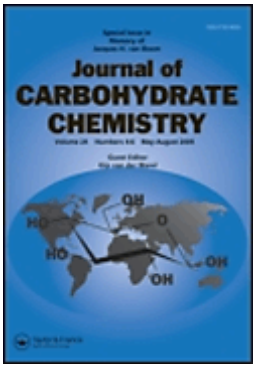

Multiply–linked cyclodextrin–aromatic hybrids: caps, hinges and clips

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Figure 2.cdx Scheme 1.cdx Scheme 2.cdx Scheme 3.cdx Scheme 4.cdx Scheme 5.cdx Scheme 6.cdx Scheme 8.cdx	

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Multiply–linked cyclodextrin–aromatic hybrids: caps, hinges and clips.

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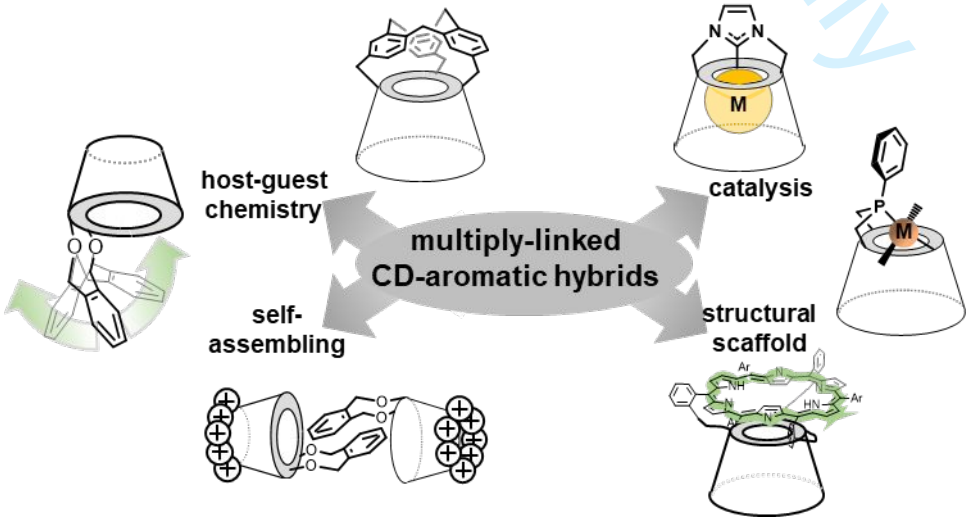
Multiply–linked cyclodextrin–aromatic hybrids: caps, hinges and clips.

The judicious combination of shaping and recognition elements in cage-type architectures represents a powerful strategy to access molecular devices with tailored receptor properties and controlled abilities to form supramolecular assemblies. Aromatic modules are particularly attractive for these endeavours: they can play the role of rigid walls to build permanent cavities, folding screens between preexisting compartments and/or act as functional components promoting noncovalent self-interactions as well as associations with third species, allowing several levels of organization to be implemented. The field of cyclodextrins has enormously benefitted from the amalgamation with aromatic building blocks to give birth to hybrids with a much broader spectrum of properties and applications. The progress in precision chemistry has further enabled the efficient preparation of multiply-linked cap, hinge or clip cyclodextrin-aromatic chimeras with unprecedented level of control, which has translated into new developments in fields like supramolecular catalysis, self-assembly or gene delivery. This review article focuses specifically in these type of compounds, highlighting the intimate relationship between structure, supramolecular properties and performance in the target application.

Keywords: capped cyclodextrins; supramolecular chemistry; transition metal catalysis; host-guest; self-assembling

Graphical abstract



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Introduction

The cyclomaltooligosaccharides (cyclodextrins, CDs) are iconic cage molecules that have been instrumental in the burst and development of supramolecular chemistry.[1] Their α-(1→4)-linked α-D-glucopyranosyl backbone features a truncated-cone toroidal shape that exhibits inner-outer amphiphilicity, enabling the inclusion of hydrophobic guest molecules on a size-fit basis (Figure 1). Upon confinement in the CD cavity, the properties of the guest (e.g. its fluorescence behavior, spectroscopic properties, stability, chemical reactivity or accessibility to enzymes or receptors) become altered, which have given rise to a broad variety of technological applications. The implementation of efficient methodologies for the functionalization of the hydroxyl groups in the native cyclodextrins through precision chemistry strategies has exponentially expanded the catalogue of available CD derivatives beyond the straight-jacketed hexa (αCD), hepta (βCD) and octamer (γCD) representatives.[2] Currently, tailored-made CDs can be accessed in single diastereomeric form with a precise orientation of functional elements, with the only limitation of one's imagination.[3] Chemical elaboration allows, for instance, overcoming the limit of the internal cavity for molecular hosting, imparting catalytic activities, programming self-assembly or promoting the association with biomolecular partners. Aromatic appendages are particularly attractive for those channels: they can play the role of rigid walls and probe elements, conveying additional noncovalent interaction and sensing abilities and allowing several levels of organization to be implemented. In most reported examples, however, the aromatic component in aromatic-CD hybrids is attached to the cyclooligosaccharide core through a single position and retains substantial mobility, which limits accurate three-dimensional definition.[4] Multiply-linked derivatives with restricted conformational freedom, reachable after point-specific positioning of the components, are better suited for

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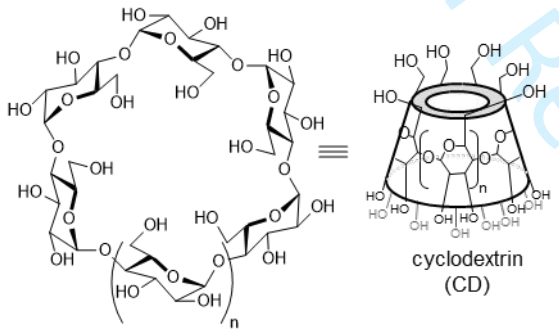
precise control of receptor topology. Depending on the relative disposition of the anchoring points, “cap”-, “hinge”- and “clip”-like architectures with diverse degrees of flexibility have been reported. This review centers specifically on such kind of molecular nanosized hybrids, with a focus on the potential of aromatic modules to trigger conformational changes and self-assembling modes impacting the CD supramolecular and functional properties. Rather than a comprehensive discussion, we will comment on selected representative examples that highlight the vigor of the field. Note that capped CD dimers incorporating aromatic segments in the tethering arm are not covered here. For an all-inclusive information, the reader is addressed to excellent reviews and recent reports.[5]



CD	i. d. (Å)	o. d. (Å)	height (Å)
αCD (n = 1)	4.7 - 5.2	14.2 - 15.0	7.9 - 8.0
βCD (n = 2)	6.0 - 6.4	15.0 - 15.8	7.9 - 8.0
γCD (n = 3)	7.5 - 8.3	17.1 - 17.9	7.9 - 8.0

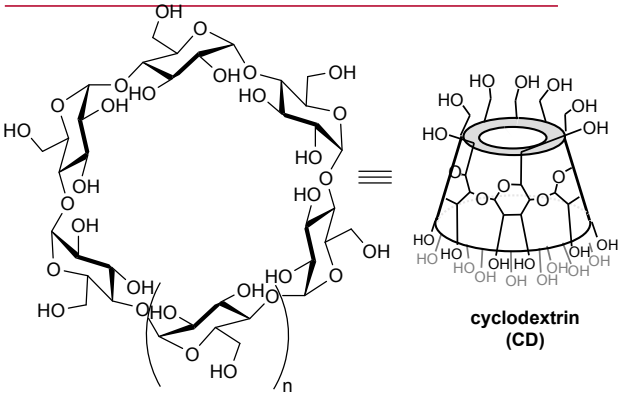


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Figure 1. General structure and dimensions of native cyclodextrins (the acronyms i. d. and o. d. refer to inner and outer diameter, respectively).

Doubly-linked heteroaromatic caps: metal chelation and catalysis

The rigid structure of CDs, with hydroxyl groups regularly disposed at precise distances, provides a versatile framework for programming concerted metal chelation after point-selective functionalization. The more readily accessible primary positions have been generally targeted for these channels. In order to limit the conformational mobility, Matt, Armspach and coworkers developed synthetic methodologies, based in the use of tritylating reagents, to access diamines for the incorporation of capping heteroaromatic ligands doubly anchored at C-6 positions in I/II, I/III or I/IV relative disposition in either α or βCD.[6] In a pioneering work, these authors described the synthesis of the 2,2'-bipyridyl-capped αCDs **1** and **2**. These hybrids exhibited distinct metal chelating properties that were governed by the orientation of the aromatic fragment: endo-oriented bipyridyl moieties preferentially stabilized metals with planar coordination geometry metals, such as Pd(II),[7] while the exo-oriented analog better adapted to octahedral metal centers, such as Ru(II),[8] (Scheme 1).

