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Anne-doriane Manick, Jean-pierre Dutasta, Alexandre Martinez. Low-Symmetry Macrocycles and Cages for Carbohydrate Recognition. *ChemPlusChem*, 2023, 88 (7), 10.1002/cplu.202300291 . hal-04383506

HAL Id: hal-04383506

<https://hal.science/hal-04383506>

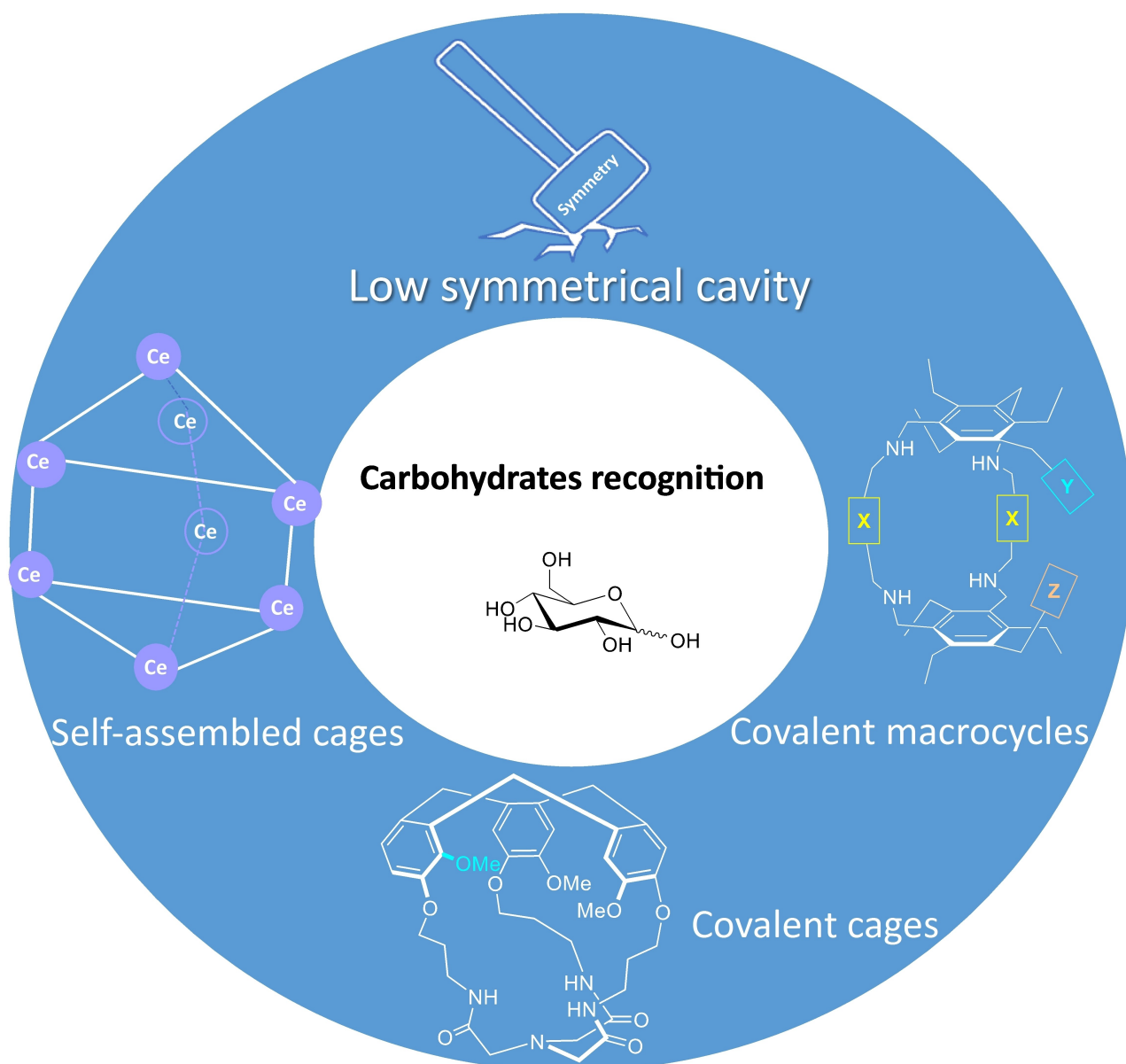
Submitted on 9 Jan 2024

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Low-Symmetry Macrocycles and Cages for Carbohydrate Recognition

Anne-Doriane Manick,^{*[a]} Jean-Pierre Dutasta,^[b] and Alexandre Martinez^{*[c]}



The recognition of carbohydrate plays a key role in numerous biological processes. Thus, artificial receptors have been synthesized to mimic these biological systems. To date, most of the receptors reported for carbohydrate complexation present highly symmetrical cavities, probably because their syntheses require less synthetic efforts and are easier to achieve and control. However, carbohydrates display complex, asymmetrical structures suggesting that hosts with low symmetry might be

more adapted to recognize these guests. Here, we described the strategies that have been used to complex carbohydrates with macrocycles and cages presenting low symmetry and the potential of this approach. Self-assembled cages are first described, then covalent macrocycles and cages are presented and for each example the binding properties of low-symmetry systems are compared to those of their higher-symmetry counterparts.

1. Introduction

Synthetic molecular cages and macrocycles attract great interest as they found a wide range of applications from receptors, to supramolecular catalysts.^[1–17] They present a well-defined cavity as those found in biological systems, like proteins or enzymes. However, if artificial cages and their inner space are highly symmetrical, natural systems display cavities with low symmetry.^[18–24] Indeed, cavities of proteins are devoid of any element of symmetry, affording highly sophisticated and distorted catalytic or recognition sites: each part of the cavity is strongly different from the other, being each composed of various amino acids. This can account for the high selectivity and specificity of biological receptors and catalysts. The high level of symmetry of artificial systems can be explained by much easier syntheses and characterizations than those of their lower symmetrical parents. Such highly symmetrical cavities are suitable for highly symmetrical, ideally spherical, guests.^[19] For instance, cryptophane hosts with D_3 symmetry display a roughly spherical cavity, capable of binding efficiently the spherical xenon atom.^[2a,25] Nevertheless, most of high-interest guests, like biomolecules, drugs or toxic compounds are mainly low-symmetrical species. Moreover, a growing interest has recently emerged for synthetic molecular cages with low symmetry which offer greater modularity of their properties. Indeed, cavities with reduced symmetry can be decorated with various different functional groups and should provide more selective receptors or nano-reactors.^[18–19]

