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Highly Selective Binding of Diverse Neutral Donor/Acceptor Substrates by a C_3 Macrotricyclic Receptor

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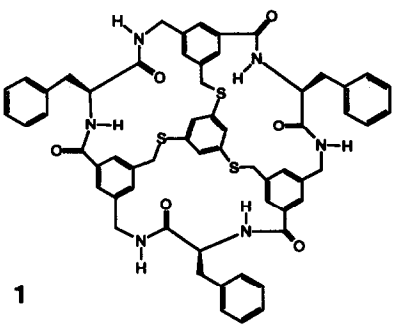
Abstract: The synthetic receptor **1** binds a variety of peptides and glycosides with high selectivity for functionality and stereochemistry. Depending upon peptide mainchain substitutents, either the C- or the N-terminus of a peptide may be directed into the binding pocket of **1**.

We recently reported a novel, C_3-symmetric receptor (**1**) which bound Boc-protected N-methylamides of α-amino acids with high selectivity.[1] In particular, **1** bound such derivatives of alanine, valine, leucine, serine and threonine with enantioselectivity corresponding to 2-3 kcal/mol (90-99% ee favoring L). It also showed selectivity between different classes of amino acids. For example, derivatives of serine and threonine were bound ≥2 kcal/mol more tightly that alanine, valine and leucine. While the high affinity of **1** for Boc, N-methylamides of L-amino acids suggests structural and electronic complementarity, we expected that certain other donor/acceptor substrates would also be bound by **1** with high selectivity. In this report, we describe two new classes of molecules, methoxycarbonyl amino acid esters and octyl glycosides, which are bound by **1** with high affinity and selectivity in chloroform.



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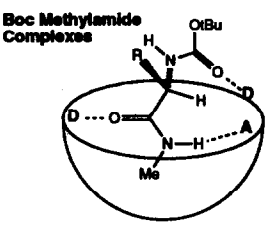
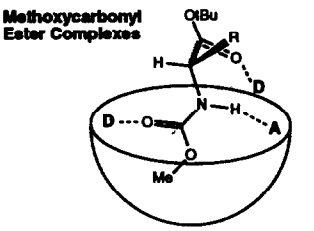
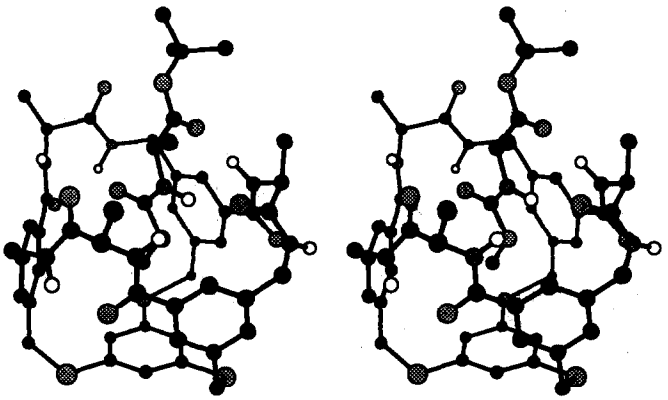




The key features of **1** which make it highly selective are a deep binding cavity with appropriately-positioned hydrogen bond donor/acceptor functionality and conformationally stability. We view **1** as a deep, apolar pit whose entrance is studded with alternating hydrogen bond donor (D) and acceptor (A) sites. Molecules which can readily form hydrogen bonds to these sites and fill the cavity should be the preferred binding partners.

Our previous NMR and molecular modeling results[1a] suggested such a binding mode for the Boc, L-amino acid N-methylamides which were tightly bound by **1** via three hydrogen bonds as illustrated above. As shown in the companion diagram, a structurally similar arrangement can be constructed with N-methoxycarbonyl amino acid esters. Interestingly, this arrangement directs the opposite, N-terminus of the amino acid substrate toward the center of the binding cavity. This simple picture also suggests that the L-configuration of such derivatives should be preferentially bound. A stereopair diagram of the complex of **1** and methoxycarbonyl alanine t-butyl ester is



shown above and was produced by simulated annealing over 500 ps starting at 300 K using the AMBER* force field and the GB/SA chloroform solvation model.[2]

The necessary methoxycarbonyl substrates were prepared from the corresponding t-butyl esters using methylchloroformate. As shown in entries 5-8 of Table 1, they are indeed bound enantioselectively with a marked preference for L-configuration.[3] In the case of dialanine derivatives (entry 8), the stability of the complex is most sensitive to the stereochemistry of the N-terminal alanine. This behavior is in contrast to the Boc dialanine N-methylamides (entry 4) which bind less selectively but with a C-terminal L-alanine being slightly preferred.

