Controlled binding of organic guests by stimuli-responsive macrocycles

Arturo Blanco-Gómez, Pablo Cortón, Liliana Barravecchia, Iago Neira, Elena Pazos, Carlos Peinador* and Marcos D. García†

Departamento de Química, Facultade de Ciencias and Centro de Investigacións Científicas Avanzadas (CICA), Universidade da Coruña, 15071 A Coruña, Spain

Chemical Society Reviews, volume 49, issue 12, pages 3834–3862, 21 June 2020
Submitted 11 February 2020, First published 12 May 2020
https://doi.org/10.1039/D0CS00109K

Abstract

Synthetic supramolecular chemistry pursues not only the construction of new matter, but also control over its inherently dynamic behaviour. In this context, classic host-guest chemistry, based on the development of a myriad of macrocyclic receptors with fine-tuned affinities and selectivities, has enormously contributed to the discovery of new chemical function under self-assembly conditions. In turn, the use of molecular switches as control units within host-guest assemblies opened the door for the regulation of their dynamic interactional behaviour, which can be translated into controlled aggregation. In this review, we will focus on different strategies developed for the regulated binding of organic molecules by switchable macrocyclic hosts. As we will see, an appropiate design using stimuli-responsive versions of well-known organic receptors, allows the molecular switches implemented within their structures to transform their regulated behaviour from the molecular to the supramolecular level.

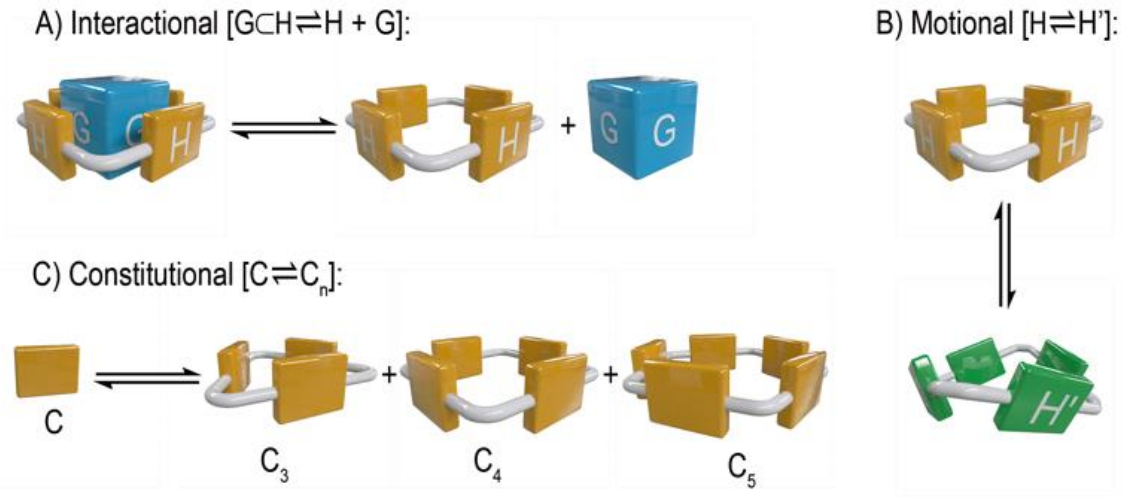
1. Introduction: from molecular to supramolecular switches.

Supramolecular chemistry has permeated every aspect of chemistry over the last 50 years, from the construction of novel matter,[1-7] to the discovery of never imagined chemical function.[8] This success is firmly cemented on the seminal works of Pedersen,[9-10] Lehn[11-12] and Cram[13] on artificial molecular hosts, and on the subsequent design and synthesis of a countless number of fine-tuned macrocyclic receptors (e.g., currently commercially available compounds such as cyclodextrins, crown ethers, calix[n]arenes or cucurbit[n]urils).[14-15] Despite the well-established synergy between host-guest and supramolecular chemistry, current trends in the field are focused not only on non-responsive

* carlos.peinador@udc.es
† marcos.garcia1@udc.es

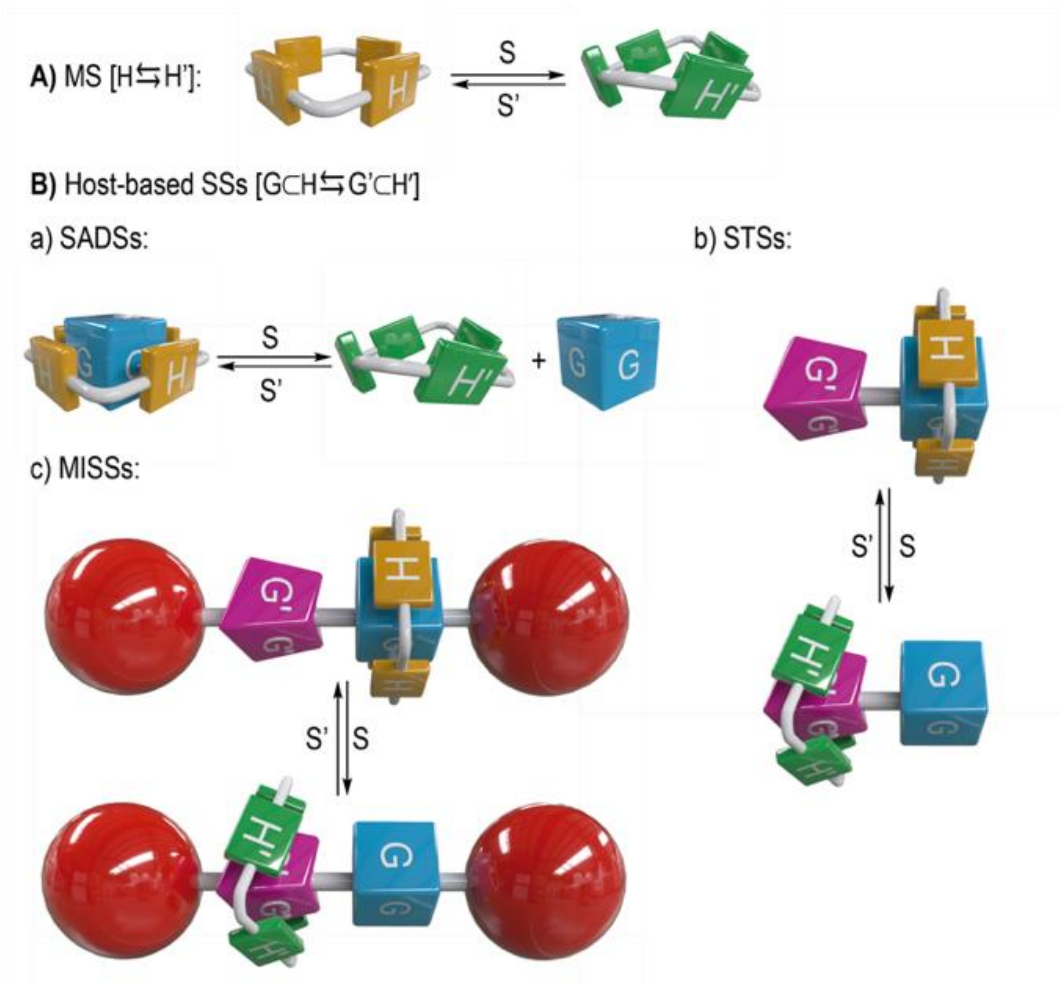
systems, but on the regulation of dynamic behaviour, in an effort to achieve spatiotemporal control over molecular aggregation, which could eventually lead towards the creation of abiotic informed matter.[16-20] Although a great deal of effort has been devoted to the development of stimuli-responsive host-guest systems and their practical applications,[21-27] in the majority of the cases, their controlled dynamic behaviour has been obtained through the use of molecular switches (MSs),[28-34] as the guest part of host-guest assemblies. Conversely, the use of stimuli-responsive versions of macrocyclic hosts has been certainly less active, probably because of their enhanced difficulty as synthetic targets.[35]

According to Lehn,[16-20,36] three different types of dynamic behavior can be envisioned for supra(molecular) systems, namely: *interactional*, *motional*, and *constitutional*, which necessarily operate under strict thermodynamic control. For a given entity, the *reactional/interactional dynamics* would account for its ability to form or disrupt (non)covalent bonds, *motional dynamics* for reversible changes in shape, conformation, or molecular motion, and *constitutional dynamics* for the reversible modification of the structure of the entity in terms of the number of self-assembled (sub)components. As shown in Scheme 1, for the particular case of a macrocyclic host H, the reversible molecular recognition of a guest G to produce G⊂H (i.e. the equilibrium [H+G⇌G⊂H]), is an example of interactional dynamics. As a case of motional dynamics, we can consider any kind of factor that reversibly changes the shape of H to H' (i.e. [H⇌H']), for instance by isomerization of double bonds or other functional groups, formation or disruption of intramolecular hydrogen bonding, etc. Finally, in terms of constitutional dynamics, we can envisage a set of cyclic species, C_n (including the molecular receptor H = C_4), in thermodynamic equilibrium with its constituent C (i.e. [n C⇌C_n]), in which the structural nature of each species is precisely defined by the number of self-assembled units.



Scheme 1. Interactional [H+G⇌G⊂H], motional [H⇌H'], and constitutional dynamism [C⇌C_n], for a given macrocycle H.

From a human point of view, control over molecular dynamism, as defined above, can be achieved by two different means: a) *intrinsic control* of the chemical equilibrium, by an aprioristic design of the structure/information gathered by the interacting units, and/or *a posteriori* modification of the interaction conditions according to Le Chatelier's principle; b) *extrinsic control*, by creating accessible metastable states attained by opposite physicochemical inputs. With this in mind, in the present review we will focus our attention on the controlled binding of organic guests by means of stimuli-responsive macrocyclic hosts or, in the terms defined above: *extrinsic control over the reactional dynamics of host-guest aggregates, attained by regulation of the motional dynamics of the macrocyclic host* (Scheme 2B).

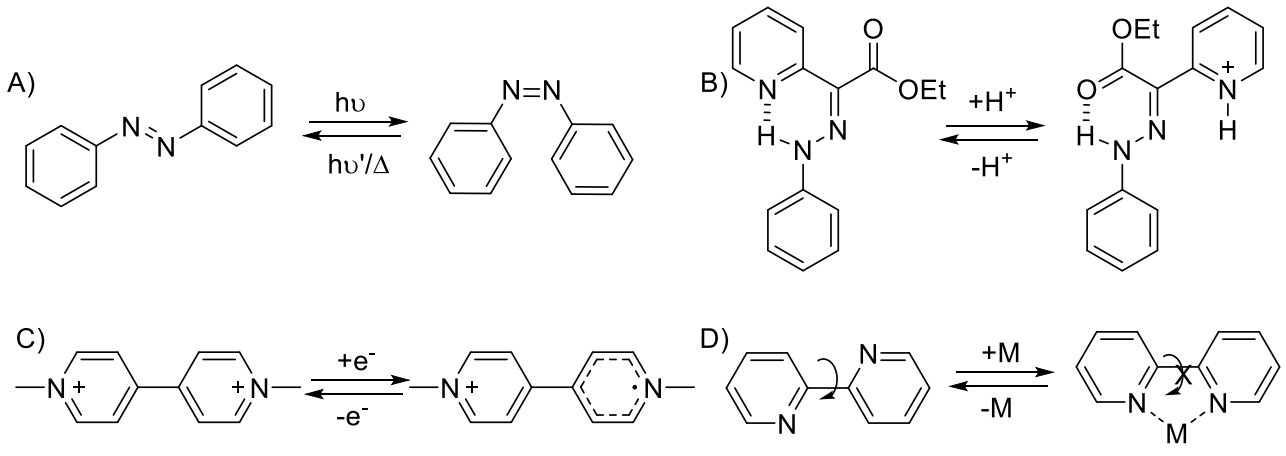


Scheme 2. A) Schematic representation of a host-based MS: [H⇄H´]. B) Implementation into extrinsically-controlled SSs: G⊂[H⇄H´].

In a phenomenological fashion, we can describe host-controlled binding in terms of swapping, produced between a basal complexing form of the macrocycle and a non-productive counterpart (represented in this work as [H⇄H´], Scheme 2). In that situation, the host acts as a MS, with a given stimulus S morphing the shape of H into H´, and a divergent

input S' producing the opposite result, *i.e.*, transformation of H' into H. Subsequently, H could be able to translate or not its behaviour from the molecular to the supramolecular level in the presence of a given guest G. If the result is the dissociation of the guest upon stimulation, the system (i.e. G⊂[H⇄H´], Scheme 2) is said to behave as a supramolecular switch (SS).[37]Particular cases of SSs include those that imply complete association-dissociation of the aggregate to the reaction media (termed in this work as SADSs = "Supramolecular Association-Dissociation Switches"), and those where a large relative movement of the position of the components within the assembly is produced (termed in this work as STSs = "Supramolecular Translocation Switches"). This later concept of switchable translocation can be further extended to mechanically interlocked molecules (resulting in MISSs = Mechanically-Interlocked Supramolecular Switches),[37] with the structural change producing the relative movement of the subunits within the aggregate. For the sake of simplification, we will discuss in this review only SADSs, since the design principles applied for switching in related STSs and MISSs can be inferred from those applied to SADSs.

Regarding the applied stimuli (Scheme 3), we will discuss those inputs capable of a reversible extrinsic control of the system (i.e. pH: S = $+H^+$ and S' = $-H^+$, redox: S = $+e^-$ and S' = $-e^-$, photochemical: S = hυ and S'= hυ'/Δ). Additionally, as this type of stimulation is sometimes referred to as allosteric (by interaction of protons, electrons or photons as effectors with specific binding moieties of a (supra)molecule), we will include in this review selected examples of other chemical effectors (E) as stimuli (allosteric stimulation: S = +E and S' = -E). To describe allosterism in host-guest systems,[38-40] we will follow the simplified classic description of the phenomenon,[41-42] which defines it as cooperative effects in the selective binding of more than one substrate to different binding sites of a given receptor. These effects produce a conformational change of the host due to the binding of E in the so-called "allosteric site", resulting in activation or deactivation of the association of another substrate at a different primary binding site.



Scheme 3. Archetypical examples of MSs involving: A) photoisomerization,[43] B) protonation-deprotonation,[44] C) oxidation-reduction,[45] and D) metal coordination.[46]

Concerning the organization of the review, first we will briefly introduce some of the most popular families of organic macrocyclic hosts,[47-50] focusing on their structure-binding relationships and, in some cases, their intrinsic behaviour as MSs and direct implementation into SSs. As we will see, these macrocycles have served as starting points for the design of SSs. Consequently, the discussion on those in this review (Sections 3-7), will be primarily organized on the basis of the design criteria applied for their construction and, when possible, the different host classes and applied stimuli.

2. The tools of the trade: well-known families of macrocyclic hosts.

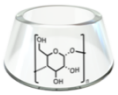
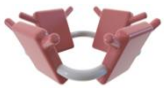
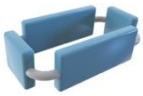
Stating the obvious, the most straightforward method to introduce switching capabilities into macrocyclic molecular receptors, and in turn to implement those into host-based SSs, would be the direct covalent post-functionalization of macrocycles, with well-defined binding abilities by themselves, with MS moieties.[14-15] Therefore, we will discuss in advance such binding abilities, in particular with organic guests, trying to correlate those features with the structure of the macrocycle. We will comment as well on the ease of chemical functionalization of these compounds, as this factor can constitute the bottleneck for the synthetic accessibility of new switchable analogues. Furthermore, Table 1 summarizes the most remarkable properties of those families of compounds regarding the topic of this review. Finally, we will discuss the particular properties as a stimuli-responsive host of the so-called "blue box" (cyclobis(paraquat-*p*-phenylene)). This iconic cyclophane is undoubtedly one of the seminal examples of macrocyclic MS, being in turn intrinsically able to perform the controlled binding of organic substrates. Consequently, the "blue box" has not only served as a model for the development of other stimuli-responsive hosts, but as well as a continuous source of inspiration for those research studies in the field of (supramolecular) chemistry.

2.1. Cyclodextrins

With more than one century of history since their discovery by Villiers,[51] naturally occurring cyclodextrins (CDs) are probably the most widely used family of macrocyclic hosts.[52] Structurally, the water-soluble, non-toxic, and commercially available α-, β-, and γ-CDs are bucket-shaped cyclic oligosaccharides consisting of six, seven, or eight glucopyranose units attached by 1,4-linkages. Due to the oligomerized glucose units, CDs exhibit hydroxyl groups on the larger primary face and hydroxymethyl functions on the secondary, making these derivatives quite easy to functionalize.[53-54] Because of these features, an extensive number of CD derivatives have been reported having a wide range of binding abilities.[55] For instance, native CDs can complex a variety of organic guests in aqueous media mostly because of the hydrophobic effect. Due to the different cavity diameters of CDs (α-: 4.9 Å;

β-: 6.2 Å; γ-: 8.0 Å), α-CD can accommodate linear alkanes and monocyclic aromatic molecules as appropriate guests, β-CD binds in turn bulky hydrocarbons, such as adamantane, or polyaromatic compounds, such as naphthalene and anthracene derivatives, and γ-CD can incorporate even larger guests, e.g. two γ-CD molecules can sandwich a fullerene, or two aromatic guests can be included in a single cavity.

Table 1. Schematic representation and comparison of relevant features for the macrocyclic host families covered in this review.

	Host family	Monomers	Functionalization (ref)	Host-Guest Aqueous Media	Host-Guest Organic Media
	**Coronands and criptands**	12-24	59-61, 65 and 69	✓	✓
	**Cyclodextrins (CD)**	6-8	52-54	✓	restricted
	**Calix[*n*]arenes (CX[*n*])**	4-8	76 and 77	✓	✓
	**Resorcin[*n*]arenes (RA[*n*])**	4	87	restricted	✓
	**[*n*]Cavitands**	4-7	79	restricted	✓
	**Pillar[*n*]arenes (PA[*n*])**	5,6	90	✓	✓
	**Exboxes (Ex$_n$Box)**	-	101	✓	✓
	**Cucurbit[*n*]urils (CB[*n*])**	5-11	98	✓	restricted

2.2. Coronands and cryptands

The invention of crown ethers (coronands) by Pedersen in 1967 can be considered as one of the most ground-breaking chemical discoveries of the 20th century,[56] being the first type of abiotic receptor capable of structure-specific metal ion recognition. Simple derivatives, usually termed as [m]crown-n ethers (m = total number of atoms, n = number of oxygen atoms), are cyclic compounds consisting of ethylene oxide repeating units in the form of (–CH_2CH_2O–)$_n$ oligomers with n > 4. Regarding their host-guest chemistry,[57] the oxygen or other heteroatoms included in the annulus of coronands, are prone to coordinate inorganic

cations, which are solubilized in organic solvents due to the hydrophobic nature of the exterior of the host. Additionally, simple crown ethers can act as well as receptors in organic media of ammonium salts, and even appropriate neutral molecules, based on multitopic hydrogen bonding.[58] Because of their easy structural modification, including oxygen, nitrogen,[59] phosphorous[60] or sulphur-containing derivatives,[61] the supramolecular chemistry of coronands has certainly exploded since their discovery.

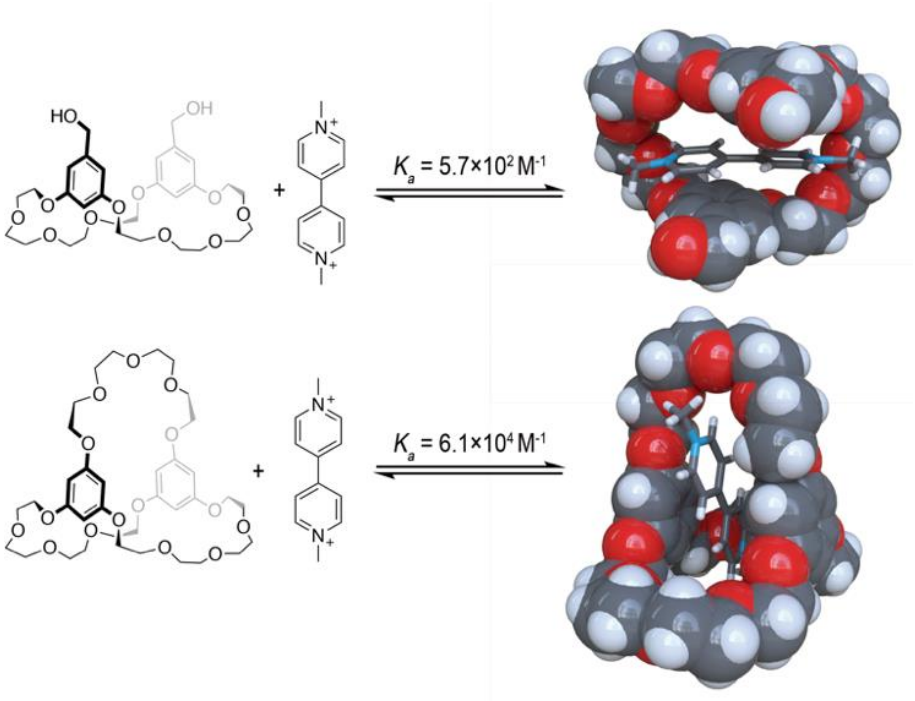
The so-called cryptands[12,62-63] are referred to as three-dimensional polycyclic analogues of crown ethers, possessing as well cyclic polyether structures, with amines (or other functional groups or structural motifs), as bridgeheads. Because of their crypt-like environment, having a more preorganized structure than that of their monocyclic congeners, these compounds are superior to coronands in terms of complexation abilities.[64] For the purpose of this review, we will especially focus our attention on those coronands and cryptands known to complex aromatic organic guests, namely, aryl-containing coronands and their cryptand-like analogues. Concerning those, Stoddart *et al.* were the first to study the interaction of simple aryl-containing coronands with organic dications,[65] showing for instance that bis (*p*-phenylene)-34-crown-10 ether was able to bind organic cations, such as the herbicide paraquat (*N*,*N*'-dimethyl-4,4'-bipyridinium cation, MV) and its derivatives (viologens, MVs), in acetone.[66] Since then, aryl-containing crown ethers, such as bis (*m*-phenylene)-32-crown-10 ether or dibenzo-24-crown-8 ether derivatives, have been extensively used not only for the preparation of host-guest complexes with MVs or ammonium salts,[67] but also for binding motifs within mechanically-interlocked molecules based on π-π interactions.[68] Concerning the recognition of organic molecules, as thoroughly demonstrated by Gibson *et al*, modification of aryl-containing coronands, to produce cryptand-like structures, renders superior hosts reaching K_a values in the 10^5-10^6 range for 1:1 complexes with MVs (Scheme 4).[69]

2.3. Cyclic arenes and related deep cavitands

2.3.1. Calix[n]arenes. Discovered by Baeyer and popularized by Gutsche,[70-71] calix[n]arenes (CX[n]s) are composed of n phenolic units linked by methylene bridges at their 2,6-(*meta*)-positions. Even-numbered CX[n]s analogues (n = 4, 6, 8) can be selectively obtained in reasonable yields by adjusting the conditions of the reaction between phenolic derivatives and formaldehyde. Conversely, odd-numbered CX[n]s (n = 5, 7, 9), and large homologues, can also be obtained but in lower yields. These macrocycles own unique calix-shaped structures, with a cone-shaped upper rim and a narrower lower edge, because of the intramolecular hydrogen bonds between phenolic moieties. The wider upper rim of the CX[n]s is hydrophobic due to the methylene bridges, while the lower is hydrophilic on account of the phenolic oxygen atoms. Their host-guest chemistry with organic substrates is based on π-π stacking, cation–π, ion–dipole, and hydrogen-bonding interactions. In that manner, CX[n]s are prone to form host–guest complexes in organic media with aromatic cationic species because of the electron-donating nature of the phenolic units.[72] By

introducing sulfonate moieties on their structures, Shinkai *et al*. reported the first water-soluble CX[n]s[73] able to form host–guest complexes not only with cationic molecules, but also with neutral organic species because of the hydrophobic effect.[74-75] Functionalization of CX[n]s has been extensively studied, with modifications being introduced on the rims, the methylene bridges and/or the *meta*- position of the phenolic rings.[76-77]

Structurally related to calixarenes,[78] cavitands are a loosely defined class of concave and rigid macrocycles constructed through rigidification of the upper rim of CX[n]s, yielding versatile receptors with a rich host-guest chemistry conditioned by their highly preorganized structures.[79]



Scheme 4. Complexation of MV by a coronand (top) and a cryptand (bottom). Adapted from ref. 69 with permission from American Chemical Society, copyright 2014.

