Saccharide Recognition

Self-Assembled Receptors that Stereoselectively Recognize a Saccharide

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Saccharide recognition is very important for many processes occurring in nature, such as cell–cell interaction, carbohydrate transportation, and carbohydrate metabolism.[1,2] X-ray crystallographic analysis of saccharide–protein complexes has revealed that neutral and charged functionalities are preorganized in the three-dimensional binding pocket that recognizes saccharide molecules through hydrogen-bonding interactions.[3] This analysis has provided valuable information for the design of artificial saccharide receptors.[4–11] These receptors generally have a covalent scaffold decorated with neutral[4–10] and charged functionalites.[11] Recently, noncovalent synthesis[12] has led to new types of artificial receptors that self-assemble through multiple noncovalent interactions such as hydrogen-bonding[13] or metal–ligand interactions.[14] Hitherto, a self-assembled receptor for saccharide recognition has not yet been reported. Herein, we report the first example of carbohydrate recognition by a receptor that is self-assembled through hydrogen bonds. More importantly, this self-assembled receptor is able to recognize *O*-alkyl pyranosides stereoselectively.

Hydrogen-bonded tetrarosette assemblies $\mathbf{1}_3\cdot(BA)_{12}/(CYA)_{12}$ and $\mathbf{4}_3\cdot(BA)_{12}/(CYA)_{12}$ are formed from 15 components: 3 calix[4]arene tetramelamines **1** or **4** and 12 barbituric acid (BA) or cyanuric acid (CYA) derivatives (Scheme 1).[15,16] A total of 72 cooperative hydrogen bonds hold the building blocks together to form a fully assembled tetrarosette structure, with each floor of the assembly corresponding to one rosette motif (Figure 1, p. 2302). Tetramelamines **1** and **4** consist of two calix[4]arene units which are covalently connected through two urea moieties.

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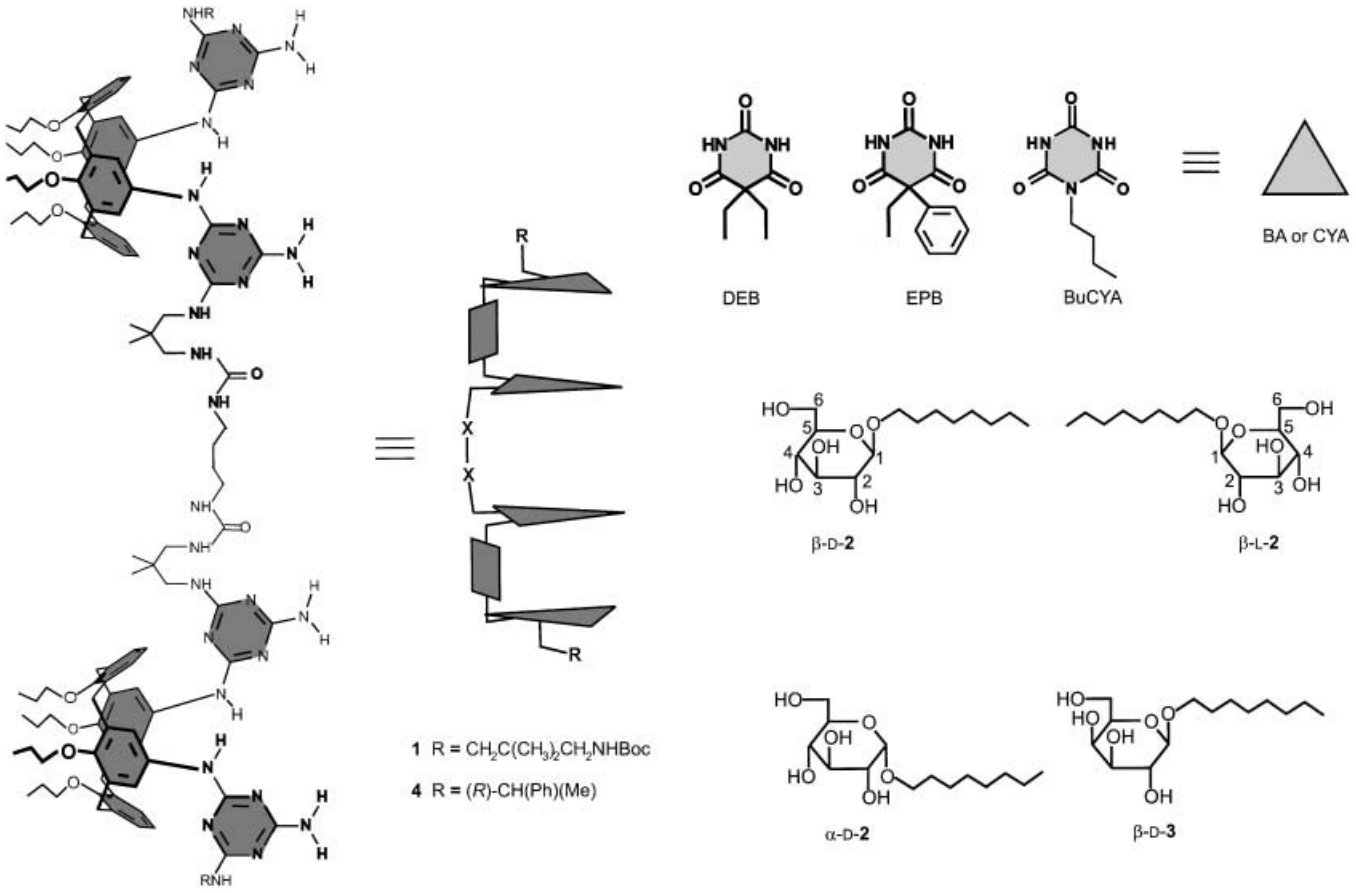


