

Selective Encapsulation of Disaccharide Xylobiose by an Aromatic Foldamer Helical Capsule

Subrata Saha, Brice Kauffmann, Yann Ferrand,* and Ivan Huc*

Abstract: Xylobiose sequestration in a helical aromatic oligoamide capsule was evidenced by circular dichroism, NMR spectroscopy, and crystallography. The preparation of the 5 kDa oligoamide sequence was made possible by the transient use of acid-labile dimethoxybenzyl tertiary amide substituents that disrupt helical folding and prevent double helix formation. Binding of other disaccharides was not detected. Crystallographic data revealed a complex composed of a D-xylobiose α anomer and two water molecules accommodated in the right-handed helix. The disaccharide was found to adopt an unusual all-axial compact conformation. A dense network of 18 hydrogen bonds forms between the guest, the cavity wall, and the two water molecules.

Saccharides constitute important molecular recognition targets, yet they remain elusive and difficult to discriminate. Indeed, they may only differ by the configuration of a single stereogenic center, and each saccharide often exists as different isomeric forms owing to anomerization and to equilibria between open chain and cyclic furanose or pyranose forms. Significant progress in synthetic saccharide receptor development has been made over the years,^[1] including combinatorial approaches and screening of libraries.^[2] Nevertheless, the ab initio design of selective saccharide receptors has remained a challenging objective except in the case of all equatorial sugars that can be sandwiched between aryl groups and for which tight and selective binding has been achieved even in water.^[3]

We and others have introduced foldamer-based helical containers in which aryl groups expose their edges to a central cavity as versatile tools for molecular recognition.^[4–7] In some designs, molecular helices possess a reduced diameter at both ends and completely surround their guest, allowing for host-guest interactions in all directions (Figure 1 a).^[5–7] Sequences

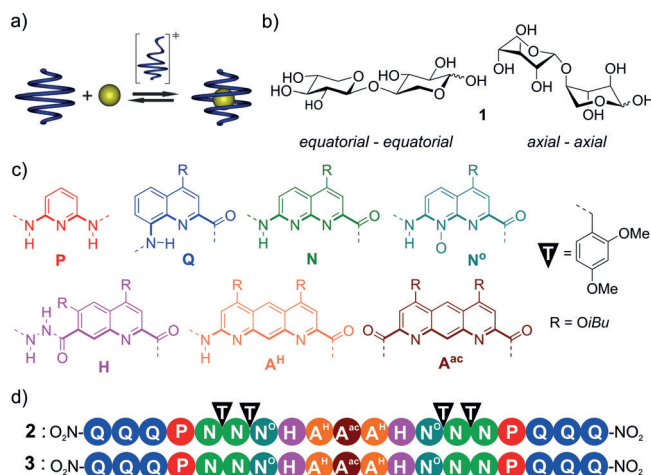


Figure 1. a) Representation of the encapsulation of a guest molecule (yellow sphere) in the cavity of a helical foldamer capsule (blue tube). b) Two possible conformations of 1,4-D-xylobiose **1**. c) Color-coded formulae and associated letters of amino acid, diamino, and diacid monomers. The inner rim of the helix is marked by thick bonds. d) Sequences of the ill-folded oligomer **2** including tertiary amide bonds (T) and of capsule **3**. The terminal nitro group replaces the 8-amino-quinoline substituent.

based on first principle design have been shown to tightly bind to polyhydroxylated guests, including monosaccharides, in organic solvents.^[6,7] Furthermore, structure elucidation allowed for iterative improvements of the designs to reach outstanding selectivity.^[6,7a] We now have expanded this approach to produce a selective disaccharide receptor that binds a dipentose, α -1,4-xylobiose **1** (Figure 1 b), whereas binding of dihexoses is negligible. Structure elucidation allowed us to decipher a binding mode that involves an induced fit of the guest, which adopts an all axial conformation to match with the capsule cavity.