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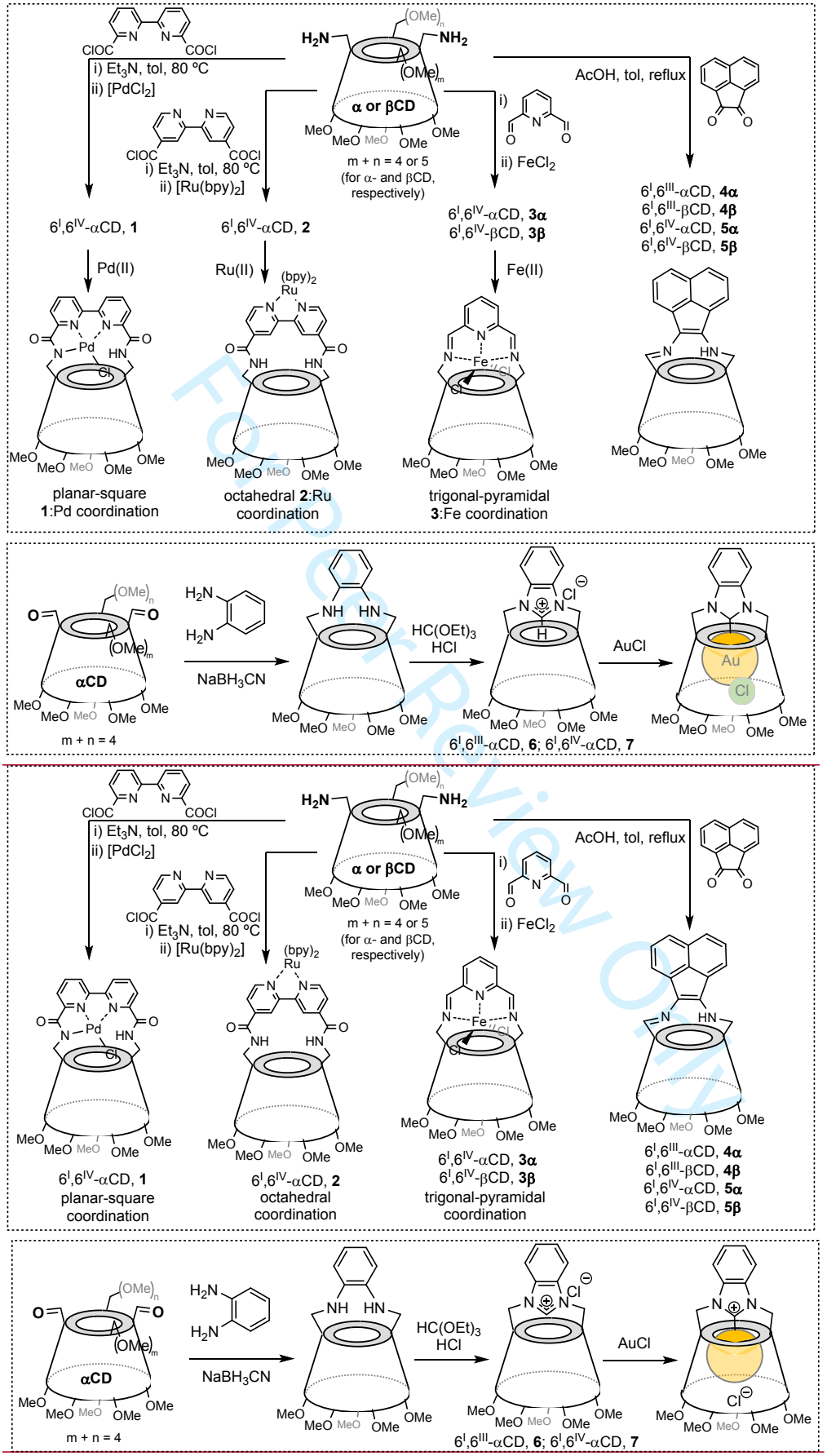

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Scheme 1. Different approaches to primary rim *N*-heterocyclic aromatic-capped CDs reported by Matt, Armspach and coworkers and their metal chelation capabilities (methoxyls at the primary rim were omitted for clarity in some of the structures).

The same laboratory reported the synthesis of α and βCD derivatives equipped with a rigid pyridine-bisimine cap bridging the distal 6^{I} and 6^{IV} positions (**3α** and **3β**). This architecture provided a suitable environment for trigonal bipyramidal chelation of Fe(II)[9] (Scheme 1), which is remarkable considering that in the absence of the CD scaffold the pyridine-bisimine motif affords octahedral Fe(II) complexes. The approach has been later extended to the installation of aromatic caps through $6^{I}/6^{III}$ and $6^{I}/6^{IV}$ unsymmetrical imine-enamine (**4** and **5**) and benzimidazole (**6** and **7**) bridges in a regioselective manner. The final compounds ~~have~~ induce inward-oriented ~~nitrogen atoms~~coordination, offering new opportunities for conducting catalytic reactions in a highly crowded chiral environment.[10] The concept has been recently demonstrated for the asymmetric cycloisomerization of 1,6-enynes promoted by complexes of Au(I) and benzimidazolium carbene-capped CDs[11] (Scheme 1).

Sollogoub and co-workers developed an efficient synthesis of *N*-heterocyclic carbene (NHC)-capped CD derivatives (**8α** and **8β**) and of their complexes with group 11 transition metals, i.e. Cu(I), Ag(I) or Au(I), and investigated the striking effects of confinement of the metal inside the CD cavity in the chemical properties. A unique C-H···M coordination sphere was evidenced that served as insulation shield from electrode surfaces and governed the catalytic activity. Thus, the regioselectivity of the Au(I)-catalyzed cycloisomerization of 1,6-enynes reverted upon switching from α to βCD-based NHC ligands.[12] Similar CD ring size effects on the regioselectivity were observed for the Cu(I)-catalyzed hydroboration reaction, which led the authors to

