Enantioselective Complexation of Carbohydrate or Crown Ether Hosts with Organic Ammonium Ion Guests Detected by FAB Mass Spectrometry

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Abstract: Enantioselective host–guest complexation has been demonstrated by FAB mass spectrometry. Among several carbohydrates, a modified β-mannofuranoside **6b** as well as chiral crown ethers **10** and **13**, differentiates a chiral ammonium ion guest such as the (1-(1-naphthyl)ethyl)ammonium ion. The relative peak intensity (RPI) method has been applied to the evaluation of such diastereomeric complex ions where the peak intensity of the target host (M)–guest (A^+) complex ion $I((M+A)^+)$ is compared to that of the internal standard host (R)–guest (A^+) ion $I((R+A)^+)$: the RPI value = $I((M+A)^+)/I((R+A)^+)$. The present enantioselectivity is characterized by the RPI ratio value $I((M+A_{(R)})^+)/I((M+A_{(S)})^+)$ in the range 1.2–1.6 (1.0 ± 0.1 nonenantioselectivity). The observed preference of the (*R*)-enantiomer guest is compatible with model examinations and related coloration results. With chiral crown ether **13**, a close correspondence exists between the FABMS/RPI enantioselection and that of strictly related solution-phase energetics in association equilibria. The usefulness of the RPI method is also shown by comparison to the relevant equilibrium constants (NMR titration) in solution.

Since 1981, fast atom bombardment mass spectrometry (FABMS) has been widely utilized for molecular weight determination and structure analysis.[1] Especially, addition of a metallic ion (Li^+ or Na^+) or an ammonium ion salt, followed by detection of generated 1:1 adduct ions, has played a powerful role.[2] However, many studies have concentrated on the molecular weight and/or sequence determination of carbohydrates,[3] peptides,[4] proteins,[5] and so on.

The 1:1 adduct ions for which multisite interaction has been well-defined as electrostatic, hydrogen-bonding, or hydrophobic, can be regarded as host–guest complex ions at present.[6] Typical host–guest complex ions of 18-crown-6 with various cationic species have been successfully clarified by mass spectrometry using various types of soft-ionization techniques (FAB,[7] CI,[8] PD,[9] etc.[10,11]). Recently, more weakly bonded complexes, for example, receptor–ligand (enzyme–substrate) complexes of immunophilins[12] or hydrogen-bonding complexes of imidazoles,[13] etc.,[14] were also identified.

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Except for the studies on 18-crown-6 and the related host systems, however, there are surprisingly few FABMS studies on such host–guest complexations. Even if FABMS target compounds are limited to carbohydrates, few reports of mono-,[15] oligo-,[16] or polysaccharides[17] with organic cations have appeared. This is in sharp contrast to the extensive studies undertaken in solution using NMR and UV methods for (1) monosaccharides with metallic cations (by Angyal)[18] and (2) cyclic oligosaccharides (cyclodextrins) with neutral molecules.[19]

Recently, we utilized the RPI (relative peak intensity) method in FABMS for quantitative comparison of 1:1 adduct ion formation (or host–guest ion formation) of modified carbohydrates with cations and determined the alkylammonium ion affinity ordering. Furthermore, we have also emphasized the importance of permethylation of carbohydrates for increasing complexation ability and sensitivity.[20]

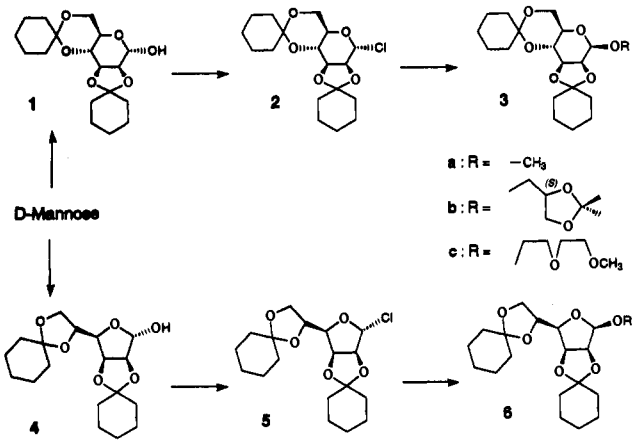
In this paper, we describe the application and applicability of the FABMS/RPI method to enantioselective host–guest complexation.[21] First, newly designed carbohydrate derivatives (**3**, **6**) are chosen as the hosts. Second, crown ether derivatives (**10**, **13**, **16**) are employed for confirmation as the typical hosts of a highly chiral environment.

To our knowledge, there are at present only two types of analytical approaches for successful detection of enantioselectivity by mass spectrometry: (1) the FABMS/MS approach for lithium-coordinated diols[22] and (2) the CIMS approach for mandelic acid aggregations.[23] This paper describes, for the first time, diastereomeric host–guest complexations involving carbohydrate or chiral crown ether hosts detected by FAB mass spectrometry.

Results and Discussion

Selection of Carbohydrate Hosts. Enantioselectivity may be achieved by incorporating chiral unit(s) into the host skeleton. Carbohydrates are chiral compounds. Therefore, if a carbohydrate derivative can act as a host molecule capable of binding an ion by more than two oxygens, a binding enantioselectivity difference toward chiral alkylammonium ion guests may appear in association equilibria. For example, in the host systems of designed chiral crown ethers[24] or the related noncyclic derivatives, enantioselectivity in association equilibria has been established mainly on the basis of intermolecular complementarity on steric grounds: crown ethers involving 1,1′-binaphthyl[25] or pyridyl units,[26] tetracyclic podand ionophores,[27] etc.[28]

Scheme I



In this study, β-D-mannose was selected as the carbohydrate host skeleton because this carbohydrate is known to have a relatively greater ability to complex with cationic species[20] and is readily available. MNDO model calculations suggest a possible site[3] for the complexation of permethylated β-D-mannopyranose (or permethylated β-D-mannofuranose) with Li^+, where three oxygens O_1, O_2, and O_{ring} (or O_1, O_2, and O_3) can bind the cation (2.2 Å for O···Li^+). Actually, for the complex ion of methyl 2,3-*O*-isopropylidene-4-*O*-methyl-β-L-rhamnopyranoside with Na^+ in acetone, three-point binding (O_1, O_2, and O_{ring}) was deduced by NMR spectrometry.[29] Furthermore, for the complex between β-D-mannofuranose and Ca^{2+}, three-point binding (O_1, O_2, and O_3) was confirmed by X-ray crystallography.[30]

Considering the above complexation sites, β-D-mannose was modified by the introduction of two functional groups: (1) another oxygen-containing group at an anomeric OH position, and (2) two cyclohexylidene groups at the remaining OH positions. The former is expected to increase complexation ability,[31] and the latter are expected to operate as potential chiral barriers.

The carbohydrate derivatives, **3a–c** and **6a–c** were synthesized by the reaction pathways shown in Scheme I.

The chiral crown ether derivatives, **10**, **13**, **16**, were prepared by the reaction pathways shown in Scheme II.

