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Cyclotrehalins: Cyclooligosaccharide Receptors Featuring a Hydrophobic Cavity**

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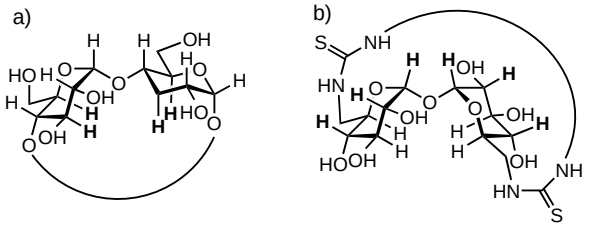
Dedicated to Dr. Jacques Defaye

Interactions between carbohydrates and other biomolecules play a prominent role in many biological recognition processes.[1] The complexity of such phenomena has stimulated the use of model systems to gather information about their nature (hydrophobic, polar, hydrogen bonds) and to unravel the factors influencing the binding specificity and the stability of carbohydrate-containing supramolecular entities.[2] Among sugar-derived model hosts, the commercially available cyclodextrins (CDs) have been by far the most extensively investigated for this purpose,[3] as they feature a hydrophobic cavity that can accommodate a guest molecule of appropriate size. The study of the resulting inclusion complex, by techniques such as NMR spectroscopy, is facilitated by the high symmetry and the rigidity of the CD structure. Yet, this strait-jacketed host has an intrinsic limitation: Exclusively contacts involving the inner α face of the D-glucopyranose units (i.e., H-3 and H-5) are observable (Scheme 1a).



Scheme 1. Representation of a) cyclodextrins (CDs) and b) trehalose cyclooligosaccharides (cyclotrehalins, CTs) incorporating thiourea intersaccharide bridges. The CH protons directed toward the inside of the corresponding cavities are in boldface.

Although much effort has been directed towards the preparation of synthetic CD analogues bearing a cavity of designed shape, size, and electrostatic potential,[4,5] no cyclooligosaccharide hosts suitable for the analysis of specific interactions involving the β face of the monosaccharides have been reported so far.

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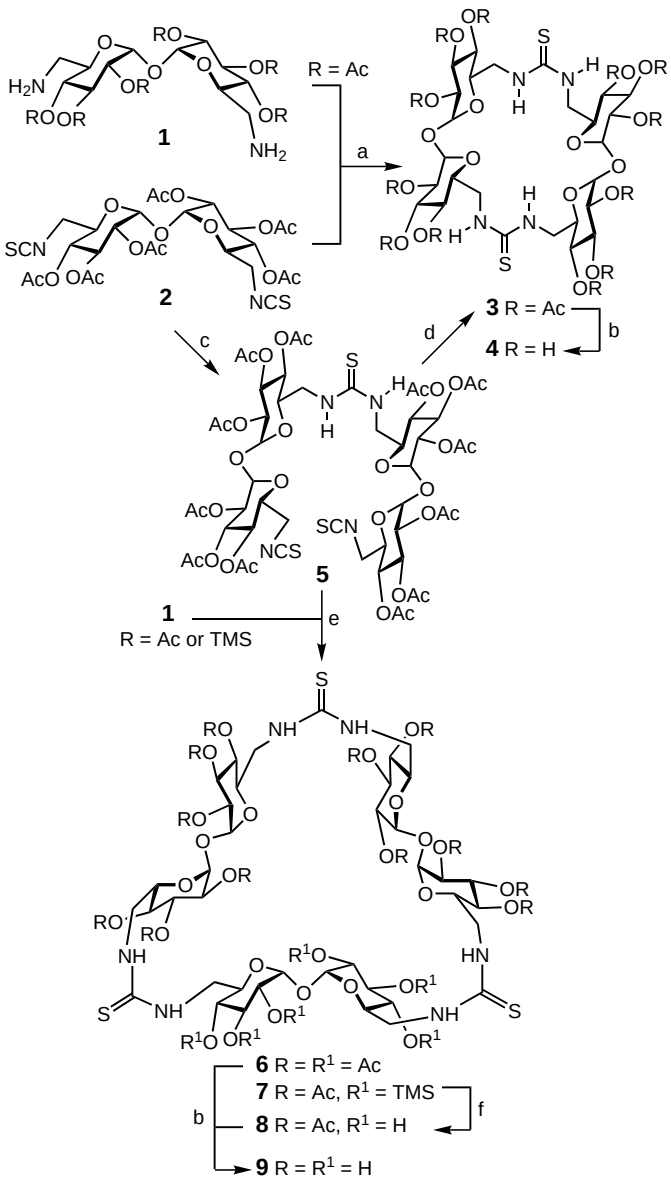
In principle, "reversed CDs", in other words cyclooligosaccharides in which the β face of the monosaccharide constituents is oriented toward the inside of a convex cavity, are deemed to exhibit inclusion capabilities analogous to those of the original CDs. To prove this concept, we have focused on the potential of cyclic arrays of desired ring size and defined secondary structure composed of alternating (6→6)-linked α,α'-trehalose moieties and thiourea groups as novel artificial receptors (Scheme 1b). Preliminary modeling studies suggested that the inner wall in these macrocycles (cyclotrehalins, CTs)[6] would expose the H-1, H-2, and H-4 protons for contacts with an included guest, provided that the conformation about the interglycosidic bonds of the trehalose segments remains identical to that of the parent disaccharide, in other words, fitting the *exo*-anomeric effect.[7] Moreover, the presence of thiourea segments in the structure might provide additional chelation points for molecular recognition and catalysis.[8]

