A Hydrogen-Bonding Receptor That Binds Cationic Monosaccharides with High Affinity in Methanol

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Abstract: A dicarboxylate host (**1**) binds cationic monosaccharides such as D-glucosamine·HCl (**2**), D-galactosamine·HCl (**3**), and D-mannosamine·HCl (**4**) with high affinity ($K_1 = 8.0 \times 10^4 - -2.0 \times 10^5\ M^{-1}$) in methanol. In circular dichroism (CD) spectroscopy a positive exciton-coupling band was observed near 290 nm; this indicates that the saccharides are recognized by multiple point interactions. Since the corresponding neutral monosaccharides are not significantly bound, one may conclude that complex formation is primarily due to the electrostatic interaction between NH_3^+ in the guest and one carboxylate in the host and secondarily due to hydrogen-bonding interactions of OH groups with the other carboxylate and/or nitrogen bases. Molar ratio plots and Job plots indicate that host **1** and cationic monosaccharide guests form CD-active, pseudo-cyclic 1:1 complexes at low guest concentration followed by the formation of CD-silent, acyclic 1:2 **1**·saccharide complexes at high guest concentration. The possible binding modes are discussed in detail on the basis of molecular mechanics calculations and chemical shift changes in ^{1}H NMR spectra. The results of competition experiments with several cationic reference compounds bearing fewer OH groups than **2**–**4** are consistent with the proposed binding model. Thus, the present study is a rare example of saccharide recognition in a protic solvent, where in general, hydrogen-bonding interactions are rarely useful because of strong solvation energy. These are apparently the strongest saccharide complexes involving noncovalent interactions between host and guest. We believe that the findings are significant as a milestone toward development of new saccharide recognition systems ultimately useful in aqueous solution.

Keywords: carbohydrates · chirality · circular dichroism · host–guest systems · hydrogen bonds

Introduction

Molecular recognition of neutral and ionic species by synthetic receptors has been a fascination of many chemists for the last few decades. In many reported synthetic receptors hydrogen-bonding interactions play a central role.[1, 2] It has been shown, however, that hydrogen-bonding interactions are effective in aprotic solvents but less effective for recognition of guests soluble only in aqueous media.[3] This limitation becomes particularly serious in saccharide recognition, because sugars are practically soluble only in water and only partially in alcoholic solvents, but they are virtually insoluble in most aprotic solvents (except a few polar aprotic solvents such as DMF and DMSO). It is known that certain proteins, such as concanavalin A and L-arabinose-binding protein, utilize hydrogen-bonding interactions for saccharide binding after excluding most (but not all) water molecules which may hamper the hydrogen bond based protein–saccharide interactions.[4] These binding modes are mimicked in aprotic solvents to some extent. For example, Rebek et al.[2a] succeeded in recognition of a saccharide analogue by a receptor designed from Kemp's acid. Davis et al.[5] and Aoyama et al.[6] demonstrated that OH groups appended to cholic acid or calix[4]resorcinarene are useful as a functional group array to bind saccharides through hydrogen bonds. Similarly, it was shown by Anslyn et al.[7] and Inouye et al.[8] that arrangement of hydrogen-bond-accepting pyridine units in complementary spatial positions is an appropriate strategy to design saccharide receptors.

The preceding experiments were conducted either in aprotic solvents (mainly in $CDCl_3$) or in two-phase extraction systems containing high concentrations of saccharides in the aqueous phase. Hence, the complexes discussed therein are relevant to protein–saccharide interactions occurring in hydrophobic environments but cannot be directly applied to saccharide recognition in aqueous solution.[9] Recently, opti-

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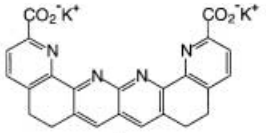
cally-active 1,1′-binaphthyl-derived cyclophane receptors were reported with central cavities including four anionic phosphodiester groups for "ionic" hydrogen bonding.[10] Very interestingly, this type of receptor[10a] can bind certain saccharides even in a protic solvent mixture (CD_3CN/CD_3OD 88:12 *v*/*v*). More recently, Král et al.[11] reported macrocyclic and open-chain porphyrins bearing polycationic groups capable of binding sugars, particularly trisaccharides, even in water. These findings suggest that ionic hydrogen-bonding interactions may be a better choice than neutral hydrogen-bonding interactions for binding saccharides in protic solvents.