Scheme 1. Structures of the building blocks. Boc = *tert*-butyloxycarbonyl.

This self-assembly process results in a total of six urea functionalities being positioned in the central cavity for saccharide recognition. In the absence of any source of chirality, the tetrarosette assembly is present as a racemic mixture of *P* and *M* enantiomers ((*P*)-$\mathbf{1}_3$·$(BA)_{12}$ and (*M*)-$\mathbf{1}_3$·$(BA)_{12}$) (Figure 1 a), while the introduction of chiral centers (*R* or *S*) in the assembly leads to the formation of exclusively one of the two possible diastereomers (Figure 1 b).[17]

Recognition of *n*-octyl β-D-glucopyranoside (β-D-**2**) by $\mathbf{1}_3$·$(DEB)_{12}$ (DEB = 5,5-diethylbarbituric acid) is reflected in the shifts and splitting of the signals in the ^{1}H NMR spectrum recorded in $CDCl_3$ (Figure 2, p. 2303). As expected, in addition to the original NH^A signal of the urea moiety, a new signal ($NH^{A'}$) corresponding to the complex formed between one of the isomers (*P* or *M*) of $\mathbf{1}_3$·$(DEB)_{12}$ and β-D-**2** is observed at lower magnetic field ($\Delta\delta = 0.05$ ppm, 10 equivalents of β-D-**2**). The downfield shift is possibly a result of the formation of one hydrogen bond between the urea carbonyl group of $\mathbf{1}_3$·$(DEB)_{12}$ and one hydroxy group of β-D-**2**. More important, similar shifts and splittings are observed for the H^{a2} and H^{c2} signals on the second and third rosette floors upon guest binding, whereas the corresponding signals on the first and fourth floors show no splitting. The intensities of the new signals ($H^{a2'}$ and $H^{c2'}$) slightly increase with the amount of β-D-**2** added, while the original signals decrease. This means that one of the two enantiomers from the racemic mixture of the *P* and *M* isomers of $\mathbf{1}_3$·$(DEB)_{12}$[15] recognizes the chiral guest stereoselectively and results in the formation of one diastereomeric complex.

