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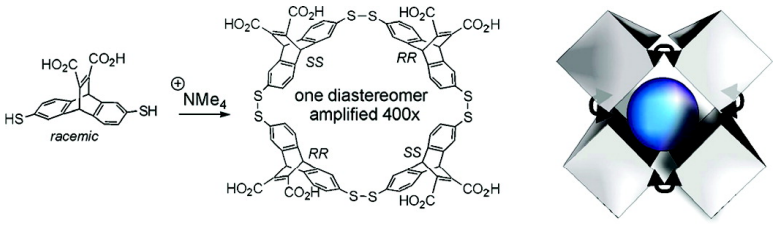

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Diastereoselective Amplification of an Induced-Fit Receptor from a Dynamic Combinatorial Library

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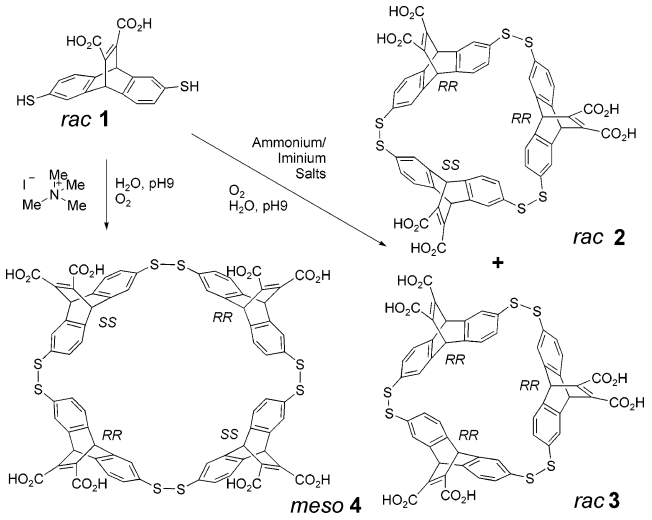
The design of artificial hosts for molecules or ions remains a considerable scientific challenge, most notably when hosts are flexible, and can undergo conformational changes on binding and when the solvent is water. Combinatorial methods in which large sets of potential hosts are screened are an attractive approach toward such challenging receptors. Dynamic combinatorial chemistry[1] is a particularly effective method, in which a pool of hosts is generated by linking relatively simple building blocks together using a reversible reaction. The continuous exchange of building blocks ensures that the library is under thermodynamic control. Upon adding a guest, the equilibrium will shift in the direction of the host(s) that bind(s) this guest with high affinity. The technique is rapidly gaining popularity for the development of supramolecular receptors in a range of solvent systems,[2] including some induced-fit hosts.[2e,f] We now report the discovery and highly diastereoselective amplification of a strongly binding induced-fit host from a dynamic combinatorial library (DCL) of macrocyclic disulfides in water.

Scheme 1. Macrocyclic Receptors Based on Dithiol **1**



We have previously used disulfide exchange[3] to generate DCLs of macrocycles bearing aromatic, hydrophobic binding sites.[4] Building block **1**, inspired by hosts reported by Dougherty et al.,[5] has been a key component of these libraries, combining a rigid, curved binding surface with thiols for reversible linking to other building blocks and carboxylates for water solubility. We have prepared **1** as a racemic mixture and have previously reported the simultaneous nondiastereoselective amplification of the diastereomeric hosts **2** and **3** using various cationic templates.[4] We now report the very efficient amplification of a new tetrameric receptor (**4**) by a guest for which we perhaps least expected this: tetramethylammonium iodide. We discovered this host while screening a DCL made from building blocks **1** and **5**. Introducing NMe_4I into this library induced the clear amplification of **4**, which was identified by ESI-MS as a cyclic tetramer of building block **1** (Figure 1a,b). Amplification of **4** is even more pronounced in the biased "library" made solely from dithiol **1** (Figure 1c,d).