Sequence **3** (Figure 1 d) was designed to fold into a helical capsule following previously described principles.^[5a] Energy minimization predicts an inner-cavity volume large enough (ca. 330 Å³) to accommodate some disaccharides.^[8] Its inner rim possesses multiple hydrogen bond donors and acceptors suitable to bind sugars in organic solvents. Furthermore, the ovoid cavity shape hints at binding of compact sugar conformations and not of extended or flat (for example, all-equatorial) guests. In the design of sequence **3**, terminal Q monomers play the role of end caps that close the cavity; large central A and H units ensure a wide-enough helix equatorial diameter; amide protons serve as hydrogen bond donors; and several monomers expose hydrogen bond acceptor functions to the binding cavity, including the endocyclic nitrogen atoms of N and A units, the hydrazide carbonyl oxygen atom of H

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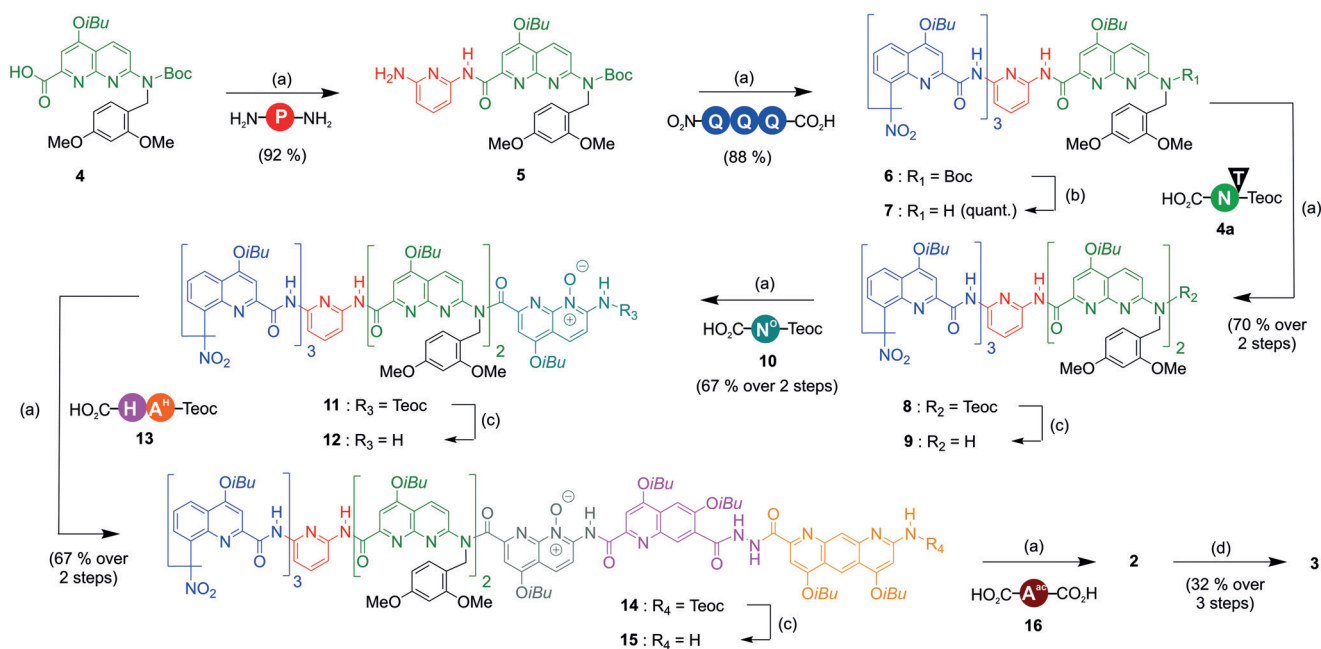
units,^[6] and the N-oxide oxygen atom of N^O units. The latter was specifically developed for this work with the intention to exploit the established hydrogen bonding capabilities of N-oxides.^[9]

The predictions outlined above can be made with relatively high confidence. Thus, the challenge of constructing an aromatic foldamer-based disaccharide receptor lay not so much in its design. It was in fact primarily a synthetic challenge owing to the number of monomers (the MW of **3** is 5 kDa) and their variety (seven different units) and because of difficulties associated with coupling long sequences. Earlier successful foldamer capsule syntheses typically entailed extending a sequence from its narrow helical end to produce a long chain, cone-like, helix having an amine function at the wide end that was eventually coupled to a central diacid.^[6,7] A limitation of that approach is that the cone-like intermediate has a propensity to self-assemble into an anti-parallel double helical duplex, all the more so that the sequence is long and that the diameter is wide.^[10] This property can be exploited on purpose to form double helical containers.^[11] Yet it constitutes an obstacle to sequence elongation because of the steric hindrance associated with the inclusion of the terminal amine functions in a double helix. In contrast, once a full unimolecular capsule is formed, the reduced diameter of the terminal Q₃ segments prevents self-assembly into a double helix:^[12] sequence **3** is expected to be monomeric. Similarly, long Q_n oligomers can be coupled without difficulties.^[13] To prevent self-assembly of synthetic intermediates, we used tertiary benzylic amides as removable disruptors of helicity with the expectation that they would also disfavor double helix formation. Aryl-alkyl tertiary amides have been shown to preferentially adopt *cis* conformations.^[14] Their use has been proposed before to reduce steric hindrance in single

helices^[15] or to disrupt aggregation in rod-like aromatic amide oligomers.^[16] We thus set to target sequence **2** as a synthetic intermediate.