General Methodology of FABMS/RPI. Our general RPI methodology in FABMS is the following: (1) Three solutions of a carbohydrate host (M), an internal standard host (R), and an

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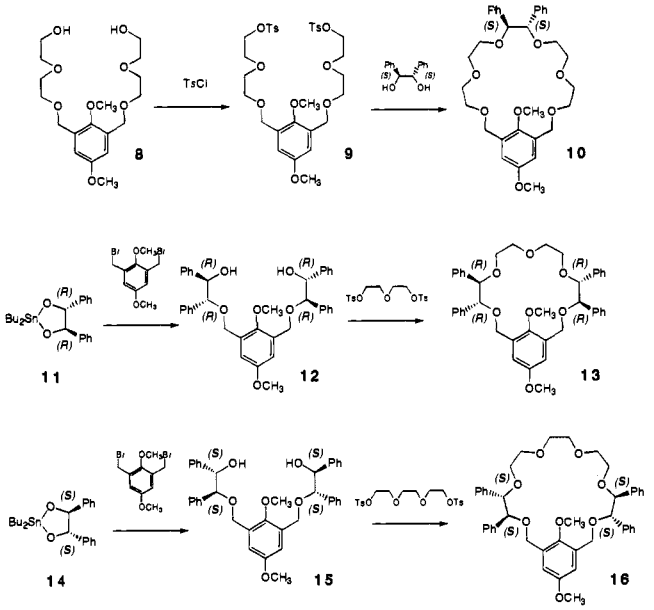
Scheme II



ammonium ion guest (A^+) are mixed with a matrix of NBA (*m*-nitrobenzyl alcohol) or glycerol (see Experimental Section). R is added to an equimolar amount of M. As the internal standard R, an achiral crown ether (or a deuterated carbohydrate derivative) having structural and functional similarity to M is usually employed. (2) FAB mass spectra are obtained in an accumulation (10 times) mode to obtain more reliable data. (3) The resultant peak intensities of the 1:1 host–guest ions which appear simultaneously in each spectrum as $(M+A)^+$ and $(R+A)^+$ ions are compared.[20]

The relative peak intensity (RPI) value is defined by the ratio of the corresponding peak intensities as $I((M+A)^+)/I((R+A)^+)$. Since the magnitude of the RPI values is primarily controlled by the choice of the internal standard, it is important to use an internal standard having an RPI value near 1.0 to obtain reliable data.[32] Using these FABMS/RPI values, we can compare the degree of ammonium ion transfer (eq 1) under FABMS conditions.

$$M + (R+A)^+ \rightleftharpoons (M+A)^+ + R \qquad (1)$$

Indeed, an ordering of cation affinity has been evaluated for a selected series of carbohydrates (M) of the same molecular weight but different stereostructures.[20] The present aim is to extend this RPI method to the detection of enantioselectivity of a selected chiral M toward an enantiomeric pair of ammonium ions ($A_{(R)}^+$ and $A_{(S)}^+$) (eqs 2 and 3). The two diastereomeric complex ions,

$$M + (R+A_{(R)})^+ \rightleftharpoons (M+A_{(R)})^+ + R \qquad (2)$$

$$M + (R+A_{(S)})^+ \rightleftharpoons (M+A_{(S)})^+ + R \qquad (3)$$

$(M+A_{(R)})^+$ and $(M+A_{(S)})^+$, might vary both in structures and in their association constants and then might exhibit different FABMS/RPI values in an appropriate host–guest pair.

Steric Effects on FABMS/RPI Values. Table I shows the steric effects of ammonium ions on RPI values. For a series of alkylammonium ions, in spite of largely different sizes of alkyl groups, carbohydrates **7** (permethylated β-D-mannopyranoside) and **6a** have values of about 4.1 and 0.6, respectively. However, **6b** shows clear alkyl size dependency; for less bulky alkyl groups, it has an RPI value of ca. 1.0, and for more bulky ones, ca. 0.3.

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Table I. RPI Values for Selected Carbohydrates (M) Complexed with Alkylammonium Ions (A^+)[a]

	$I((M+A)^+)/I((R+A)^+)$		
A^+ (Cl^-)	M = **7**[b]	M = **6a**	M = **6b**
NH_4^+	3.5	0.6	1.0
$C_2H_5NH_3^+$	4.6[c]	0.8	1.4
n-$C_4H_9NH_3^+$	4.1	0.5	0.7
n-$C_8H_{17}NH_3^+$	4.5[c]	0.4	0.2
1-adamantyl-NH_3^+	3.8	0.4	0.3
trityl-NH_3^+	4.0	0.8	0.4

[a] R = 12-crown-4. Matrix = NBA. Accumulation of 10 scan times (scans 10–20). [M]:[R]:[A^+] = 1:1:4. Standard deviation (SD) is within ±0.2 (n = 3). [b] Permethylated β-mannopyranoside. [c] SD is within ±0.6.

These results suggest that carbohydrate **6b** is relatively sensitive to the size of the alkyl moiety of alkylammonium ions on the RPI scale.

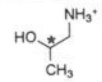
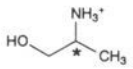
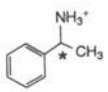
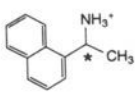
Enantioselectivity of Carbohydrates. In Table II the RPI values of some selected complex pairs are listed together with their enantioselectivities which are evaluated as the ratio of RPI values for an enantiomeric ammonium ion pair; i.e., $RPI_{(R)}/RPI_{(S)} = I((M+A_{(R)})^+)/I((M+A_{(S)})^+)$. Hardly any of the complex pairs show enantioselectivity on the basis of RPI values. That is, the (*R*)- and (*S*)-ammonium ions give equal RPI values, so that the RPI ratio is 1.0 (nonenantioselectivity). However, when M is the carbohydrate **6b** and A^+ is a (1-(1-naphthyl)ethyl)ammonium ion, it is observed that the $RPI_{(R)}$ value is 20% larger than the $RPI_{(S)}$ value;[21] that is, the RPI ratio is 1.2. This is the first example of enantioselectivity of a modified carbohydrate being established in diastereomeric host–guest complex ions using FABMS. This finding is supported by similar results for some chiral crown ether hosts (see later). Therefore, the observation shows that at least the carbohydrate **6b** must bind the ammonium ion at a particular complexation site. On the other hand, when the guest is changed to a less bulky (1-phenylethyl)ammonium ion, such enantioselectivity of **6b** vanishes. The larger size of the naphthyl unit likely results in chiral differentiation because of steric effects.

On the other hand, the host **6c**–guest (1-(1-naphthyl)-ethyl)ammonium ion combination does not show any enantioselection. We propose that a complexation site of the β-mannofuranose moiety moves so that cyclohexylidene steric barriers become less effective in this host–guest pair. In a recent report by Still et al., enantioselectivity of noncyclic podand ionophores toward chiral ammonium ions has been confirmed by X-ray crystallography.[27] According to this report, the most tightly bound oxygen atoms of the host vary in the different structures of the related hosts. This lends support to our prediction.

Observed RPI values are plotted against scan times in Figure 1a (1b) in order to check the constancy of RPI values, where M is **6b** (**6c**), R is 12-crown-4 (15-crown-5), and A^+ is an enantiomeric pair of the (1-(1-naphthyl)ethyl)ammonium ion ((1-phenylethyl)ammonium ion). Two lines are clearly distinctive in Figure 1a, never crossing each other, and are very constant for a sufficient period of time, showing appreciable enantioselectivity. On the other hand, in the case of **6c**, the RPI values fall on a single line, as shown in Figure 1b, demonstrating nonenantioselectivity in this type of plot.

