

Molecular amplification of two different receptors using diastereomeric templates†

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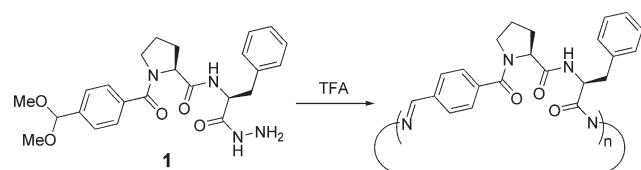
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Two different macrocyclic members of a pseudo-peptide hydrazone dynamic combinatorial library were amplified using the diastereomeric templates quinine and quinidine.

The development of synthetic receptors that differentiate between similar guests still represents a challenge for supramolecular chemists. Dynamic combinatorial chemistry (DCC)¹ provides access to new host–guest systems that may be difficult to synthesize using traditional design approaches.² This is accomplished through the preparation of dynamic combinatorial libraries (DCLs) that invite guests to recognize their preferred receptor from a mixture. Under appropriate conditions,³ the concentration of recognized receptors can then be amplified by means of the reversible chemistry involved in the maintenance of the DCLs. However, the level of subtlety achievable in a DCL has yet to be fully explored.

It has recently been demonstrated that a template molecule can recognize and amplify a preferred diastereomer from a mixture of potential receptors⁴ and some evidence has been presented for enantioselective recognition in another DCL.⁵ In addition, it has been observed that two different receptors can be amplified by exposure of one single DCL to two significantly different templates.⁶ However, similar template molecules tend to induce amplification of the same library receptor, albeit to different levels.⁷ We report here the amplification of two different macrocyclic receptors by exposure of one single small dynamic pool of polyhydrazones to diastereomeric cinchona alkaloids.

We have previously described the preparation of a dynamic system of macrocycles from building block **1** (Scheme 1). The mixture consists of a series of macrocyclic polyhydrazones ranging from dimer to at least undecamer; it responds to the presence of



Scheme 1 Dynamic library of macrocycles prepared from **1**.

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† Electronic supplementary information (ESI) available: Fig. S1: HPLC traces of the library: (a) in the presence of 6-OMe-quinoline and quinuclidine, (b) in the presence of cinchonine, (c) in the presence of cinchonidine. See DOI: 10.1039/b705620f

alkaline metal cations by amplifying the cyclic trimer,^{7b,8} and to acetylcholine by producing a catenane consisting of two interlocked trimers.²

When the library was exposed to the cinchona alkaloid quinine (Fig. 1) a significant shift in the product distribution toward the cyclic tetramer at the expense of the other macrocycles was observed by HPLC: the percentage of tetramer was increased from 63 to 91% (Fig. 2(a) and (b)).‡§

The template molecule quinine can be regarded as a quinoline moiety attached to one quinuclidine moiety by a one-carbon bridge. Both moieties are very similar to previously reported templates for the molecular amplification of different macrocyclic receptors from DCLs;^{6,9} in an attempt to determine which of those moieties was responsible for the molecular amplification observed, quinuclidine and 6-OMe-quinoline were tested, individually and simultaneously, as potential templates. The lack of any amplification observed for either template (see ESI†) suggests that the binding is driven by an interaction involving both moieties in the template. This was supported by the observation that the cinchonidine also produced amplification of the cyclic tetramer. Electrospray mass spectrometry analysis of the reaction mixture allowed the detection of the complex between the cyclic tetramer and the protonated alkaloid cinchonidine (Fig. 3).¶ Under the acidic library conditions the template will be protonated.

In order to test the importance of the relative positions of the moieties, we tested the template effect of quinidine, a diastereomer of quinine that possesses different configuration in two of the four stereogenic centres of the molecule (Fig. 1). No amplification of the cyclic tetramer was observed; on the contrary, the concentration of this species along with other macrocycles in the mixture decreased to feed molecular amplification of the cyclic dimer from 9 to 45% (Fig. 2(c)). The same result was observed with cinchonine, showing that, as in the quinine case, the 6-substituent is not involved in recognition.

As in Gagné's system,⁵ it has not proved possible to obtain association constants by direct experimental measurement because

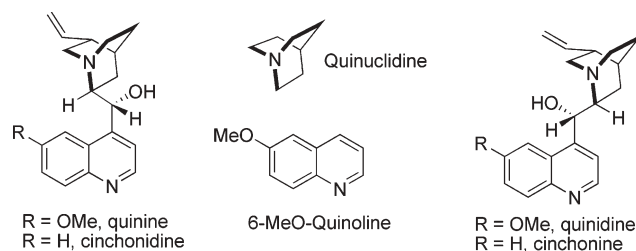


Fig. 1 Templates used for diastereoselective amplification of macrocycles.

