Chiral Molecular Recognition in Fast Atom Bombardment Mass Spectrometry (FAB-MS) Enantiomerlabeled (EL) Guest Method Using New Chiral Bis-pyridino-18-crown-6

Jae-Kon Kim, Jong Gun Lee, Sungeun Lee, Jung Ju Seo,[†] Jongki Hong,[‡] and Hongsuk Suh[*]

*Department of Chemistry and Chemistry Institute for Functional Materials, Pusan National University,
Kumjungku Jangjundong San 30, Pusan 609-735, Korea*
[†]Korea Basic Science Institute, Sungbookku Anamdong 5ka 102, Seoul 136-701, Korea
[‡]Korea Basic Science Institute, Yusungku Yeoeundong 52, Taejeon 305-333, Korea
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Recently, in the more highly structured host-guest complex systems, chiral recognition has been detected by Sawada and his co-workers using fast atom bombardment mass spectrometry (FAB-MS) and electrospray ionization mass spectrometry (ESI-MS).[1-2] In this reports, the enantiomer-labeled (EL) guest method is utilized. This method requires isotopic labeling of one of the 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 ($G_{S\text{-}dn}^+$). Chiral recognition of a given host is simply measured with a given guest from the peak intensity ratio of the two diastereomeric host-guest complex ions as I [(H + G_R^+)]/I [(H + $G_{S\text{-}dn}^+$)] = $I_R/I_{S\text{-}dn}$ *IRIS*. Therefore, (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 cannot differentiate the chirality of the given guests.

The new chiral crown ether host **5** was designed and synthesized in such a way that the interaction options available for the incoming chiral guest are limited. The synthesis of the new chiral bis-pyridino-18-crown-6 **5**, substituted with urea and diphenyl substituents, is summarized in Scheme 1.

Diol **1** was synthesized from (S)-(+)-mandelic acid over 5 steps by using the method which was reported by us previously.[3] Diol **1** was coupled with diiodide **8** using sodium hydride in THF to obtain bispyridino-18-crown-6 **3** in 58% yield. The diiodide **8** was prepared from chelidamic acid (**6**). Esterification of the chelidamic acid (**6**), by using ethanol and sulfuric acid, followed by alkylation, by using 7-bromo-heptanenitrile and potassium carbonate, provided compound **7** in 65% yield. The resulting ester **7** was treated with sodium borohydride followed by thionyl chloride and sodium iodide to generate the diiodide **8** in 45% overall yield.

The nitrile group of the macrocycle **3** was reduced to amine **4** with LiAlH$_4$ and diethyl ether in 57% yield. Treatment of the reduced primary amine **4** with ethyl isocyanate

provided the desired chiral host **5**[4] substituted with urea and diphenyl groups as final product in 30% yield.

Another new chiral bis-pyridino-18-crown-6 **2**, with only
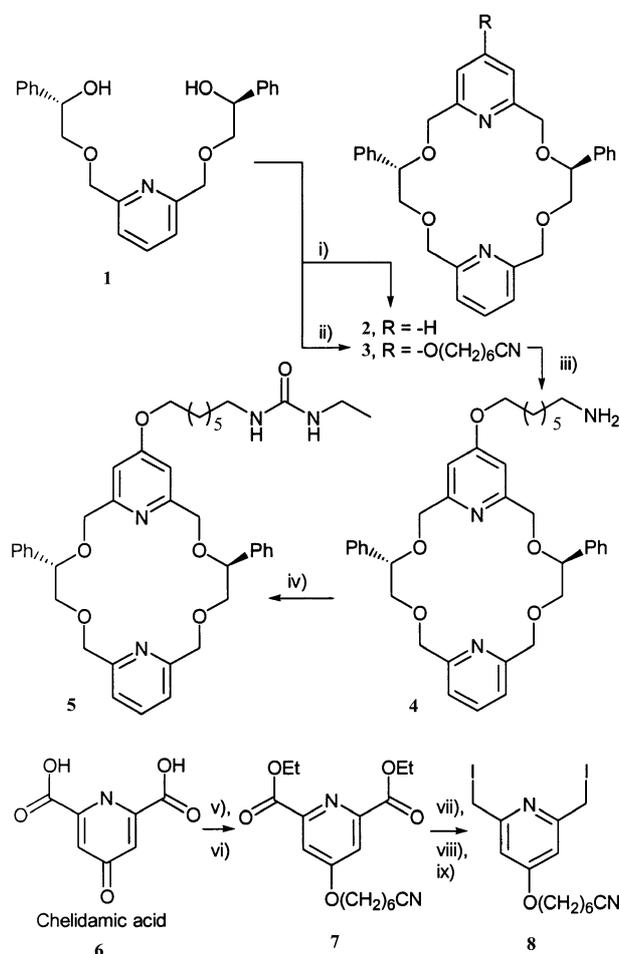
Scheme 1. *Reaction conditions*; i) 2,6-bis(iodomethyl)pyridine, NaH, THF, room temp. to reflux, 47%; ii) **8**, NaH, THF, room temp. to reflux, 58%; iii) LiAlH$_4$, CH$_2$Cl$_2$/diethyl ether, 0 °C to room temp., 8 h, 57%; iv) ethyl isocyanate, CH$_2$Cl$_2$, room temp., 8 h, 30%; v) EtOH, *Conc*. H$_2$SO$_4$ (cat), reflux, 80 °C, 24 h, 89%; vi) Br(CH$_2$)$_6$CN, K$_2$CO$_3$, acetone, room temp. to 80 °C, 15 h, 73%; vii) NaBH$_4$, EtOH, 0 °C to room temp., 4 h, 58%; viii) SOCl$_2$, CH$_2$Cl$_2$, 0 °C to 50 °C, 93%; ix) NaI, acetone, reflux, 70 °C, 12 h, 83%.

diphenyl substituents, was also synthesized to be compared with the chiral crown ether **5**. Diol **1** was coupled with 2,6-bis(iodomethyl)pyridine[13] using sodium hydride in THF to obtain bispyridino-18-crown-6 **2** in 47% yield.

