Complexation of Alkyl Glycosides with Cyclic Resorcinol Tetramer in Apolar Organic Media: Geometrical Requirement for the Intracomplex Sugar–Sugar Interaction

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(Received January 11, 1993)

Synopsis. ^{1}H NMR and circular dichroism spectroscopic investigation of the complexation of octyl glycoside derivatives of various monosaccharides as guests with cyclic resorcinol tetramer as host in chloroform indicates that the complexation-responsible intracomplex sugar–sugar interaction is markedly dependent on the stereochemistry of the sugar glycosides.

We have recently shown that cyclic resorcinol tetramer **1** exhibits a novel binding behavior toward a lipophilic glucose derivative.[1] Host **1** binds four molecules of octyl α- or β-glucopyranoside (**2**α and **2**β) in chloroform in a highly cooperative manner with a Hill coefficient $n\approx4$. The suggested structure of the 1 : 4 (host to guest) complex is schematically shown in structure **3**. The host–guest hydrogen bonding at the four unit-binding sites of the host (A—D) gives rise to a 1 : 4 stoichiometry and the intracomplex guest–guest hydrogen bonding involving the 2- and 6-OH groups provides the orgin of the remarkable cooperativity ($n\approx4$) in the guest binding. In the present work, we have investigated the complexation behaviors of a number of other monosaccharides. We report here that the cooperative binding involving a novel sugar–sugar interaction is specific to the glucose derivative.

Result

In addition to those of 2-deoxy-D-glucose (**6**) and D-xylose (**9**) previously reported,[1] octyl glycosides, all in the α-configuration, of D-mannose (**4**), D-galactose (**5**), D-ribose (**7**), and D-arabinose (**8**) were newly prepared (Chart 1). All of them are readily soluble in chloroform. The complexation between host **1** and guests **4**—**9** was monitored by circular dichroism (CD) and ^{1}H NMR spectroscopy.

A $CHCl_3$ solution of **1** (1.0 mM, 1 M=1 mol dm^{-3}) and mannoside **4** ([**4**]$\leq$30 mM) exhibited induced CD with first (longer wavelength) negative and second (shorter wavelength) positive Cotton effects. On the other hand, at a sufficiently higher concentration of **4** was observed a practically nonsplit positvie Cotton effect in a longer wavelength region. The actual spectra at [**4**]=20 and 300 mM are shown in Figs. 1a and 1b. In the inset of this Figure is shown the correlation between θ (observed ellipticity) at 305 nm and [**4**] in a range $0\leq$[**4**]$\leq$80 mM. The ^{1}H NMR spectra for a series of solutions of **1** (1.0 mM) and guest **4** also showed a biphasic behavior. At lower guest concentrations ([**4**]$\leq$30 mM) there were observed upfield-shifted CH-proton resonances of the guest at $\delta\approx0$. The intergration of these resonances changed with changing [**4**], while the chemical shifts remained practically unaffected. At higher guest concentrations ([**4**]=120 mM), these high-field resonances of the guest disappeared with concomitant shifts of the host-proton resonances; in particular, the OH-protons and the higher-field component of the aromatic protons underwent upfield (ca. 1 ppm) and downfield (ca. 0.15 ppm) shifts, respectively. The previously studied 1 : 4 glucoside complex **1**·**42** (refer to structure **3**)[1] showed similar trends in the CD and NMR spectra (a simple, i.e., nonsplit, positive Cotton effect (Fig. 1c) and guest-induced shifts of the host-proton resonances) as observed here in the presence of a sufficiently excess amount of **4**. On the other hand, the split Cotton effects and the upfield-shifted guest-proton resonances observed at lower [**4**] are characteristic of the 1 : 1 **1**-sugar complexes, where sugar is bound in the cavity of the host.[2,3]

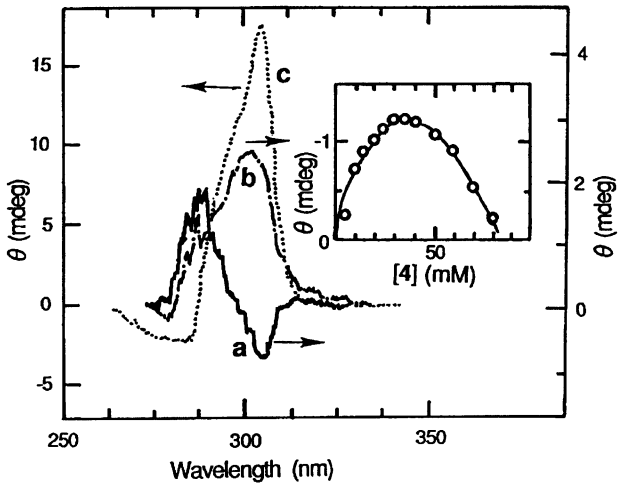

Fig. 1. Induced circular dichroism spectra for $CHCl_3$ solutions (0.1-cm path length) of host **1** (1.0 mM) and a guest: (a) guest=**4** (20 mM), (b) guest is **4** (300 mM), and (c) guest is **2**β (80 mM). Inset: correlation of θ at 305 nm and [**4**].