This conclusion is supported by the induced signal in the circular dichroism (CD) spectrum. The racemic mixture of (*M*)-$\mathbf{1}_3$·$(DEB)_{12}$ and (*P*)-$\mathbf{1}_3$·$(DEB)_{12}$ is CD silent. The addition of β-D-**2** to this mixture induces a negative Cotton effect around 290–310 nm, clear evidence for the formation of a *P* rosette assembly (Figure 3; p. 2303).[17] As a result of the chiral recognition, the *P* enantiomer, which binds β-D-**2** more strongly, is amplified in the mixture as both enantiomers (*P* and *M*) are in dynamic equilibrium (Figure 4; p. 2304).[18] A ^{1}H NMR titration was also performed with *n*-octyl β-L-glucopyranoside (β-L-**2**). The chiral recognition of β-L-**2** by (*M*)-$\mathbf{1}_3$·$(DEB)_{12}$ is also reflected in the shifts and splitting of the signals in the ^{1}H NMR spectra recorded in $CDCl_3$. As expected, the appearance of a positive Cotton effect around 290–310 nm in the CD spectrum was observed, thus indicating the amplification of the *M*-rosette assembly.

The binding constants for the complexations of $\mathbf{1}_3$·$(DEB)_{12}$ with β-D-**2** and β-L-**2** can be estimated on the basis of the CD data to be approximately $20\,M^{-1}$ (ca. 9 % diastereomeric excess).[19] The 1:1 stoichiometry of the complexes (*P*)-$\mathbf{1}_3$·$(DEB)_{12}$·(β-D-**2**) and (*M*)-$\mathbf{1}_3$·$(DEB)_{12}$·(β-L-**2**) was determined from a Job plot (see the Supporting Information).[20,21]

While similar chiral recognition of β-D-**2** by the different assembly $\mathbf{1}_3$·$(EPB)_{12}$ (EPB = 5-ethyl-5-phenyl barbituric acid) was found by ^{1}H NMR and CD spectroscopy, the cyanuric