Table 1. Binding of **1** and Simple Peptides in $CDCl_3$.

Entry	Substrate	Binding Energy (-ΔG, kcal/mol)				Enantioselectivity
1[1a]	Boc-Ala-NHMe	L: 3.9	D: 1.7			95% ee
2[1a]	Boc-Val-NHMe	L: 4.4	D: 1.5			99% ee
3[1a]	Boc-Ser-NHMe	L: >6.1	D: 3.8			>96% ee
4	Boc-Ala-Ala-NHMe	LL: 2.9	DD: 2.0	LD: 2.8	DL: 3.3	64, 40% ee
5	MeO_2C-Ala-OtBu	L: 4.8	D: 2.3			97% ee
6	MeO_2C-Val-OtBu	L: 3.7	D: 1.5			95% ee
7	MeO_2C-Ser-OtBu	L: ≥7.0	D: 4.7			≥96%ee
8	MeO_2C-Ala-Ala-OtBu	LL: 4.7	DD: 2.2	LD: 4.4	DL: 2.7	97, 89% ee
9	Pr-Ala-OtBu	L: 3.8	D: 2.3			85% ee
10	Ac-Ala-OtBu	L: 3.0	D: 1.5			85% ee
11	Boc-Ala-OMe	L: 1.5	D: 1.2			15% ee
12	Boc-Ser-OMe	L: 4.7	D: 2.9			90% ee
13	Boc-Thr-OMe	L: 4.7	D: 3.1			87% ee
14	Boc-His-OMe	L: 3.5	D: 2.7			58% ee
15	Boc-Asn-OMe	L: 3.1	D: 2.2			64% ee
16	Boc-Gln-OMe	L: 4.2	D: 2.2			93% ee
17	Boc-Glu(OMe)-OMe	L: 2.9	D: 1.4			84% ee

The N-terminal methoxycarbonyl group appears particularly appropriate for binding to **1**. For comparison, the isostructural N-propanoyl alanine derivative (entry 9) binds less tightly by 1.0 kcal/mol in the case of the L enantiomer. The smaller N-acetyl derivative (entry 10) is bound even more weakly. Evidence for the above-proposed structure of the methoxycarbonyl amino acid derivatives is limited at this time; however, we do observe ~1 ppm upfield shifts in the ^{1}H NMR of N-terminal methoxycarbonyl methyls upon binding. Similar, though larger (~3 ppm), upfield shifts of the C-terminal N-methyl of Boc methylamides were observed when they bound to **1**.[1a] Such shielding is compatible with placement of methyls in the binding site near the face of the aromatic rings defining the cavity walls.

We also examined a series of Boc amino acid methyl esters which generally showed weak binding and poor enantioselectivity (e.g. alanine, entry 11) unless the sidechain was functionalized by hydrogen bond donor and/or acceptor groups. For such amino acid derivatives (entries 12-17), L was always favored with enantioselectivities ranging from 0.8 to 2.0 kcal/mol.

