chiral catalysis.[5]

We recently described rigid macrocyclic receptor **1** (Fig. 1),[6] a host that can simultaneously bind a mono-alkylammonium cation and its counteranion.[7] An important feature in the formation of **1** is the incorporation of an amino acid (glycine) residue in one of the latter synthetic steps. This strategy allows a common precursor (**4** in Scheme 1) to serve as a starting point for the formation of a range of targets. In this paper we report the synthesis of chiral macrocycles **2** and **3** (Fig. 1), and examine their enantioselective[8–10] and ditopic recognition properties.

The synthesis of receptors **2** and **3** is readily achieved by coupling **4**[6] with the respective *N*-Boc amino acids (Scheme 1 and supplementary information†). Hydrolysis of the ester groups of **5** and **6** with 1 equivalent of NaOH afforded the corresponding carboxyl acids. The Boc groups of these derivatives were then removed with either aqueous HCl solution or HCl–ethyl acetate, to yield respectively the cyclization precursors **7** and **8**. Cyclization under high dilute conditions, using DPPA as coupling reagent, gave macrocycle **2** and **9**. Removal of the *t*-butyl group of **9** gave macrocycle **3**.



**1** R = H
**2** R = $CH_2Ph$
**3** R = $CH_2OH$

**Fig. 1** The structures of macrocycle **1–3**.

Host **1** is not planar but dish-shaped. Furthermore, the directionality of its peptidic moiety (anticlockwise N → C terminus as shown) precludes the existence of any vertical mirror-plane in this dish. Hence the molecule is chiral, with ring flipping interconverting one enantiomer into the other. In addition to this element of circular chirality,[11] hosts **2** and **3** each possess a chiral center. Thus, ring flipping amounts to diastereomer interconversion. This flipping is facile; an examination of the NMR spectrum of **2** down to −50 °C did not lead to signal decoalescence. It was therefore not possible to identify which diastereomeric form of **2** and **3** predominates in solution. In addition to engendering a chiral center, the side-chains in hosts **2** and **3** can contribute to the ensemble of non-covalent interactions between host and guest. For host **2**, the benzyl group may take part in π–π stacking or cation–π interactions. In the case of **3**, its hydroxy group has the opportunity to hydrogen bond to anions or acceptors on the cation. It may also of course form intramolecular hydrogen bonds with other functionalities in the macrocycle.

NMR was used to determine the enantioselective recognition properties of receptors **2** and **3** (supplementary information†). Titration experiments in 40% $CD_3CN$–$CDCl_3$ using nitrate salts, gave a good balance between complexation strength and solubility, and led to fast exchange (at 400 MHz) between the free host and complex.[6] As expected, binding fitted a 1 : 1 isotherm and induced a downfield shift of the NMR signals.

Macrocycles **2** and **3** exhibit mild to good enantioselectivity for various α-amino acid methyl ester salts, with a preference for *S*-isomers (Table 1). For both hosts, the smaller and/or the more flexible guests bound more strongly. Thus the threonine and alanine salts proved to be the best guests, with the former proving the stronger binder presumably because it can form an additional hydrogen bond with the host. All the guests examined were noted to bind more strongly to host **2**. This suggests that either the benzyl group in **2** forms cation–π interactions with the guest, or that the hydroxy group of **3** is involved in intramolecular hydrogen bonding in such a manner as to inhibit guest binding. Two factors are evidently important in enantioselective recognition (Table 1). First, the larger and or more rigid the guest the better the discrimination. Second, added functional groups, such as the hydroxy group of the threonine salt, also led to better discrimination. It is interesting to note that for the series alanine, valine, phenylalanine and phenylglycine, the decrease in the $K_a$ of the *S*-isomers (*S*-alanine : *S*-phenylglycine $K_a$ ratio = 5.4 : 1) is much smaller than the decrease in the $K_a$ for the *R*-isomers (*e.g.*, *R*-alanine : *R*-phenylglycine $K_a$ ratio = 13.3 : 1). This suggests that

† Electronic supplementary information (ESI) available: synthesis and characterization, NMR spectra, binding isotherms and Job's plots. See http://www.rsc.org/suppdata/cc/b5/b501774b/