Two sample solutions involving diastereomeric complex ions as a pair were carefully and successively measured under the same machine conditions of FABMS. We would expect hydrophobicity to be nearly identical for (*R*)- and (*S*)-alkylammonium ions. The different RPI values in a diastereomeric pair should be derived from the different stabilities of the diastereomeric complex ions and by their different degrees of association. Although conventional (EBE type) FABMS/MS spectra (MI and CID) show no differences between daughter ion patterns of two diastereomeric complex ions,[21] this may be supported by the fact that equal RPI values are observed in most cases in Table

Table II. Comparison of RPI Ratio Values for Carbohydrates Complexed with Enantiomeric Alkylammonium Ions[a]

A^+ (Cl^-)	$I((M+A_{(R)})^+)/I((M+A_{(S)})^+)$ M = **3a**	M = **3b**	M = **6a**	M = **6b**	M = **6c**
			1.0 (0.74/0.74)	1.0 (1.2[b]/1.2[b])	
	1.0 (0.4[b]/0.4)	1.0 (1.4[b]/1.4[b])	1.0 (0.57/0.57)	1.0 (1.1[b]/0.9[b])	
	1.0 (0.8/0.8)	1.0 (1.3/1.4)	1.0 (0.57/0.53)	1.0 (1.64[b]/1.67)	1.0 (0.68/0.70)[c] 1.0 (4.0/3.9)
	1.0 (0.4/0.4)	1.0 (1.3/1.5[b])	1.0 (0.71/0.65)	1.2[d] (1.6/1.3) 1.2[e] (1.6/1.4)	1.0 (5.1[b]/5.0[b])

[a] RPI ratio: $I((M+A_{(R)})^+)/I((M+A_{(S)})^+) = RPI_{(R)}/RPI_{(S)}$. Here, $RPI_{(R)} = I((M+A_{(R)})^+)/I((R+A_{(R)})^+)$ and $RPI_{(S)} = I((M+A_{(S)})^+)/I((R+A_{(S)})^+)$, which are shown in parentheses as ($RPI_{(R)}/RPI_{(S)}$). R = 12-crown-4. Matrix = NBA. SD is within ±0.05 (n = 5–15). Concentration ratio [M]:[R]:[A^+] = 1:1:4. [b] SD is within ±0.1. [c] R = 15-crown-5. [d] (1.6 ± 0.03)/(1.3 ± 0.08). [e] (1.59 ± 0.05)/(1.36 ± 0.03).

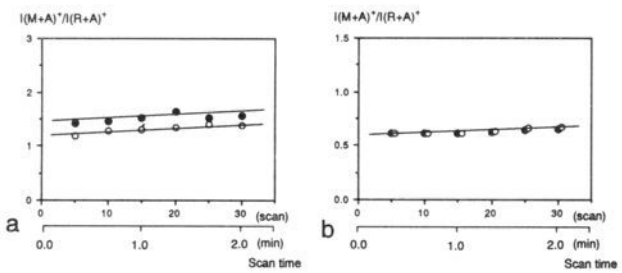
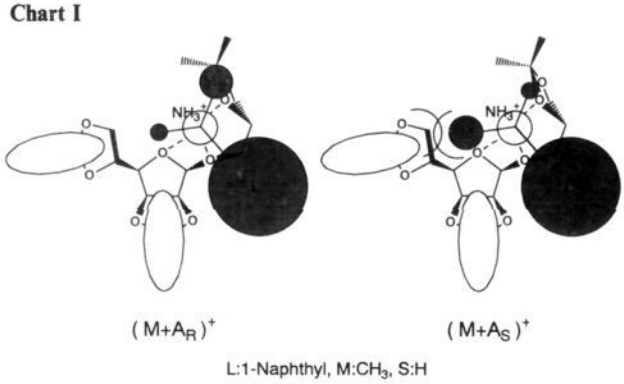


Figure 1. Plots of RPI values versus scan times (●, $RPI_{(R)}$; ○, $RPI_{(S)}$): (a) M = **6b**, R = 12C4, A^+ = (1-Naph)CH(Me)NH_3^+; (b) M = **6c**, R = 15C5, A^+ = PhCH(Me)NH_3^+.

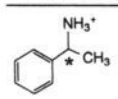
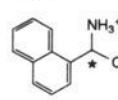
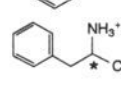
Chart I



I (RPI ratio = 1.0 ± 0.1). Therefore, as far as a comparison is limited to a diastereomeric complex pair, the host–guest complex ion with a larger RPI value is more stable. This provides practical and useful direct information obtained from the FABMS/RPI approach.

The observed preference for an (*R*)-ammonium ion in the complex is compatbile with the following predicted models. According to MNDO model calculations on the 1:1 complex ion between **6b** and Li^+, it is expected that the three oxygens O_1, O_{ring}, and $O_{dioxolane}$ can bind the Li^+ cation. CPK models of the two complex ions are then constructed using the same host structure as the above in a first-order approximation (Chart I). Judging from these CPK models, the methyl group in the host–(*S*)-guest complex ion $(M+A_{(S)})^+$ is sterically repulsive to the framework of the C_5–C_6 moiety in the host. It is then predicted that the $(M+A_{(S)})^+$ ion is energetically less favorable than the $(M+A_{(R)})^+$ ion on steric grounds. Therefore, the complex ion having the larger RPI value corresponds to the energetically favorable diastereomeric complex ion.

Table III. Comparison of RPI Ratio Values for Chiral Crown Ethers Complexed with Enantiomeric Alkylammonium Ions[a]

A^+ (Cl^-)	$I((M+A_{(R)})^+)/I((M+A_{(S)})^+)$ M = **10**	M = **13**	M = **16**
	1.1 (0.84/0.75)		
	1.2 (0.90/0.74)[b] 1.2 (0.85/0.69)[b]	1.2 (2.0/1.6)[c] 1.2 (0.98/0.81)[c,e]	1.0 (1.32/1.32)[d]
	0.9 (1.43/1.60)	1.4 (0.71/0.50)[f] 1.5 (1.81/1.22)[d,f] 1.6 (1.85/1.13)[d,f,g]	1.1 (1.47/1.29)

[a] Presentation is the same as that in Table II. R = 15-crown-5. Concentration ratio [M]:[R]:[A^+] = 1:1:1. [b] (0.90 ± 0.02)/(0.74 ± 0.02); (0.85 ± 0.01)/(0.69 ± 0.02). [c] (1.96 ± 0.02)/(1.58 ± 0.05); (0.98 ± 0.03)/(0.81 ± 0.05). [d] [M]:[R]:[A^+] = 1:1:2. [e] [M]:[R]:[A^+] = 1:1:0.5. [f] (0.71 ± 0.01)/(0.50 ± 0.02); (1.81 ± 0.03)/(1.22 ± 0.01); (1.85 ± 0.03)/(1.13 ± 0.01). [g] Racemic A^+; RPI = 1.57 ± 0.01.

Nonenantioselectivity for the corresponding carbohydrate **3b** is informative. From CPK model examinations, the β-mannopyranoside skeleton (six-membered ring) is more planar than the β-mannofuranoside one (five-membered ring) and, thus, is not effective for guest differentiation. This structural requirement of the pyranoside host seems to be the reason for such nonenantioselection.

Enantioselectivity of Chiral Crown Ethers. Table III is a summary of the RPI values and RPI ratios for the three chiral crown ethers. Two of the three crowns (**10** and **13**) successfully show enantioselectivity toward an enantiomeric pair of (1-(1-naphthyl)ethyl)ammonium ions. The RPI ratio is 1.2 in both cases, showing a preference for the (*R*)-ammonium ion (Figure 2a). In addition, for the enantiomeric guest of the methyl ester of phenylalaninium chloride, chiral crown **13** has the largest RPI ratio value which we have observed (Figure 3). The observed RPI values of the racemic ammonium ion are also plotted against scan times in Figure 2b, illustrating the intermediate nature of these $RPI_{(R)}$ and $RPI_{(S)}$ values. Thus, the FABMS/RPI results demonstrate that, with chiral crowns **10** and **13**, the (*R*)-enantiomers of the two guests were bound more strongly than the (*S*)-types.