As summarized in Table 2, receptor **1** also forms complexes with various chloroform-soluble octyl glycosides.[3,4] Though the multitude of possible intermolecular hydrogen-bonding arrangements makes it difficult to determine the structures of such complexes, we do find that **1** binds glycosides with a marked dependence upon carbohydrate stereochemistry. Thus, anomers bind with energy differences typically 0-1 kcal/mol but as much as 1.9 kcal/mol in the case of mannose (entry 6). Selectivity does not however appear directed solely by the anomeric center: the α-anomer (entry 6) is bound preferentially in the case of D-mannose, but the β-anomers of both D- and L-glucoside (entries 1,2) are preferred. Altering the stereochemistry of certain ring hydroxyls also has a marked effect on binding. Thus, relative to α-D-glucoside, inverting C2 increases binding by 1.6 kcal/mol (entry 6), inverting C3 decreases binding by 1.3 kcal/mol (entry 9) and inverting C4 has little effect on binding (entry 7). It is interesting that one sugar derivative, α-D-mannoside, is bound by **1** significantly more tightly than any other sugar studied. Its binding is also accompanied by a significant (0.25 ppm) downfield shift in the NMR signal for the anomeric hydrogen.

Table 2. Binding of **1** and Simple Glycosides in $CDCl_3$.

Entry	Substrate	Binding Energy (-ΔG, kcal/mol)	
1	1-O-Octyl-D-glucopyranoside	α: 3.5	β: 4.4
2	1-O-Octyl-L-glucopyranoside	α: 3.0	β: 3.6
3	1-O-Octyl-6-OAc-D-glucopyranoside	α: 2.6	β: 2.5
4	1-O-Octyl-6-OBz-D-glucopyranoside	α: 2.7	β: 2.3
5	1-O-Octyl-2-deoxy-D-glucopyranoside	α: 3.9	β: 3.7
6	1-O-Octyl-D-mannopyranoside	α: 5.1	β: 3.2
7	1-O-Octyl-D-galactopyranoside	α: 3.3	β: 3.8
8	1-O-Octyl-2-deoxy-D-galactopyranoside	α: 2.2	
9	1-O-Octyl-D-allopyranoside	α: 2.2	

The above experiments demonstrate that 1 is capable of binding the stereoisomers of a variety of donor/acceptor substrates both tightly and with high selectivity. Considering the ready availability of 1 on large scale,[1b] the results reported here suggest that 1 and its derivatives may be of value as stereoselective chromatographic stationary phases. While many of the structural details of 1's binding selectivity remain to be clarified (especially those with carbohydrates whose association properties are complicated by the differing solvation energies of the substrates and a multitude of potential binding modes), it is clear that 1 has structural characteristics which make it a highly selective receptor. We believe that the key such characteristic is conformational inflexibility which in 1 positions unassociated (not internally hydrogen bonded) donors and/or acceptors at well defined positions at the binding site. This pattern of such donors and acceptors on the periphery of the binding site seems complementary to many substrate structural types.[5]

Notes and References:

1. a. J.-I. Hong, S.K. Namgoong, A. Bernardi and W.C. Still, *J. Am. Chem. Soc.*, **113**, 5111 (1991); b. Synthesis: S.D. Erickson, J.A. Simon and W.C. Still, *J. Org. Chem.*, in press (1993).

2. a. D.Q. McDonald and W.C. Still, *Tetrahedron Lett.*, **33**, 7747 (1992); b. W.C. Still, A. Tempczyk, R.C. Hawley and T. Hendrickson, *J. Am. Chem. Soc.*, **112**, 6127 (1990).

3. Binding energies were measured by ^{1}H NMR titration of 0.5 mM 1 in $CDCl_3$ at 23 °C by the substrates indicated. Substrate concentrations varied from 20 mM for tightly bound substrates to 200 mM for the most weakly bound substrates. The concentration and chemical shift results were fit by a nonlinear least squares procedure to a binding equation of the form A + B -> AB to give binding energies. Binding energies in the range 3-5 kcal/mol are accurate to within 0.2 kcal/mol. No corrections for substrate aggregation were made.

4. For previous synthetic carbohydrate receptors, see: Y. Aoyama, Y. Tanaka and S. Sugahara, *J. Am. Chem. Soc.*, **111**, 5397 (1989); R.P. Bonar-Law, A.P. Davis and B.A. Murray, *Angew. Chem. Int. Ed.*, **29**, 1407 (1990); K.M. Bhattarai, R.P. Bonar-Law, A.P. Davis and B.A. Murray, *J. Chem. Soc., Chem. Commun.*, 752 (1992).

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