One group included in the present investigation has developed a number of fused-pyridine receptors for recognition of creatinine, guanidinium, urea, and related molecules.[1f, 12–14] Among them, host **1** (Figure 1) has two carboxylate anions and four basic nitrogens capable of forming both ionic and neutral hydrogen-bonding interactions. Careful



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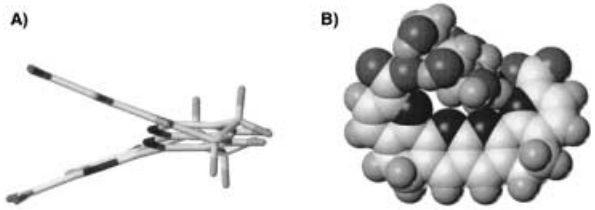
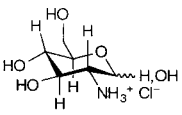


Figure 1. A) Side view of **1** in minimum-energy conformation (SYBYL; NCCN torsions −22°). (B) Space-filling (CPK) model of D-glucosamine docked in cavity of receptor **1**.

examination of the molecular structure of **1** reveals that i) the naphthyridine ring and adjacent pyridine rings are expected to be twisted to some extent to avoid an energetically unfavorable eclipsed conformation in the CH_2CH_2 linkages, and ii) the size of the cleft composed of four basic nitrogens is comparable to the size of monosaccharides (Figure 1). These structural characteristics suggest that **1** would act as an excellent saccharide receptor and the binding event could be read out by induced circular dichroism (ICD) arising from the twisting direction of the naphthyridine–pyridine NCCN torsional angle.

Investigations of saccharide recognition using hydrogen-bonding interactions have so far been conducted mainly in aprotic solvents to avoid the strong solvation energy of protic solvents. However, it is clear that a saccharide recognition system useful even in protic (particularly, aqueous) solution should be more important from a practical viewpoint. Again, examination of the molecular structure of **1** suggests that the combination of both electrostatic and hydrogen-bonding interactions would enable the binding of "cationic" monosaccharides even in protic solvents. With these objectives in mind, we compared the recognition ability of **1** toward cationic monosaccharides [D-glucosamine·HCl (**2**), D-galactosamine·HCl (**3**), and D-mannosamine·HCl (**4**)] with that toward neutral monosaccharides and cyclic primary ammonium reference compounds **5**–**8**. Very interestingly, we have found that cationic monosaccharides **2**–**4** are bound by **1** even in 100% methanol, inducing circular dichroism and exciton coupling associated with the heterocyclic chromophore of this receptor.



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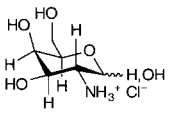

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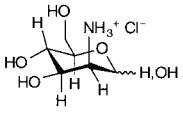

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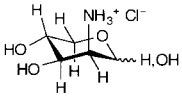

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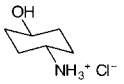

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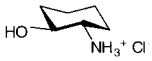

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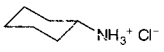

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Results and Discussion

Absorption spectra: The UV/Vis absorption spectra of dipotassium salt **1** were recorded in water and in methanol in the absence and the presence of guests **2**–**4** (Figure 2). The spectrum of **1** in methanol is very similar to that in water.[14] In titration studies,[15] addition of the first two equivalents of HCl in methanol produce no significant UV shifts; this indicates that **1** exists as a dianionic species in this solvent. A plot of the absorbance (255 nm) versus the concentration of **1** [$(0.5–2.0)\times10^{-5}$ M] showed a linear relationship, $R=0.998$; the plot is not shown here. This implies that **1** does not aggregate but exists as a monomeric species in methanol over this concentration range. Figure 2 also shows that the spectrum in methanol is only slightly affected by addition of guests **2**–**4**. This result is similar to that observed in the complexation of **1** with various aliphatic amines, in which no proton transfer was

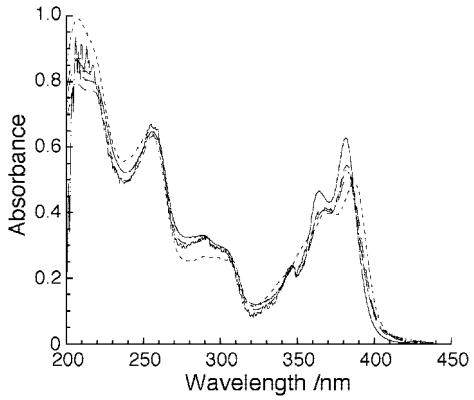

Figure 2. UV/Vis absorption spectra of **1** (2.00×10^{-5} M) in water (pH 8.0 - - - -) and methanol (——) in the presence of **2** (– –), **3** (–––) and **4** (—--): 25 °C, [**2**, **3**, or **4**] = 1.00×10^{-3} M.