In the case of the azophenolic derivative of **13**, Kaneda et al. have already reported enantioselective coloration with chiral

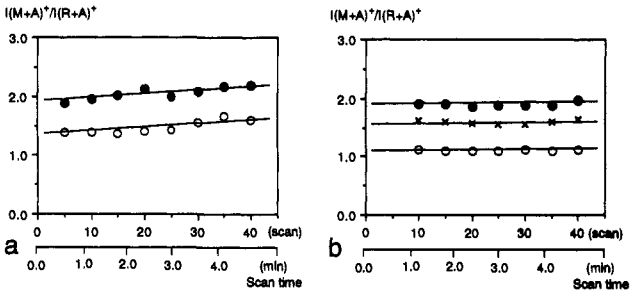


Figure 2. Plots of RPI values versus scan times (●, $RPI_{(R)}$; ○, $RPI_{(S)}$; ×, $RPI_{(racemic)}$): (a) M = **13**, R = 15C5, A^+ = (1-Naph)CH(Me)NH_3^+, [M]:[R]:[A^+] = 1:1:1; (b) M = **13**, R = 15C5, A^+ = $PhCH_2CH$-(COOMe)NH_3^+, [M]:[R]:[A^+] = 1:1:2.

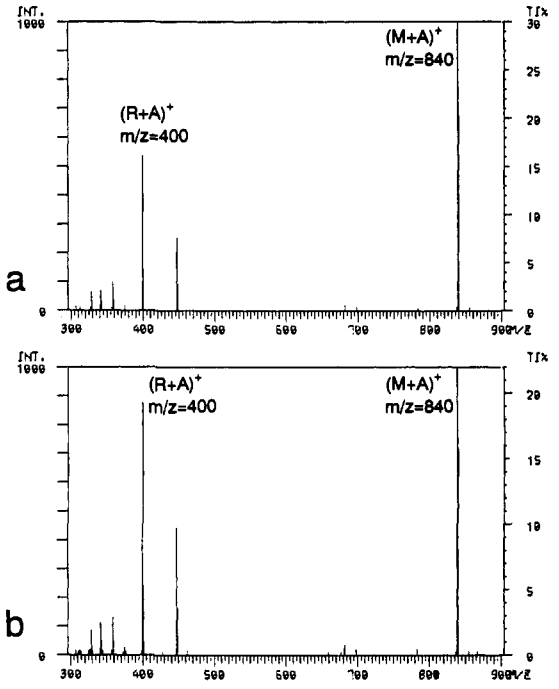


Figure 3. FAB mass spectra (accumulation mode) for a mixture of chiral crown **13**, 15C5, and an enantiomer of the methyl ester of phenylalaninium chloride with NBA matrix: (a) (*R*)-ammonium isomer; (b) (*S*)-ammonium isomer.

amines in ethanol, where the corresponding azophenolic (*R,R,R,R*)-crown host binds more effectively to the (*R*)-(1-(1-naphthyl)ethyl)amine guest than to the other enantiomeric (*S*)-amine.[33] Therefore, the present finding by the FABMS/RPI approach that crown host **13** prefers the (*R*)-ammonium ion guest is consistent with the previous finding by the coloration system.

On the other hand, crown **16** shows no chiral differentiation. These results are understandable on the basis of the structural complementarity of the corresponding host–guest complex ions. The larger size of the crown ring and an accompanying shift of the attached phenyl groups (chiral barriers) result in looser intermolecular complementarity with the guest ammonium ion, even if a sterically bulky naphthyl unit exists.

Association Constants for the Complexation of Carbohydrates or Chiral Crown Ethers with Ammonium Ions in Solution. Table IV shows association constants (K_s) for the complexation of some carbohydrates and crowns with the ethylammonium ion or the (2-phenylethyl)ammonium ion in acetonitrile at 25 °C. A nonlinear (in the case of $K_s > 1$) or a linear method (in the case of $K_s < 1$; $[A^+]_0/[M]_0 > 70$) was employed for K_s determination

(33) (a) Kaneda, T.; Hirose, K.; Misumi, S. *J. Am. Chem. Soc.* **1989**, *111*, 742–743. (b) Kaneda, T. In *Crown Ethers and Analogous Compounds*; Hiraoka, M., Ed.; Elsevier: Amsterdam, 1992; Chapter 6.

Table IV. K_s Values Determined by ^{1}H-NMR Titration in CD_3CN at 25 °C[a]

M	A^+ (PF_6^-) CH_3-$CH_2NH_3^+$	A^+ (PF_6^-) C_6H_5-$CH_2CH_2NH_3^+$	A^+ (ClO_4^-) (1-Naph)-CH(Me)NH_3^+
β-Glc-p[b]	0.2 ± 0.02 (2)[c]		
3b	0.5 ± 0.02 (3)[c]		
6b	0.7 ± 0.3 (5)[c]		
3a		0.9 (1)	
β-Rib-f[b]	2.1 (1)		
α-Man-p[b]	3.9 ± 0.7 (9)	9.4 ± 1.0 (7)[d]	
α-Man-f[b]	6.4 ± 1.0 (4)	25.6 ± 6.9 (3)[c]	
6c	26.1 ± 1.3 (6)		
β-Man-f[b]	26.4 ± 4.3 (9)	40.6 ± 4.4 (5)	
α-Tal-p[b]		44.0 ± 0.9 (4)	
12-crown-4[e]	200 (1)	75.6 (1)	
13			32.9 ± 2.3 (4)[f]
13			16.5 ± 1.9 (4)[g]

[a] Numbers in parentheses show number of independent protons followed ($\Delta\delta^{obs}_{max} > 5$ Hz). [b] Permethylated monosaccharide. [c] $\Delta\delta^{obs}_{max} > 3$ Hz. [d] Previously determined as approximately 3 M^{-1} by using a linear method (^{1}H-NMR titration).[20a] [e] K_s with $NH_4^+SCN^-$ in CD_3OD (commercially available without purification) at 25 °C equals 6.1. [f] (*R*)-Ammonium ion in acetone-d_6 at 25 °C. [g] (*S*)-Ammonium ion in acetone-d_6 at 25 °C.

by ^{1}H-NMR titration.[34] In the former case, the calculated K_s values were averaged for the various target protons where the maximum induced shift value ($\Delta\delta^{obs}_{max}$) equals more than 5 Hz in our measurements (see Experimental Section). The results are listed in Table IV.

Recently, the ability of polyols and their permethylated derivatives to complex with cations in water was reported to be almost absent.[18] Alternatively, we selected acetonitrile as a dipolar aprotic solvent and successfully determined weak K_s values between permethylated carbohydrates and alkylammonium ions using the ^{1}H-NMR approach.

All the K_s values obtained for carbohydrates **3a**, **3b**, and **6b** are less than 1. The utilization of a high concentration of A^+ is, at least, required for observing an appreciable induced shift. In this sense, detection of chiral differentiation by K_s values in solution would be impossible for these carbohydrate cases. The K_s values for carbohydrates in Table IV are generally smaller than the value for 12-crown-4. As far as the comparison is limited to a series of permethylated carbohydrates, the more the MeO groups of M are located toward the upper side of the ring in Mills' formulas, the larger the K_s values are. Cf. the K_s ordering of α-Man-p < α-Tal-p, α-Man-p < α-Man-f, and α-Man-f < β-Man-f. These observations also suggest the importance of electrostatic interaction between oxygen atoms of carbohydrates and cations, which has been well-defined in host–guest complexation involving various crown ether hosts.