2.3.2. Calix[4]pyrroles. Calix[4]pyrroles (CP[4]s),[80] are shape-analogues of CX[4]s, as being constructed by four pyrrole rings linked through the α- (i.e. pyrrolic carbon atoms 2 and 5) or *meso*-like positions by sp^3 hybridized carbon atoms. Although this family of macrocycles has been popularized by Sessler *et al*, primarily for the recognition of inorganic anions[81] or ion pairs,[82] their ease of functionalization[83] has rendered a number of congeners able to serve as well as receptors for organic molecules.[83-85]

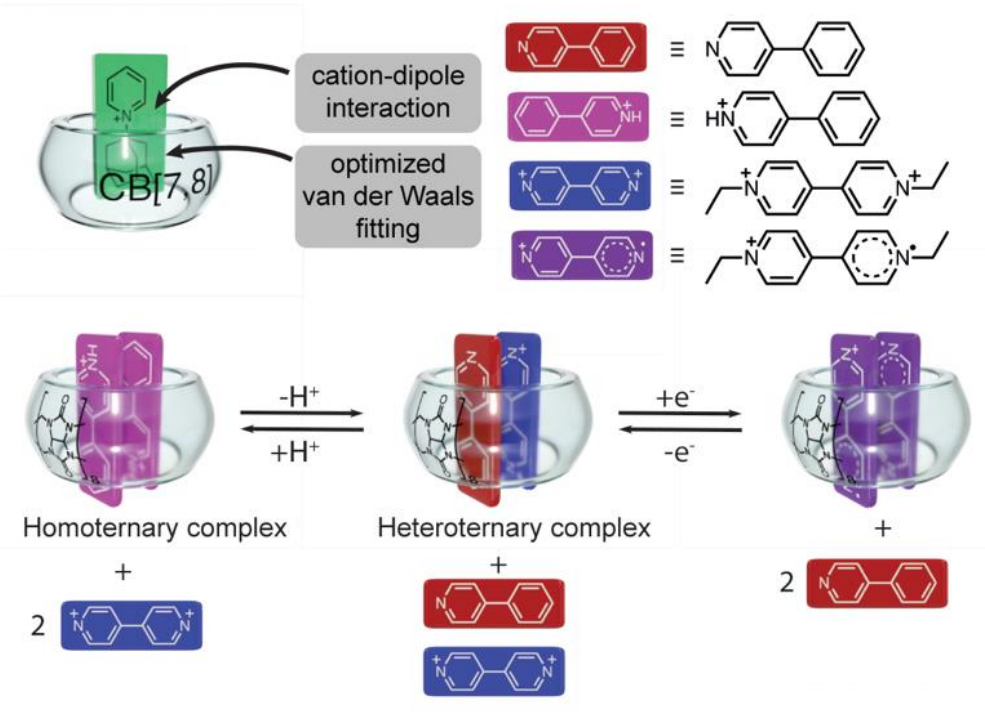
2.3.3. Resorcin[n]arenes. Resorcin[n]arenes (RA[n]s),[86] are cyclic arenes produced by the acid-catalysed condensation of resorcinol with aliphatic or aromatic aldehydes. By far, the most commonly studied resorcinarenes are RA[4]s. As CX[4], RA[4] owns in terms of

structure two different rims. The upper rim of the parent RA[4] includes eight hydroxyl groups that can participate in hydrogen bonding interactions, whereas substitution on the lower rim, and therefore its properties, depend on the constitution of the starting aldehyde. Since RA[4]s possesses phenolic hydroxyl groups available for further functionalization,[87] and shares a very similar host-guest chemistry compared to CX[n]s, it is not surprising to find RA[4]s complexes with a variety of guest molecules in organic media (e.g. dicarboxylic acids, sugars, terpenes or steroids).[88]

2.3.4. Pillar[n]arenes. Pillar[n]arenes, or simply pill[n]arenes (PA[n]s), are a relatively new class of cyclophanes discovered by Ogoshi *et al*,[89] composed of hydroquinone (HQ) units linked by methylene bridges at *para*- positions. PA[n]s (n = 5-15) are symmetrical and rigid, easy to mono-/di-/per- functionalize,[90] and their derivatives are appropriately soluble in aqueous or organic solvents, where they display a very rich host-guest chemistry.[91-92] Due to the HQ rings, native PA[n]s display an electrondonor (ED) core and ionophoric rims, which make these macrocycles appropriate hosts for electron acceptor (EA) organic dications, such as MVs, in organic media. Furthermore, PA[n]s have as well the ability to complex a wide range of neutral organic guests by dipole–dipole, π···π, C–H···π, and hydrogen bonding interactions, as exemplified by the complexation ability of PA[5] with aliphatic nitriles, alcohols, esters, aldehydes and ketones or haloalkanes.[93]

2.4. Cucurbiturils.

Cucurbiturils (CB[n]s, n = 5-11), are a family of pumpkin-shaped macrocycles formed by condensation of n glycoluril units joined together by 2n methylene bridges, producing hollow molecules with inner hydrophobic cavities accessible through two identical carbonyl-laced portals.[94] Due to these structural features, CB[n]s display a rich host-guest chemistry that has been extensively reviewed (Scheme 5).[95] In a nutshell, CB[n]s are able to form diverse binary aggregates with neutral/cationic organic species, substrates that are recognized by these hosts by a conjunction of cation-dipole interactions, hydrophobic forces, and optimization of host-guest packing coefficients. Additionally, the special characteristics of CB[8] should be noted because, due to its hydrophobic but polar large cavity, it is able to form as well complexes of the types: homoternary 1:2 (HG_2) and heteroternary 1:1:1 (HGG', G = ED/G' = EA). This latter case of host-guest aggregates is unique, taking advantage of increased charge transfer interactions stablished between two complementary guests.[96] Regarding the stimuli-responsiveness of CB[n]s, they can be considered as intrinsic pH-based MSs. For instance CB[7], with pK_a = 2.2, reversibly forms hydrogels in acidic aqueous media.[97] However, as a probable consequence of their non-trivial functionalization,[98] no other CB[n] derivatives behaving as MSs have been reported to date.



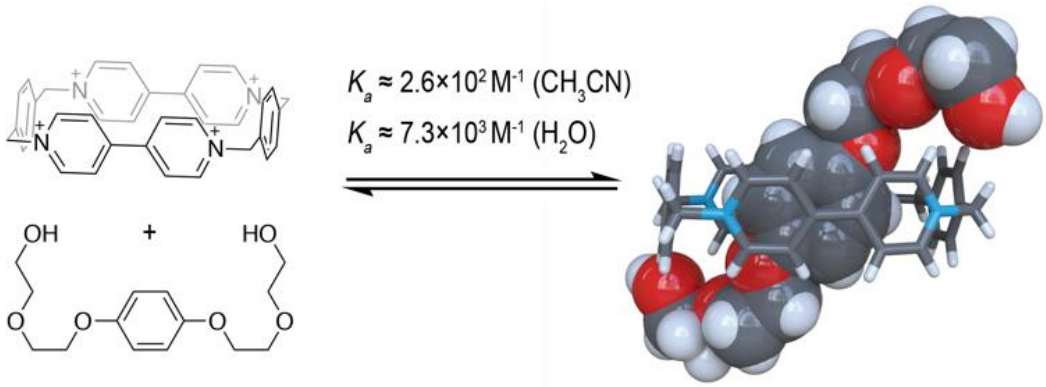
Scheme 5. 1:1 binary (top), 1:2 homoternary and 1:1:1 heteroternary (bottom) CB[*n*]-based inclusion complexes, and implementation of the later types into an orthogonal pH/redox CB[8]-based supramolecular switch. Adapted from ref. 100 with permission from The Royal Society of Chemistry, copyright 2017.

Although the primary concern of this work is the controlled binding of unaltered organic guests by stimulation of macrocyclic hosts, this is not the only case in which the catch and release of an unaltered guest can be achieved upon stimulation of a host-guest system. Based on the ability of CB[8] able to form unusual 1:1:1 heteroternary complexes, a huge amount of CB[8]-based supramolecular switches have been developed, by using appropriate EDs or EAs as stimuli-responsive guests.[99] As a remarkably simple example of this interesting behaviour, Schalley *et al.* have recently shown dual-responsiveness within a CB[8]:MV:ED heteroternary complex, by combining the characteristics of an MV as redox-responsive EA, and a phenylpyridine derivative as pH-sensitive ED.[100] As designed, the aggregate orthogonally responds in aqueous media to both redox potentials and pH, generating a multifunctional switch (Scheme 5).

2.5. Exboxes.

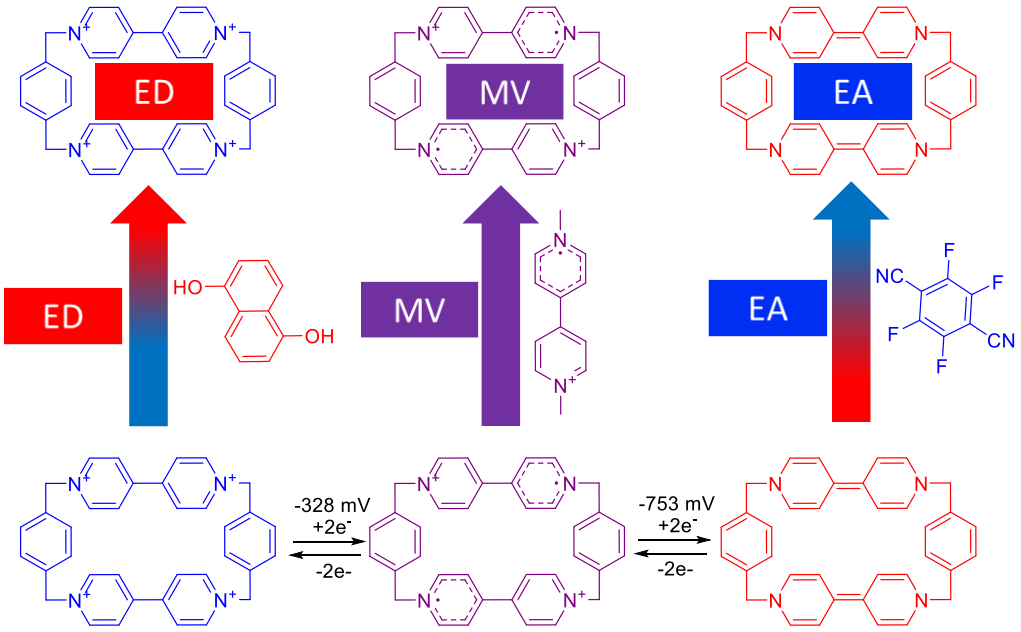
2.5.1. Host-guest chemistry. The Exboxes, and related macrocycles, comprise a family of pyridinium-based polycationic cyclophanes developed by Stoddart *et al.*[101] Structurally, the simplest derivative is the so-called "blue box" (Ex_0Box^{4+}, cyclobis(paraquat-*p*-phenylene)cyclophane, Scheme 6).[102] This rectangular macrocycle comprises two MV units on the large sides separated by *p*-phenylene moieties, and is able to form host-guest aggregates with appropriate electron rich aromatics in organic media[103] or water.[104] Expansion of the large side by introducing aryl-extended MVs results in Ex_nBox^{4+} analogues (n = 0–3 = number of *p*-phenylene

linkers introduced on each of the two MV subunits). Other, more exotic, analogues have been reported, including different modifications on the nature of the short/large sides of the macrocycle,[101] as well as cage-like derivatives.[105,106]



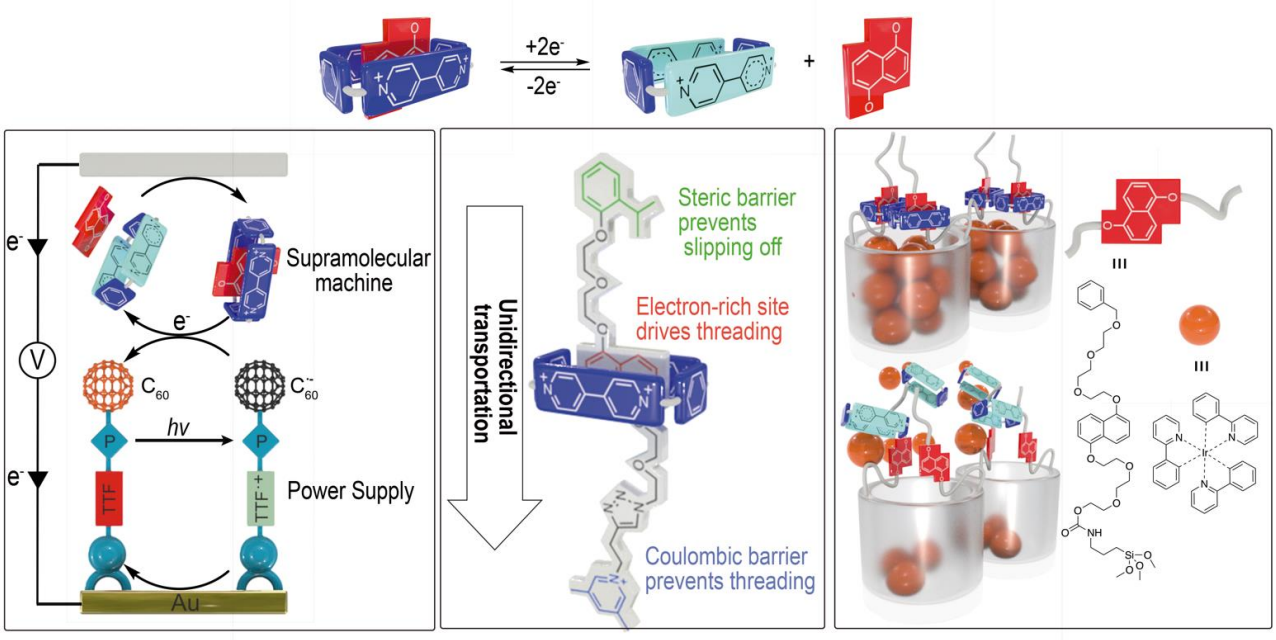
Scheme 6. Complexation of a hydroquinone (HQ) derivative by the "blue box" in CH_3CN[103] and water.[104]

As a result of its structure (i.e. the presence of the MV units in the macrocyclic annulus), the "blue box" has two accessible redox states [$E_{1/2}$ ($Ex_0Box^{4+}\rightarrow Ex_0Box^{2(+\bullet)}$)= -328 mV, $E_{1/2}$($Ex_0Box^{2(+\bullet)}\rightarrow Ex_0Box$ = -753 mV)], a feature translated in a very different behaviour of the macrocycle as a host depending on its reduction state.[107] Consequently, the macrocycle forms inclusion complexes of the types: (i) ED⊂Ex_0Box^{4+} (ED = aromatic electron donors) by π-donor/π-acceptor interactions (ii) $MV^{+\bullet}$⊂$Ex_0Box^{2(+\bullet)}$ by radical pairing and, (iii) EA⊂Ex_0Box^{4+} (EA = aromatic electron acceptors) *via* van der Waals interactions (Scheme 7).



Scheme 7. Types of inclusion complexes formed by the molecular host "blue box" depending on its reduction state. Adapted from ref. 107 with permission from American Chemical Society, copyright 2015.

2.5.2. Supramolecular responsiveness. In the context of the present review, the "blue box" is the archetypical example of a macrocyclic-based MS, able to translate its stimuli-responsiveness from the molecular to the supramolecular level. Since the first report on the responsiveness of the G⊂ [Ex_0Box^{4+}⇄$Ex_0Box^{2(+•)}$] system (Scheme 8),[103] other "blue box"-based SSs have been extensively explored, and not only within the realm of MISSs.[108] Due to the low potential needed for the first two electron reduction of Ex_0Box^{4+} (*vide supra*), the switching can be conveniently achieved electrochemically,[109-110]or indirectly by photoinduced electron transfer (PET), using a variety of sensitizers.[111-112] Interestingly, a tetrathiafulvalene (TTF)-porphyrin-C_{60} molecular triad, able to form self-assembled monolayers (SAMs) on gold-electrode surfaces, has also been reported to generate a switchable photocurrent capable of fueling the "blue box"-based redox SS (Scheme 8).[113-114] Another more recent example of photoreduction of the tetracationic cyclophane has been reported by Stoddart's lab, achieving in this work a unique supramolecular behavior: the unidirectional threading and dethreading of the host from an appropriately designed dumbbell component (Scheme 8).[115]

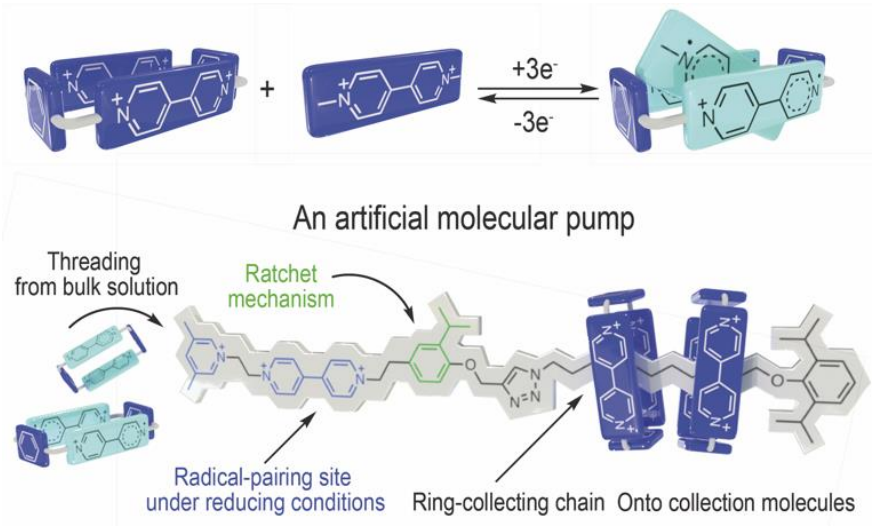


Scheme 8. Top: schematic representation of the classic "blue box"-based SS ED⊂[Ex_0Box^{4+}⇄$Ex_0Box^{2(+•)}$] (exemplified with ED = naphthalene derivative]. Bottom (from left to right): indirect fuelling of the SSs by a TTF-P-C_{60} triad[113-114] (adapted from ref. 114 with permission from John Wiley and Sons, copyright 2007); redox-controlled unidirectional transport of the "blue box" along an asymmetrically-stoppered dumbbell component (adapted from ref. 115 with permission from American Chemical Society, copyright 2013); implementation of the "blue box" as a redox-responsive gatekeeper into mesoporous silica-based nanocontainers (adapted from ref. 118 with permission from American Chemical Society, copyright 2004).

Regarding the implementation of this type of Ex_0Box^{4+}-based SSs into surfaces, it has been reported to work when the host is covalently attached to silica substrates[116] but, conversely,

not when included into gold SAMs.[117] Furthermore, the SS has also been implemented as a gating mechanism into mesoporous silica-based nanovalves.[118-119] For instance, the nanocontainers can be filled with luminescent $Ir(ppy)_3$ molecules by diffusion, and the opening and closing of the channels appropriately operated by pseudorotaxanation, using the "blue box" as a stimuli-responsive gatekeeper (Scheme 8).

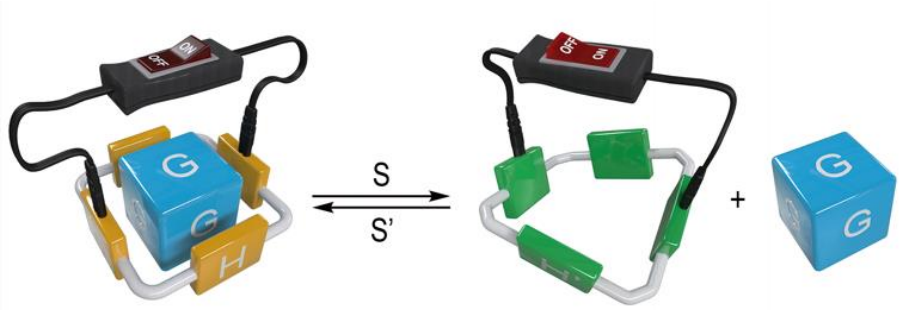
Finally, concerning other potential switching mechanisms for "blue box"-based complexes, the discovery of the enhanced stability of tricationic trisradical inclusion complexes of the type $MV^{+\bullet}\subset Ex_0Box^{2(+\bullet)}$ (Scheme 38),[120] has translated on an increased current interest in the study of $[MV^{2+}\rightleftarrows MV^{+\bullet}]\subset[Ex_0Box^{4+}\rightleftarrows Ex_0Box^{2(+\bullet)}]$ SSs, particularly MISSs.[121] As an example of the potential utility of this new redox-controlled processes involving radical pairing, Stoddart *et al.* have recently reported its implementation on molecular machinery, being able not only to carry out unidirectional movement of the host, but to perform it uphill (Scheme 9). [122-124]



Scheme 9. Top: Schematic representation of the non-standard "blue-box"-based SS: $[MV^{2+}\rightleftarrows MV^{+\bullet}]\subset[Ex_0Box^{4+}\rightleftarrows Ex_0Box^{2(+\bullet)}]$. Bottom: Implementation of the SS into a energetically demanding molecular pump. Adapted from ref. 123 with permission from Macmillan Publishers Limited, copyright 2015.

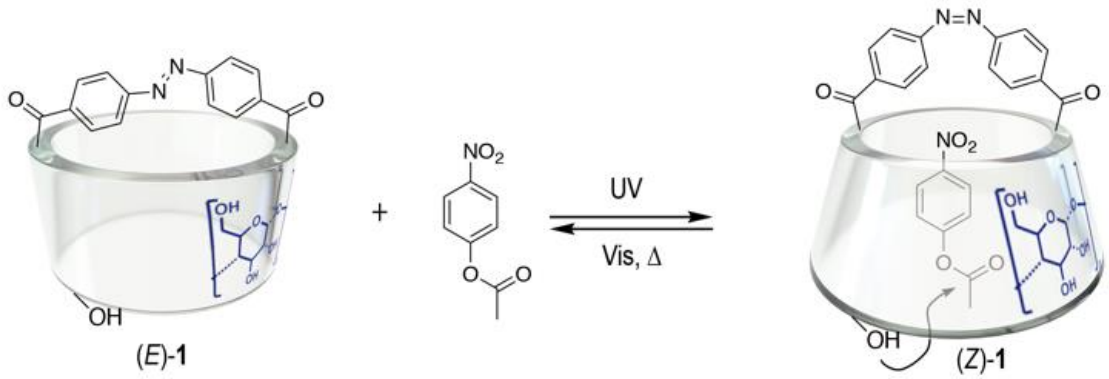
3. Capping of macrocyclic hosts with molecular switches.

As we have shown in the introduction, and besides the remarkable properties of the "blue box" as a stimuli-responsive receptor, the vast majority of the families of classical macrocyclic hosts are inherently non-responsive. Consequently, the most intuitive form of introducing regulated dynamism into those would be its functionalization with MSs. In the capping strategy, we will discuss the conversion of popular macrocycles into bicyclic cryptand-like analogues having a stimuli-responsive arm (Scheme 10). Crucially, this moiety must be attached by at least two positions to the binding site of the host, enabling the efficient transmission of the change in the shape of the MS into the binding site.



Scheme 10. Capping: supramolecular switching by conversion of known macrocycles into stimuli-responsive cryptands.

As long ago as in 1979, Ueno *et al.* reported the development of a CD-based supramolecular switch,[125] a study that latter on would become a paradigmatic example of the capping strategy (Scheme 11). In this pioneering work, the use of an azobenzene moiety (AzB) as the capping moiety of β-CD, results in the photoresponsive cryptand-like host **1**, able to easily switch between the (*E*)- and (*Z*)-isomers of the AzB moiety. Crucially, photoisomerization alters the extent of association produced by the host, with smaller K_a values for selected organic guests in the case of the isomer (*E*)-**1** than those for (*Z*)-**1**. The most extreme example corresponds to 4,4'-bipyridine, since only (*Z*)-**1** is able to bind the guest with a K_a = 4.5 x 10^2 M^{-1}. Furthermore, as a remarkable early example of the potential applicability of SSs, the authors reported the *p*-nitrophenol acetate⊂[(*E*)-**1**⇄ (*Z*)-**1**] system as a case of switchable catalysis.[126] In this work, contextualized on the CD-mediated hydrolysis of esters, the change in geometry upon irradiation of the AzB moiety translates into an alteration of the depth of the hydrophobic pocket of β-CD. Thus, (*E*)-**1** effectively prevents the binding of the model ester in the cavity, which impedes its hydrolysis, whereas the formation of (*Z*)-**1** upon irradiation with 365 nm light results in up to a 5-fold increase in the hydrolysis reaction rate, remarkably, with only a 38% of the (*Z*)-isomer being present in the photostationary state.



Scheme 11. Application of the photoresponsive β-CD-based cryptand **1**[125] for the controlled hydrolysis of esters. Adapted from ref. 126 with permission from The Royal Society of Chemistry, copyright 1981.

Although the interest of professor Shinkai at Nagasaki University, has been primarily focused on the controlled binding of metallic cations more than organic compounds,[127] his research group reported, nearly at the same time as Ueno *et al*, the conversion of 1,10-diaza-18-crown-6 ether into the AzB-containing photoresponsive cryptand **2** (Table 2).[128] The authors found that (*E*)/(*Z*)-**2** showed different affinity towards the ammonium group, with the isomer (*E*)-**2** displaying an increased affinity for a model alkylammonium guest.[129]

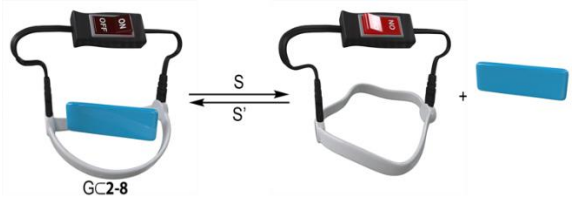
Quite some time later, the extensive work of Stoddart *et al.* on the development of aryl-containing crown ethers for the complexation of organic compounds,[65,130] opened the door for the development of coronand-based SSs. For instance, Huang *et al*,[131] and Yang *et al*,[132] developed similar coronand-based photoswitches **3** and **4**, able to catch and release MVs, a fact related to the enhanced binding affinity of these organic cations, upon photoirradiation of the more compact (*Z*)-isomers of AzB or stilbene moieties (Table 2).

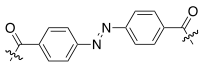
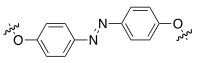
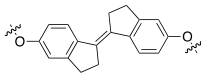
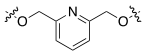
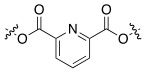
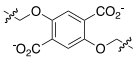
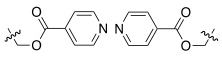
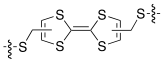
In a similar vein, Gibson *et al.* employed the modification of bis (m-phenylene) crown ethers for the development of pH-responsive cryptands.[133] Consequently, introduction of a pyridine moiety as the capping part of the crown ether results in the pH-responsive cryptand **5a**, able to bind in its neutral form the paraquat dication, and release it upon protonation. As in many other related pH-based SSs, the release of the guest is produced because of electrostatic repulsions between the charged binding site and the cation. Analogous results were obtained with similar cryptands **5b** and **6** (Table 2), all of them having ionizable moieties capable of regulating the binding of MVs by modulation of the electrostatic interactions.[134-136]

Control over the accessibility to the binding site of crown ethers can be achieved as well by the controlled self-assembly of pseudocryptand structures, as described by Huang *et al*.[137] Taking advantage of two pyridines as pendant groups, those arrange in the pseudocryptand **7**, which complexes a MV derivative in acetone with K_a = 9.6 x 10^2 M^{-1}, circa 8 times the value obtained for the corresponding crown ether without the pyridine pendants. Protonation of those moieties on the receptor produces a large positive electrostatic barrier, which hampers the inclusion of the organic salt on the nested polyether zone of the cryptand-like structure (Table 2). Some of the authors have reported that removal of carbonyl groups in **7** results in a receptor able to bind paraquat but, interestingly, not able to release it upon protonation.[138]

Finally, redox-responsiveness has also been reported for bis (*m*-phenylene) crown ether derivatives, based on the increased electrostatic repulsions between the oxidized form of the host and a cationic guest. In particular, Wang *et al.* synthesized the redox-responsive TTF-containing tricycle **8** by introducing the redox-responsive moiety as the third arm of bis(*m*-phenylene)-32-crown-10.[139] The host exhibited on/off binding abilities to MVs, which are controlled by selective chemical oxidation and reduction of the TTF moiety, apparently without altering the redox-responsive guest (Table 2).