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observed. In any case, absorption spectroscopy is not a sensitive method for detecting the interaction of saccharides with host **1**.

CD Spectra: As expected from the computational studies (Figure 1), free host **1** should exist in solution as two enantiomeric conformations in which the torsions between the naphthyridine ring and the pyridine rings are twisted in either the right- or left-handed direction. When this equilibrium is shifted to either direction by saccharide binding, one enantiomer will exist in excess over the other, and therefore the binding event should be easily read out by CD spectroscopy.

Figure 3 shows CD spectra of **1** (2.00×10^{-5} M) in methanol in the presence of **2**–**4** (1.00×10^{-4} M). As expected, these cationic monosaccharides resulted in CD-active species, whereas methanol solutions containing neutral saccharides (e.g., D-glucose, D-galactose, D-mannose, D-xylose, and D-fructose) were totally CD-silent.

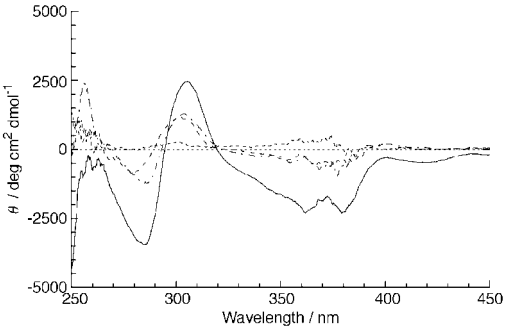

Figure 3. CD spectra of **1** (2.00×10^{-5} M) in the absence (----) and the presence of monosaccharides (1.00×10^{-4} M) at 25 °C in methanol: —— **2**, —·—**3**, – – – **4**.

In general, when a host molecule binds a saccharide, the resulting complex becomes optically active. It has been established through CD spectroscopic studies on saccharide recognition[16] that the complex becomes strongly CD-active only when the saccharide is recognized by the host at multiple points,[17] forming a pseudo-cyclic structure. Thus, the difference observed between cationic and neutral saccharides indicates that the primary contact with the cationic saccharide guest is achieved by electrostatic interaction between NH_3^+ and COO^- and the secondary contact is due to hydrogen-bonding interactions of OH with N and/or COO^- as a pseudo-intramolecular process. Here, it is particularly noteworthy that i) electrostatic interactions can overcome the strong solvation energy operating between saccharides and methanol solvent molecules and ii) hydrogen-bonding interactions between **1** and saccharides become significant in methanol only when they occur in a pseudo-intramolecular fashion. When water was added to the solution, the CD intensity decreased with increasing water concentration and the CD spectra completely disappeared at a methanol/water ratio of 4:1 (*v*/*v*). This result implies that the hydrogen-bonding sites involved in the complex are more strongly solvated in water, suppressing complexation. Moreover, addition of D-lysoxylamine·HCl (**5**) to methanol solutions of **1** did not produce CD activity. D-Mannosamine·HCl (**4**) is identical to **5** except that **4** bears a 6-hydroxymethyl group; this suggests that this hydrogen-bonding site may be necessary to produce a CD-active complex.

To specify the stoichiometry of the CD-active species, the CD intensity (305 nm) was plotted against [**1**]/([**1**]+[**2**]) (Job plot: Figure 4). It is clearly seen from Figure 4 that the CD maximum appears at [**1**]/([**1**]+[**2**])=0.5; this indicates that the CD-active species consists of a 1:1 complex between **1** and **2**. The same 1:1 stoichiometry was also confirmed for the complexes with **3** and **4**.