The K_s values for complexation between crown **13** and an enantiomeric (1-(1-naphthyl)ethyl)ammonium perchlorate in acetone at 25 °C could be successfully determined by ^{1}H-NMR titration. The K_s value with the (*R*)-ammonium ion is clearly larger than the K_s value with the (*S*)-ammonium ion. This is enantioselectivity from the viewpoint of energetics in solution (eqs 2 and 3). The result is identical to that derived from the FABMS/RPI approach.

The present investigation has demonstrated that our FAB mass spectrometric method is applicable to the detection of molecular enantioselective recognition. Emphasis is put on the fact that the FABMS/RPI values are parallel to their energetics in equilibria shown in eqs 2 and 3. Enantioselection of a carbohydrate which exhibits very weak complexation ability in solution can be readily observed by this type of FAB mass spectrometry, even if it is difficult to detect by NMR spectrometry: a great merit of mass

(34) (a) Takai, Y.; Okumura, Y.; Takahashi, S.; Sawada, M.; Kawamura, M.; Uchiyama, T. *J. Chem. Soc., Chem. Commun.* **1993**, 53–54. (b) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386.

spectrometry. We postulate that this advantage results from the gas-phase character of the FABMS/RPI approach, although present data do not allow us to distinguish whether the FABMS/RPI values reflect energetics in the solution or in the gas phase. This is an area we hope to explore in a future study.

Experimental Section

Materials. Ten carbohydrate derivatives (**1–6**) were obtained from D-mannose by following the procedures described in the literature (Scheme I).[35–37] The compounds were mainly purified by silica gel column chromatography and characterized by ^{1}H-NMR, FTIR, and EI or FAB mass spectrometry.

Methyl 2,3:4,6-di-*O*-cyclohexylidene-β-D-mannopyranoside (3a): mp 127–128 °C (recrystallized from hexane), lit. mp 128–129 °C;[36] ^{1}H NMR ($CDCl_3$) δ 4.69 (d, 1H, $^3J_{1,2}$ = 2.4 Hz, H_1), 4.29 (dd, 1H, $^3J_{1,2}$ = 2.4 Hz, $^3J_{2,3}$ = 5.7 Hz, H_2), 4.13 (dd, 1H, $^3J_{2,3}$ = 5.7 Hz, $^3J_{3,4}$ = 7.6 Hz, H_3), 3.94 (dd, 1H, $^3J_{3,4}$ = 7.6 Hz, $^3J_{4,5}$ = 10.2 Hz, H_4), 3.92 (dd, 1H, $^3J_{5,6'}$ = 4.5 Hz, $^2J_{6,6'}$ = 10.3 Hz, $H_{6'}$), 3.81 (t, 1H, $^3J_{5,6}$ = 10.3 Hz, $^2J_{6,6'}$ = 10.3 Hz, H_6), 3.58 (s, 3H, CH_3), 3.22 (dt, 1H, $^3J_{4,5}$ = 10.2 Hz, $^3J_{5,6}$ = 10.3 Hz, $^3J_{5,6'}$ = 4.5 Hz, H_5), 1.93–1.36 (m, 10H, cyclohexylidene group). Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.34; H, 8.62. A single-crystal X-ray structure determination confirmed the structure of **3a** (see later).

(2′*S*)-2′,3′-(Isopropylidenedioxy)propyl 2,3:4,6-Di-*O*-cyclohexylidene-β-D-mannopyranoside (3b). Compound **2** (1.2 g, 2.64 mmol) was added to a stirred mixture of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol (0.31 g, 2.33 mmol), Ag_2CO_3 (0.96 g), and 4A molecular sieves (5.1 g) in dry CH_2Cl_2 (12 mL). The mixture was stirred under a N_2 atmosphere in the dark at room temperature for 3.5 d, filtered with Celite, and concentrated. Purification on a silica gel column (eluent 8:1 CH_2Cl_2/CH_3COOEt) yielded the syrupy compound **3b** (0.36 g, 32% yield): ^{1}H NMR ($CDCl_3$) δ 4.92 (d, 1H, $^3J_{1,2}$ = 2.8 Hz, H_1), 4.36 (dd, 1H, $^3J_{1,2}$ = 2.8 Hz, $^3J_{2,3}$ = 5.7 Hz, H_2), 4.26–4.13 (m, 3H, H_3, H_4, dioxolane 1H), 4.03–3.94 (m, 3H, $H_{6'}$, dioxolane 2H), 3.87 (t, 1H, $^3J_{5,6}$ = 10.5 Hz, $^2J_{6,6'}$ = 10.3 Hz, H_6), 3.22 (dt, 1H, $^3J_{4,5}$ = $^3J_{5,6}$ = 10.5 Hz, $^3J_{5,6'}$ = 4.5 Hz, H_5), 1.51 (s, 3H, dioxolane CH_3), 1.45 (s, 3H, dioxolane CH_3), 1.85–1.46 (m, 10H, cyclohexylidene group); FABMS (NBA matrix) *m*/*z* 454 (M^+). Anal. Calcd for $C_{24}H_{38}O_8$: C, 63.42; H, 8.43. Found: C, 63.51; H, 8.25.

3′,6′-Dioxaheptyl 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranoside (3c): syrup; ^{1}H NMR ($CDCl_3$) δ 4.71 (d, 1H, $^3J_{1,2}$ = 2.4 Hz, H_1), 4.13 (dd, 1H, $^3J_{1,2}$ = 2.4 Hz, $^3J_{2,3}$ = 5.9 Hz, H_2), 3.96 (dd, 1H, $^3J_{2,3}$ = 5.9 Hz, $^3J_{3,4}$ = 7.6 Hz, H_3), 3.85 (dd, 1H, $^3J_{3,4}$ = 7.6 Hz, $^3J_{4,5}$ = 10.4 Hz, H_4), 3.73 (dd, 1H, $^3J_{5,6'}$ = 5.5 Hz, $^3J_{6,6'}$ = 10.8 Hz, $H_{6'}$), 3.63 (dd, 1H, $^3J_{5,6}$ = 10.4 Hz, $^3J_{6,6'}$ = 10.8 Hz, H_6), 3.22 (s, 3H, OMe), 3.07 (dt, 1H, $^3J_{4,5}$ = $^3J_{5,6}$ = 10.4 Hz, $^3J_{5,6'}$ = 5.5 Hz, H_5), 1.75–1.24 (m, cyclohexylidene group).

2,3:5,6-Di-*O*-cyclohexylidene-α-D-mannofuranose (4): mp 120 °C (recrystallized from ether/hexane), lit. mp 122 °C;[37] ^{1}H NMR ($CDCl_3$) δ 5.39 (d, 1H, $^3J_{1,OH}$ = 2.3 Hz, H_1), 4.78 (dd, 1H, $^3J_{2,3}$ = 6.0 Hz, $^3J_{3,4}$ = 3.9 Hz, H_3), 4.60 (d, 1H, $^3J_{2,3}$ = 6.0 Hz, H_2), 4.42 (dd, 1H, $^3J_{4,5}$ = 6.0 Hz, H_5), 4.25 (dd, 1H, $^3J_{3,4}$ = 9.0 Hz, $^3J_{4,5}$ = 6.0 Hz, H_4), 4.08–4.03 (m, 2H, H_6, $H_{6'}$), 2.94 (d, 1H, $^3J_{1,OH}$ = 2.3 Hz, OH), 1.68–1.32 (m, 10H, cyclohexylidene group); ^{13}C NMR ($CDCl_3$) δ 113.4, 109.4, 101.5 ($^1J_{CH}$ = 175.0 Hz, C_1), 85.2, 80.5, 79.4, 73.1, 65.9, 36.4, 35.7, 34.7, 34.2, 25.2, 25.1, 24.1, 24.0, 23.9, 23.7.