Among the asymmetrical guest, carbohydrates are of particular interest.^[26] Their numerous stereogenic centers make them one of the most information-rich biomolecules and their complexations are involved in key biological processes like cell-cell recognition,^[27] infection by pathogens^[28] or tumour metastases.^[29] Thus, bio-inspired molecular hosts have been built to mimic lectins. These artificial receptors are able to recognize carbohydrates, even in water for some remarkable hosts, and could find applications in medicine, for instance in the diagnostic of diseases or the monitoring of carbohydrate concentrations.^[26] Various strategies have been proposed to complex carbohydrates: from acyclic receptors^[30] to macrocyclic hosts,^[31] covalent or self-assembled cages,^[32,33] or even foldamers.^[34] In particular, the recognition of glucose, has been extensively studied by the Davis's group, and remarkable recognition properties have been reached with these synthetic lectins.^[32,35] The β anomer of glucose presents all its alcohol functions in equatorial positions and C–H bonds in axial positions, and could be considered as the less asymmetrical sugar allowing a carbohydrate-binding "temple" strategy of its complexation.^[26a,36] Nevertheless, other carbohydrates differ from glucose by the configuration of one or more stereogenic centers and therefore display a lower regularity. Consequently their recognition by artificial receptors is still highly challenging and their efficient and selective recognition should probably involve receptors with cavities that fit with the size and shape of these low-symmetrical guests, i.e., cavities with low symmetrical inner space. Thus, lowering the symmetry of host molecules can appear as a promising strategy to recognize carbohydrates. In this review, we describe the advances that have been made to obtain low symmetrical macrocycles and cages for sugar recognition.

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2. Self-assembled cages

Metal-organic polyhedra (MOPs) generated via coordination-driven self-assembly between metal ions and organic ligands show considerable potential as molecular containers in the field of metallosupramolecular chemistry. New self-assembly approaches that combine precise control of the size, shape, and functionalization of low-symmetrical cage cavities were developed, allowing for the selective binding of lower-symmetry guests.^[19a] In this context, Duan et al. described several cerium-based assemblies with amide-containing tetrapod or tripod ligands for the selective recognition by luminescence of natural saccharides.^[37] First, they designed tetrapod ligands with

chromophore units and two bis carboxyhydride salicylzone tridentate chelating groups. The ligand L_1 with ethylene spacer form the cubic $Ce_8(L_1)_6$ structure (Figure 1a). Each Ce^{IV} center at the cube corners is coordinated by three tridentate chelating groups of L_1 ligands with their long axes aligned. The replacement of the ethylene linker in L_1 by a larger tetrasubstituted *p*-phenylene moiety in L_2 influences the shape of the architecture. As confirmed by the crystal structures of $Ce_8(L_1)_6$ and $Ce_8(L_2)_6$, the flexibility of the ligand L_2 provides a twist configuration. The four metal centers connected to the same ligand L_2 are not coplanar yielding a bicoronal trigonal prism of lower symmetry (Figure 1b). Differences between the inner volume or the narrow edge of the opening of these two cage structures have been observed: the regular cube $Ce_8(L_1)_6$ presents smaller inner volume (500 \AA^3 vs 750 \AA^3) and more narrow edge of the opening (5.0 \AA vs 8.0 \AA) than the bicoronal trigonal prism $Ce_8(L_2)_6$. Therefore, this latter appears as potentially a better mono- and disaccharides chemosensor. The fluorescence responses of $Ce_8(L_2)_6$ were recorded in DMF for natural carbohydrates (e.g., glucose, lactose, sucrose) and revealed a low selectivity (Figure 1e, blue bars).^[37a] The importance of increasing the selectivity led the authors to develop similar ligands keeping a low symmetry structure, with more hydrogen binding sites in order to improve cage-saccharide interactions. They were able to synthesize ligand L_3 incorporating a terephthalamide moiety with two “free” amide groups. This flexible ligand forms an octa-nuclear bicoronal triangular prism $Ce_8(L_3)_6$ (Figure 1c).^[37b] Six cerium centers are connected to three of the six ligands yielding a tricycle prism, and two metal centers linked by three additional ligands form a helical pillar inside the tricycle prism. The modification of the cage environment with multiple hydrogen binding sites in the confined space (two “free” amide groups per ligand) is probably

responsible for the lactose-selective recognition over other saccharides as shown by fluorescence spectroscopy (Figure 1e, yellow bars).^[37b] The design of the new tripod ligand L_4 with three “free” amide groups, conserving the carboxyhydride salicylzone tridentate chelating units, impacted the topology of the cage formed (Figure 1d). The tetranuclear tetrahedron $Ce_4(L_4)_4$ is obtained via the chelation of each cerium ion by three different ligands, each ligand being positioned on the four faces of the tetrahedron. Fluorescence analysis in DMF/acetonitrile (1:9) showed that $Ce_4(L_4)_4$ only binds the disaccharide sucrose underlining the impact of the topology of self-assembled MOPs on the selectivity (Figure 1e, green bar).^[37b] These sensing selectivity discrepancies can be explained by the ligands used, which affect the symmetry of the receptor as well as the size of the inner space and the spatial organization of weak non-covalent interactions.

3. Covalent molecular cages and macrocycles

Covalent molecular cages with a rigid cavity and macrocyclic compounds constructed via covalent bonds were developed to entrap a wide range of guests, including saccharides. The main benefit of this class of containers is the variety of structures accessible by traditional organic synthesis, but often requires multi-step syntheses.^[38] The possibility of creating macrocyclic or cage structures with specific cavity to bind lower-symmetry saccharide guests has attracted interest of chemists and some examples are compiled and discussed in the next section.



Anne-Doriane Manick completed her Ph.D. degree under the supervision of Prof. G. Prestat at Sorbonne Paris Cité in organometallic catalysis. She undertook her 1st postdoc in the group of Prof. Kanai (Tokyo, Japan) and worked on photocatalysis. Then she joined iSm2 (Marseille, France) and gets an expertise in supramolecular chemistry and chirality in the Chirosciences group led by Prof. A. Martinez. She obtained, in 2022, a position of CNRS researcher in the Institut de Chimie Radicalaire (Marseille) to develop new methodologies for the synthesis of chiral enantiopure polymers.