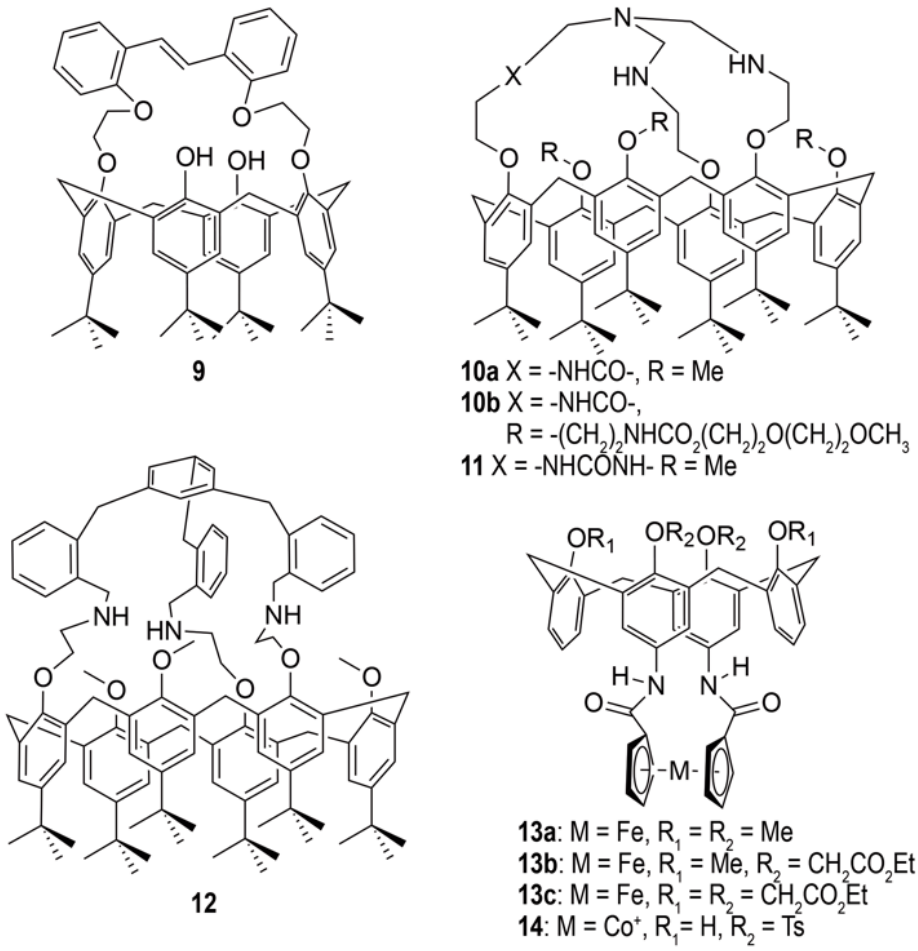
Table 2. Catch and release of organic salts by switchable (pseudo)cryptands.



	Molecular switch	Coronand	Guest	Stimulus	Ref.
2		Diaza18C6[1]	AM[2]	light	129
3		BMP32C10[1]	MVs[3]	light	131
4		BMP32C10[1]	MVs[3]	light	132
5a		BMP32C10[1]	MVs[3]	pH	133
5b		BMP32C10[1]	MVs[3]	pH	136
6		BMP32C10[1]	MVs[3]	pH	134
7		BMP32C10[1]	MVs[3]	pH	137
8		BMP32C10[1]	MVs[3]	e^-	139

[1]BMP = bis(*meta*-phenylene), [2]AM = ammonium salt, [3]MVs = viologen derivatives.

Capping of CX[n]s has been used as well by different authors aiming for switchable ionophores (Scheme 12). For instance, the stilbene-containing CX[4] derivative **9**,[140] is not able to complex alkali cations, but instead behaves as a partial SS with small organics of the likes of acetonitrile or nitromethane, preferring to complex the neutral molecules on its more compact (*Z*)-form. By expanding the size of the cavity to CX[6] analogues, Jabin *et al.* reported similar pH-responsive cryptand-like compounds termed calix[6]cryptamides (**10a-b**),[141-142] calix[6]cryptoureas (**11**),[143] and calix[6]azacryptands (**12**).[144] Similarly, redox-responsiveness was also reported for CX[4] derivatives containing amide ferrocene (Fc) units at the wide rim (compounds **13a-c**),[145] with the oxidized metallocene having increased affinity for carboxylates as anionic guests due to increased electrostatic interactions. Similarly, Beer *et al.* reported analogous results for the cobaltocenium (Cc^+) derivative **14**.[146]

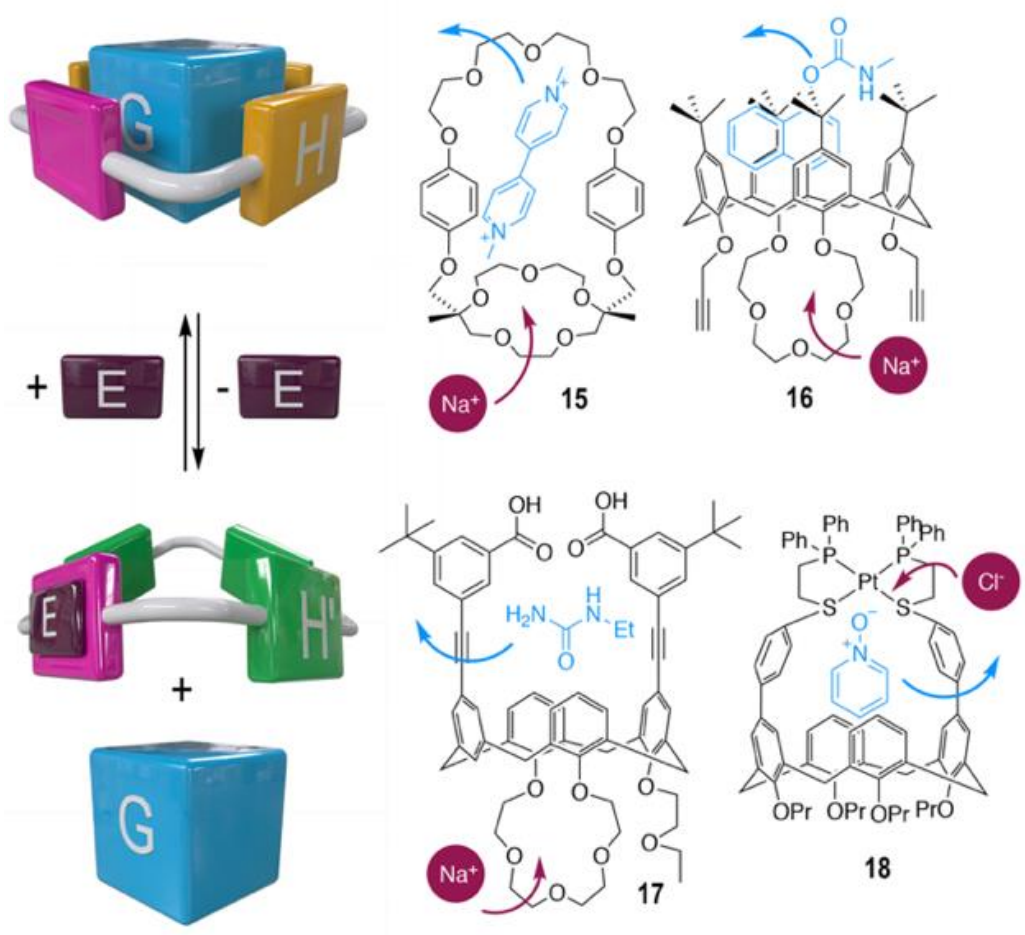


Scheme 12. Examples of capped switchable calix[n]arenes.

Concerning the use of the capping strategy for the development of allosterically regulated hosts, Muraoka *et al.* designed the cryptand **15**,[147] having two different crown ether moieties merged: a primary binding site having electron-rich HQ moieties for the complexation of paraquat, and a secondary allosteric site for the complexation of Na^+ (Scheme 13). The binding of the organic substrate is regulated by the alkali cation, which causes the expulsion of the organic guest from the primary site because of the appearance of electrostatic repulsions. A related example, reported by Li *et al*,[148] uses the CX[4]-crown ether chimera **16** for the controlled release of the pesticide carbaryl, a guest having a naphthalene group able to interact with the CX[4] moiety through π-π interactions. In this case, the primary and secondary binding sites do not share similar binding preferences, so the allosteric regulation is due to a stretching of the CX[4] binding site produced upon complexation of the effector.

Fukazawa *et al.* reported a similar derivative (compound **17**, Scheme 13), with the binding site not located within the annulus of the calixarene.[149] Here, the macrocycle rather serves as a convenient structural scaffold, allowing the installation of a crown-ether-based allosteric site on the lower rim, and two benzoic acid moieties on the upper rim as the primary binder motifs. As for **16**, the conformation of the primary site in **17** is controlled by using Na^+

addition or removal. Nevertheless, the alkali cation acts in this case as a positive heterotropic effector, producing an enhanced binding of the corresponding ureas used as guests (e.g. 29-fold increase for 1-ethylurea).



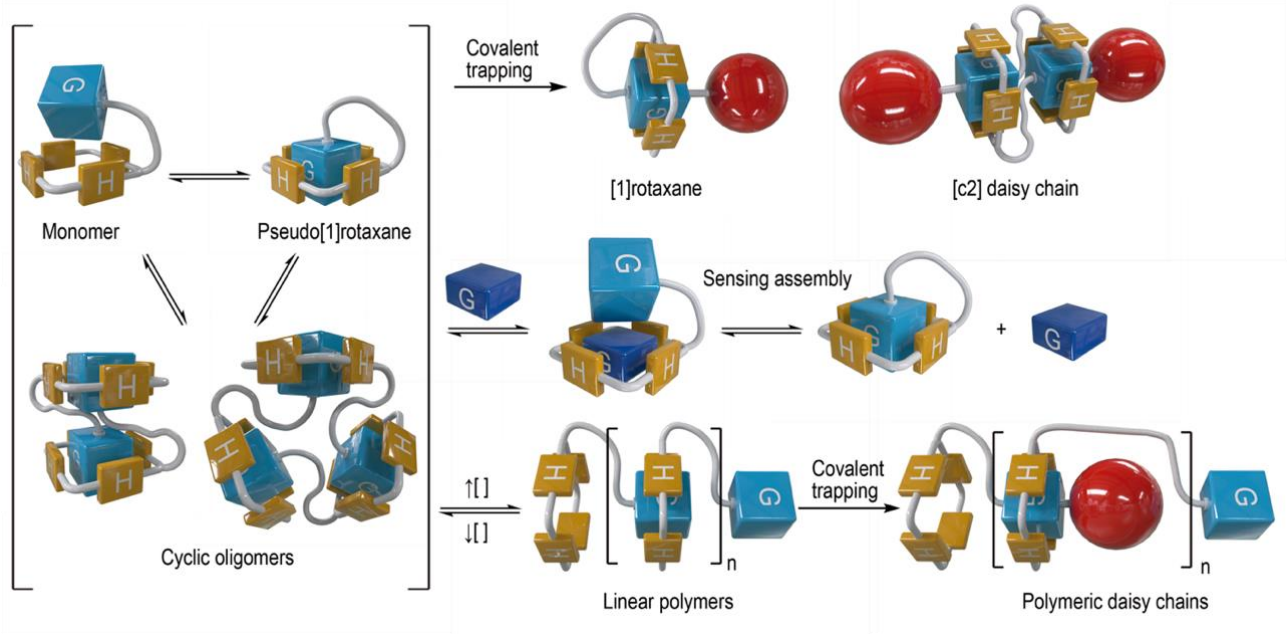
Scheme 13. Examples of allosteric SSs based on the capping strategy.[147-150]

Finally, in an interesting example of synergy between coordination and host-guest chemistry, Mirkin *et al.* have developed the coordination-controlled switchable calixarene **18** (Scheme 13).[150] In this compound, a CX[4] moiety serves as a primary binding location, being capped with an allosteric site on the upper rim composed of hemilabile phosphine alkyl thioether ligands (P,S) chelated to a Pt(II) centre. The environment at this regulatory Pt(II) centre dictates the charge and structural conformation of the entire assembly, resulting in three accessible configurations: a closed inactive state and two open, active states. One of the active arrangements, the semi-open state, recognizes pyridine *N*-oxide as a neutral model guest, which is conveniently captured and released by switching the receptor between the closed and semi-open configurations using Cl^- as an effector.

4. Molecular cannibalism: appending MSs to macrocyclic hosts.

4.1. Dynamic behavior of pseudo[1]rotaxanes.

Molecular architectures consisting of a macrocyclic host covalently attached to a guest through a linker, are intrinsically interesting for many reasons (Scheme 14). Firstly, host-guest aggregation can be produced intermolecularly with the species acting as classic examples of *AB*-type heteroditopic monomers, which are able to form cyclic or linear supramolecular oligomers/polymers via host-guest self-recognition.[151] On the other hand, intramolecular association can take place leading to self-inclusion, which in turn has interest on its own (i.e. producing intermediates upon the construction of [1]rotaxanes[152] and interlocked daisy chains,[153]or as macrocycle/dye conjugates in indicator displacement assays for analyte sensing[154]). In this section, we will show how reversible stimulation can be conveniently used in this type of systems to regulate the cannibalistic behaviour at the molecular level, and used in turn for the controlled binding of external organic guests by the macrocycle. Consequently, different situations would be analysed, namely, stimulation of MSs located on the host, internal guest or linker parts of the pseudo[1]rotaxane structure.

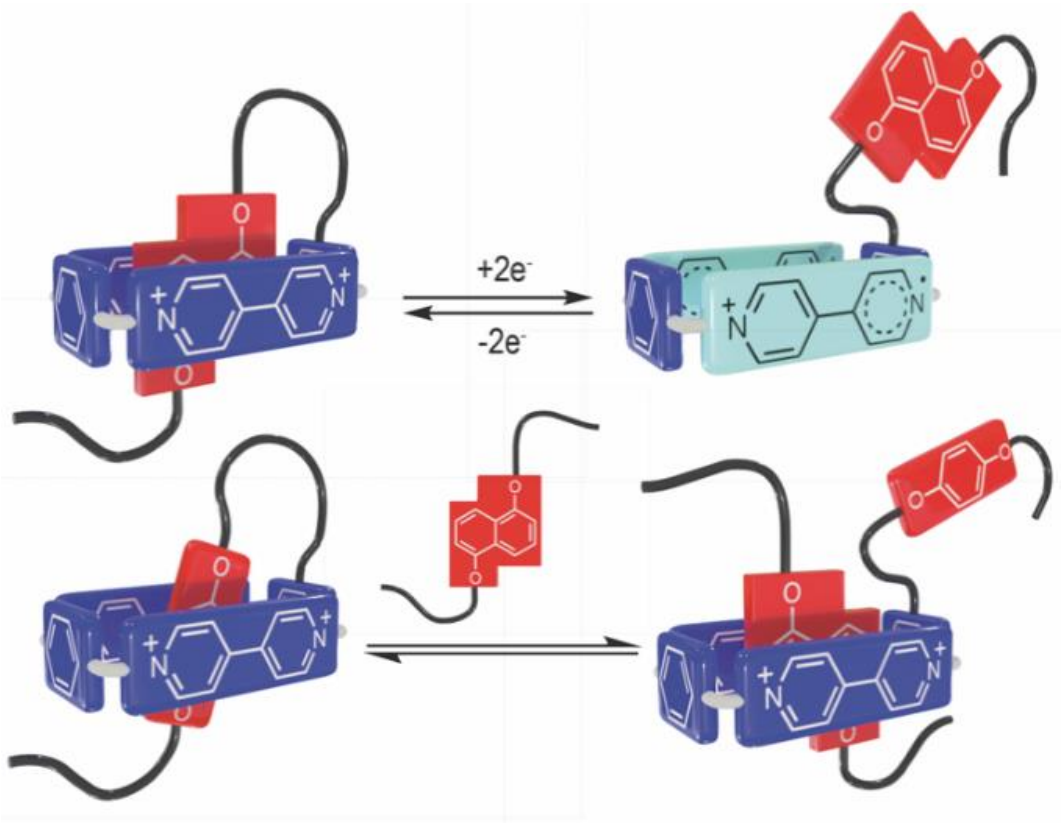


Scheme 14. Dynamic behaviour and applicability of covalently attached host-guest molecules.

4.2. "Blue box"-based pseudo[1]rotaxanes.

As in many other aspects of the development of modern supramolecular chemistry, Stoddart *et al.* soon realized the potential of pseudo[1]rotaxanes, in particular, those involving the unique responsiveness of the "blue box". In two seminal communications published in 1997, Stoddart's lab reported the synthesis of a series of scorpion-like inclusion complexes, structures comprising the "blue box" attached through an appropriate linker to aromatic EDs

(Scheme 15).[155-156] Two important observations were made; the corroboration of the expected redox-responsive nature of these molecules, and the possibility of exchange between the internal and external guests disrupting self-complexation. Because of these observations, the authors wrote: "*Our next goal will be the construction of a reversible system in which the complexation will be switched off and on again when it is perturbed by some external stimuli which could be either chemical, electrochemical or photochemical in nature*."[156]Nevertheless, a number of other "blue box"-based pseudo[1]rotaxanes have been reported over the years but, to the best of our knowledge, none has been implemented in the anticipated controlled binding of external guests,[157-161] which can be potentially achieved at least on the particular case of the redox-controlled catch and release of MVs assisted by radical pairing (see section 2.5.2).

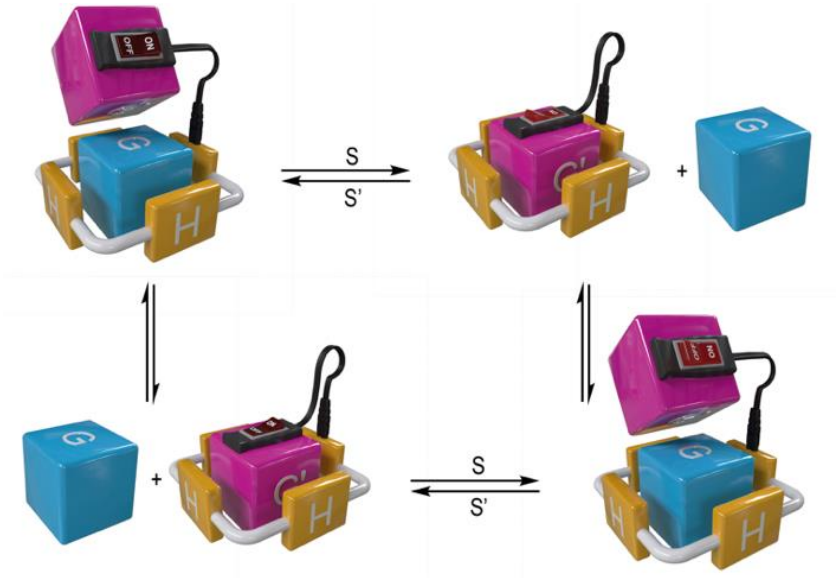


Scheme 15. Examples of "blue box"-based pseudo[1]rotaxanes showing: redox-responsiveness (adapted from ref. 155 with permission from John Wiley and Sons, copyright 1997) (top); exchange between internal and external guests (adapted from ref. 156 with permission from Elsevier, copyright 1997) (bottom).

4.3. Molecular switches as internal guests.

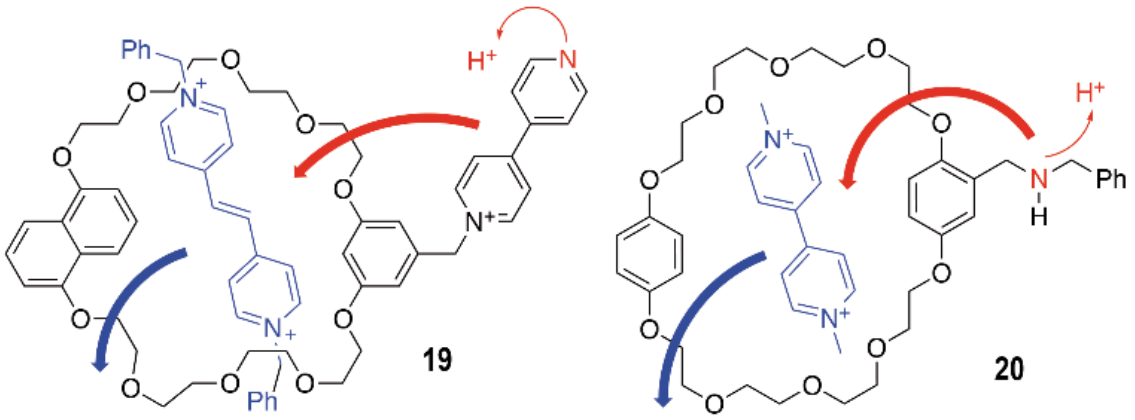
In contraposition to the capping strategy, the exocyclic group in stimuli-responsive pseudo[1]rotaxanes would have the potential not only to work as an MS-based control moiety but, being attached to the macrocycle through only one position, the pendant would also be able to act as an appropriate responsive internal guest. In that fashion, stimulation of this group can be used to lock the dynamism by a gating mechanism, which hampers the

accessibility to the binding site of a given external substrate. In other words, the switching mechanism is not produced by the transmission of a change in shape on the MS to the binding site, but rather by opening or closing the access to the binding site by regulated self-complexation (Scheme 16). This situation would imply, a priori, a potential inherent drawback on the subsequent SS. As the binding site of the macrocycle is not affected by the external stimulation, the efficiency of the SS would directly depend on the different affinities between the binding site and three different guests: the basal and stimulated forms of the internal guest and the static external substrate.



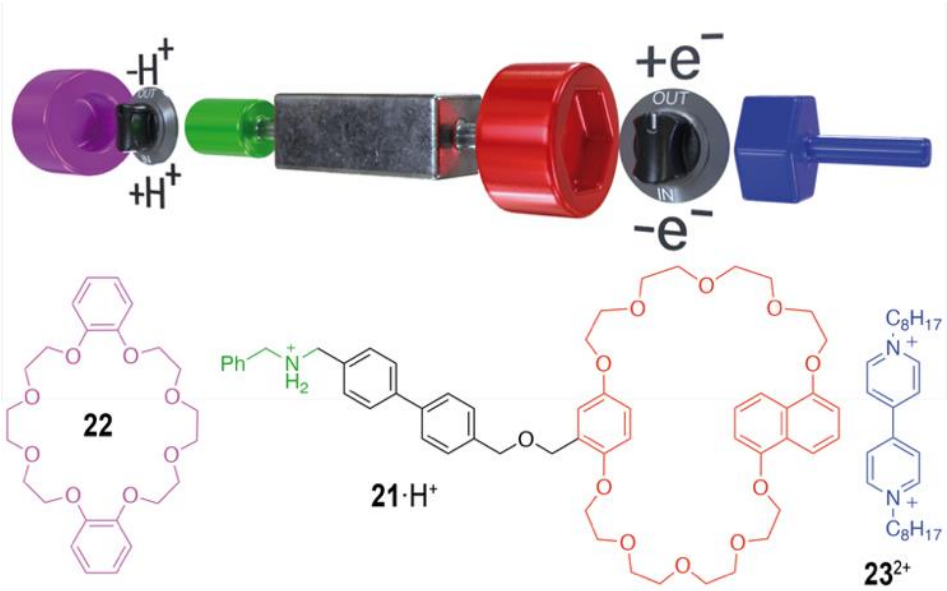
Scheme 16. Supramolecular switching by a guest-induced gating mechanism.

A very simple example of this type of controlled binding using crown ether derivatives was reported by Balzani, Stoddart *et al*, who used the pH-responsive macrocycle **19**, for the controlled binding of a MV (Scheme 17).[162] **19** is composed of a macrocyclic polyether with 1,5-dioxynaphthalene and 1,3-dioxybenzene ED units, with the latter moiety bearing a covalently linked 4,4'-bipyridinium monocationic tail. Upon protonation of the remaining N atom of the pendant with trifluoroacetic acid, the electron deficient moiety is self-included within the cavity of the crown ether, and conveniently excluded upon addition of tributylamine as a base. This pH-based MS could be satisfactorily translated to the supramolecular level, using *trans*-1,2-bis(1-benzyl-4-pyridinium)ethylene as an external guest. More recently, Chen *et al.* reported a very similar SS for the complexation of paraquat.[163]In this case, the bis (*p*-phenylene)-34-crown-10-based macrocycle **20** (Scheme 13), bearing a dibenzylamine side arm, forms a sailboat-shaped self-complex, in which the arm of the substituted macrocycle sticks into the cavity of the coronand only when the amine is protonated.