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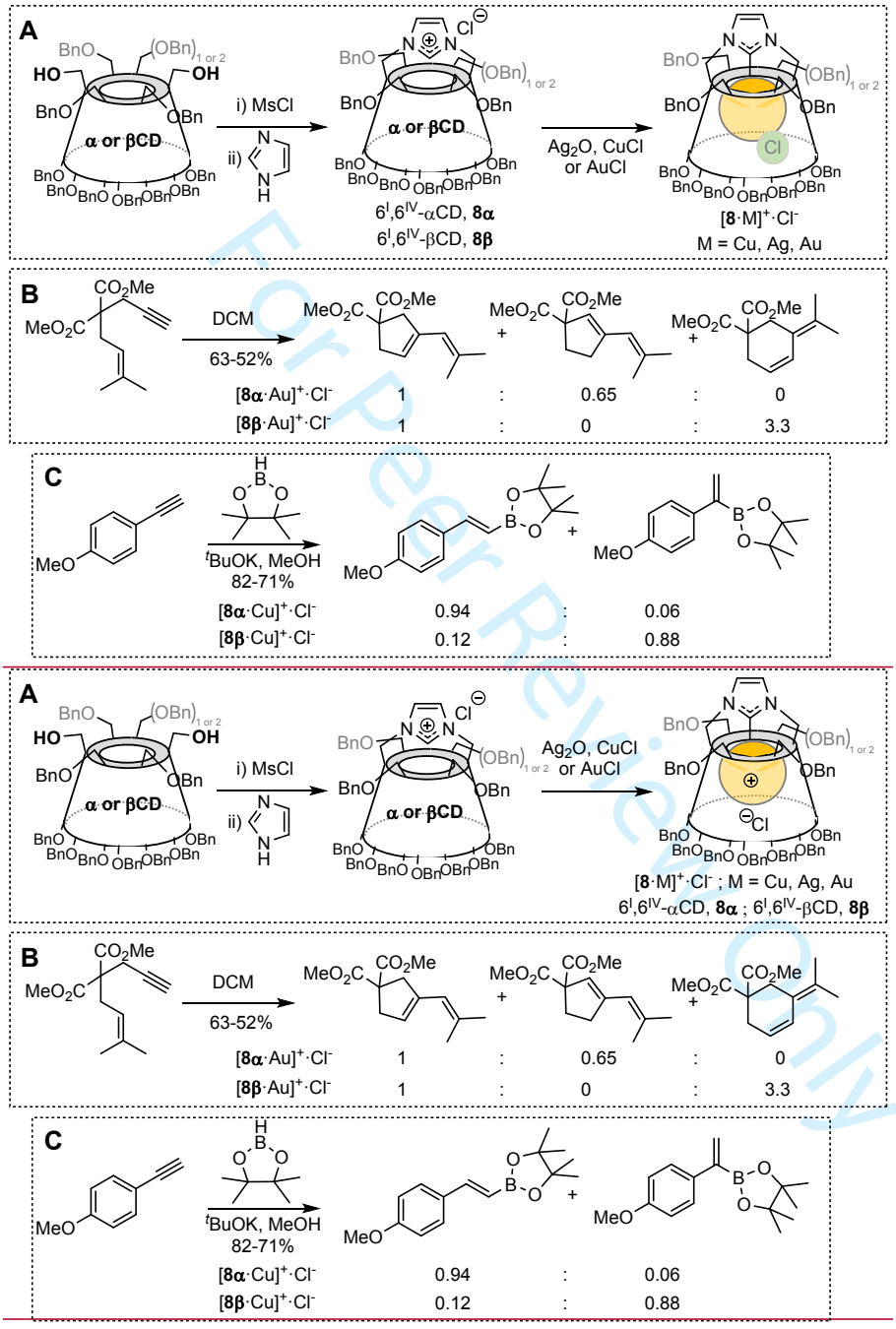
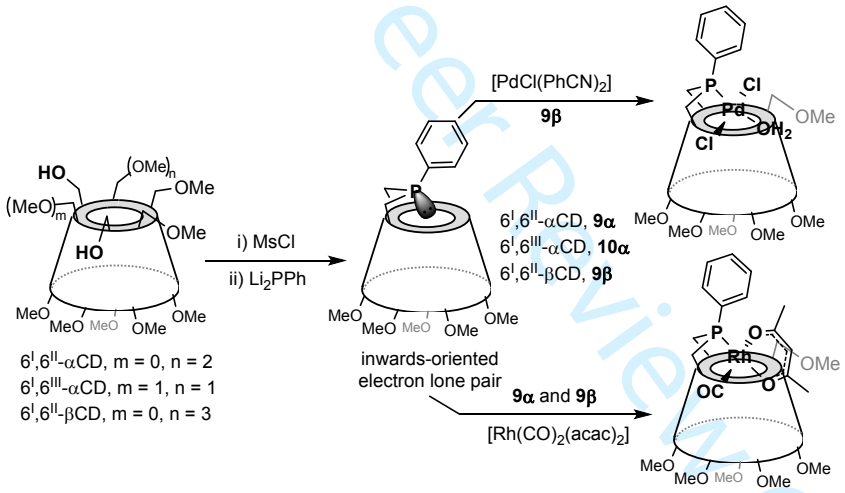
proposed different catalytic pathways for αCD- and βCD-derived NHC/Cu(I) complexes[13] (Scheme 2).



Scheme 2. (A) Synthesis of NHC-capped CDs **8α** and **8β** described by Sollogoub and coworkers and their performance in 1,6-enyne cycloisomerization (B) and hydroboration reactions (C) catalysed by Au(I) and Cu(I), respectively.

In a parallel series of reports, Matt, Armspach and coworkers described the synthesis of primary rim aromatic phosphine-capped αCD derivatives from multiply O-6 mesylate esters. The phosphorous atom in the adducts can bridge either the $6^{I}/6^{II}$ (**9α** and **9β**) or $6^{I}/6^{III}$ (**10α**) positions in the cyclooligosaccharide.[14] The authors demonstrated that the rigid inter-6^{I},6^{II} phosphine tether orients metal ligation towards the inner cavity, which constitutes a unique coordination sphere that largely influences the enantiomeric outcome of catalytic reactions, as evidenced for the Rh(I)-catalyzed hydroformylation reaction[15,16] (Scheme 3).



Scheme 3. Synthesis of the inner-oriented phosphine-capped CDs described by Matt and Armspach.

Triply-linked aromatic caps: innovative allosteric host-guest systems

Hemicryptophanes, which combine a cyclotriveratrylene (CTV) unit with another C_3-symmetric moiety, are chiral molecular cages that exhibit remarkable properties in molecular recognition and supramolecular catalysis.[17] With the idea to generate extended cavities, Chambron and co-workers conceived the preparation of αCD

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hemicriptophane-type hybrid cavitants combining αCD and CTV halves. Initially, the reaction of a CTV triphenol (CTV-OH) with the tri-mesylated derivative of the $6^{I},6^{III},6^{V}$-tri-~~*O*-mesylated~~ol αCD ~~derivative~~ **11** ~~with a CTV triphenol (CTV-OH) partner~~ was attempted, but the target hybrid adduct could not be detected (Scheme 4, left). An alternative approach, based on the cyclotrimerization of CTV precursor moieties anchored in αCD alternating primary positions trough ethylene spacers, afforded the desired compound **12**, as a mixture of the corresponding *M* and *P* diastereomers, in modest yield (5-8%).[18] Interestingly, the more flexible *anti*-diastereomer showed solvent and temperature dependent self-inclusion properties that were detectable by NMR and circular dichroism.[19] Looking for higher synthetic efficiencies, the same authors proposed a different αCD/CTV hybrid prototype containing disulfide bridges. The reaction of the C_3-symmetric $6^{I},6^{III},6^{V}$-trithio αCD derivative **13** and CTV-SH under oxidative conditions produced the target hemicryptophane **14**, as a mixture of the *M* and *P* diastereomers, in 11% yield upon equilibration, a meritorious result results taking into account the number of potential combinations[20] (Scheme 4, right).

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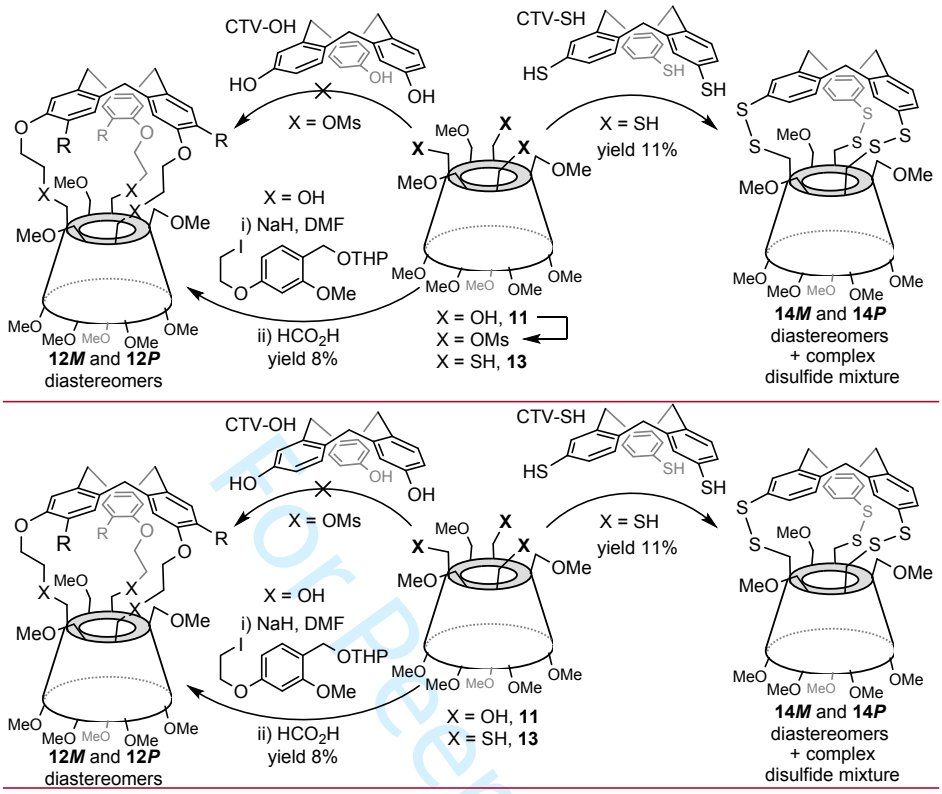

Scheme 4. Synthetic strategies towards triply-linked CTV-capped CDs **12** and **14** explored by Chambron and coworkers.