Jean-Pierre Dutasta obtained his Ph.D. (1980) under the supervision of Prof. J.-B. Robert, at the University of Grenoble, where he obtained a CNRS researcher position. After a postdoctoral internship at UCLA (USA) in the group of Prof. D.J. Cram, he was appointed to the University of Grenoble, where he started research on supramolecular chemistry of phosphonate cavitands. In 1988 he joined the Chemistry Laboratory of the École Normale Supérieure de Lyon, where he is currently Emeritus Research Director. His research activities focus on stereochemistry and supramolecular chemistry of host-guest systems based on molecular cages.



Alexandre Martinez obtained his Ph.D. degree under the supervision of Dr. B. Meunier, in asymmetric catalysis. Then, he works on supramolecular chemistry as Postdoc in the team of J. Lacour in Geneva and was recruited as associated professor in the group of J.-P. Dutasta at the ENS Lyon. He is now a full professor at the Ecole Centrale Marseille, his research topics focus on supramolecular chemistry, stereochemistry and catalysis.

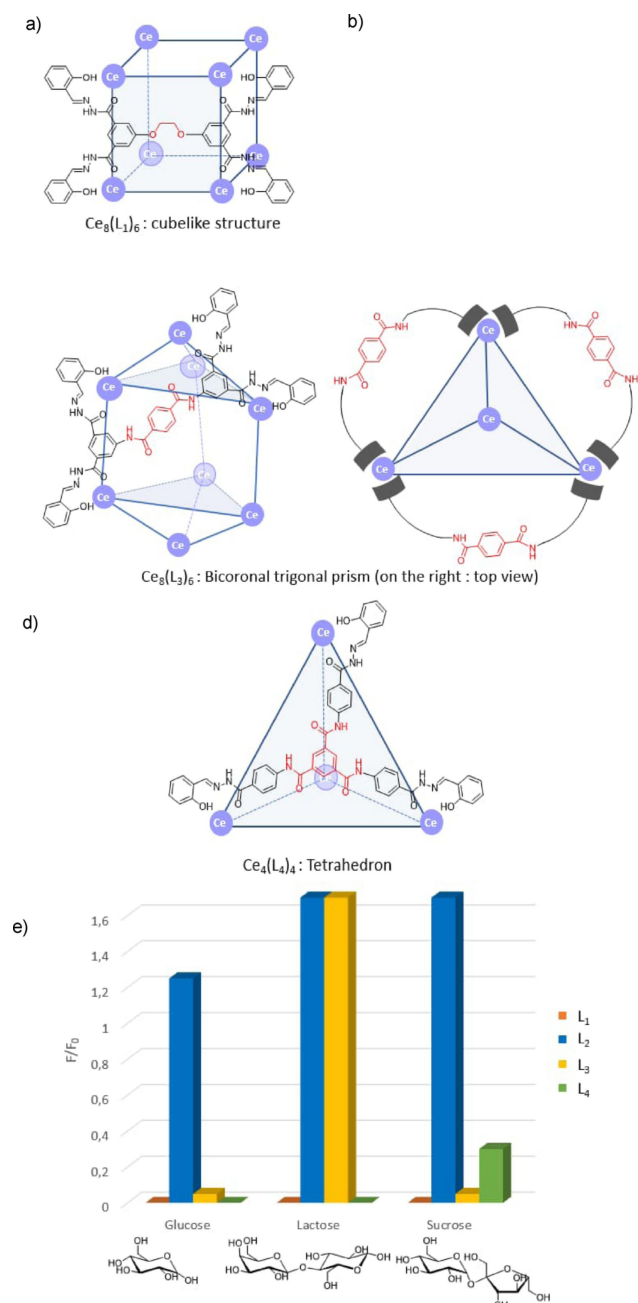


Figure 1. With $\text{Ce}^{\text{III}}(\text{NO}_3)_3$, tetrapotic ligand L_1 (a), flexible tetrapotic ligands L_2 and L_3 (b and c) and tripod ligand L_4 (d) form cuboid, bicoronal trigonal prisms and tetrahedron respectively. e) Fluorescence responses of Ce-L_1 (orange bars), Ce-L_2 (blue bars), Ce-L_3 (yellow bars), Ce-L_4 (green bars) for saccharides mentioned (solvent: DMF for L_1 and L_2 , DMF/acetonitrile (1:9) for L_3 and L_4).

3.1. Macrocyclic receptors

The design of macrocyclic receptors equipped with noncovalent interaction sites has been considered as a promising strategy for the selective molecular recognition of saccharides.

In this context, Diederich et al. reported the synthesis of chiral receptors presenting similar structures with the same noncovalent interaction sites (e.g., hydrogen-bond donor

groups). They used chiral BINOL-derived spacers affording trimeric receptors endowed with a rigid cavity.^[39] Depending on the enantiomer spacers employed, four diastereomeric receptors have been synthesized: (i) (*S,S,S*)- and (*R,R,R*)- D_3 -symmetrical receptors and (ii) (*R,S,S*)- and (*S,R,R*)- C_2 -symmetrical receptors. For this section, we will focus on receptors (*S,S,S*)- D_3 -symmetrical **1** and (*R,S,S*)- C_2 -symmetrical **2** with different substituents (Figure 2a). Interestingly, these receptors share a circular array of six H-bonding groups (OH groups) that are essential for the interactions with the monosaccharide guests. Nonetheless, molecular modeling of these receptors, without substituents, reveals that the D_3 -symmetrical host has a more planar overall shape, whereas the C_2 -symmetrical host is distorted from planarity with reduced cavity size (Figure 2b). These differences impact the binding properties toward monosaccharides especially octyl-glucosides in CDCl_3 (Figure 2c). The D_3 -symmetrical host (*S,S,S*)-**1** displayed moderate binding affinities

