Pergamon

Tetrahedron Letters, Vol. 35, No. 14, pp. 2117-2120, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0279-7

Synthesis and Properties of A_4B_6 Cyclooligomeric Receptors

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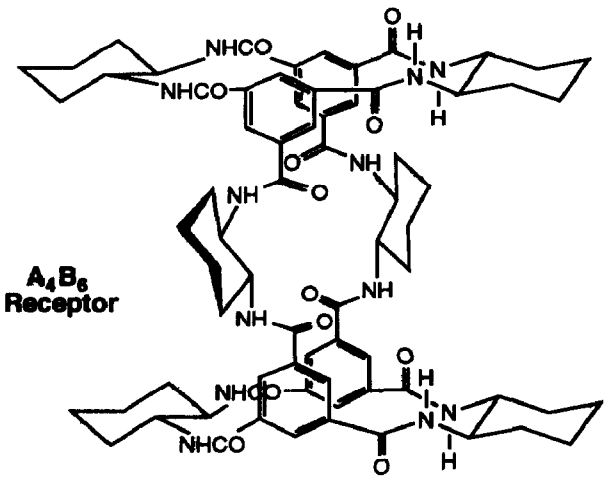
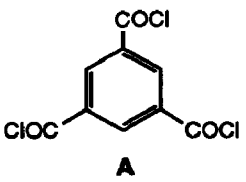
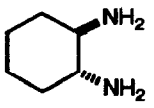
Abstract: The highly selective peptide-binding properties of A_4B_6 macrotricyclic receptors are not limited to previous structures where B = *trans*-1,2-diaminocyclohexane as we demonstrate by preparation and study of new $A_4B'_6$ receptors derived from acyclic diamines.

We recently described the preparation and properties of a novel receptor for peptides.[1] This molecule, the A_4B_6 macrotricycle shown below, is remarkable for several reasons. First, it self-assembles in a single step from two commercially available materials, the acid chloride **A** and the diamine **B**. Though the yield of this extraordinary reaction is only 13%, the receptor is readily isolated because it is the most chromatographically mobile of the products formed. Second, A_4B_6 is a highly selective receptor for neutral peptides. For example, it binds derivatives of L amino acids with enantioselectivities as high as 99% ee and can also distinguish between peptides based on the steric requirements of their sidechains. In some cases, this sidechain selectivity can be quite large and exceed 3 kcal/mol even when the peptides being compared differ only by a single methylene (e.g. phenylglycine vs phenylalanine). When we designed the A_4B_6 receptor, we chose the conformationally rigid building blocks **A** and **B** to minimize its flexibility. In this Letter, we describe the synthesis and properties of two related A_4B_6 cyclooligomers which are constructed from more conformationally flexible acyclic diamines B1 and B2. As we will show, binding properties in this series of receptors are sensitive to structure of the components used to assemble them, but rigid cyclic building blocks need not be used to obtain high binding selectivity.

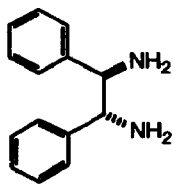




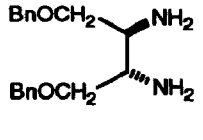
A



B



B1



B2

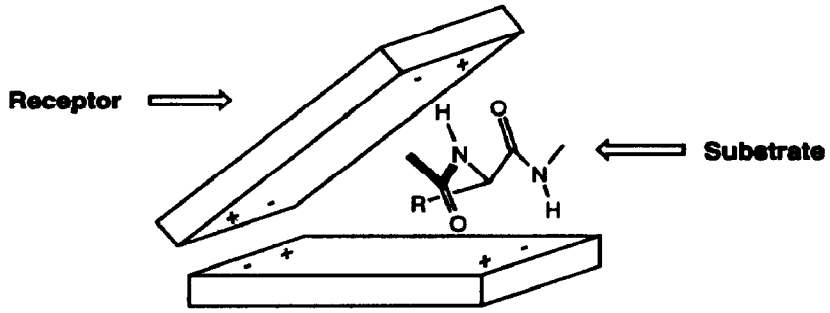
To prepare the new receptors, we carried out the simple one-step coupling of the amines shown and the triacid chloride **A** as described for A_4B_6.[1] With **B1**, the A_4B1_6 receptor was obtained in 10% yield when the coupling was carried out at a concentration corresponding to 6 mM in receptor.[2] With **B2**, we had to use a more dilute 1 mM concentration and were able to prepare A_4B2_6 in 7% yield. Both products were readily isolated as the most mobile reaction product on silica gel and were identified by mass spectroscopy and by their symmetry as revealed by ^{13}C and ^{1}H NMR.

