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A Chiral A_2B_2 Macrocyclic Minireceptor with Extreme Enantioselectivity

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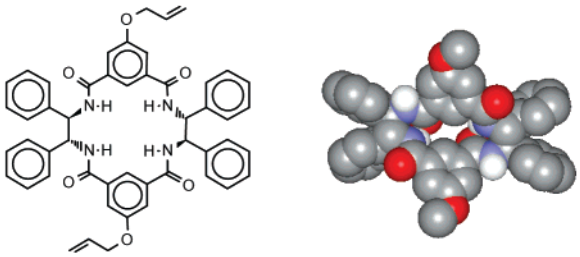
ABSTRACT



We describe a novel macrocyclic minireceptor that is assembled from a chiral 1,2-diamine and 5-allyloxyisophthalic acid. After immobilization on HPLC silica, the chiral macrocycle preferentially binds the L-enantiomers of simple amino acid derivatives, with enantioselectivities values up to 3.0 kcal/mol.

The investigation of molecular recognition phenomena occurring in living systems is greatly facilitated by synthetic model structures that mimic the mode of action of their natural counterparts. One convenient way to study in detail the specific interactions between artificial receptors and their binding partners is offered by chromatographic systems in which surface-linked species are screened for the ability to differently retain the components of a pool of potential ligands. This approach has been recently applied in both achiral[1] and chiral[2] systems and proved to give results that closely match those observed in free solution. Highly enantioselective synthetic receptors share some structural properties that seem closely related to their discrimination ability: conformational homogeneity, cagelike structure, and the presence of functional groups with a high degree of directionality (e.g., H-bond donor−acceptor functionalities). Here we report on the properties of the new chiral minireceptor **1**, which incorporates the above structural features and shows receptorlike enantioselectivities ($\Delta_{R,S}\Delta G_{25}$ °C in the 2−3 kcal/mol range) for simple amino acid derivatives.

The macrocyclic minireceptor **1** was prepared in a single step from 5-allyloxyisophthaloyl chloride (A) and commercially available, chiral 1,2-(*R*,*R*)-diphenylethylenediamine (B, Scheme 1). Simply mixing equimolar amounts of the A and B components in the presence of Hunig base in THF at 4 mM concentrations results in the formation of the neutral, A_2B_2 18-membered macrocycle **1** in 60% unoptimized yield.[3] The more polar oligomeric, linear byproducts are easily removed by chromatography on silica gel.

Spectroscopic data are in agreement with a neutral A_2B_2-type structure. Molecular modeling was carried out in an attempt to gain information on the structural features of **1**. A Monte Carlo conformational search within Macromodel/Batchmin V. 5.0,[4] Amber* force field, and the GB/SA solvation[5] model for $CHCl_3$ yielded a minimum energy structure for **1** (allyl groups modeled by methyls) featuring an open cavity delimited by the two aromatic isophthalic

(1) Zimmerman, S. C.; Saionz, K. W. *J. Am. Chem. Soc.* **1995**, *117*, 1175−1176. Zimmerman, S. C.; Kwan, W. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2404−2406. Bianco, A.; Gasparrini, F.; Maggini, M.; Misiti, D.; Polese, A.; Prato, M.; Scorrano, G.; Toniolo, C.; Villani, C. *J. Am. Chem. Soc.* **1997**, *119*, 7550−7554. Gasparrini, F.; Misiti, D.; Della Negra, F.; Maggini, M.; Scorrano, G.; Villani, C. *Tetrahedron* **2001**, *57*, 6997−7002.

(2) Gasparrini, F.; Misiti, D.; Villani, C.; Borchardt, A.; Burger, M. T.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 4314−15. Gasparrini, F.; Misiti, D.; Villani, C.; Wennemers, H.; Still, W. C. *J. Org. Chem.* **1997**, *62*, 8221−24. Pieters, J.; Cuntze, J.; Bonnet, M.; Diederich, F. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1891−1900. Cuntze, J.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 897−911.

