An Exceptional Synthetic Receptor for Peptides

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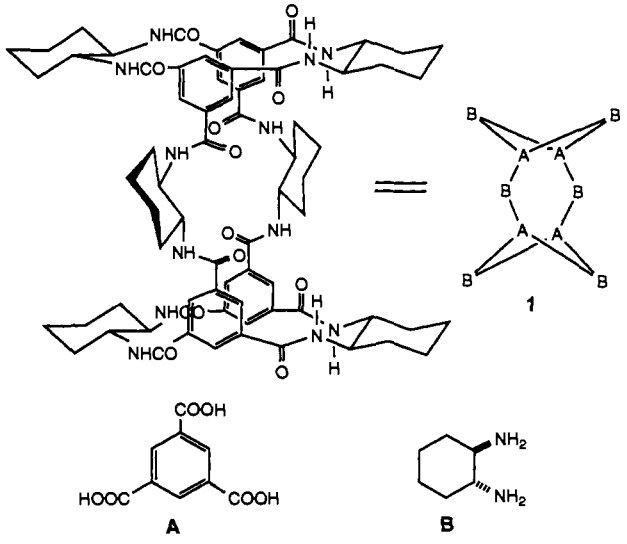
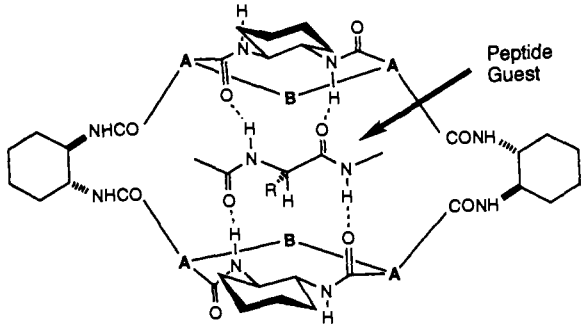
Unlike most synthetic host molecules,[1] biological receptors are conformationally well defined and large enough to almost fully encapsulate the substrates which they often bind with exquisite selectivity. Constructing analogous synthetic receptors is challenging because such structures seem to require complex atomic networks to form large binding sites and position binding functionality. In this communication, we describe one example of a large synthetic receptor which has only minimal structural complexity and yet has binding selectivities approaching those of biological receptors. It can also be assembled by the simplest of syntheses. This new receptor (**1**) is an A_4B_6 cyclooligomer of trimesic acid (A) and (*R,R*)-diaminocyclohexane (B). It binds amino acid residues in peptide chains with very high selectivities for chirality (up to 99+% ee) and side-chain identity (up to 3+ kcal/mol).



In designing **1**, we aimed for minimal receptor flexibility by using fragments having few opportunities for conformational isomerism and by joining them with planar amide bonds. Because one of the fragments (A) has three joining points, the neutral, nonpolymeric condensation products of A and B will be bridged polycyclics. Among the ways in which A and B can be combined, structure **1** is appealing because of its well-defined binding cavity and appropriately positioned hydrogen-bonding groups.

We synthesized **1** by first preparing an amide-linked Boc-B-A-B-A-B-Boc oligomer having the two internal carboxylates activated as pentafluorophenyl esters. When this material was deprotected (TFA, anisole) and slowly added to iPr$_2$NEt/THF, it dimerized to **1** in 39% yield (see supplementary material). Alternatively, **1** could be prepared in a single step (13% yield) by simply mixing commercially available A acid chloride and B at 3 mM concentration with iPr$_2$NEt in dry THF.

^{1}H NMR titrations in $CDCl_3$ showed that **1** formed 1:1 complexes with certain peptides and that *N*-Ac-L-Val-NHtBu was particularly well bound. To predict the structure of the most stable complex, we carried out a 5000-step MacroModel/SUMM conformational search[2] using AMBER*[3] and GB/SA chloroform.[4] The most stable structure found is shown in the color diagram (Chart I). The complex is held together by four intermolecular hydrogen bonds forming a structure resembling a peptidic three-strand β-sheet as shown front-on in the schematic:



A related pair of intramolecular hydrogen bonds (between B's) closes the unbound end of **1** to produce a deep cavity which fully encapsulates the side chain (R) of a bound L-peptide. With L-valine, this structure places the side-chain isopropyl near the face of the four aromatic rings (A) of **1**. It is compatible with the ^{1}H NMR of the corresponding L-valine methylamide complex, which shows a 2.5 ppm upfield shift for the side-chain methyls and an ~1 ppm downfield shift of only one of the three different types of host NH's.