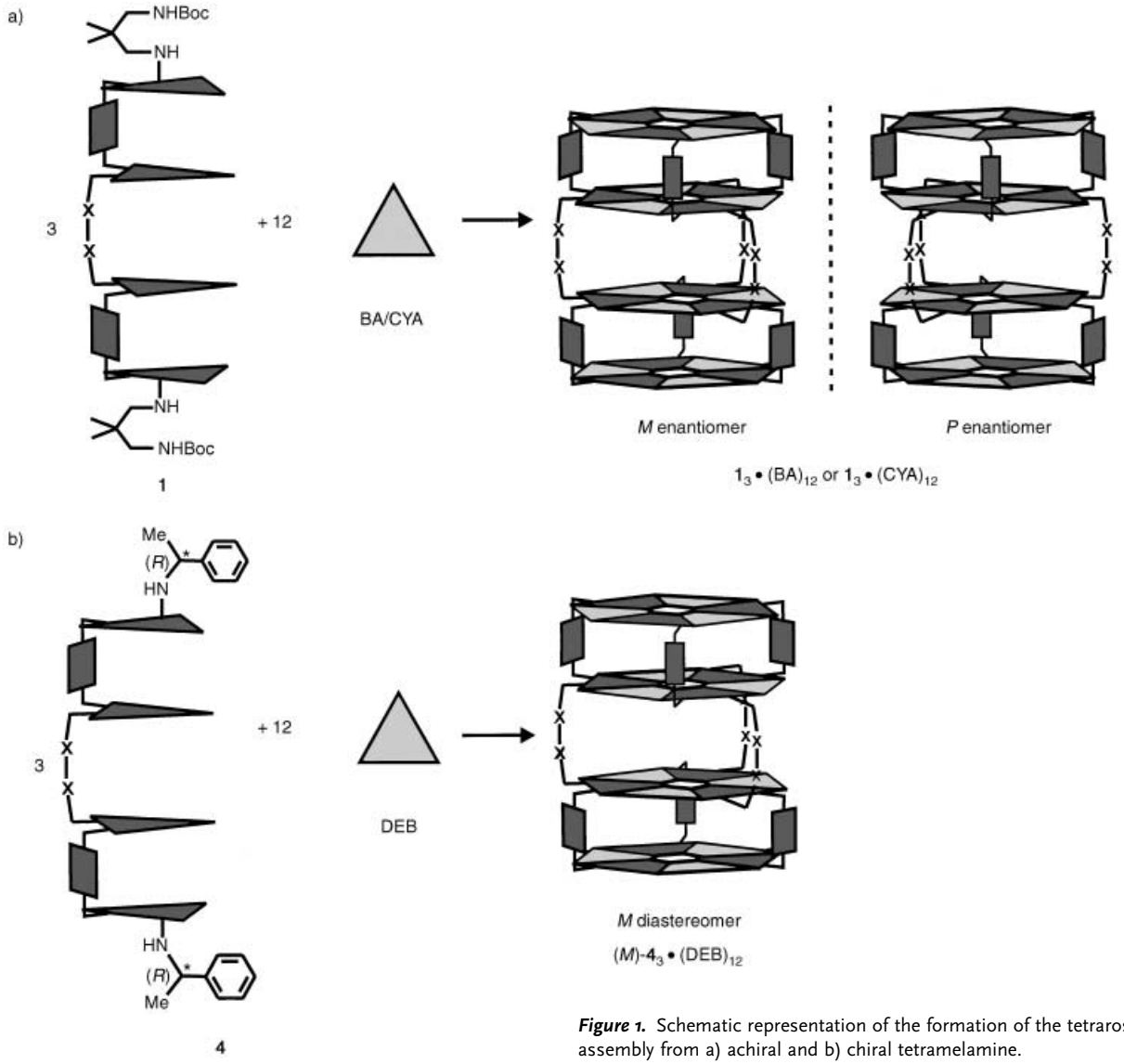


Figure 1. Schematic representation of the formation of the tetrarosette assembly from a) achiral and b) chiral tetramelamine.

acid based assembly $\mathbf{1}_3\cdot(\mathrm{BuCYA})_{12}$ did not show any shift or splitting in the ^{1}H NMR spectrum. Furthermore, the CD spectrum of this assembly upon addition of β-D-**2** remained unchanged.[22] Thus, this assembly does not complex the saccharide. This distinct behavior is most probably a consequence of the difference in the orbital electron distribution of BA and CYA.[23]

Computational studies (gas-phase MM calculation, Quanta 97/CHARMm 24.0) confirmed the observed enantioselectivity. In the complex with (P)-$\mathbf{1}_3\cdot(\mathrm{DEB})_{12}$, β-D-**2** is located in the cavity without any steric hindrance (Figure 5, p. 2304). A urea carbonyl group in the receptor forms a hydrogen bond with the hydroxy group at the 4-position of β-D-**2**. In contrast, the modeling study of the "mismatching" complex (P)-$\mathbf{1}_3\cdot(\mathrm{DEB})_{12}\cdot$(β-L-**2**) shows that the alkyl chain of β-L-**2** breaks the hydrogen-bonding network on the second rosette floor.

In contrast to β-D-**2**, its α isomer, *n*-octyl α-D-glucopyranoside (α-D-**2**), and epimer, *n*-octyl β-D-galactopyranoside (β-D-**3**), were not recognized by $\mathbf{1}_3\cdot(\mathrm{DEB})_{12}$, as indicated by the absence of shifts or splittings in the signals in the ^{1}H NMR spectra and the absence of CD signals. This trend in the complexation can be rationalized by the strength of the intramolecular hydrogen bonds in the pyranosides.[6–8]

Complexation experiments using chiral assemblies (M)-$\mathbf{4}_3\cdot(\mathrm{DEB})_{12}$ were performed to further probe the stereoselectivity of the recognition of saccharide by the tetrarosette assemblies. In this case, instead of the racemic mixture of receptors (P)-$\mathbf{1}_3\cdot(\mathrm{DEB})_{12}$ and (M)-$\mathbf{1}_3\cdot(\mathrm{DEB})_{12}$, the diastereomeric assembly (M)-$\mathbf{4}_3\cdot(\mathrm{DEB})_{12}$ was used as a complexing molecule.