Sequence **2** possesses four removable dimethoxybenzylic (DMB) amide substituents. We hypothesized that the tertiary amides would prevent the self-assembly of the Q₃PN₂N^OHA^H precursor into a double helix and allow for its coupling to diacid monomer A^{ac} to produce **2**. As shown in Scheme 1, DMB groups were installed on protected naphthyridines **4** and **4a** (see the Supporting Information). Sequence elongation involved the PyBOP-mediated coupling of O₂N-Q₃-CO₂H with the primary amine group of **5** yielding pentaamide **6**. After Boc cleavage, the amine of pentaamide **7** was coupled to the acid of **4a** to give hexaamide **8**. Tertiary amides were found to be prone to base-mediated hydrolysis. The terminal secondary amine of **8** was thus deprotected to give **9** using TBAF in presence of succinic acid to keep the medium slightly acidic. The coupling of **9** with the acid function of the newly prepared naphthyridine N-oxide **10** (see the Supporting Information) yielded heptaamide **11**. Deprotection and addition of dimer **13** gave nonaamide **14**. As expected, the ¹H NMR spectrum of oligomer **14** exhibits a single set of sharp resonances reflecting the absence of undesired self-assembly (Supporting Information, Figure S1). Teoc deprotection of the amine followed by the final coupling step to diacid **16** provided the ill-folded intermediate oligomer **2**. The folded capsule **3** was eventually obtained in moderate yield on a 40 mg scale after acidic treatment to cleave the four DMB groups. Pure samples of **3** were produced by crystallization.

The folding of **3** into a helical capsule was evidenced in the solid state. Single crystals suitable for X-ray crystallographic analysis were obtained by NMR-tube layering of *n*-hexane above a chloroform solution. The structure was solved in the



Scheme 1. Synthetic pathway to capsule **3**: a) PyBOP, DIEA, CHCl₃, 35 °C; b) HCl 4.0 M in dioxane, 25 °C; c) TBAF 1 M in THF, succinic acid, THF:DMF, 25 °C; d) TFA, CH₂Cl₂, 25 °C. Teoc = trimethylsilylethyl-oxycarbonyl.