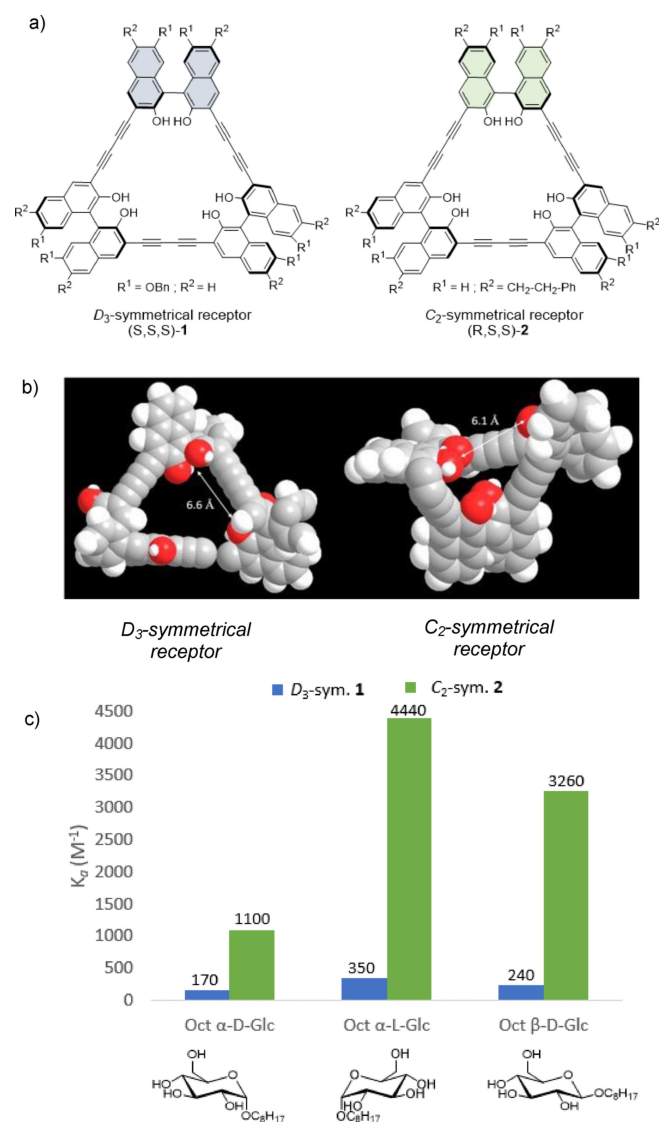


Figure 2. a) Structures of **1** and **2**; b) 3D chemical structures; c) Association constants K_d (M^{-1}) for 1:1 complexes of receptor **1** (blue bars) or receptor **2** (green bars) with the mentioned monosaccharides in CDCl_3 .

($170 \text{ M}^{-1} < K_a < 240 \text{ M}^{-1}$) and selectivities (enantio- and diastereoselectivity), while the less planar C_2 -symmetrical host (R,S,S)-**2** formed 1:1 complexes with Oct- α -D-Glc, Oct- α -L-Glc and Oct- β -D-Glc, yielding K_a ten times higher than those obtained with macrocycle **1** ($1100 \text{ M}^{-1} < K_a < 4440 \text{ M}^{-1}$). Moreover, this host demonstrated remarkable enantioselectivity and diastereoselectivity toward Oct- α -L-Glc underlining the efficiency of the less planar receptor.

Roelens and co-workers reported the two-steps synthesis of the C_{3h} -symmetric cage **3** endowed with hydrogen-bonding donor groups (e.g., pyrroles and amines groups on the cage's arms) (Figure 3).^[32f] Complementary CH- π and Van der Waals interactions were expected between the hexasubstituted benzene moiety (roof and floor of cage **3**) and the aliphatic backbone of the carbohydrate. Using ^1H NMR titration experiments, they proved the unprecedented exclusive recognition of Octyl- β -D-glucopyranoside (Oct β Glc) ($K_a = 4.83 \times 10^4 \text{ M}^{-1}$ in CDCl_3) over its α anomer that differs only by the stereochemistry at C_1 . Moreover, α and β anomers of the galacto- and manno-pyranoside series were not recognized by the cage. Interestingly, they noticed a slow exchange between the free species and the host-guest complex in chloroform on the NMR timescale as well as a desymmetrization of the cage upon the encapsulation. Indeed, a split of the single signal for the three equivalent pyrrolic NH protons into three singlets and a split of the pyrrolic CH signal into three coupled nonequivalent signals were observed. These highlighted details might suggest a partial encapsulation of Oct β Glc. Despite the ability of cage **3** to bind exclusively the Oct β Glc, Roelens's group envisaged a new

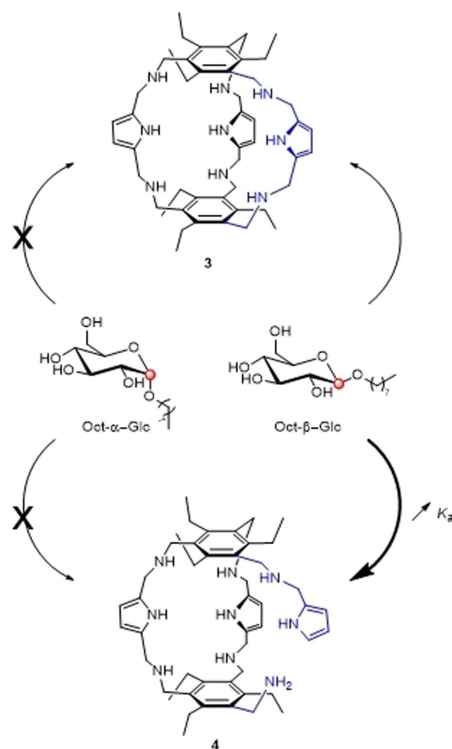


Figure 3. Structures of receptors **3** and **4** as host and Oct- α -Glc and Oct- β -Glc as guests.

strategy based on less preorganized and lower symmetry system to improve the binding properties.^[40] They cleaved one of the three arms of the cage while preserving noncovalent interaction sites (Figure 3). This cleavage resulted in the non-symmetric aminopyrrolic receptor **4** with a monocyclic core and a side arm, which provided the necessary adaptivity toward the guest. The receptor **4** showed the same selectivity toward Oct β Glc, however, deconstructed architecture **4** gave a significant threefold increase in affinity over the more preorganized and higher symmetrical parent **3** ($K_a = 12.3 \times 10^4 \text{ M}^{-1}$ and $4.83 \times 10^4 \text{ M}^{-1}$, respectively in CDCl_3). In contrast to cage **3**, ^1H NMR titration experiments using receptor **4** revealed the formation of two 1:1 species: (i) one in a slow exchange regime and (ii) one in a fast exchange regime on the NMR timescale. By combining NMR spectroscopies with molecular modeling calculations, they proposed two types of complexes. The monosaccharide is located inside a cleft between the benzyl parts but with two different orientations. In the case of the complex in slow exchange, the octyl chain threads the macrocycle such as a rotaxane shape. Concerning the complex in fast exchange, the octyl chain of the saccharide is located outside the macrocycle.