The "mismatch" combination of receptor (M)-$\mathbf{4}_3\cdot(\mathrm{DEB})_{12}$ and β-D-**2** (Figure 6, p. 2305) does not show any changes in the ^{1}H NMR spectrum (see the Supporting Information). In contrast, recognition of *n*-octyl-β-L-glucopyranoside (β-L-**2**) by (M)-$\mathbf{4}_3\cdot(\mathrm{DEB})_{12}$ in the matching pair is reflected in the corresponding shifts in the ^{1}H NMR spectra recorded in $CDCl_3$ (see the Supporting Information). Similarly as observed for assembly $\mathbf{1}_3\cdot(\mathrm{DEB})_{12}$, the urea proton NH^A shifts to a lower magnetic field ($\Delta\delta = 0.10$ ppm, 10 equiva-

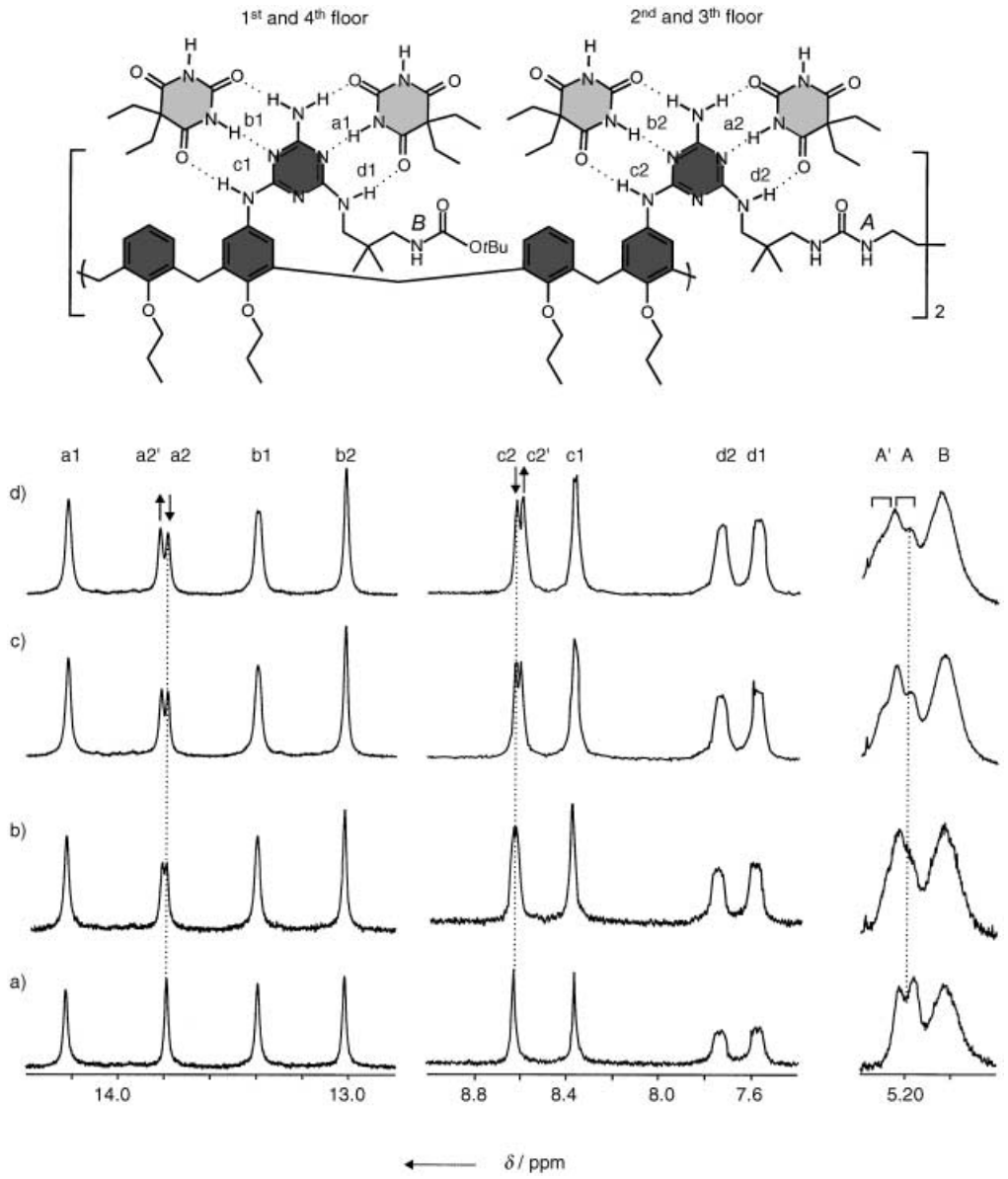
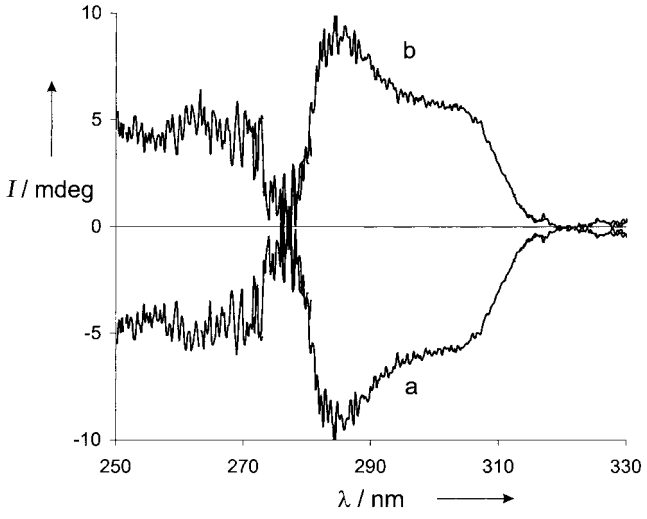