A typical solution of FAB-MS sample was prepared by mixing the following three solutions: (1) 5 μL portion of a 0.3 M MeOH solution of 1 : 1 mixture of unlabeled (*R*) and labeled (*S-d3*) ester guests ([G_R^+] = 0.15 M and [G_{S-d3}^+] = 0.15 M), (2) 5 μL portion of a 0.05 M CHCl$_3$ solution of the given host, and (3) 30 μL of the *m*-nitrobenzyl alcohol (NBA) matrix. After MeOH and CHCl$_3$ being evaporated in the ion source, the concentrations in NBA were calculated to be [H] = 0.0083 M, and [G^+] = 0.05 M ([G_R^+] = 0.025 M, [G_{S-d3}^+] = 0.025 M), which means [H] : [G_R^+] : [G_S^+] = 1 : 3 : 3. All of the amino acid methyl ester hydrochlorides, guests, were synthesized and purified according to the previously reported methods[5] using commercially available (Sigma-Aldrich) (*R*)-amino acids and (*S*)-amino acids. In case of (*S*)-amino acids, the amino acids were treated with CD$_3$OD and anhydrous HCl gas to generate the isotopic labeled (*S-d3*)-amino acid methyl ester hydrochlorides.

Results and Discussion

The structures of newly synthesized chiral macrocycles **5** and **2** were identified by ^{1}H-NMR, ^{13}C-NMR, and FAB-MS. The new chiral bis-pyridino-18-crown-6 **5**, substituted with urea and diphenyl groups, was selected as the host compound. Another new chiral bis-pyridino-18-crown-6 **2**, with only diphenyl substituents, was also used as the host compound to be compared with the macrocycle **5**. Isotopic labeled (*S-d3*)-methyl ester hydrochlorides and unlabeled (*R*)-amino methyl ester hydrochlorides of leucine, phenylglycine, and phenylalanine were chosen as the chiral guest compounds. The length of the chain which connects the urea and the macrocycle was chosen by using HyperChem for the optimal binding of the final macrocycles with the amino acid methyl ester hydrochlorides.[6]

The results of the chiral recognition properties of the hosts toward the employed guests were listed in Table 1. The chiral host **5** exhibits IRIS values ranging from 1.12 to 1.44, which means preference of binding with (*R*)-enantiomer as like our expectation. In case of the chiral host **2**, the IRIS values for chiral recognition were lower than those of the host **5**.

The complex, between the macrocycle **5** and amino acid methyl ester hydrochloride, is 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. In addition to this, another hydrogen bonding interac-

Table 1. IRIS values of synthesized hosts toward representative amino acid methyl ester hydrochloride guests by the FAB-MS EL method[a]

Host	Guest		
	LeuOMe$^+$	PGlyOMe$^+$	PheOMe$^+$
2	1.18	1.28	1.07
5	1.25	1.44	1.12

[a]Averaged with two measuring using two sample solutions prepared separately. For one measurement, the IRIS value was obtained from an average of those of three scans (Nos. 10, 20, 30).

tions between urea hydrogens of the host and ester oxygen of the guest could be possible to exist. With these possible hydrogen bonding interactions between the chiral macrocycle **5** and the amino acid methyl ester hydrochloride, the complex with the (*R*)-amino acid methyl ester hydrochloride will have less severe steric repulsion between the alkyl group on the chiral carbon of the guest and the phenyl group of the host as compared to that with the (*S-d3*)-amino acid methyl ester hydrochloride.

In summary, we successfully synthesized new chiral macrocycles, and evaluated their ability of chiral molecular recognition using fast atom bombardment mass spectrometry (FAB-MS) enantiomerlabeled (EL) guest method. The host showed (*R*)-enantiomer preference as like our expectation.

References and Notes

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4. Compound **5**: yellow powder, mp 146-147 ℃, FAB-MS (NBA) *m/z* 683 (MH$^+$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.87-1.04 (m, 5H), 1.09-1.5 (m, 8H), 2.65 (t, 2H, *J* = 7.8 Hz), 2.80-3.30 (m, 4H), 3.67 (dd, 2H, *J* = 2.4, 10 Hz), 3.84 (t, 2H, *J* = 7.8 Hz), 4.26 (dd, 2H, *J* = 8.4, 3 Hz), 4.48-4.99 (m, 10H), 5.80 (br s, 2H), 6.50 (s, 2H) 7.07-7.66 (m, 12H), 7.69 (t, 1H, *J* = 7.8); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.1, 159.1, 158.9, 157.4, 155.6, 138.1, 137.1, 129.0, 128.5, 127.4, 126. 8, 120.5, 107.4, 79.8, 77.6, 77.2, 76.3, 75.0, 72.3, 70.8, 67.0, 39.9, 34.6, 30.1, 28.8, 28.5, 26.6, 25.6, 15.4.

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