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New Artificial Host Compounds Containing Galactose End Groups for Binding Chiral Organic Amine Guests: Chiral Discrimination and Their Complex Structures

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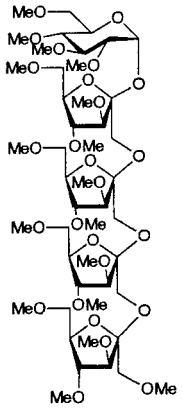
New linear host (**1**) and cyclic hosts (**2** and **3**), which have galactopyranose skeletons as chiral origins and oxyethylenes skeletons as binding sites, were designed based on the structural features extracted from the fructo-oligosaccharide derivatives, having a large chiral discrimination ability, and were then synthesized. These hosts showed chiral discrimination toward chiral organic ammonium salts. For example, the chiral discrimination ability (the ratio of association constants: K_R/K_S) of host **1**, which has the highest value among them, was $K_R/K_S = 3$ for Trp-O-^{i}Pr$^+$ and $K_R/K_S = 0.7$ for 1-(1-naphthyl)ethylammonium (NEA$^+$) at 298 K in $CHCl_3$. It was clarified that host **1** changed the conformation from a linear structure to the pseudo-ring structure by complexation with cations such as alkali metallic ions and chiral organic ammonium ions. The ^{1}H NMR induced shifts of host **1** by adding the NEA$^+$ guests showed that the host−guest complex structures are clearly different, depending upon the chirality of the guest; in the complex with (*R*)-NEA$^+$, the naphthyl group of the guest is located above the oxyethylene skeleton of the host and in the complex with (*S*)-NEA$^+$, and the naphthyl group is located between the edges of the pseudo-ring of the host. The clearly different structure of the complex of host **1** with NEA$^+$ may be caused by the dynamic molecular recognition, thus the induced-fitting mechanism.

Introduction

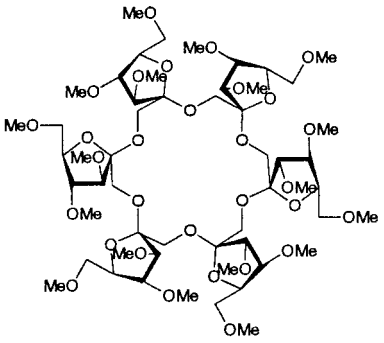
Molecular recognition, especially chiral recognition, is one of the fundamental and significant processes in living systems. Recently, it has been determined that sugar chains play important roles in molecular recognition on the surfaces of cells and enzymes in vivo.[1]

We have now clarified the chiral discrimination of various permethylated oligosaccharides toward organic amines and their complex structures.[2] It was determined that permethylated fructo-oligosaccharides, especially the permethylated 1^F−fructonystose (MeFruNys), have a remarkable chiral discrimination ability (Chart 1).[2b] The structural features of their oligosaccharides are as follows: (i) linear structure, (ii) saccharide moiety as chiral origin, and (iii) oxyethylene skeletons as binding site for cation guests. However, cyclic fructo-oligosaccharides (MeCF6) showed only a low chiral discrimination ability through the rigid structure.[3] The reasons why the linear fructo-oligosaccharides have a

CHART 1



MeFruNys



MeCF6

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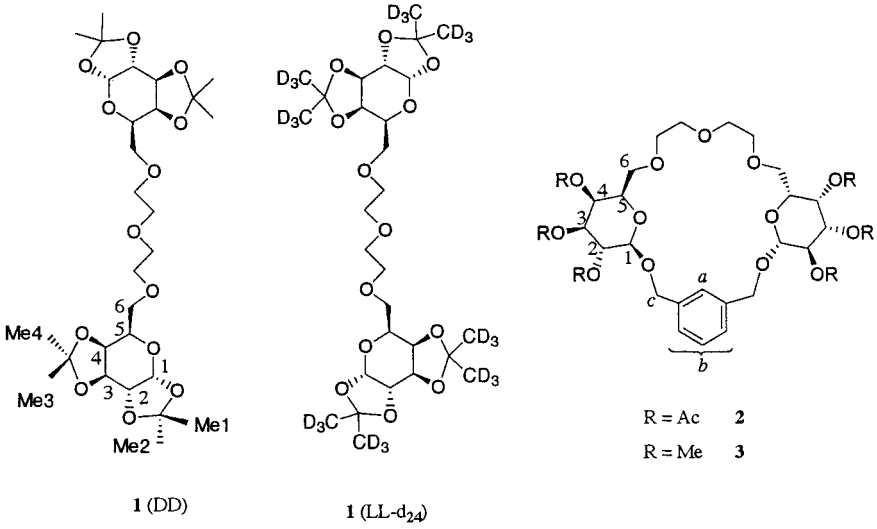
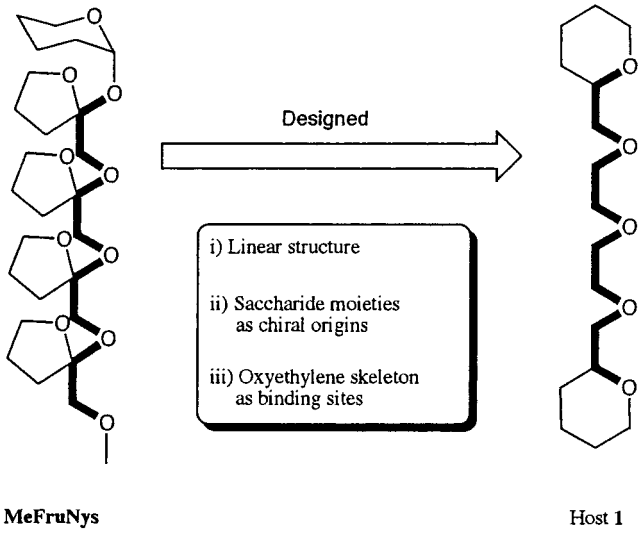
CHART 2



1 (DD) **1** (LL-d_{24})

SCHEME 1



greater chiral discrimination ability would be the low molecular symmetry and the dynamic chiral recognition mechanism. The dynamic conformation changes emphasize the difference in the host−guest complex stability.

Recently, dynamic molecular recognition of various linear hosts has been reported.[4] These hosts recognized the guests by intermolecular interactions such as electrostatic, hydrophobic, and hydrogen bonding interaction which occur due to the drastic conformation changes induced by the complexation with the guest. In the complex structures, the guests fit in with the hosts' changed conformations. The molecular recognition of cyclic hosts via dynamic conformation changes in the hosts of the flexible ring skeletons or the branch moieties in the hosts has also been reported.[5] Some cyclic hosts have saccharide moieties and are expected to distinguish the chirality of the guests.[6]

In this paper, we report that new linear host and flexible cyclic hosts (**1**, **2**, and **3**) having a C_2-symmetry axis were designed and synthesized based on the structural feature of MeFruNys, the high chiral discrimination ability of which we had previously found (Scheme 1 and Chart 2). These new hosts showed a chiral discrimination toward chiral ammonium salts, and the host−guest complex structures were clarified.

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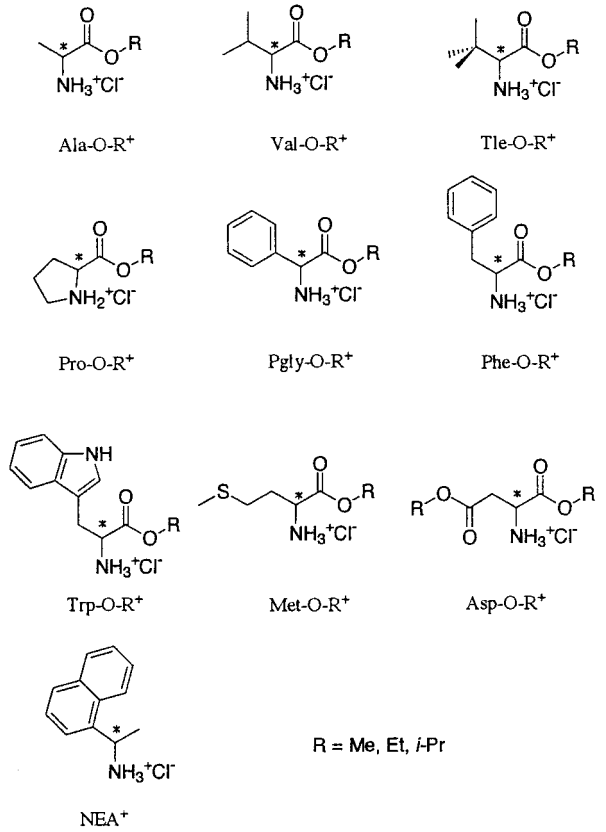
CHART 3



Results

Qualitative Evaluation of Chiral Discrimination Ability. (a) The FAB Mass Spectrometry (MS)/ Enantiomer Labeled (El) Guest Method. The chiral discrimination ability of hosts **1**, **2**, and **3** toward various chiral ammonium salts (Chart 3) was qualitatively/ semiquantitatively evaluated using fast atom bombardment (FAB) mass spectrometry.[7] In this method, the FAB mass spectra of the three component samples in a solution (3-nitrobenzyl alcohol: NBA matrix) containing the hosts (H) and a 1:1 mixture of the (*S*)-enantiomeric guest labeled with deuteriums (G_{S-dn}^+) and the unlabeled (*R*)-enantiomeric guest (G_R^+) were measured at room temperature, and the two diastereomeric 1:1 complex ion peaks differing in molecular weight ($\Delta M = n$, *n*: the number of deuteriums) were compared in intensity in order to estimate the chiral discrimination ability of the host toward the guest. The relative intensity $[I(H + G_R)^+/I(H + G_{S-dn})^+ = I_R/I_{S-dn}]$ values of hosts **1**, **2** and **3** with chiral organic ammonium salts as guests are shown in Table 1. Their hosts showed a chiral discrimination toward some guests.The I_R/I_{S-dn} values in NBA have been reported to be in good agreement with the chiral discrimination ability (the relative association constants, K_R/K_S) in organic solvent such as chloroform.[7] FAB typical mass spectra are shown in Figure 1. In their spectra, fragment ions from the matrix, guests, and host, free guests including fragments from the complex ions, matrix adduct ions, and the host−guest complex ions were observed.