Binding energies were measured by titrating 0.5 mM solutions of receptor in $CDCl_3$ with various N-acetyl amino acid methylamides and monitoring the receptor protons by 400 MHz NMR. In general, signals which showed the largest shifts upon binding were certain aromatic (H-C) and amide (H-N) protons. The binding energies we found are given in the Table and all represent averages of at least two different binding measurements. Scatchard treatment of binding data indicated 1:1 complexes in all cases.

Table. Peptide-Binding Properties of Macrotricyclic Receptors in $CDCl_3$.

	A_4B_6		A_4B1_6		A_4B2_6	
Peptide Substrate[a]	$-\Delta G$[b]	$\Delta\Delta G$[c]	$-\Delta G$[b]	$\Delta\Delta G$[c]	$-\Delta G$[b]	$\Delta\Delta G$[c]
GLY	1.9[d]		1.4		1.5	
L-ALA	3.5[d]	1.3[d] (80 %ee)	4.1	1.8 (90 %ee)	3.7	1.7 (89 %ee)
D-ALA	2.2[d]		2.3		2.0	
L-VAL	5.0[d]	2.6[d] (98 %ee)	4.5	2.4 (96 %ee)	3.8	1.5 (84 %ee)
D-VAL	2.4[d]		2.1		2.3	
L-ILE	4.3[d]	1.9[d] (92 %ee)	4.2	2.2 (95 %ee)	2.6	0.4 (32 %ee)
D-ILE	2.4[d]		2.0		2.2	
L-LEU	3.4[d]	1.0[d] (68 %ee)	3.6	1.5 (84 %ee)	2.5	0.3 (24 %ee)
D-LEU	2.4[d]		2.1		2.2	
L-PHE	NC[d]	-	NC	-	NC	-
D-PHE	2.0[d]		1.5		1.4	
L-Phenylglycine	5.9[d]	3.0[d] (>99 %ee)	5.7	3.9 (>99 %ee)	3.4	1.6 (87 %ee)
D-Phenylglycine	2.9[d]		1.8		1.8	
L-Ethylglycine	5.7	3.3 (>99 %ee)	5.5	3.4 (>99 %ee)	5.5	3.3 (>99 %ee)
D-Ethylglycine	2.4		2.1		2.2	
L-Propylglycine	6.0	3.5 (>99 %ee)	5.7	3.5 (>99 %ee)	4.8	2.5 (97 %ee)
D-Propylglycine	2.5		2.2		2.3	
L-Butylglycine	3.9	1.4 (82 %ee)	3.8	1.6 (87 %ee)	2.5	0.2 (16 %ee)
D-Butylglycine	2.5		2.2		2.3	

a. All peptides are N-acetyl, methylamides; b. binding energy (kcal/mol); c. enantioselectivity (kcal/mol); d. from reference 1. NC = no complexation observed.



The binding results obtained with all three receptors support the general picture of the complex suggested previously[1] and illustrated above. In the diagram, '+' and '-' represent receptor hydrogen bond donors (H-N) and acceptors (O=C) respectively. We believe these functionalities not only bind the peptidic substrate by hydrogen bonds but also associate to close the other end of the receptor to create a conical binding cavity which can encapsulate the sidechain (R) of a bound L amino acid.

The binding data in the Table reveals a number of notable trends. First, all receptors bind all D amino acid substrates with roughly the same binding energy (2.0-2.5 kcal/mol). Thus the high enantioselectivities observed originate from especially favorable binding to L peptide substrates, not by destabilization of binding to D substrates. Second, both the original A_4B_6 receptor and the new A_4B1_6 analog have similar binding selectivities despite the construction of the latter from an acyclic diamine. Indeed, A_4B1_6 binds six of the eight substrates studied with higher enantioselectivity than does A_4B_6.