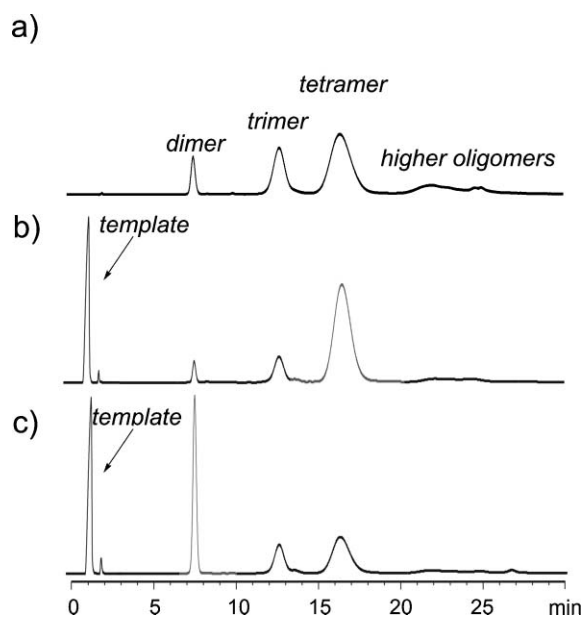


Fig. 2 HPLC traces of the library: (a) control without template, (b) in the presence of quinine, (c) in the presence of quinidine.

the acidic conditions required to produce protonated template induce library equilibration. However, values of around 10^4 M^{-1} are implied by the templates' ability to alter population distributions in millimolar solutions.

These results show the potential of dynamic combinatorial chemistry for the discovery of very different receptors that are able to differentiate between similar diastereomeric compounds. This is particularly remarkable, considering that the amplified macrocyclic polyhydrazones are rather flexible.^{7b,8} The design of such flexible diastereoselective receptors still represents an unaccomplished challenge for chemists.

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Notes and references

‡ HPLC analysis was carried out using a Hewlett-Packard 1050 instrument, coupled to a HP 1050 DAD; data were analysed using HP ChemStation. Reverse phase HPLC separations were carried out using a 15 cm × 4.6 mm i.d. 3 μm particle size, Supelco ABZ + C18 alkylamide column using acetonitrile and water gradients.

§ The general procedure for cyclization experiments entailed dissolution of monomer **1** (5 mM) in CHCl_3 -MeOH (98 : 2) containing 1.5% of TFA at room temperature. The equilibrium is reached within 5 days. The amplification observed is achieved by addition of 5 equiv. of template (with respect to **1**) either when the reaction is started or after it has reached equilibrium.

¶ Electro spray mass spectra were recorded on a Micromass Quattro-LC triple quadrupole apparatus fitted with a z-spray electrospray source. The electrospray source was heated to 100 °C and the sampling cone voltage was 65 V. Samples were introduced into the mass spectrometer source with

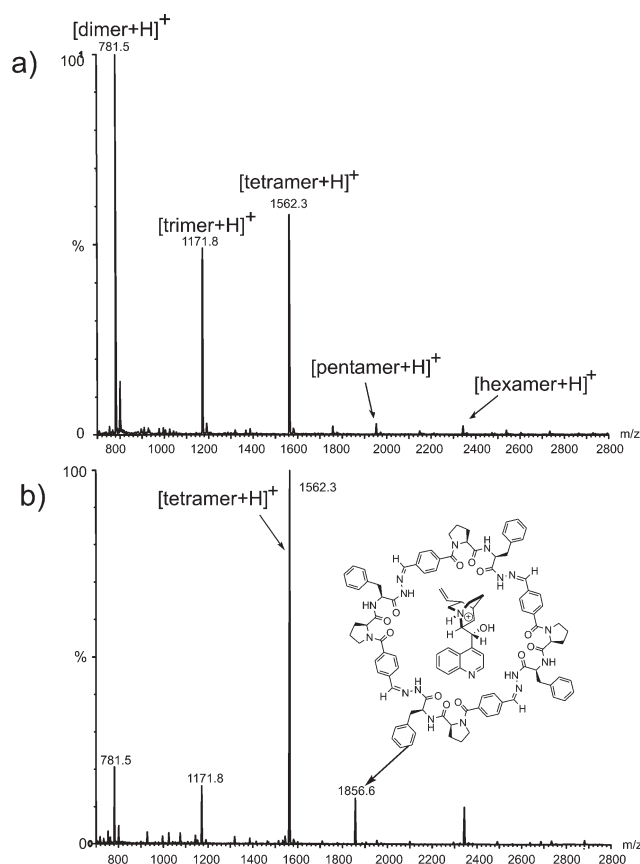


Fig. 3 ESI-MS analysis of the DCLs: (a) control without template, (b) in presence of the template cinchonidine.

an LC pump (Shimadzu LC-9A LC pump) at a rate of 4 mL min^{-1} of $\text{MeCN-H}_2\text{O}$ (1 + 1).

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