TABLE 1. The Relative Intensity of the Diastereomeic Complex Ions (I_R/I_{S-dn}) and Sampling Concentration Conditions in FAB Mass Spectrometry

	host			
guest[a]	**1**	**2**	**3**	condition[f]
Ala-O-^{i}Pr$^+$ [b]	1.43	1.46	1.40	A
Val-O-^{i}Pr$^+$ [b]	0.85	1.39	1.18	A
Tle-O-^{i}Pr$^+$ [b]	1.03	1.57	1.63	A
Pro-O-^{i}Pr$^+$ [b]	1.98	1.77	1.09	A
Pgly-O-^{i}Pr$^+$ [b]	0.76	0.96	0.55	A
Phe-O-^{i}Pr$^+$ [b]	1.78	1.88	0.85	A
Trp-O-^{i}Pr$^+$ [c]	2.64	2.09	1.91	A
Met-O-^{i}Pr$^+$ [b]	1.33	1.50	1.27	A
Asp-O-^{i}Pr$^+$ [b]	1.00	0.96	0.90	A
NEA$^+$ [d]	0.63	1.61	0.96	B
Ala-O-Me$^+$,[d]	1.15			B
Leu-O-Me$^+$ [d]	1.11			B
Phe-O-Me$^+$ [d]	1.27			B
Pgly-O-Et$^+$ [e]	0.62			B
Phe-O-Et$^+$ [e]	1.47			B
Trp-O-Et$^+$ [e]	2.30			B

[a] The (*S*)-enantiomers of all guests were labeled with deuteriums: [b]−$CD(CD_3)_2$; [c]−$CH(CD_3)_2$, [d]−CD_3; [e]−C_2D_5. [f]The sampling concentration condition is as follows: condition A, [H] = 0.2 M × 5 μL (in chloroform), $[G_R^+ + G_{S-dn}^+]$ = 0.67 M × 10 μL (in methanol) into NBA 15 mL; condition B, [H] = 0.05 M × 5 μL (in chloroform), $[G_R^+ + G_{S-dn}^+]$ = 0.30 M × 5 mL (in methanol) into NBA 15 μL. All the I_R/I_{S-dn} values were averaged (n = 11), and the error ranges were ±0.03.

(b) The FABMS/EL Host Method. Another enantiomeric host **1** (LL-d_{24}) labeled with 24 deuteriums was synthesized from L-galactose instead of D-galactose. The 1:1 mixture of host **1**-DD and **1**-LL-d_{24} were added to the optically pure chiral ammonium salts in NBA. The solution's FAB mass spectra were measured, and the chiral discrimination ability was evaluated from the relative peak intensity of the two diastereomeric complex ions $[I(H_{DD} + G)^+/I(H_{LL-d24} + G)^+ = I_{DD}/I_{LL-d24}$ values] using the above method (Table 2).[8] In this case, the I_{DD}/I_{LL-d24} values showed a chiral discrimination ability of the guest toward host **1**. Some chiral organic amine guests also showed chiral discrimination toward host **1**.

Association Constants. The association constants (*K*) of the hosts with chiral organic ammonium picrates (G^+Pic^-) in chloroform at 298 K were successfully deter-

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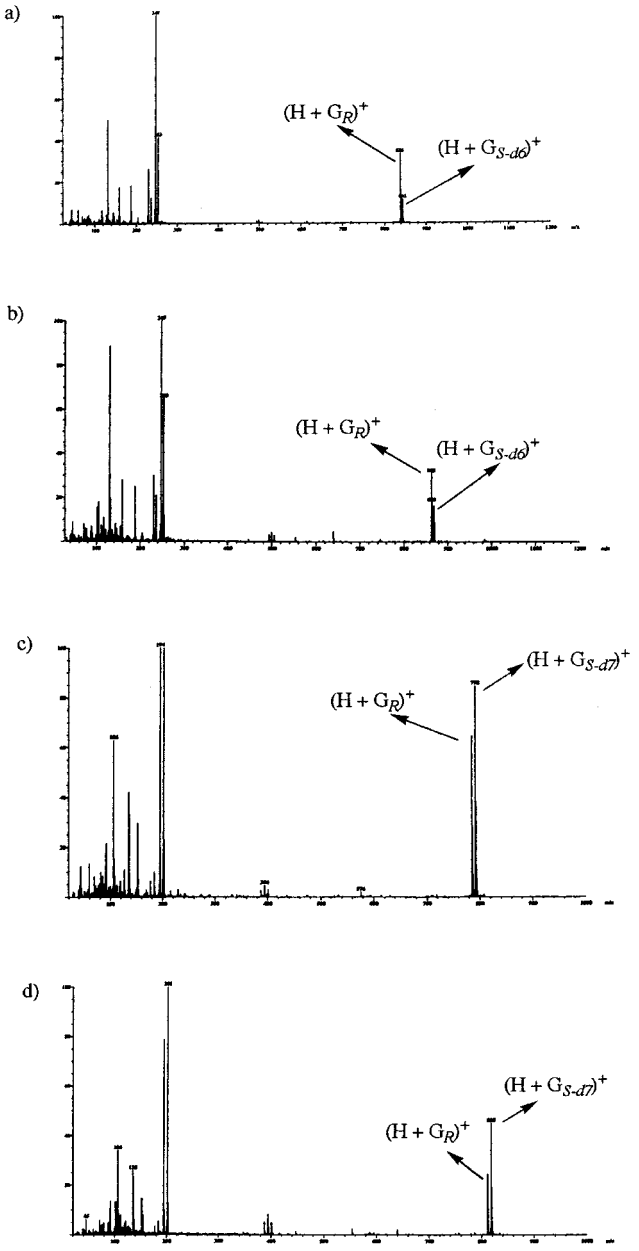

FIGURE 1. Typical FAB mass spectra: (a) host, **1**, guest, Trp-O-^{i}Pr$^+$; (b) host, **3**, guest, Trp-O-^{i}Pr$^+$; (c) host, **1**, guest, Pgly-O-^{i}Pr$^+$; (d) host, **3**, guest, Pgly-O-^{i}Pr$^+$. Matrix, 3-nitrobenzyl alcohol.

mined by UV−visible spectrometry.[2b,3c,9] The cation and picrate anion, which exist as a tight ion pair in a low-polar solvent, become a separated ion pair by the association of the cation with the host. Therefore, the electrostatic interaction between the cation and the picrate anion is decreased to induce the delocalization of the π-electrons in the picrate anion part. The change in the electron state is reflected as a bathochromic shift ($\Delta\lambda$) in the λ_{max} of the picrate anion in the UV−visible spectrum. A typical UV−visible spectrum is shown in Figure 2 (host **1**, (*R*)-NEA$^+$Pic$^-$). Each enantiomer of NEA$^+$Pic$^-$, Trp-O-^{i}Pr$^+$Pic$^-$, and Pro-O-^{i}Pr$^+$Pic$^-$ was used as a guest. In the case of host **1**, the bathochromic shifts of (*R*)-, (*S*)-NEA$^+$Pic$^-$, and (*R*)-, (*S*)-Trp-O-^{i}Pr$^+$Pic$^-$ were 5, 7, 4, and 2 nm, respectively. In host **2**, the bathochromic shifts of (*R*)-, (*S*)-NEA$^+$Pic$^-$, and (*R*)-, (*S*)-Trp-O-^{i}Pr$^+$-Pic$^-$ were 2, 1, 2, and 2 nm, respectively. The bathochromic shift by host **3** was observed only in TrpOiPr$^+$Pic$^-$ ((*R*)-isomer, 2 nm, (*S*)-isomer, 1 nm). For all hosts, no shifts in Pro-O-^{i}Pr$^+$Pic$^-$ were observed. Some *K* values were calculated for the clear absorbance changes at some fixed wavelengths (Table 3). The chiral discrimination ability (K_R/K_S) from the ratio of the determined *K* values are also shown in Table 3.

^{1}H NMR Cation-Induced Shifts and Coupling Constant Changes. To clarify the position of the binding site between the hosts and the cationic moiety in organic ammonium, the ^{1}H NMR induced shifts by adding a

TABLE 2. The Relative Intensity of the Diastereomeic Complex Ions (I_{DD}/I_{LL-d24}) of the 1:1 Deuterium-Labeled LL-/DD-Unlabeled Host 1 with Various Organic Ammonium Ion Guests in FAB Mass Spectrometry[a]

guest cation (counteranion: Cl$^-$)	I_{DD}/I_{LL-d24}
(*S*)-NEA$^+$	1.52 (0.66)
(*R*)-NEA$^+$	0.64 (0.64)
(*R*)-*N*-benzyl -*N*-1-phenylethylammonium ion	0.74
(*R*)-2-butylammonium ion	0.96
(*S*)-2-butylammonium ion	0.97
(*S*)-1-phenylethylammonium ion	0.99
(*R*)-1-(2-hydroxyl)-phenylethylammonium ion	0.98
(*S*)-Trp$^+$	0.88
(*S*)-Phe$^+$	0.96
(*S*)-Asp	0.95
(*S*)-Trp-O-^{i}Pr$^+$	0.42 (2.38)
(*R*)-Trp-O-Me$^+$	1.55
(*S*)-Phe-O-Me$^+$	0.77 (1.30)
(*R*)-Ala-O-Me$^+$	1.09 (1.09)
(*S*)-Val-O-Me$^+$	1.49
(*S*)-Lys-OMe^{2+} [b]	0.99
(*S*)-Pro-O-Bn$^+$	0.68

[a] The deuterium-labeled LL-host **1** was prepared by acetalization with acetone-d_6 (see the experimental part). [b]The peak was detected as the single charged complex ion associated with chloride anion (H + G + Cl)$^+$. The values translated as corresponding to the I_R/I_{S-dn} values in the guest method are in parentheses. In *(S)*-guest, the I_{DD}/I_{LL-d24} values have to be inverted in order to compare with the I_R/I_{S-dn} values in Table 1. All the I_{DD}/I_{LL-24} values were averaged (n = 30) and the error ranges were ±0.03.

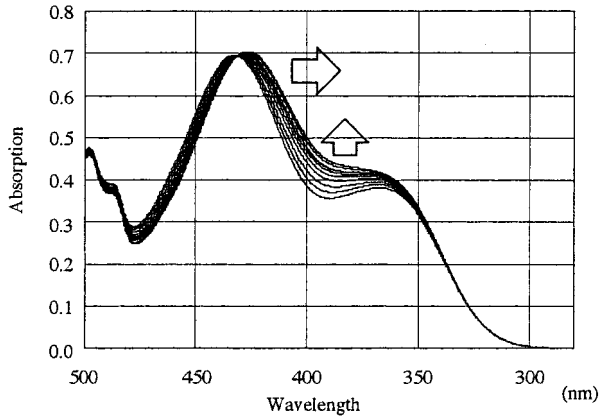

FIGURE 2. UV-visible spectral changes of (*R*)-NEA$^+$(Pic$^-$) induced by host **1** at 298 K in $CHCl_3$. [G$^+$Pic$^-$] = 4.4 × 10^{-4} M, [H] = 0 ∼ 5.20 × 10^{-2} M^{-1}. The bathochromic shift ($\Delta\lambda$) of λ_{max} of the picrate anion was 5 nm (from 347 to 352 nm).