In 2010, the same group developed the synthesis of a new generation of chiral tripodal receptors keeping the hexasubstituted benzene moiety as the receptor's floor, but replacing the amino groups in the linker with *trans*-1,2-diaminocyclohexane.^[41] The enantiomerically pure monocycles (*R*)-**5** and (*S*)-**5** were synthesized allowing to study the effect of the chirality of the receptors on the enantioselective recognition of monosaccharides (Figure 4). It is worth noting that the corresponding more preorganized bicyclic cage was not obtained. With these monocyclic receptors in hand, they demonstrated a higher affinity for mannosides with axial polar substituents. They employed BC_{50}^0 as an affinity descriptor to assess the receptor's binding properties and to account for the fact that several complex species contribute to the overall binding affinity.^[42] The BC_{50}^0 or intrinsic median binding concentration is known as the total concentration of receptor required to bind 50% of the guest. This value reflects the dissociation constant (K_d). Notably, the (*S*)-receptor exhibited a high affinity for the Octyl- β -D-mannoside (Oct β Man) and strong enantioselectivity ($\text{BC}_{50}^0 = 83 \mu\text{M}$ and $\text{BC}_{50}^0 = 1222 \mu\text{M}$ for (*S*)-**5** and (*R*)-**5** respectively in CD_3CN ; 15:1 enantioselectivity). No enantio-discrimination was obtained using Oct α Man ($\text{BC}_{50}^0 = 299 \mu\text{M}$ and $\text{BC}_{50}^0 = 286 \mu\text{M}$ for (*R*)-**5** and (*S*)-**5** respectively in CD_3CN). These discrepancies were explained using NMR experimental data and molecular modeling calculations, which revealed significant hydrogen bonding between pyrrolic moiety and axial hydroxyl group of mannoside, as well as Van der Waals interactions of the β -face of the saccharide with the benzene moiety.

Using a similar approach of combining a macrocyclic backbone with flexible side arms, Mazik et al. underlined the importance of the nature of the bridge units (X) and the side-arms (Y) in the recognition process (Figure 5a).^[32g] They prepared macrocycles with benzene or pyrrole bridges and two side-arms bearing carbonate or carbamate functions. They

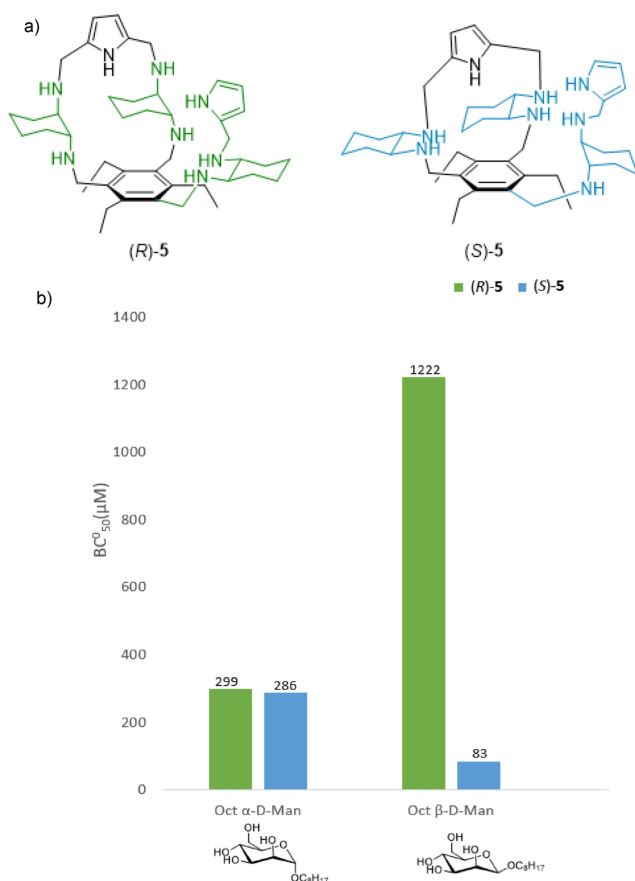


Figure 4. a) Structures of receptors (R)-5 and (S)-5; b) BC_{50}^0 (μM) for 1:1 complexes of receptor (R)-5 (green bars) or receptor (S)-5 (blue bars) for mentioned monosaccharides in CD_3CN .

measured the binding constants in CDCl_3 using Oct- β -D-Glc as guest by NMR and ITC experiments (Figure 5b). The results demonstrated that the receptor with pyrrole-containing bridges 7 is more efficient than the receptor 6 with benzene-based bridge units ($K_a = 79000 \text{ M}^{-1}$ and $K_a = 4810 \text{ M}^{-1}$ respectively in CDCl_3). Furthermore, the presence of hydrogen bond donor group in the flexible arms enhanced the recognition properties. A 23-fold increase in binding affinity was observed between the pyrrole-based receptor containing CH_2OBoc (8, $K_a = 3400 \text{ M}^{-1}$ in CDCl_3) and that with the CH_2NHBoc moiety in the flexible arms (7, $K_a = 79000 \text{ M}^{-1}$ in CDCl_3). The synthesis of an efficient system 9 including benzene-based bridge units and cyclohexyl groups in flexible side arms has been also achieved.^[43] The nature of these units allowed the combination of hydrogen bonding, $\text{CH}-\pi$ interactions and Van der Waals contacts with the saccharides resulting in a good K_a of 12500 M^{-1} compared to the receptor 6 bearing the CH_2NHBoc moiety ($K_a = 4810 \text{ M}^{-1}$ in CDCl_3). The combination of these interactions in the recognition process was validated by 2D NMR investigations and molecular modeling.