Ménand, Le Gac and coworkers accomplished the preparation of triply-linked hexaphyrin-αCD hybrids through a synthetic route that involved the use of the αCD triol **15**, obtained via the corresponding $6^{I},6^{III},6^{V}$-tri-*O*-trityl-αCD following the method of Kraus and coworkers,[21] as the key starting material.[22] The free OH-groups in **15** served as anchoring points for benzaldehyde moieties and the resulting trisaldehyde **16** was finally engaged in macrocyclization reactions with 5-aryldipyrromethanes to afford the target compounds (e.g. **17**) in low (5%) but reproducible yields (Scheme 5). Circular dichroism, UV-visible-near infrared spectroscopy, NMR and molecular modeling of the different oxidation states of the hexaphyrin moiety revealed remarkable physicochemical features, including switchable Hückel aromaticity/antiaromaticity (reversible $26e^{-}$-to-$28e^{-}$ system switch between **17** and **18**), nonsymmetrical capping

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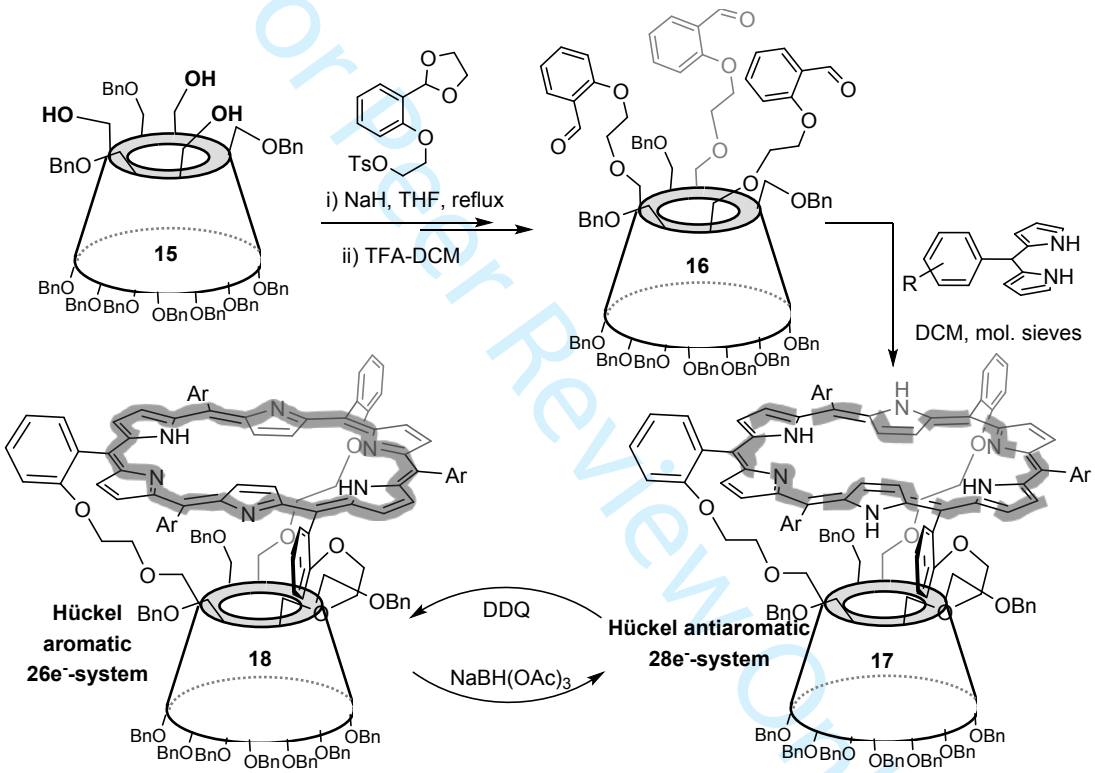
affording coordination-site discrimination and restricted rotational motion of the hexaphyrin cap, supporting much potential for the fields of aromaticity, supramolecular catalysis and switchable devices. As a proof of concept, the authors demonstrated that protonated hexaphyrin-αCD conjugates undergo a rectangular-to-triangular shape-shifting of the cap that allosterically affects the number of encapsulated methanesulfonate counterions and their positioning in the hybrid cavity.[23]



Scheme 5. Synthesis of triply bridged hexaphyrin–αCD hybrids **17** and **18** through a [1+3]-macrocyclization strategy developed by Ménand, Le Gac and coworkers.

In a recent contribution, the same laboratories reported the extension of the αCD-assisted hexaphyrin synthesis to the preparation of hybrids in which the hexaphyrin platform is sandwiched between two αCD macrocycles, both of them triply linked to the expanded porphyrin system.[24] The methodology implies the same αCD

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trisaldehyde precursor but now the 5-aryldipyrromethane partner is also anchored in three copies to the αCD triol **15**. The new doubly capped porphyrin edifices displayed switchable oxidation states with interconvertible conformational forms, namely rectangular and dumbbell arrangements, with redox and thermal responsiveness. The possibility to reconfigure the whole structure in a controlled manner offers unprecedented opportunities for the design of multiaddressable allosteric receptors and catalysts.

Cyclic ether aromatic hinges: programming self-assembly

The *m*-xylylene group was first introduced in carbohydrate chemistry by Schmidt and coworkers[25] as a benzyl ether bidentate rigid segment in intramolecular glycosylation strategies: upon tethering the glycosyl acceptor and the glycosyl donor, the conformational restrictions imposed by the macrocyclic structure of the final product can be advantageously exploited to control the stereochemistry of the newly formed glycosidic bond.[26] The concept was later extended by Ortiz Mellet, García Fernández and coworkers to the use of *o*-, *m*- and *p*-xylylene intersaccharide bridges for the stereoselective synthesis of di-D-fructose dianhydrides (DFAs),[27] a family of spiroketal cyclic disaccharides present in caramel that exhibit interesting prebiotic properties.[28,29] In the course of their work, the authors realized that the separation distance provided by the *o*-xylylene moiety enabled the efficient protection of vicinal diols through formation of an eight-membered cyclic diether.[30] The presence of the fused aromatic ring translates into a preference for the *trans*-diequatorial disposition of the oxygen centers, which allows controlling the stereochemical outcome of transformations implying conformational transitions. This was demonstrated by the same authors in the synthesis of DFAs[31] as well as by Lowary and coworkers[32] and Ando and coworkers[33] for

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glycosylation reactions in the furanose series.

Given that the OH-2 and OH-3 *vic*-diol segments at the secondary rim in cyclodextrins are *trans*-diequatorially oriented in their ground state conformation, the possibility of employing the *o*-xylylene group for their selective differentiation was particularly appealing. The installation of the doubly-linked aromatic module at the entrance of the CD cavity was expected to impact the inclusion properties of the host, which represented an additional motivation. It was found that fully unprotected α, β and γCD reacted with α,α'-dibromo-*o*-xylene in DMSO in the presence of lithium diisopropylamide (LDA) to give the corresponding $2^{I},3^{I}$-*O*-(*o*-xylylene) derivatives in 28-33% yield after a conventional silica gel column chromatography[34] (Scheme 6). The utility of this strategy for transient point-selective protection was confirmed after methylation of the remaining hydroxyls (to give **22**-**24**) and removal of the xylylene cyclic ether by hydrogenolysis in the presence of formic acid to give the corresponding diols. Reaction conditions to incorporate the *o*-xylylene motif in per-(6^{I}-*O*-*tert*-butyldimethylsilyl)-βCD were also optimized.[35]