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TABLE 3. Association Constants (*K*) of Host with Chiral Organic Ammonium Picrate in $CHCl_3$ at 298 K

host	guest	association constant (M^{-1})	K_R/K_S
1	(*R*)-NEA^+	$(9.2 \pm 0.4) \times 10^2$	0.71
1	(*S*)-NEA^+	$(1.3 \pm 0.4) \times 10^3$	
1	(*R*)-Trp-O-^{i}Pr$^+$	$(2.2 \pm 0.3) \times 10^3$	3.2
1	(*R*)-Trp-O-^{i}Pr$^+$	$(6.2 \pm 0.2) \times 10^2$	
2	(*R*)-NEA^+	$(9.8 \pm 0.5) \times 10^2$	1.6
2	(*S*)-NEA^+	$(1.6 \pm 0.7) \times 10^3$	
3	(*R*)-Trp-O-^{i}Pr$^+$	$(3.8 \pm 0.5) \times 10^2$	2.0
3	(*S*)-Trp-O-^{i}Pr$^+$	$(1.9 \pm 0.2) \times 10^2$	

TABLE 4. ^{1}H NMR Downfield Limiting Shifts and the Association Constants of the Hosts with Potassium and Ammonium Thiocyanate in Acetone-d_6 at 298 K[a]

host	guest	proton peak	limiting shift (ppm)	association constant (M^{-1})
1	$K^+(SCN^-)$	H1	0.19	$(6.4 \pm 0.6) \times 10$
		H2	0.10	
		H3	0.05	
		H4	0.06	
		H5	0.13	
		Me1	0.06	
		Me2	0.08	
		Me3	0.03	
		Me4	0.01	
1	$NH_4^+(SCN^-)$	H1	0.11	$(1.5 \pm 0.3) \times 10$
		H2	0.07	
		H3	0.04	
		H4	0.04	
		H5	0.09	
		H6	0.06	
		H6′	0.12	
		oxyethylenes	0.06	
		Me1	0.04	
		Me2	0.05	
		Me3	0.02	
		Me4	0.01	
2	$K^+(SCN^-)$	H1	0.13	6.0 ± 2.0
		H2	−0.02	
		H3	−0.01	
		H4	0.04	
		H5	0.14	
		H*c*	0.04	
		OAc	0.03	
		OAc	0.10	
		OAc	0.03	
3	$K^+(SCN^-)$	H1	0.20	$(1.2 \pm 0.1) \times 10$
		H*a*	0.14	
		H*b*	0.03	
		H*c*	0.07	
		OMe	0.00	
		OMe	0.05	
		OMe	0.02	

[a] Methyl protons of host **2** (acetyl group) and host **3** (acetal group) could not be assigned.

simple cation such as potassium and an unsubstituted ammonium (counteranion: SCN^-) were measured and the *K* values were determined in acetone-d_6 at 298 K. The limiting shifts were calculated from the determined *K* values, the initial concentrations of the hosts and the guests, and the observed shifts (Table 4). The limiting shifts are corresponding with the shifts of the complexing hosts, and the magnitudes of the downfield shifts suggest that there is the positive charge near the protons.

In host **1**, similar specific shifts were observed for both K^+ and NH_4^+. The proton peaks of H1, H5, and Me1 of the acetal moiety showed relatively large downfield shifts

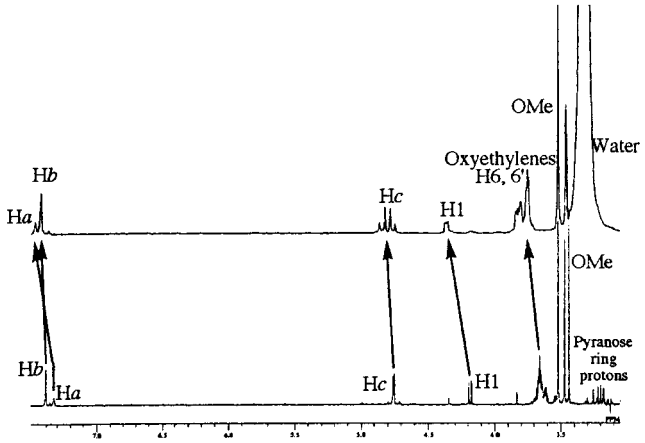

FIGURE 3. ^{1}H NMR induced shifts of host **3** by adding $K^+(SCN^-)$ at 298 K in acetone-d_6.

TABLE 5. Coupling Constant Changes (Hz) of Host Protons by Complexation with Metallic and Ammonium Ions in Acetone-d_6 at 298 K

host	guest	protons	free host	complex
1[a]	$NH_4^+(SCN^-)$	H5, H6	$^3J = 6.2$	$^3J = 3.1$
1[a]	$NH_4^+(SCN^-)$	H5, H6′	$^3J = 6.2$	$^3J = 8.3$
2[b]	$K^+(SCN^-)$	H*c* (geminal protons)	$^2J = 0.0$[c]	$^2J = 11.7$
3[b]	$K^+(SCN^-)$	H*c* (geminal protons)	$^2J = 10.6$	$^2J = 11.7$

[a] ^{1}H NMR, 600 MHz. [b] ^{1}H NMR, 270 MHz. [c] The protons were observed as a singlet peak.

(Figure 3). The peak of H1 and H5 in host **2**, and H1 in host **3**, also showed relatively large downfield shifts. Furthermore, the changes in the coupling constants between some protons were also induced by the complexation (Table 5). In host **1**, the coupling constants (^3J) between H5 and H6, and between H5 and H6′, changed by complexation with the simple cations. In hosts **2** and **3**, the singlet peak of methylene Hb changed to doublet peaks (^2J). The *K* values of host **1** with K^+ was the largest of these values for the given hosts.

NOESY of Host 1 Complex with $NEA^+(PF_6^-)$. The ^{1}H-NOESY of host **1** and its complex with $NEA^+(PF_6^-)$ was measured in chloroform-*d*. The spectrum of the complex is shown in Figure 4. The cross-peak between H4 and H6′ was observed in the complex, although the cross-peak was not observed in the free host. From the other observed cross-peaks between the pyranose ring protons and acetal protons, the acetal groups were assigned (see Experimental Section).

^{1}H NMR Induced Shifts of Host 1 by Adding $NEA^+PF_6^-$. The ^{1}H NMR shift changes of host **1** in chloroform-*d* were induced by adding each enantiomer of $NEA^+PF_6^-$ (Table 6). In the case of the (*R*)-enantiomer, relatively large upfield shifts by the H1 and H4 peaks were observed (Figure 5). On the other hand, the proton peaks of the oxyethylene moiety showed upfield shifts in the (*S*)-enantiomer. Also, the changes in the coupling constants (^3J) between H5 and H6, and H5 and H6′ were observed after adding each enantiomeric guest ($^3J_{5,6} = {}^3J_{5,6'} = 7$ Hz → $\Delta^3J_{5,6} = 3$ Hz, $^3J_{5,6'} = 8$ Hz) as well as the unsubstituted ammonium ion. The association constants were estimated at the following values: $(1.50 \pm 0.04) \times 10^3$ M^{-1} with (*S*)-$NEA^+(PF_6^-)$; $(1.04 \pm 0.08) \times 10^3$ M^{-1}

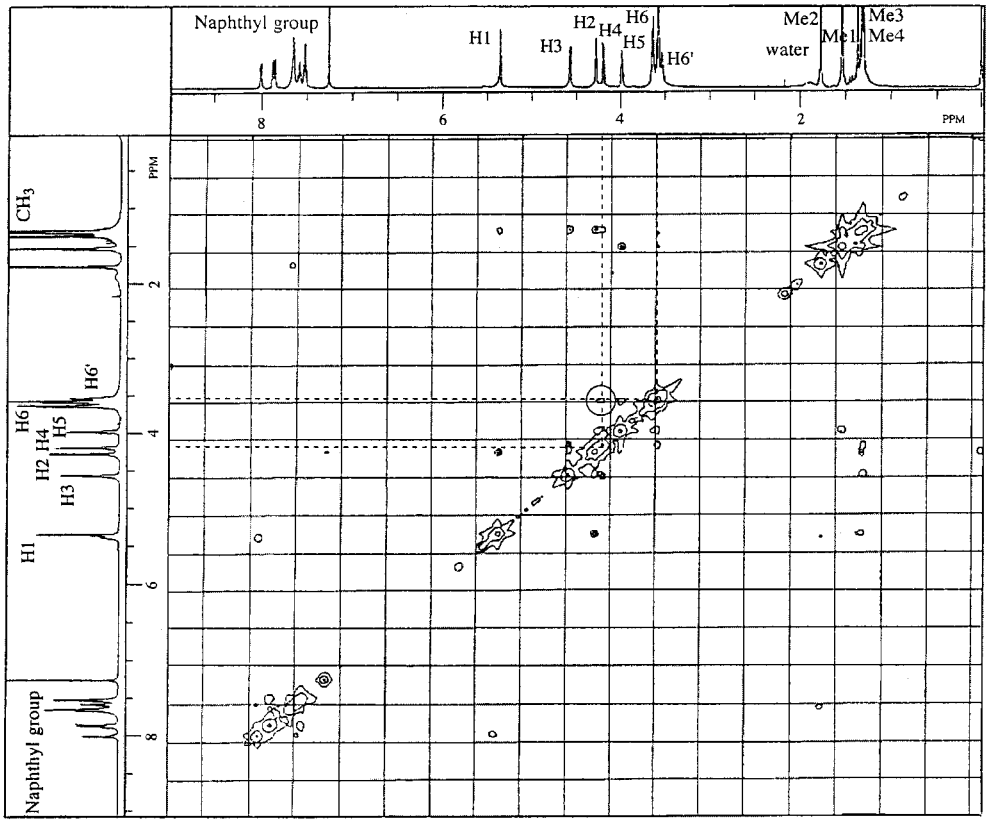

FIGURE 4. ^{1}H NMR NOESY of complex of host **1** with (*S*)-NEA$^+$(PF_6^-) in $CDCl_3$.

TABLE 6. ^{1}H NMR Upfield Limiting Shifts (ppm) of Host 1 by Complexation with NEA$^+$(PF_6^-) in $CDCl_3$ at 298 K

proton	(*S*)-NEA$^+$	(*R*)-NEA$^+$
H1	0.28	0.16
H2	0.05	0.03
H3	0.05	0.02
H4	0.12	0.10
H5	0.02	0.00
oxyethylenes	0.10	0.17
Me1	0.16	0.02
Me2	−0.01	−0.01
Me3	0.01	0.09
Me4	−0.06	0.01

with (*R*)-NEA$^+$(PF_6^-). The K_R/K_S value (0.69) was in good agreement with the results of the FABMS/EL guest method and the UV−visible titrations.

^{1}H NMR Induced Shifts of Host 2 and 3 by Adding Organic Ammonium PF6$^-$ Salts. The ^{1}H NMR shift changes of hosts **2** and **3** in chloroform-*d* induced by adding each enantiomer of NEA$^+$$PF_6^-$ were observed (Table 7). By adding (*S*)-NEA$^+$(PF_6^-) to host **2**, the proton peaks of the benzene ring moiety and one of the attached methylenes in host **2** showed upfield shifts. On the other hand, adding the (*R*)-enantiomer induced the relatively large upfield shifts of H2 and H6.

By adding (*R*)-Trp-O-^{i}Pr$^+$(PF_6^-) to host **3**, the peaks of the benzene ring moiety, H1, and H2 in host **3** induced upfield shifts (Figure 6). In the case of the (*S*)-enantomer, relatively large upfield shifts of the oxyethylene moiety in host **3** were observed.