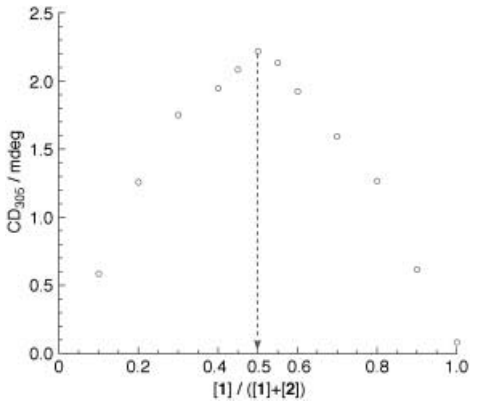

Figure 4. Job plot of the CD intensity (305 nm) versus [**1**]/([**1**]+[**2**]); the ([**1**]+[**2**]) value was maintained constant (2.00×10^{-4} M, 25 °C, methanol).

Next, to estimate the association constants (*K*) for 1:1 complex formation, the CD spectra were measured as a function of the saccharide concentrations (the example for **2** is shown in Figure 5). The CD spectra changed with two well-defined isosbestic points, suggesting that only one CD-active species is produced in the complexation process.

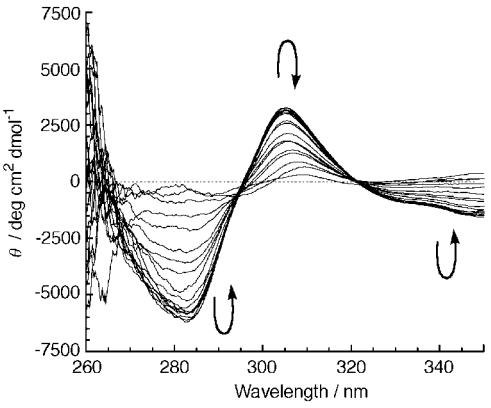

Figure 5. CD spectral change in **1** (2.00×10^{-5} M): [**2**]=0–2.00×10^{-2} M at 25 °C in methanol. The CD spectra in the presence of **3** or **4** showed similar changes.

We plotted the CD intensity against the saccharide concentration, as shown in Figure 6. The CD intensity increased at [saccharide]=0–0.1 mM (Figure 6A) and then decreased with further increase in the saccharide concentration (Figure 6B). As mentioned above, the CD-active species has 1:1 stoichiometry and features multi-point interactions

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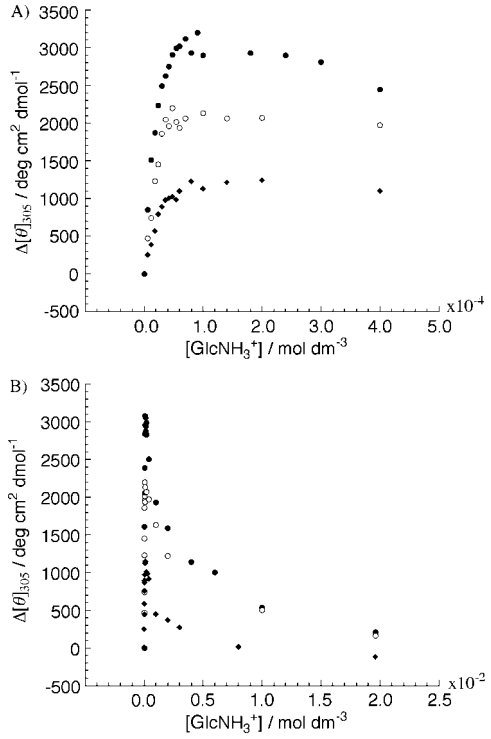


Figure 6. Plots of $\Delta[\theta]_{305}$ versus saccharide concentration: $[\mathbf{1}] = 2.00 \times 10^{-5}$ M, ● **2**, ○ **3**, ◆ **4**: [saccharide] $= 0.00 - 4.00 \times 10^{-4}$ M (A), $0.0 - 1.96 \times 10^{-2}$ M (B); at 25 °C in methanol.

forming a pseudo-cyclic structure. Taking these facts into consideration, the biphasic $\Delta\theta$ dependence is rationalized by Scheme 1 consisting of the initial formation of a CD-active pseudo-cyclic 1:1 complex at low saccharide concentration followed by a CD-silent, noncyclic 1:2 **1**·saccharide complex at high saccharide concentration. A similar biphasic dependence frequently appears in other saccharide recognition systems and has been rationalized in an analogous manner.[16]

