Enantiomeric Recognition in Host-Guest Complexation Using Chiral Bis-pyridino-18-crown-6 Ethers, by Electrospray Ionization Mass Spectrometry (ESI-MS) Enantiomer-Labelled (EL) Guest Method

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Enantiomeric recognition of chiral amino acids by synthetic and natural host compounds is one of the most challenging subjects in modern host-guest chemistry.[1] Host-guest chiral recognition plays an important role in biological process, resolution of enantiomers, and asymmetric catalysis reactions.[2] A number of synthetic model compounds have been designed and synthesized as chiral host molecules that help chemists understand the basis of the mechanism of host-guest complexations and their chiral recognitions. Hence, the successful design, synthesis, and application of chiral macrocyclic ligands with the selective recognition of the guests have attracted much attention for the investigations of catalysis,[3] separations,[4] and enzyme mimics.[5] To determine the chiral recognition of these hosts, various methods of extraction/NMR, extraction/polarimetry, NMR titration, variable temperature NMR, nuclear overhauser effects (NOE), UV-vis titration, HPLC, capillary electrophoresis, transport, and membrane electrode have been used.[6] A high degree of chiral recognition was observed in these studies.

In the host-guest complex systems, chiral recognition has been detected by Sawada and his co-workers using fast atom bombardment mass spectrometry (FAB-MS)[7] and electrospray ionization mass spectrometry (ESI-MS).[8] In this reports, ESI-MS enantiomer-labeled (EL) guest method is utilized. This method requires the isotopic labeling of guest (G^+) enantiomers, and detects the complexation of a target host (H) compound with a 1:1 mixture of the unlabeled (G_R^+) and labeled enantiomer guests ($G_{S\text{-}dn}^+$). The peak intensity ratio, $I[(H + G_R)^+]/I[(H + G_{S\text{-}dn})$, of two diastereomeric host-guest complex, which appeared simultaneously with n mass-unit difference in one ESI mass spectrum, was abbreviated as '*IRIS*' for shot and adopted here as a critical measure for detecting chiral recognition ability. This method is a direct and operationally simple method, and it is a major feature of the stream needed for rapid screening of enantiomeric recognition.

We studied the synthesis of chiral bis-pyridino-18-crown-6 ethers,[9] and the chiral recognition of α-amino acids and chiral amines by FAB-MS EL guest method,[9a] UV-vis titration,[9b] and ^{1}H-NMR titration.[9c] Our interest has been focused on the enantiomeric recognition of amino acids by utilizing synthetic chiral bis-pyridino-18-crown-6 ether. We report herein the synthesis of chiral bis-pyridino-18-crown-6, (*R*,*R*,*R*,*R*)-**5** and **6** with tetraethyl tetracarboxylate and tetramethyl tetracarboxamide groups as chiral barriers, and their enantiomeric recognition of several amino acid methyl ester hydrochlorides (**7**-**16**) by ESI-MS EL guest method. The *IRIS* values for the enantiomeric recognition of amino acid methyl ester hydrochlorides (**7**-**16**) using chiral bis-pyridino-18-crown-6 ether, (*R*,*R*,*R*,*R*)-**5** and **6**, were detected by ESI-MS EL guest method.