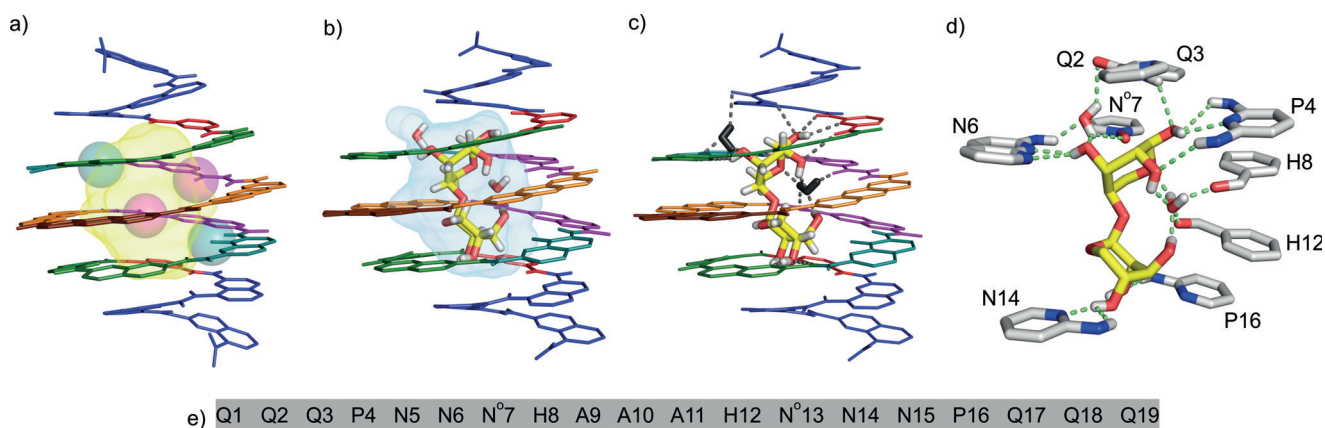


Figure 2. Side views of the crystal structures of: a) *P*-3; b) and c) *P*-3-D-1·(H₂O)₂.^[21] In (a), (b), and (c) the helix appears in tube representation. Monomers are color-coded as in Figure 1. In (a) the cavity (321 Å³) is shown as a transparent yellow isosurface, whereas hydrogen bond acceptors (oxygen atoms) of the H and N^o monomers are shown as magenta and green transparent CPK spheres. In (b) and (c) xylobiose and water molecules are shown in tube representation. In (b) the cavity (360 Å³) is shown as a transparent light blue isosurface. One of the terminal trimeric quinoline caps is slightly tilted allowing a water molecule to protrude out of the cavity. In (c) the two included water molecules are colored in black for clarity, whereas the 18 hydrogen bonds found in the complex are shown as grey dashes. d) Zoom on the cavity of *P*-3-D-1·(H₂O)₂ showing the binding mode between the xylobiose, the water molecules, and the inner wall of the foldamer. The disaccharide, the water molecules, and those heterocycles that interact with them are shown in tube representation. Non-polar hydrogens have been removed. Green dashed lines indicate hydrogen bonds. Details of these hydrogen bonds (distances, angles) can be found in the Supporting Information. In all representations, isobutoxy side chains and solvent molecules were omitted for clarity. e) Numbering of the units used in (d).

P $\bar{1}$ space group (Figure 2a). Both the overall helix shape and cavity volume (ca. 320 Å³) matched well with the initial prediction.

The binding of several disaccharides, namely D-cellobiose, D-lactose, D-maltose, D-sucrose, and D-xylobiose, to capsule **3** was assessed in DMSO/CHCl₃ mixtures (20:80 vol/vol) by using circular dichroism (CD). This screen assumes that binding, if it occurs, is likely to show some diastereoselectivity with respect to *P*-3 or *M*-3. It should thus result in some helix handedness induction detectable by CD. In this medium, dipentose D-xylobiose **1** was the sole disaccharide to generate a response.

Larger sugars, that is, dihexoses, did not induce any CD. The positive CD induced by **1** was too weak to allow for a trustworthy determination of the binding constant. However, saturation of the host took place after addition of slightly more than 1 equiv of guest [D-**1**] (Supporting Information, Figure S3). The weak CD induction thus did not reflect a weak binding but rather a poor diastereoselectivity, with a preference of D-**1** for *P*-3. Host-guest complex formation was also monitored by ¹H NMR spectroscopy in the same solvent mixture. Upon titrating **3** (250 μM) with D-**1**, the initial set of resonances corresponding to free capsule **3** (Figure 3a) was replaced by three sets of signals that could all be attributed to disaccharide–capsule complexes (Figure 3b–d): a major set (black triangles) and two sets of weaker signals (black squares) integrating together for almost the same intensity as the major one. The presence of several sets of sharp signals presumably reflects the poor diastereoselectivity observed by CD (D-sugar in *P* or *M* helices) as well as a possible weak discrimination of the α and β sugar anomers. Each set of resonances account for 20 non-equivalent amide or hydrazide protons which denotes a loss of symmetry of the sequence upon complexing **1**. Exchanges between the free

capsule and the carbohydrate–capsule complexes are slow on the NMR timescale. Integration of the corresponding signals thus allowed us to estimate an overall affinity constant (*K*_a) of about 20000 L mol⁻¹.

The complexity of the NMR spectra made it impossible to elucidate a host–guest complex structure in solution as was achieved previously for monosaccharides.^[6] We thus turned