Both A_4B_6 and A_4B1_6 show surprisingly high selectivity among L amino acids which are distinguished only by the size and shape of their unfunctionalized, hydrocarbon sidechains. Amino acids having branched sidechains bind well only when the branch occurs at the substrate β-carbon. Thus valine and isoleucine (R = *i*-Pr, *s*-Bu) bind well but leucine (R = *i*-Bu) does not. The receptors also distinguish substrates by sidechain length. Thus while alanine and butylglycine (R = Me, *n*-Bu) are rather poorly bound, ethylglycine and propylglycine (R = Et, *n*-Pr) are among the best substrates. All three receptors distinguish phenylglycine and phenylalanine by >3 kcal/mol. These observations are compatible with the conical-cavity model which favors substrates having more steric bulk near the enlarged, open end of the binding cavity. Substrates with sidechains that are either too small to fill the cavity or too long to be accommodated are poorly bound. While binding selectivity based on steric effects is known,[3] the subtle differences in sidechain bulk which our receptors are able to distinguish energetically by 1-2 kcal/mol is unusual with synthetic receptors. The key to such high steric selectivity appears to coincide with the receptor's ability to fully encapsulate the chemical substructure being distinguished.

Like A_4B_6 and A_4B1_6 which bind L-peptides based on the steric requirements of their sidechains, receptor A_4B2_6 also distinguishes peptide sidechains sterically but with different selectivity. In particular, A_4B2_6 selects for L-peptides whose sidechains are small and compact:

thus alanine, valine and ethylglycine are well-bound while isoleucine, leucine, phenylglycine, propylglycine and butylglycine are more weakly bound relative to the other receptors. Thus A_4B2_6 appears to have a smaller binding cavity, a property which may follow from cavity occupancy by benzyloxymethyl substituents or from partial cavity collapse due to the flexible nature of the B2 fragment.

These findings suggest that the highly selective binding we found with the original A_4B_6 receptor may be general to cyclooligomeric molecules of this class and that binding selectivity can be altered by starting with different A and B fragments. Thus it should not be difficult to prepare a wide range of interesting receptors by similar routes. It may also be noted that these receptors incorporate B fragments in two different structural environments: the upper and lower macrocycles include four equivalent B's while two other B's link those macrocycles together. By varying these distinct B fragments independently, even more receptor diversity can be generated. We will be reporting on the properties of such receptors in the near future.[4]

Notes and References.

1. S.S. Yoon and W.C. Still, *J. Am. Chem. Soc.*, **115**, 823 (1993).

2. Synthesis of A_4B1_6: To an ice cold solution of (1R,2R)-diphenylethylenediamine (66 mg, 0.31 mmol) and iPr_2NEt (0.16 mL, 0.63 mmol) in THF (100 mL) and dimethylacetamide (10 mL) was added 1,3,5-benzenetricarbonyl trichloride (55 mg, 0.21 mmol) as a single portion with stirring. After 2 hours at O °C, the mixture was allowed to warm to room temperature and then to stand for an additional 12 hours. Volatile materials were removed at reduced pressure and the crude product was purified by flash chromatography on silica gel (3% methanol in methylene chloride). A_4B1_6 was the most mobile compound chromatographically and was isolated as an amorphous white solid (9.8 mg, 10%): TLC (5% MeOH in CH_2Cl_2) R_f = 0.71; ^1H NMR ($CDCl_3$) δ 9.03 (d, 1H, J = 5.2 Hz), 8.57 (d, 1H, J = 9.2 Hz), 8.47 (s, 1H), 8.27 (s, 1H), 7.70 (s, 1H), 7.46-7.12 (m, 15H), 6.81 (m, 1H), 5.60 (m, 2H), 5.38 (dd, 1H, J = 10.7, 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.7, 165.8, 164.7, 141.8-128.5 (m), 64.7, 62.8, 60.0; IR (neat) 3345, 2933, 1652, 1538, 1321 cm^{-1}; MS (FAB) *m/z* 1899 (M+1).

3. For example: F. Diederich, K. Dick and D. Griebel, *J. Am. Chem. Soc.*, **108**, 2273 (1986); W.L. Mock and N.-Y. Shih, *J. Am. Chem. Soc.*, **110**, 4706 (1988); M.A. Petti, T.J. Shepodd, R.E. Barrans and D.A. Dougherty, *J. Am. Chem. Soc.*, **110**, 6825 (1988); D.J. Cram, M.E. Tanner, S.J. Keipert and C.B. Knobler, *J. Am. Chem. Soc.*, **113**, 8909 (1991); K. Naemura, K. Ueno, S. Takeuchi, Y. Tobe, T. Kaneda and Y. Sakata, *J. Am. Chem. Soc.*, **115**, 8475 (1993); L. Garel, B. Lozach, J.-P. Dutasta and A. Collet, *J. Am. Chem. Soc.*, **115**, 11652 (1993).

4. We acknowledge support by NSF Grant CHE92 08254.

(*Received in USA* 9 *November* 1993; *revised* 30 *December* 1993; *accepted* 1 *February* 1994)