Figure 2. ^{1}H NMR spectra of $\mathbf{1}_3\cdot(DEB)_{12}$ (1 mM) in $CDCl_3$ at 20 °C in the presence of a) 0, b) 3, c) 5, and d) 10 equivalents of β-D-**2**.



lents of β-L-**2**) and shifts for H^{a2} and H^{c2} on the second and third rosette floors were observed, whereas the corresponding signals (H^{a1} and H^{c1}) on the first and fourth floors remained unchanged.

In contrast to what occurred in the complexation studies with the racemic mixture (M/P)-$\mathbf{1}_3\cdot(DEB)_{12}$, the addition of β-L-**2** to the chiral assembly (M)-$\mathbf{4}_3\cdot(DEB)_{12}$ does not result in measurable changes in the CD spectra (see Supporting Information). This observation means that the CD changes observed (see above) for the assembly $\mathbf{1}_3\cdot(DEB)_{12}$ definitely arise from the amplification of one of the enantiomers upon complexation.

Figure 3. CD spectra of $\mathbf{1}_3\cdot(DEB)_{12}$ (1 mM) in the presence of 10 equivalents of a) β-D-**2** and b) β-L-**2** in $CDCl_3$ (in a 0.01 cm width cell at 20 °C).

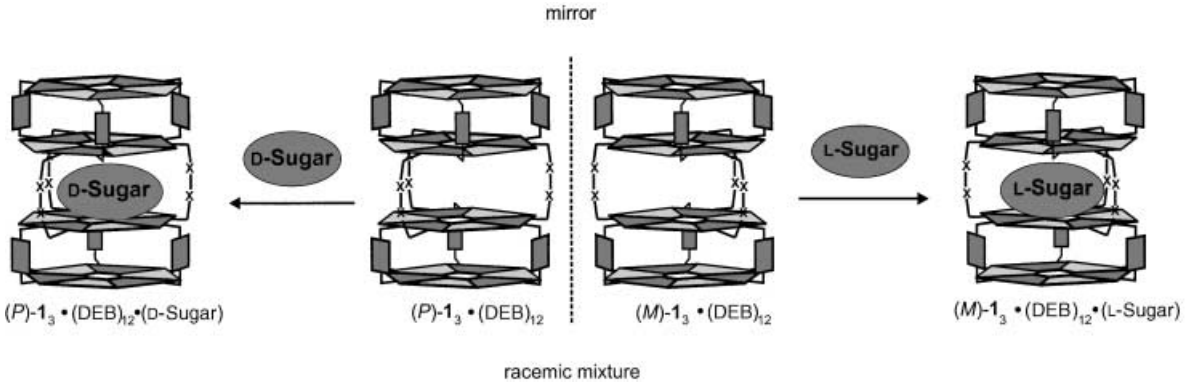


Figure 4. Schematic representation of the enantioselective recognition of saccharides by a racemic mixture of assemblies.

