Synthesis and Characterization of Pyridine-Based Polyamido-Polyester Optically Active Macrocycles and Enantiomeric Recognition for D- and L-Amino Acid Methyl Ester Hydrochloride

Hongwu Zhao and Wenting Hua*

Department of Chemistry, Peking University, Beijing 100871, PR China

Received August 30, 1999

Five new chiral macrocycles, **3a**−**e**, have been prepared by the acylation cyclization of chiral diamine dihydrobromide intermediates **2a**−**c** with 2,6-pyridinedicarbonyl dichloride in highly diluted solution at room temperature. The chiral diesters **1a**−**c** needed for the preparation of the macrocycles were obtained from condensation of corresponding *N*-(*Z*)-L-amino acids and 2,6-bishydroxymethyl pyridine in the presence of DCC and DMAP. The enantiomeric recognition of chiral macrocycles **3a**−**e** for D- and L-amino acid methyl ester hydrochlorides has been characterized by fluorescence spectra, which indicate that some of them exhibited significant chiral recognition for the enantiomers of D- and L-amino acid methyl ester hydrochlorides. The stoichiometry and binding constants of **3a**-L-Am_2 and **3c**-L-Am_2 complexes have been determined. An X-ray analysis of the chiral macrocycle **3b** show that the chiral ligand is rather rigid and strained.

Introduction

Molecular recognition exists in many biochemical processes. Some examples are antibody−antigen interactions, biocatalysis reactions, the DNA double helix, and the use of single enantiomeric forms of amino acids and sugars in metabolic pathways. The successful design, synthesis, and use of chiral macrocyclic ligands capable of the selective recognition of other species is of great interest to workers in catalysis,[1,2] separations,[3,4] enzyme mimics,[5−7] and other areas involving chiral molecular recognition. The study of the enantiomeric recognition of amines and protonated amines by chiral macrocyclic ligands[8−12] is of significance because these compounds are basic blocks of biological molecules with versatile abilities to form complexes with a variety of molecules. Careful characterization of such synthetic systems could lead to better understanding of natural systems. Cram and co-workers have reported enantiomeric recognition of organic ammonium salts by solvent extraction techniques,[13−15] transport of amides through liquid membranes,[16] and partial resolution of amino acids on silica gel or polystyrene to which chiral host materials are bonded.[17] Lehn and co-workers have found that reactivity of the thiolyzation reaction of certain *p*-nitrophenyl esters increased dramatically after the addition of chiral host molecules.[18] In 1987, the Nobel Prize was awarded to three pioneers in this field, Pedersen, Lehn, and Cram. From then on, molecular recognition has attracted more and more chemists. Our interest has focused on the enantiomeric recognition of the synthetic chiral macrocycles for D- and L-amino acid methyl ester hydrochloride (Am).

We here reported the synthesis of five new chiral macrocyclic receptors, **3a**−**e**, and their enantiomeric recognition for different amino acid methyl ester hydrochlorides (Am_1 = alanine-OMe·HCl; Am_2 = phenylalanine-OMe·HCl; Am_3 = histidine-OMe·2HCl). We also report the X-ray crystal structure of **3b** and the stoichiometry and binding constant of **3a**-L-Am_2 and **3c**-L-Am_2 complexes.

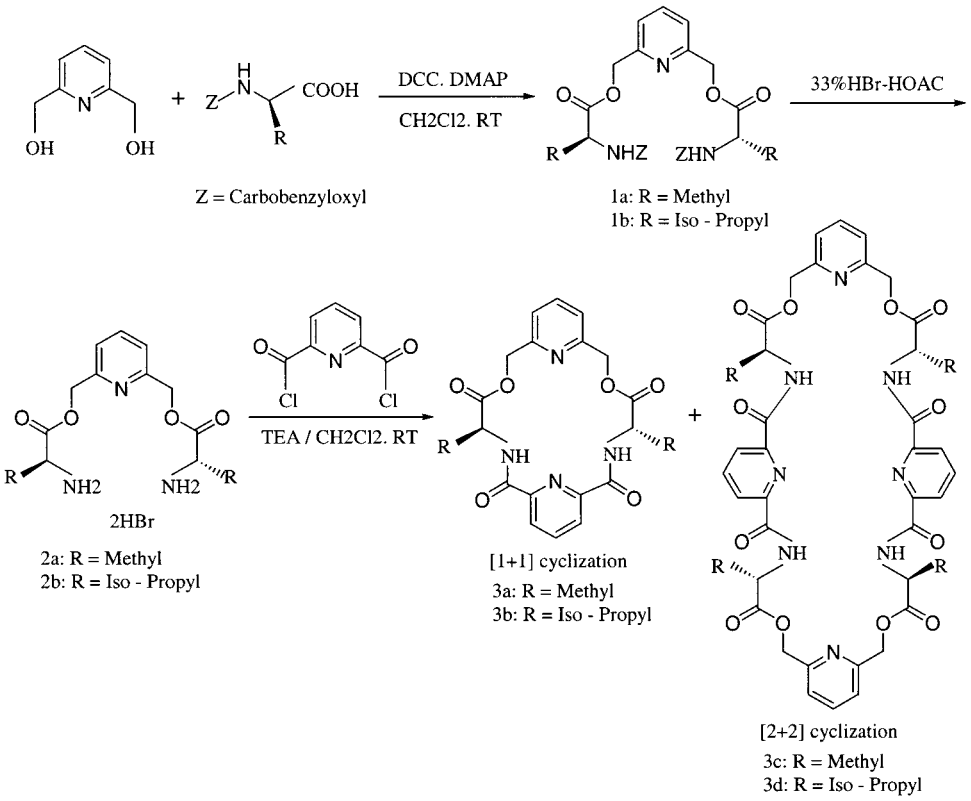
Results and Discussion

Five new chiral macrocycles were prepared by acylation of chiral diamine dihydrobromide intermediates **2a**−**c** with 2,6-pyridinedicarbonyl dichloride in highly diluted solution at room temperature as shown in Schemes 1 and 2.