Scheme 17. Crown ethers used on pH-based SSs by a guest-induced gating mechanism.[162-163]

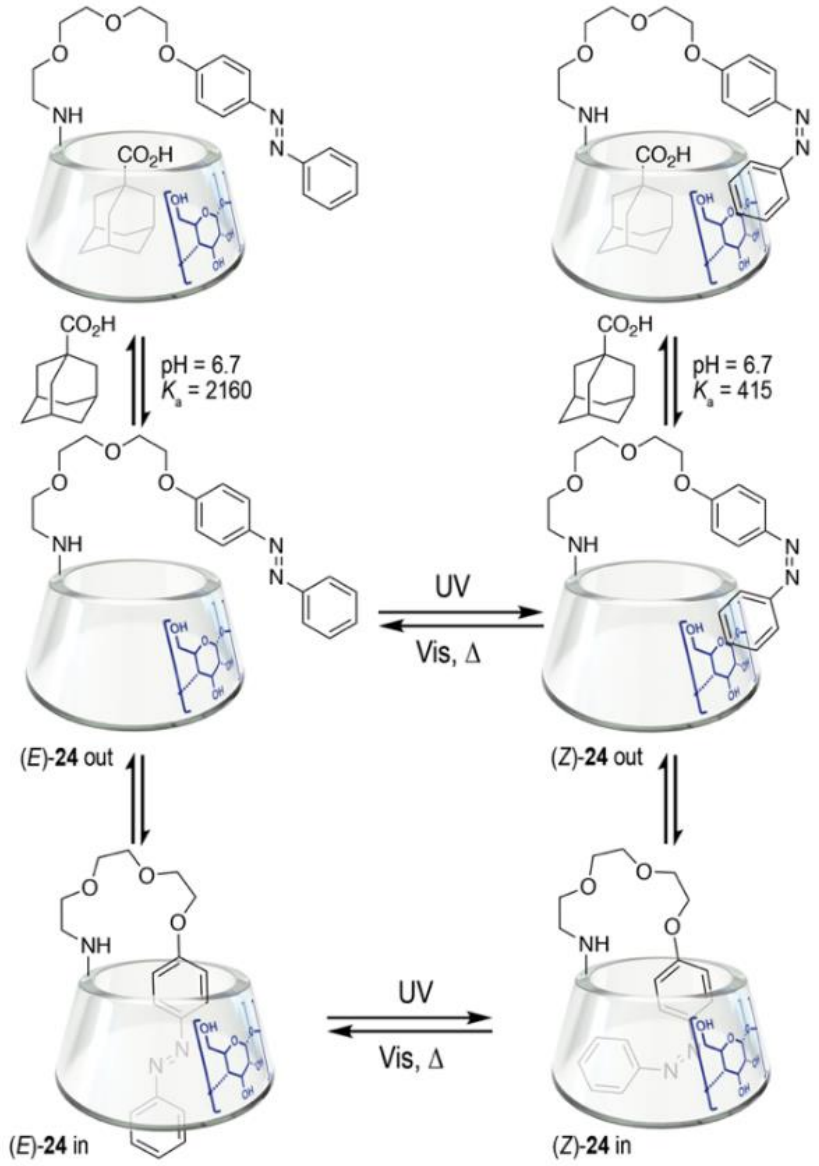
In an impressive example of implementation of this type of self-complexing crown-ethers into more sophisticated systems, Stoddart *et al.* reported its utilization on the development of "supramolecular plug-socket connectors" (Scheme 18).[164-165] For instance, using the coronand-based pseudo[1]rotaxane **21**·H^+ as a molecular extension cable, control over the two connections on the ternary complex **23**$^{2+}$⊂**21**·H^+⊂**22** can be achieved by acid-base means [**23**$^{2+}$⊂**21**·H^+⊂**22**⇄**21** + **22**⊂**23**$^{2+}$], or electrochemically [**23**$^{2+}$⊂**21**·H^+⊂**22**⇄**23**$^{+\bullet}$ + **21**·H^+⊂**22**].[165]



Scheme 18. A supramolecular plug-socket connector. Adapted from ref. 165 with permission from the American Chemical Society, copyright 2007.

Concerning cyclodextrins, and as in the case of the capping strategy, Ueno *et al.* reported an early example of the guest-induced gating strategy, describing a SS based on the *exo*-functionalization of β-CD with an AzB moiety (Scheme 19).[166] UV irradiation of compound

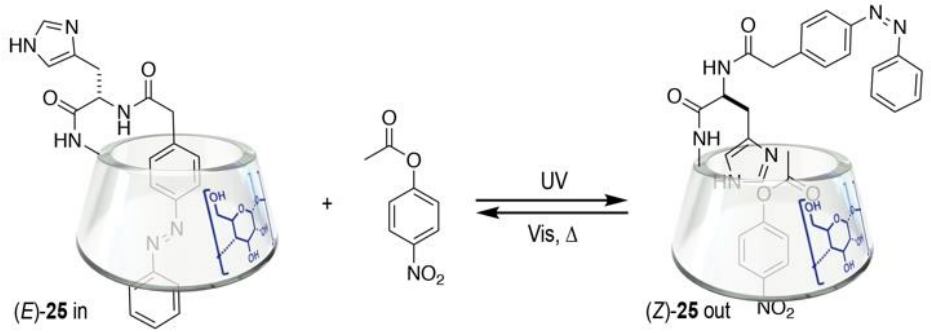
24 efficiently promotes (*E*) to (*Z*) isomerization of AzB, with visible light reverting the process. Although the structural change of the internal guest upon photoisomerization is not large enough, so both the (*E*)/(Z)-isomers form self-inclusion complexes, the gating mechanism still produces significantly different association constants for both forms of the receptor with selected external guests, such as adamantane (AD) derivatives.



Scheme 19. β-CD functionalized with a photoresponsive AzB moiety. Adapted from ref. 166 with permission from The Royal Society of Chemistry, copyright 1990.

Considering similar AzB-appended β-CDs, Ma *et al.* employed those for the photocontrolled complexation of the typical phosphor *α*-bromonaphthalene (*α*-BrNp).[167] Based on the different binding affinities of the three potential guests ((*E*)-AzB > α-BrNp > (*Z*)-AzB), the authors describe the translation of the photocontrolled host-guest system optical output into a chemical INHIBIT logic gate. Partial photocontrolled supramolecular switching has been

obtained as well with AzB-modified γ-CDs,[168-169] which in turn have been subjected to covalent immobilization on silica particles for their use as photoresponsive stationary phases in micro-HPLC.[170]

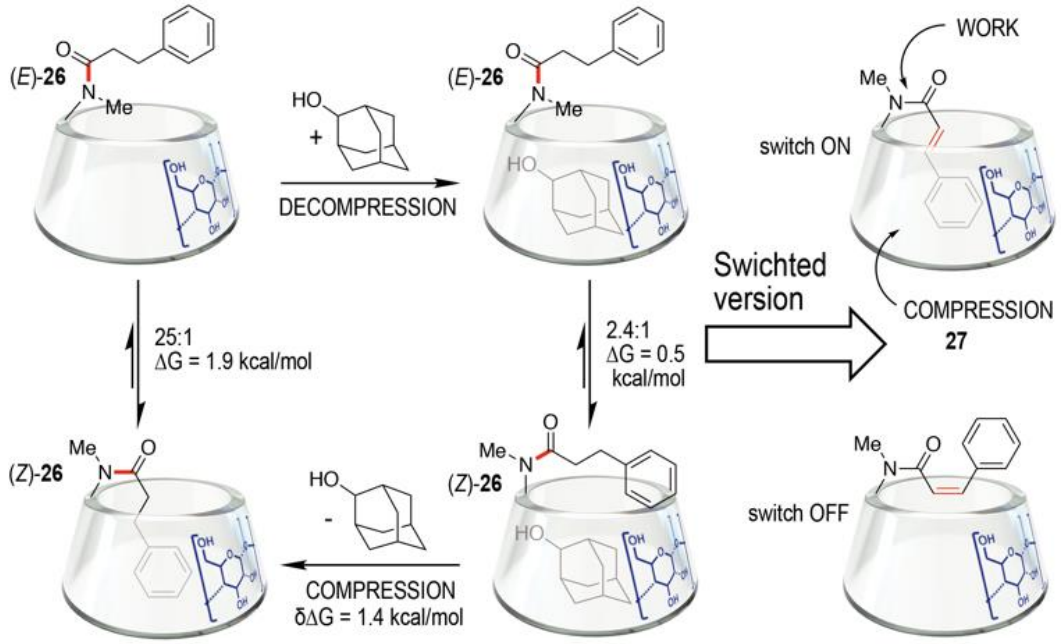


Scheme 20. Photocontrolled ester hydrolysis catalysed by an AzB-appended β-CD. Adapted from ref. 171 with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, copyright 2001.

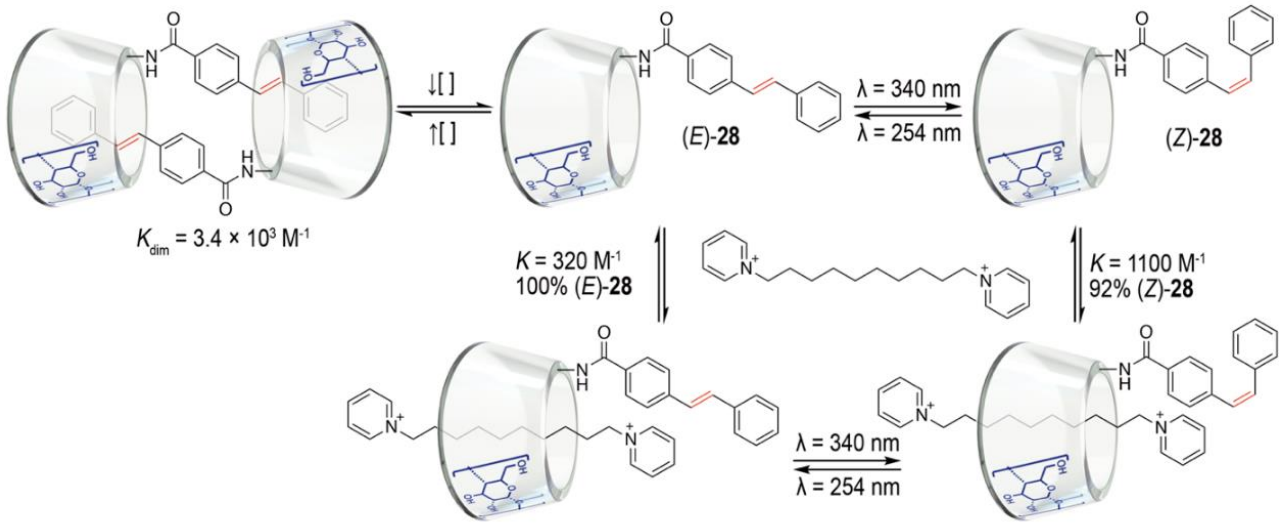
An example reported by Ueno's group also demonstrates the potential applicability of this type of photoresponsive *exo*-functionalized CDs in the field of supramolecular catalysis.[171] In this case, scorpionane **25**, a linker-modified version of the β-CD analogue **24**, was explored for the photocontrolled imidazole-catalysed hydrolysis of esters. In compound **25**, an imidazole group was attached to an AzB-based pendant, in a way that the catalytic moiety is available to the active site of the host only once the (*E*) to (*Z*) isomerization is produced. In consequence, (*E*)-**25** cannot act as an effective catalyst as no substrate can be included in the host cavity because of the tight self-inclusion of the (*E*)-AzB moiety (intramolecular inhibition). Conversely, (*Z*)-**25** acts as an effective catalyst in the hydrolysis of a *para*-nitrophenyl ester, with the binding site being available for the insertion of both the substrate and the catalytic heterocyclic moiety, which is properly oriented towards the substrate (Scheme 20).

Another quite interesting example of applicability for β-CD-based pseudo[1]rotaxanes is the molecular pumps developed by Easton and co-workers (Scheme 21).[172] The first prototype of the nanomachine comprises an *N*-methyl-3-phenylpropanamido pendant as piston, connected to a β-CD moiety as the cylinder molecule **26**, which is fuelled by inclusion of 1-adamantanol (AD). The compression and decompression strokes involve the binding processes of the amide (*Z*)-isomer with AD, and the amide (*E*)-isomer with AD in a reverse sequence, with the difference in the binding-free energies being the work generated by and stored within the engine.[173-174] As discussed by the authors, a more refined version of the engine can be envisaged, one that can be reversibly switched off and on, just by introducing a photoisomerizable double bond on the propanamide moiety within compound **27**. In this case, the on/off states are regulated by the isomerization of the *N*-methylcinnamide moiety,

as the (*Z*)-form of the pendant is unable to self-include within the cavity of the β-CD, precluding in that manner the compression stroke.



Scheme 21. Representation of the β-CD-based nanopump and its photoswitched version. Adapted from ref. 172 with permission from the American Chemical Society, copyright 2006.

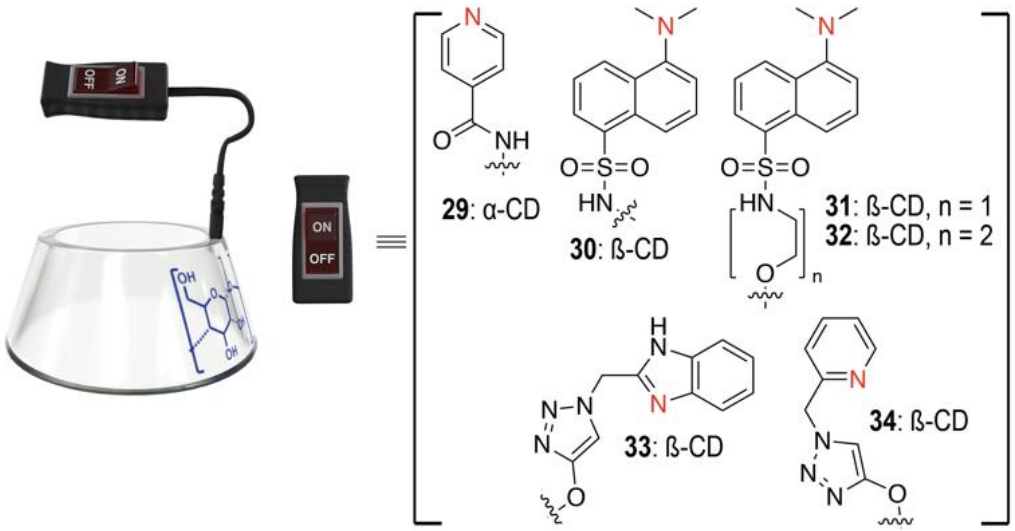


Scheme 22. Partial gating of α-CD by photocontrolled (*E*) to (*Z*) isomerization of a stilbene moiety. Adapted from ref. 175 with permission from American Chemical Society, copyright 2011.

As previously discussed, self-inclusion is only one of the dynamic possibilities that covalently-attached host-guest systems can display, as exemplified by Harada *et al.* on the photocontrolled system based on α-CD **28** (Scheme 22).[175] In **28**, a rigid stilbene moiety is

directly attached to α-CD through an amide bond. By doing so, the formation of pseudo[1]rotaxane is always precluded, but instead the system is more prone to form dimeric Janus [2]pseudorotaxanes with increasing concentrations of the monomer. The authors showed a quite significant difference in the complexation behaviour of the modified host and a dipirydinium-based axel as the guest, as photoisomerization conveniently precludes molecular cannibalism.

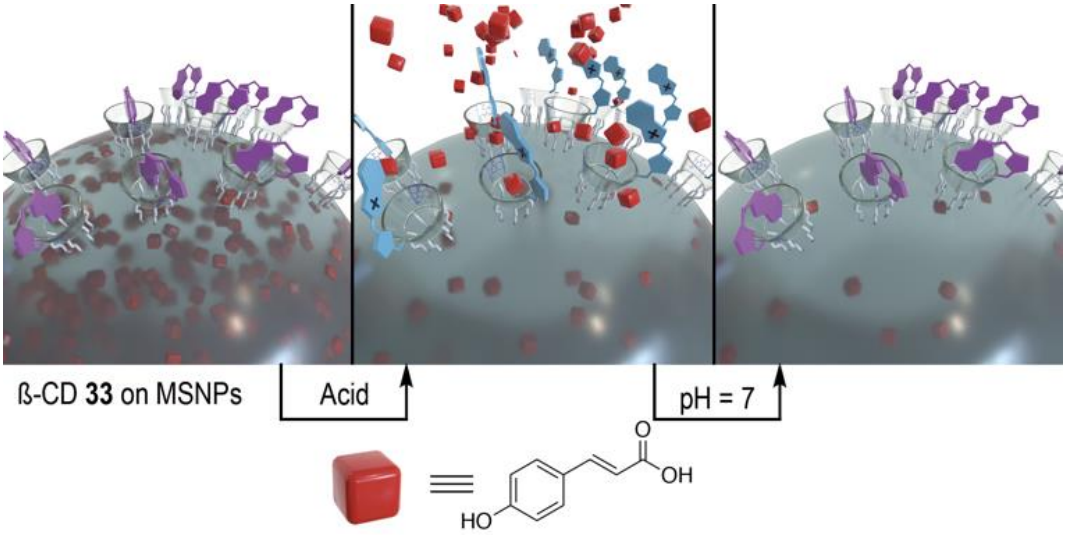
Interestingly, the authors have also described the pH-controlled complexation of the same external guest, simply modifying α-CD by the replacement of the stilbene moiety attached to the macrocyclic core by a pyridyl-pendant (compound **29**, Scheme 23).[176] In this occasion, the differences in binding between the acid or basic forms of **29** are attributed to the obvious electrostatic repulsions between the external/internal guests upon protonation. In a similar example, Feiters and co-workers prepared a series of β-CDs bearing a dansyl group pendant (compounds **30**-**32**),[177] finding different (self)-complexation behaviours of the hosts in water depending on the protonation state of the dimethylamine moiety.



Scheme 23. Base-appended CDs used in SSs.[176-179]

pH-Responsive CD-based self-inclusion complexes have been used by Fu *et al*., in the construction of nanocontainer-based SSs for the controlled release of drugs.[178] Specifically, the authors designed the mono-benzimidazole functionalized β-CD **33** (Schemes 23 and 24), which was found to be able to reversibly block the macrocycle's cavity upon protonation/deprotonation of this responsive aromatic pendant. Implementation of the host-based MS **33** as nanovalves into mesoporous silica nanoparticles (MSNPs) loaded with *p*-coumaric acid, produces pH-responsive particles able to release their cargo upon stimulation. A similar approach, using the pyridine-functionalized β-CD **34** (Scheme 23), has been used by the same research group for the release of cinnamaldehyde as cargo.[179]

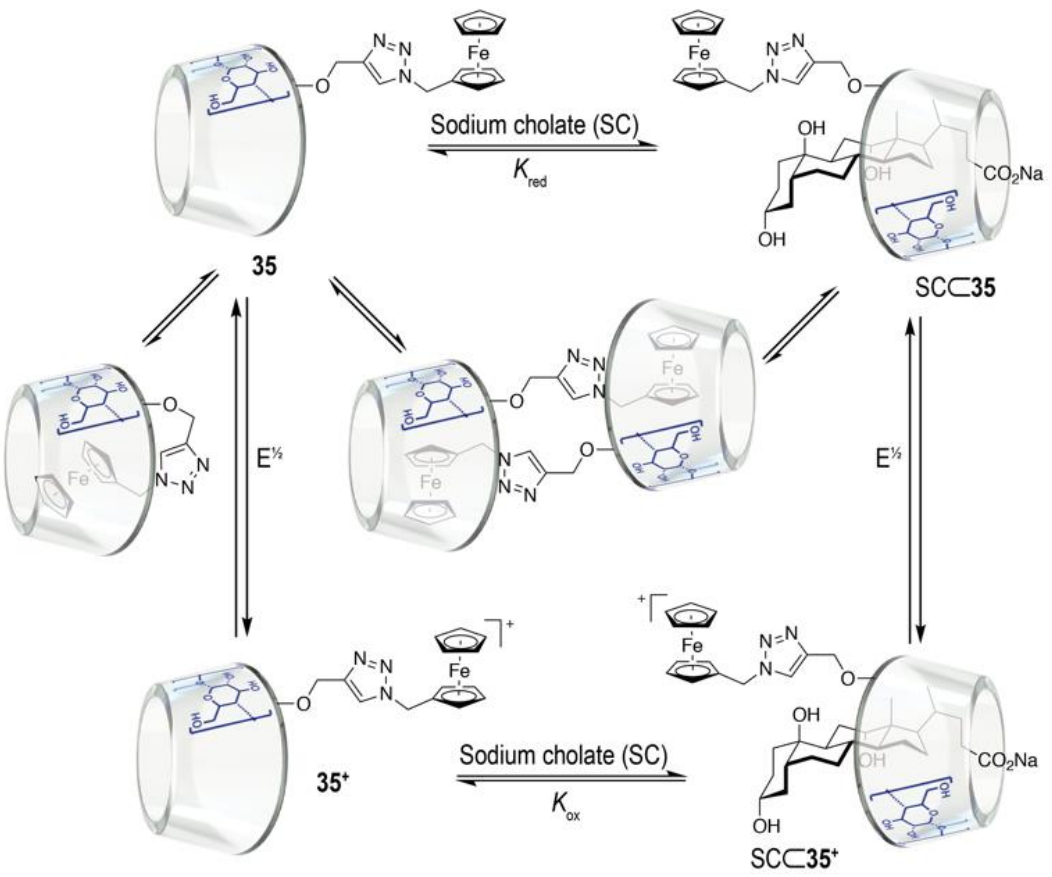
Finally, this type of MSNPs β-CD-based nanogates have also been reported for the release of different cargos.[180-181]



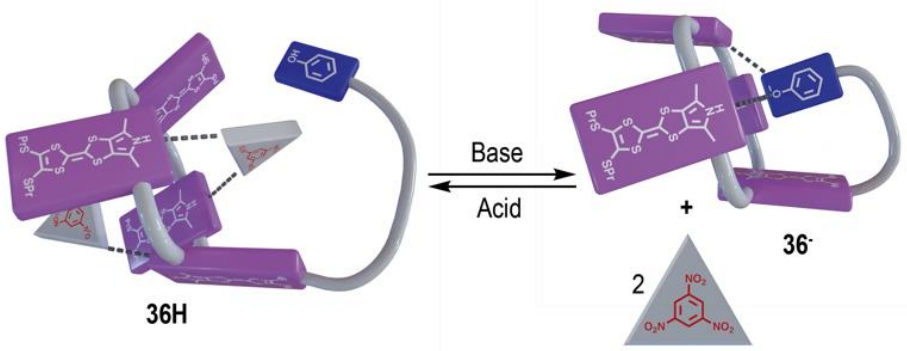
Scheme 24. Benzimidazole-appended β-CD **33** as pH-responsive nanovalves within MSNPs. Adapted from ref. 178 with permission from the Royal Society of Chemistry, copyright 2014.

In a related example, concerning in this case redox-responsiveness, Vargas-Berenguel *et al.* designed the Fc-β-CD conjugate **35**, which introduces the ferrocene-based responsive pendant on the wider rim of the CD.[182] As shown in Scheme 25, the reduced and oxidized forms of **35** showed different self-association behaviours. It was found that the conjugate forms a redox-controllable head-to-head Janus [2]pseudorotaxane, in equilibrium with a monomeric form in which the Fc moiety is intramolecularly self-included within the β-CD cavity. By contrast, only one distinguishable form of the oxidized state of the conjugate is detectable in aqueous solution, corresponding to the Fc^+ cation posed outside the cavity of the host. This difference between the reduced and oxidized forms of the receptor was used by the authors for the detection of bile salts, which have higher association constants with the oxidized form of the electroactive conjugate, as analysed on the basis of the half wave reduction potentials for the compound without ($E_{1/2}$) and with ($E^{O}_{1/2}$) the guest.

Finally, Nielsen *et al.* reported on the use of an asymmetric self-complexing tetraTTF-CP[4] cavitand for the acid/base-controlled complexation of 1,3,5-trinitrobenzene (TNB).[183] The receptor **36H** is composed of three identical TTF units and a fourth appended with a phenol moiety, which allows swapping between locked and unlocked states of the host by using base or acid as the inputs. In the unlocked state, the receptor is able to accommodate two TNB guest molecules, whereas these external guests are not able to bind to the host in the locked state (Scheme 26).



Scheme 25. A Fc-β-CD conjugate as a SS and its application in the sensing of SC. Adapted from ref. 182 with permission from John Wiley and Sons, copyright 2009.



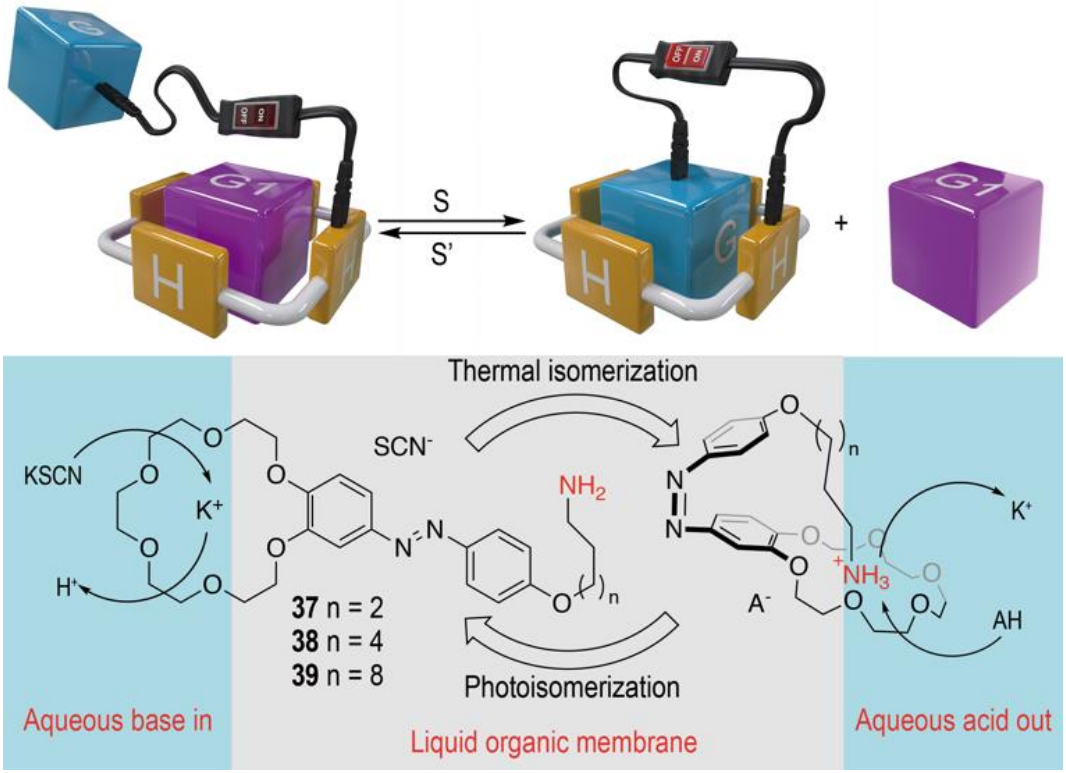
Scheme 26. Controlled self-inclusion for the catch and release of TNB. Adapted from ref. 183 with permission from John Wiley and Sons, copyright 2011.