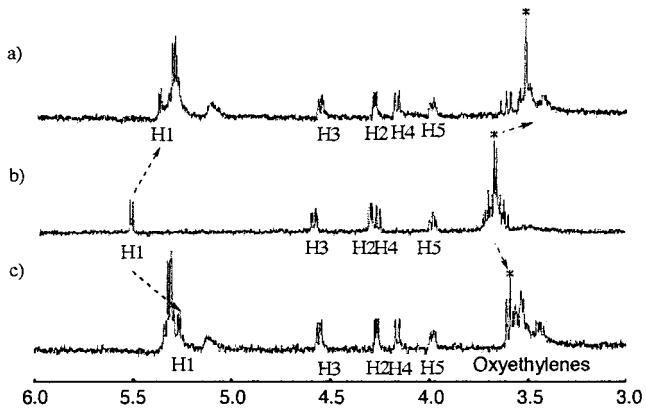

FIGURE 5. ^{1}H NMR induced shifts of host **1** by adding NEA$^+$(PF_6^-) at 298 K in $CDCl_3$. [H] = 0.2 mM. (a) Host **1** and (*R*)-NEA$^+$(PF_6^-), [G]/[H] = 5.7; (b) free host **1**; (c) host **1** and (*S*)-NEA$^+$(PF_6^-), [G]/[H] = 5.7.

Discussion

The FABMS/EL Method. The chiral discrimination ability (I_R/I_{S-dn} values) of hosts **1**, **2**, and **3** evaluated by FAB mass spectrometry was in good agreement with the ratio of the stability constants (K_R/K_S) of the corresponding host−guest complexation in chloroform as determined by the UV titration method. The I_R/I_{S-dn} values of host **1** by the labeled guest method and the I_{DD}/I_{LL-d24} values by the labeled host method agreed with each other (Table 2).[8f] For example, $I_R/I_{S-dn} = 0.63$ in the guest method for NEA$^+$, $I_{DD}/I_{LL-d24} = 0.64$ in the host method for (*R*)-NEA$^+$; $I_R/I_{S-dn} = 2.64$ in the guest method for Trp-O-^{i}Pr$^+$, and $I_{DD}/I_{LL-d24} = 0.42$ (the inverted values, 2.38) in the host

TABLE 7. ^{1}H NMR Induced Downfield Shifts (ppm) of Hosts 2 and 3 by Complexation of Chiral Organic Ammonium Hexafluorophosphates in $CDCl_3$ at 298 K[a]

	host **2**			host **3**		
guest	$NEA^+(PF_6^-)$	(*R*)-isomer	(*S*)-isomer	Trp-O-^{i}Pr$^+$(Cl^-)	(*R*)-isomer	(*S*)-isomer
proton	Ph-*b*	−0.04	0.05	Ph-*b*	0.04	−0.13
	H*c*	−0.04	0.03	H*c*, H*c*′	0.02	−0.02
	H*c*′	0.00	0.00	H1	0.00	−0.09
	H1	0.00	0.20	H2	−0.10	−0.20
	H2	−0.02	−0.08	oxyethylenes	−0.06	0.01
	H3	−0.05	0.00			
	H4	−0.06	0.21			
	H5	−0.10	0.06			
	H6	−0.08	−0.09			

[a] The concentration of the host was 0.5 mg/0.6 mL. The mole ratio of the guest for the host was as follows: (*R*)-guest/host **2** = 4.2; (*S*)-guest/host **2** = 4.2; (*R*)-guest/host **3** = 3.6; (*S*)-guest/host **3** = 3.9.

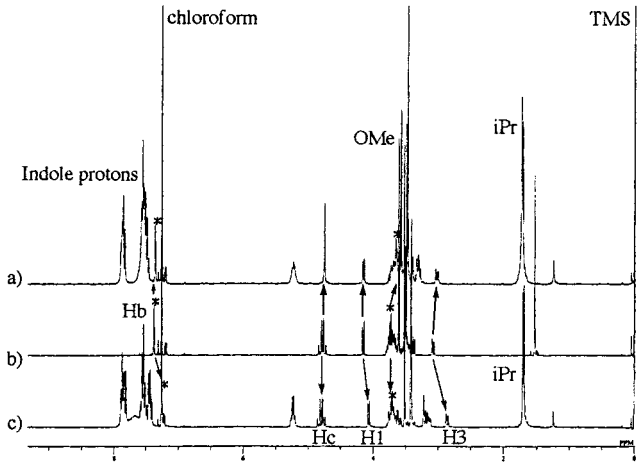

FIGURE 6. ^{1}H NMR induced shifts of host **3** by adding Trp-O-^{i}Pr$^+$(PF_6^-) at 298K in $CDCl_3$. [H] = 0.8 mM. (a) host **3** and (*R*)-Trp-O-^{i}Pr$^+$(PF_6^-), [G]/[H] = 3.6; (b) free host **3**; (c) host **3** and (*S*)-Trp-O-^{i}Pr$^+$(PF_6^-), [G]/[H] = 3.8.

method for (*S*)- Trp-O-^{i}Pr$^+$. As the product of the I_R/I_{S-dn} values of each NEA^+ enantiomer with host **1** in the labeled host method was ca. 1 (1.52 × 0.64 = 0.94), the cross-chirality relationship held fairly well.[7e] Therefore, the results by the FABMS method seems to reflect the behaviors of the hosts and the guest in the organic solution.

The concentration ratio $[(H + G_R)^+/(H + G_S)^+]$ of the diastereomeric complex ions in the three-component equilibrium solution of the chiral host and racemic guests depends on the concentration of the initial concentration of the host and the guests. In the case of large excess guests for the host, the concentration ratio $[(H + G_R)^+/(H + G_S)^+]$ corresponds approximately to the ratio of the stability constants (K_R/K_S), independent of the magnitude of *K*. On the other hand, the concentration of the complex ions $[(H_R + G)^+/(H_S + G)^+]$ in the three-component solution of the racemic hosts and chiral guest also corresponds approximately to the ratio of the stability constants (K_R/K_S). Under our sample concentration conditions in the FAB mass spectrometric experiments, the initial guest concentration in the labeled guest method and the initial host concentration in the labeled host method are in excess for the host concentration and for the guest concentration, respectively. Therefore, the concentration ratio of the complex ions in NBA is assumed to be approximately consistent with the ratio of the *K*'s in NBA. Generally, the concentration ratio of the chemical species in the matrix are not directly reflected in the ratio of the peak intensity in mass spectrometry because of the difference in the ionization efficiency and transferability effect on the gas-phase such as the solvent effect, etc. However, the I_R/I_{S-dn} in the FABMS/EL method was reflected in the ratio of the peak intensity only in the case of the diastereomeric complex ions $[(H + G_R)^+/(H + G_{S-dn})^+]$.[7a,8f,10] Chiral discrimination ability in chloroform by the UV and NMR titration may be in agreement with that in NBA using the FABMS/EL method, because the ability was represented as the ratio values to offset most of the solvent effects.[7g]

Chiral Discrimination Ability and Enantioselectivity. Linear host **1** showed the largest chiral discrimination ability of hosts **1**, **2**, and **3**. Host **1**, differing from hosts **2** and **3**, has rigid and steric 2-propylidene groups which may be playing a significant role in the inducement of chiral discrimination. Indeed, the larger bathochromic shifts (4−7 nm) in λ_{max} of the picrate anion in the UV−visible spectra were observed by adding host **1** to an organic ammonium picrate solution in comparison to the cyclic hosts (0−2 nm). The bathochromic shifts are observed as the case where the picrate anion is separated from the countercation of the ammonium ion. The larger shifts suggest that the 2-propylidene groups in host **1** are effectively functioning as repulsion barriers to construct the stereochemical binding site. Furthermore, the CH_3 moiety of the 2-propylidene groups in host **1** may be interacting with the π-electrons of the aromatic groups in the guest because of the observation of the specific ^{1}H NMR induced upfield shift of the Me1 peak by adding NEA^+ -containing naphthyl groups.[11]

For cyclic hosts **2** and **3**, the enantioselectivity toward Pro-O-^{i}Pr$^+$, Phe-O-^{i}Pr$^+$, Pgly-O-^{i}Pr$^+$, and NEA^+ was different for each of them. This suggests that the complex structure of the host substituted with methyl groups is different from that of the host substituted with acetyl groups.

Structure of Diasteromeric Host−Guest Complex. (a) Complex of Host 1 with NEA^+. The downfield limiting shifts of the H1 and H5 peaks by complexation with K^+ or NH_4^+, and the difference in the induced shift of H6 from that of H6′, which are geminal protons to each other, suggest that the cation guest is located in the

(10) Hiraoka, K. *J. Mass Spectrom. Soc. Jpn.* **1999**, *47*, 140−148.
(11) Nishio, M. In *The CH/p Interaction. Evidence, Nature, and Consequence*; Wiley-VCH: New York, 1998.

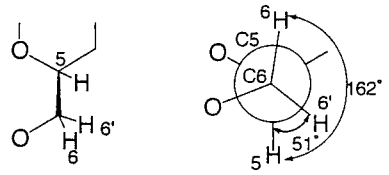

FIGURE 7. The pseudo-cyclic structure of host **1** in the complex with cation suggested by ^{1}H NMR induced shift and NOESY.

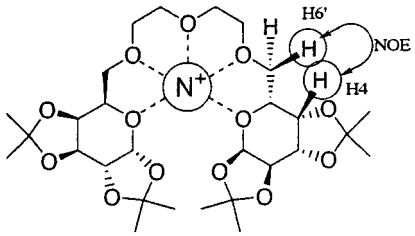

FIGURE 8. The dihedral angles of H5−C5−C6−H6(H6′) arrangement calculated with the Karplus equation from the actual coupling constants of the complex of host **1** with (*S*)-NEA$^+$(PF_6^-).

pseudo-binding site which consists of a five-oxyethylene chain containing oxygens of the galactopyranose rings. The differences in the coupling constants between H5 and H6, and H5 and H6′, which had the same constants in free host **1**, were induced by the complexation with NH_4^+ or NEA$^+$. The changes in the coupling constants suggest a fixed rotation of the C5−C6 bonds by the complexation. Two conformations (dihedral angles) of the eclipse and gauche forms in the C5−C6 bonds were calculated from the coupling constants using the Karplus equation.[12] The illustration of the gauche conformation, which seems to be more stable, is shown in Figure 7. In this conformation, H4 and H6 are positioned in the *trans*-1,3-form to each other. The NOE observation between H4 and H6 in the complex with NEA$^+$, though the NOE between these protons was not observed in free host **1**, shows that the geometric relationship of H4 and H6 was the *trans*-1,3-form and also supports the fact that the host in the complex has a the pseudo-ring structure which consists of oxyethylenes containing the gauche conformation of C5−C6 bonds (Figure 8). This conformation is the same as that of the oxyethylenes in the complex of 18-crown-6 with $K^+(SCN^-)$ from the X-ray crystalline analysis.[13]

The upfield shift of the oxyethylene moiety induced by the complexation with (*R*)-NEA$^+$ in the ^{1}H NMR suggests that the naphthyl group of the guest is located above the oxyethylene moiety (Figure 9a,c). However, in the complex with (*S*)-NEA$^+$, the upfield shifts of H1 and Me1 were observed. The complex structure is suggested such that the naphthyl group is located at the incision of the pseudo-ring of host **1** (Figure 9b,d). This suggested structure of the complex with the (*S*)-guest may be considered to be more stable than that with the (*R*)-guest because of the least repulsion between the host and the naphthyl group and probably stabilization by the CH-π interaction. These structures support the results of the FABMS/EL method and the *K* values.