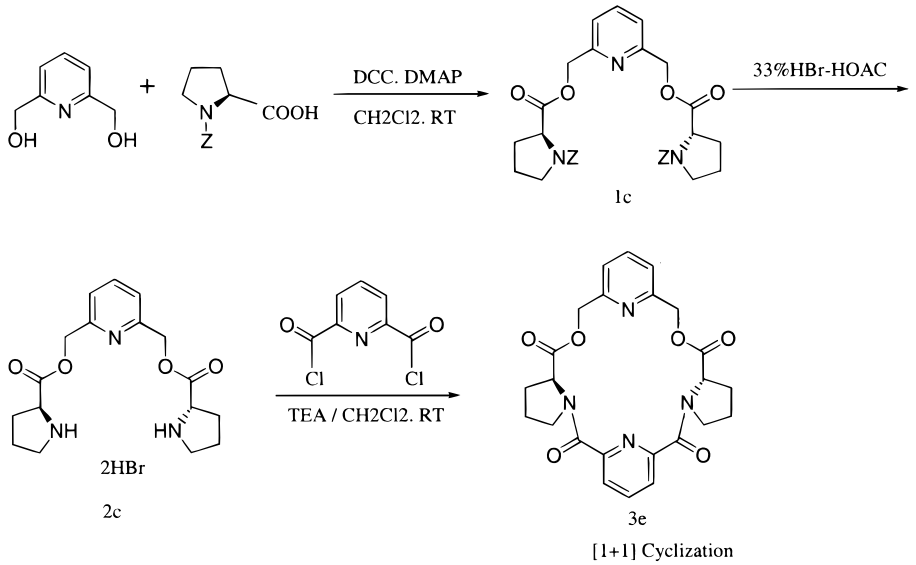
(1) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628.
(2) O'Malley, S.; Kodadek, T. *Organometallics* **1992**, *11*, 2299.
(3) Helgson, R. C.; Koga, K.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 3021.
(4) Gasparrini, F.; Misiti, D.; Borchardt, A.; Burger, M. T.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 4314.
(5) Breslow, R.; Czanik, A. W.; Lauer, M.; Leppkes, R.; Winkler, J.; Zimmerman, S. *J. Am. Chem. Soc.* **1986**, *108*, 1969.
(6) Talma, A. G.; Jouin, P.; De Vries, J. G.; Troostwijk, C. B.; Werumeus Buning, G. H.; Waninge, J. K.; Visscher, J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 3981.
(7) Chao, Y.; Cram, D. J. *J. Am. Chem. Soc.* **1976**, *98*, 1015.
(8) Huszthy, P.; Bradshaw, J. S.; Zhu, C. Y.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1991**, *56*, 3330.
(9) Naemura, K.; Mizo-oku, T.; Kamada, K.; Hirose, K.; Tobe, Y.; Sawada, M.; Takai, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1549.
(10) Echegoyen, L.; Martinez-Diaz, M. V.; de Mendoza, J.; Torres, T.; Vicente-Arana, M. J. *Tetrahedron* **1992**, *48*, 9545.
(11) Naemura, K.; Ogasahara, K.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 19.
(12) Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1111.
(13) Gokel, G. W.; Timko, J. M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1975**, 394.
(14) Lingenfelter, D. S.; Helgeson, R. C.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393.
(15) Artz, S. P.; deGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* **1985**, *50*, 1486.
(16) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4941.
(17) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035.
(18) Lehn, J. M.; Sirlin, C. *J. Chem. Soc., Chem. Commun.* **1978**, 949.

10.1021/jo9913715 CCC: $19.00
Published on Web 04/19/2000

Scheme 1. Preparation of Chiral Macrocycles 3a−d



Scheme 2. Preparation of Chiral Macrocycle 3e



The key intermediates **1a−c** were prepared from condensation of the corresponding *N*-(*Z*)-L-amino acids and 2,6-bishydroxymethyl pyridine in the presence of DCC and DMAP. The acylation of chiral diamine dihydrobromide **2a** with 2,6-pyridinedicarbonyl dichloride afforded [1 + 1] cyclization product **3a** and [2 + 2] cyclization product **3c** simultaneously. Similarly, **2b** gave [1 + 1] product **3b** and [2 + 2] product **3d**. However, for the reaction of **2c** with 2,6-pyridinedicarbonyl dichloride under the same conditions, only the [1 + 1] product **3e** was obtained, with no detectable [2 + 2] product. In general, the yields of [1 + 1] products are higher than those of the corresponding [2 + 2] products. Structures of these macrocycles are identified by ^{1}H NMR, MS, IR, and elemental analysis.