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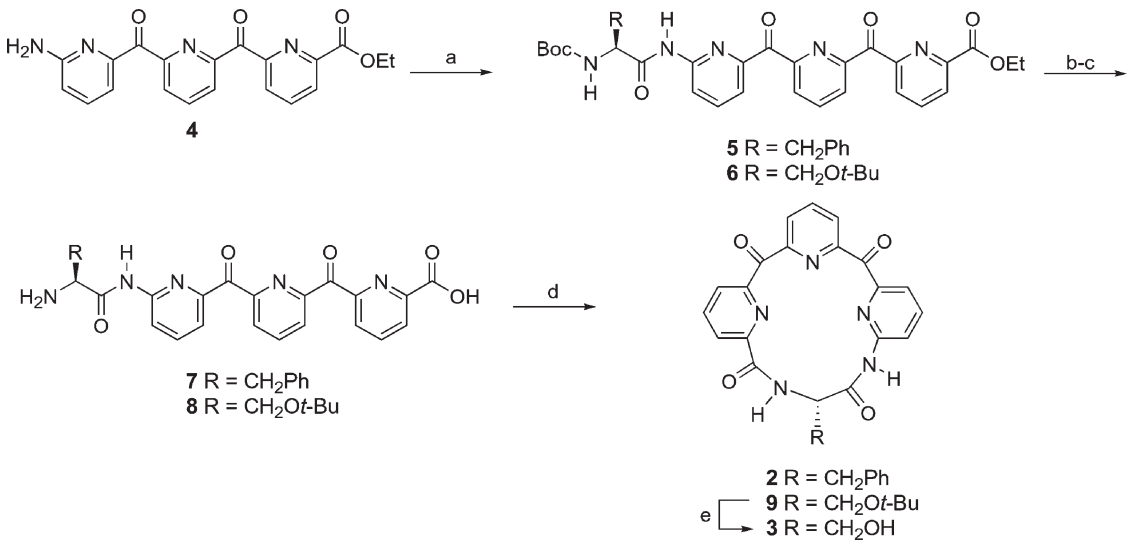


**Scheme 1** Synthesis of **2** and **3**. *Reagents and Conditions*: (a) respective *N*-Boc amino acid, HBTU, HOBt (60–65%); (b) 1.0 equiv. NaOH (85%); (c) for the phenyl alanine derivative, 10% HCl (88%), for the serine derivative, HCl–ethyl acetate 85%; (d) DPPA–DMF (38–40%). (e) HCOOH, 65%.

**Table 1** Association constants[a,b] for macrocycles **2** and **3** with various amino acid methyl ester ammonium salts

| Host | Guest[c] | $K_{S\text{-isomer}}$/ $10^{-3}$ $M^{-1}$ | $K_{R\text{-isomer}}$/ $10^{-3}$ $M^{-1}$ | $K_S/K_R$ |
|---|---|---|---|---|
| **2** | $NH_3^+$–alanine–OMe | 15.4 | 11.9 | 1.3 |
| **2** | $NH_3^+$–valine–OMe | 9.5 | 5.0 | 1.9 |
| **2** | $NH_3^+$–phenylalanine–OMe | 5.0 | 1.9 | 2.6 |
| **2** | $NH_3^+$–phenylglycine–OMe | 2.8 | 0.9 | 3.0 |
| **2** | $NH_3^+$–threonine–OMe | 18.1 | 6.4 | 2.8 |
| **3** | $NH_3^+$–alanine–OMe | 8.5 | 7.3 | 1.2 |
| **3** | $NH_3^+$–valine–OMe | 4.8 | 3.2 | 1.5 |
| **3** | $NH_3^+$–phenylalanine–OMe | 2.9 | 1.5 | 1.9 |
| **3** | $NH_3^+$–phenylglycine–OMe | 2.1 | 0.8 | 2.6 |
| **3** | $NH_3^+$–threonine–OMe | 11.0 | 4.7 | 2.3 |

[a] At 25 °C, initial [host] = 1.0 mM. [b] NMR titrations were carried out in 40% $CD_3CN$–$CDCl_3$. [c] Guests were added as nitrate salts.

the improved enantiomeric recognition for the larger guests arises through unfavorable non-covalent forces in the mismatched host–guest pairs, rather than more favorable interactions in the matched pairs.

As was the case for host **1**,[6] macrocycles **2** and **3** were expected to possess ditopic properties. Focusing on the more discriminating host **2**, we examined the binding of chloride, bromide and tosylate salts of the two of phenylalanine ester enantiomers (Table 2). The observed trend in $K_a$ values, $NO_3^- > Cl^- > TsO^- \approx Br^-$ is essentially the same as that determined for host **1**.[6]

**Table 2** Association constants[a,b] for macrocycle **2** and various ammonium salts of phenylalanine methyl ester

| Host | $A^-{\cdot}NH_3^+$–phenylalanine–OMe | $K_{S\text{-isomer}}$/ $10^{-3}$ $M^{-1}$ | $K_{R\text{-isomer}}$/ $10^{-3}$ $M^{-1}$ | $K_S/K_R$ |
|---|---|---|---|---|
| **2** | $Cl^-$ | 4.4 | 1.7 | 2.6 |
| **2** | $Br^-$ | 1.7 | 0.7 | 2.5 |
| **2** | $TsO^-$ | 2.0 | 0.8 | 2.5 |

[a] At 25 °C, initial [host] = 1.0 mM. [b] NMR titrations were carried out in 40% $CD_3CN$–$CDCl_3$.

Although these hosts are capable of both enantiomeric and ditopic recognition, the two properties do not appear to be linked. In other words, while the more tightly binding nitrate salt might be expected to lead to better enantioselectivity, this is not the case. Thus, although the nature of the anion is important in determining the overall $K_a$, the ion pair does not seem to be tight enough such that any improved anion binding can be reflected in the binding of its chiral counterion.

In conclusion, we have examined the binding properties of receptors **2** and **3**. Both show moderate to good enantioselectivities. Our results also confirm similar ditopic properties to those observed in the parent macrocycle. We are continuing to investigate the properties of these and related ligands.

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