(b) Complexes of Host 2 with NEA$^+$ and Host 3 with Trp-O-^{i}Pr$^+$. For the complex of host **2** with NEA$^+$ and the complex of host **3** with Trp-O-^{i}Pr$^+$, the structure would be also assumed on the basis of the induced ^{1}H NMR shifts by the complexation. The downfield shifts of the H1 and H5 protons and the separation of the methylene H*c* peak induced by adding the potassium ion suggest that these hosts form a complex with the cation moiety at the cyclic binding site in the center of the hosts. The naphthyl group and the indole moiety in each guest induce the upfield shifts of the adjacent proton peaks due to the shielding effect by the conjugated π-electrons. Therefore, the position of these substituent groups would be expected from the assigned protons which showed the induced upfield shifts. The expected structures of the complexes from the above spectral changes are illustrated in Figure 10. In the complexes of host **2** with both enantiomers of NEA$^+$, the upfield shifts of H2 protons in the pyranose rings was observed and suggest that the naphthyl group locates above one pyranose ring. On the other hand, the induced shifts suggest the indole moiety in the complex of host **3** with the (*S*)-guest locates above one pyranose and the aryl moiety of the host, and the moiety in the complex with (*R*)-guest locates above the oxyethylene moiety.

Summary

These new flexible linear and cyclic hosts were designed on the basis of the features of remarkable chiral recognition of the oligosaccharide derivatives. They were then synthesized and evaluated for chiral discrimination ability. Further, the complex structure between the host and chiral amine guests were also clarified. The flexibile ring skeleton of the cyclic hosts had less effect on chiral discrimination ability against our expectation. While, linear host **1** showed relatively higher chiral recognition via the dynamic complexation. Another enantiomer of the host $\mathbf{1}_{DD}$ can be more easily synthesized than that of MeFruNys. The optical purity of several chiral amines are evaluated using the deuterium-labeled/unlabeled host pair in FAB mass spectrometry, as reported previously.[8d,8e] The chiral discrimination ability for the evaluation of optical purity by the FABMS method is required to be I_R/I_{S-dn} (I_{DD}/I_{LL-24}) > 1.4 or I_R/I_{S-dn} (I_{DD}/I_{LL-24}) < 0.7. The chiral discrimination ability of host **1** was smaller than that of MeFruNys.[2b] However, the chiral discrimination ability of host **1** towrad some given guests was enough to evaluate the optical purity. One of advantages of the evaluation of optical purity using mass spectrometry is the remarkable high sensitivity. The structures of the complexes of host **1** with both enantiomer of NEA$^+$ were clarified from the ^{1}H NMR induced shifts, etc. This clarification of the complex structure and the chiral recognition mechanism would be useful to research new chiral guests which have never been distinguished, for example, by mass spectrometry, gas or liquid chromatography, capillary electrophresis, etc.

Experimental Section

General. ^{1}H NMR spectra were recorded at 270 or 600 MHz, and ^{13}C NMR spectra were recorded at 70 or 150 MHz.

(12) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11−15. (b) Karplus, M. *J. Phys. Chem.* **1960**, *64*, 1793−1798. (c) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870−2871. (d) Hoch, J. C.; Dobson, C. M.; Karplus, M. *Biochemistry* **1985**, *24*, 3831−3841.

(13) Seiler, P.; Dobler, M.; Dunitz, J. D. *Acta Crystallogr.* **1974**, *B30*, 2744−2745.

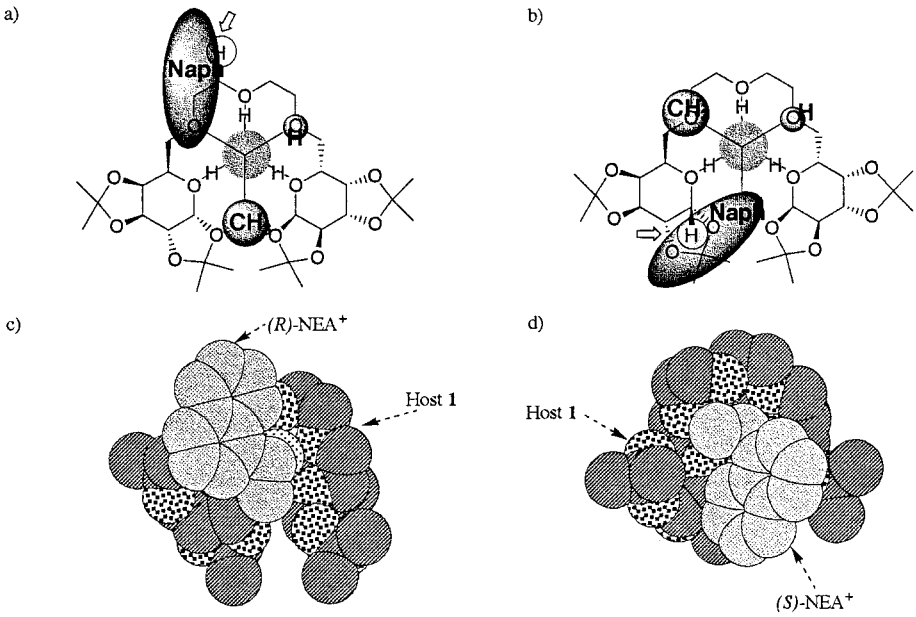

FIGURE 9. The structure of the complex of the cyclic hosts with guest cations suggested by ^{1}H NMR induced shifts. (a) The complex of host **2** with NEA$^+$; (b) the complex of host **3** with Trp-O-^{i}Pr$^+$.

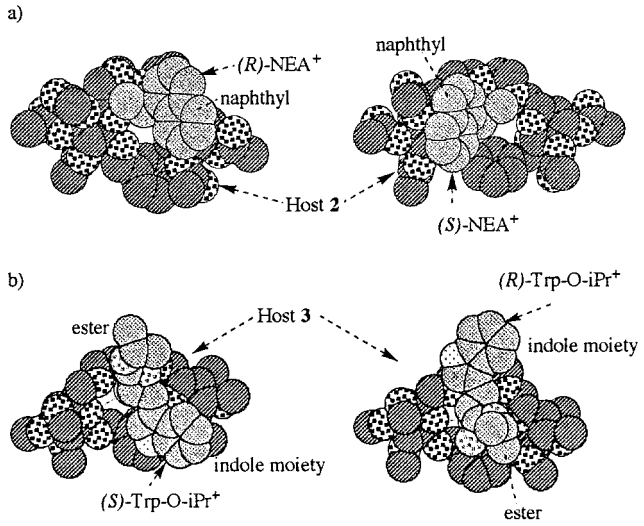

FIGURE 10. The structure of the complex of host **1** with NEA$^+$ suggested by ^{1}H NMR induced shifts. The arrows show the proton observed the upfield induced shifts by adding NEA$^+$. (a) Illustration of the complex of host **1** with (*S*)-NEA$^+$; (b) illustration of the complex of host **1** with (*R*)-NEA$^+$; (c) space fill model of the complex of host **1** with (*S*)-NEA$^+$; (d) space fill model of the complex of host **1** with (*S*)-NEA$^+$.

TMS was used as the internal standard. Liquid column chromatography for the isolation and the purification of hosts was carried out with an RI detector under an appropriate medium pressure.

Materials. 18-Crown-6 was used without further purification. Potassium and ammonium thiocyanate was used after dryness under reduced pressure with vacuum pump at 100 °C over 8 h. Spectral grade $CHCl_3$ was used as solvent for UV−visible measurement without purification. $CDCl_3$ (99.9 at. % D) and acetone-d_6 (99 at. % D) was used as solvent for NMR measurement without purification. 3-Nitrobenzyl alcohol was used as FABMS matrix without purification.

Preparation of Organic Ammonium Salts. Amino acid 2-propyl ester hydrochlorides were synthesized according to the standard esterification method from commercial D-amino acid and l-amino acid with propan-2-ol or propan-2-ol-d_8 (99+ atom % D).[14] L-Tryptophan 2-propyl-d_6 ester hydrochloride was prepared by esterification with propan-2-ol-d_6, (99.5 at. % D) to avoid H/D exchange of the indole moiety. The proportion of the deuterium-labeled amino acid ester hydrochloride depends on that of the alcohol. The deuterium content of the labeled amino acid hydrochlorides was >99%. The above products were dried in vacuo at 40 °C before the FABMS measurements.

Amino acid 2-propyl ester picrates and 1-(1-naphthyl)-ethylammonium picrate were prepared by neutralization of picric acid and amino acid 2-propyl ester or 1-(1-naphthyl)-ethylamine in benzene and recrystallized in benzene and ethyl acetate.[15] The products were dried in vacuo for 5−10 h at 50 °C and used in the UV−visible titrations. Dried picrate salts should be carefully treated because of the explosive properties. The element analyses of the products were as follows: (*R*)-NEA$^+$(Pic$^-$). Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 13.99. Found: C, 54.11; H, 3.99; N, 13.91. (*S*)-NEA$^+$(Pic$^-$). Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 13.99. Found: C, 54.20; H, 3.95; N, 13.95. (*R*)-Trp-O-^{i}Pr$^+$(Pic$^-$). Anal. Calcd for $C_{20}H_{21}N_5O_9$: C, 50.53; H, 4.45; N, 14.73. Found: C, 50.74; H, 4.25; N, 14.52. (*S*)-Trp-O-^{i}Pr$^+$(Pic$^-$). Anal. Calcd for $C_{20}H_{21}N_5O_9$: C, 50.53; H, 4.45; N, 14.73. Found: C, 50.77; H, 4.28; N, 14.49. (*R*)-Pro-O-^{i}Pr$^+$(Pic$^-$). Anal. Calcd for $C_{14}H_{18}N_4O_9$: C, 43.53; H, 4.70; N, 14.50. Found: C, 43.66; H, 4.56; N, 14.21. (*S*)-Pro-O-^{i}Pr$^+$(Pic$^-$). Anal. Calcd for $C_{14}H_{18}N_4O_9$: C, 43.53; H, 4.70; N, 14.50. Found: C, 43.56; H, 4.62; N, 14.42.

Organic ammonium hexafluorophosphate was prepared according to the anion exchange method between the corresponding organic ammonium chloride and $AgPF_6$.[16] Typical procedures and the characterization were as follows: (*R*)-1-(1-naphthyl)ethylammonium hexafluorophosphate [(*R*)-NEA$^+$-(PF_6^-)]. Commercial 1-(1-naphthyl)ethylamine (165 mg, 0.96 mmol) was dissolved in dichloromethane, and the solution was bubbled with dry HCl gas. The precipitate was filtered, washed with dichloromethane, and dried at 60 °C in vacuo overnight.