4.4. Molecular switches as stimuli-responsive host-guest linkers.

In opposition to the examples discussed in the previous section, that imply transient modification of an internal guest attached to the macrocyclic host, external stimulation can also be performed on the linker part of the pendant. In that fashion, the approach of the internal guest to the binding site of the receptor can be precisely controlled by the geometry of the attachment (Scheme 27). This type of linker-induced gating mechanism renders

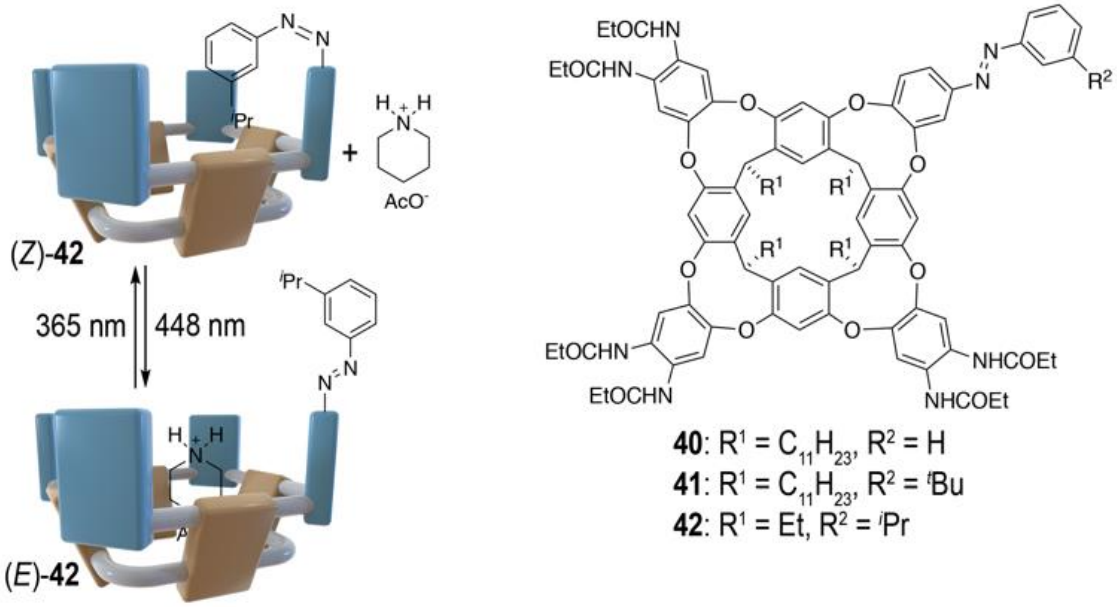
locked in/out states of the binding site independent of the static internal guest, so competition is restricted between the external and internal substrates.

A seminal illustration of this type of assembly was reported by Shinkai *et al*, reflecting how a careful design of the linker-based MS can translate into a SS.[184] Even though the responsive host is eventually used for the controlled binding of metallic cations and not organic substrates, this example is worth mentioning because of its intrinsic beauty and design value. In this work, appropriate alkylammonium groups are attached though an AzB-based linker to a benzo crown ether, leading to compounds **37-39** (Scheme 27). In acidic aqueous media, and upon (*E*)- to (*Z*)- photoisomerization, the compounds were found to self-complex (or "self-bite") because of the adequate positioning of the ammonium tail relative to the binding site of the coronand on the (*Z*)-isomer. This "molecular autosarcophagic" behaviour reflects the relative affinities of the isomers for alkali-metal cations, with the binding being significantly reduced upon UV-Vis light irradiation. The result was found to be especially noticeable for the larger analogues **38** and **39**, which showed almost no metal-binding ability in their (*E*)-forms. Furthermore, the authors used this significant difference in the metal binding ability to produce light-controlled passive or active ion-transport of ions across a liquid membrane. Another example worth mentioning, and conceptually related to that of Shinkai, was reported by Feringa *et al*, using the acid-base controlled self-complexation to unlock or lock a molecular rotary motor.[185]



Scheme 27. Top: Supramolecular switching by a linker-induced gating mechanism. Bottom: Schematic representation of K^+ transport by photoinduced intramolecular complexation in **37**-**39**. Adapted from ref. 184 with permission from The Royal Society of Chemistry, copyright 1985.

Moving our attention to the controlled binding of organic molecules as guests, Rebeck's group has reported three structurally related RA[4]-based cavitands (**40**-**42**, Scheme 28).[186-187] The more significant difference in these compounds is the substitution on one of the phenyl groups with an AzB moiety, installed within the four walls of RA[4]. These three compounds are a nice example of the subtleties implicit to a good molecular design, as only compounds **40** and **41** are able to translate the molecular photoresponsiveness into a supramolecular switching behaviour. That is nicely illustrated by comparing the behaviour of **40** and **41**, which displayed very similar association constants in their (*E*)-forms with AD derivatives as guests. Nevertheless, only **41** acts as a SS in the AD⊂[(*E*)-**41**⇄(*Z*)-**41**] system, with the photoisomerization of the AzB moiety producing the complete ejection of the guests from the cavity of the host.

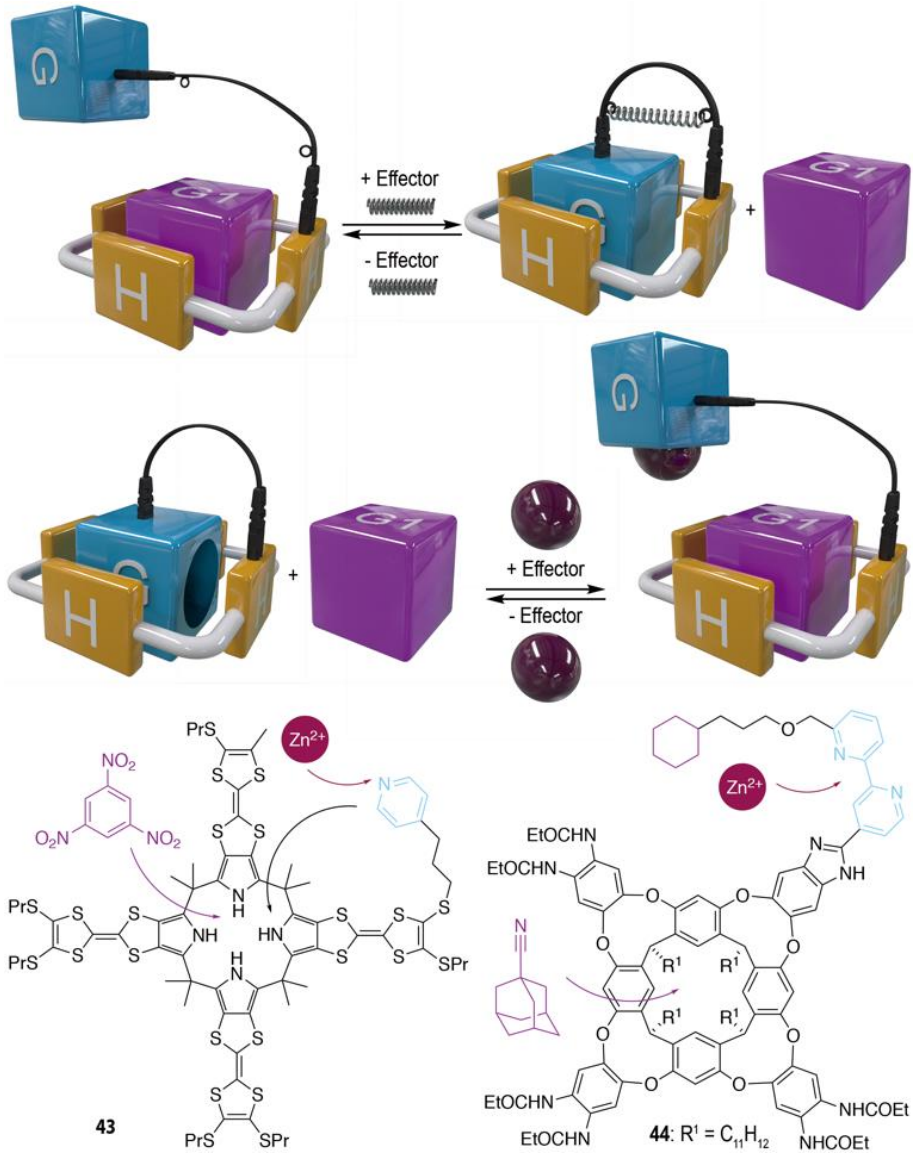


Scheme 28. Right: Structure of cavitands **40**-**42**.[186-187] Left: Photocontrolled switchable Knoevenagel catalysis. Adapted from ref. 187 with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, copyright 2011.

In the case of **42**,[187] it was used for the light-controlled encapsulation of the piperidinium cation (PPH^+) as organocatalyst of the Knoevenagel condensation (Scheme 28). In the (*E*)-state, the cavitand binds to the catalyst and, surprisingly, accelerates the rate of the reaction between malononitrile and aromatic aldehydes, producing up to a 3.5-fold increase in reaction rate compared to the process carried out with PPH^+ alone. Conversely, photoisomerization generates the (*Z*)-isomer of the host inducing self-complexation, releasing the PPH^+ catalyst out of the binding site, and inhibiting the reaction slightly. Based on NOESY analysis, the authors postulated that the ammonium group of the PPH^+ cation within PPH^+⊂[(*E*)-**42**] protrudes from the open end of the cavitand, easing the catalytic activity. As the substrates are not guests in the complex, a wide range of aldehydes are tolerated as substrates for the catalysed condensation reaction.

4.5. Allosteric regulation.

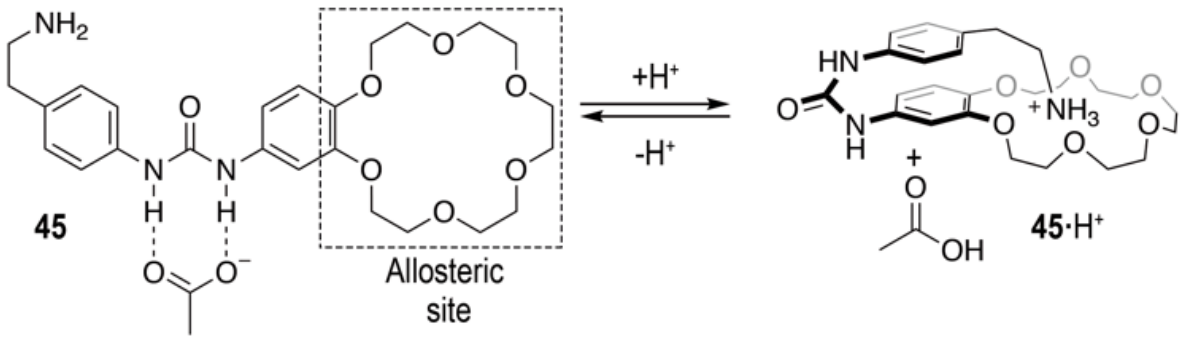
Regarding the allosteric regulation of intrinsic host-guest systems, it has been reported for the two situations discussed in sections 4.2 and 4.3 (i.e. using an "allosteric linker" or an "allosteric internal guest", Scheme 29). Regarding the latter case, Nielsen *et al.* have reported the TTF-substituted CP[4] receptor **43**, appended with a pyridine moiety that acts both as an internal guest and allosteric site.[188] This cavitand shows a self-complexing behaviour in its basal form, with the pyridine ring inserted on the annulus of the host, rendering a highly preorganized receptor able to complex TNB as an external guest. Addition of Zn^{2+} salts produces coordination to the internal guest, and in turn a coordination-induced switching of the receptor into its random conformation, which shows a positive cooperativity with TNB.



Scheme 29. Schematic depictions of allosteric switching stimulation of a linker (top) or internal guest (middle). Examples of SSs showing allosterically controlled self-inclusion (bottom). Adapted from ref. 188 and 189 with permission from John Wiley and Sons, copyright 2013 and Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, copyright 2010, respectively.

On the other hand, Rebek *et al.* reported the development of a SS using the RA[4]-based cavitand **44** (Scheme 29).[189] Here, one of the walls of the host is functionalized with a bipyridyl switching unit linked to a cyclohexyl group as an internal guest. Given that the cavitand has an appropriately large flexible linker, the self-inclusion complex is enthropically favoured, and thus the tethered cyclohexane prevents the entry of external guests. Crucially, Zn^{2+} ions are able to block the bipyridine ligand on a *syn* conformation, which in turn forces a conformational change that pulls the internal guest out of the cavity, leaving it accessible to an AD derivative as external guest. After removal of the metal ion, the initial configuration is regenerated, and the guest released.

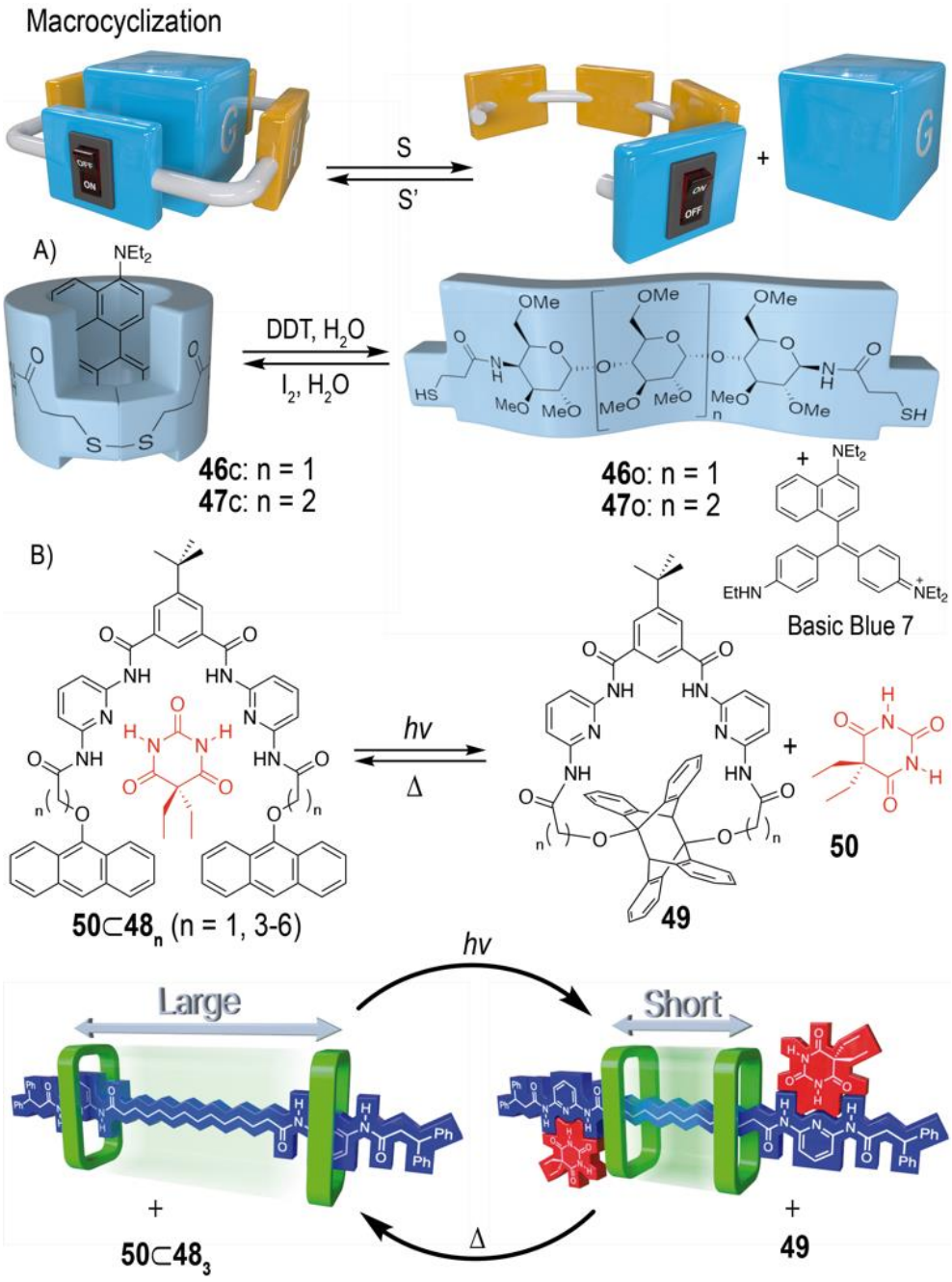
Another interesting example of allosteric regulation was reported by Brand *et al*, who developed modified versions of Shinkai's tail-biting system, replacing the AzB moiety by a triaminotriazine-based hydrogen bonding donor-acceptor-donor motifs or ditopic donors like urea moieties (Scheme 30).[190] As a result, exemplified for the latter case with compound **45**, the system self-complexes upon protonation of the terminal ammonium moiety and, conversely, deprotonation disrupts the complexation with the crown ether, making the secondary binding site available for the recognition of complementary guests like acetate. It should be noted that in this example of SS, the macrocycle cannot be considered as the primary binding site, as no guest is released from it to the bulk reaction media.



Scheme 30. Allosteric regulation by self-complexation.

5. Controlled (pre)organization of macrocyclic hosts.

As classically defined by Cram, "*the smaller the changes in organization of host and guest, the stronger the binding*".[191] It is well-known that preorganization has been thoroughly used in supramolecular chemistry to overcome entropic penalties on binding, and it can be considered as the basis of the field of host-guest chemistry itself. Therefore, we can easily envisage the stimuli-responsive modification of the (pre)organization of a host as a strategy for the development of macrocycle-based SSs, not altering in this occasion the structure of the receptor or the accessibility to its binding site, but rather controlling the creation/destruction of the host itself (Scheme 31).



Scheme 31. Supramolecular switching by stimuli-responsive macrocyclizations. A) Redox-based dithiol-disulfide interconversions in α- and β-CDs. Adapted from ref. 192 with permission from American Chemical Society, copyright 2007. B) Photoregulated catch and release of barbiturates,[193-194] and its use on the controlled gliding of the ring component of a [2]rotaxane. Adapted from ref. 198 with permission from the American Chemical Society, copyright 2017.

5.1. Controlled macrocyclization.

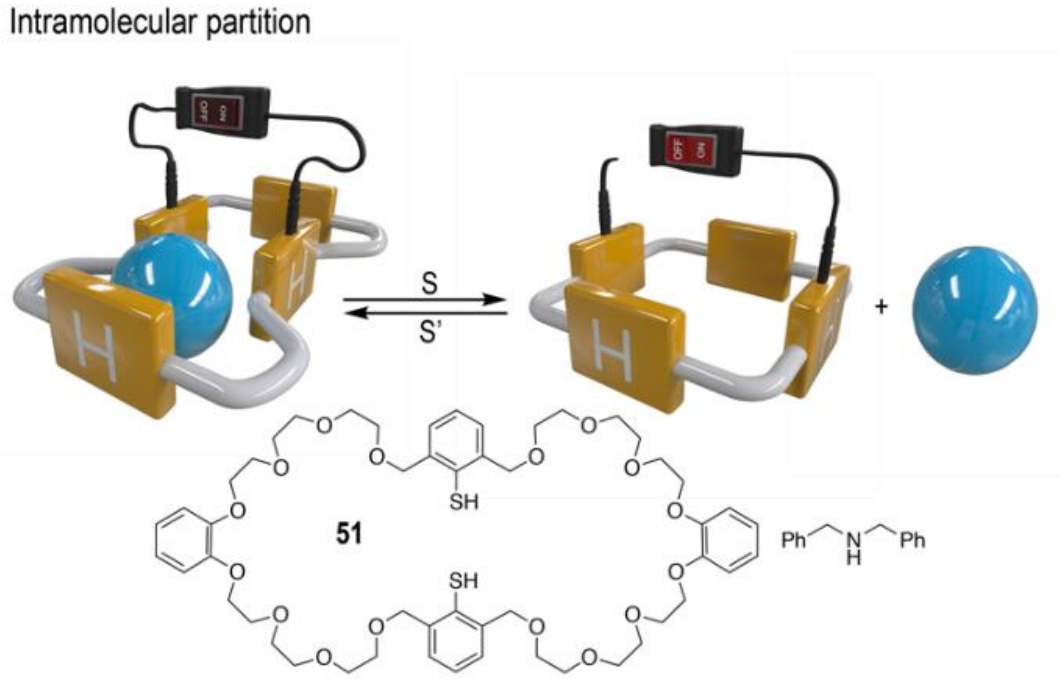
In theory, the most obvious way to control the (pre)organization of a macrocyclic host would consist in controlling the macrocyclization reaction itself. However, as any chemist would recognize, these reactions are nothing but difficult to control, with the stimuli potentially unleashing the inherent competition with oligomerization. A case that clearly exemplifies these difficulties was reported by Akashi *et al.*[192] Specifically, the

permethylated CD derivatives **46**$_o$-**47**$_o$ (Scheme 31A), having thiol moieties that upon oxidation yield disulfide bridges inserted into α- and β-CD rings, were developed for controlling their hosting ability by the opening and closing of their corresponding rings, based on redox-based dithiol-disulfide interconversions. Consequently, macrocycles **46**$_c$-**47**$_c$ showed higher inclusion ability towards the dye Basic Blue 7 (BB7) with K_a values in the 10^4 M^{-1} range, similar to those obtained for native per-methylated CDs. On the other hand, a significant drop in the binding is found for the open analogues **46**$_o$-**47**$_o$, showing K_a values in the 10^3 range. As it would be expected, the main drawback of the switching mechanism, apart from the $K_{a(c)}/K_{a(o)} \sim 10$, corresponds to the low yield of the oxidative macrocyclization reaction with I_2, producing the closed forms in moderate yields because of the competitive oligomerization. Nevertheless, the actual (I_2/DTT)-triggered SS BB7⊂[**46**$_o$/**47**$_o$↔**46**$_c$/**47**$_c$] was not assayed in this work, so the effect of the guest as template on the cyclization was not evaluated.

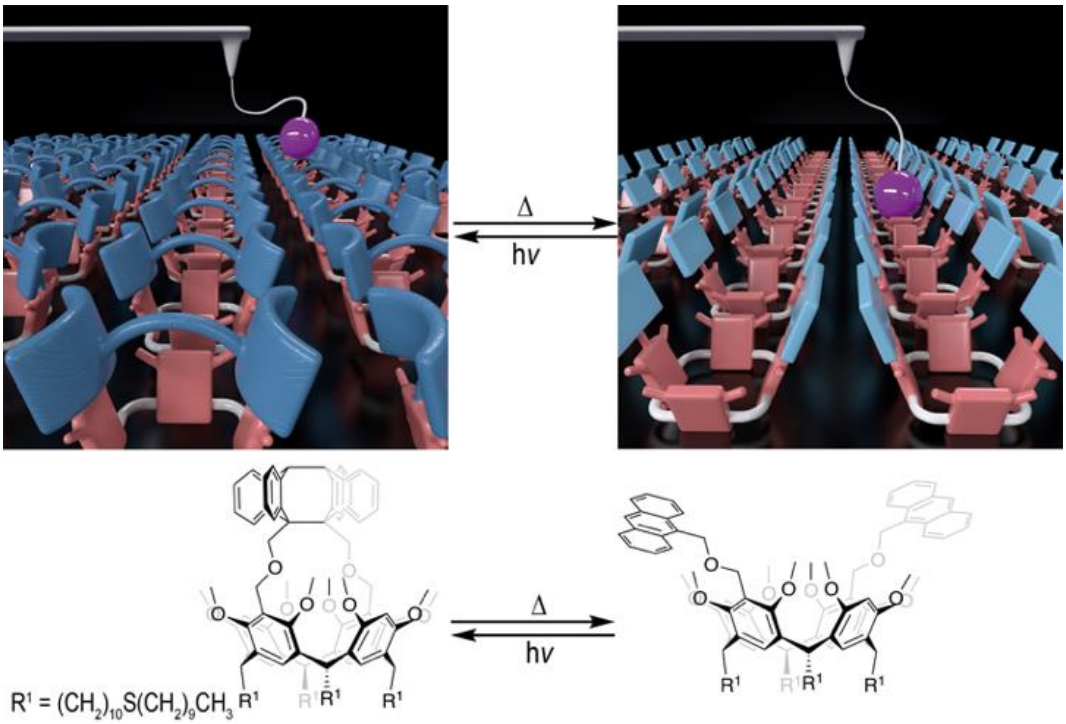
More efficient examples of the reversible macrocyclization strategy have been reported by Tucker and Desvergne *et al.* on the context of barbiturate receptors.[193-194] In those examples, a well-established acyclic Hamilton-like binding site,[195] was connected by alkyl spacers of variable length to two anthracene units, resulting in compounds **48$_n$** (n = 1, 3-6). By using the $4\pi + 4\pi$ photocycloaddition reaction, the authors were able to efficiently exchange between acyclic and cyclic forms of the receptors. Due to the steric constrictions imposed by the photoadduct on the binding site, the authors found exceedingly large differences in their binding abilities depending on the linker length, as large as a 1000-fold decrease in the binding ability of the dimerized receptor **48$_3$** (Scheme 31B). More recently, the photocontrolled macrocyclization described above has been incorporated into Au SAMs,[196] used as a clipping mechanism in the synthesis of [2]rotaxanes[197] and, remarkably, for the remote actuation on the ring gliding in a [2]rotaxane *via* the photoregulated catch and release of a barbiturate guest/effector (Scheme 31B). [198]

5.2. Controlled intramolecular partition of the binding site.

The organization of the macrocycle can be modified not only by the regulated conversion of a linear precursor into a macrocycle, but also by intramolecular partition of a binding site. This idea can be traced back to the work of Shinkai *et al.* on the development SSs for metallic cations, using for the task the reversible redox-controlled conversion of aza crown ethers to aza cryptands, by intramolecular transformation of dithiols into disulfides.[199-200] Using this very same strategy, Nabeshina *et al.* reported a SS for the catch and release of the dibenzyl ammonium cation based on the reversible formation of a disulfide bridge, which halves the crown ether host **51** (Scheme 32).[201] In this case, the oligomerization of the receptor is not a significant problem, due to the highly organized cyclic nature of the starting and final products of the partition reaction.



Scheme 32. Supramolecular switching by stimuli-responsive intramolecular partition of a binding site.



Scheme 33. Photoresponsive RA[4] and its application to the study by AFM of host-guest chemistry at the single molecule level. Adapted from ref. 202 with permission from the American Chemical Society, copyright 2007.