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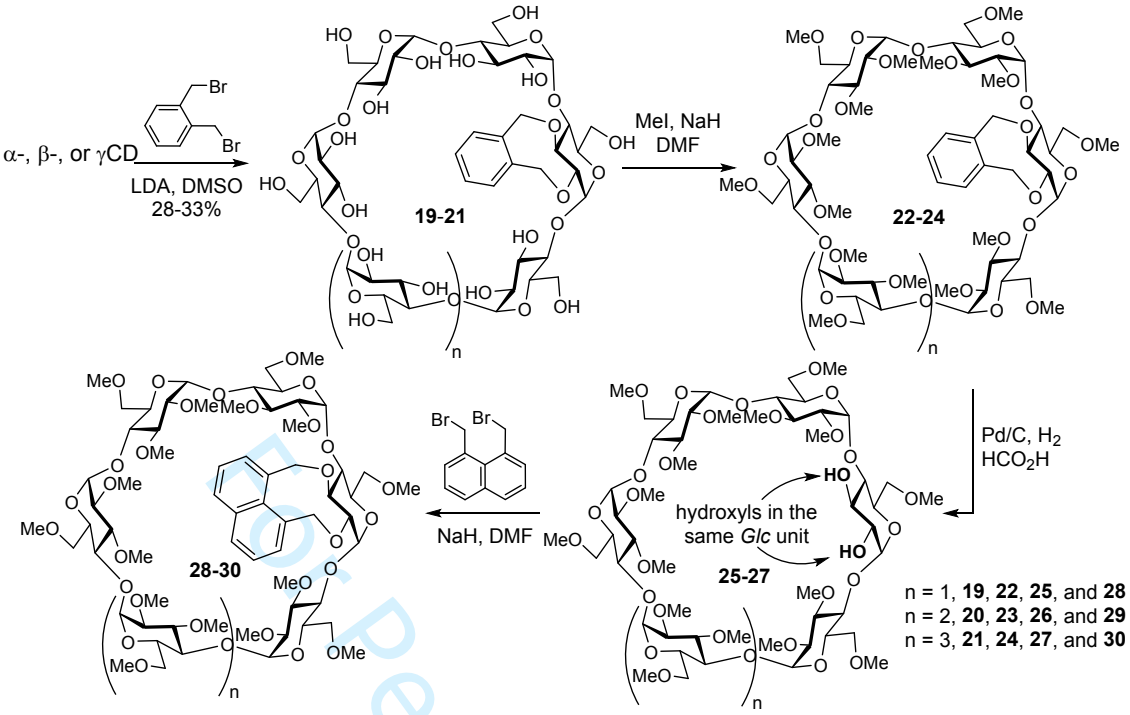

Scheme 6. Synthesis of hinged-type cyclodextrin-aromatic hybrids by direct $2^I,3^I$-*O*-(*o*-xylylenation) of native CDs described by Ortiz Mellet, García Fernández and coworkers.

The $2^I,3^I$-*O*-(*o*-xylylene)-equipped permethylated CD derivatives **22-24** exhibited negative solubility temperature coefficients in water: when heated, clear (25 °C) solutions became immediately turbid, returning to the limpid original state upon cooling. This was ascribed to reversible dimerization processes: in the dimer state, the hydrophobic aromatic moiety is likely sandwiched between the two self-assembling CD monomers, becoming shielded from the bulk. This arrangement facilitates solvation and preventing unspecific clusterization at low temperatures, whereas heating results in dimer disruption, uncovering of the aromatic ring and precipitation. The thermodynamic parameters for the monomer-to-dimer equilibrium was extensively characterized by steady-state and time-resolved fluorescence techniques (based on the fluorescence of the bidentate xylylene moiety), NMR and computational studies (molecular mechanics

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and molecular dynamics; MM and MD). The data were consistent with a restricted mobility of the xylylene hinge, which can adopt close and open conformations relative to the CD cavity, but do not undergo self-inclusion. The formation of head-to-head (HH) dimers in semi-open conformation is then strongly favored.[36] A similar behavior was observed for α, β and γCD derivatives incorporating the $2^I,3^I$-*O*-(1,8-dimethylnaphthylene) hinge **28**-**30**, obtained from the corresponding diols by reaction with 1,8-dibromomethylnaphthalene[37] (Scheme 6). Interestingly, the presence of the aromatic hinge in the CDs enhances the 1:1 association constants towards hydrophobic guests such as octyl β-D-glucopyranoside or methyl 2-naphthalenecarboxylate (2MN; a fluorescent probe sensitive to medium polarity), by about three-fold as compared with the fully methylated hosts, by providing additional favorable contacts. It is worth noting that inclusion of the guest requires dimer disruption, which could be used for the spatiotemporal control of the self-assembling properties (Figure 2).

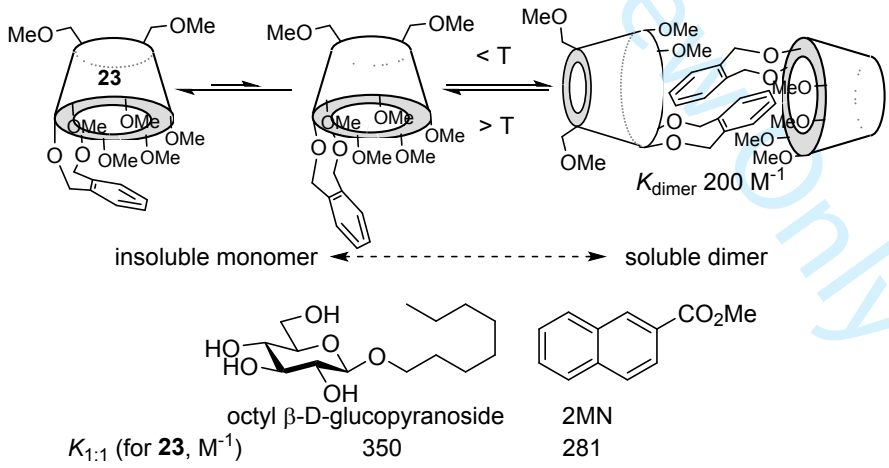

Figure 2. Schematic representation of the conformational and aggregation equilibria for $2^I,3^I$-*O*-(*o*-xylylenated)-βCD **23**.

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The possibility of controlling the propensity of CD derivatives to form HH-dimers in aqueous environments offers new opportunities for programming reversible hierarchical processes requiring the antiparallel orientation of functional elements located at the primary face of the cyclooligosaccharide platform. The co-assembly of cyclodextrin-based multihead/multitail amphiphiles with nucleic acids to afford nanocomplexes with transfectious capabilities represents an archetypic example.[38,39] Nanometric molecular gene delivery systems (molecular nanoparticle-based vectors)[40,41] of this family spontaneously form bilayers between quasi-parallel nucleic acid chains (DNA or RNA) by the interplay of electrostatic interactions between the cationic clusters and the polyphosphate backbone[42] and hydrophobic interactions involving the lipophilic domains,[43] concertedly leading to desolvation and compaction of the genetic material. HH-dimers with cationic clusters oriented in opposite directions emulate the smallest structural element of a bilayer and are therefore pre-organized to undergo nucleic acid-templated nanocondensation[44] (Figure 3).

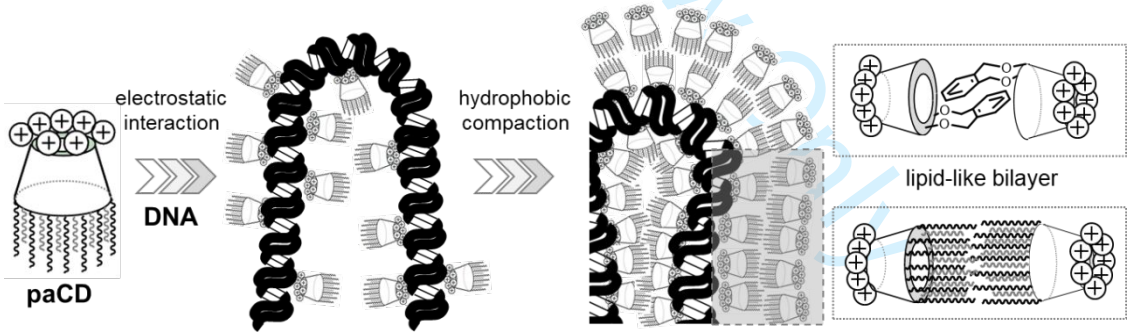

Figure 3. Schematic representation of the process leading to nucleic acid condensation in the presence of polycationic CD amphiphiles emphasizing on the relevance of the spontaneous formation of CD amphiphile bilayers.