The enantiomeric recognition for D- and L-amino acid methyl ester hydrochlorides by these chiral macrocyclic receptors has been characterized by fluorescence spectra. It is evident from the differences in fluorescence intensity and fluorescence maximum that these chiral ligands exhibit significant chiral recognition for the enantiomers of amino acid methyl ester hydrochlorides.

As shown in Table 1, the enantiomeric recognition for D- and L-alanine methyl ester hydrochlorides (Am_1) by chiral macrocycles **3a−e** differs, among which **3c** and **3e** show chiral recognition better than that of the others.

Table 1. Chiral Recognition Data Determined by Fluorescence Spectra for the Interactions of Pyridine-Containing Chiral Ligands with Enatiomers of Amino Acid Methyl Ester Hydrochlorides

ligand	cation	λ_{max} (nm)	$\Delta\lambda$ (nm)	I/I_0 (rel intensity)
3a		350		
	D-Am_1	342	8	0.68
	L-Am_1	350		0.68
	D-Am_2	350	50	0.84
	L-Am_2	400		1.25
	D-Am_3	350	0	0.67
	L-Am_3	350		0.66
3b		392		
	D-Am_1	362	12	1.08
	L-Am_1	374		0.84
	D-Am_2	360	10	1.32
	L-Am_2	350		1.21
	D-Am_3	362	38	0.91
	L-Am_3	400		0.98
3c		348		
	D-Am_1	400	52	0.37
	L-Am_1	348		0.85
	D-Am_2	352	48	0.69
	L-Am_2	400		1.50
	D-Am_3	352	1	0.72
	L-Am_3	351		0.77
3d		392		
	D-Am_1	354	12	1.19
	L-Am_1	366		0.96
	D-Am_2	380	14	1.01
	L-Am_2	366		1.19
	D-Am_3	350	16	1.96
	L-Am_3	364		0.82
3e		350		
	D-Am_1	400	50	0.78
	L-Am_1	450		4.69
	D-Am_2	350	50	0.84
	L-Am_2	400		1.25
	D-Am_3	348	8	1.05
	L-Am_3	340		0.99

Shimadzu RF540 spectrofluorophotometer was used to recall all Fluorescence specrta. Equimolar amounts of ligand and salt was dissolved in the solvent (CH_3OH/CH_2Cl_2=1:3, v/v). Am_1 = Alanine Methyl Ester Hydrochloride.Am_2 = Phenylalanine Methyl Ester Hydrochloride. Am_3 = Histidine Methyl Ester Dihydrochloride.

Chiral ligands **3a**, **3c**, and **3e** all show excellent chiral recognition for enantiomers of phenylalanine methyl ester hydrochloride (Am_2), whereas **3b** and **3d** do not. As for D- and L-histidine methyl ester dihydrochloride (Am_3), only **3b** exhibits good recognition, and **3a**, **3c**, **3d**, and **3e** show little or no enantiomeric recognition.

The structure of chiral ligand **3b** has been determined by X-ray crystallography and is shown in Figure 1. Although the structure of the ligand allows for symmetry including a 2-fold axis, the conformation of the molecule in the solid state does not contain any such symmetry. The dihedral angle between the two aromatic pyridine rings is 37.4°, which makes the chiral ligand rather rigid and strained. The asymmetric steric structure of **3b** will contribute to chiral recognition.

CPK molecular model examination and molecular structure of compound **3b** show that the **3b**-L-Am and **3b**-D-Am complexes each have two possible conformations. In the two conformations of the **3b**-L-Am complex, there exists steric repulsion between the alkyl group on the chiral carbon of amino acid methyl ester hydrochloride and the isopropyl on the chiral carbon of compound **3b**. However, in one of the two possible conformations of the **3b**-D-Am complex, such steric repulsion is less severe. The different degree of steric repulsion leads to the

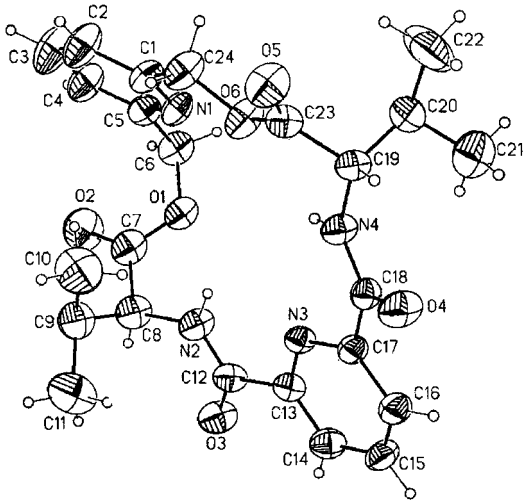


Figure 1. The molecular structure of compound **3b** with the atom-labeling scheme. Displacement ellipsoids are shown at the 50% probability level for non-H atoms; H atoms are shown as spheres of arbitrary radii.