A related example of stimuli-responsive enthropically favoured dimerization in a SS has been reported for the study of host-guest chemistry using atomic force microscopy (AFM).[202] In this work, the authors prepared a self-assembled monolayer of a bis

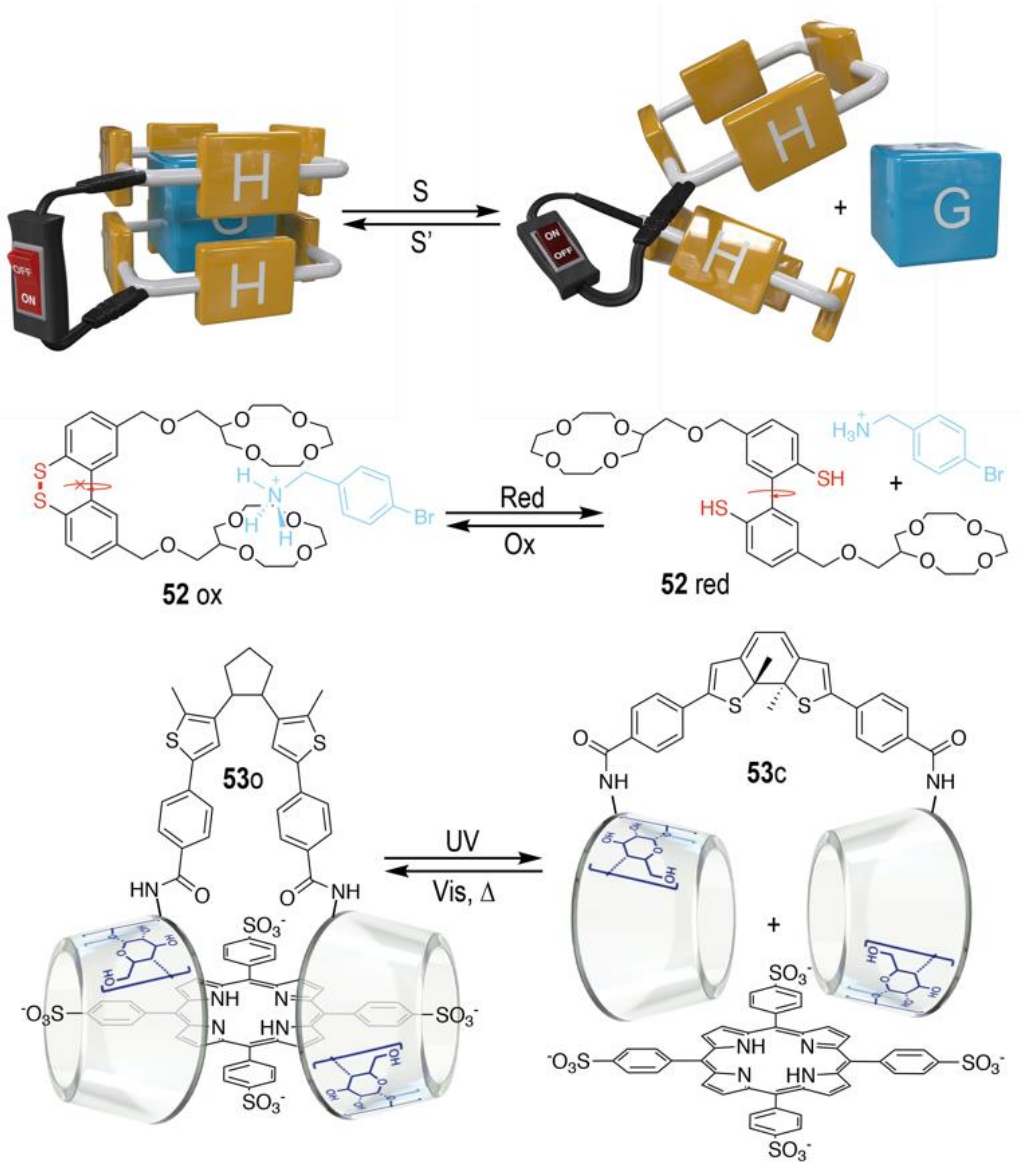
anthracene-appended RA[4], capable of photoresponsive reversible dimerization (Scheme 33). By attaching to an AFM tip an ammonium ion as the guest, the authors demonstrate that the system is reversibly switched between two cavitands with different binding abilities, probing the reversibility at the single-molecule level.

6. Controlled cooperativity of dimerized macrocyclic hosts.

Another intuitive way to alter the organization of a given host corresponds to the case of regulated intermolecular predimerization. For this strategy, we should invoke the host-guest chemistry of simple crown ethers with metallic salts, and the known fact that indicates that when a cation is too big to be accommodated by only one host, sandwich complexes are formed, with two crown ethers coordinating the same cation.[203] Considering as well that the stability of the complex can be enhanced by increasing preorganization, by linking two host molecules together, we will soon realize the possibility offered by the attachment of those two hosts through an appropriate stimuli-responsive linker. In this fashion, the linker can regulate the cooperative effect, resulting in the controlled binding of a given guest, preferentially in the more preorganized form of the host (Scheme 34).[204]

Nabeshima *et al.* reported a nice example of the strategy based on the quantitative dithiol-disulfide interconversion of **52**red⇄**53**ox.[205] The binding affinity of **52**ox to the cationic guest *p*-bromobenzylammonium is significantly higher than that of the reduced form, as the former compound is appropriately preorganized to bind the guest in a face-to-face cooperative fashion (Scheme 34). In a similar vein, Reinhoudt *et al.* have reported the use of β-CD dimers, linked by photoresponsive dithienylethene moieties, for the switchable complexation of a porphyrin derivative as a model guest.[206-208] In the open form **53**o, the intramolecularly linked β-CD cavities have a certain amount of flexibility to bind the guest tightly in a cooperative fashion, while the binding is much less favourable in the photogenerated closed rigid form **53**c (Scheme 34). Years later, Liu *et al.* demonstrated that a similar system, using an AzB-tethered cyclodextrin dimer as the host, and a porphyrin molecule as the guest, could be used for the photocontrolled reversible conversion of nanotubes into nanoparticles (intra to intermolecular complexation).[209] Finally, in an interesting applicative example, Monti *et al.* reported on the use of a similar β-CD dimer for the photocontrolled release of the antimalarial drug artimisinin.[210]

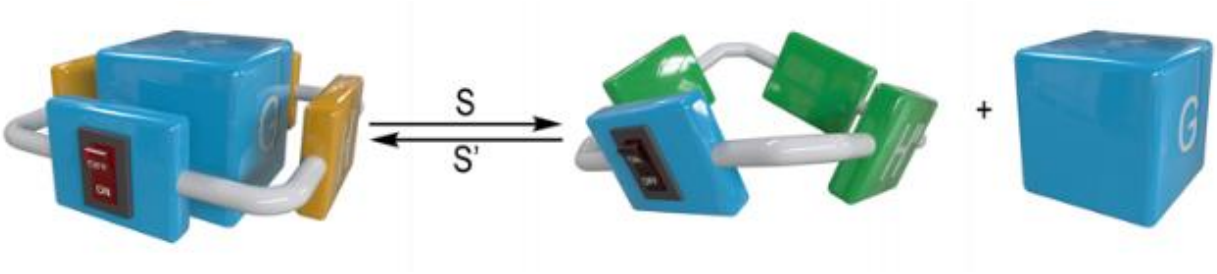
Allosteric regulation has been used for the development of SSs based on the control of the face-to-face conformation of binding sites within dimerized molecular hosts. In particular, a quite popular strategy is the transition metal-triggered allosteric modulation of dimerized crown ethers,[211]RA[n]s,[212-214] or CDs,[215-216] joined together through 2,2'-bipyridil-based linkers. In these examples, various metal cations can be used as positive or negative heterotropic effectors, although the stimulation is only partially reversible due to the difficulties associated with the removal of the chelated effector.[46]



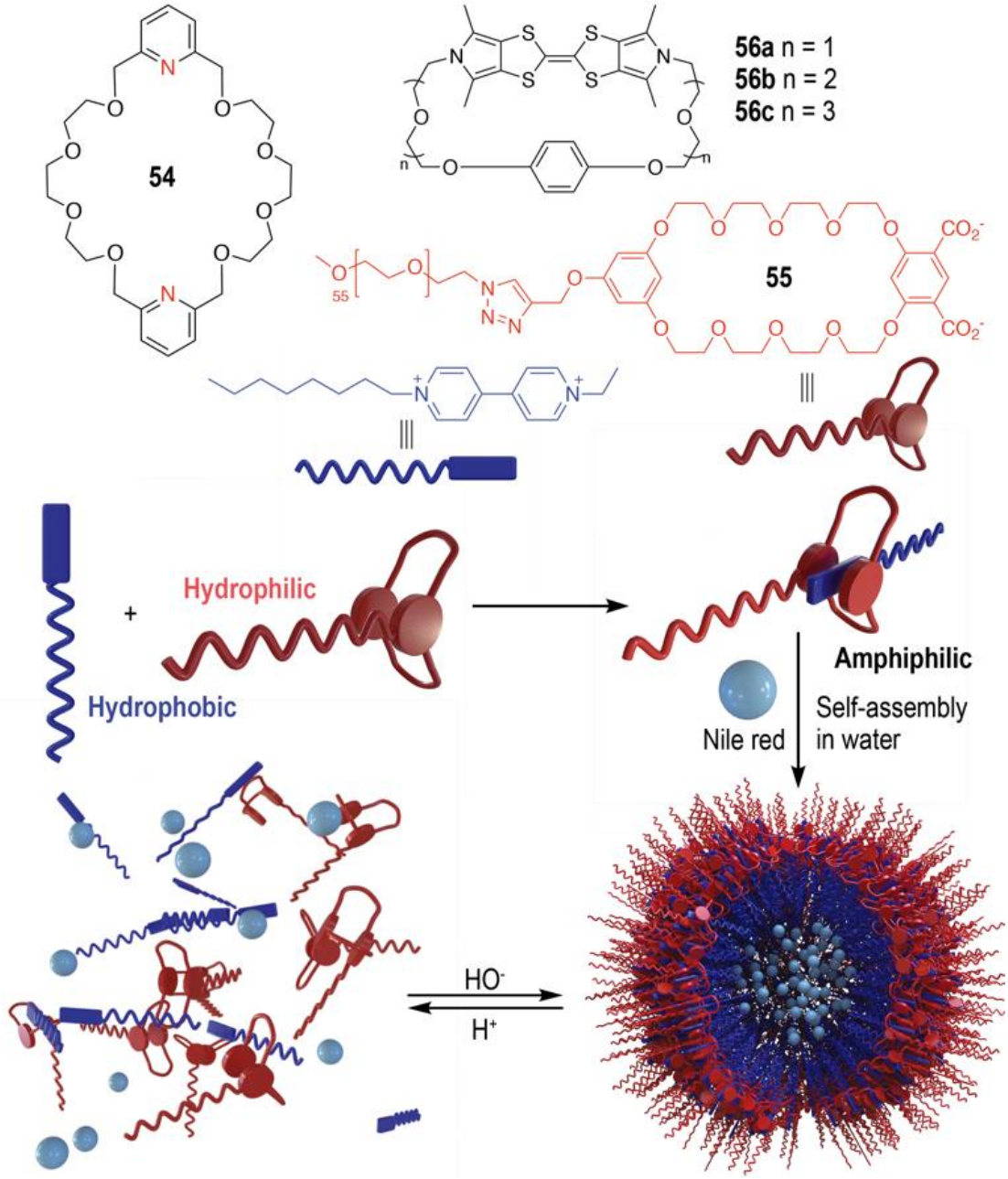
Scheme 34. Top: SS by stimuli-responsive intermolecular predimerization. Middle: Example of redox. Adapted from ref. 205 with permission from Elsevier, copyright 1989. Bottom: Photocontrolled SSs. Adapted from ref. 206 with permission from The Royal Society of Chemistry, copyright 2002.

7. Evolving the binding site of known macrocyclic hosts

Although the direct introduction of MSs within the binding site of well-known hosts is in principle a quite appealing strategy (Scheme 35), assuring the complete transmission of the structural change from the switch to the macrocycle, two main reasons preclude its generalization. The most obvious is that the binding site modification can be directly translated into unpredictable changes upon host-guest association. The second limitation corresponds to synthetic accessibility, as modifications can entail from subtle changes on the macrocycle's rim/s to a more drastic restructuring of the macrocyclic annulus. Nevertheless, it should be emphasised that the alternative to this approach, the *de novo* design of stimuli-responsive binding sites, has been scarcely reported in the literature.[217-223]



Scheme 35. SSs obtained by introduction of stimuli-responsive units within the binding site of well-known hosts.



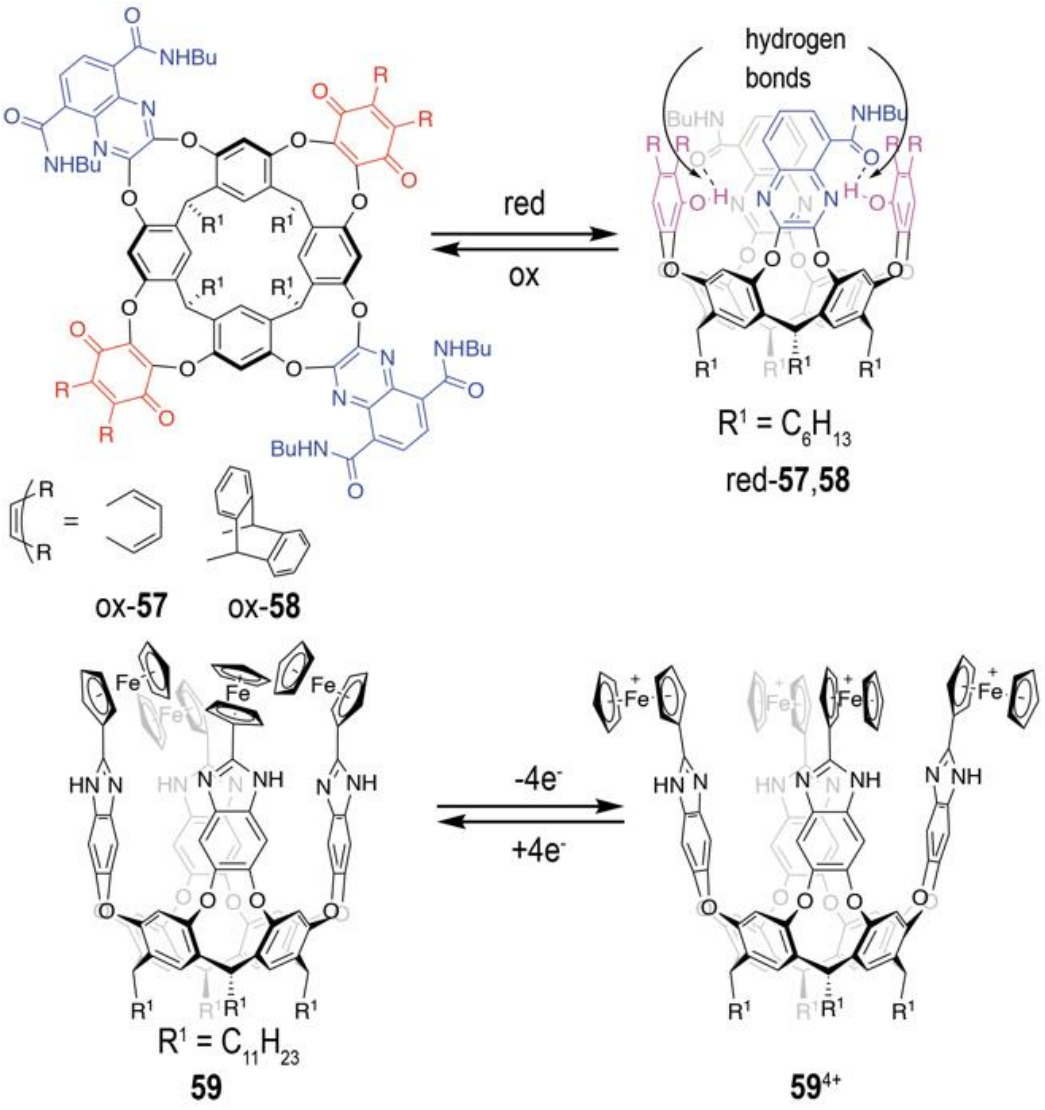
Scheme 36. Top: Examples of pH-responsive coronands **54**[224], **55**[225]and **56a-c**[226] obtained by direct modification of the annulus. Bottom: MV-mediated self-assembly of **55** into a pH-responsive micelle. Adapted from ref. 225 with permission from the American Chemical Society, copyright 2012.

7.1. Evolving coronands.

The modification of the binding site of dibenzo-18-crown-6 ethers is perhaps the simpler example of the binding site modification strategy for the development of SSs (Scheme 36). As previously discussed, this class of coronands are well known for their affinity to MVs, so a slight modification of their annulus by replacing the benzene rings by appropriate ionizable moieties should, in principle, render pH-responsive hosts for those organic cations. Indeed, as reported by Zhang *et al*, the approach nicely works with the *N*,*N*′-dimethyl-2,7-diazapyrenium cation as the guest being trapped and released by dipyrido[30]crown-10 ether **54**, which is able to control the binding of the guest by protonation-triggered electrostatic repulsions.[224] Implementation of ionizable carboxylate functions into related bis (*m*-phenylene)-32-crown-10 ethers produces similar results, improving the affinity of the receptor for MVs in water, due to the introduction of favourable electrostatic host-guest interactions, as demonstrated by Huang *et al.* in the development of a pH-responsive micelle based on compound **55**.[225] Finally, modification of coronands to produce redox-responsive crown ethers has also been explored, in particular by introduction of pyrrolo-tetrathiafulvalene units within the annulus, resulting in macrocyclic compounds **56a-c** capable of catching and releasing MV derivatives.[226]

7.2. Modification of the rims and annulus in cyclic [n]arenes.

In the context of the extensive work on the development of switchable RA[4] cavitands as molecular grippers, Diederich and co-workers have shown that an appropriate modification of the upper rim of those receptors would not only control their kite-vase conformations, but result in supramolecular switching.[227-229] For instance, cavitands **57**-**58** are characterized by two redox-responsive quinone (Q)-based walls,[230] and two quinoxaline walls with two hydrogen bonding carboxamide groups. The oxidized form of the Q moieties favors the kite form of the cavitand, due to the poor stabilization of the closed form and the steric hindrance between the amide and Q groups. In contrast, the reduced form of the hydroquinone establishes hydrogen bonding interactions with carboxamide groups, stabilizing and favoring the vase form of the cavitand. As a result, the binding of different cycloalkanes is highly controllable by redox stimulation, with K_a (red-**58**)/K_a (ox-**58**) reaching values of up to 217 (Scheme 37). Peris *et al.* have developed a similar redox-responsive cavitand **59**,[231] characterized by the presence of four Fc units on the host walls. The redox controlled Fc to Fc^+ transformation is not translated in this compound into the vase-kite swap in conformation, but instead into a slight opening upon reduction of the basal kite conformation. Consequently, **59** is only able to complex ammonium salts in its oxidized form (Scheme 37).

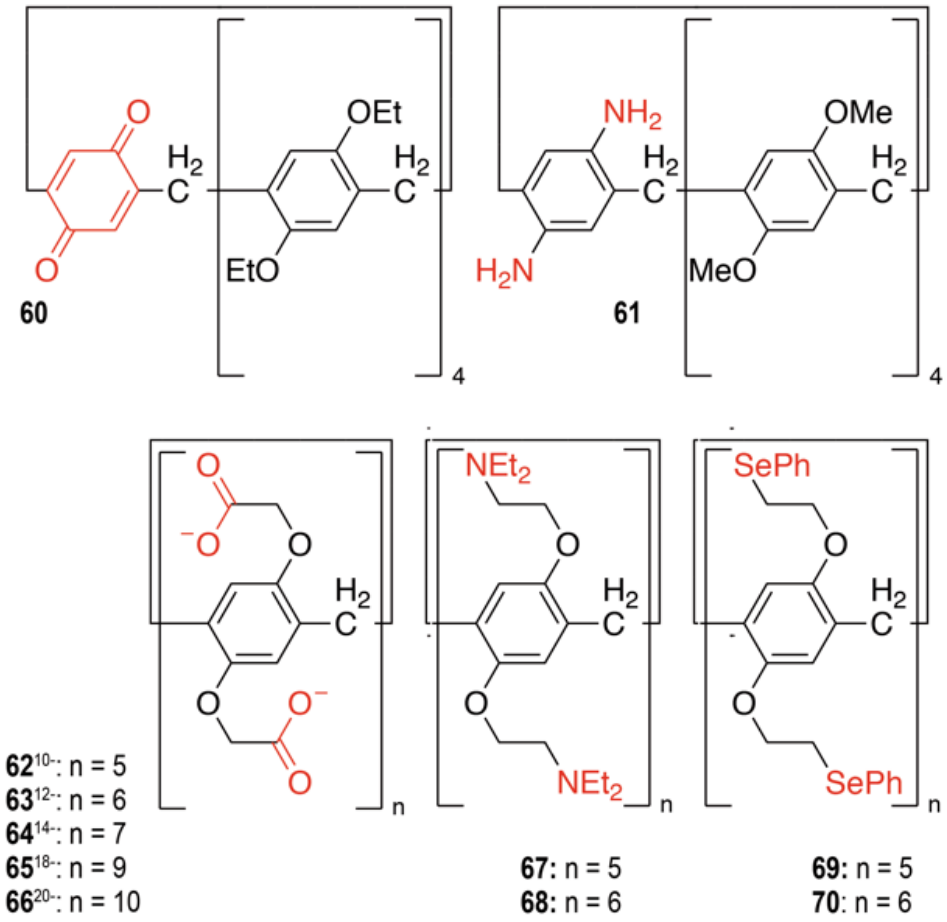


Scheme 37. Examples of redox-controlled SSs based on RA[4] cavitands **57**-**58**[230]and **59**.[231]

As previously discussed in this review, the host-guest chemistry of pillar[n]arenes has exploded in the last decade or so, mostly because of the ease of functionalization of these versatile hosts.[90] In particular, the hosting ability of the binding site can be easily adjusted by introduction of stimuli-responsive units on the rims or annulus of the PA[n]s. Regarding the later, Ogoshi *et al.* reported the synthesis of the PA[5] derivative **60** containing one Q unit (Scheme 38).[232] The authors found that **60**·H_2 formed a host–guest complex with 4-dicyanobutane with a K_a 50 times lower than its parent compound. In consequence, the authors studied the redox SS G⊂[**60**⇄**60**·H_2] (G = a bis-triazolyl based axel). The oxidized form of the pair does not form a very stable complex with the guest (K_a ~30 M^{-1}), because of the decreased π-electron density of the cavity caused by the Q ring within the annulus. Upon addition of a reductant, the subsequently generated HQ unit produces more than a 10-fold increase on the guest binding. Wen *et al.* have also demonstrated that supramolecular pH-responsiveness can be achieved in a similar fashion, by a slight modification of the annulus of PA[5].[233] In this example, the analogue **61** is obtained through replacement of the

hydroxy groups in one of the rings by primary amine functions, displaying a quite moderate binding to the 1,3-dihexyl-*1H*-imidazol-3-ium cation in $CDCl_3$ (K_a ~200 M^{-1}), which disappears upon acid treatment leading to **61**·H_2.

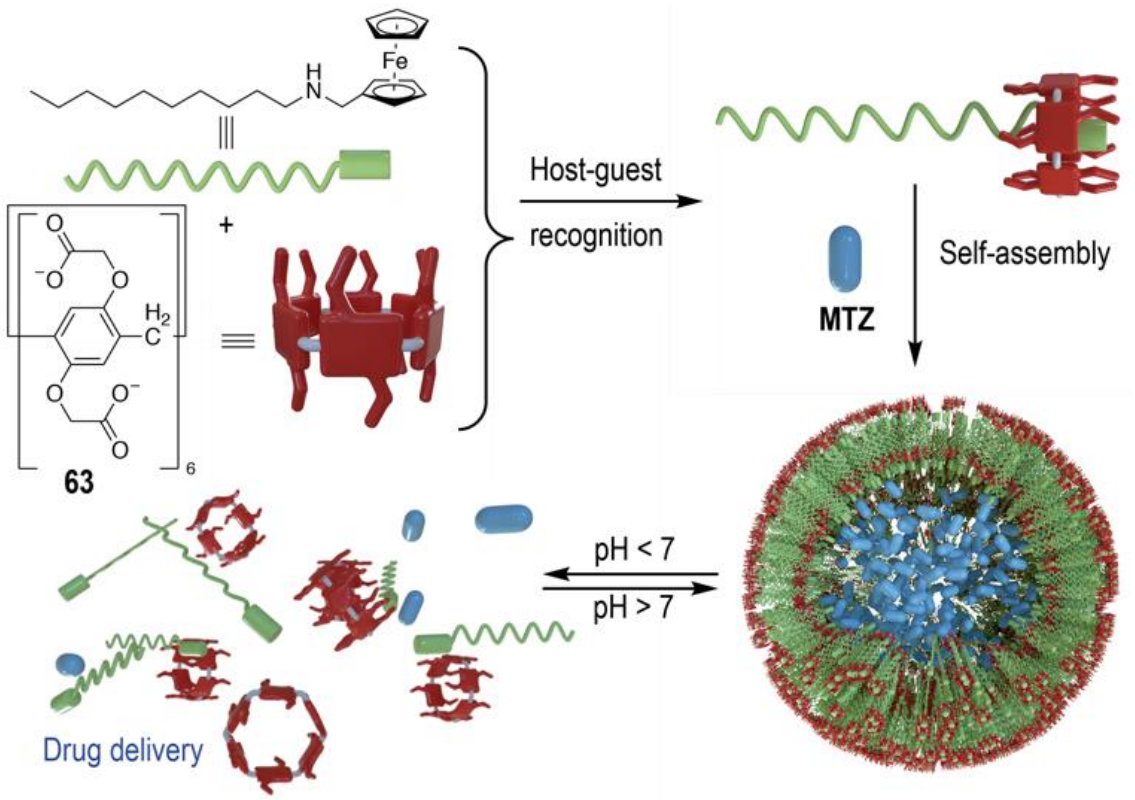
Regarding rim derivatization, Huang`s lab[234-238] and others[239] have extensively shown how this strategy can be successfully applied to the construction of SSs based on PA[n] derivatives. In this situation, carboxylate per-functionalized analogues $_{PC}$PA[n] (n =5-7,9-10, compounds **62**-**66**, Scheme 38) can be appropriately switched on and off for the controlled binding of MVs. The carboxylate groups in these hosts not only increase water-solubility but improve as well the complexation of positively charged guests, by means of electrostatic interactions. Once protonated, these macrocycles reduce their substrate affinities, producing the disassembly of the corresponding host-guest aggregate.



Scheme 38. PA[n]-based hosts **60**-**70** displaying supramolecular responsiveness.