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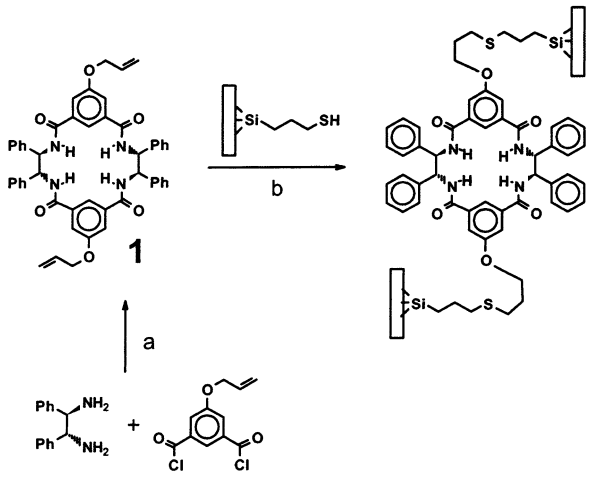
Scheme 1. Synthesis of Minireceptor **1** and Its Immobilization on HPLC Silica Particles[a]



[a] (a) THF, (^{i}Pr)$_2$NEt, 25 °C, 0 °C for 1 h, then rt for 12 h. (b) AIBN, $CHCl_3$, 55 °C in a closed vessel, 6 days.

rings, whose planes are oriented at a relative angle of 120°. This disposition generates a cleft that is closed on the left and right sides by the phenyl rings of the chiral diamines. The four amides take an alternate conformation with the carbonyl oxygens pointing in turn inside and outside the macrocycle cavity, producing an array of alternating H-bond donor and acceptor sites along the macrocycle border.

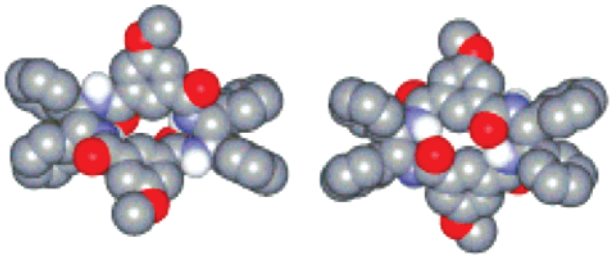


Figure 1. Low-energy conformation of **1** (population = 25%) found by molecular mechanics calculations. Front and back views showing free and H-bond-associated amide fragments.

Within each B unit, one carbonyl oxygen and the adjacent amidic NH point toward the bottom of the cavity and are intramolecularly H-bonded. The remaining amide fragments are outwardly directed, exposed to the solvent and available for H-bonding with the guests. The molecule has an overall twist induced by the chiral B units, with chirality transferred from the outside of the macrocycle to the interior of the cavity. The above structural features were found on all the other relative minima found within 3 kcal/mol.

Available spectroscopic data are in agreement with the above picture. FT-IR spectra of **1** in $CDCl_3$ solutions show a sharp band at 3437 cm^{-1} and a broad band centered at 3358 cm^{-1}. These bands are observed in the 1−5 mM concentration range and are consistent[6] with the presence of associated and unassociated amide NHs.

Covalent attachment of **1** to spherical γ-mercaptopropyl silica was realized via AIBN radical addition of the silica thiol groups across the pendant allylic double bonds. Grafting to the silica surface occurred smoothly in methylene chloride at 55 °C, giving the chiral stationary phase (**CSP1**) with a receptor loading of 0.17 mmol per gram of matrix (about 1.2 μmol/m^2).[7]

After packing by standard methods into a 250 × 4 mm ID column and end-capping with HMDS,[8] we started a screening process to identify some specific classes of compounds showing enantioselective association with the immobilized receptor.

It must be emphasized that when studying enantioselective associations by monitoring differential retentions in an HPLC system, one must consider the observed selectivities as limiting lower values, which approach the values in free solution when the underlying support (unreacted silica) has no affinity for the examined compounds.[9,10]

Preliminary examination of several chiral test solutes indicated that minireceptor **1** binds certain amino acid derivatives in organic media (see Figure 2 and Table 1) with

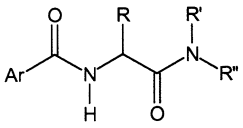


Figure 2. General structure of amino acid derivatives used in enantioselective binding studies (see Table 1).

enantioselection as high as 3.0 kcal/mol, a value among the highest recorded for simple, totally synthetic receptors.[11]