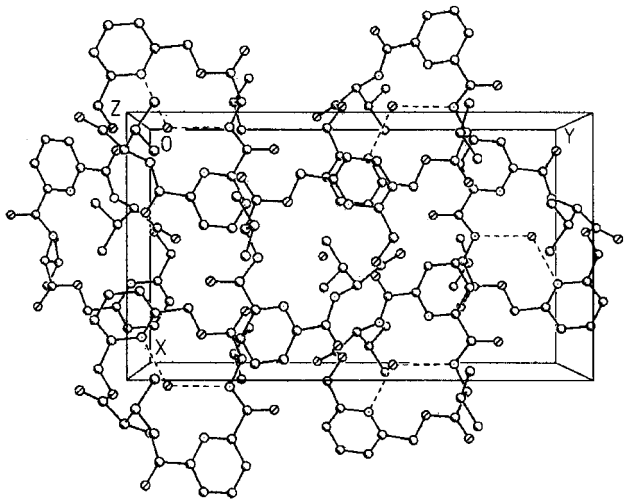


Figure 2. The packing diagram of the unit cell along the *C* axis of **3b** with H-atoms omitted.

different stabilities of **3b**-L-Am and **3b**-D-Am complexes. Therefore, we conclude that the different stability of the two diasteromeric complexes can result in enantiomeric recognition of compound **3b** for D- and L-amino acid methyl ester hydrochlorides. The facts have also demonstrated that structural complementarity between host and guest must be responsible for the enantiomeric recognition.

The X-ray structure of **3b** reveals that a water molecule is bonded to the chiral macrocycle by hydrogen bonds, as shown in Figure 2. It could be inferred that amino methyl ester hydrochlorides are anchored to the chiral macrocycles via tripod hydrogen bonding. It is likely that two pyridine nitrogen atoms and an amide nitrogen of compound **3b** with three hydrogen atoms of the ammonium cation are involved and that the interaction imparts stability to the diastereomeric complexes **3b**-D-Am and **3b**-L-Am. The fact that only **3c** and **3e** show marked chiral recognition for D- and L-Am_1 leads to the conclusion that the steric repulsive interaction between the alkyl groups on the chiral carbon of hosts and guests is responsible. In addition, we also noticed that chiral

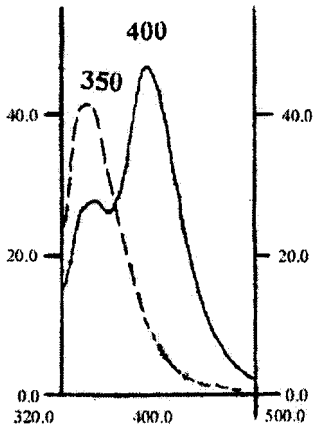


Figure 3. Fluorescence emission spectra changes of **3a** in the absence and the presence of equimolar amounts of L-Am_2: **3a** (- - -); **3a** + L-Am_2 (—). The excitation wavelength was 300 nm.

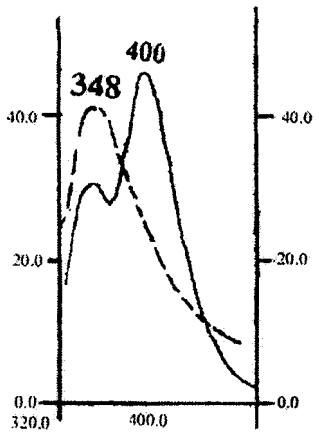


Figure 4. Fluorescence emission spectra changes of **3c** in the absence and the presence of equimolar amounts of L-Am_2: **3c** (- - -); **3c** + L-Am_2 (—). The excitation wavelength was 300 nm.

macrocycles **3a**−**e** each show better chiral recognition for Am_2 than for Am_1, and that suggests that not only steric effects and hydrogen bond but also $\pi-\pi$ stacking between the aromatic groups of hosts and guests may play an important role in chiral recognition. The reason that the chiral macrocycles **3a**, **3c**, and **3e** show little or no enantiomeric recognition for D- and L-Am_3 is not clear. The fact mentioned above indicates that hydrogen bonding and $\pi-\pi$ stacking between hosts and guests lead to the formation of the complex, while steric interaction contributes to enantiomeric recognition.

As shown in the Figure 3, when L-Am_2 is added to the system of **3a**, a new fluorescent emission peak for the **3a**-L-Am_2 complex can be observed at 400 nm. Similar fluorescence emission spectra have also been observed when L-Am_2 is added to the system of **3c** as shown in Figure 4; the peak at 400 nm is ascribed to the **3c**-L-Am_2 complex.

To determine the binding constant, we first tried to estimate the stoichiometry of the complex formed between chiral macrocycle and L-amino acid methyl ester hydrochloride. Figure 5 shows that the fluorescence emission intensity of the **3a**-L-Am_2 complex at 400 nm increases with increasing concentration of L-Am_2 until the mole ratio of L-Am_2 to the chiral macrocycle **3a** is near 0.92. However, as the mole ratio keeps on increasing, the maximum fluorescence emission intensity of the

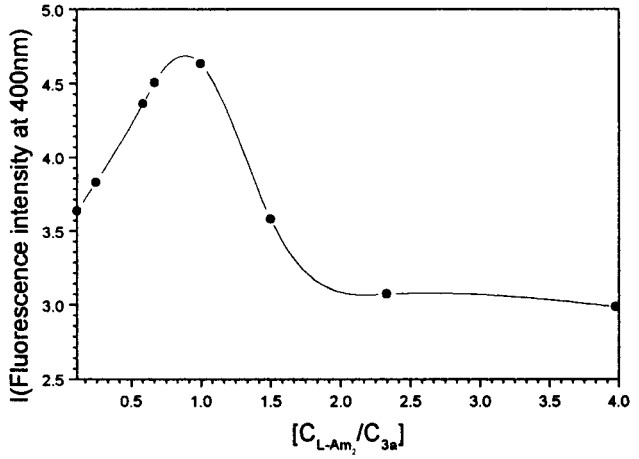


Figure 5. The Job's plot of fluorescence intensity (*I*) vs [L-Am_2]/[**3a**]; total moles 5×10^{-4}, the molar ratio of L-Am_2 to **3a** was varied: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2.