As a proof of concept, Ortiz Mellet, Mendicuti, García Fernández and coworkers prepared the polycationic $2^{I},3^{I}$-*O*-(*o*-xylylene)-βCD derivatives **32** and **34** by xylylenation of the per-(C-6)-azido βCD followed either by reduction of the azido groups or by copper(I)-catalyzed azide-alkyne coupling (CuAAC) reaction with the propargyl-functionalized amine dendron **33** and final deprotection[45] (Scheme 7). NMR, fluorescent decay measurements and computational studies supported the existence of pH-dependent dimerization equilibria in water: whereas the dimers are rather stable at neutral pH, decreasing the pH results in higher protonation degrees of the polyamine domains and, consequently, stronger coulombic repulsion of the CD constituents. Upon formulation with plasmid DNA (pDNA), multilayer co-assemblies endowed with pH-responsiveness were obtained. This is conceptually very interesting for applications in gene therapy, since the weakening of the dimers after nanoparticle cell uptake destabilizes the whole CD-DNA supramolecular edifice, facilitating endosome escape and DNA cargo release. Indeed, evaluation of the transfection capabilities in COS-7 (renal epithelial green monkey) cells, using a luciferase-encoding reporter pDNA, afforded efficiencies that paralleled (**32**) or overpassed by 10-fold that of the nonviral vector gold standard polyethyleneimine [45].

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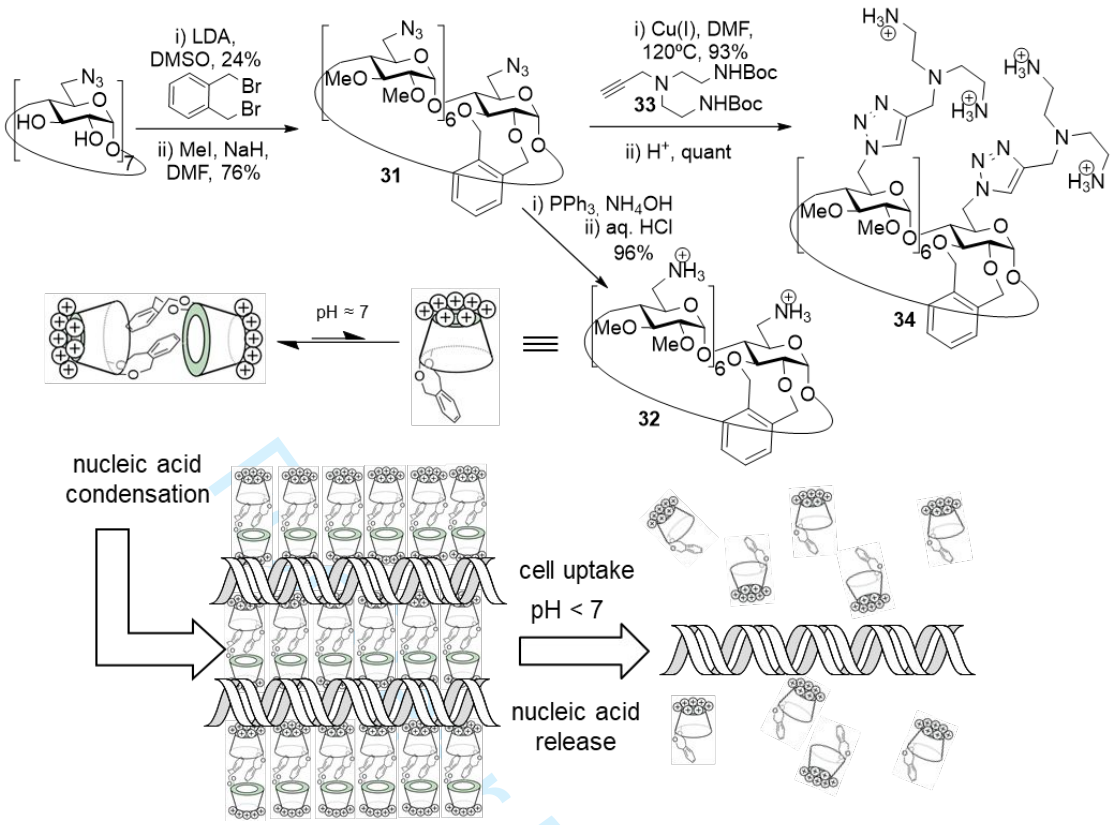

Scheme 7. Synthesis of polycationic 2^{I},3^{I}-*O*-(*o*-xylylene)-βCD derivatives **32** and **34** and proposed mechanism for the pH-sensitive hierarchical condensation and release of DNA. At neutral pH, the xylylene group promotes dimerization through hydrophobic interactions, preorganizing the system for the next DNA condensation step. Acidification leads to increased electrostatic repulsion, destabilizing the condensate and facilitating DNA release.

Cyclic ether aromatic clips: control over molecular topology

Yamada and coworkers developed an elegant strategy to achieve completely β-selective glycosylation by using a glycosyl fluoride donor bearing an *o*-xylylene bridge between the 3-*O* and 6-*O* positions of D-glucopyranose.[46] The rationale behind is that the rigid tether connecting the nonconsecutive positions in the monosaccharide forces a distorted conformation of the six-membered ring that determines the stereochemical outcome of the reaction. Moving to the field of cyclodextrins, Ortiz Mellet, Mendicuti, García

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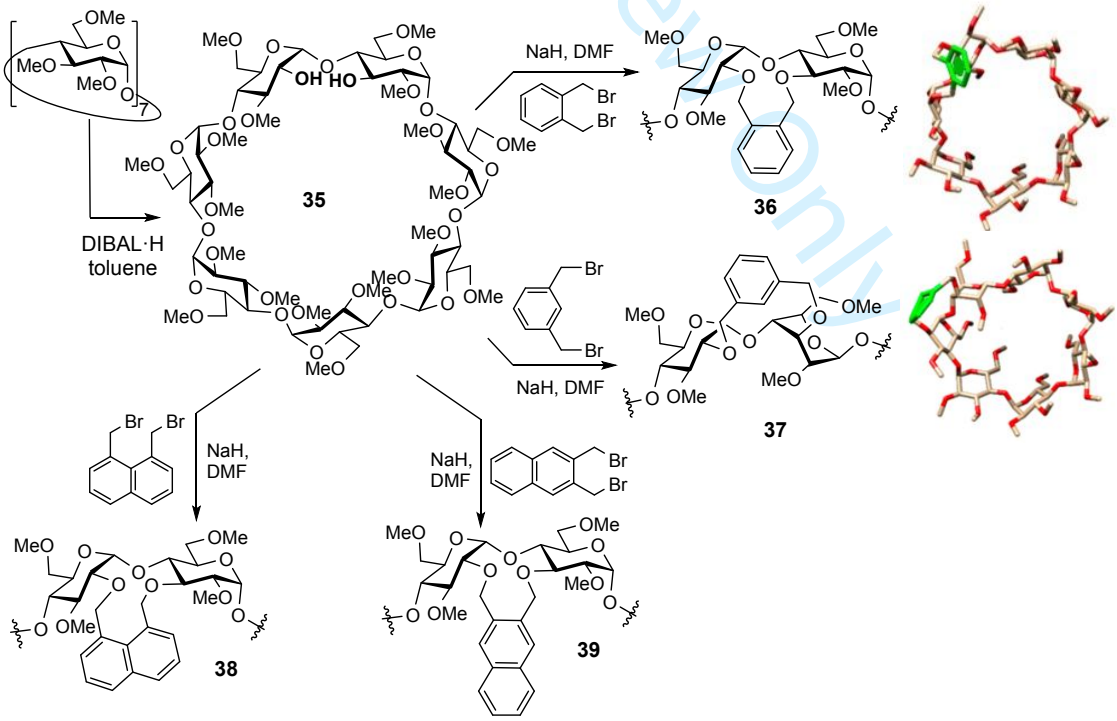
Fernández and coworkers conceived that aromatic "clips" could similarly be inserted between nonconsecutive hydroxyls to force a conformational change in the cyclooligosaccharide macroring, thereby modifying the topology of the cavity.[47] Starting from the βCD diol derivative **35**, accessed by regioselective bis-demethylation of permethylated βCD with diisopropylaluminum hydride (DIBAL·H) following the methodology of Sollogoub and coworkers,[48] the reaction with 1,2- or 1,3-dibromomethylbenzene, afforded the corresponding $2^{I},3^{II}$-di-*O*-(*o*- or *m*-xylylene)-βCD derivatives **36** and **37**, respectively (Scheme 8). As predicted from theoretical calculations, the *o*-xylylene "clipped" isomer **36** preserved the $^{4}C_{1}$ chair conformation of the glucopyranosyl residues and the toroidal shape characteristic of CDs. Sharply differently, the *m*-xylylene clip in **37** provoked a shift to the $^{1}C_{4}$ conformation in the (O-3)-substituted monosaccharide residue, which results in a substantial alteration of the overall shape of the host to an elliptic geometry.