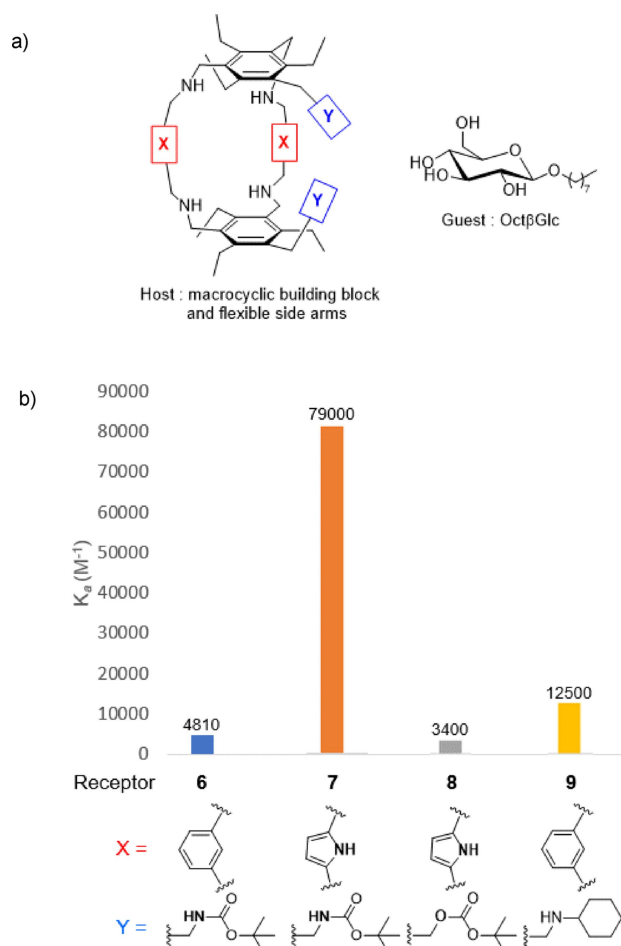


Figure 5. a) Macrocycles bearing two flexible side arms as host and Oct- β -Glc as guest; b) Association constants K_a (M^{-1}) for 1:1 complexes of mentioned receptors 6–9 for Oct- β -Glc in CDCl_3 .

3.2. Covalent molecular cages

The Davis group has focused its research on the development of novel carbohydrate receptors with improved selectivity and efficiency in organic and also in aqueous solution, which is still an important challenge.^[44] Inspired by natural lectins (carbohydrate-binding proteins), they designed a cage with an amphiphilic cavity from two aromatic surfaces (the cage's floor and roof) and four pillars (Figure 6). The apolar faces allow for

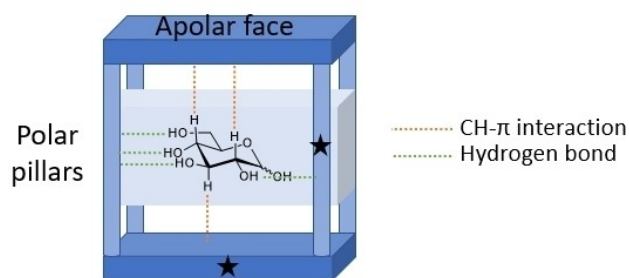


Figure 6. Design of synthetic lectin as saccharide receptor. Stars are for modifiable parts.

hydrophobic and CH- π interactions with the saccharides while the pillars (e.g. isophthalamide) can establish hydrogen bonds with the polar groups of sugars. Moreover, the addition of substituents on pillars allows the solubilization and non-aggregation of the cage in water. From these simpler modifiable cages, Davis team identified three main approaches to obtain desymmetrical receptors in order to increase the selectivity and binding properties toward saccharides: (i) the modification of the pillars, (ii) the use of different apolar faces and (iii) the preparation of chiral cage. These modifications are listed in the following part.

In the 2000's, this group reported the synthesis of tricyclic polyamide receptors for carbohydrates in water and organic media.^[45] These receptors were built from two apolar biphenyl surfaces and isophthalamide units as pillars (Figure 7). With a K_a of 980 M^{-1} , the cage **10** with four $-\text{OC}_5\text{H}_{11}$ substituents recognizes selectively octyl- β -glucopyranoside over octyl- α -glucopyranoside and octyl- β -galactopyranoside in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (92:8).^[45a] The substitution of $(-\text{OC}_5\text{H}_{11})$ alkyl groups with charged dodecarboxylate, as substituents on the pillars, resulted in the water-soluble cage **11**.^[45b] Interestingly, receptor **11** showed the same selectivity for methyl β -D-glucoside in the more competitive D_2O solvent but with a lower K_a (27 M^{-1}). Molecular modeling of this type of receptor revealed that one pillar did not participate in the hydrogen bond network with

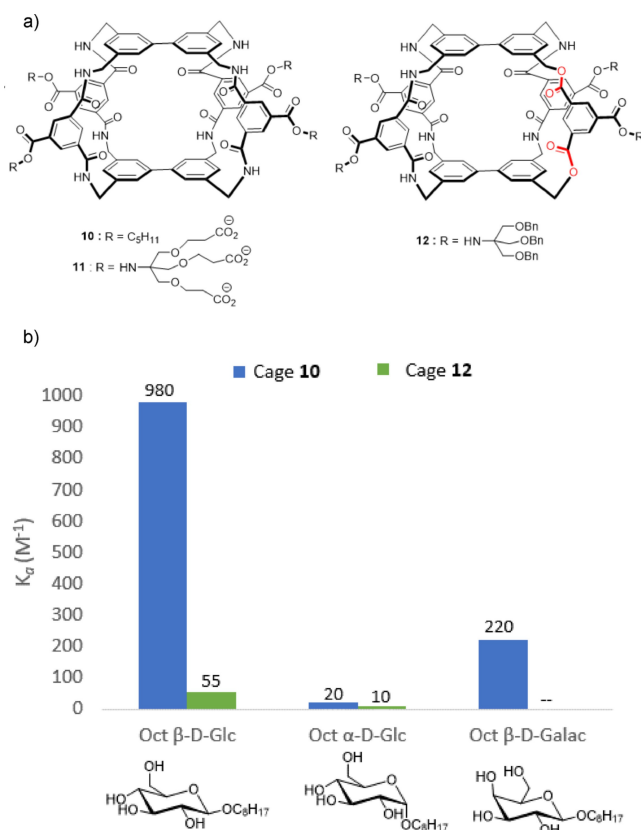


Figure 7. a) Synthetic lectin **10** and its water-soluble counterpart **11**; The lower-symmetry cage **12**; b) Association constants K_a between receptors **10** and **12** and octyl glycosides in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (92:8) measured by ^1H NMR titration.

the guest, therefore they modified only one pillar while preserving the three other spacers with isophthalamide units.^[46] The replacement of one isophthalamide motif with a diester unit, which cannot act as hydrogen-bond donor, resulted in the less symmetrical receptor **12** that could better match the asymmetry of the carbohydrate guests (Figure 7). It should be noticed that they also changed the nature of the R substituents (R = benzyloxy). The authors showed previously a comparable binding of **10** (R = C_5H_{11}) and the variant with benzyloxy substituents toward Oct- β -D-Glc ($K_a = 920\text{ M}^{-1}$ vs $K_a = 720\text{ M}^{-1}$ respectively in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (92:8)).^[45c] Unfortunately, while maintaining the same selectivity, the binding constant toward octyl- β -glucopyranoside reduced dramatically in organic media ($K_a = 55\text{ M}^{-1}$ in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (92:8)). The relevance of the hydrogen bond donor sites on each corner of the cage might explain this low binding value. Indeed, in the case of the symmetrical cage **10**, there are four equal guest orientations. These configurations become non-equivalent in the modified cage **12**. As a result, the entropic cost must be considered, and a reasonable compromise between receptor symmetry and binding entropy must be found.