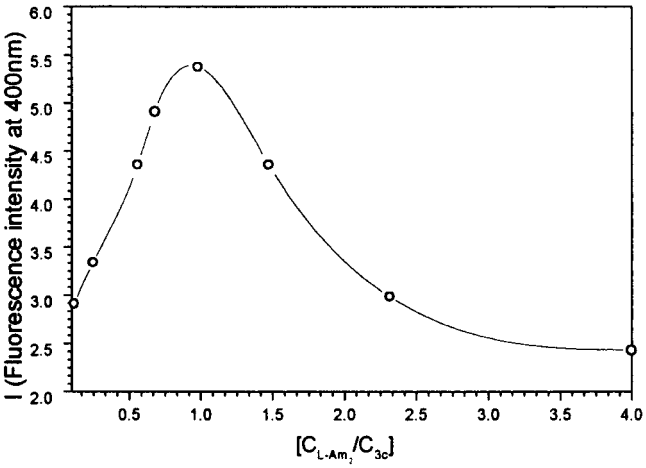


Figure 6. The Job's plot of fluorescence intensity (*I*) vs [L-Am]/[**3c**]; total moles 5×10^{-4}, the molar ratio of L-Am_2/**3c** was varied: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2.

3a-L-Am_2 complex decreases. A similar phenomenon was also found for the interaction of **3c** with L-Am_2, as shown in Figure 6. The maximum fluorescence emission intensity corresponded to a mole ratio of 1:1.

From results mentioned above, it can be concluded that the stoichiometry of **3a**-L-Am_2 and **3c**-L-Am_2 complexes is approximately 1:1. The binding of L-Am_2 to **3a** and **3c** may be described in terms of the Scatchard equation. Substituting for $\bar{N}$ and n in the Scatchard equation, $\bar{N}/[C] = n/K_d - \bar{N}/K_d$, [19] yields $F/[C] = F_\infty/K_d - F/K_d$, where [C] is the free L-Am_2 concentration and K_d is the dissociation constant. F is the measured fluorescence intensity, and F_∞ is the fluorescence intensity in the presence of infinite L-Am_2 concentration. K_d may be found from the slope of a linear plot of $F/[C]$ versus F.

A series of assay mixtures were made up to contain a constant concentration of **3a** and **3c** of 1×10^{-5} mol L^{-1}. These mixtures varied in L-Am_2 content from 1.65×10^{-4} mol L^{-1} to 8.00×10^{-4} mol L^{-1}. The results are shown in Figures 7 and 8. From the linear Scatchard plot, we can obtain the binding constant for the interaction of **3a** with L-Am_2 as 8.84×10^2 M^{-1} and that of **3c** with L-Am_2 as 9.52×10^2 M^{-1}.

(19) Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 660.

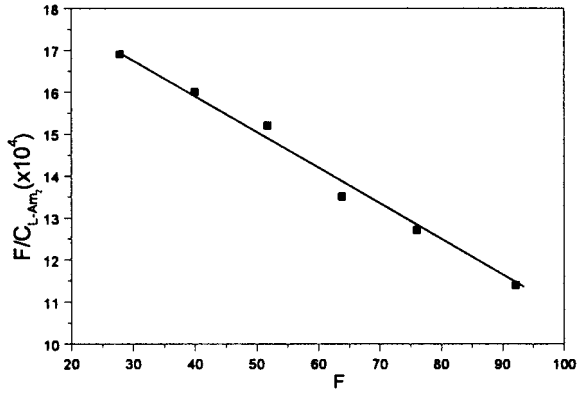


Figure 7. Scatchard plot of L-Am_2 binding to **3a**. Concentrations in the systems: [**3a**] 1.0×10^{-5} mol L^{-1}, [L-Am_2] = 2.5×10^{-4}, 3.4×10^{-4}, 4.0×10^{-4}, 5.5×10^{-4}, 6.8×10^{-4}, 7.5×10^{-4} mol L^{-1}, respectively.