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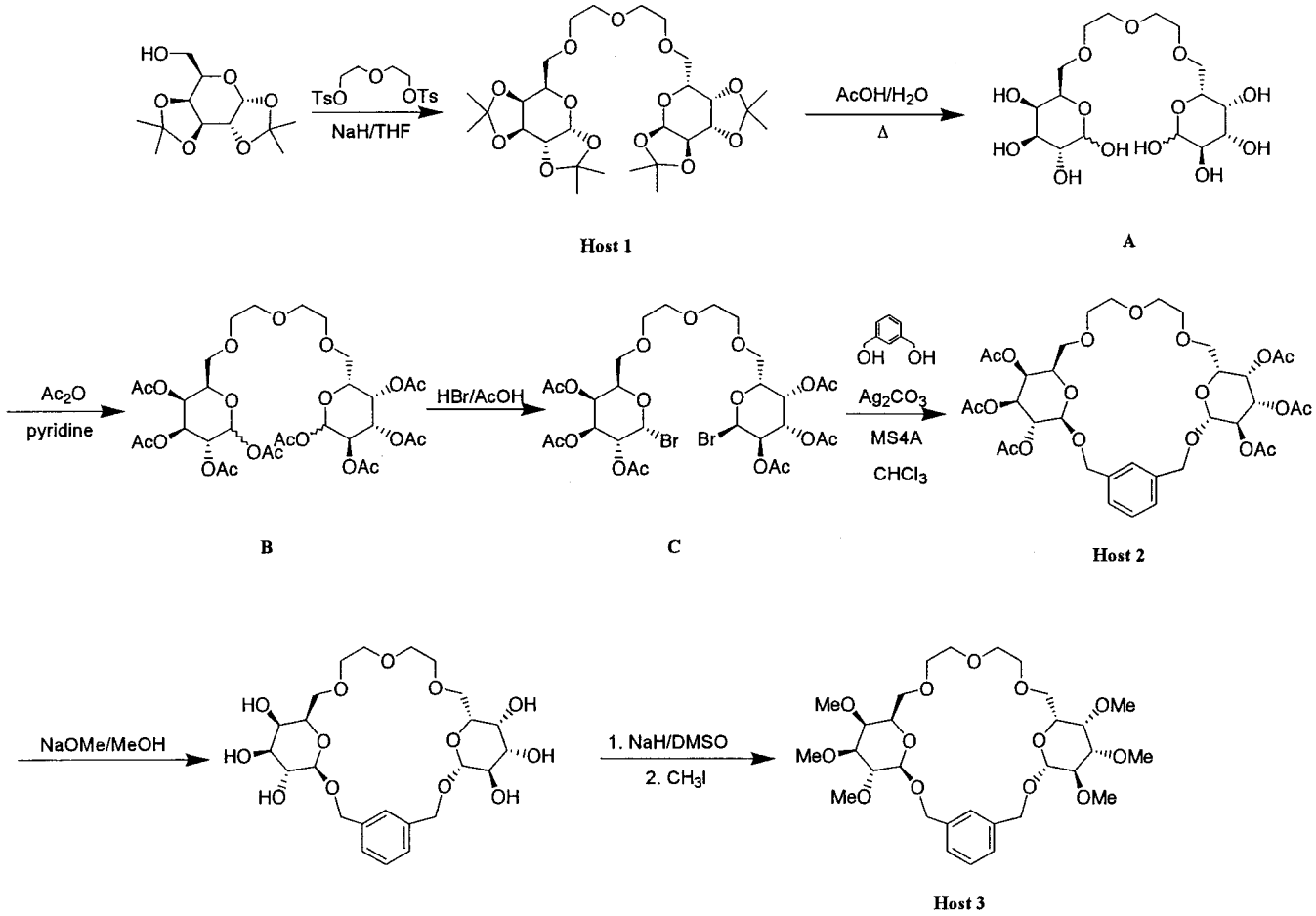
SCHEME 2



The obtained chloride (200 mg, 0.96 mmol) was dissolved into a 5 mL of water. While, the equimolar $AgPF_6$ (243 mg) was also dissolved into a 5 mL of water. The aqueous solutions were mixed, and the produced precipitate (AgCl) was removed by filtration. The water was removed from the filtrate by freeze drying. The quantitatively obtained white powder was further dried in vacuo before the ^1H NMR experiments. Anal. Calcd for $C_{12}H_{14}F_6N_1P_1$: C, 45.44; H, 4.45; N, 4.42. Found C, 46.92; H, 4.52; N, 4.59. (*S*)-NEA$^+$(PF_6^-). Anal. Calcd for $C_{12}H_{14}F_6N_1P_1$: C, 45.44; H, 4.45; N, 4.42. Found C, 46.97; H, 4.52; N, 4.59. (*R*)-Trp-O-^{i}Pr$^+$(PF_6^-). Anal. Calcd for $C_{14}H_{19}F_6N_2O_2P_1$: C, 42.87; H, 4.88; N, 7.14. Found C, 43.64; H, 4.93; N, 7.31. (*S*)- Trp-O-^{i}Pr$^+$(PF_6^-). Anal. Calcd for $C_{14}H_{19}F_6N_2O_2P_1$: C, 42.87; H, 4.88; N, 7.14. Found C, 43.61; H, 4.97; N, 7.44.

Synthesis of Hosts. Hosts **1**, **2**, and **3** were synthesized as following procedures (Scheme 2): 6,6′-*O*- (2,2′-oxydiethyl)-bis-(1,2:3,4-di-*O* -2-propylidene α-D-galactopyranose) ether (host **1**): 1,2:3,4-di-*O* -2-propylidene α-D-galactopyranose (1.61 g, 6.19 mmol) and sodium hydride (ca. 3.00 g, ca. 13 mmol) in dry distilled tetrahydrofran (100 mL) were stirred at room temperature, and a 50 mL solution of diethylene glycol di-*p*-toluenesulfonate[17] (1.28 g, 3.09 mmol) in tetrahydrofuran was added dropwise to the slurry and heated under reflux overnight. The reaction mixture was cooled to room temperature, filtered, and evaporated, and chloroform (150 mL) was added. The organic layer was three times washed with water and dried over anhydrous magnesium sulfate. After filtration, the organic solution was evaporated and purified with liquid chromatography (silica gel, ethyl acetate:*n*-hexane = 1:1, v/v) under a medium pressure to yield 1.67 g colorless syrup (91.5%). $[\alpha]_D^{20} = -60.7$ (c = 0.2, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 5.52 (d, 2H, $^3J_{H1,H2}$ = 5.0 Hz, H1) 4.59 (dd, 2H, $^3J_{H2,H3}$ = 2.3 Hz, $^3J_{H3,H4}$ = 8.3 Hz, H3) 4.30 (dd, 2H, $^3J_{H1,H2}$ = 5.0 Hz, $^3J_{H2,H3}$ = 2.3 Hz, H2) 4.26 (dd, 2H, $^3J_{H3,H4}$ = 7.9 Hz, $^3J_{H4,H5}$ = 1.7 Hz, H4) 3.98 (m, 2H, $^3J_{H4,H5}$ = 1.7 Hz, H5) 3.73−3.58 (m, 12H, Ha, Hb, H6, H6′) 3.70 (dd, $^3J_{H5,H6}$ = 5.9 Hz, $^2J_{H6,H6'}$ = 10.2 Hz, H6) 3.62 (dd, $^3J_{H5,H6'}$ = 3.6 Hz, $^2J_{H6,H6'}$ = 10.2 Hz, H6′) 1.54 (s, 6H, Me2) 1.44 (s, 6H, Me1) 1.34 (s, 6H, Me4) 1.33 (s, 6H, Me3) from TMS. ^{13}C NMR (70 MHz, $CDCl_3$) δ (ppm) 109.0, 108.3, 96.2, 71.0, 70.6, 70.5, 70.3, 69.7, 66.6, 25.9, 25.8, 24.8, 24.3 from TMS. FT-IR(cm^{-1}) 2988, 2956 (C−H), 1169, 1142, 1109, 1071 (acetal, ether). FABMS *m*/*z* 629 $(M + K)^+$. Anal. Calcd for $C_{28}H_{46}O_{13}$: C, 56.94; H, 7.85. Found: C, 56.90; H, 7.86.

Their methyl protons of acetal groups were assigned from NOESY. The cross-peaks were observed between Me1 and H2, Me2 and H5, and, Me3 and H4 protons, respectively. Their proton pairs are near each other in CPK model. Me4 was not observed the cross-peak for other proton because there are not other protons near Me4.

6,6′-*O*-(2,2′-Oxydiethyl)-bis(D-galactopyranose) (**A**).[18] D-Galactose derivative host **1** was heated under reflux in 80% acetic acid over 1 h. The solution was cooled to room temperature, and acetic acid was removed under reduced pressure. The residue was purified with liquid chromatography (Dowex-AG

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50X, K, Ca form, water) and evaporated to give 1.09 g of white solid (yield 90%). mp ~200 °C (decomp.). ^{1}H NMR (270 MHz, D_2O) δ (ppm) 5.28 (d, $^3J_{H1,H2}$ = 3.6 Hz, α-isomer H1) 4,61 (d, 2H, $^3J_{H1,H2}$ = 7.9 Hz, β-isomer H1).

6,6′-*O*-(2,2′-Oxydiethyl)-bis(1,2,3,4-tetra-*O*-acetyl-D-galactopyranose) (**B**).[19] **A** (1.00 g, 2.33 mmol) was stirred in acetic anhydrate (45 mL) and dry pyridine (80 mL) at room-temperature overnight. The solution was evaporated and added to chloroform. The organic layer was three times washed with water and dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated and purified with liquid chromatography (silica gel, ethyl acetate:*n*-hexane = 1:1 v/v) to yield octaacetyl anomeric mixture 1.04 g (59%). ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 6.36 (α-isomer H1) 6.31 (d, $^3J_{H1,H2}$ = 4.6 Hz, β-isomer H1).

Dibromo-bis-6,6′-*O*-(2,2′-oxydiethyl)-bis(2,3,4-tri-*O*-α-D-galactopyranoside) (**C**).[20] **B** (1.03 g, 1.34 mmol) was stirred in a 20% hydrobromide acetic acid solution (10 mL) at room temperature in darkness overnight. The reaction mixture was poured into ice−water (50 mL). After three times extraction with chloroform, the organic layer was three times washed with sat. aq $NaHCO_3$ and water, respectively. The solution was treated with silica gel for a few minutes, filtered, evaporated, purified with liquid chromatography (silica gel, ethyl acetate:*n*-hexane = 2: 1) to yield 0.62 g of a slight brown syrup (57%). ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 6.71 (d, 2H, $^3J_{H1,H2}$ = 4.0 Hz, H1) 5.55 (dd, 2H, $^3J_{H3,H4}$ = 3.0 Hz, H4) 5.40 (dd, 2H, $^3J_{H2,H3}$ = 10.6 Hz, $^3J_{H3,H4}$ = 3.0 Hz, H3) 5.04 (dd, 2H, $^3J_{H1,H2}$ = 4.0 Hz, $^3J_{H2,H3}$ = 10.6 Hz, H2) 4.45 (m, 2H, H5) 3.58 (m, 12H, ethylene, H6, H6′) 2.14 (s, 6H, −$COCH_3$) 2.11(s, 6H, −$COCH_3$) 2.00 (s, 6H, −$COCH_3$) from TMS. ^{13}C NMR (70 MHz, $CDCl_3$) δ (ppm) 170.0, 169.8, 169.6, 88.7, 72.1, 71.0, 70.5, 68.4, 68.2, 68.0, 67.5, 20.7, 20.5, 20.5 from TMS.