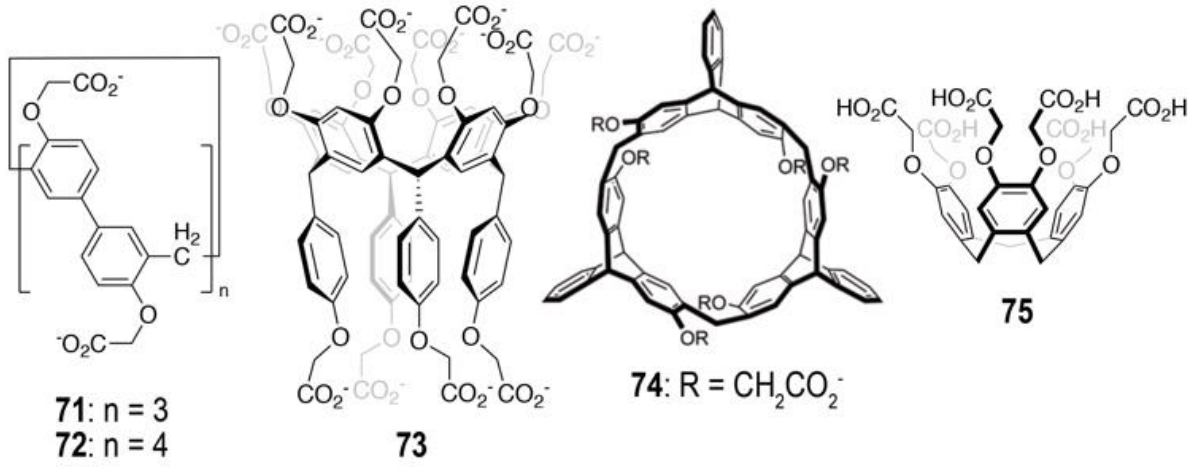
The adequate water solubility of $_{PC}$PA[n]s, in conjunction with their pH-triggered switching mechanism and their rich host-guest chemistry, based on the hydrophobic effect, π–π and electrostatic interactions,[240] have made these macrocycles excellent candidates for the development of practical applications. For instance, those have been extensively used in the

construction of pH-responsive extended architectures, in the context of controlled drug delivery.[241-242] As exemplified in Scheme 39, this strategy was successfully applied by Wang *et al.* for the controlled release of the drug mitoxantrone (MTZ).[243] First, a supramolecular amphiphile is prepared by conjunction of PCPA[6] **63** as the head and a Fc-based molecule as the hydrophobic tail. The amphiphile is then self-assembled in water, forming appropriate vesicles that can be loaded with the drug. Taking advantage of the well-known intra-/extracellular pH differences, the responsive MTZ-loaded vesicles were used to conveniently deliver their cargo inside cancer cells, as observed by cell imaging techniques.



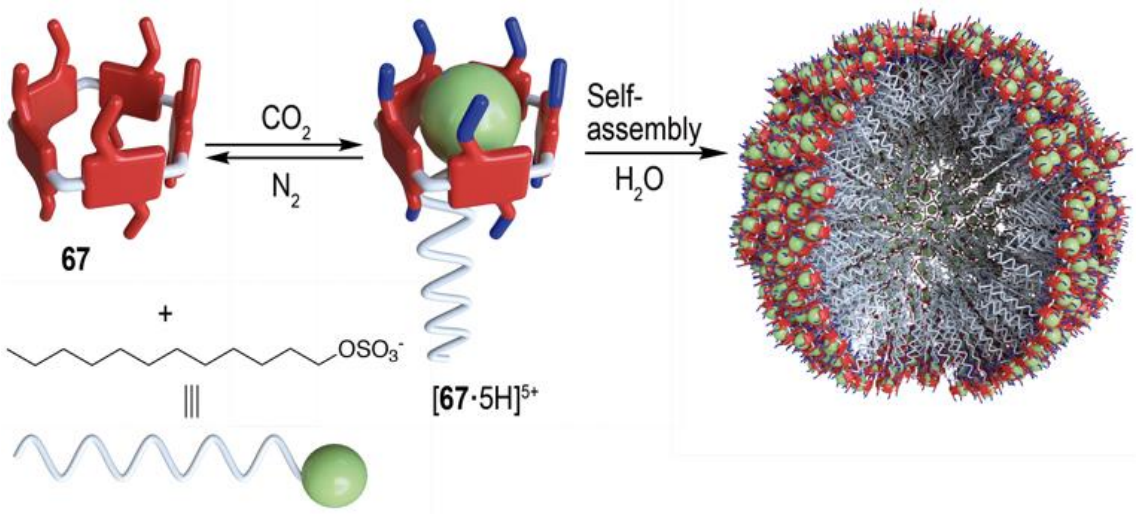
Scheme 39. PCPA[6]-based pH-responsive supramolecular drug delivery system. Adapted from ref. 243 with permission from the American Chemical Society, copyright 2013.

On a side note, rim perfunctionalization with carboxylate groups has been reported in other cyclic arenes, aiming for water solubility and supramolecular pH-responsiveness, as demonstrated with per-carboxylated biphen[3,4]arenes (**71**-**72**),[244-245] RA[4]s (**73**),[246] 2,6-helic[6]arenes (**74**),[247] or cyclotriveratrylenes (**75**)[248] (Scheme 40).



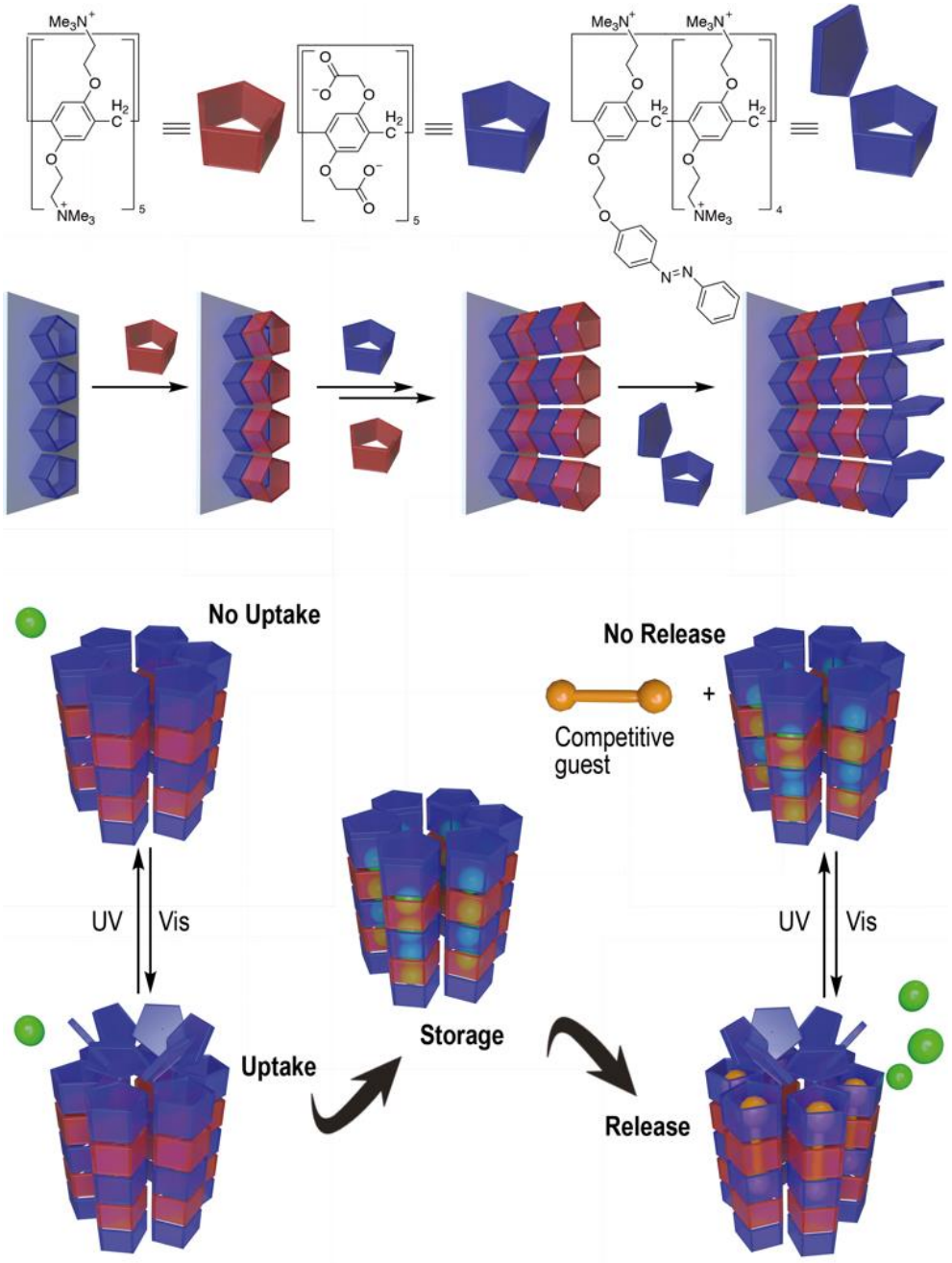
Scheme 40 Assorted per-carboxylated cyclic arenes implemented into pH-responsive SSs.

Following our discussion on modified PA[n]s, rim per-functionalization with ionizable tertiary amines has also produced pH-responsive compounds; for instance, the modified PA[5] derivative **67** (Schemes 38 and 41), was found able to bind in a controlled fashion the surfactant dodecyl sulphate.[249] The neutral form of the host can be reversibly protonated by carbonic acid in water, producing the electrostatically enhanced binding of the surfactant. The inclusion complex acts as a supramolecular amphiphile, which self-assembles into spherical bilayer vesicles in aqueous media that can be easily disrupted upon N_2 bubbling of the solution. This CO_2/N_2-responsive system has been employed in this scenario for the catch and release of the dye calcein. Similar [CO_2/N_2]-based pH-responsiveness was also reported in similar amphiphilic PA[n]s by Huang *et al.*[250] and Xue *et al.*[251]



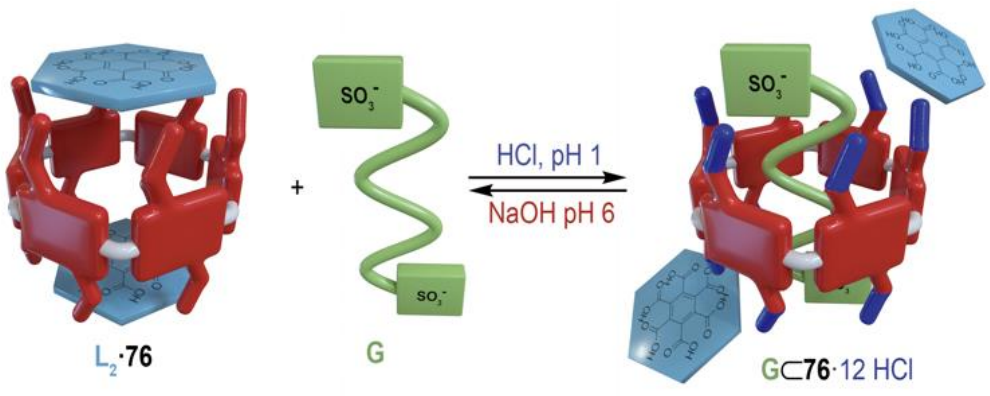
Scheme 41. Self-assembly of CO_2/N_2-responsive micelles using per-amino-PA[5] **67**. Adapted from ref. 249 with permission from the American Chemical Society, copyright 2015.

Interestingly, Ogoshi *et al.* have realized not long ago that charge complementary PA[n] derivatives (i.e. per-carboxylated and per-amino-PA[5]s), can be used for the efficient construction of microporous multilayer films (prepared by layer-by-layer assembly, LbL), and are capable of efficient guest encapsulation.[252] A slight modification on one of the self-assembled building blocks, by introducing an azobenzene moiety on the per-amino-host (azo-PA[5]$^+$), allowed the self-assembly of the three components into a film showing photo-regulated guest uptake, storage, and release (Scheme 42).[253]



Scheme 42. Top: Chemical structures of cationic PA[5]$^+$, azo-PA[5]$^+$, and anionic PA[5]$^-$ building blocks. Middle: LbL assembly by consecutive adsorption of PA[5]$^+$, PA[5]$^-$ and azo-PA[5]$^+$. Bottom: Schematic representation of the catch and release mechanism. Adapted from ref. 253 with permission from the American Chemical Society, copyright 2018.

Another refreshing twist on the use of per-alkylamino pillarenes in SSs has been reported by Cohen *et al*, who created pH-responsive, water-soluble PA[6]-based supramolecular boxes based on multiple charge-assisted hydrogen bonds (Scheme 43).[254] For instance, addition of mellitic acid **L** as a "supramolecular lid" to the hexane disulfonate⊂**76**$^{12+}$ inclusion complex, immediately led to guest escape along with formation of the closed box **L**$_2$**76**. This process was found to be reversible and pH-dependent, thus paving the way for the easy and modular preparation of many pH-responsive supramolecular hydrogen-bonded boxes.



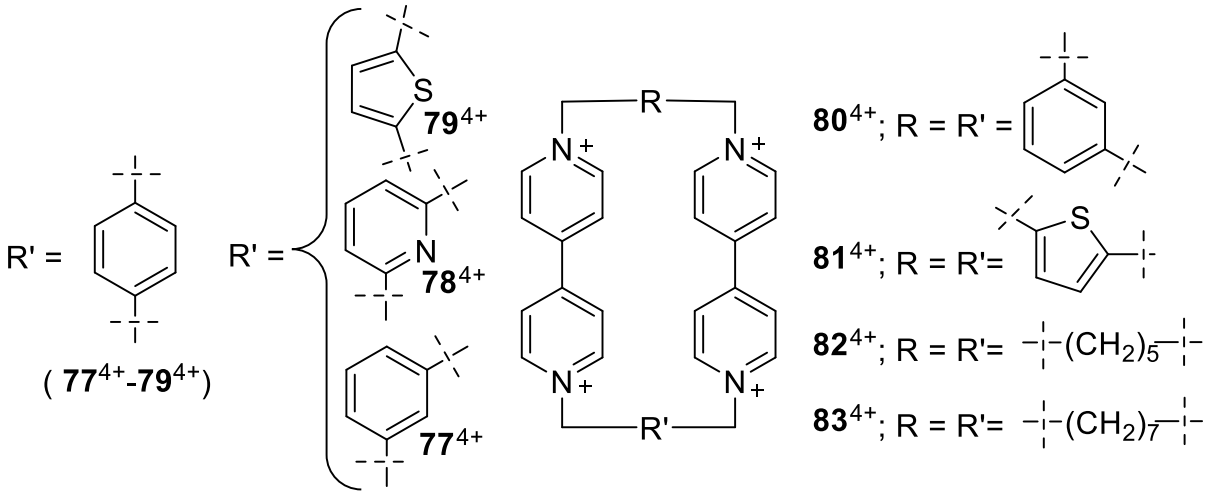
Scheme 43. Schematic representations of the pH-response of the water-soluble box **76**$^{12+}$, along with guest release and encapsulation upon addition of NaOH or HCl, respectively. Adapted from ref. 254 with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, copyright 2019.

Supramolecular redox responsiveness has also been reported by Huang *et al.* in the realm of pillarene chemistry, by using PA[5,6]s per-functionalized in both rims with alkyl phenyl selenides (compounds **69**-**70**, Scheme 38).[255-257] The reversible interconversion between selenide and selenoxide can be efficiently produced by, respectively, oxidation with H_2O_2 and treatment with vitamin C. In turn, the process produces the transformation of the pillarene derivative into an amphiphilic building block. The compounds are able to self-assemble in water by themselves, forming micelles that can be filled with appropriate cargos, which are subsequently liberated upon stimulation using ascorbic acid as a reductant. This switching mechanism can be translated into supramolecular responsiveness when a pyridinium-based amphiphile guest forms the corresponding inclusion complex with ox**70**, self-assembling into vesicles that can be disrupted by reduction upon exposure to vitamin C.

7.3. Blue box-inspired hosts.

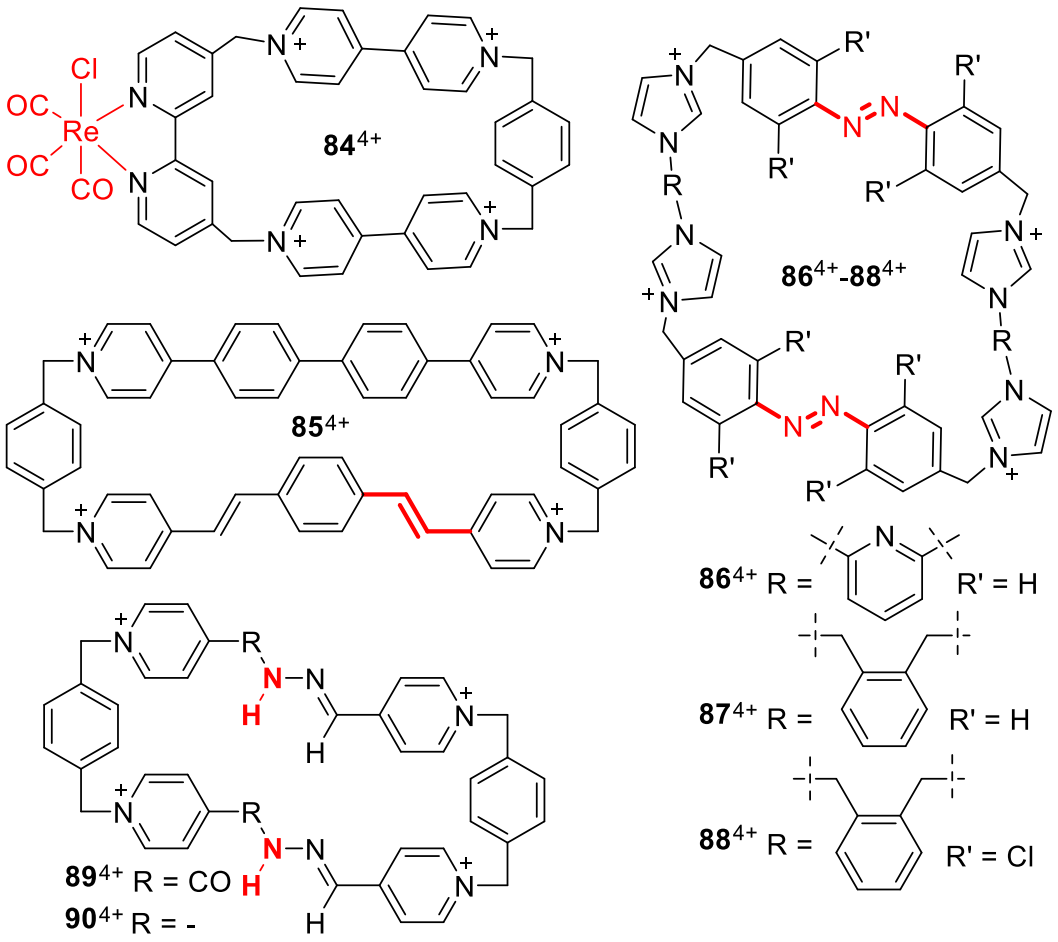
The well-stablished binding and molecular switching abilities discussed for the "blue box" (Sections 2.5 and 4.2), have obviously served as the starting point for the development of new macrocycles having, at least in theory, supramolecular redox-responsiveness. Those analogues are not restricted to new hosts with enlarged cavities (i.e. the Ex$_n$Box$_m$$^{4+}$ family of

macrocycles).[101] As shown in Scheme 44, more exotic modifications have been developed which maintain the viologen-based scaffold on the large side of the molecular rectangle, adjustments that include compounds with decreased cavity volumes (**77**$^{4+}$-**81**$^{4+}$)[258] or increased flexibility (**82**$^{4+}$-**83**$^{4+}$).[259] Interestingly, these molecular hosts have been reported to complex MVs in a redox-controlled fashion by radical pairing-assisted processes.



Scheme 44. Examples of redox "blue box"-based SSs **77**-**83**.[258-259]

Apart from these modifications on the "blue box" annulus, designed to maintain the redox behaviour of the model compound, the implementation of other types of stimuli-responsiveness in "blue box"-like cyclophanes has been as well achieved (Scheme 45). Firstly, Stoddart *et al.* have reported some interesting modifications of the original redox-responsiveness of the tetracationic cyclophane. Substitution of one of the phenylene linkers on the short side of the host by a 2,2'-bipyridine moiety, results in a "blue box" analogue with the ability of complexing a Re(I) metal center, resulting in compound **84**$^{4+}$. The metal moiety serves here as the internal photosensitizer, allowing for the photoredox-controlled binding of appropriate aromatic substrates.[260] More recently, the same research group reported another "blue box"-inspired photo-responsive host, **85**$^{4+}$.[261] In this case, due to the photoactive oligo (*p*-phenylenevinylene) pyridinium unit within its macrocyclic scaffold, the configurations of the cyclophane can go back and forth between (*EE*)- and (*EZ*)-isomers, upon alternating blue light irradiation and heating. While in its basal (*EE*)-configuration, **85**$^{4+}$ is capable of binding aromatic guests with different characteristics (e.g., anthracene and perylene as electron donors or 9,10-anthraquinone and 5,12-tetracenequinone as acceptors); when irradiated with blue light, its binding ability is switched off as a result of the (*EE*)- to (*EZ*)- transformation, and it is conveniently restored upon heating.

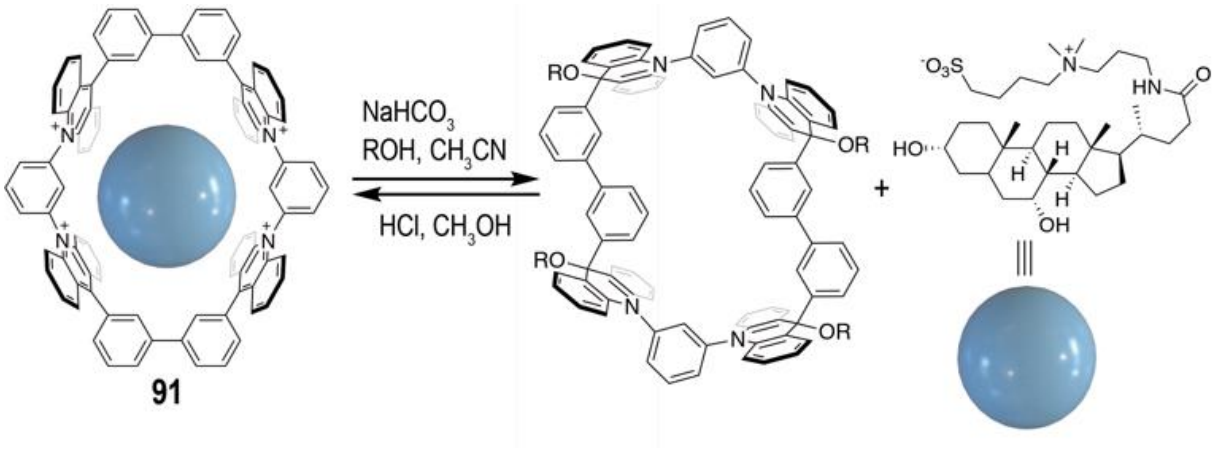


Scheme 45. "Blue box"-like compounds **84**$^{4+}$-**90**$^{4+}$ capable of supramolecular photo- and pH-responsive switching.

Another family of receptors inspired by the "blue box" are the tetracationic imidazolium-based macrocycles, known as the Texas-sized molecular boxes and developed by Sessler *et al*.[262] Among the different analogues obtained by this research group, the AzB-containing compound **86**$^{4+}$ (Scheme 45),[263] able to show supramolecular responsiveness, has been recently reported. It was found that the cavity shape of the receptor can be controlled through photoirradiation, so that in the absence of UV light the cationic macrocycle acts as an effective receptor in DMSO-d6 for model aryl anions, while exposure to UV light induces guest release. Other very similar examples of related light-responsive macrocycles (**87**$^{4+}$ and **88**$^{4+}$, Scheme 45) have been also reported.[264-265]

The introduction of pH-responsiveness into "blue box"-like cyclophanes has been reported by García *et al*, who developed a series of hydrazone-based analogues of the receptor, which include accessible pH-responsiveness (**89**$^{4+}$-**90**$^{4+}$, Scheme 45).[266-267] In the particular case of the so called "red box" **90**$^{4+}$,[267] the cyclophane is able to complex a variety of aromatic compounds in organic media, but only in its acidic form, resulting in supramolecular pH-responsiveness of the G⊂[**90**$^{4+}$⇄**90**$^{2+}$] system. Finally, another recent example of pH-responsive tetracationic macrocycle has been reported by Yoshizawa *et al*,[268] who developed compound **91**$^{4+}$, having an open/closed pH-based switching function within its framework.

The installation of pH-responsive acridinium rings into the macrocycle translates into a cyclophane with the ability to catch and release large hydrophilic molecules in water (Scheme 46).



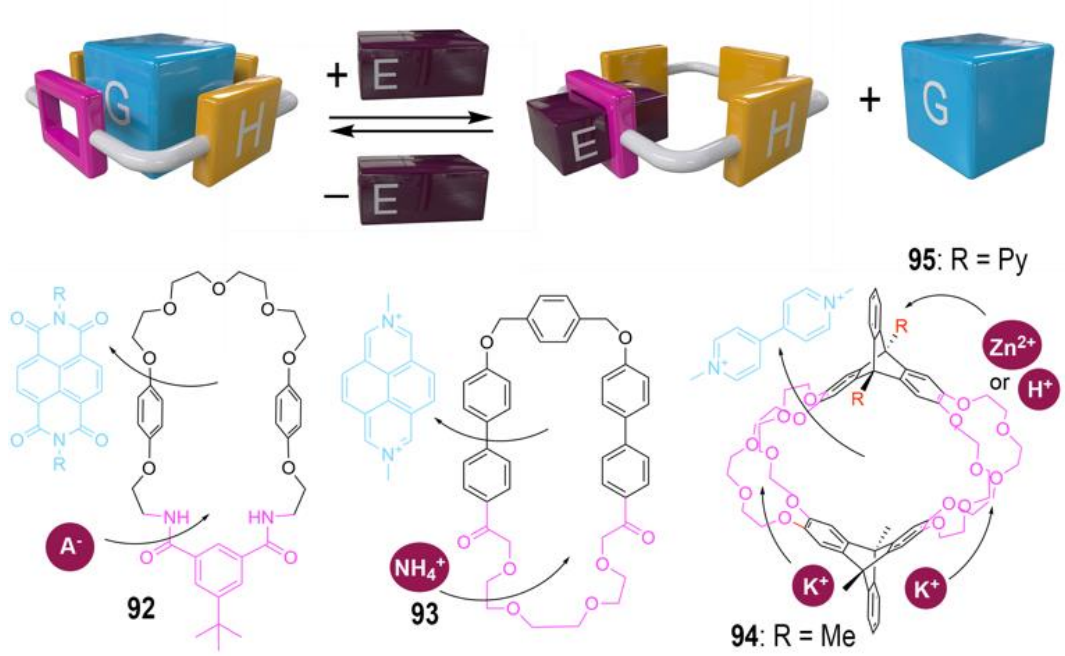
Scheme 46. pH-responsive SS based on the aromatization-dearomatization of acridinium rings within the tetracationic host **91**$^{4+}$. Adapted from ref. 268 with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, copyright 2017.