2,3:5,6-Di-*O*-cyclohexylidene-α-D-mannofuranosyl chloride (5): syrup; ^{1}H NMR ($CDCl_3$) δ 6.01 (s, 1H, H_1), 4.95 (d, 1H, $^3J_{2,3}$ = 5.8 Hz, H_2), 4.85 (dd, 1H, $^3J_{2,3}$ = 5.8 Hz, $^3J_{3,4}$ = 3.8 Hz, H_3), 4.45 (m, 1H, $^3J_{4,5}$ = 6.7 Hz, $^3J_{5,6}$ = 5.2 Hz, $^3J_{5,6'}$ = 6.3 Hz, H_5), 4.26 (dd, 1H, $^3J_{3,4}$ = 3.8 Hz, $^3J_{4,5}$ = 6.7 Hz, H_4), 4.07 (dd, 1H, $^3J_{5,6'}$ = 6.3 Hz, $^2J_{6,6'}$ = 8.7 Hz, $H_{6'}$), 3.99 (dd, 1H, $^3J_{5,6}$ = 5.2 Hz, $^2J_{6,6'}$ = 8.7 Hz, H_6), 1.80–1.33 (m, 10H, cyclohexylidene group).

Methyl 2,3:5,6-di-*O*-cyclohexylidene-β-D-mannofuranoside (6a): syrup; ^{1}H NMR ($CDCl_3$) δ 4.61 (dd, 1H, $^3J_{2,3}$ = 5.6 Hz, $^3J_{3,4}$ = 3.9 Hz, H_3), 4.55 (m, 2H, H_1, H_2), 4.37 (dt, 1H, $^3J_{4,5}$ = 6.3 Hz, $^3J_{5,6}$ = 5.8 Hz, H_5), 4.01 (d, 2H, $^3J_{5,6}$ = 5.8 Hz, H_6, $H_{6'}$), 3.53 (dd, 1H, $^3J_{3,4}$ = 3.9 Hz, $^3J_{4,5}$ = 6.3 Hz, H_4), 3.42 (s, 3H, CH_3), 1.72–1.19 (m, 10H, cyclohexylidene group).

(2′*S*)-2′,3′-(Isopropylidenedioxy)propyl 2,3:5,6-di-*O*-cyclohexylidene-β-D-mannofuranoside (6b): syrup; ^{1}H NMR ($CDCl_3$) δ 4.75 (d, 1H, $^3J_{1,2}$ = 3.9 Hz, H_1), 4.68 (dd, 1H, $^3J_{2,3}$ = 6.2 Hz, $^3J_{3,4}$ = 3.9 Hz, H_3), 4.61 (dd, 1H, $^3J_{1,2}$ = 3.9 Hz, $^3J_{2,3}$ = 6.2 Hz, H_2), 4.42 (dt, 1H, $^3J_{4,5}$ = 6.5 Hz, $^3J_{5,6}$ = 6.0 Hz, H_5), 4.30 (m, 1H, dioxolane 1H), 4.05 (m, 3H, H_6, $H_{6'}$, dioxolane 1H), 3.90 (m, 1H, dioxolane 1H), 3.86 (m, 1H, dioxolane 1H), 3.67 (dd, 1H, $^3J_{3,4}$ = 3.9, $^3J_{4,5}$ = 6.5 Hz, H_4), 3.64 (m, 1H, dioxolane 1H), 1.77–1.26 (m, cyclohexylidene), 1.42 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); FABMS (NBA matrix) *m*/*z* 454 (M^+). Anal. Calcd for $C_{24}H_{38}O_8$: C, 63.42; H, 8.43. Found: C, 63.53; H, 8.70.

3′,6′-Dioxaheptyl 2,3:5,6-di-*O*-cyclohexylidene-β-D-mannofuranoside (6c): syrup; ^{1}H NMR ($CDCl_3$) δ 4.78 (d, 1H, $^3J_{1,2}$ = 3.8 Hz, H_1), 4.67 (dd, 1H, $^3J_{1,2}$ = 3.8 Hz, $^3J_{2,3}$ = 6.1 Hz, H_2), 4.62 (dd, 1H, $^3J_{2,3}$ = 6.1 Hz, $^3J_{3,4}$ = 3.8 Hz, H_3), 4.44 (m, 1H, H_5), 4.06 (m, 2H, H_6, $H_{6'}$), 3.94 (m, 1H, diethylene glycol), 3.81 (m, 2H, diethylene glycol), 3.65 (m, 3H, diethylene glycol), 3.54 (m, 2H, diethylene glycol), 3.38 (s, 3H, CH_3).

Permethylated α-D-mannofuranose and permethylated β-D-mannofuranose were obtained by a slight modification of the well-known Hakomori method[38] from the corresponding methyl α-D-mannofuranoside[39] and methyl β-D-mannofuranoside,[40] respectively.

Chiral Crown Ethers (10, 13, 16). These compounds are the synthetic intermediates of the corresponding azophenolic derivatives already reported in the literature.[33] The synthesis and characterization of the chiral crowns are as follows.

2,6-Bis-(7-hydroxy-2,5-dioxaheptyl)-1,4-dimethoxybenzene (8). 2,6-Bis(bromomethyl)-1,4-dimethoxybenzene prepared according to the literature procedure[41] (10.0 g, 340 mmol) was mixed with diethylene glycol (55 mL) and NaOH (3.0 g, 75 mmol), and the mixture was stirred at 110 °C for 2 h. After dilution with H_2O, extraction with $CHCl_3$, and evaporation in vacuo, the product was purified by silica gel column chromatography. Diol **8** was obtained in quantitative yield (10.7 g) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.93 (s, 2H, Ar), 4.60 (s, 4H, benzyl), 3.79 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 3.75–3.53 (m, 16H, ether chain), 2.60 (b s, 2H, OH); EIMS *m*/*z* 374 (M^+). Anal. Calcd for $C_{18}H_{30}O_8$: C, 57.74; H, 8.08. Found: C, 57.64; H, 7.94.

2,6-Bis(7-((*p*-tolylsulfonyl)oxy)-2,5-dioxaheptyl)-1,4-dimethoxybenzene (9). To a pyridine solution (50 mL) of diol **8** (2.00 g, 5.34 mmol) which had been cooled with an ice bath was added tosyl chloride (5.09 g, 26.7 mmol), which was dissolved with stirring. The solution was allowed to stand for 3 d in a refrigerator. The reaction mixture was poured into a mixture of ice and water, and the product was extracted with methylene chloride. The organic layer was washed with a 6 N HCl solution, dried over anhydrous K_2CO_3, and evaporated in vacuo to afford ditosylate **9** in 95.3% yield (3.48 g) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 4H, Ts), 7.29 (d, *J* = 8.0 Hz, 4H, Ts), 6.85 (s, 2H, Ar), 4.53 (s, 4H, benzyl), 4.33–3.40 (m, 16H, ether chain), 3.75 (s, 3H, inner CH_3O), 3.68 (s, 3H, outer CH_3O), 2.42 (s, 6H, CH_3 of Ts); EIMS *m*/*z* 683 (M^+).