In conclusion, we have shown for the first time the complexation of a saccharide by a self-assembled receptor through hydrogen-bonding interactions. More importantly, the recognition of the monosaccharide occurs enantioselectively. This enantiomeric recognition of the saccharide allows the amplification of the best receptor from a racemic mixture of self-assembled receptors. Furthermore, the tetrarosettes are quite stable even in polar media (up to at least 60% methanol in $CDCl_3$). Further studies on saccharide recognition with similar assemblies in a polar environment are under investigation.

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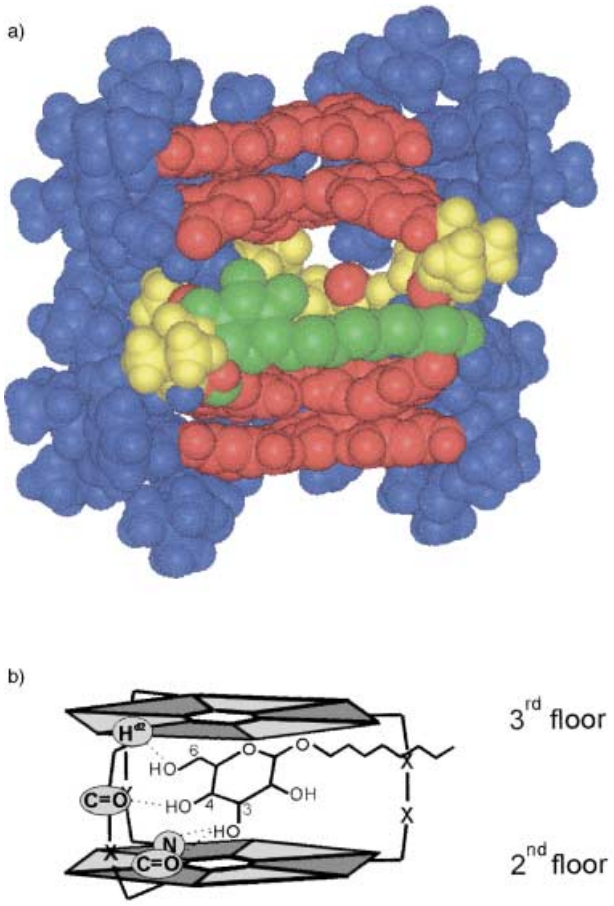

Figure 5. a) Computer simulated structures of (*P*)-**1**$_3$·(DEB)$_{12}$·(β-D-**2**) (a cross-sectional view of the assembly is depicted to show the environment inside the cavity occupied by the sugar; blue = calix[4]arene; red = rosette floors; green = saccharide; yellow = urea groups). b) Cartoon representation of (*P*)-**1**$_3$·(DEB)$_{12}$·(β-D-**2**) (for clarity reasons only the second and third floors of the tetrarosette assembly are shown).

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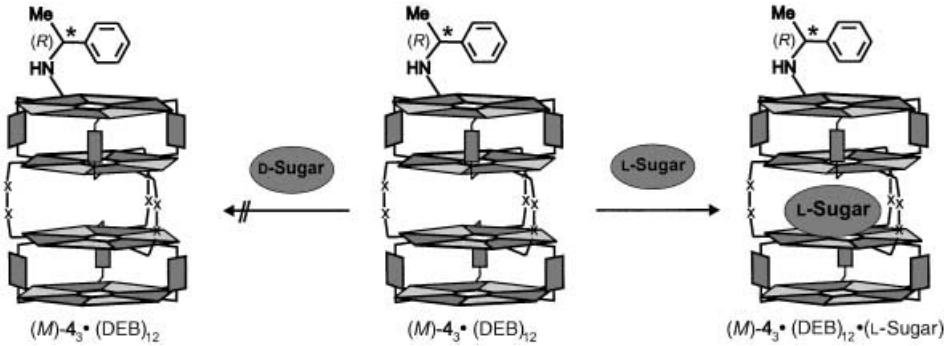

Figure 6. Schematic representation of the enantioselective recognition of saccharides by a chiral tetrarosette.