Larger cavity receptors have been developed for the encapsulation of biomimetic disaccharides (Figure 8).^[32c,47] These structures were constructed using the same two building blocks: (i) isophthalamide pillars substituted with carboxylate groups to afford hydrogen bond donor sites and solubility in water and (ii) two terphenyl motifs as the cage's roof and floor. The addition of one extra pillar to the receptor **13** resulted in the more-preorganized cage **14**, improving complementarity and conformational selectivity for disaccharides. However, the simplest receptor **13** better recognized disaccharides in water ($K_a = 4500\text{ M}^{-1}$ for methyl β -D-cellobioside) than the pre-organized one **14** ($K_a = 850\text{ M}^{-1}$).

These previous examples demonstrated a selectivity for all-equatorial carbohydrates with identical hydrophilic faces. To tailor the selectivity to carbohydrates with axial polar substitu-

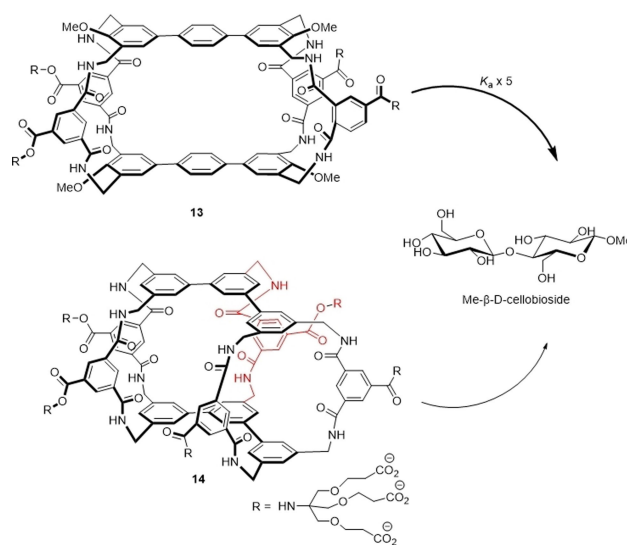


Figure 8. Recognition of disaccharides by pre-organized receptor **14** and simpler receptor **13**.

ents, Davis et al. suggested the synthesis of cages with two distinct apolar surfaces. Indeed, these guests should be accommodated by receptors that are desymmetrized, with one face becoming more polar while retaining the amphiphilic cavity. In this context, they synthesized water-soluble macrobicyclic **15** bearing a small apolar surface (biphenyl unit) and a larger apolar surface (pyrene unit) (Figure 9a).^[48] They found no difference in selectivity when compared to usual symmetric receptors. Monosaccharides having axial polar groups (e.g., mannose, galactose) are only faintly recognized.

The other strategy envisaged by Davis et al. is to maintain the apolar faces identical but stagger the roof and the floor of the cage to modify the environment of the cavity.^[36b] They

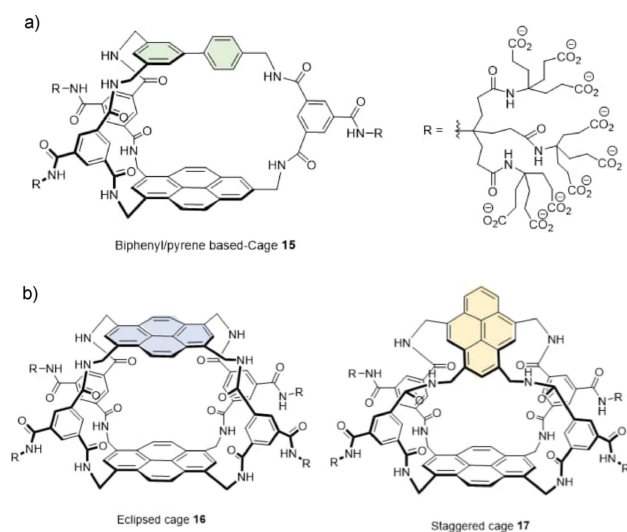


Figure 9. a) Dissymmetric biphenyl/pyrene based cage **15**; b) Eclipsed architecture **16**, and staggered cage **17**.

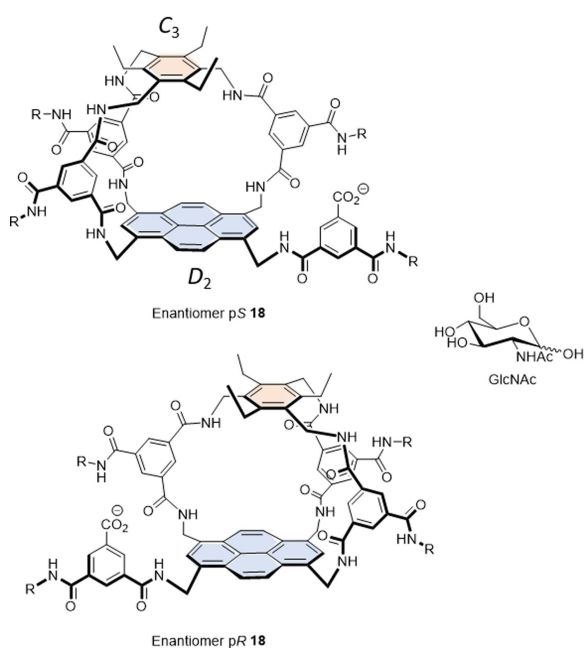


Figure 10. Chiral receptor combining C_3 and D_2 -symmetrical units.

replaced classical biphenyl faces with pyrene units so as to expand and rigidify hydrophobic surfaces (Figure 9b). Interestingly, the staggered pyrene-based cage **17** proved more effective than the eclipsed one **16** and the biphenyl-based receptor **15** ($K_a = 18200, 2100, 630 \text{ M}^{-1}$ for β -N-acetylglucosaminyl in water and cages **17**, **16**, **15**, respectively). Despite the excellent association constant obtained for the staggered receptor with β -N-acetylglucosaminyl, the monosaccharides with axial polar substituents such as mannose and galactose showed poor binding with this less symmetrical cage. These results underlined the difficulties in developing receptors for a large range of saccharides.