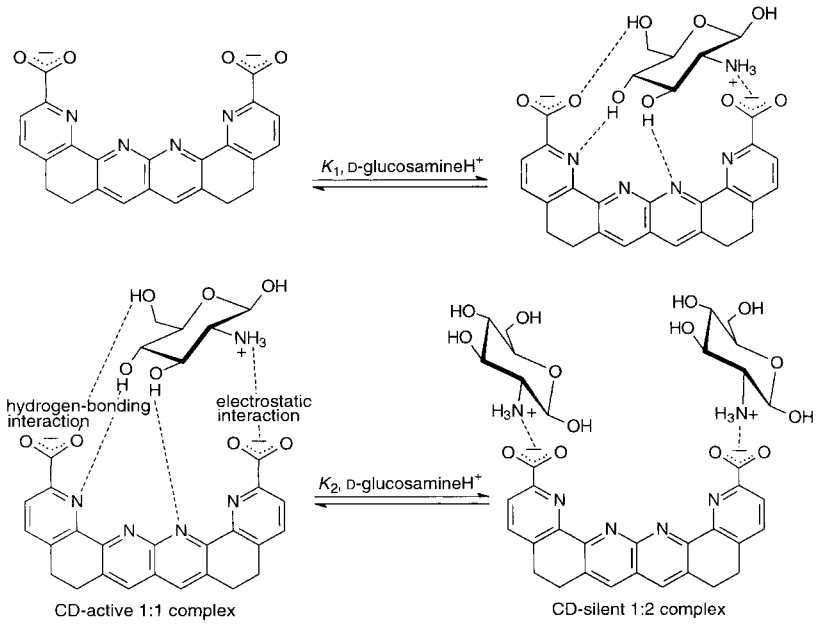
The K values for the formation of 1:1 and 1:2 complexes (K_1 and K_2, respectively) were estimated by a nonlinear least-squares method.[16f,i, 18] The results are summarized in Table 1 with the CD spectral parameters. Examination of Table 1 reveals several interesting aspects characteristic of the present

Table 1. Association constants (K_1 and K_2) and λ_{max} and $[\theta]_{max}$ in the CD spectra of complexes of **1**.[a]

Guest	K_1 [M^{-1}]	K_2 [M^{-1}]	λ_{max} [nm] ($[\theta]_{max}$ [deg cm^2 dmol^{-1}])	
2	2.0×10^5	6.5×10^2	305 (3054)	283 (−5860)
3	1.5×10^5	5.0×10^2	305 (2133)	283 (−3931)
4	8.0×10^4	6.0×10^2	305 (1150)	283 (−1158)
5	7.0×10^4			
6	6.0×10^4			
7	2.3×10^4			
8	1.7×10^4			

[a] At 25 °C, methanol.

electrostatic/hydrogen-bonding cooperating system, namely, i) both the K_1 and K_2 values are similar for complexes of the three guests, the largest difference being observed between the K_1 for **2** and that for **4** (only 2.5-fold), ii) the K_1 values appear in the order of **2** > **3** > **4** which is the same as the order of $[\theta]_{max}$, that is, the stronger the CD bands are, the larger the K_1 values are, and iii) on the other hand, the K_2 values ($500 \sim 650\,M^{-1}$) are more similar than the K_1 values. Aspect (i) implies that the electrostatic interaction which should commonly operate in the binding of **2**–**4** acts as a primary binding force; the hydrogen-bonding interaction, which may be useful to discriminate among the three saccharides, plays only a secondary role. It should be noted, however, that such strong CD bands cannot appear without the contribution of the hydrogen-bonding interaction which stabilizes the guest saccharide in a pseudo-cyclic structure. Then, aspect (ii) suggests that the magnitude of the hydrogen-bonding interaction is the origin of the difference both in the K_1 values and the CD intensity. The K_2 values reflect the conversion of the pseudo-cyclic 1:1 complexes into the noncyclic 1:2 complexes. As in the formation of the 1:1 complexes, the second saccharide is also bound primarily by an electrostatic interaction in the cases of all three saccharide guests. This is why the K_2 values are almost the same in the three cases.



Scheme 1. Model explaining dependence of CD activity on saccharide concentration.