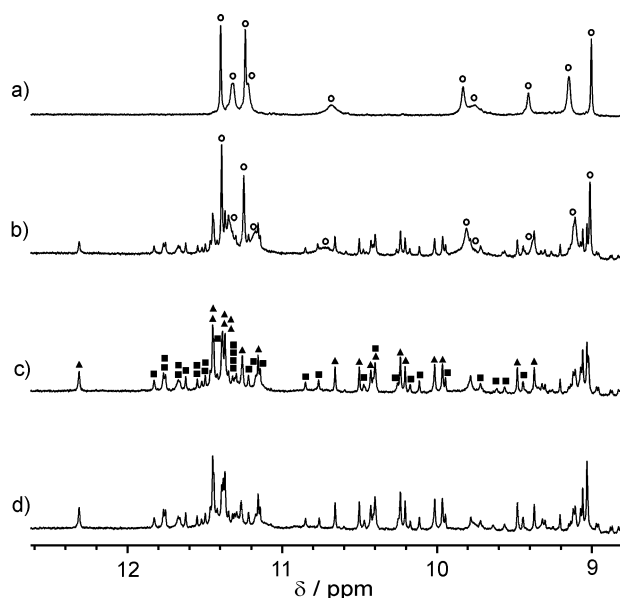


Figure 3. Excerpt of the amide and hydrazide resonances of the ¹H NMR spectrum of capsule **3** (700 MHz, 298 K) at 0.25 mm in a CDCl₃/[D₆]DMSO (80:20 vol/vol) mixture in the presence of: a) 0 equiv; b) 0.25 equiv; c) 1 equiv; and d) 1.5 equiv of **1**. ○ empty host, ■, ▲ signals of the different carbohydrate–capsule species.

towards X-ray crystallography. Racemic crystallography has proven very efficient in our hands to crystallize saccharide host–guest complexes,^[6,7c,17] but it could not be implemented here owing to the unavailability of L-1. Fortunately, single crystals of P-3 \supset α -D-1, that is, the helix handedness that prevails in solution, were obtained by the successive diffusion of first *n*-hexane then diethyl ether in a chloroform/DMSO solution (99:1 vol/vol) initially containing racemic P/M-3 capsule with D-1 as a guest. Crystals diffracted at 0.86 Å resolution and the structure was solved in the chiral space group P2₁2₁2₁. The structure revealed the presence of a molecule of α -D-1 and of two water molecules in the cavity of P-3 (Figure 2b–d). In its bound conformation, α -D-1 has all hydroxy groups in an axial position except the α anomeric OH (Figure 1b), instead of the equatorial conformation previously observed for this sugar bound to a protein.^[18] This unexpected compact conformation was interpreted as an induced fit imposed by the shape of the cavity, which is probably not complementary to the most stable conformer of the guest. Out of the 18 hydrogen bonds observed in the quaternary complex P-3 \supset D-1·(H₂O)₂, only nine consist of direct contacts between the sugar and the foldamer. Nine additional bonds are mediated by the water molecules which bridge the guest to the cavity wall. Two hydrazide carbonyl groups and one N-oxide function are involved in hydrogen bonding. The superposition of the aromatic backbones of 3 and 3 \supset D-1·(H₂O)₂ did not reveal significant differences of helical backbone folding except a small gap between one distal Q₃ segment and the adjacent naphthyridine that allows space for the inclusion of a water molecule. The cavity space was found to be slightly larger in 3 \supset D-1·(H₂O)₂ (ca. 360 Å³) than in 3 (ca. 320 Å³). The volume of the guests 1·(H₂O)₂ (ca. 222 Å³) leads to a packing coefficient of 0.62, a value close to that of other helical capsule–monosaccharide host–guest complexes.^[6]

It was not possible to assess the binding of dipentoses other than D-1 for lack of commercial availability. Molecular modeling revealed that dihexoses D-sucrose and D-cellobiose were not well accommodated in the cavity because the helical backbone folding was perturbed by the presence of the guest. This could be a consequence of the overall shape of the guests rather than of their size as acceptable packing coefficients of 0.68 were predicted for both dihexoses. Unlike for monosaccharides, very few synthetic receptors for disaccharides have been reported.^[14,3b,19] Reports on oligosaccharide recognition are even fewer.^[20] None of the earlier studies provided detailed structural information on disaccharide–receptor complexes. The crystal structure of 3 \supset D-1·(H₂O)₂ reported herein is the first structure of an artificial receptor–disaccharide host–guest complex.

In conclusion, we have prepared a foldamer-based helical capsule with a cavity large enough to accommodate xylobiose. The synthesis of the nineteen-unit-long sequence required new approaches to overcome undesired aggregation into double helices. The encapsulation of xylobiose validates our approach based on first principle design of artificial receptors. The foldamer possesses a slightly larger-than-necessary cavity that could be the starting point of a structure-based iterative reduction of cavity size and increase of shape complementar-

ity via mutations and deletions in the sequence, as previously demonstrated for other guests.^[6] Advanced predictive computational tools are desirable at this stage to guide initial sequence design and subsequent iterative modifications and accelerate receptor optimization.

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Conflict of interest

The authors declare no conflict of interest.

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- [21] CCDC 1854295 and 1854296 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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