The last strategy proposed by Davis et al. is to form a chiral framework so as to promote enantioselective carbohydrate recognition.^[49] Indeed, carbohydrates, are chiral and naturally predominate in the D-form. To generate asymmetric receptors, they combined roof and floor units of different symmetries: C_3 -symmetrical substituted benzene as roof and D_2 -symmetrical pyrene as floor (Figure 10). The resolution of the enantiomers of **18** were unsuccessful. They could, however, investigate the binding properties of both cages using ^1H NMR titration experiments on the racemate. They demonstrated that one enantiomer of **18** had a strong affinity for N-Acetyl-D-glucosamine (GlcNAc), with an excellent enantioselectivity of 16:1 (K_a of 1280 M^{-1} and 81 M^{-1} for the diastereomeric complexes formed during the titration experiments in D_2O). They were able to determine the structure of the stronger binding enantiomer pR-**18** based on extensive NMR studies. Furthermore, they detected also enantiodiscrimination for D-glucose and D-mannose with greater K_a than with the prior cage, emphasizing the relevance of the chirality of the receptor.

Hemicryptophanes which are built from a chiral cyclo-tribenzylene unit (CTB), exhibit remarkable binding properties toward neutral or charged guests.^[2a,50] They appear to be a potential saccharide host due to the formation of hydrogen bonds with polar functions on the cage's arms and $\text{CH}\cdots\pi$ interactions with the aromatic rings of the CTB moiety. Martinez et al. developed an efficient method for the synthesis of enantiopure hemicryptophane C_3 -**19** and enantiopure parent C_1 -**20** with a lower symmetry due to the unexpected arrangement of the substituents of the CTB upper part (Figure 11).^[51] These cages, combining a CTB moiety with an amino-trisamide unit present the same recognition sites, but the main difference is their level of symmetry. This low symmetry has a significant influence both on the binding properties and on the stereo and substrate selectivities. In fact, in CDCl_3 , the C_1 -symmetrical receptor recognizes glucose, galactose, and mannose derivatives, more efficiently than the C_3 -symmetrical counterpart (i.e. $K_a = 4656 \text{ M}^{-1}$ vs 573 M^{-1} for Oct- α -Glc with cages C_1 -(-) and C_3 -(-), respectively). Compared to Davis's synthetic lectins, hemicryptophanes may recognize carbohydrate with axial polar substituents with a significant binding constant (up to 2236 M^{-1} for α -mannose with cage C_1 -**20**) and have a preference for α -anomers (α : β diastereoselectivity up to 100:1) except for galactose derivatives. Finally, hemicryptophane C_1 -**20** is able to discriminate β -galactose from β -glucose. The authors were able to explain the difference in selectivity between a low symmetry

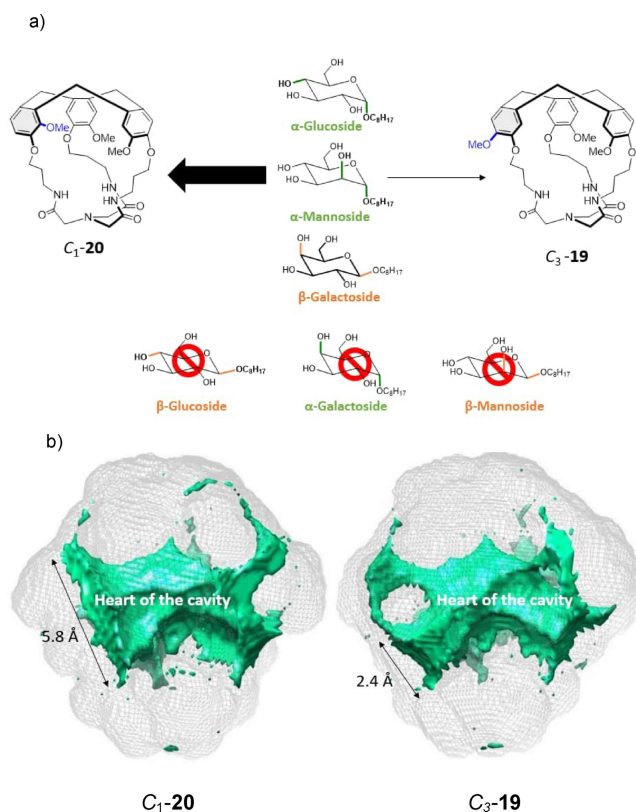


Figure 11. a) C_3-19 and C_1-20 hemicryptophanes with C_3 - and C_1 -symmetry, respectively, and saccharides guests; b) Views of the shape of the inner cavities of the hemicryptophanes C_1-20 and C_3-19 .

receptor and its more symmetrical counterpart using DFT calculations. Both cages have similar cavity sizes and recognition units however the lower symmetrical cage C_1-20 displays a wider window than its C_3-19 counterpart (5.8 Å vs 2.4 Å) allowing for closer access to the recognition sites (Figure 11).

4. Summary and Outlook

In this review, we have described recent strategies that have been developed to obtain low symmetrical macrocycles and cages for carbohydrates recognition. Reducing the symmetry of artificial receptors can more accurately mimic the pocket of proteins. Most of these low symmetry hosts display higher binding constant and selectivity for carbohydrates complexation than their more symmetrical counterparts. Indeed, these guests present various stereogenic centers and an overall shape with low regularity that are probably more suitable to enter a cavity of low symmetry. Although the syntheses and characterizations of hosts with reduced symmetry reveal more complex and challenging than their higher symmetrical parents, these formers provide original and more sophisticated inner space that can better fit with the complex structure of carbohydrates. Thus, this strategy – lowering the symmetry of cages – opens new way for the selective and efficient complexation of carbohydrates. New convenient approaches and synthetic

methods will likely be further developed to obtain more easily low symmetry receptors.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: cages · carbohydrate recognition · low symmetry · macrocycles · supramolecular chemistry

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Manuscript received: June 14, 2023
Revised manuscript received: June 26, 2023
Accepted manuscript online: July 3, 2023
Version of record online: ■■■