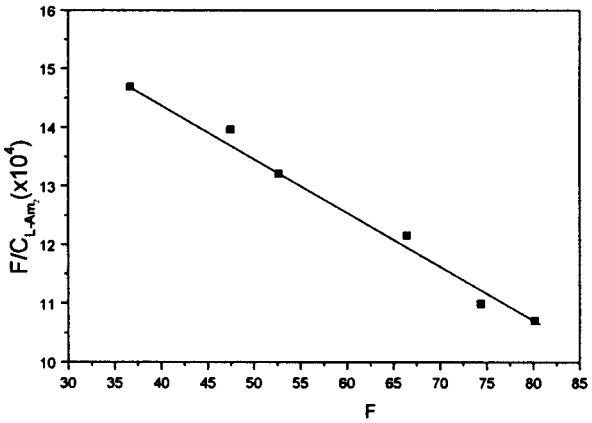


Figure 8. Scatchard plot of L-Am_2 binding to **3c**. Concentrations in the systems: [**3c**] 1.0×10^{-5} mol L^{-1}, L-Am_2 = 2.5×10^{-4}, 3.4×10^{-4}, 4.0×10^{-4}, 5.5×10^{-4}, 6.8×10^{-4}, 7.5×10^{-4} mol L^{-1}, respectively.

In summary, we can draw the following conclusions from the above-mentioned facts: (1) The chiral macrocycles **3a**−**e** show evident interaction with amino acid methyl ester hydrochloride, and some of them recognize D- and L- enantiomers of amino acid methyl ester hydrochloride remarkably. (2) It is a simple method to use fluorescent spectra to determine the degree of interaction of enatiomeric recognition for D- and L-enantiomers of amino acid methyl ester by these artificial receptors.

Experimental Section

Infrared spectra were obtained on a Bruker Vector22 instrument.^{1}HNMR spectra were recorded on a Bruker ARX 400 spectrometer. Chemical shifts are indicated in δ values (ppm) downfield from internal TMS. Multiplicities were recorded as s (singlet), d (double), t (triplet), and m (multiplet). FAB−mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Elemental analyses were carried out on Carlo-Erba-106 or Elementar Vario EL instruments. Melting points were taken on an XT-4 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC. Commercial grade solvents were used without further purification unless specified. CH_2Cl_2 was distilled from calcium hydride. Starting materials were purchased from the Acros chemical company unless otherwise noted. The 2,6-pyridinedimethanol and pyridine 2,6-bisdicarbonyl chloride were prepared as reported.[20,21]

Preparation of *N*-Carbobenzyloxyl-L-alanine Diester 1a. In dry CH_2Cl_2 (75 mL) were dissolved 2,6-pyridinedimethanol (500 mg, 3.6 mmol), *N*-carbobenzyloxyl-L-alanine (1.8 g, 8 mmol), 4-(dimethylamino)pyridine (200 mg, 1.62 mmol), and 1.3-dicyclohexylcarbodiimide (1.7 g, 8.16 mmol). After the reaction was stirred overnight at room temperature, the resulting white suspension was filtered. The filtrate was evaporated. The residue was chromatographed on silica gel using petroleum ether/ethyl acetate 1/1 as eluent to give a colorless oil (yield 1.5 g, 75.8%). $[\alpha]^{25}_D = -15.5$ (*c* 1, CH_2Cl_2). MS(FAB$^+$): m/z 550 $(M + H)^+$. ^{1}H NMR: δ 7.8 (m, 3H), 7.3 (m, 10H), 5.2 (m, 4H), 5.0 (s, 4H), 4.2 (t, 2H), 1.3 (d, 6H). IR (KBr): 3349, 1747, 1689, 1532, 1456, 1261, 1076 cm^{-1}. Anal. Calcd for $C_{29}H_{31}N_3O_8$ (549): C63.38, H5.69, N7.65, O23.28. Found: C63.08, H5.89, N7.78, O23.25.

Preparation of *N*-Carbobenzyloxyl-L-valine Diester 1b. Compound **1b** was prepared as described above as a colorless oil (yield 92%). $[\alpha]^{25}_D = -12.6$ (*c* 1, CH_2Cl_2). MS-(FAB)$^+$: *m/z* 606 (M + H). ^{1}H NMR: δ 7.8 (m, 3H), 7.3 (m, 10H), 5.2 (m, 4H), 5.0 (m, 4H), 4.0 (m, 2H), 2.11 (m, 2H), 0.9 (d, 12H). IR (KBr): 3371, 2966, 1713, 1593, 1527, 1459, 1228, 1192, 1044 cm^{-1}. Anal. Calcd for $C_{33}H_{39}N_3O_8$ (605): C65.44, H6.49, N6.94, O21.13. Found: C65.29, H6.54, N6.90, O21.27.

Preparation of *N*-Carbobenzyloxyl-L-proline Diester 1c. Compound **1c** was prepared as described above as a colorless oil (yield 92.4%). $[\alpha]^{25}_D = -81.0$ (*c* 1, CH_2Cl_2). MS-(FAB$^+$): *m/z* 602 $(M + H)^+$. ^{1}H NMR δ 7.26−7.56 (m, 13H), 5.27 (d, 2H), 5.11 (m, 6H), 4.51 (m, 2H), 3.64 (m, 4H), 2.26 (d, 2H), 2.11(brs, 2H), 1.95 (m, 4H). IR (KBr): 3328, 2944, 1751, 1706, 1417, 1353, 1169 cm^{-1}. Anal. Calcd for $C_{33}H_{35}N_3O_8$ (601): C65.88, H5.86, N6.98, O21.28. Found: C66.18, H5.89, N7.22, O20.98.