Replacement of the classical O-glycosidic intersaccharide linkages in cycloglucans with achiral thiourea functional groups permits a convergent retrosynthetic analysis for CTs, involving the coupling reaction of C_2-symmetric diamine and diisothiocyanate precursors. Actually, this approach proved successful in the preparation of dimer **3** from the hexa-*O*-acetylated derivatives **1** (R = Ac) and **2** (Scheme 2).[9] Confirmation of the reversed CD conformation of the unprotected receptor **4** was, however, prevented by the limited dimensions of the cavity.

A similar strategy for the synthesis of the trimer homologue requires prior desymmetrization of the trehalose building blocks. Our solution to this problem involved the water-promoted self-condensation of diisothiocyanate **2**, directly affording the linear pseudotetrasaccharide **5** in which the α,α'-trehalose subunits are already desymmetrized and appropriately functionalized.[10] Compound **5** can be cyclized in situ to give the cyclic dimer **4** or, alternatively, coupled with the per-*O*-acetylated diamine **1** to give the cyclic pseudohexasaccharide **6** in modest (25%) yield. When the silyl ether derivative (**1**, R = TMS) was used the corresponding cyclic trimer **7** was obtained in 70% yield.

The NMR spectra of the per-*O*-acetate **6** exhibit signals for a single D-glucopyranose subunit, as expected for a D_3-symmetric structure. The symmetry is reduced to C_2 in the case of compound **7** and its desilylated derivative **8** which results in the presence of three distinct spin systems in their NMR spectra. NOE experiments indicate close contacts between the H-1/H-1′, H-1/H-5′, and H-5/H-1′ protons of the magnetically nonequivalent D-glucopyranose moieties of the acetylated trehalose fragments (Figure 1a). This points unequivocally to a rigid conformation about the glycosidic linkages dictated by the exo-anomeric effect in agreement with our original hypothesis.

The three-dimensional model of the D_3-symmetric, unprotected CT **9** depicts a truncated-cone structure with the hydroxy groups located at both rims, reminiscent of the CDs (Figure 1).[11] Contrary to the dimeric CT **4**, for which the macrocyclic ring imposes a *Z*,*E* configuration about the NH–C(=S) bonds, in **9** the possibility of both *Z*,*E*- and *Z*,*Z*-rotameric dispositions at the semirigid thiourea segments



Scheme 2. Modular and convergent synthesis of cyclotrehalins **4** and **9** from symmetric trehalose precursors: a) pyridine, 40°C, 48 h (40%); b) NaOMe, MeOH, then H_2O, room temperature (96–99%); c) pyridine/H_2O (15:1), 40°C, 6 h (43%); d) pyridine/H_2O (10:1), 60°C, 48 h (38% overall from **2**); e) from **1** (R = Ac), pyridine, 40°C, 24 h (25%); from **1** (R = TMS), CH_2Cl_2, 12 h (70%); f) H_2O/AcOH (10:1) in $CHCl_3$/MeOH/H_2O (4:3:1), 60°C, 15 h, (89%). TMS = trimethylsilyl.