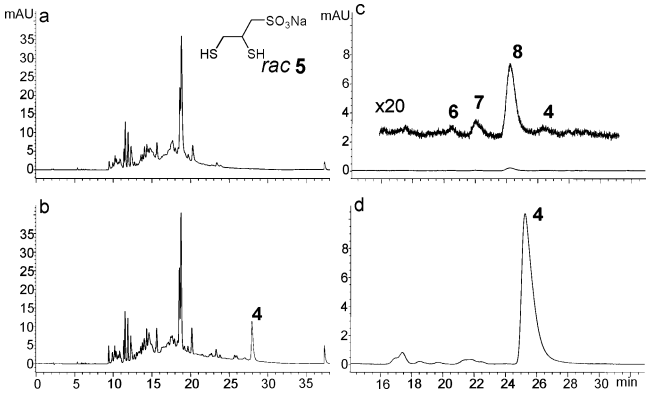


Figure 1. HPLC analysis of DCLs made from **1** and **5**, in the (a) absence and (b) presence of NMe_4I, and from only **1**, in the (c) absence and (d) presence of NMe_4I, zooming in on the tetramers.

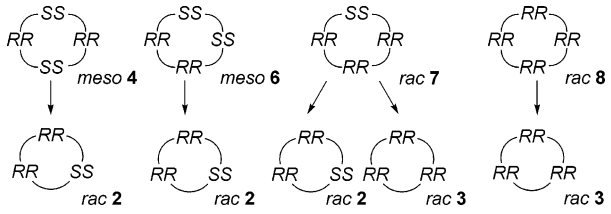


Figure 2. Correlation between trimer and tetramer diastereomers upon re-equilibration.

Since **1** is racemic, various stereoisomeric tetramers (**4**, **6**−**8**) can be formed (see Figure 2). We have been able to achieve baseline separation of all four diastereomeric products by HPLC (Figure 1c), which revealed that amplification is highly diastereoselective (Figure 1d). One of the four diastereomers is amplified around 400-fold, whereas the other three have amplification factors of not more than[6] 3, 13, and 0.3. Strikingly, the diastereomer that is strongly favored in the presence of the template (62% of the "library") is one of the least favored tetramers in its absence.

The structures of the diastereomers have been assigned using NMR and structural correlation through re-equilibration. The ^1H NMR spectrum of the most amplified diastereomer (as the neutral acid in CD_3OD) indicates a highly symmetric structure with only four different C−H environments. Whereas this observation rules out diastereomers **6** and **7** on symmetry grounds, it does not discriminate between **4** and **8**. To distinguish **4** from **8** we have studied the early stages of the re-equilibration of the tetramers. The most amplified diastereomer was isolated by preparative HPLC and dissolved in a pH 9 solution. Over a period of 7 days, a buildup of small amounts of other oligomeric products was observed, principally cyclic trimer. Unlike the tetramers, the structural assignment

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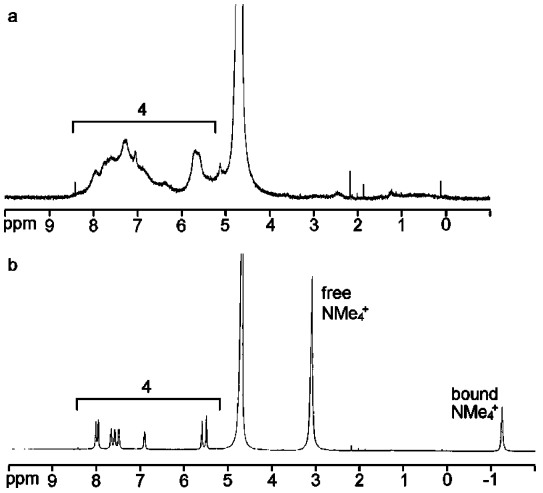

Figure 3. ^{1}H NMR spectra of **4** in D_2O, (a) without and (b) with NMe_4I.

of the two possible diastereomeric trimers (**2** and **3**) follows unambiguously from ^{1}H NMR analysis and symmetry considerations (see Supporting Information). We found that after 7 days only **2** was produced in significant amounts and only traces of **3** were detected, indicating that diastereomer **4**, built up from four units of **1** with alternating chirality, is preferred by NMe_4^+.