The picture which emerges from association energy measurements (see table) is also in accord with the above binding mode which projects L-amino acid side chains into the central cavity of the receptor. Thus peptide derivatives are bound with high selectivity for the L-configuration except when side chains are large (entries 7 and 8). Valine and phenylglycine side chains appear to fit the binding cavity quite well, but substantial reductions in binding occur when even single methylenes are added (entries 3 vs 4 and 5 and 6 vs 7 and 8). Removal of side-chain bulk from a near-optimal side chain (iPr) also diminishes binding. Thus stepwise truncation of side-chain iPr to Me to H costs 1.5 kcal/mol per step with L-amino acids. The effect is less significant with D-amino acids, which the model suggests to have side chains projecting away from the binding site and into solvent. Finally, the large binding energies in entries 14 and 15 suggest that **1** can interact associatively with as many as three residues, a feat that

Table I. Binding Energies (kcal/mol) of Receptor **1** and Peptides[a]

entry	peptide	$-\Delta G$ (L)	$-\Delta G$ (D)	$\Delta\Delta_G$[b] (% ee)
1	*N*-Ac-Gly-NHMe	1.9		
2	*N*-Ac-Ala-NHMe	3.5	2.2	1.3 (80)
3	*N*-Ac-Val-NHMe	5.0	2.4	2.6 (97)
4	*N*-Ac-Ile-NHMe	4.3	2.4	1.9 (92)
5	*N*-Ac-Leu-NHMe	3.4	2.4	1.0 (68)
6	*N*-Ac-PGly[c]-NHMe	5.9	2.9	3.0 (>99)
7	*N*-Ac-Phe-NHMe	NC[d]	2.0	>-2.0 (<93)
8	*N*-Oc[e]-Tyr-NHMe	NC[d]		
9	*N*-Ac-Ser-NHMe	3.5	3.4	0.1 (8)
10	*N*-Ac-HSer[f]-NHMe	5.1	3.7	1.4 (83)
11	*N*-Ac-Thr-NHMe	3.5	2.9	0.6 (46)
12	*N*-Boc-Val-NHMe	2.8	1.7	1.1 (70)
13	*N*-Boc-Val-NH_2	4.9	3.7	1.2 (76)
14	*N*-Boc-Gly-Val-NHMe	6.2	3.2	3.0 (>99)
15	*N*-Boc-Gly-Val-Gly-NHBn	>7.2	4.6	>2.6 (>97)

[a] By NMR titration at 25 °C of 0.5 mM **1** in $CDCl_3$ (each binding energy is the average of two to five independent measurements on different protons, and the largest deviation from the average is ≤0.2 kcal/mol). [b] Enantioselectivity favoring L. [c] PGly, phenylglycine. [d] NC, no complex observed. [e] Oc, octanoyl. [f] HSer, homoserine.

(1) Notable exceptions: Petti, M. A.; Shepodd, T. J.; Barrans, R. E.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 2697. Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4527. Jeong, K.-S.; Muehldorf, A. V.; Rebek, J. *J. Am. Chem. Soc.* **1990**, *112*, 6144. Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111. Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554. Tanner, M. E.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1992**, *57*, 40.

(2) Goodman, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110.
(3) McDonald, D. Q.; Still, W. C. *Tetrahedron Lett.* **1992**, *33*, 7743.
(4) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127. $CHCl_3$ parameter set: Hollinger, F.; Still, W. C., unpublished results.

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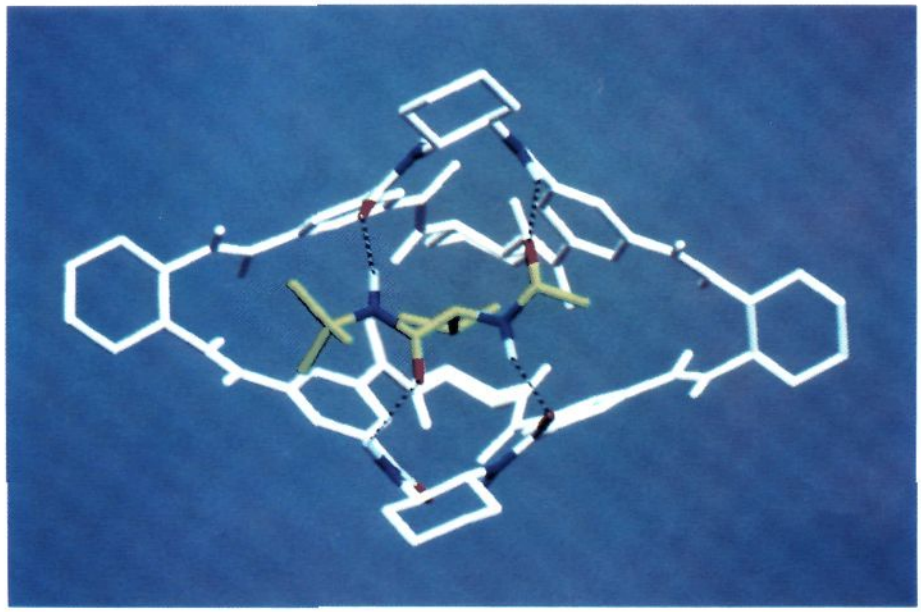
Chart I



appears unique among synthetic receptors. Presumably the terminal residues of such peptides are able to form additional hydrogen bonds to the outlying amides of the host (NHCO and CONH in the schematic).

Thus it is possible to assemble a large, conformationally well-defined receptor with remarkable binding properties starting from a few conformationally restricted subunits and trivial synthetic operations. There are doubtless many other such readily accessible heterooligomeric assemblies which have structural and binding properties analogous to those we associate with macromolecular receptors.[5]

Supplementary Material Available: Experimental procedure and spectral data for **1** (1 page). Ordering information is given on any current masthead page.

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