The structure of **1**·**2** was modeled by molecular mechanics to suggest the host–guest interactions responsible for the stability and induced CD of this 1:1 complex. A total of 22 different host–guest arrangements were minimized in the absence of solvent. The mini-

mum energy structure shown in Figure 7 supports the proposed pseudo-cyclic structure of this complex. One end of the twisted receptor molecule is anchored by the primary association between the NH_3^+ and COO^- groups. Primary hydrogen-bond contacts (dashed lines) occur between NH donors and carboxylate and adjacent pyridine acceptors, and a long-range NH/naphthyridine nitrogen interaction is present, but not shown in Figure 7. The other carboxylate of **1** forms a

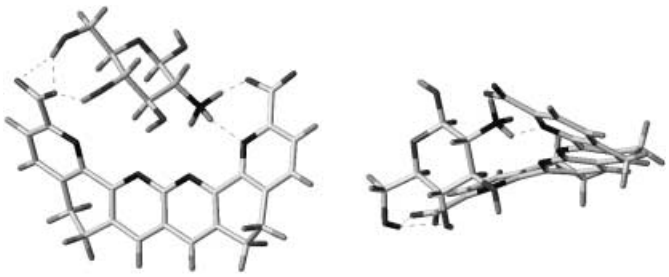


Figure 7. Energy minimized structure of complex **1·2** (SYBYL; NCCN torsions, -16, -26°); primary hydrogen bonds are shown by dashed lines.

hydrogen-bonded network with the 6-OH and 4-OH groups of **2**. The approximately coplanar arrangement of these hydrogen bonding groups and the orientation of the C–NH_3^+ bond nearly perpendicular to the array of COO^-, pyridine N and naphthyridine N donor groups at the other end of **1** are apparently responsible for a counterclockwise (M-helical) bias of the two NCCN torsions in the receptor. We also attempted to energy minimize **1·2** with P-helical twists of these torsions. The resulting local minimum energy structure, with NCCN torsions of $+15$ and $+25^\circ$, is 3.3 kcal mol^{-1} higher in energy and the 6-OH and 4-OH groups lie on either side of the carboxylate plane. These calculations produce reasonable NCCN torsional angles, which are $+18.8$ and -19.8° in the *N*-ethylguanidinium complex of **1**.[14] It is likely that there are several M-helical complexes that are in dynamic equilibrium with that shown in Figure 7.

The conformation of host **1** in the energy minimized structure of its complex (Figure 7) displays a counterclockwise twist (M-helicity) between adjacent pyridine and 1,8-naphthyridine rings, apparently producing the positive CD couplet at about 295 nm (Figure 3). This corresponds approximately to the broad absorption band centered at 290 nm (cf. Figure 2). The longest wavelength absorption band at ca. 380 nm produces only a very weak CD signal. In a CD study of an M-helical 2,2*N*′-bipyridine derivative,[19] a negative CD couplet was associated with the longest wavelength band (300 nm) and a positive CD couplet was observed for the next higher energy electronic transition (230 nm). Assignment of electronic transitions in the present case consisting of one 1,8-naphthyridine and two pyridine chromophores is more complicated, but the two cases are consistent if one considers that a positive CD couplet is observed for the second longest wavelength band in both cases.

The binding of neutral saccharides could not be detected by any spectroscopic method used (e.g., UV/Vis, CD, and ^{1}H NMR spectroscopy). Hence, it is difficult to estimate the "absolute" affinity of **1** with neutral saccharides in methanol. However, one can estimate the relative affinity by the competition method, monitoring the CD intensity of the **1·2** complex. Thus, to methanol solutions containing **1** (2.00×10^{-5} M) and **2** (1.00×10^{-4} M) were added several neutral saccharides (D-glucose, D-galactose, D-mannose, etc.) up to 2.00×10^{-2} M. We found that the CD spectrum of the **1·2** complex was scarcely affected even at the ratio: [neutral saccharide]/[**2**] = 200. This result indicates that host interaction with these neutral saccharides is weaker by more than two orders of magnitude than that with cationic saccharides.