Experimental Section

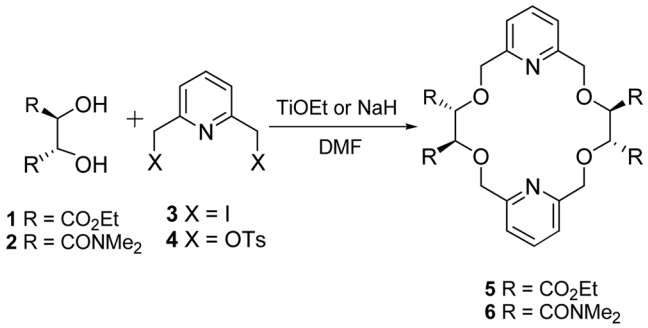
General. ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on a Varian Unity Plus 5 (500 MHz). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer under fast atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix, in the Korea Basic Science Institute (Seoul), Korea. Column chromatography was performed using E. Merck silica gel (60, particle size 0.040-0.063 mm) and alumina 60 (Merck, 70-230 mesh). Analytical thin layer chromatography (TLC) was performed using pre-coated TLC plates with silica Gel 60 F_{254} (E. Merck no. 5715-7) and alumina 60 (Merck, 70-230 mesh). All reactions were carried out under argon atmosphere with dry solvent, unless otherwise noted. Dimethyl formamide (DMF) were distilled from sodium/benzophenone immediately prior to use and acetone was dried from calcium chloride.

All chemicals were reagent grade unless otherwise specified. Commercial samples (Sigma-Aldrich) of (*D*)-methyl alaninate hydrochloride, (*D*)-methyl methionate hydrochloride were used without purification. All other amino acid methyl ester hydrochlorides were synthesized and purified according to the standard[7] methods using commercially available (Sigma-Aldrich) (*D*)-amino acids and (*L*)-amino acids. In case of (*S*)-amino acids, the amino acids were treated CD_3OD and anhydrous hydrochloride gas to generate

the isotopic labelled (*S*-d_3)-amino acid methyl ester hydrochlorides. The 2,6-bis(iodomethyl)pyridine (**3**),[9d] 2,6-bis-(benzenesulfonylmethyl)pyridine (**4**) was prepared using the reported methods.[11]

Synthesis of Tetraethyl (4*R*,5*R*,15*R*,16*R*)-3,6,14,17-tetraoxa-23,24-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaene-4,5,15,16-tetracarboxylate (5). To a stirred solution of diethyl-*L*-tartrate (**1**) (7 g, 33.95 mmol) in dry DMF (700 ml) at room temperature under argon was added thallous ethoxide (16.9 g, 67.9 mmol) over a period of 15 min and the resulting white suspension was stirred for 30 min. A solution of 2,6-bis(iodomethyl)pyridine (**3**) (16 g, 52.28 mmol) in dry DMF (50 mL) was added dropwise and the mixture stirred for a further 1 h. Then temperature was raised to 70 °C in about 1 h and maintained at that temperature for 12 h. The orange thallous iodide was removed by filteration through a pad of sand (3 cm height) over alumina (5 cm height) on *Büchnner* funnel, and concentrated under reduced pressure. The residue was purified by chromatography on alumina 60 (Merck, 70-230 mesh, R_f 0.31, 100% $CH_2Cl_2 \rightarrow$ 3% MeOH-CH_2Cl_2) to give (*R*,*R*,*R*,*R*)-**5** (4.40 g, 21%) as a pale yellow oil.

$[\alpha]_D^{24}$ = +78.5° (c = 0.1, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.32 (t, 12 H, J = 6.8 Hz), 4.16-4.28 (m, 8 H), 4.4 (s, 4 H), 4.7 (s, 8 H), 7.27 (d, 4 H, J = 6.6 Hz), 7.60 (t, 2 H, J = 7.6 Hz; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.0, 61.4, 73.5, 79.2, 120.8, 137.1, 156.8, 169.0; HRMS (FAB, NBA) calcd 619.2503 for $C_{30}H_{38}N_2O_{12}$ $(M + H)^+$, found 619.2499.



Scheme 1. Synthetic Routes for Chiral Bis-pyridino-18-crown-6 Ethers.

