mg, 45%): ^{1}H NMR ($CDCl_3$) δ 4.12 (s, 2H) 6.94 (s, 1H) 8.31 (s, 2H) 8.56 (s, 1H).

A solution of 40 mg of hexakis(pentafluorophenyl)ester (0.0253 mmol) and 63 mg of N-(Disperse Red I)succinyl-(3R,4R)-pyrrolidine diamine diTFA salt[2(a)] (0.0835 mmol) in 10 mL of DMA was added to a solution of 0.19 ml of DIPEA (1.09 mmol) in 200 mL of THF at room temperature for 20 hr by syringe pump. After the stirring for 5 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 10% MeOH in methylene chloride to give an amorphous red solid (18 mg, 32%): ^{1}H NMR ($CDCl_3$/CD_3OD) δ 0.72 (t, 3H, J=7.0 Hz) 2.43 (m, 2H) 3.01 (q, 2H, J=7.0 Hz) 3.26 (s, 2H) 3.45 (m, 2H) 3.64 (m, 1H) 3.82 (m, 1H) 4.22 (m, 4H) 4.56 (m, 1H) 4.67 (m, 1H) 6.67 (d, 2H, J=9.1 Hz) 6.98 (m, 1H) 7.78 (m, 5H) 7.98 (m, 1H) 8.15 (d, 2H, J=9.1 Hz) 8.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm) 172.11, 170.54, 170.02, 168.23, 151.24, 141.61, 138.87, 137.97, 136.03, 135.66, 132.55, 128.07, 126.66, 126.22, 125.36, 124.65, 123.21, 122.21, 119.58, 111.23, 54.32, 50.34, 48.70, 45.34, 37.07, 28.77, 28.54, 28.18, 28.12; IR (neat) 3325, 2825, 1723, 1675, 1576 cm^{-1}; MS (FAB) *m/z* 2061 (M+1); HRMS (FAB) 2061.3164 (2061.3144 calcd for $C_{102}H_{109}O_{21}N_{21}S_3$)

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5. All possible combinations of R=methyl (Me), ethyl (Et), isopropyl (*i*Pr), *t*-butyl (*t*-Bu), neopentyl (neoPe), trifluoromethyl (TFA), methoxymethyl (MOM), acetoxymethyl (AcOM), cyclopropyl (cPr), cyclobutyl (cBu), cyclopentyl (cPe), phenyl (Ph), morpholino (Mor), dimethylamino (Me2N) and AA1-AA3=Gly, D-Ala, L-Ala, D-Ser(OtBu), L-Ser(OtBu), D-Val, L-Val, D-Pro, L-Pro, D-Asn(Tr), L-Asn(Tr), D-Gln(Tr), L-Gln(Tr), D-Lys(N-Boc), L-Lys(N-Boc).
6. Although **1** and a known receptor (**2**)[3] show the similar selectivities at R (Me and Me_2N) and AA3 site (Gln) of tetrapeptide substrate, there are selectivity differences at AA2 (**1** prefers Ala, **2** prefers Pro) and AA1 (**1** prefers Pro, **2** shows virtually no selectivity) site. These support the notion that this class of receptors recognize total structual features not just the direct interaction region of tetrapeptide substrate.
7. Since **1** was sparingly soluble in $CDCl_3$, it was not possible to study complexation properties of **1** in $CDCl_3$. See related approach; 2(a) and Smith, P.W.; Chang, G.; Still, W.C. *J. Org. Chem.* **1988**, *53*, 1587.
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An Enantioselective Peptide-Binding Receptor

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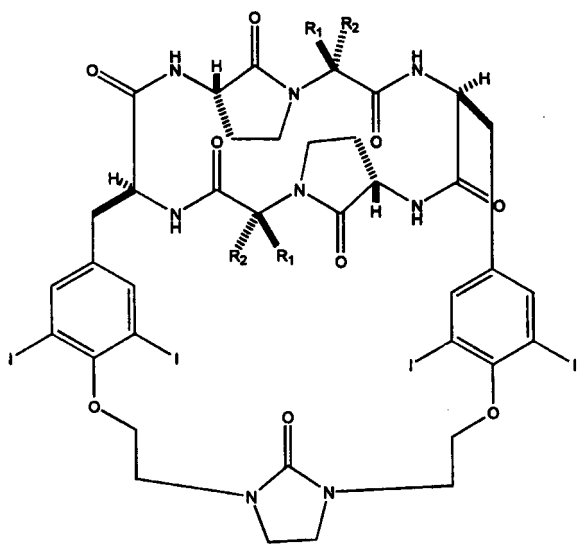
The enantioselective complexation of peptides by synthetic receptors has been widely studied because this would increase the understanding of basic principles on molecular recognition mechanism seen in biological systems such as enzyme and antibody, and lead to the selective catalysts, novel pharmaceuticals, novel analytical and separative tools.[1]