The association constants (K_1 values) for 1:1 complexes of **1** with reference compounds **5**–**8** were estimated by competition with the 1:1 complex **1·2**. Each reference compound was incrementally added to a methanol solution of **1** (2.0×10^{-5} M) and D-glucosamine·HCl (1.0×10^{-4} M), which showed maximum CD intensity indicating predominant formation of the 1:1 complex. The K_1 values were calculated from the decrease in CD intensity (305 nm), assuming 1:1 substitution, and are listed in Table 1. Cyclohexylamine·HCl (**8**) forms the weakest complex, as expected from its lack of OH groups. The K_1 values for *trans*-4-aminocyclohexanol·HCl (**6**) and *trans*-2-aminocyclohexanol·HCl (**7**) are somewhat larger, showing the significant influence of a single OH group on binding strength. A 4-OH group may be more effective than 2-OH because the distance between the *trans*-4-OH and NH_3^+ groups is large enough to bridge between the two carboxylate groups of **1**. The K_1 for D-lysoxylamine·HCl (**5**) is similar to that of **6**, apparently because additional OH···N hydrogen-bonding interactions compensate for the fact that the *trans*-1,3-disposed NH_3^+ and OH groups are not far enough apart to bridge the two carboxylates of **1**. This bridging interaction appears to be necessary to produce CD activity in the time-averaged interaction of **1** with a chiral, cationic guest.

^{1}H NMR Spectra: The foregoing spectral data and modeling results support the view that cationic saccharides are bound to host **1** by both electrostatic and hydrogen-bonding interactions. According to the model of complex **1·2** presented in Figure 7, the host conformation is controlled by hydrogen-bonding interactions with NH_3^+ and OH groups located on opposite sides of **2**. Guests **3** and **4** are stereoisomeric at carbons 2 and 4, so the conformations of **1** in **1·3** and **1·4** should differ. This results in different induced CD intensities, and we measured the ^{1}H NMR spectra of the complexes in CD_3OD to probe differences in the complexation modes.

Both the pyridyl protons (a and b) and the naphthyridyl protons (c) shift to lower field when **3** is added. On the other hand, no significant peak shift was induced by the addition of D-galactose. The results again indicate the importance of an electrostatic interaction as a primary driving-force for guest binding. Similar downfield shifts were also induced by the addition of **2** or **4**, while reference compounds **6** and **8** mainly deshielded protons a and c. The chemical shift changes are summarized in Table 2, which shows that the $\Delta\delta$ values (with respect to the δ values in the absence of saccharide) for **3** are larger than those for **2** and **4**. The basic difference between **2** and **3** is related to the absolute configuration of C-4; that is, **2** possesses an equatorial 4-OH whereas **3** possesses an axial 4-OH group. In other words, the 4-OH in **2** is *trans* and that in

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3 is *cis* with respect to the equatorial 6-CH_2OH group. The structure of **1·3**, was energy minimized by molecular mechanics, and the result is shown in Figure 8. In **3** the axial

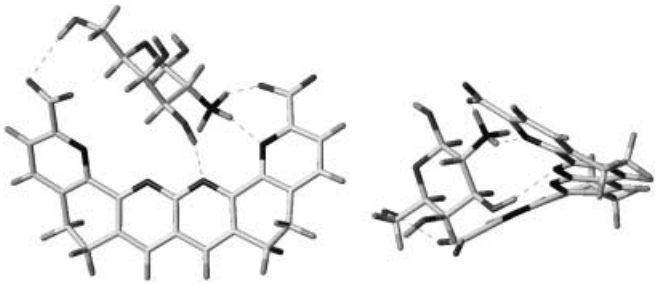
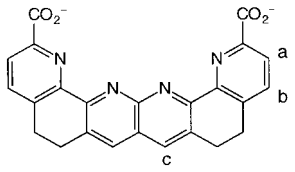


Figure 8. Energy minimized structure of complex **1·3** (SYBYL; NCCN torsions, −26, −19°); primary hydrogen bonds are shown by dashed lines.

4-OH group is too far away to bind to the COO^-, but the loss of this interaction (relative to **1·2**) is partially compensated by hydrogen bonding of the 3-OH to the naphthyridine group of **1**. This explains the relatively large $\Delta\delta$ value for the naphthyridine (c) protons in **1·3** (cf. Table 2). Cyclohexylamine·HCl (**8**) and *trans*-4-aminocyclohexanol·HCl (**6**) cause a smaller downfield shift of the naphthyridine protons of **1**; this suggests N ··· COO^- bridging via their NH_3^+ groups.[20]

Table 2. Chemical shift changes induced by the addition of various guests to methanol solutions of receptor **1**.[a]