Results and Discussion

Since the symmetry of macrocycle is crucial for chiral molecular recognition, we focused on synthesis of C_2-symmetirc chiral bis-pyridino-18-crown-6 ether (*R*,*R*,*R*,*R*)-**5** and **6**. The synthesis of (*R*,*R*,*R*,*R*)-**5** and **6** is summarized in Scheme 1. The new chiral bis-pyridino-18-crown-6 ether (*R*,*R*,*R*,*R*)-**5** and **6**, substituted with tetraethyl tetracarboxylate and tetramethyl tetracarboxamide groups as chiral barriers, were selected as the host compound. The synthesis of (*R*,*R*,*R*,*R*)-**5** and **6** is based on a modified *Williamson* synthesis of ethers derived that described by Seebach *et al.*[12] Chiral bis-pyridino-18-crown-6 ether (*R*,*R*,*R*,*R*)-**5** and **6**[10] were prepared from diethyl-*L*-tartrate (**1**) or *N*,*N*,*N*′,*N*′-tetramethyl tartaramide (**2**) with 2,6-bis(iodomethyl)pyridine (**3**) in the presence two equivalent of thallous ethoxide as the base under high dilution conditions, which yields are 19-21% respectively. However, when the sodium hydride as the base was used in the synthesis of (*R*,*R*,*R*,*R*)-**5** and **6**, the yield dropped in 8-9%, respectively. When the di-*p*-toluenesulfonate **4** was used, instead of the diiodide **3**, in the synthesis of (*R*,*R*,*R*,*R*)-**5** and **6**, the yield also decreased from 21% to 7%, and no appreciable alkylation with the corresponding dichloride occurred. The structures of (*R*,*R*,*R*,*R*)-**5** and **6** were identified by ^{1}H-NMR, ^{13}C-NMR, and FABMS.

The enantiomeric recognition of amino acid methyl hydrochlorides by chiral bis-pyridino-18-crown-6 ether (*R*,*R*,*R*,*R*)-**5** and **6** have been evaluated by ESI-MS EL guest method. We used (*R*,*R*,*R*,*R*)-**5** and **6** as the host and amino acid methyl ester (CH_3 and CD_3) hydrochlorides (**7**-**16**) as the guest in Figure 1. The *IRIS* values, I $[(H + G_R)^+]$ / I $[(H + G_{S\text{-}d3})^+]$, were detected by the ESI-MS EL guest method using various amino acid methyl ester hydrochlorides were summarized in Table 1, and the values are corrected by the natural abundance of the (M+3) isotope. *IRIS* values in Table 1 can be classified as following three types, (1) *IRIS* > 1.0 means that a given chiral host binds more strongly the (*R*)-enantiomer of a given guests; (*R*)-enantiomer preference. The larger the $I_R/I_{S\text{-}dn}$ value from unity, the higher the degree of chiral recognition of the host. (2) In contrast, *IRIS* < 1.0 means that a given chiral host binds more strongly the (*S*)-enantiomer of a given guests; (*S*)-enantiomer preference. (3) *IRIS* = 1.0 ± 0.05 means that a given chiral host compound

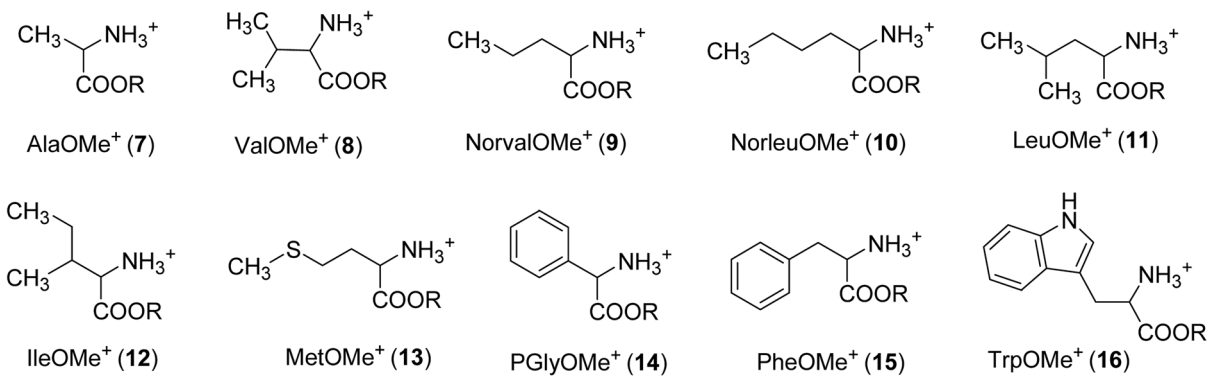


Figure 1. The chemical structure of amino acid methyl ester hydrochlorides (CH_3 and CD_3 esters) (**7**-**16**) used in experiments.