(3) **Minireceptor 1.** 5-Allyloxyisophthaloyl chloride (0.63 g, 2.45 mmol) dissolved in 1 mL of THF was added at once to a cooled (0 °C) solution of *(R,R)*-1,2-diphenylethylenediamine (0.28 g, 2.45 mmol) and diisopropylethylamine (0.85 mL, 4.9 mmol) in 400 mL of THF. After the mixture was stirred for 12 h at 25 °C, the solvent was removed at reduced pressure, the residue was dissolved in CH_2CI_2, and the organic solution was washed with 0.1 N HCl and brine, dried over Na_2SO_4, and after solvent removal, purified by preparative HPLC (LiChroprep Si 60, 15−25 μm, 250 × 20 mm i.d. axially compressed column, 0.5% MeOH in CH_2Cl_2) to afford receptor **1** as a white solid (0.50 g, 63%). IR ($CDCl_3$): 3437, 3358, 1657, 1593, 1527, 1507 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.54 (brs, 4H), 8.28 (s, 2H), 7.60−7.45 (m, 24H), 5.96−5.77 (m, 2H), 5.60−5.47 (m, 4H), 5.30−5.15 (m, 4H), 4.484.29 (m, 4H). ^{13}C NMR ($CDCl_3$): 168.4, 158.7, 138.1, 135.9, 132.3, 128.6, 128.0, 127.8, 118.5, 117.8, 116.5, 69.1, 61.2. MS (FAB) *m/z*: 797 (M + H$^+$).

(4) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379−4386.

(5) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6129

(6) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164−1173.

(7) A slurry of γ-mercaptopropyl silica (Hypersil, 3.2 g. Anal. Found: C, 4.43; H, 0.92; 0.74 mmol per gram of matrix or 4.9 μmol/m^2), minireceptor **1** (0.46 g), and AIBN (0.03 g) in 20 mL of CH_2Cl_2 was stirred for 6 days in a closed reactor at 55 °C. After the mixture was cooled to room temperature, the modified silica was collected by filtration and washed with CH_2Cl_2, MeOH, CH_2Cl_2, and hexane and dried under reduced pressure. Anal. Found: C, 11.08; H, 1.43; N, 0.83. FT-IR (KBr): 1653, 1595, 1531 cm^{-1}.

(8) Pirkle, W. H.; Readnour, R. S. *Anal. Chem.* **1990**, *63*, 16−20.

Table 1. Enantioselection of Aminoacid Derivatives by Minireceptor **1** in 99/1 CH_2Cl_2/2-propanol at 25 °C

compd	Ar	R	R′	R″	$-\Delta\Delta G^{a,b,c}$
2	3,5-DNP[d]	Me	hexyl	H	1.5
3		Et	hexyl	H	2.4
4		Pr	hexyl	H	2.8
5		Bu	hexyl	H	3.0
6		^{i}Pr	hexyl	H	3.0
7		^{s}Bu	hexyl	H	3.0
8		^{i}Bu	hexyl	H	2.0
9		^{t}Bu	hexyl	H	1.4
10		Ph	hexyl	H	2.2
11		Bn	hexyl	H	1.3
12		$MeSCH_2CH_2$	hexyl	H	2.5
13		^{i}Pr	Et	Et	0.6
14		^{i}Pr	^{t}Bu	H	2.3
15		^{i}Pr	1-Adm[e]	H	2.4
16	Ph	^{i}Bu	hexyl	H	0.9
17	C_6F_5	^{i}Bu	hexyl	H	1.6
18	1-naphthyl	^{i}Bu	hexyl	H	0.5

[a] In kcal/mol, calculated from $\Delta\Delta G = -RT\ln\alpha$, where α is the chromatographic enantioselectivity factor, *T* the absolute temperature, and *R* the gas constant. [b] Values are accurate to ±50 cal/mol. [c] Enantioselectivity favoring the L-enantiomers. [d] 3,5-DNP = 3,5-dinitrophenyl. [e] 1-Adm = 1-adamantyl.

Enantioselectivity data for neutral amino acid derivatives, expressed as the difference in the free energy of binding ($-\Delta\Delta G$) between the two enantiomers and the immobilized receptor, are gathered in Table 1. Minireceptor **1** differentially binds the enantiomers of the examined compounds with selectivities that strongly depend on the side chain nature and on the type of modification at both carboxy- and amino-termini. The stereochemical preference is always in favor of the guests with the L-configuration. In all cases, the D-enantiomers of the guests are loosely bound and elute close to the column void volume. The differences in the free energies of interaction for D- and L-enantiomers span a range of 2.5 kcal/mol, with the extremes at 0.5 and 3.0 kcal/mol. Among *N*-3,5-dinitrobenzoyl amino acid hexylamides, enantioselectivity increases with side chain length (cf. **2**−**5** and **12**) and reaches a maximum value of 3 kcal/mol for the linear four-carbon atom chain. The same value is observed for *β*-branched ^{i}propyl and ^{s}butyl side chains, while ^{i}butyl and ^{t}butyl side chains disfavor enantioselectivity.