(10*S*,11*S*)-22,24-Dimethoxy-10,11-diphenyl-3,6,9,12,15,18-hexaoxabicyclo[18.3.1]tetracosa-1(24),20,22-triene (10). To a suspension of NaH (1.38 g, 57.5 mmol) in THF (400 mL) was slowly added with stirring and refluxing a THF solution (400 mL) of **9** (4.91 g, 7.19 mmol) and (*S*,*S*)-hydrobenzoin[42] (1.54 g, 7.19 mmol). After removal of the solvent in vacuo, the product was extracted with hot hexane, purified by silica gel column chromatography, and recrystallized from MeOH. Chiral crown ether **10** was obtained as colorless plates in 20.9% yield (830 mg): mp 106.5–107.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.14–6.98 (m, 10H, Ph), 6.93 (s, 2H, Ar), 4.62 (s, 4H, benzyl), 4.43 (s, 2H, PhCH=), 4.03 (s, 3H, inner CH_3O), 3.82 (s, 3H, outer OCH_3) 3.69–3.38 (m, 16H, ether chain); $[\alpha]_D$ = +28.2° (*c* 1.00, $CHCl_3$); EIMS *m*/*z* 552 (M^+). Anal. Calcd for $C_{32}H_{40}O_8$: C, 69.55; H, 7.30. Found: C, 69.63; H, 7.15.

(4*R*,5*R*)-2,2-Dibutyl-4,5-diphenyl-1,3,2-dioxastannolane (11). A mixture of (*R*,*R*)-hydrobenzoin[42] (2.00 g) and dibutyltin oxide (2.32 g) in benzene (50 mL) was refluxed with stirring for 1 d by using a Soxhlet extractor in which 4A molecular sieves (8.0 g) were placed into a filter-paper thimble for dehydration. After evaporation of the solvent, the

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product was recrystallized from hexane to give colorless needles of dioxastannolane **11** in 61.5% yield (2.56 g): mp 136.0–137.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.17–6.97 (b s, 10H, Ar), 4.28 (b s, 2H, PhCH═), 1.78–0.89 (m, 18H, *n*-Bu); $[\alpha]_D$ = +28.6° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{32}H_{40}O_8$: C, 59.36; H, 6.79. Found: C, 59.59; H, 6.67.

(3*R*,3′*R*,4*R*,4′*R*)-2,6-Bis(3,4-diphenyl-4-hydroxy-2-oxabutyl)-1,4-dimethoxybenzene (12). A suspended 1,1,2,2-tetrachloroethane solution (10 mL) of **11** (2.00 g, 4.49 mmol) and 2,6-bis(bromomethyl)-1,4-dimethoxybenzene[41] (713 mg, 2.20 mmol) was refluxed for 3 h. To the reaction mixture were added water (3 mL) and EtOH (10 mL), and the mixture was further refluxed for 2 h. After removal of the solvent, the product was triturated with MeOH. The colorless precipitate was filtered out, and the filtrate was evaporated. The product was purified by silica gel column chromatography (eluent $CHCl_3$) to give a colorless viscous oil of diol **12** in 99.2% yield (1.29 g): ^{1}H NMR ($CDCl_3$) δ 7.19–7.00 (m, 20H, Ph), 6.89 (s, 2H, Ar), 4.71 (d, 2H, *J* = 8.0 Hz, PhCH═), 4.48 (d, 2H, *J* = 11.7 Hz, benzyl), 4.40 (d, 2H, *J* = 11.7 Hz, benzyl), 4.38 (d, 2H, *J* = 8.0 Hz, PhCH═), 3.73 (s, 3H, inner CH_3O), 3.51 (s, 3H, outer CH_3O), 3.51 (b s, 2H, OH); $[\alpha]_D$ = −18.0° (*c* 1.00, $CHCl_3$); EIMS *m*/*z* 590 (M^+). Anal. Calcd for $C_{38}H_{38}O_6$: C, 77.27; H, 6.48. Found: C, 77.13; H, 6.35.

(4*R*,5*R*,13*R*,14*R*)-19,21-Dimethoxy-3,6,9,12,15-pentaoxa-4,5,13,14-tetraphenylbicyclo[15.3.1]heneicosa-1(21),17,19-triene (13). To a suspension of NaH (148 mg, 6.16 mmol) in THF (50 mL) was slowly added with stirring and refluxing a THF solution (50 mL) of diol **12** (910 mg, 1.54 mmol) and diethylene glycol ditosylate (639 mg, 1.54 mmol). After concentration of the solvent, the product was extracted with hot hexane, purified by silica gel column chromatography (eluent benzene/hexane (1:1)), and recrystallized from hexane to afford chiral crown ether **13** as colorless columns in 58.8% yield (600 mg): mp 178.5–179.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.19–6.94 (m, 20H, Ph), 6.60 (s, 2H, Ar), 4.61 (s, 3H, inner CH_3O), 4.59 (d, 2H, *J* = 8.7 Hz, PhCH═), 4.58 (d, 2H, *J* = 10.1 Hz, benzyl), 4.49 (d, 2H, *J* = 8.7 Hz, PhCH═), 4.29 (d, 2H, *J* = 10.1 Hz, benzyl), 3.71 (s, 3H, outer CH_3O), 3.51–3.36 (m, 8H, ether chain); $[\alpha]_D$ = −57.6° (*c* 1.07, $CHCl_3$); EIMS *m*/*z* 660 (M^+). Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 76.05; H, 6.88.

(4*S*,5*S*)-2,2-Dibutyl-4,5-diphenyl-1,3,2-dioxastannolane (14). This dioxastannolane was prepared by the same method as **11** using (*S*,*S*)-hydrobenzoin[42] to give colorless needles (2.56 g, 61.5%): mp 136.0–137.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.17–6.97 (m, 10H, Ph), 4.28 (b s, 2H, PhCH═), 1.76–0.89 (m, 18H, *N*-Bu); $[\alpha]_D$ = −28.6° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{32}H_{40}O_8$: C, 59.36; H, 6.79. Found: C, 59.55; H, 6.58.

(3*S*,3′*S*,4*S*,4′*S*)-2,6-Bis(3,4-diphenyl-4-hydroxy-2-oxabutyl)-1,4-dimethoxybenzene (15). This diol was prepared by the same method as **12** using **14** instead of **11** to give a colorless viscous oil (1.17 g, 90.0%): ^{1}H NMR ($CDCl_3$) δ 7.19–7.00 (m, 20H, Ph), 6.89 (s, 2H, Ar), 4.71 (d, 2H, *J* = 8.0 Hz, PhCH═), 4.48 (d, 2H, *J* = 11.7 Hz, benzyl), 4.40 (d, 2H, *J* = 11.7 Hz, benzyl), 4.38 (d, 2H, *J* = 8.0 Hz, PhCH═), 3.73 (s, 3H, inner CH_3O), 3.51 (s, 3H, outer CH_3O), 3.51 (b s, 2H, OH); $[\alpha]_D$ = +25.5° (*c* 1.00, $CHCl_3$); EIMS *m*/*z* 590 (M^+). Anal. Calcd for $C_{38}H_{38}O_6$: C, 77.27; H, 6.48. Found: C, 77.01; H, 6.25.

(4*S*,5*S*,16*S*,17*S*)-22,24-Dimethoxy-3,6,9,12,15,18-hexaoxa-4,5,16,17-tetraphenylbicyclo[18.3.1]tetracosa-1(24),20,22-triene (16). To a suspension of NaH (650 mg, 27.1 mmol) in THF (200 mL) was slowly added with stirring and refluxing a THF solution (200 mL) of diol **15** (4.00 g, 6.77 mmol) and triethylene glycol ditosylate (3.11 g, 6.77 mmol). After evaporation of the solvent, the product was extracted with hot hexane, purified by silica gel column chromatography (eluent $CHCl_3$), and further purified by gel-permeation liquid chromatography to afford a colorless viscous oil of chiral crown ether **16** in 56.6% yield (2.70 g): ^{1}H NMR ($CDCl_3$) δ 7.23–6.96 (m, 20H, Ph), 6.71 (s, 2H, Ar), 4.59 (d, 2H, *J* = 8.3 Hz, PhCH═), 4.58 (d, 2H, *J* = 11.2 Hz, benzyl), 4.51 (d, 2H, *J* = 11.2 Hz, benzyl), 4.42 (d, 2H, *J* = 8.3 Hz, PhCH═), 4.18 (s, 3H, inner CH_3O), 3.72–3.47 (m, 12H, ether chain), 3.68 (s, 3H, outer CH_3O); $[\alpha]_D$ = +26.9° (*c* 1.0, $CHCl_3$); EIMS *m*/*z* 704 (M^+). Anal. Calcd for $C_{44}H_{48}O_8$: C, 74.98; H, 6.86. Found: C, 74.79; H, 6.60.