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[19] In this chiral complexation, we assumed that the binding constant (K_P) of β-D-**2** with (*P*)-**1**$_3$·(DEB)$_{12}$ is much larger than that (K_M) with (*M*)-**1**$_3$·(DEB)$_{12}$. The K_P value can be obtained according to equations (1–5):$K_P = [(P)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}\cdot(\beta\text{-D-}\mathbf{2})]/[(M)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]/[\beta\text{-D-}\mathbf{2}]$ (1)$[(P)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}] = [(M)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}] = \{(1-(de/100))/2\}\times[\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]_0$ (2)$[\beta\text{-D-}\mathbf{2}] = [\beta\text{-D-}\mathbf{2}]_0-(de/100)\times[\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]_0$ (3)$[(P)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}\cdot(\beta\text{-D-}\mathbf{2})] = (de/100)\times[\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]_0$ (4)$de\,(\%) = (\mathrm{CD}_{obs}/\mathrm{CD}_{100\%\,de})\times 100$ (5)in which $[(P)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}\cdot(\beta\text{-D-}\mathbf{2})]$, $[(M)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]$, $[(P)\text{-}\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]$, and $[\beta\text{-D-}\mathbf{2}]$ are the concentrations of the corresponding species, $[\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]_0$ and $[\beta\text{-D-}\mathbf{2}]_0$ are the initial concentrations of the host and guest, and *de*(%) is the diastereomeric excess of the *P* assemblies obtained from the ratio of observed and standard CD intensities (CD_{obs} and $\mathrm{CD}_{100\%\,de}$). The CD intensity (67 mdeg) at 300 nm in completely chiral (*M*)-**4**$_3$·(DEB)$_{12}$ is used as the reference ($\mathrm{CD}_{100\%\,de}$) because the CD spectral shape of (*M*)-**4**$_3$·(DEB)$_{12}$ almost coincides with that of **1**$_3$·(DEB)$_{12}$·(β-D-**2**) complex (see the Supporting Information). When $[\mathbf{1}_3\cdot(\mathrm{DEB})_{12}]_0 = 1$ mM, $[\beta\text{-D-}\mathbf{2}]_0 = 10$ mM, $\mathrm{CD}_{obs\,300\,nm} = 6$ mdeg, and $de = 9\%$, a K_p value can be estimated to be $20\,\mathrm{M}^{-1}$.

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[21] We also measured the MALDI-TOF mass spectra by using the Ag^+-labeling technique to detect the complex. However, only the parent ion peak of the assembly was observed at $m/z =$ 9978.0 (calcd for $C_{528}H_{684}N_{114}O_{78}Ag$, 9976.2). For a description of the MALDI-TOF mass spectrometry technique using Ag^+-labeling, see P. Timmerman, K. A. Jolliffe, M. Crego-Calama, J.-L. Weindmann, L. J. Prins, F. Cardullo, B. H. M. Snellink-Ruel, R. Fokkens, N. M. M. Nibbering, S. Shinkai, D. N. Reinhoudt, *Chem. Eur. J.* **2000**, *6*, 4104 – 4115.

[22] **1**$_3$·(BuCYA)$_{12}$ was obtained by two different methods:[15] 1) from **1**$_3$·(DEB)$_{12}$ upon exchange of DEB for BuCYA and 2) the direct mixing of **1** and BuCYA in toluene and subsequent heating (100 °C) and evaporation. Complexation with β-D-**2** was observed in neither case, even after two weeks or higher temperature (55 °C).

[23] The three-dimensional structure of DEB, which arises from the presence of a sp^3 carbon atom in the six-membered ring, is better suited for guest encapsulation, while the flatter structure of BuCYA is less favored because the complexed guest could be expelled more easily.