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Scheme 8. Synthesis of *O*-2^{I},*O*-3^{II}-xylylene- (**36** and **37**) and dimethylnaphthylene-clipped (**38** and **39**) βCD derivatives. The MM-optimized 3D-structures of **36** and **37** (secondary rim view) of their structures are depicted at the right hand side.

Prearranging the CD topology through aromatic clipping enables the control over the inclusion properties. Thus, circular dichroism experiments established that the *o*-xylylene module in **36** adopts a semi-open conformation that permits the inclusion of hydrophobic molecules fitting the size of the βCD cavity. The guest can additionally benefit from favorable contacts with the aromatic clip in the complex, as confirmed for adamantane-1-carboxylate (AC). Dissimilarly, the elliptic cavity of **37** is unable to host globular molecules, even though the *m*-xylylene moiety adopts a fully open arrangement, selecting instead planar guests such as methyl 2-naphthoate. Fluorescence decay measurements and computational calculations further evidenced a direct relationship between molecular shape and self-assembling behavior: compound **36** formed an HH-dimer in water solution whereas the conformationally distorted analogue **37** existed in monomeric form at any concentration.[47]

The potential of aromatic clips to modulate the self-assembling properties of CDs has been further demonstrated by preparing the *O*-2^{I},*O*-3^{II}-linked 1,8- and 2,3-dimethylnaphthylene derivatives **38** and **39**, respectively. In both cases the conformation of the glucopyranosyl units and the CD macroring remain essentially unaltered. However, the relative orientation of the aromatic platform significantly differs: the 1,8-dimethylnaphthalene module in **38** adopts a rather rigid open conformation whereas the more flexible 2,3-dimethylnaphthalene appendage in **39** can accommodate a semi-open arrangement. Both compounds form rather stable HH-dimers in water solution, but whereas the aromatic motifs act as extension walls in the case of **38**-dimer, they behave as folding screens between the secondary rims of the monomer

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constituents in the case of **39**-dimer. Remarkably, the dimer architecture has a strong impact in the inclusion capabilities. Thus, the AC guest was found to enter the **38**-dimer extended cavity through the bulk-exposed βCD narrower rim to form a ternary complex AC/**38**-dimer. In other words, **38**-dimer can accept hydrophobic cargos while preserving the self-assembled structure. Contrarily, inclusion of AC triggered **39**-dimer disruption to give the bimolecular AC/**39** complex species (Figure 4). The possibility of implementing different supramolecular organization levels (e.g., self-assembly and/or inclusion and/or spatiotemporal controlled dissociation) with aromatic clips offers then a rational strategy to program the behavior of CD-based devices in biological environments for (bio)molecular encapsulation and controlled release.[49]

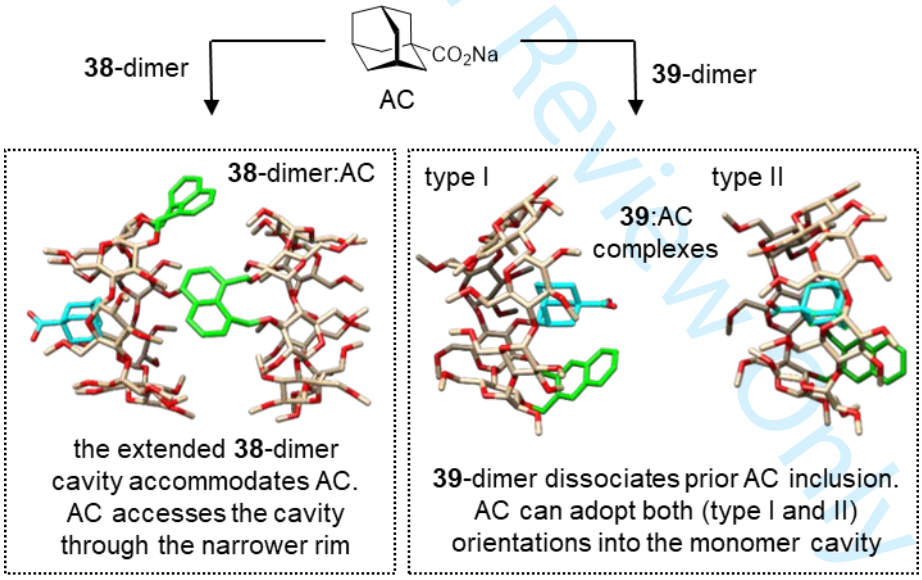

Figure 4. Schematic representation of the structure of AC/**38** and AC/**39** complexes illustrating the disparate molecular inclusion dimer formation capabilities imposed by their corresponding dimethylnaphthalene appendages.

Concluding remarks

The ensemble of contributions commented in the above sections illustrates the potential of strategies based in combining CD hosts and aromatic modules to generate precise molecular topologies and programming several levels of supramolecular organization. Beyond predefining interactions with target guest for sensing purposes, aromatic moieties can drive self-assembly as well as co-assembly with biomolecular partners to afford nanocomplexes capable of performing specific tasks. Polyfunctional CD-aromatic hybrids can further be designed to reversibly self-arrange into stimuli responsive multivalent constructs with predictable orientations and densities of the key appended motifs. The current applications have focused mainly in supramolecular catalysis[50] and molecular vectors for non-viral gene delivery[51] because of the critical dependence of the efficiency of these processes on molecular and supramolecular preorganization.[52] Cyclodextrins have been broadly used to synthesize multivalent ligands in other research areas such as carbohydrate-protein interactions,[53] pore-forming toxin blockers[54] or enzyme inhibition[55] that are also expected to benefit from similar approaches. New developments will certainly arise in the near future from the intimate merging of cyclodextrin and aromatic units in purpose-conceived hybrid architectures.

Disclosure statement

No potential conflict of interest was reported by the authors.

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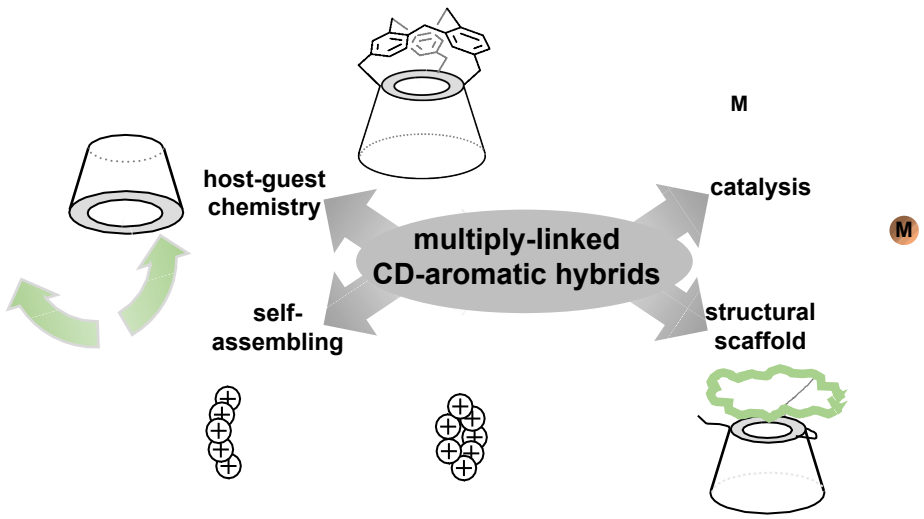
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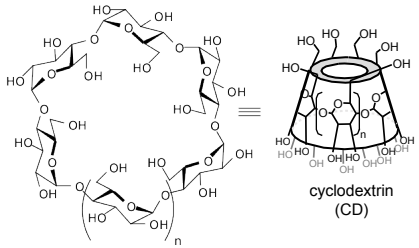
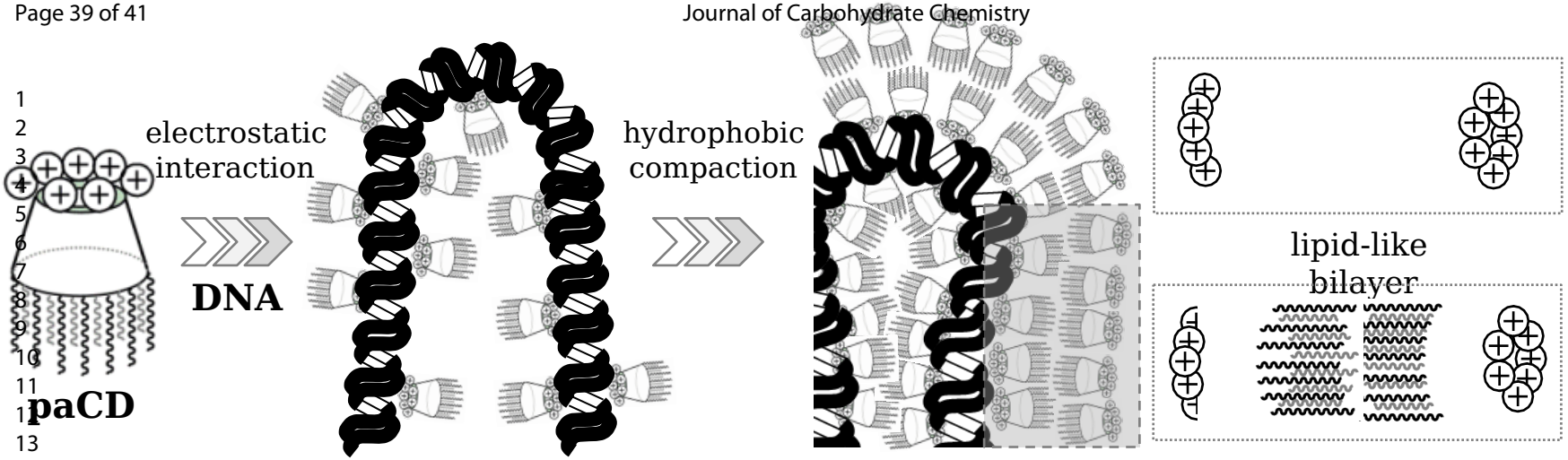