A $CHCl_3$ solution of host **1** and galactoside **5** showed no induced CD. In addition, in the ^{1}H NMR spectra

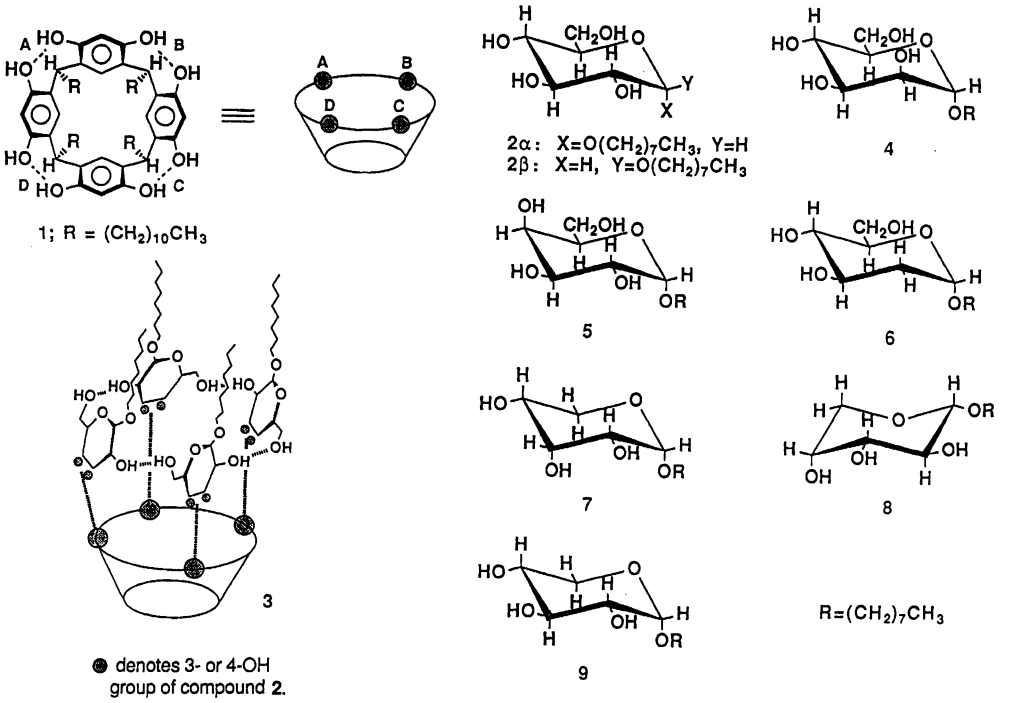

Chart 1.

neither host-induced upfield-shifted resonances for the guest nor guest-induced shifts for the host protons were observed. This was also the case for aldopentose derivatives **7** and **8**. These results indicate that galactoside **5** and aldopentosides **7** and **8** are hardly bound to host **1**. This was also confirmed by a competitive method. A $CHCl_3$ solution of host **1** (1.0 mM) and glucoside **2**β (20 mM) exhibited a positive Cotton effect with θ=17.4 mdeg at 305 nm. The CD intensity at 305 nm for a ternary system of **1**(1.0 mM), **2**β (20 mM), and **5**, **6**, **7**, **8**, or **9** (20 mM) was $\geq$98, ca. 95,[1] $\geq$98, $\geq$97, or $\geq$97%,[1] respectively, of that for the binary system of **1** (1.0 mM) and **2**β (20 mM). These results indicate that the binding of guests **5**—**9**, if any, is too weak to compete with glucoside **2**β. The relative binding ability of mannoside **4** was evaluated in a similar manner. A solution of **1** (1.0 mM) and mannoside **4** (20 mM) exhibits a negative Cotton effect with θ=−1.0 mdeg at 305 nm (Fig. 1a), as opposed to a positive one at this wavelength for glucoside **2**β (vide infra). The observed ellipticity for a ternary mixture of **1** (1.0 mM), **2**β (20 mM), and **4** (20 mM) was θ=13.1 mdeg, i.e., 75% of that (17.4 mdeg) for the binary system of **1** ans **2**β. A qualitative implication of this result is that the glucoside/manoside competition is in favor of the former.