A phenyl ring directly bound to the stereogenic carbon gives higher enantioselectivity compared to the more flexible benzyl side chain (**10** vs **11**). Increasing the steric bulk at the carboxy terminus lowers enantioselctivity by 0.6−0.7 kcal/mol (**6** vs **14** and **15**). Replacing the amidic NH H-bonding site in **6** with a tertiary amide, as in **13**, costs 2.4 kcal/mol in enantioselectivity. With leucine hexylamides, variations of the electronic properties of the aryl ring at the amino terminus result in a loss of 1.1−1.5 kcal/mol in enantioselectivity for the *π*-basic phenyl (**16**) and 1-naphthyl rings (**18**), compared to the *π*-acidic 3,5-dinitrophenyl ring. With the pentafluorophenyl ring, the selectivity loss amounts to only 0.4 kcal/mol.

In addition, immobilized minireceptor **1** shows less pronounced enantioselctive association ($\Delta_{R,S}\Delta G_{25}$ °C in the 0.1−0.5 kcal/mol range) with a set of structurally diverse compounds such as aryl carbinols, axially chiral atropisomeric amides and imides, sulfoxides, Troger's base, η^6-arene chromium tricarbonyl complexes, and metal *β*-diketonates.

It is worth noting that the closely related minireceptor **19** prepared from (*R*,*R*)-1,2-diaminocyclohexane,[12] after immobilization on HPLC silica (CSP2), shows only modest enantioselctivities (up to 0.4 kcal/mol, see Supporting Information) for DNB-amino acid derivatives. Molecular mechanics calculations predict similar low-energy structures for the two receptors, suggesting the four peripheral phenyl rings of minireceptor **1** are responsible for its extremely high affinity for the L-enantiomers of the guests.

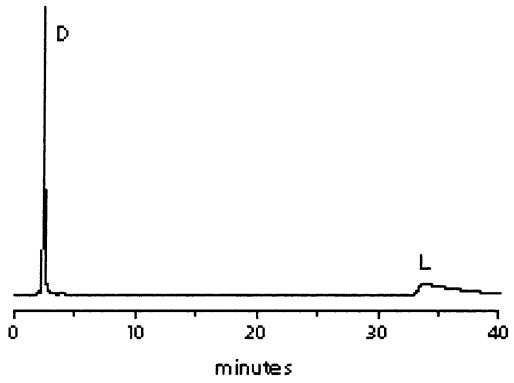


Figure 3. Chromatographic resolution of compound **14** on silica-bound minireceptor **1**. Eluent: 99/1 CH_2Cl_2/2-propanol. Flow rate 2.0 mL/min. $T = 25$ °C. UV detection at 254 nm.

Preliminary ^{1}H NMR free-solution complexation studies of **1** and L-**6** add direct structural information to chromato-

(9) Fornstedt, T.; Götmar, G.; Andersson, M.; Guiochon, G. *J. Am. Chem. Soc.* **1999**, *121*, 1664−1774

(10) Control experiments showed that under the same experimental conditions used with immobilized minireceptor **1**, none of the examined compounds is retained on *γ*-mercaptopropyl silica.

(11) Cram, D.; Cram, J. M. *Acc. Chem. Res*. **1978**, *11*, 8. Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155−163. Schmidtchen, F. P.; Berger, M. *Chem. Rev*. **1997**, *97*, 1609−1646. Ogoshi, H.; Mizutani, T. *Acc. Chem. Res*. **1998**, *31*, 81−89. You, J.-S.; Yu, X.-Q.; Zhang, G.-L.; X., Q.-X.; Lan, J.-B.; Xie, R.-G. *Chem. Commun*. **2001**, *18*, 1816−1817. Sansone, F.; Baldini, L.; Casnati, A.; Lazzarotto, M.; Ugozzoli, F.; Ungaro, R. *Proc. Nat. Acad. Sci*. **2002**, *99*, 4842−4847. Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc*. **1994**, *116*, 4240−4250. For nonmacrocyclic chiral receptors, see: Pirkle, W. H.; Murray, P. G. *J. Chromatogr*. **1993**, *641*, 11−19. Welch, C. J.; Ganapati, B.; Protopopova, M. N. *J. Comb. Chem*. **1999**, *1*, 364−367. Lah, J.; Maier, N. M.; Lindner, W.; Vesnaver, G. *J. Phys. Chem. B* **2001**, *105*, 1670−1678. Botana, B.; Ongeri, S.; Arienzo, R.; Demarcus, M.; Frey, M. J.; Piarulli, U.; Potenza, D.; Gennari, C.; Kilburn, J. D. *Chem. Commun.* **2001**, 1358−1359.