Preparation of L-Alanine Diester Diamine Dihydrobromide 2a. *N*-Carbobenzyloxyl-L-alanine diester (1 g, 1.8 mmol) was dissolved in 10 mL of 33% HBr−HOAc. The mixture was stirred at room temperature for 2 h, and the solution was the concentrated to dryness. After that, 10 mL of anhydrous ethyl ether was added to the residue, and the mixture was stirred for an additional 1 h and filtered to give a light yellow powder (yield 0.80 g, ca. 100%). MS(FAB$^+$): *m/z* 282 $(M + H)^+$. ^{1}H NMR: δ 8.43 (brs, 6H), 7.93 (t, 1H), 7.46 (d, 2H), 5.31 (m, 4H), 4.27 (t, 2H), 1.49 (d, 6H). IR (KBr): 3416, 2931, 2560, 1764, 1628, 1512, 1235, 1186, 1117 cm^{-1}.

Preparation of L-Valine Diester Diamine Dihydrobromide 2b. Compound **2b** was prepared as described above as a light yellow powder (yield ca. 100%). MS(FAB$^+$): *m/z* 338 $(M + H)^+$. ^{1}H NMR: δ 8.43 (brs, 6H), 7.93 (t, 1H), 7.52 (m, 2H), 5.36 (m, 4H), 4.06 (brs, 2H), 2.23 (m, 2H), 1.06 (m, 12H). IR (KBr): 3426, 2969, 1749, 1629, 1510, 1465, 1289, 1216, 1162, 1041 cm^{-1}.

Preparation of L-Proline Diester Diamine Dihydrobromide 2c. Compound **2c** was prepared as described above as a light yellow powder (yield ca. 100%). MS(FAB$^+$): *m/z* 334 $(M + H)^+$. ^{1}H NMR: δ 9.61 (brs, 2H), 8.99 (brs, 2H), 7.93 (t, 1H), 7.49 (d, 2H), 5.34 (m, 4H), 4.55 (m, 2H), 3.25 (m, 4H), 2.31 (m, 2H), 2.10 (m,2H), 1.96 (m, 4H). IR (KBr): 3416, 2925, 2548, 1890, 1753, 1649, 1626, 1569, 1391, 1242, 1197, 1064 cm^{-1}.

Preparation of Chiral Macrocyclic Ligands 3a and 3c. A solution of freshly prepared pyridine 2,6-bisdicarbonyl chloride (200 mg, 0.97 mmol) in dry dichloromethane (10 mL) was added dropwise to a well-stirred solution of diester diamine dihydrobromide **2a** (0.43 g, 0.97 mmol) and triethylamine (0.66 mL, 4.12 mmol) in dry CH_2Cl_2 (120 mL) at 0 °C over 30 min. The reaction mixture was stirred for an additional 12 h at room temperature. The resulting white suspension was filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel using dichlormethane/ethyl acetate/petroleum ether/methanol (2/1/0.1/0.1) as eluent to give

(20) Baker, W.; Buggle, K. M.; Mcomie, J. E. W.; Watkins, D. A. M. *J. Chem. Soc.* **1958**, 3594.
(21) Markees, D. G. *J. Org. Chem*. **1958**, *23*, 1030.

Table 2. Crystal Data and Structure Refinement for 3b

empirical formula	$C_{24}H_{28}N_4O_7$
formula weight	484.50
temperature	293(2) K
wavelength	0.71073 A
crystal system, space group	orthorhombic, *P*2(1) 2(1) 2(1)
unit cell dimensions	$a = 11.816(2)$ Å, $\alpha = 90°$ $b = 20.541(4)$ Å, $\beta = 90°$ $c = 10.066(2)$ Å, $\gamma = 90°$
volume	2443.1(8) Å^3
Z, calcd density	4,1.317 mg/m^3
absorption coefficient	0.098 mm^{-1}
F(000)	10 024
crystal size	0.45 mm × 0.35 mm × 0.15 mm
θ range for data collection	2.25° to 24.99°
index ranges	$0 \le h \le 14$, $0 \le k \le 24$, $0 \le l \le 11$
reflections collected/unique	2429/2429 [*R*(int) = 0.0000]
completeness to 2θ	24.99 99.0%
absorption correction	ψ scan
max and min transmisson	1.00000 and 0.5874
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	4517/5/512
goodness-of-fit on F^2	1.029
final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0598$, $WR_2 = 0.1514$
R indices (all data)	$R_1 = 0.0849$, $WR_2 = 0.1691$
absolute structure parameter	−1(2)
extinction coefficient	0.009(3)
largest diff. peak and hole	0.291 and −0.356 e/Å^3

3a (60 mg, 14.9%) and **3c** (20 mg, 2.48%) as white solids. **3a**: $[\alpha]^{25}_D = -79.64$ (*c* 1, CH_2Cl_2). Mp 186−188 °C. MS(FAB$^+$): *m*/*z* 413 (M + H)$^+$. ^{1}H NMR: δ 9.19 (d, 2H), 8.14 (m,3H), 7.76 (t,-1H), 7.40 (d, 2H), 5.21 (d, 2H), 5.08 (d, 2H), 4.70 (t, 2H), 1.52 (d, 6H). IR (KBr): 3397, 3295, 2993, 2939, 1741, 1679, 1652, 1528, 1452, 1239, 1136, 1113, 1059 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_4O_6$ (412): C58.25, H4.89, N13.59, O23.28. Found: C58.16, H4.98, N13.38, O23.48. **3c**: $[\alpha]^{25}_D = -26.8$ (*c* 1, CH_2Cl_2). Mp 118−120 °C. MS(FAB$^+$): *m*/*z* 825 (M + H)$^+$. ^{1}H NMR: δ 9.54 (d, 4H), 8.23 (m,6H), 7.69 (m,2H), 7.26 (d, 4H), 5.21 (m, 8H), 4.63 (m, 4H), 1.54 (d, 12H). IR (KBr): 3448, 2938, 1746, 1671, 1532, 1453, 1176, 1135, 1059 cm^{-1}. Anal. Calcd for $C_{40}H_{40}N_8O_{12}$ (824): C58.25, H4.89, N13.59, O23.28. Found: C58.02, H4.97, N13.37, O23.64.