Discussion

Both CD and ^{1}H NMR spectroscopy suggests that the complexation of host **1** and mannoside **4** is at least biphasic. Although a 1 : 4 (host to guest) complex **1**·**4**4 plausibly results at higher guest concentrations, intermediate complex(es) **1**·x**4** ($x\leq$3) accumulates at lower guest concentrations. This is in marked contrast to the formation of glucoside-complex (**1**·**4**2), where host **1** *simultaneously* binds four molecules of **2** in an essentially single step owing to a very strong cooperativity ($n\approx$4) in the **2**-binding process.[1] Rather surprising is the behavior of galactoside **5**. It forms neither 1 : 4 nor 1 : 1 host–guest complex, in spite of its apparent similarity to glucoside **2** and mannoside **4**. These results, coupled with the relative binding abilities of **2**>**4**,[4] indicate that cooperativity in the guest binding dramatically decreases on going from glucoside **2** through mannoside **4** to galactoside **5**.

We have previously demonstrated that the cooperativity in the binding of glucoside **2** arises from intracomplex intermolcular hydrogen bonding involving the 2-OH and 6-OH groups in adjacent guest molecules (refer to structure **3**).[1] This conclusion was based on the finding that neither 2-deoxyglucoside **6** having no 2-OH group nor xyloside **9** having no 6-OH group forms stable complex with host **1**. The present findings not only further reinforce this conclusion but also newly uncover the following points. (1) The presence of 6-OH group is indeed essential. None of aldopentose derivatives **7**—**9** having various stereochemisty of the 2-, 3-, and 4-OH groups are readily bound. (2) The stereochemistry of the 2-OH group is important. Thus, mannoside **4** having axial 2-OH exhibits a less pronounced cooperativity as compared with that for glucoside **2** where 2-OH is equatorial. (3) The trans or the equatorial-equatorial stereochemistry for the 3-OH and 4-OH groups of glycoside guest is also important.[5] Readily bound glucoside **2** has such a trans stereochemisty, while the correspond-

ing groups in hardly bound galactoside **5** is cis or axial-equatorial.

To summarize, the affinities of octyl glycoside derivatives of otherwise closely related aldohexoses and aldopentoses decrease dramatically in the order glucoside **2**>mannoside **4**>galactoside **5**≅aldopentosides≅0. This is because the complexation-responsible host–guest and guest–guest interactions are markedly dependent on the stereochemisty of the OH groups. Phenomenologically, it is interesting to note a solvophobicity/solvophilicity control of the selectivity. The glucose structure is least suited for the 1 : 1 complexation with host **1**. In fact, glucose shows the lowest affinity to **1** in the extraction of monosaccharides from water into CCl_4 upon formation of a 1 : 1 **1**-sugar complex.[3] In marked contrast, the glucose derivative **2** shows the highest affinity to **1** in the *homogeneous* binding of lipophilic octyl glycoside derivatives in chloroform, where potential guest–guest interaction becomes more important. The implication of this work may be two-fold. First, a slight difference in stereochemisty does lead to remarkable discrimination among otherwise closely related sugars. Second, direct sugar–sugar interaction does take place in a highly selective manner. Hakomori, et al., have recently demonstrated that cell–cell adhesion is initiated by direct interaction of the oligosaccharides on the cell surfaces.[6]

Experimental

Preparation of octyl glycosides **5**—**9** has been described.[1] Octyl α-D-mannopyranoside (**4**) was obtained in a similar manner. Thus, a mixture of mannose (15 g) and 1-octanol (200 ml) containing concd hydrochloric acid (1.25% by weight) was stirred at 50—60 °C for 5 d. Workup and chromatography on silica gel with acetone as eluant gave the desired compound **4**, which was recrystallized from ethyl acetate: yield 6.9 g (21%); mp 54—55 °C. The ^{13}C NMR spectrum for a $CDCl_3$ solution showed a single resonance for 1-C at $\delta=100.1$, thus confirming the α-configuration.[7]

^1H NMR and CD spectra were taken as described, using a JEOL JNM EX-400 spectrometer and a JASCO J-500C spectropolarimeter, respectively.[1]

References

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4) There is no significant difference in the binding abilities of glucoside epimers **2**α and **2**β to host **1**; $K=1.9\times10^8$ and 3.2×10^8 M^{-4} for **2**α and **2**β, respectively.[1] On the other hand, the estimated binding constant for the equilibrium, $\mathbf{1}+\mathbf{44}\rightleftharpoons\mathbf{1}\cdot\mathbf{44}$, is $K=10^4$—10^5 M^{-4}. This is based on computer simulation of the buildup of 1 : 4 complex **1**·**44** (Fig. 1).

5) Investigation of the binding abilities of *cis*- and *trans*-1, 2-cyclohexanediol indicates that the former is better bound to host **1** than the latter by a factor of 2.5 : Y. Kikuchi, Y. Kato, Y. Tanaka, H. Toi, and Y. Aoyama, *J. Am. Chem. Soc.*, **113**, 1349 (1991).

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