Chiral Alkylammonium Ions for FABMS. Commercially available chiral alkylamines were converted into hydrochloride salts. They were recrystallized from methanol/ether and used after checking the rotation: (*R*)- and (*S*)-(1-(1-naphthyl)ethyl)amines (Wako), (1-phenylethyl)-amines (Tokyo Kasei), 1-amino-2-propanols (Tokyo Kasei), (*R*)-2-amino-1-butanol (Fluka), (*S*)-2-amino-1-butanol (Aldrich). (*R*)- and (*S*)-methyl esters of phenylalaninium chlorides were purchased and used without purification (Sigma).

Alkylammonium Salts for K_s Measurements. (2-Phenylethyl)ammonium hexafluorophosphate was prepared by the standard method using $AgPF_6$ and purified to give a colorless crystal, mp 184–186 °C. Ethylammonium hexafluorophosphate was prepared in the same manner to give a colorless crystal, mp 118–120 °C. (*R*)- and (*S*)-(1-(1-naphthyl)ethyl)ammonium perchlorates were prepared by the standard method using $HClO_4$ and purified by recrystallization to give colorless needles, mp 186–187 °C.

FAB Mass Spectra. All positive-ion FAB mass spectra were recorded on a JEOL JMS-DX300 operating at an accelerating voltage of 3 kV with a mass range of *m*/*z* 20–800. The instrument was equipped with a standard JEOL FAB source and an ion gun. Argon was used as the atom beam accelerated to 6 eV with an emission current of 20 mA. The source pressure was typically ca. 3×10^{-6} Torr. Spectra were obtained with a magnet scan rate of 3 s per scan, and the data were processed with a JMA 3100 data processing system.

A typical FABMS sample solution was prepared by mixing the following two solutions: (1) a 5-μL portion of a mixture of 10 μL of a 0.5 M MeOH solution of **6b**, 10 μL of a 0.5 M MeOH solution of 12-crown-4, and 40 μL of NBA matrix; (2) 2.5 μL of a 0.7 M MeOH solution of (*R*)- or (*S*)-(1-(1-naphthyl)ethyl)ammonium chloride. The resulting sample solution was mixed with a vibrator ([M]:[R]:[A^+] = 1:1:4), and 1.0 μL was deposited on a FAB probe tip. The internal standard compound of 12-crown-4 was purified by solidification at liquid nitrogen temperature in hexane.

A mass range of *m*/*z* 300–700 was set up, and 10 successive spectra of the first enantiomeric sample solution were accumulated (usually, scans 15–25) and averaged. The resulting RPI was obtained from the average of several runs. Under the same conditions, measurements soon followed for the second enantiomeric sample solution.

Association Constant Determinations by ^{1}H-NMR Titration. The association constant for 1:1 complexation is defined by eqs 4 and 5. Here,

$$K_s = x/([M]_0 - x)([A^+]_0 - x) \quad (4)$$

$$x = [M]_0(\Delta\delta/\Delta\delta_c) \quad (5)$$

x is the concentration of the 1:1 complex ion in the equilibrium, $[M]_0$ and $[A^+]_0$ are initial concentrations of carbohydrate and ammonium ion, respectively, $\Delta\delta$ is the induced change in chemical shift of a selected (carbohydrate) proton signal, and $\Delta\delta_c$ is the limiting shift, corresponding to the induced change after 100% complexation.

$$\Delta\delta = [1/K_s + [M]_0 + [A^+]_0 - \{(1/K_s + [M]_0 + [A^+]_0)^2 - 4[M]_0[A^+]_0\}^{1/2}]\Delta\delta_c/(2[M]_0) \quad (6)$$

From a series of measured $\Delta\delta$ together with known $[A^+]_0$ and $[M]_0$ values, the K_s value could be determined by means of a nonlinear least-squares method (modified Newton–Gauss type).[28b,34,43]

For the complexation of permethylated β-mannofuranose with $EtNH_3^+PF_6^-$ in CD_3CN at 25 °C, 10 proton signals are followed with 7 different concentrations of $[A^+]_0$ ($[M]_0$ = 0.0036 M, $[A^+]_0$ = 0–0.102 M (*n* = 7)). The K_s value in this system was calculated to be 26.4 ± 4.3 M^{-1} (*n* = 9) by an average of the 9 sets ($\Delta\delta^{obs}_{max}$ > 5 Hz) (see Table IV).

When the condition $[A^+]_0 \gg [M]_0$ was applied (i.e., K_s < 1), the K_s value could be determined by a linear method (eq 7).[44] Carbohydrates

$$1/\Delta\delta = 1/\{K_s[A^+]_0\Delta\delta_c\} + 1/\Delta\delta_c \quad (7)$$

3a, **3b**, **6b**, and β-Glc-p in Table III are the cases for which this procedure was used.

X-ray Structure Analysis. Crystals for X-ray analysis of **3a** ($C_{19}H_{30}O_6$) were obtained by slow evaporation from a hexane solution. Crystal data for **3a** are as follows: orthorhombic space group $P2_12_12_1$, *a* = 10.618 (17) Å, *b* = 23.793 (32) Å, *c* = 7.405 (10) Å, *v* = 1871 Å^3, *z* = 4, D_c = 1.259 g cm^{-3}. A total of 4915 reflections were recorded on a Rigaku AFC-5FOS four-circle diffractometer using graphite-monochromated Mo Kα

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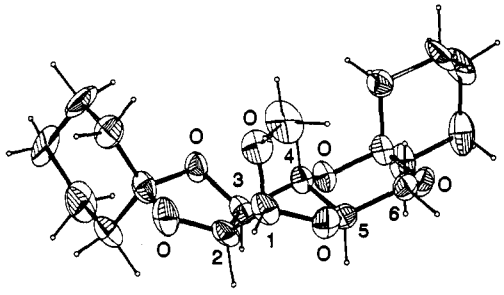

Figure 4. X-ray structure of **3a** (ORTEP drawing).

radiation. Of these, 2192 [with $I > 3\sigma(I)$] were judged as observed reflections. The structure was solved using MULTAN 84.[45]

As shown in Figure 4, the central pyranose ring of carbohydrate **3a** has a boat conformation.

MNDO Calculations. Calculations of geometries and energies for the 1:1 complex ion formed between the model (diisopropylidene derivative instead of the dicyclohexylidene one) of **3b** (**6b**) and Li^+ were carried out on a FACOM S3500 computer (ANCHOR in the TASMAC system) by using standard MNDO programs (MOPAC 5 and MNDOC).[46] For the initial geometry of the mother skeleton, the present crystal data (for the β-mannopyranose skeleton) or the reported data (for the β-mannofuranose skeleton)[47] were used.

A lithium atom was introduced within certain coordination distances of some oxygens of the model carbohydrate derivative.[3,48] The lithium position and several torsional angles in the dioxolane-linkage part were partially optimized. The heats of formation were compared for different structures in order to determine a stable structure or structures of the 1:1 adduct ion.

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