Similar re-equilibration experiments were conducted with **6** and **7** (see Supporting Information), allowing the complete assignment of all HPLC peaks shown in Figure 1c.

The binding of NMe_4I to diastereomer **4** was studied using isothermal tritration microcalorimetry (ITC), giving an approximate (see Supporting Information) binding constant of 4×10^6 M^{-1} in 10 mM pH 9 borate buffer, and thermodynamic parameters of $\Delta G^\circ = -38$ kJ mol^{-1}, $T\Delta S^\circ = -1$ kJ mol^{-1}, $\Delta H^\circ = -39$ kJ mol^{-1}. Binding is strongly enthalpy driven, similar to our previous observations on binding of organic cations to trimers **2** and **3** and in agreement with cation$-\pi$ interactions as the dominant driving force for binding.[5] In comparison, the trimer **2** binds NMe_4I with a binding constant of only 8×10^2 M^{-1}. The micromolar affinity observed for **4** compares favorably with the affinity of previously reported receptors for NMe_4^+ in water, which have binding constants in the order of 10^4 M^{-1} at most.[7]

Evidence for induced-fit recognition comes from an NMR study of this receptor. The ^{1}H NMR signals of **4** in D_2O (pD 8.7) are exceedingly broad (see Figure 3a), suggesting the existence of a variety of conformations and/or aggregates. The addition of an excess of NMe_4I dramatically transforms the spectrum into a set of clearly resolved peaks. Separate peaks for the unbound and bound guest were observed at $\delta = 3.09$ and $\delta = -1.25$ ppm, respectively. The strong ring-current-induced upfield shift ($\Delta\delta = -4.34$ ppm) indicates an intimate association between the guest protons and the aromatic rings of the host. Integration of signals of the host and the bound guest indicates that a 1:1 complex is formed.

The presence of the guest appears to reduce the symmetry of the host:[8] eight peaks are observed instead of the four seen when a spectrum of **4** is recorded in the absence of guest in MeOD (vide supra). However, when the temperature is raised from 300 to 360 K the spectrum in D_2O simplifies to four signals.

A tentative mode of binding can be deduced from CPK models (Figure 4). There is a clear size mismatch between host and guest when the host adopts an extended conformation. However, we found that **4** could easily fold into a four-stave barrel shape, enclosing a

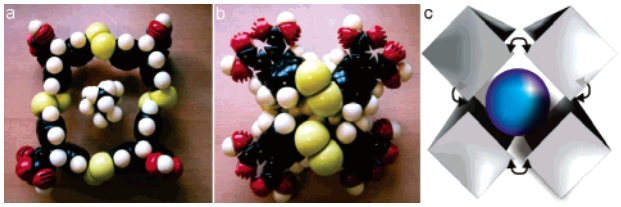

Figure 4. CPK models of **4** and NMe_4^+ in extended (a) and folded (b) conformations and a cartoon representation rationalizing the observed diastereoselectivity (c).

cavity ideally sized to accommodate the guest. Strikingly, it turned out to be impossible to fold any of the other three diastereomers **6**−**8** into the same conformation. This conformation also provides a plausible explanation for the observed diastereoselectivity: linking the corners of the building blocks with disulfides as indicated in Figure 4c results in a cyclic tetramer in which the subunits have alternating chirality.

In summary, through dynamic combinatorial chemistry we have discovered an unexpected high-affinity, induced-fit receptor **4**. Use of a racemic mixture of building block **1** gives a range of subtly but profoundly different structures from which the best is selected with impressive selectivity. The new receptor is amplified approximately 400-fold and binds tetramethylammonium iodide with submicromolar affinity in water.

Acknowledgment. We are grateful to Ana Belenguer for valuable assistance with the HPLC equipment, and we acknowledge financial support from the Royal Society and EPSRC.

Supporting Information Available: Materials and methods, ITC traces, NMR assignment of the two diastereomeric trimers, and HPLC traces from re-equilibration experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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