Learned from molecular recognition studies on receptor/substrate binding, criteria for the design of selective receptors were identified. The primary requirement to such receptors is a conformationally rigid system with proper arrays of functional groups complementary to those found in substrates.[2] In efforts to develop such receptors, chemists have constructed cyclic and multi-cyclic structures from conformationally rigid building blocks having the suitable functionalities for the binding with given substrates. Obviously, there exist a variety of readily available building blocks. Among those are cyclohexapeptides. Cyclohexapeptides are conformationally homogeneous due to intramolecular hydrogen bondings. Moreover, various functionalities can be



1 R_1 = Me, R_2 = H
2 R_1 = H, R_2 = Me

Structure of 1 of 2.

introduced to periphery of cyclohexapeptides by using amino acids with various sidechain functional groups.

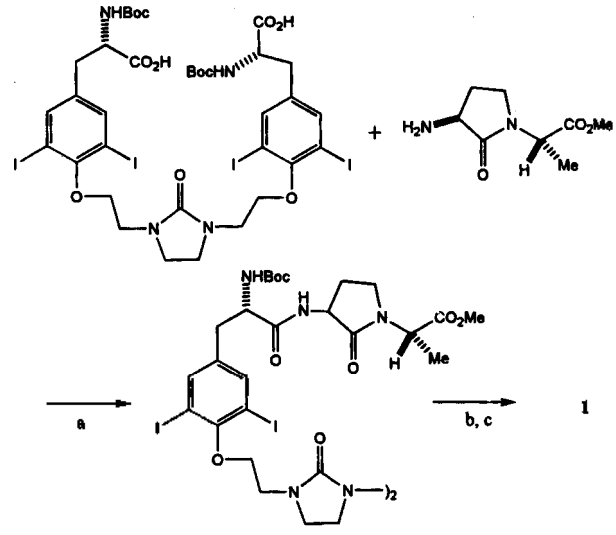
Here, to explore the possibility that cyclohexapeptides can be used as novel building blocks for the construction of molecular receptors, C_2-symmetric cyclohexapeptide-derived receptors (**1** and **2**) are described.[3]

In **1** and **2**, γ-lactam derived alanine dipeptides[4] were used to prevent conformational isomerism and the cyclic structure was constructed to further reduce the number of accessible low energy conformation. Thus a number of well-defined hyrogen bonding donor/acceptors are available for the selective interactions with peptides. As will be shown, a synthetic receptor (**1**) binds peptides enantioselectively and its peptide-binding ability is markedly sensitive to the subtle changes in structure of receptor.

Synthesis of **1** begins with N-Boc-L-diiodotyrosine derived diacid as shown in Scheme 1. A double DCC-promoted amide formation with the γ-lactam amine led to the dimethylester. Ester hydrolysis and subsequent EDC coupling with pentafluorophenol furnished the cyclization precursor. Macrocyclization was then carried out as a double intramolecular amide formation by syringe pump addition of bis(pentafluorophenyl)ester diamine diTFA salts to THF containing excess iPr_2NEt at room temperature. This cyclization provided the receptor **1** in 35% yield. Receptor **2** was prepared by following the essentially same procedures except using γ-lactam derived D-alanine dipeptide instead of L-isomer for receptor **1** with 32% yield.

The peptide-binding properties were evaluated by the standard NMR titration method. The results are summarized in Table 1.

The binding data in Table 1 reveal a number of notable trends. First, although **1** showed 1 : 1 complex formation with peptides, **2** is unable to bind with the same peptides. Thus stereochemical inversion of alanine of **1** reduce binding with (D)-serine derived peptide as large as 4 kcal/mol. It is remarkable that such subtle structural changes of receptor greatly affect the peptide-binding properties of receptor. Second, receptor **1** showed the enantioselectivies for peptides. For example, **1** shows the enatioselection corresponding to 1.2 kcal/mol favoring D-isomer of serine derived peptide. Interestingly, deletion of hydroxy group in side chain of serine reduced the enantioselection of **1**. Thus, **1** was found to bind the alanine derived peptide with the the low enantioselection within experimental error. Third, sidechain functional groups as well as carboxyl and amino terminal groups of substrates have the profound effects on binding with **1**. Changes in N-terminal group from acetyl to trifluoromethyl and C-terminal group from amide to ester reduce binding by 3 kcal/mol. Also, benzyl protection of sidechain groups in serine derived peptides reduced greatly binding with receptor **1**.