Preparation of Chiral Macrocyclic Ligands 3b and 3d. Compounds **3b** and **3d** were prepared as described above as white solids. **3b**: yield 12.5%. $[\alpha]^{25}_D = -211.15$ (*c* 1, CH_2Cl_2). Mp 156−158 °C. MS(FAB$^+$): *m*/*z* 469 (M + H)$^+$. ^{1}H NMR: δ 8.5 (d, 2H), 8.20 (m, 3H), 7.83 (t, 1H), 7.44 (d, 2H), 5.49 (d, 2H), 5.05 (d, 2H), 4.66 (m, 2H), 2.32 (m, 2H), 0.85 (m, 2H). IR (KBr): 3410, 2964, 1751, 1682, 1519, 1443, 1373, 1279, 1228, 1043 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_4O_6$ (468): C61.53, H6.02, N11.96, O20.49. Found: C61.56, H6.31, N11.66, O20.47. **3d**: yield 5.2%. $[\alpha]^{25}_D = -60.7$ (*c* 1, CH_2Cl_2). Mp 84−86 °C. MS-(FAB$^+$): *m*/*z* 937 (M + H)$^+$. ^{1}H NMR: δ 9.05 (d, 4H), 8.21 (t, 6H), 7.76 (t, 2H), 7.36 (d, 4H), 5.23 (m, 8H), 4.45 (m, 4H), 2.31 (m, 4H), 0.90 (m, 24H). IR (KBr): 3409, 2965, 2875, 1745, 1684, 1524, 1462, 1447, 1391, 1372, 1315, 1187 cm^{-1}. Anal. Calcd for $C_{48}H_{56}N_8O_{12}$ (936): C61.53, H6.02, N11.96, O20.49. Found: C61.68, H6.10, N11.77, O20.45.

Preparation of Chiral Macrocycle Ligand 3e. Compound **3e** was prepared as described above as a white solid. **3e**: yield 17.3%. $[\alpha]^{25}_D = -213.36$ (*c* 1, CH_2Cl_2). mp 258−260 °C. MS(FAB$^+$): *m*/*z* 46 5(M + H)$^+$. ^{1}H NMR: δ 8.0 (m, 1H), 7.9 (t, 2H), 7.7 (t, 1H), 7.3 (d, 1H), 7.2 (d, 1H), 5.5 (m, 1H), 5.1 (m, 2H), 4.7 (s, 2H), 4.5 (d, 1H), 4.0 (s, 1H), 3.9 (s, 1H), 3.7 (s, 1H), 3.6 (s, 1H), 2.2 (s, 1H), 2.1 (d, 1H), 2.0 (m, 2H), 1.9 (m, 4H). IR (KBr): 3451, 2969, 2930, 1750, 1634, 1579, 1441, 1399, 1175, 1086 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_4O_6$ (464): C62.06, H5.21, N12.06, O20.67. Found: C62.21, H5.27, N11.85, O20.67.

X-ray Structural Determination of Compound 3b. Computing data collection: MSC/AFC Diffractometer Control Software (Molecular Structure Corporation, 1994). Cell refinement: MSC/AFC Diffractometer Control Software. Data reduction: SHELXS 97 (Sheldrick, G. M., 1997). Structure solution: SHELXS 97. Structure refinement: SHELXL 97. Molecular graphics: Interactive Molecular Graphics XP, Version 4.2 for MS DOS (1990). Crystal data and experimental conditions are shown in Table 2.

Acknowledgment. We thank Prof. Hongcheng Gao, Department of Technical Physics, Peking University, for his assistance in determining the stoichiometry and binding constants of the complexes and Prof. Xianglin Jin, Department of Chemistry, Peking University, for the X-ray crystal structure determination of compound **3b**.

Supporting Information Available: Fluorescence spectra data of enatiomeric recognition for D- and L-amino acid methyl ester hydrochloride (2.0×10^{-3} M) by chiral macrocycles **3a**−**e** (2.0×10^{-5} M) (25 °C, CH_3OH/CH_2Cl_2 = 1:3 v/v, host/guest = 1:1 mol/mol); atomic coordinates ($\times 10^4$) and equivalent istropic displacement coefficients (mtmex 10^5 nm^3) of chiral macrocyclic ligand **3b**, U_{eq} defined as one-third of the trace of the orthogonalized U_{ij} tensor (Table 3); and ring torsion angles (deg) of **3b** with esd values (Table 4). This material is available free of charge via the Internet at http://pubs.acs.org.

JO9913715