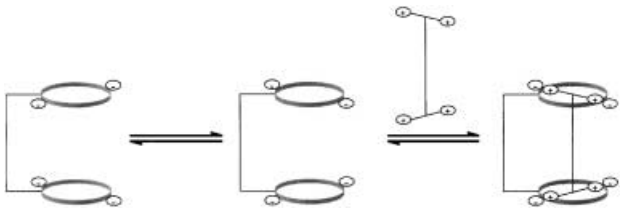
Guest	δ (Δδ (ppm))					
	a		b		c	
none	8.088		7.872		8.266	
2	8.093	(0.005)	7.900	(0.028)	8.325	(0.059)
3	8.130	(0.043)	7.913	(0.041)	8.337	(0.071)
4	8.098	(0.011)	7.892	(0.020)	8.316	(0.050)
D-galactose	8.086	(−0.002)	7.871	(0.001)	8.265	(−0.001)
6	8.100	(0.012)	7.865	(−0.007)	8.291	(0.025)
8	8.105	(0.017)	7.874	(0.002)	8.300	(0.034)

[a] [**1**] = 4.00×10^{-4} M, [guest] = 2.00×10^{-3} M, 25 °C; error ± 0.005 ppm.

Rapid equilibration of a number of structures of all three cationic monosaccharide complexes is shown by the symmetry of the ^{1}H NMR spectra, and downfield shifts of a, b and c protons may be attributed to contributions of structures in which the various pyridine and naphthyridine nitrogens form hydrogen bonds with OH groups of the guests. While these downfield shifts are relatively small, most exceed experimental error (0.005 ppm) and they are consistent with those observed upon complexation of **1** with guanidinium ion.[14] This indicates that they are structurally significant, but unfortunately they were too small to be used for accurate measurement of association constants. No correlations were observed in NOESY two-dimensional NMR spectra, which is consistent with the large distances expected between protons of host and guest, as well as the rapid exchange observed on the NMR time scale.

Conclusion

Dicarboxylate receptor **1** has been shown to bind various aminoglycosides (**2**–**4**) with substantial degrees of induced circular dichroism. This ICD effect is caused by the formation of pseudo-cyclic 1:1 complexes involving multiple point interactions. Dianion **1** forms 1:2 host–guest complexes at higher guest concentrations, but such complexes are CD-silent because they lack pseudo-cyclic structures. The positive signs of the CD-couplets corresponding to the second longest wavelength transition of the heterocyclic chromophore are consistent with M-helical NCCN twists expected in lowest-energy complexes, according to the results of molecular mechanics calculations for the complex of **1** with D-glucosamine (**2**). In the calculated structure, the twisted conformation of **1** is stabilized by a planar array of carboxylate and guest OH groups at one end of the receptor and by the guest R-NH_3^+ group binding perpendicular to the O,N,N plane at the other end of the receptor. The results of CD competition and NMR experiments with several cationic reference compounds bearing fewer OH groups than **2**–**4** are consistent with this model. The ICD mechanism is conceptualized in Scheme 2, showing pre-equilibration of enantiomeric host



Scheme 2. Conceptual model for induced circular dichroism resulting from the complexation of aminoglycosides **2**–**4** by dicarboxylate receptor **1**.

conformations and stabilization of one enantiomer by pairing of host hydrogen bond acceptor groups (minus signs) with guest hydrogen bond donor groups (positive signs). The results and conclusions of this study are an important step toward the development of saccharide recognition systems of practical use in aqueous media.

Experimental Section

The synthesis of compound **1** was reported previously.[14] Saccharides **2**, **3**, and **4** were pure grade and were purchased from Tokyo Kasei Co. Ltd., Wako Pure Chem. Co. Ltd., and Funakoshi Co. Ltd., respectively. Reference compounds **6** and **7** were obtained from Aldrich Chemical Co., while **5** and **8** were purchased from Funakoshi Co. Ltd. and Tokyo Kasei Co. Ltd., respectively. UV/Vis, ^{1}H NMR, and CD spectra were recorded on a Shimadzu UV-160A spectrophotometer, a Bruker DMX 600 spectrometer, and a JASCO J-720 spectrometer, respectively. Molecular mechanics calculations were carried out by means of the SYBYL computer program using the Tripos force field, Gasteiger–Marsili charges and the Powell method of minimization.

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[20] The smaller downfield shifts observed for proton c when **6** or **8** are added to **1**, relative to the shifts for **2** – **4**, are not simply a consequence of the smaller K_1 values for **1**·**6** and **1**·**8**. Under the conditions of the NMR experiment, even for the weakest complex (**1**·**8**), receptor **1** is more than 98% in the complexed form.

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