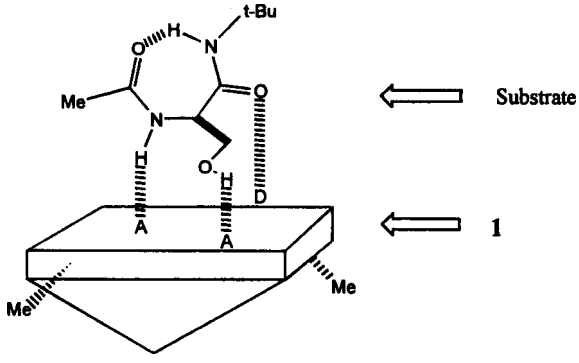


Scheme 1. (a) DCC/HOBT (78%), (b) i. NaOH, ii. C_6F_5OH/EDC (45%), (c) DIPEA, THF (35%).

Table 1. Association Energy (kcal/mol) of **1** and **2** with peptides[a]

Peptides	1		1
	$-\Delta G$	$\Delta\Delta G^b$	
N-Ac-gly-NH'Bu	2.82		NC
N-TFA-Gly-NH'Bu	NC[c]		
N-Ac-Gly-O'Bu	NC		
N-Boc-Gly-NH'Bu	NC		
N-Ac-(L)Ala-NH'Bu	2.31		NC
N-Ac-(D)Ala-NH'Bu	2.02	0.29	NC
N-Ac-(L)Val-NH'Bu	1.82		
N-Ac-(D)Val-NH'Bu	1.46	0.36	
N-Ac-(L)Ser-NH'Bu	2.92		NC
N-Ac-(D)Ser-NH'Bu	4.10	− 1.23	NC
N-Ac-(L)Thr-NH'Bu	2.45		
N-Ac-(D)Thr-NH'Bu	3.59	− 1.14	
N-Ac-(L)Ser(OBn)-NH'Bu	NC		
N-Ac-(L)Ser(OBn)-NH'Bu	NC		

[a] By NMR titration at 25 °C of 0.5 mM [receptor] in $CDCl_3$ (each binding energy is obtained using a nonlinear least-square data treatment and is the average of 2-5 independent measurements on different protons and the largest deviation from the average is <0.2 kcal/mol), [b] enantioselectivity favoring L-isomer, [c] no complex formation.



Scheme 2. D: Hydrogen bond donor (N-H), A: Hydrogen bond Acceptor (C=O).

To get the insight on these findings, conformational searching on receptors **1** using MACROMODEL/AMBER force field was carried out.[5] This study shows that the expected binding cavity of **1** is collapsed[6] and suggests that the binding with peptides occurs from the convex surface of **1** as shown in Scheme 2. The complex is mainly held by hydrogen bonds between **1** and substrates. Thus removal and Bn-protection of hydroxy group in serine derived peptides reduce the binding strength as well as selectivity with **1**. Also, changes in carboxyl and amino terminal groups of substrates from amide and acetyl to ester and trifluoroacetyl weaken the binding by reduction of hydrogen binding ability of substrates. Conformational searching on **2** reveal that the low energy conformer of **2** has the structure similar to that of **1** except stereochemical inversion of alanine. As a result, methyl groups of alanine in **2** place on the expected binding surface. Presumably, these two methyl groups weakened greatly the binding of **2** with peptides by steric hindrance.[7]

Although the exact nature on the binding selectivity of **1** is not clear, further structural studies on complex using computation, NMR and X-ray crystallography will clarify this issue.[8]

In summary, a readily accessible macrocyclic receptor (**1**) derived from a cyclohexapeptide has the enantioselective peptide binding properties. Also, this study shows clearly that cyclohexapeptides can be used as building blocks for the novel synthetic receptors. Currently, work directed to cyclohexapeptides-derived receptors with the novel peptide binding properties is in progress.