1,3-(Dimethylene)benzenediyl 6,6′-*O*-(2,2′-Oxydiethyl)-bis-(2,3,4-tri-*O*-acetyl-β-D-galactopyranoside) (host **2**):[21] Under nitrogen atmosphere, **C** (3.07 g, 3.79 mmol), 1,3-dimethanol benzene (0.502 g, 3.79 mmol), silver carbonate (0.503 g), and powdered molecular sieves 4A (12.5 g) were stirred in dry chloroform at room temperature in darkness for 72 h. The reaction mixture was filtered through celite on a glass filter, and the filtrate was evaporated and purified with chromatography (silica gel, ethyl acetate:*n*-hexane = 3:2). The portion was evaporated to give a white solid that was recrystallized from ethyl acetate/*n*-hexane to yield 2.59 g of colorless crystals (87%). mp 135−137 °C. $[\alpha]_D^{20} = -5.0$ (c = 0.2, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 7.40−7.31 (m, 4H, aryl proton) 5.32 (dd, 2H, $^3J_{H3,H4}$ = 3.0 Hz, H4) 5.26 (dd, 2H, $^3J_{H1,H2}$ = 7.9 Hz, $^3J_{H2,H3}$ = 10.6 Hz, H2) 4.93 (dd, 2H, $^3J_{H2,H3}$ = 10.2 Hz, $^3J_{H3,H4}$ = 3.3 Hz, H3) 4.85 (d, 2H, $^2J_{Ha,Hb}$ = 11.9 Hz, Ha) 4.76 (d, 2H, $^2J_{Ha,Hb}$ = 12.2 Hz, Hb) 4.37 (d, 2H, $^3J_{H1,H2}$ = 8.3 Hz, H1) 3.81−3.54 (m, 14H, ethylene, H5 H6, H6′) 2.15 (s, 6H, −$COCH_3$) 2.07 (s, 6H, −$COCH_3$) 1.96 (s, 6H, −$COCH_3$) from TMS. ^{13}C NMR (60 MHz, $CDCl_3$) δ (ppm) 170.3, 170.0, 169.5, 136.3, 129.6, 98.2, 73.2, 71.6, 71.1, 70.7, 70.4, 69.6, 69.0, 68.3, 20.7, 20.6, 20.5 (19 peaks) from TMS. FT-IR (cm^{-1}, KBr-disk) 2921, 2882 (C−H), 1748 (C═O), 1633 (benzene ring), 1456 (CH_2), 1371 (CH═CH), 1250, 1225 (ester), 1067 (ether). FABMS *m*/*z* 823 $(M + K)^+$. Anal. Calcd for $C_{36}H_{48}O_{19}$: C, 55.10; H, 6.15. Found: C, 55.08; H, 6.07.

1,3-(Dimethylene)benzenediyl 6,6′-*O*-(2,2′-Oxydiethyl)-bis-(2,3,4-tri-*O*-methyl-β-D-galactopyranoside) (host **3**).[22] Host **2** (2.00 g, 2.55 mmol) was stirred in a 5% sodium methoxide methanol solution (10 mL) at room temperature for 3 h. Cation-exchange resin H-form which was washed with methanol was added to the solution in order to neutralize and stirred for 30 min. After filtration, the solution was evaporated and dried at 50 °C under reduced pressure with a vacuum pump overnight to give 1.33 g of solid. Under a nitrogen flow, the residue (0.60 g) was reacted at room temperature for 4 h with dimethylsulfinyl carbanion which was prepared from sodium hydride (50 mg) and dimethyl sulfoxide (8 mL), and methyl iodide (5 mL) was added dropwise to the solution keeping ca. 10 °C and stirred overnight. After extraction with chloroform, the organic layer was washed three times with saturated aq $Na_2S_2O_3$ and water, respectively, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was evaporated to give a white solid which was recrystallized from diethyl ether to yield 45 mg of colorless crystals (45%). mp 151−153 °C. $[\alpha]_D^{20} = -47.3$ (c = 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.38 (m, 3H, aryl proton) 7.18 (m, 1H, aryl proton) 4.82 (d, 2H, $^2J_{Ha,Hb}$ = 12.3 Hz, Ha) 4.76 (d, 2H, $^2J_{Ha,Hb}$ = 12.3 Hz, Hb) 4.17 (d, 2H, $^3J_{H1,H2}$ = 7.7 Hz, H1) 3.80−3.65 (m, 12H, ethylene, H6, H6′) 3.62(s, 6H, methoxy) 3.54 (s, 6H, methoxy) 3.52 (m, 2H, $^3J_{H3,H4}$ = 2.9 Hz, H4) 3.50 (s, 6H, methoxy) 3.48 (m, 2H, H5) 3.39 (dd, 2H, $^3J_{H1,H2}$ = 7.7 Hz, $^3J_{H2,H3}$ = 9.7 Hz, H2) 3.09 (dd, 2H, $^3J_{H2,H3}$ = 9.5, $^3J_{H3,H4}$ = 2.9 Hz, H3) from TMS. ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 136.7, 129.1, 127.7, 100.7, 83.9, 80.5, 76.2, 74.6, 71.6, 71.2, 70.7, 69.7, 61.3, 60.7, 58.6 (15 peaks) from TMS. FT-IR (KBr-disk, cm^{-1}) 2930, 2874 (C−H), 1468, 1383 (H−C−H, H−C−C), 1129, 1111, 1078, 1065 (ether). FABMS *m*/*z* 655 $(M + K)^+$. Anal. Calcd for $C_{30}H_{48}O_{13}$: C, 58.43; H, 7.84. Found: C, 58.18; H, 7.86.

Deuterium-labeled LL-host **3**-d_{24}, 6,6′-*O*-(2,2′-oxydiethyl)-bis(1,2:3,4-di-*O*-2-propylidene-d_6 α-L-galactopyranose) ether (host **1**). 1,2:3,4-Di-*O*-2-propylidene-d_6 α-L-galactopyranose (0.17 g, 0.64 mmol) and sodium hydride (ca. 0.10 g, ca. 2.5 mmol) in dry distilled tetrahydrofran (10 mL) were stirred at room temperature, and a 3 mL solution of diethylene glycol di-*p*-toluenesulfonate[17] (0.13 g, 0.32 mmol) in tetrahydrofuran was added dropwise to the slurry and heated under reflux overnight. The reaction mixture was cooled to room temperature, filtered, and evaporated, and chloroform (20 mL) was added. The organic layer was washed three times with water and dried over anhydrous magnesium sulfate. After filtration, the organic solution was evaporated and purified with liquid chromatography (silica gel, ethyl acetate:*n*-hexane = 1:1, v/v) under medium pressure to yield 0.40 g colorless syrup (22%). $[\alpha]_D^{20} = +64.0$ (c = 0.307, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 5.53 (d, 2H, $^3J_{H1,H2}$ = 5.0 Hz, H1) 4.59 (dd, 2H, $^3J_{H2,H3}$ = 2.2 Hz, $^3J_{H3,H4}$ = 8.0 Hz, H3) 4.30 (dd, 2H, $^3J_{H1,H2}$ = 5.0 Hz, $^3J_{H2,H3}$ = 2.2 Hz, H2) 4.26 (dd, 2H, $^3J_{H3,H4}$ = 8.0 Hz, H4) 4.00−3.96 (m, 2H, $^3J_{H4,H5}$ = 1.7 Hz, H5) 3.72−3.60 (m, 12H, Ha, Hb, H6, H6′) from TMS. FABMS *m*/*z* 637 $(M + Na)^+$. Anal. Calcd for $C_{28}H_{22}D_{24}O_{13}$: C, 54.70; H, 7.54 (calculated D as H). Found: C, 55.92; H, 7.62.

The FAB Mass Spectrometry (MS)/Enantiomer Labeled (EL) Guest Method. FAB mass spectra (positive mode) were measured with a JEOL JMS-600 mass spectrometer operating at an accelerating voltage of 6 kV with a mass range of *m*/*z* 20−2300. The instrument was equipped with a standard JEOL FAB source and an ion gun. Xenon was used as the atom beam with an emission current of 0.5 mA and an acceleration of 3 kV. The ion source pressure was typically ca. 2×10^{-6} Torr. The spectra were obtained with a magnet scan rate of 5 s per scan (to *m*/*z* 2300), and the data were processed with a JEOL JMA data processing system on a Microsoft Windows 98. The calibration was carried out with CsI.

(a) Preparation of Sample Solutions. A sample solution was prepared by mixing three solutions under two conditions as follows: microsyringes and a vibrator were used. FABMS measurements were performed, after the solution stood overnight, with a deposit of a 1 μL aliquot of the mixed solution on a FAB probe tip. Condition A: (1) 10 μL of a 0.67 M MeOH solution of a 1/1 mixture of (*R*)-unlabeled and (*S*)-labeled guests ($[G_R^+] = [G_{S-dn}^+] = 0.33$ M), (2) 5 μL of a 0.20 M $CHCl_3$ host solution, and (3) 15 μL of NBA matrix. The last concentrations in NBA were calculated to [H] = 0.067 M, [G] = 0.45

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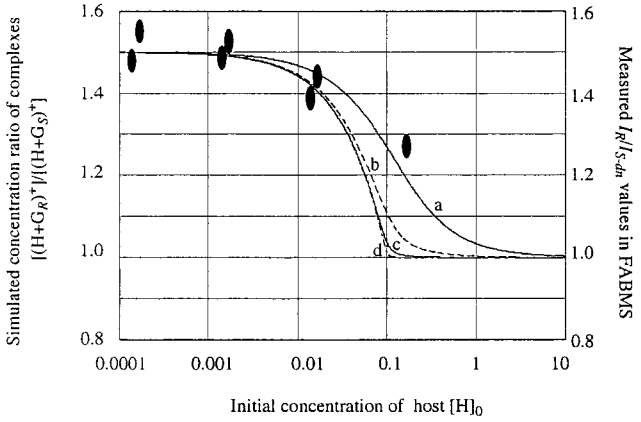

FIGURE 11. Plots of the simulated concentration ratio of the complex ions $[(H + G_R)^+]/[(H + G_S)^+]$ vs the initial concentration of the host $[H]_0$ with the measured I_R/I_{S-dn} values (●) in FABMS. Host: **1**, guest: Phe-O-Et$^+$(Cl$^-$), matrix, NBA. (a) $K_R = 15$ M^{-1}, $K_S = 10$ M^{-1}, (b) $K_R = 150$ M^{-1}, $K_S = 100$ M^{-1}, (c) $K_R = 1500$ M^{-1}, $K_S = 1000$ M^{-1}, (d) $K_R = 15000$ M^{-1}, $K_S = 10000$ M^{-1}. $[G_R^+] = [G_S^+] = 0.10$ M are assumed.