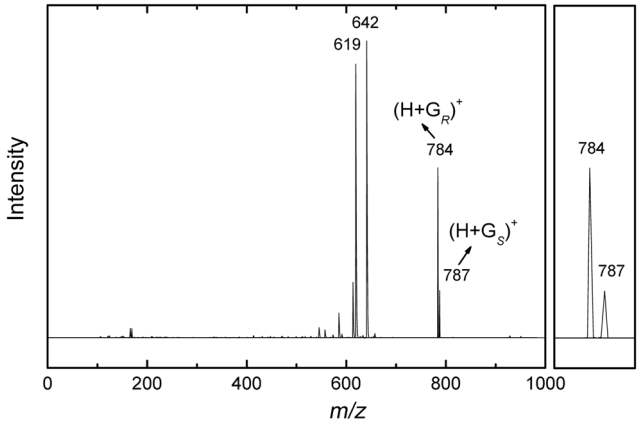


Figure 2. An expansion of the ESI mass spectrum for the complexation between (*R*,*R*,*R*,*R*)-**5** and 1: 1 mixture of (*R*)-**13** and (*S*)-**13**-d_3.

cannot differentiate the chirality of the given guests.[8] The representative ESI-MS spectrum for the complexation between (*R*,*R*,*R*,*R*)-**5** and 1:1 mixture of (*R*)-**13** and (*S*)-**13**-d_3 was shown in Figure 2. As shown in the Table 1, the (*R*,*R*,*R*,*R*)-**5** exhibited *IRIS* values range from 1.30 to 7.66, and showed (*R*)-enantiomer preference toward all guests. (*R*,*R*,*R*,*R*)-**5** also showed the highest degree of (*R*)-enantiomer predominance toward guest **7** in this experiments. Especially, (*R*,*R*,*R*,*R*)-**5** showed a characteristic pattern when R is only primary alkyl group (guests **7**, **9**, **10** and **13**) in amino acid methyl ester hydrochlorides (RCH(COOMe)NH_3^+). As R alkyl chain length increases (guest **7** → guest **13**), *IRIS* values showed a slight decline (7.66 → 1.94). In the same way, (*R*,*R*,*R*,*R*)-**6** evaluated from 0.22 to 2.31 in *IRIS* values for chiral recognition, and showed inconsistent preference as compared with (*R*,*R*,*R*,*R*)-**5.**

The origin of the enantiomeric recognition for the complex between host and guest has been estimated on the basis of complex ion structure. We performed molecular modeling and an optimization of these complexes by Spartan '02 software with semi-empirical force (PM3).[13] The minimized conformations of the complexes between (*R*,*R*,*R*,*R*)-**5**, **6** and LeuOMe$^+$ **(11)** are shown in Figure 3. The complexes are basically possible to have tripod hydrogen bonding between the one nitrogen and two oxygen of the host and three hydrogen of the ammonium cation of the guest.[9] As expected from PM3 calculation, tetraethyl tetracarboxylate group of (*R*,*R*,*R*,*R*)-**5** is located almost upper side relative to the macrocyclic ring plane in Figure 3. Since (*R*,*R*,*R*,*R*)-**5** is expected to be