Experimental

Di-Boc, Dimethyl ester. To a solution of 0.50 g of di-Boc, diacid (0.415 mmol) and 0.16 g of γ-lactam amine (0.914 mmol) in 30 mL of THF were added 0.12 g of HOBT (0.914 mmol) and 0.19 g of EDC (1.01 mmol). After stirring for 12 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 5% MeOH in methylene chloride to give an amorphous white solid (0.49 g, 78%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.78 (s, 2H) 7.50 (d, 1H, *J*=7.0 Hz) 5.05 (bs, 1H) 4.85 (dd, 1H, *J*=10.5, 5.0 Hz) 4.65 (q, 1H, *J*=7.5 Hz) 4.36 (dd, 1H, *J*=7.5, 3.6 Hz) 4.08 (t, 2H, *J*=5.3 Hz) 3.95 (s, 3H) 3.80 (s, 2H) 3.50 (t, 2H, *J*=5.3 Hz) 3.34 (m, 2H) 3.05 (dd, 1H, *J*=10.5, 5.0 Hz) 2.88 (dd, 1H, *J*=13.5, 10.5 Hz) 2.68 (m, 1H) 2.57 (m, 1H) 1.40 (s, 9H) 1.25 (d, 3H, *J*=7.5 Hz); MS (FAB) *m/z* 1517 (M+1).

1. To a solution of 0.14 g of di-Boc, dimethyl ester (0.0923 mmol) in 5 mL of THF, 3 mL of MeOH and 1 mL of water was added 0.46 mL of 1 N NaOH solution. After stirring for 5 hr at r.t., the reaction mixture was acidified with 1 N HCl solution and extracted with EtOAc (3×50 mL). The crude dicarboxylic acid was dissolved in 3 mL of THF and 10 mL of methylene chloride, and then 0.15 g of pentafluorophenol (0.84 mmol) and 0.16 g of EDC (0.84 mmol) were added. After stirring for 8 hr at r.t., all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 20% acetone in methylene chloride to give di-Boc, bis(pentafluorophenyl) ester as an amorphous white solid (86 mg, 31.9%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.78 (s, 2H) 7.50 (d, 1H, *J*=7.0 Hz) 5.05 (bs, 1H) 4.85 (dd, 1H, *J*=10.5, 5.0 Hz) 4.75 (q, 1H, *J*=7.5 Hz) 4.36 (dd, 1H, *J*=7.5, 3.6 Hz) 4.08 (t, 2H, *J*=5.3 Hz) 3.80 (s, 2H) 3.50 (t, 2H, *J*=5.3 Hz) 3.34 (m, 2H) 3.05 (dd, 1H, *J*=10.5, 5.0 Hz) 2.88 (dd, 1H, *J*=13.5, 10.5 Hz) 2.68 (m, 1H) 2.57 (m, 1H) 1.40 (s, 9H) 1.31 (d, 3H, *J*=7.5 Hz).

To a solution of 0.12 g of di-Boc, bis(pentafluorophenyl) ester and 0.1 mL of anisole in 10 mL of methylene chloride was added 3 mL of TFA. After stirring for 2 h at r.t., all volatiles were removed at reduced pressure. The crude bis (pentafluorophenyl)ester diTFA salts were used the next reaction without further purification.

A solution of 0.1 g of bis(pentafluorophenyl)ester diTFA salts (0.0551 mmol) in 10 mL of DMA was added to a solution of 0.19 mL of DIPEA (1.09 mmol) in 200 mL of THF at room temperature for 20 hr by syringe pump. After the stirring for 5 hr at room temperature, all volatiles were removed at reduced pressure. The residue was purified by flash chromatography on silica gel using 10% MeOH in methylene chloride to give an amorphous white solid (25 mg, 35%): ^{1}H NMR ($CDCl_3$) δ (ppm) 8.02 (d, ^{1}H, *J*=7.5 Hz) 7.83 (s, 2H) 7.74 (d, 1H, *J*=7.0 Hz) 4.11 (dd, 1H, *J*=10.5, 5.0 Hz) 4.05 (q, 1H, *J*=7.5 Hz) 3.95 (dd, 1H, *J*=7.5, 3.6 Hz) 3.88 (t, 2H, *J*=5.3 Hz) 3.74 (s, 2H) 3.50 (t, 2H, *J*=5.3 Hz) 3.14 (m, 2H) 3.01 (dd, 1H, *J*=10.5, 5.0 Hz) 2.70 (dd, 1H, *J*=13.5, 10.5 Hz) 2.48 (m, 1H) 2.37 (m, 1H) 1.35 (d, 3H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.32, 172.11, 170.53, 163.21, 142.32, 141.34, 139.43, 80.62, 75.33, 64.21, 55.23, 56.13, 47.32, 37.12, 26.45, 22.34; IR (neat) 3322, 2820, 1723, 1675, 1625, 1576 cm^{-1}; HRMS (FAB) 1276.4456 (calcd for $C_{39}H_{44}O_9N_8I_4$ 1276.4448).