M. Condition B: (1) 5 μL of a 0.30 M MeOH solution of a 1/1 mixture of (*R*)-unlabeled and (*S*)-labeled guests ($[G_R^+] = [G_{S-dn}^+] = 0.15$ M), (2) 5 μL of a 0.05 M $CHCl_3$ host solution, and (3) 15 μL of NBA matrix. In these concentration conditions after evaporation of MeOH and $CHCl_3$ solvents in the ion source, the concentrations in NBA were calculated to [H] = 0.0167 M, [G] = 0.10 M ($[H]/[G_R^+]/[G_{S-dn}^+] = 1/3/3$). ($[H]/[G_R^+]/[G_{S-dn}^+] = 1/3.3/3.3$). The accuracy of the 1/1 equivalent concentration of *R*- and *S*-enantiomers was confirmed by the following check: (1) whether the relative intensity (I_R/I_{S-dn}) values with 18-crown-6, which is an achiral host, were experimentally obtained as unity (1.00 ± 0.03) or not, (2) whether the relative peak areas were observed as unity in HPLC (column: Daicel CROWNPAK CR; eluent aq $HClO_4$ pH 1.5) or not (in the case of Phe-O-^{i}Pr$^+$).

(b) Determination of Sampling Concentration Condition. The relative peak intensity of I_R/I_{S-dn} value depends on the sampling concentration condition. Under a certain concentration of the 1/1 mixture of NEA$^+$ guests ($[G_R^+] = [G_{S-dn}^+] = 0.15$ M), various concentrations of host **1** NBA solutions were prepared, and the FAB mass spectra were measured. The concentration ratios of the complex ions, $(H + G_R)^+$ and $(H + G_S)^+$, calculated from the different magnitudes of association constants, which were assumed the ratio K_R/K_S as 1.5, were plotted versus the initial concentration of host $[H]_0$ with the I_R/I_{S-dn} values of the FAB mass spectra in Figure 11. The I_R/I_{S-dn} values were in good agreement with the curves. Under condition B ($[H]_0 = 0.0083$ M), the I_R/I_{S-dn} value was approximately equal to the K_R/K_S. Therefore, these sampling concentration conditions were employed. Under condition A, the I_R/I_{S-dn} value was also approximately equal to the K_R/K_S.

(c) Corrections of Observed I_R/I_{S-d3} Values. The observed peak intensity of a host·(*S*)-guest complex ion contains a contribution from an amount of the (M + 3) natural abundant isotope derived from the peak intensity of a host·(*R*)-guest complex ion. Therefore, all I_R/I_{S-d3} values were corrected by the theoretical distribution of (M + 3) ion corresponding to the host−guest complex ions on the basis of the natural abundant isotope.[7a]

(d) Effects of the Label Position with Deuteriums on the I_R/I_{S-dn} Values. Steric effects are an important factor for chiral discrimination. The position labeled with deuteriums is a very important point to evaluate the chiral discrimination ability. We confirmed that the labeling of the ester group had little influence on the chiral discrimination, i.e., the I_R/I_{S-dn} values by the following experiments. (i) FAB mass spectra of a sample mixture between an oligosaccharide and a 1:1 achiral amino acid mixture of labeled glycine 2-propyl-d_7 ester hydrochloride and unlabeled glycine 2-propyl ester hydrochloride were measured and the I/I_{d7} values were ca. 1.00. ii) The I_R/I_{S-dn} value of host **1**, **2** and **3** with a 1:1 mixture of particularly labeled (*R*)-Val-O-^{i}Pr$^+$ and unlabeled (*S*)-Val-O-^{i}Pr$^+$ was 1.15, 0.66, and 0.86. The multiplication of the I_R/I_{S-dn} value and the I_S/I_{R-dn} value was almost unity (0.85 × 1.15 = 0.98, 1.39 × 0.66 = 0.92, 1.18 × 0.86 = 1.01).

The FAB Mass Spectrometry (MS)/Enantiomer Labeled (El) Host Method. A sample solution was prepared by mixing three solutions under the conditions as follows: (1) 5 μL of a 0.16 M MeOH solution of a 1/1 mixture of DD-unlabeled and LL-labeled hosts ($[H_{DD}^+] = [G_{LL-d24}^+] = 0.08$ M), (2) 5 μL of a 0.08 M $CHCl_3$ guest solution, and (3) 30 μL of NBA matrix. FABMS measurements were performed with a deposit of a 1 μL aliquot of the mixed solution. The accuracy of the 1/1 equivalent concentration of (*R*)- and (*S*)-enantiomers was confirmed by whether the relative intensity (I_{DD}/I_{LL-d24}) values with glycine methyl ester hydrochloride, which is an achiral guest, were experimentally obtained as unity (1.00 ± 0.03) or not.

UV−Visible Experiments. The bathochromic shifts ($\Delta\lambda$) of λ_{max} and the *K* values of the organic ammonium picrates followed by adding the given hosts in $CHCl_3$ at 298 K were determined as follows. The host solution (in $CHCl_3$) was gradually added to a 5 × 10^{-2} mM $CHCl_3$ solution of a given organic ammonium picrate stirred magnetically in a UV cell until no shift was observed or until the isosbestic relationship disappeared. To maintain the UV cell at 298 K, water regulated in a LAUDA RM6 endocal refrigerated circulating bath was allowed to flow into a circulating cell holder.

As a typical example, the case of host **1** with (*R*)-NEA$^+$(Pic$^-$): 50 mL of a 5.00 × 10^{-5} M (*R*)-NEA$^+$(Pic$^-$) $CHCl_3$ solution was prepared. A 3 mL volume of the solution was charged into a UV cell, and the cell was placed on the cell holder with a reference cell. A 2 mL volume of a 4.41 × 10^{-4} M host **1** $CHCl_3$ solution was prepared and added stepwise to the solution in the UV cell through a microsyringe (total eight times). The concentration ratio [H]/[G] was 0, 2.83, 8.49, 17.0, 25.5, 33.9, 42.4, 56.6, and 70.7, respectively. The *K* values were determined from the spectral changes at various wavelengths (eight points, from 365 to 400 nm) using the Rose−Drago method.[23] The stoichiometry of the host and the guest was estimated from the inflection point the titration curve (mol ratio method).[24] The *K* values calculated at each wavelength were 962, 923, 898, 886, 882, 884, 875, and 850 M^{-1}, respectively. The averaged *K* value was 895 M^{-1}, and the standard deviation (SD) was 34. The averaged values calculated by two titration experiments was applied as the *K* value (917 ± 42 M^{-1}).

^{1}H NMR experiments. (a) The *K* values with metallic cations and the limiting shifts. The induced shifts of proton peaks of the host by adding stepwise guest cation were monitored at 298 K, and from the spectral changes the *K* values were determined using the 1:1 nonlinear method. A typical example was as follows: 0.6 mL of a 5.47 mM host **1** acetone-d_6 solution was prepared in a 5 mm NMR tube with a septa cap. ^{1}H NMR spectra were measured at 298 K by step of adding six portions of KSCN acetone-d_6 solution to the host solution. The molar ratio [G]/[H] was 0, 0.60, 1.79, 4.17, 8.94, 17.9, and 29.8, respectively. The signals of H1, H3, H2, H4, H5, and three OMe's protons were followed, and the *K* values were calculated from their shift changes by means of the typical 1:1 nonlinear method, respectively.[25] The averaged *K* value was 64.0 M^{-1}, and the SD was 5.6.

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In the case of a 1:1 complexation equilibrium, the following eq 1 holds.

$$[H] = [(K[G]_0 + K[H]_0 + 1) - \{(K[G]_0 + K[H]_0 + 1)^2 - 4K[H]_0\}^{1/2}]/2K \quad (1)$$

Here, [H] represents the host concentration in the equilibrium. $[H]_0$, $[G]_0$, and K were the initial concentration of the host and the guest, and the association constant, respectively. The limiting shift (δ_{lim}) is represents by the following eq 2.

$$\delta_{lim} = ([H]_0\delta_{obs} - [H]\delta_0)/([H]_0 - [H]) \quad (2)$$

Here, δ_{obs} and δ_0 represent the observed shift and the initial shift. Therefore, the limiting shifts are calculated from eqs 1 and 2.

(b) The *K* Values and Induced Shifts by Organic Ammonium Hexafluorophosphates. Until no or little shifts were observed, the organic ammonium salt $CDCl_3$ solution was added stepwise into the host $CDCl_3$ solution in a 5 mm NMR tube keeping room temperature, and then the induced shifts were measured. The coupling constant changes for some proton signals were observed. In the case of host **1** with $NEA^+(PF_6^-)$, the association constants were determined by the NMR titration method.

Under the conditions $[G^+] > 0.1$ mM, the self-association between the protonated amino acid ester guests (PF_6^-) was observed as ^{1}H NMR spectral changes. In the case of NEA^+ guest, the self-association was hardly observed. Therefore, $NEA^+(PF_6^-)$ was selected as guest. The association constants were determined using a homemade computer program (1:1 nonlinear least-squares method). The errors are typically estimated within ±5%.

A host solution was prepared by mixing 0.080 mg of host **1** and 600 μL of $CDCl_3$ (0.226 mM). A stock guest solution, which was prepared by mixing 0.480 mg of *S*-$NEA^+(PF_6^-)$ and 200 μL of $CDCl_3$, was successively added (A^{total}, μL) to above host solution using a microsyringe: A^{total} = 0, 1, 3, 6, 10, 15, 21, 28, 36, 45, 55, or 66 mL (n = 12). The different solutions in the NMR tube were allowed to stand ca. 10 min to approach and maintain the probe temperature (298 K). Volume corrections were done for the calculation of host and guest concentrations: the final concentrations were [H] = 0.212 mM and $[G^+]$ = 0.750 mM. The H-1 proton was followed due to the easy observation. The shift change ($\Delta\delta$) was as follows: 5.32, 9.28, 16.80, 23.82, 30.37, 42.21, 50.11, 59.50, 67.76, 76.76, and 84.53 Hz. The association constant and the error was estimated at 1.5×10^3 M^{-1}, 0.28 ppm, and 1%.

(c) NOESY. The NOESY spectra of 0.7 mL of a 15 mM host **1** with (*R*)- or (*S*)-$NEA^+(PF_6^-)$ $CDCl_3$ solution, and a 15 mM free host **1** solution were measured. The NOE signals were assigned in comparison to the corresponding ^{1}H NMR COSY spectra.

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Supporting Information Available: The I_R/I_{S-dn} values of achiral host toward amino acid 2-propyl esters hydrochlorides are summarized in Table S1. Typical FAB mass spectra of achiral hosts or guest are shown in Figure S1. This material is avaliable free charge via the Internet at http://pubs.acs.org.

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