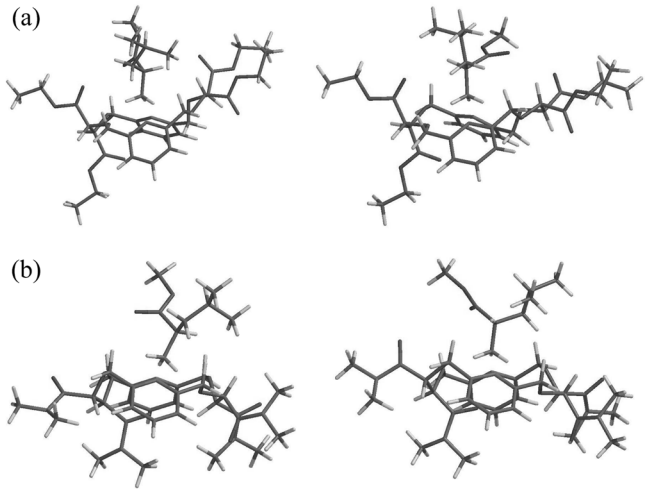


Figure 3. Structures of the diasteromeric host-guest complex ions between host (*R*,*R*,*R*,*R*)-**5**, **6** and guest LeuOMe$^+$ **(11)** estimated from PM3 calculations (a side view): (a) host (*R*,*R*,*R*,*R*)-**5** plus guest (*R*)-**11** (left) and host (*R*,*R*,*R*,*R*)-**5** plus (*S*)-**11** (right), (b) host (*R*,*R*,*R*,*R*)-**6** plus guest (*R*)-**11** (left) and host (*R*,*R*,*R*,*R*)-**6** plus (*S*)-**11** (right).

conformationally less mobile than (*R*,*R*,*R*,*R*)-**6**, tetraethyl tetracarboxylate group will effectively block the complexation space, and serve as an efficient chiral barrier for the complexation. It is indicated that the complexes with (*R*,*R*,*R*,*R*)-**5** have more steric repulsion between the alkyl or aromatic group on the chiral carbon of the amino acid methyl ester hydrochloride and tetraethyl tetracarboxylate of the host as compared with tetramethyl tetracarboxamide of the (*R*,*R*,*R*,*R*)-**6**. Based on the molecular mechanics and experimental result, it is possible to say that (*R*,*R*,*R*,*R*)-**5** forms more stable complex and shows enantiomeric recognition toward amino acid methyl ester hydrochlorides as compared to the case of (*R*,*R*,*R*,*R*)-**6**.

In conclusion, the synthesis and enantiomeric recognition of chiral bis-pyridino-18-crown-6 ether, (*R*,*R*,*R*,*R*)-**5** and **6**, with tetraethyl tetracarboxylate and tetramethyl tetracarboxamide groups as chiral barriers are reported. The *IRIS* values for the enantiomeric recognition of amino acid methyl ester hydorchlorides (**7-16**) using chiral bis-pyridino-18-crown-6 ether, (*R*,*R*,*R*,*R*)-**5** and **6**, were detected by electrospray ionization (ESI) mass spectrometry (MS) with the enantiomer-labeled (EL) guest method. (*R*,*R*,*R*,*R*)-**5** forms more stable complexes and has a good enantiomeric recognition toward amino acid methyl ester hydrochlorides as compared to the case of (*R*,*R*,*R*,*R*)-**6**.

Table 1. *IRIS* Values[a] using the ESI-MS Guest Method[b]

Host	Guest[c]									
	7	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
5	7.66	1.65	3.41	2.36	5.59	1.30	1.94	4.17	1.80	3.44
6	0.22	0.82	2.27	0.52	1.06	2.31	0.81	0.52	1.68	2.23

[a]The values are corrected by the natural abundance of the corresponding (M + 3). For one measurement, the IRIS value was obtained from an average of those of three times (Nos. 10, 20, 30). [b]Concentration condition; [G^+] = 0.909 mol dm^{-3}([G_R^+] = [G_S^+] = 0.454 mol dm^{-3}), [H] = 0.0909 mol dm^{-3}, [G^+]/[H] = 0.909/0.0909 mol dm^{-3} = 10. [c]amino acid methyl ester hydrochloride salt.

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