2. ^{1}H NMR ($CDCl_3$) δ 8.22 (d, 1H, *J*=7.5 Hz) 7.93 (s, 2H) 7.64 (d, 1H, *J*=7.0 Hz) 4.54 (dd, 1H, *J*=10.5, 5.0 Hz) 4.31 (q, 1H, *J*=7.5 Hz) 4.05 (dd, 1H, *J*=7.5, 3.6 Hz) 3.98 (t, 2H, *J*=5.3 Hz) 3.84 (s, 2H) 3.40 (t, 2H, *J*=5.3 Hz) 3.44 (m, 2H) 3.11 (dd, 1H, *J*=10.5, 5.0 Hz) 2.75 (dd, 1H, *J*=13.5, 10.5 Hz) 2.38 (m, 1H) 2.17 (m, 1H) 1.30 (d, 3H, *J*=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.95, 171.87, 170.53, 163.21, 142.32, 141.34, 139.43, 81.54, 74.25, 63.12, 55.21, 56.43, 43.32, 35.76, 26.45, 20.11; IR (neat) 3320, 2823, 1722, 1677, 1632, 1571 cm^{-1}; HRMS (FAB) 1276.4497 (calcd for $C_{39}H_{44}O_9N_8I_4$ 1276.4448).

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6. A conformer with the open cavity exists 1.5 kcal/mol above the global minimun conformer with the collapsed cavity.
7. To confirm this idea, a receptor **3** (R_1=R_2=Me) was prepared from α-methyl alanine. CPK modeling study on **3** suggest that the low energy conformer of **3** has the structure similar to that of **1** except the substitution Me for H on binding surface of **1**. As a result, methyl groups of alanine in **3** place on the expected binding surface. Subsequent binding studies revealed that **3** is unable to bind peptides. Although the subtle conformational changes of receptors by substituents of receptors cannot be ignored, this implies that the steric effects between Me in receptors (**2** and **3**) and peptides play an important role in receptor's peptide-binding ability.[9]
8. NOE study on complex of **1** and N-Ac-(D)Ser-NHtBu support partially the proposed structure of complex as shown in Scheme 2. Although many expected NOE signals between protons in the complex were not observed, a NOE signal was found between the acetyl protons of N-Ac-(D)Ser-NHMe and α-protons of γ-lactams in **1** which are placed on the convex surface of **1**. This observation is partially in accord with the binding mode of **1** emerged from binding studies.
9. Further support on this notion comes from the observation of the intermolecular self-complexation properties of **1** and **2**. Within 1~10 mM concentration range, **1** shows moderate self-complexation properties although **2** shows no self-complexation. This suggests that Me groups in **2** prevent the self-complexation because of the steric hindrances between them.

Alternate Organic and Inorganic Molecular Layers Assembled by Electrostatic Attraction

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Ultrathin films formed by electrostatic attraction of macromolecules of opposite charge have received considerable attention in recent years.[1-17] Specifically, in 1991 Decher and Hong[1] reported a technique of constructing multilayer assemblies by alternating adsorption of anionic and cationic bipolar amphiphiles on charged surfaces. Later they extended the concept to multipolar compounds such as polyelectrolytes.[2,3] In 1994, Keller *et al.*[6] applied the technique to sequential layering of structurally well-defined, two dimensional colloidal inorganic polyanions with a variety of oligomeric and polymeric cations.

When a multilayered film is prepared using bipolar cations and anions that have two identical charges at each end, the bipolar molecules are usually assumed to align perpendicularly with respect to the substrate underneath.[1] Based on a small angle X-ray scattergram, Decher and Hong[2] concluded that the bipolar anion should not be tilted from the layer normal when a multilayered film was formed between bipolar anionic amphiphiles and polymeric cations such as poly-4-vinylbenzyl-(*N*,*N*-diethyl, *N*-methyl) ammonium ion.

We hope to report that alternating multilayered film can be also assembled between organic and inorganic molecules. As observed using ellipsometry, UV absorption spectroscopy, and quartz crystal microbalance (QCM) measurements, organic bipolar cations appeared to adopt a rather flat stance when they formed multilayered films with the inorganic colloidal polyanions, α-$Zr(HPO_4)_2$.

Experimental

Cationic bola-amphiphile (Bola), (see Figure 1(a)), and α-zirconium phosphate (ZrP) were synthesized and purified following the procedure reported in the literature.[1,18] All other chemicals were reagent grade and used as received unless specified. Aqueous solutions were prepared by using tri-

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