(12) Minireceptor **19** was obtained in a manner similar to minireceptor **1** starting from *(R,R)*-1,2-diaminocyclohexane (40% yield). IR (KBr): 1646, 1581, 1530, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.64 (s, 2H), 7.44 (brs, 2H), 7.24 (s, 4H), 6.07−5.88 (m, 2H), 5.37 (dd, 2H, $J = 17.20$, 1.47 Hz), 5.27 (dd, 2H, $J = 10.40$, 1.35 Hz), 4.62, 4.45 (m, 4H), 3.88 (brs, 2H). ^{13}C NMR ($CDCl_3$): 168.6, 158.5, 136.1, 132.4, 118.3, 117.8, 116.1, 69.0, 55.2, 31.9, 24.7. MS (FAB) *m/z*: 601 ($M + H^+$). Immobilization to give **CSP2** was obtained as for **CSP1**. Anal. Found: C, 9.22; H, 1.35; N, 0.82 (corresponding to 0.19 mmol of receptor per gram of matrix (ca. 1.3 μmol/m^2)). FT-IR (KBr): 1655, 1523 cm^{-1}. See also: Hu, K.; Bradshaw, J. S.; Dalley, N. K.; Krakoviak, K. E.; Wu, N.; Lee, M. L. *J. Heterocycl. Chem.* **1999**, *36*, 381−387.

graphically derived energetic data. In the ^{1}H NMR spectrum of the 1:1 complex (10 mM in $CDCl_3$, 20 °C), the amidic NHs at the carboxy and amino termini of L-**6** undergo a 0.3 ppm downfield shift relative to free L-**6**, indicating H-bond formation with **1**. Furthermore, in the ^{1}H NMR spectrum of the 1:1 complex of **1** and racemic **6** (10 mM in $CDCl_3$, 20 °C), both the amidic NH signals of **6** are split by 0.2−0.3 ppm, with the signals of L-**6** undergoing a more pronounced shift.

All these data suggest to us a model in which the enantioselective recognition originates from a blend of different interactions, including H-bonding and $\pi-\pi$ aromatic stacking interactions, and is modulated by the identity of the amino acid side chains and functionalities present at the carboxy and amino termini.

Similar interaction modes involving a combination of aromatic−aromatic and H-bonding interactions have been described for a nonmacrocyclic *N*-aryl-amino acid amide selector[13] that, after immobilization on a chromatographic support, differentiates the enantiomers of DNB-amino acids with high enantioselectivity (chromatographic selectivity for DNB-leucine butylamide equal to 98, corresponding to a $\Delta_{R,S}\Delta G_{25}$ °C of 2.7 kcal/mol). The selectivity observed in this case originates from the fine-tuned selector structure and from the effective masking of nonspecific interaction sites obtained by incorporation of the chiral units into a linear siloxane copolymer. The chromatographic enantioselectivity of minireceptor **1** for some DNB-amino acid amides (compounds **4**−**7**) approaches the record value of 148, and stems from the nearly perfect fit of only one enantiomeric guest with the (unoptimized) macrocyclic host. A precise stereoelectronic host−guest fitting imparts extreme selectivity to the system; a less than perfect structural matching, on the other hand, produces only marginal enantioselection as observed with non-aminoacidic guests.

In conclusion, we have shown the properties of a new chiral minireceptor that combines broad-range enantioselectivity with receptorlike ability to discriminate between the enantiomers of amino acid derivatives in organic media.

Further work aimed at a deeper understanding of the observed selectivities is currently underway in our laboratory.

Acknowledgment. We are thankful for financial support from MURST (Contract 2001033797_004) and Centro di eccellenza BEMM.

Supporting Information Available: Retention and enantioselectivity data for amino acid derivatives on immobilized minireceptors **1** and **19** and general structures of chiral compounds resolvable on immobilized **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026363G

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