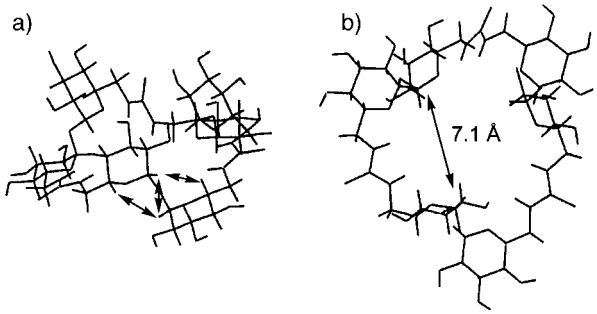


Figure 1. Structure of receptor **9** according to MM2 calculations in water: a) side view showing the intramolecular ROE contacts (observable in the C_2-symmetric derivatives **6** and **7**); b) top view (narrower rim).

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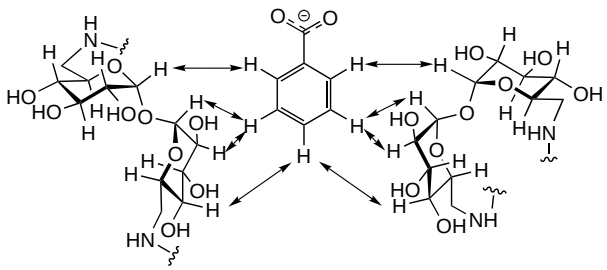
provides the structure with limited flexibility. However, this flexibility does not affect significantly either the topology or the size of the internal cavity (medium internal diameter 7.1 Å), which is estimated to be intermediate to that of α- and β-CDs (5.7 and 7.8 Å, respectively). Accordingly, receptor **9** binds benzoate anion in water. We determined the 1:1 stoichiometry for the complex (Job plot)[12] and an association constant (K_{ass}) of $8 \pm 2\,M^{-1}$ by ^1H NMR titration.[13] The high-field shift of the H-1, H-2, and H-4 protons upon addition of tetrabutylammonium benzoate suggests that the aromatic ring is bound in the cavity through hydrophobic interactions involving the β face of the monosaccharide subunits, while the carboxylate group is still solvated. There are a number of intermolecular ROE contacts, which indicate the mutual orientation of both complexation partners. The result is exactly as predicted: The phenyl ring is located inside the cavity, and the carboxylate group protrudes through the wider rim of the cone, remaining in contact with bulk water (Scheme 3). It is noteworthy that this situation is significantly different from that reported for the corresponding inclusion complexes of α- and β-CDs and benzoate: Whereas the association constants are in the same range ($10–11\,M^{-1}$),[3a] the CD structure does not induce a precise orientation of the guest in the cavity.[14]



Scheme 3. Intermolecular ROE interactions in the complex formed between host **9** and benzoate anion. The thiourea linkers and one of the three α,α'-trehalose subunits are omitted for clarity.

For further information about the dimensions of the cavity and the inclusion capabilities of CT **9**, 2-naphthalene sulfonate (NS) and 1-adamantanecarboxylate (AC) were investigated as guests. In both cases the 1:1 complex stoichiometry was confirmed, indicative of a size-matched host–guest combination, with K_{ass} values of 235 ± 15 and $4.6 \pm 0.4 \times 10^4\,M^{-1}$, respectively.[13] The CT complex with the NS guest is more stable than that with benzoate, a finding parallel to that encountered in the corresponding complexes with α-CD (K_{ass} for α-CD:NS $363 \pm 8\,M^{-1}$)[3a] and can be ascribed to the naphthalene hydrophobic part of NS being deeply embedded in the hydrophobic cavity in the longitudinal direction. The much higher stability of the **9**:AC complex, even more stable than the corresponding β-CD:NS complex ($K_{ass} = 3.9 \pm 0.3 \times 10^4\,M^{-1}$),[3a] is in accord with the size-fit concept and the symmetric complementarity between host and guest.

In summary, we have designed new carbohydrate-based receptors for the study of specific interactions between the β face of the constituent saccharides and guest molecules. This class of cyclic oligomers could become versatile tools for ligand binding and molecular recognition.

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