CD	i.d.(Å)	o.d.(Å)	height(Å)
αCD (n=1)	4.7-5.2	14.2-15.0	7.9-8.0
βCD (n=2)	6.0-6.4	15.0-15.8	7.9-8.0
γCD (n=3)	7.5-8.3	17.1-17.9	7.9-8.0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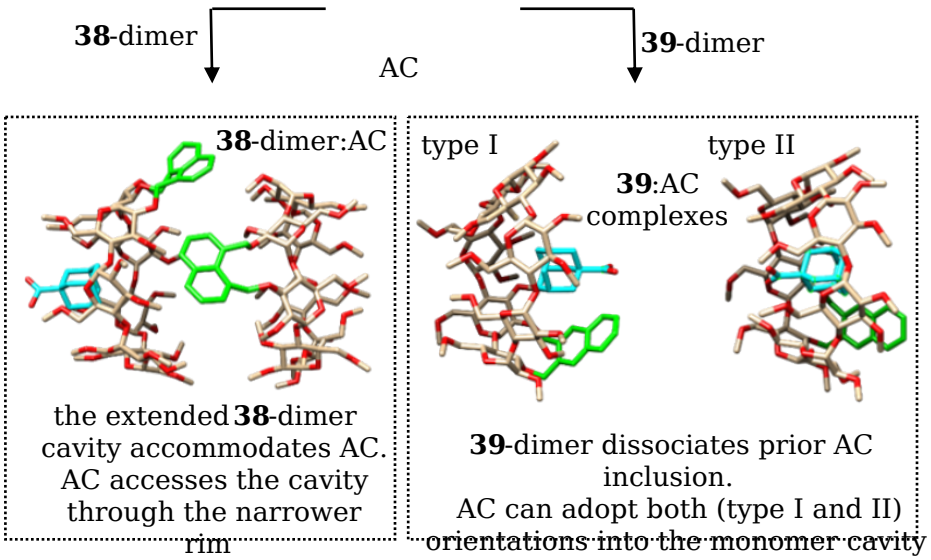
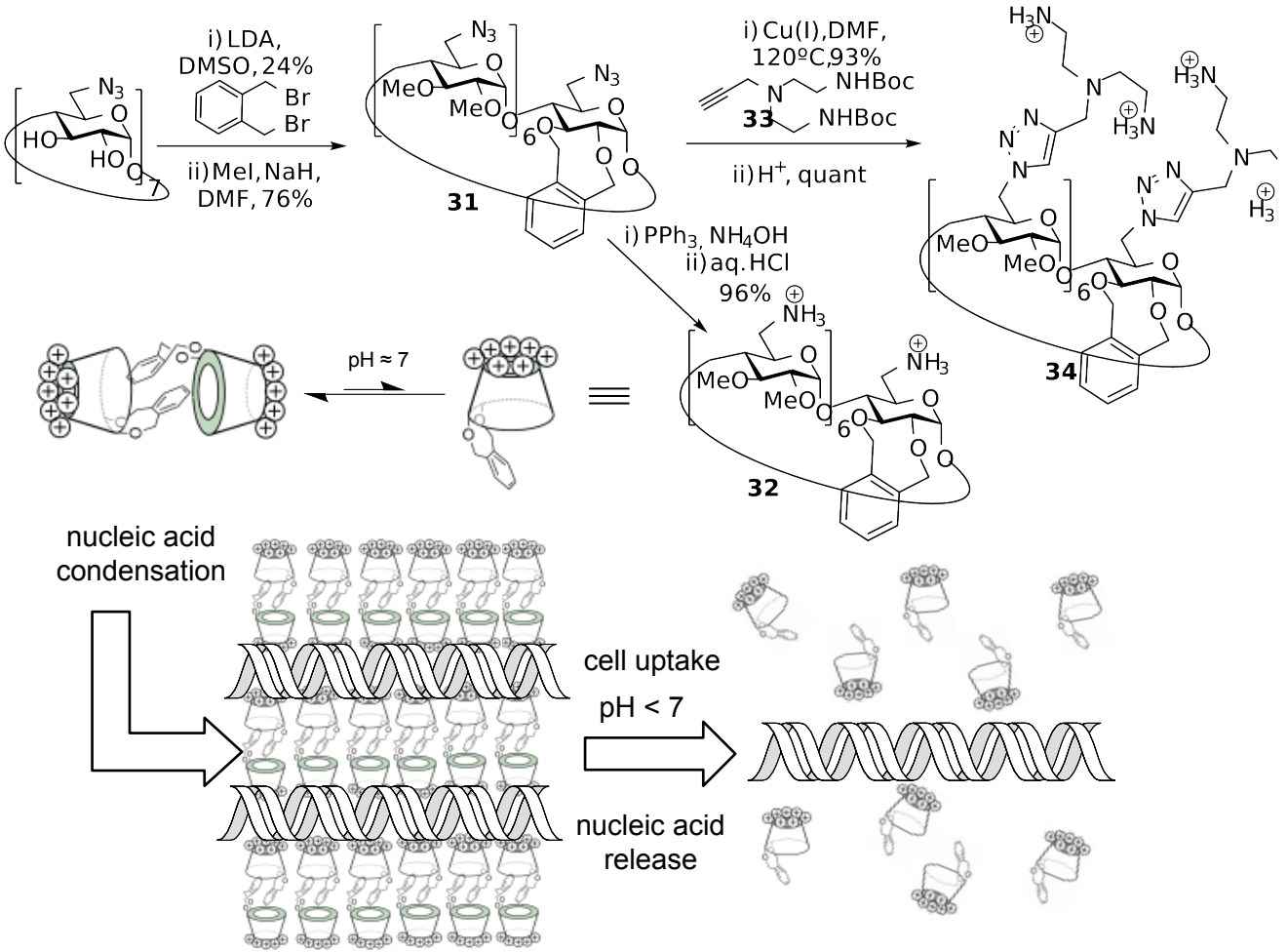

38-dimer
AC
39-dimer
38-dimer:AC
type I
type II
39:AC
complexes
the extended **38**-dimer cavity accommodates AC. AC accesses the cavity through the narrower rim
39-dimer dissociates prior AC inclusion.
AC can adopt both (type I and II) orientations into the monomer cavity


i) LDA, DMSO, 24%
Br
Br
ii) MeI, NaH, DMF, 76%
31
i) Cu(I), DMF, 120ºC, 93%
33
NHBoc
NHBoc
ii) H+, quant
34
i) PPh3, NH4OH
ii) aq. HCl
96%
32
pH ≈ 7
nucleic acid condensation
cell uptake
pH < 7
nucleic acid release