7.4. Allosteric regulation: orthogonal binding motifs within the same macrocyclic cavity.

As previously discussed, the introduction of allosteric regulation into a given receptor necessarily implies the creation of a secondary binding site for the effector. In the case of the direct evolution of binding sites, allosteric regulation necessarily implies the coexistence of the primary and allosteric site on the annulus of the macrocycle (Scheme 47). In that manner, in order to effectively achieve controlled binding, guest complexation and positive or negative allosteric regulation should be necessarily orthogonal.

A quite beautifully simple example of this design principle was reported by Beer *et al.*, as a part of their extensive work on the development of anion receptors based on mechanically interlocked molecules.[269] Similar to the idea of regulating the binding of viologens to dibenzo-18-crown-6 ethers, by introducing ionizable functional groups within the binding site (*i.e.* with a proton acting as a heterotropic negative allosteric effector in host **54**, Scheme 36),[224] the authors developed the coronand-based host **92** (Scheme 47),[270] which preserves two electron rich HQ moieties on the cyclic structure, as well as an isophthalamide moiety capable of complexing anions. Consequently, the host is able to complex the electron deficient naphthalene diimide thread in $CDCl_3$ (K_a = 355 M^{-1}), with anion complexation at the isophthalamide motif of the macrocycle causing the dissociation of the guest. In a similar example, Chiu *et al.* designed the macrocycle **93**,[271] which comprises a ring-expanded [18]crown-6 unit, for binding to ammonium ions, and a biphenyl-based aromatic motif capable of recognizing the 2,6-dimethyl diazapyrenium cation (Scheme 47). With a K_a = 630

M^{-1} for G⊂**93** in $CD_3CN/CDCl_3$ 4 : 1, the complexed and non-complexed states can be controlled through the sequential addition of an acid and a base (NH_4^+ and proton sponge, respectively).



Scheme 47. SS by interference of allosteric effectors and the primary guests within the macrocyclic annulus of **92**-**95**.

Finally, iptycene-based crown ethers have recently arisen as an interesting class of host molecules, combining rigid iptycene moieties and flexible crown ether chains.[272] Among other interesting features, these hosts can own two orthogonal binding sites sharing a common space on the core of the macrocycle (i.e. the crown/s ether/s moieties and the cavity created around the iptycene-moieties). In this context, Chen *et al.* have extensively shown how the complexation of organic cations can be controlled by appropriate inorganic salts, able to act as heterotropic negative allosteric effectors occupying the crown binding sites, and consequently producing electrostatic repulsions within the cavity of this type of hosts with the charged organic guests. For instance, the cylindrical macrotricyclic polyether **94** (Scheme 47) acts as an efficient receptor for the complexation of viologens, and addition and removal of potassium ions, as chemical effectors, conveniently acts on the allosteric (crown ether) sites of the host producing the ejection of the guest.[273] In another interesting example by this research group, an additional bipyridine-based allosteric site was introduced within a similar triptycene-derived host **95** (Scheme 47).[274] In this fashion, the complexation of MVs by the host can be switched not by intervention on the crown ether binding sites (although theoretically possible), but by protonation or coordination with Zn^{2+} of the pyridine moieties, a fact that produces the necessary electrostatic repulsions on the binding site to provoke the expulsion of the organic cation.

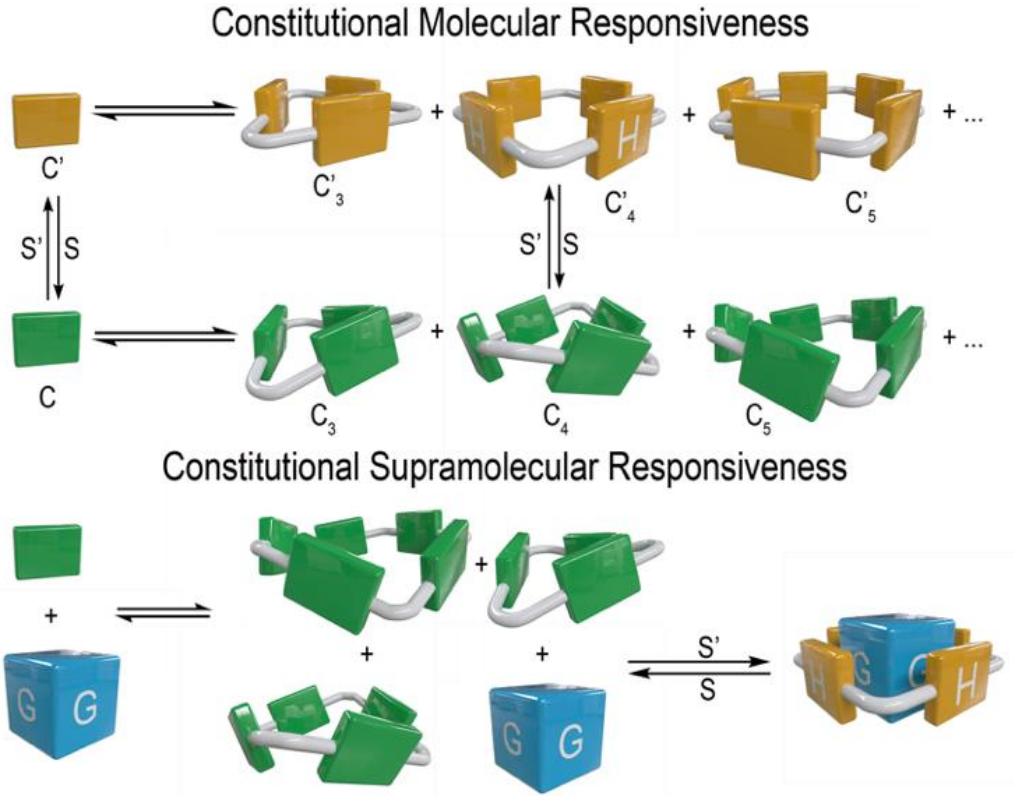
8. Summary and outlook: towards the construction of stimuli-responsive hosts by control over constitutional dynamism.

In the present review, we have highlighted different design strategies for the introduction of regulated dynamic behaviour into host-guest systems, by manipulation of well-known organic macrocyclic receptors, and implying the catch and release of organic guests. In all the examples discussed, the desired supramolecular responsiveness was achieved by controlling the motional dynamics of the macrocycle, which in turn controls the reactional dynamics of the host-guest aggregate.

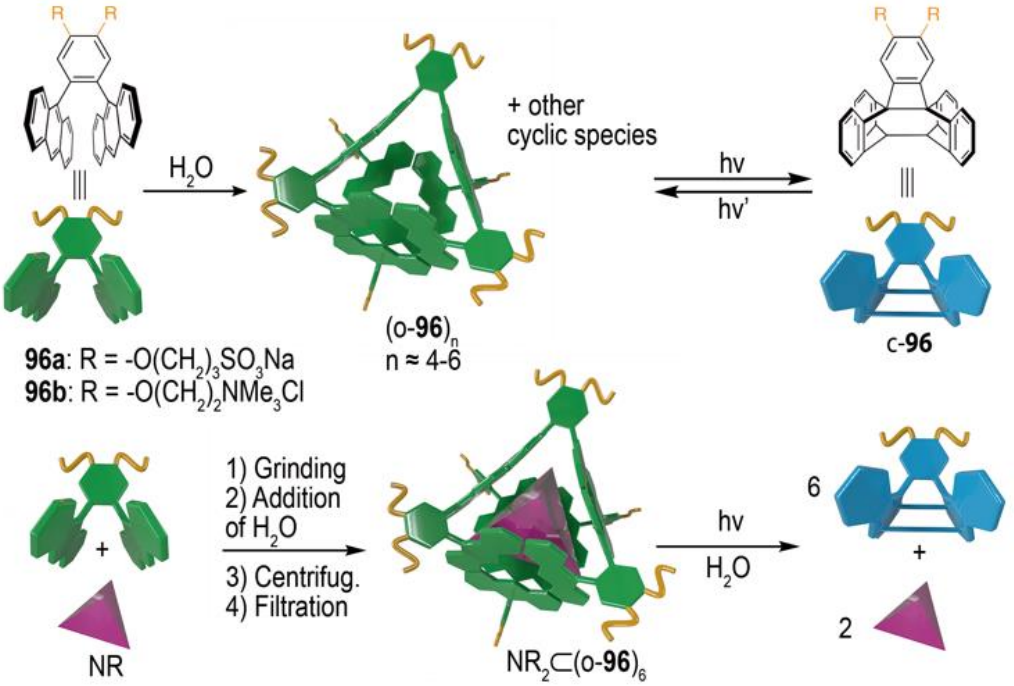
Despite the substantial deal of effort on the development of such host-based SSs, there is still plenty of room for improvement. Regarding practical applicability, important factors should be addressed, such as the efficiency of the MSs, the controlled complexation of challenging guests (e.g. neutral substrates, ion pairs, homomeric and heteromeric substrate assemblies, etc.), or the robust design of appropriate SSs capable of exerting their function in complex biological milieus.

Synthetically speaking, the use of self-assembled organic macrocycles can pave the way not only for increased yields on the macrocyclization reactions, but as well for the introduction of constitutional dynamism on the host-guest assemblies. In this context, it should be noted than the desired goal of controlled binding can be achieved by other means apart from the use of stimuli-responsive hosts or guests. In that manner, as shown in Scheme 48, a stimuli responsive constitutionally dynamic library (CDL) can be envisaged in the form [C_n⇌C⇄C'⇌C'$_n$], in which at least one form of the molecular constituents C or C' is in thermodynamic equilibria with oligomeric cyclic or linear species (C_n or C'$_n$).[275-277] In the presence of a given guest G, if the CDL is able to produce an appropriate host (let's arbitrarily say C_4' = H), the system G⊂[C_n⇌ C⇄C'⇌C'n'] would behave as an SS. In other words, the regulation of the constitutional dynamics of a molecular subcomponent is translated into the controlled binding of a desired guest.

A nice example of this strategy has been recently reported by Yoshizawa *et al.* (Scheme 49).[278] By using amphiphilic anthracene dimers as photoresponsive units, they self-assemble in water to produce different oligomeric aggregates, which organize into small spherical assemblies (o-**96**)$_n$ with a narrow size distribution (n~4-6). Addition of an appropriate aromatic substrate, like the dye Nile Red (NR), produces the shift of the CDL to the production of the complex NR_2⊂(o-**96**)$_6$. Crucially, photoirradiation generates the non-complexing component c-**96**, facilitating the release of the substrate from the self-assembled capsule. Although the recognition of the substrate is not produced by a macrocyclic host, but rather by a non-covalent capsule, the example appropriately exemplifies the advantages of introducing controllable constitutional dynamism into host-guest assemblies.



Scheme 48. Controlled binding by regulation of constitutional dynamic behaviour.



Scheme 49. Polyaromatic nanocapsules as photoresponsive hosts in water. Adapted from ref. 278 with permission from Springer Nature, copyright 2019.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the Ministerio de Economía y Competitividad (MINECO FEDER, Grant CTQ2016-75629-P), Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER) (CTQ2017-89166-R), and Xunta de Galicia (ED431C 2018/39). E. P. thanks the funding received from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 851179), the UDC-Inditex InTalent Pro- gramme for her research contract and funding and the Xunta de Galicia for the Oportunius Programme. I. N. thanks the MECD (FPU program) for financial support.

Notes and references

1 G. Vantomme and E. W. Meijer, *Science*, 2019, **363**, 1396-1397.

2 A. J. Savyasachi, O. Kotova, S. Shanmugaraju, S. J. Bradberry, G. M. O'Máille and T. Gunnlaugsson, *Chem*, 2017, **3**, 764-811.

3 H. Yang, B. Yuan, X. Zhang and O. A. Scherman, *Acc. Chem. Res.*, 2014, **47**, 2106-2115.

4 T. R. Cook, Y.-R. Zheng and P. J. Stang, *Chem. Rev.*, 2013, **113**, 734-777.

5 G. R. Desiraju, *J. Am. Chem. Soc.*, 2013, **135**, 9952-9967.

6 D. A. Uhlenheuer, K. Petkau and L. Brunsveld, *Chem. Soc. Rev.*, 2010, **39**, 2817-2826.

7 M. Grzelczak, J. Vermant, E. M. Furst and L. M. Liz-Marzan, *ACS Nano*, 2010, **4**, 3591-3605.

8 The recent progress on the development of nanomachinery is probably a paradigmatic example of supramolecular chemistry as an enabling strategy for the discovery of new chemical function. For a relevant recent review on the topic, see: S. Kassem, T. van Leeuwen, A. S. Lubbe, M. R. Wilson, B. L. Feringa and D. A. Leigh, *Chem. Soc. Rev.*, 2017, **46**, 2592-2621.

9 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 2495-2496.

10 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017-7036.

11 B. Dietrich, J.-M. Lehn and J.-P. Sauvage, *Tetrahedron Lett.*, 1969, **10**, 2885-2888.

12 B. Dietrich, J.-M. Lehn and J.-P. Sauvage, *Tetrahedron Lett.*, 1969, **10**, 2889-2892.

13 E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 2564-2571.

14 Z. Liu, S. K. M. Nalluri, and J. F. Stoddart, *Chem. Soc. Rev.*, 2017, **46**, 2459-2478.

15 J. Murray, K. Kim, T. Ogoshi, W. Yao and B. C. Gibb, *Chem. Soc. Rev.*, 2017, **46**, 2479-2496.

16 J.-M. Lehn, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, **99**, 4763-4768.

17 J.-M. Lehn, *Science*, 2002, **295**, 2400-2403.

18 J.-M. Lehn, *Angew. Chem. Int. Ed.*, 2013, **52**, 2836-2850.

19 J.-M. Lehn, *Angew. Chem. Int. Ed.*, 2015, **54**, 3276-3289.

20 J.-F. Lutz, J.-M. Lehn, E. W. Meijer and K. Matyjaszewski, *Nat. Rev. Mater.*, 2016, **1**, 16024.

21 S. Mura, J. Nicolas and P. Couvreur, *Nat. Mater.*, 2013, **12**, 991-1003.

22 E. S. Gil and S. M. Hudson, *Prog. Polym. Sci.*, 2004, **29**, 1173-1222.

23 P. M. Mendes, *Chem. Soc. Rev.*, 2008, **37**, 2512-2529.

24 J. Zhuang, M. R., Gordon, J. Ventura, L. Li and S. Thayumanavan, *Chem. Soc. Rev.*, 2013, **42**, 7421-7435.

25 F.-X. Coudert, *Chem. Mater.*, 2015, **27**, 1905-1916.

26 V. Blanco, D. A. Leigh and V. Marcos, *Chem. Soc. Rev.*, 2015, **44**, 5341-5370.

27 E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem. Int. Ed.*, 2007, **46**, 72-191.

28 *Molecular Switches*, ed. B. L. Feringa, Wiley-VCH, Weinheim, 2001.

29 A. Fihey, A. Perrier, W. R. Browned and D. Jacquemin, *Chem. Soc. Rev.*, 2015, **44**, 3719-3759.

30 D. Bléger and S. Hecht, *Angew. Chem. Int. Ed.*, 2015, **54**, 11338–11349.

31 W. R. Browne and B. L. Feringa, *Chimia*, 2010, **64**, 398-403.

32 A. E. Kaifer and M. Gómez-Kaifer, Supramolecular Electrochemistry, Wiley-VCH, Weinheim, 1999.

33 K. C. Leung, C. Chak, C. Lo, W. Wong, S. Xuan and C. H. Cheng, *Chem. Asian J.*, 2009, **4**, 364-381.

34 H. Frisch and P. Besenius, *Macromol. Rapid Commun.*, 2015, **36**, 346-363.

35 V. Martí-Centelles, M. D. Pandey, M. I. Burguete and S. V. Luis, *Chem. Rev.*, 2015, **115**, 8736−8834.

36 J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151-160.

37 R. Klajn, J. F. Stoddart and B. A. Grzybowski, *Chem. Soc. Rev.*, 2010, **39**, 2203-2237.

38 M. Takeuchi, M. Ikeda, A. Sugasaki and S. Shinkai, *Acc. Chem. Res.*, 2001, **34**, 865-873.

39 L. Kovbasyuk and R. Krämer, *Chem. Rev.*, 2004, **104**, 3161-3187.

40 C. Kremer and A. Lützen, *Chem. - Eur. J.*, 2013, **19**, 6162-6196.

41 J. Monod, J.-P. Changeux and F. Jacob, *J. Mol. Biol.*, 1963, **6**, 306-329.

42 D. E. Koshland Jr., G. Némethy and D. Filmer, *Biochemistry*, 1966, **5**, 365-385.

43 H. M. D. Bandaraband and S. C. Burdette, *Chem. Soc. Rev.*, 2012, **41**, 1809-1825.

44 X. Sua and I. Aprahamian, *Chem. Soc. Rev.*, 2014, **43**, 1963-1981.

45 L. Striepe and T. Baumgartner, *Chem. - Eur. J.*, 2017, **23**, 16924-16940.

46 C. Kaes, A. Katz and M. W. Hosseini, *Chem. Rev.*, 2000, **100**, 3553-3590.

47 The stimuli-responsive versions of molecular capsules or cages, even if macrocycle-based, would not be covered in this review, as their host:guest chemistry imply to a great extent the physical trapping of the guest within the confined nanospace defined by the capsule. For reviews on stimuli-responsive containers, see ref. 48-50

48 T. Y. Kim, R. A. S. Vasdev, D. Preston and J. D. Crowley, *Chem. - Eur. J.*, 2018, **24**, 14878-14890.

49 A. Díaz-Moscoso and P. Ballester, *Chem. Commun.*, 2017, **53**, 4635-4652.

50 S. Rieth, K. Hermann, B.-Y. Wang and J. D. Badjic, *Chem. Soc. Rev.*, 2011, **40**, 1609-1622.

51 G. Crini, *Chem. Rev.*, 2014, **114**, 10940-10975.

52 M. Sollogoub, *Synlett*, 2013, **24**, 2629-2640.

53 A. R. Khan, P. Forgo, K. J. Stine and V. T. D'Souza, *Chem. Rev.*, 1998, **98**, 1977-1996.

54 A. P. Croft and R. A. Bartsch, *Tetrahedron*, 1983, **39**, 1417-1474.

55 M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875–1918.

56 C. J. Pedersen and H. K. Frensdorff, *Angew.Chem. Int. Ed. Engl.*, 1972, **11**, 16-25.

57 G. W. Gokel, W. M. Leevy and M. E. Weber, *Chem. Rev.*, 2004, **104**, 2723-2750.

58 R. M. Izatt, J. S. Bradshaw, K. Pawlak, R. L. Bruening and B. J. Tarbet, *Chem. Rev.*, 1992, **92**, 1261-1354.

59 E. Krakowiak, J. S. Bradshaw and D. J. Zamecka-Krakowiak, *Chem. Rev.*, 1989, **89**, 929-972.

60 A.-M. Caminade and J.-P. Majoral, *Chem. Rev.*, 1994, **94**, 1183-1213.

61 S. R. Cooper, *Acc. Chem. Res.*, 1988, **21**, 141-146.

62 J. M. Lehn, *Acc. Chem. Res.*, 1978, **11**, 49-57.

63 J. M. Lehn, *Pure Appl. Chem.*, 1978, **50**, 871-892.

64 S. O. Kang, J. M. Llinares, V. W. Day and K. Bowman-James, *Chem. Soc. Rev.*, 2010, **39**, 3980-4003.

65 For a succinct account by the author on this work, see: J. F. Stoddart, *Pure Appl. Chem.*, 1988, **60**, 467-472.

66 B. L. Allwood, N. Spencer, H. Shahriari-Zavareh, J. F. Stoddart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 1064-1066.

67 P. R. Ashton, P. J. Campbell, E. J. T. Chrystal, P. T. Glinke, S. Menzer, D. Philp, N. Spencer, J. F. Stoddart, P. A. Tasker and D. J. Williams, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 1865-1869.

68 G. Barin, A. Coskun, M. M. G. Fouda and J. F. Stoddart, *ChemPlusChem*, 2012, **77**, 159-185.

69 M. Zhang, X. Yan, F. Huang, Z. Niu and H. W. Gibson, *Acc. Chem. Res.*, 2014, **47**, 1995-2005.

70 C. D. Gutsche, *Calixarenes*, The Royal Society of Chemistry, Cambridge, 1989.

71 C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161-170.

72 S. Shinkai, *Tetrahedron*, 1993, **49**, 8933-8968.

73 S. Shinkai, S. Mori, T. Tsubaki, T. Sone and O. Manabe, *Tetrahedron Lett.*, 1984, **25**, 5315-5318.

74 D.-S. Guo, K. Wang and Y. Liu, *J. Inclusion Phenom. Macrocyclic Chem.*, 2008, **62**, 1−21.

75 D.-S. Guo and Y. Liu, *Acc. Chem. Res.*, 2014, **47**, 1925−1934.

76 V. Böhmer, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 713-745.

77 C. D. Gutsche and L. G. Lin, *Tetrahedron*, 1986, **42**, 1633-1640.

78 J. R. Moran, S. Karbach and D. J. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 5826-5828.

79 S. M., Biros and J. Rebek, Jr., *Chem. Soc. Rev.*, 2007, **36**, 93-104.

80 P. A., Gale, J. L. Sessler, V. Kral and V. Lynch, *J. Am. Chem. Soc.*, 1996, **118**, 5140-5141.

81 I. Saha, J. T. Lee and C.-H. Lee, *Eur. J. Org. Chem.*, 2015, 3859-3885.

82 S. K. Kim and J. L. Sessler, *Acc. Chem. Res.*, 2014, **47**, 2525-2536.

83 J. L. Sessler, P. Anzenbacher, Jr., K. Jursikova, H. Miyaji, J. W. Genge, N. A. Tvermoes, W. E. Allen and J. A. Shiver, *Pure Appl. Chem.*, 1998, **70**, 2401-2408.

84 W. E. Allen, P. A. Gale, C. T. Brown, V. M. Lynch and J. L. Sessler, *J. Am. Chem. Soc.*, 1996, **118**, 12471-12472.

85 S. Bahring, H. D. Root, J. L. Sessler and J. O. Jeppesen, *Org. Biomol. Chem.*, 2019, **17**, 2594-2613.

86 P. Timmerman, W. Verboom and D. N. Reinhoudt, *Tetrahedron*, 1996, **52**, 2663-704.

87 V. K. Jain and P. H. Kanaiya, *Russ. Chem. Rev.*, 2011, **80**, 75-102.

88 H. J. Schneider, and U. Schneider, *J. Inclusion Phenom. Macrocyclic Chem.*, 1994, 19, 67-83.

89 T. Ogoshi, S. Kanai, S. Fujinami, T. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022-5023.

90 N. L. Strutt, H. Zhang, S. T. Schneebeli and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2631-2642.

91 M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294-1308.

92 T. Ogoshi, T. Yamagishi and Y. Nakamoto, *Chem. Rev.*, 2016, **116**, 7937-8002.

93 Y. Wang, G. Ping, and C. Li, *Chem. Commun.*, 2016, **52**, 9858-9872.

94 J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, and K. Kim, *Acc. Chem. Res.* 2003, **36**, 621-630.

95 For a recent and comprehensive review on the topic see: J. Barrow, S. Kasera, M. J. Rowland, J. del Barrio, and O. A. Scherman, *Chem. Rev.* 2015, **115**, 12320-12406.

96 Y. H. Ko, E. Kim, I. Hwanga, and K. Kim, *Chem. Commun.*, 2007, 1305-1315.

97 I. Hwang, W. S. Jeon, H. J. Kim, D. Kim, H. Kim, N. Selvapalam, N. Fujita, S. Shinkai and K. Kim, *Angew. Chem. Int. Ed.*, 2007, **46**, 210-213.

98 K. Kim, N. Selvapalam, Y. H. Ko, K. M. Park, D. Kim, and J. Kim, *Chem. Soc. Rev.*, 2007, **36,** 267-279.

99 E. Pazos, P. Novo, C. Peinador, A. E. Kaifer and M. D. García, *Angew. Chem. Int. Ed.*, 2019, **58**, 403-416.

100 S. Schoder, and C. A. Schalley, *Chem. Commun.*, 2017, **53,** 9546-9549.

101 E. J. Dale, N. A. Vermeulen, M. Juríček, J.C. Barnes, R. M. Young, M. R. Wasielewski and J. F. Stoddart, *Acc. Chem. Res.* 2016, **49**, 262-273.

102 B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1547-1550.

103 P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietraszkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vicent and D. J. Williams, *J. Am. Chem. Soc.*, 1992, **114**, 193-218.

104 M. Bria, G. Cooke, A. Cooper, J. F. Garety, S. Gunatilaka, H. M. Nutley, G. Rabani and P. Woisel, *Tetrahedron Lett.*, 2007, **48**, 301–304.

105 E. J. Dale, N. A. Vermeulen, A. A. Thomas, J. C. Barnes, M. Juríček, A. K. Blackburn, N. L. Strutt, A. A. Sarjeant, C. L. Stern, S. E. Denmark and J. F. Stoddart, *J. Am. Chem. Soc.*, 2014, **136**, 10669-10682

106 W. Liu, S. Bobbala, C. L. Stern, J. E. Hornick, Y. Liu, A. E. Enciso, E. A. Scott, and J. F. Stoddart, *J. Am. Chem. Soc.*, 2020, **142**, 3165-3173.

107 M. Frasconi, I. R. Fernando, Y. Wu, Z. Liu, W.-G. Liu, S. M. Dyar, G. Barin, M. R. Wasielewski, W. A. Goddard III and J. F.Stoddart, *J. Am. Chem. Soc.*, 2015, **137**, 11057-11068.

108 J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2017, **56**, 11094-11125.

109 M. Asakawa, P. R. Ashton, V. Balzani, A. Credi, G. Mattersteig, O. A. Matthews, M. Montalti, N. Spencer, J. F. Stoddart and M. Venturi, *Chem. - Eur. J.* 1997, **3**, 1992-1996.

110 V. Balzani, M. Gómez-López, and J. F. Stoddart, *Acc. Chem. Res.*, 1998, **31**, 405-414

111 R. Ballardini, V. Balzani, M. T. Gandolfi, L. Prodi, M. Venturi, D. Philp, H. G. Ricketts and J. F. Stoddart, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1301-1303.

112 L. Scarpantonio, A. Tron, C. Destribats, P. Godard, and N. D. McClenaghan, *Chem. Commun.*, 2012, **48**, 3981–3983.

113 S. Saha, L. E. Johansson, A. H. Flood, H.-R. Tseng, J. I. Zink, and J. F. Stoddart, *Small*, 2005, **1**, 87-90.

114 S. Saha, E. Johansson, A. H. Flood, H.-R. Tseng, J. I. Zink, and J. F. Stoddart, *Chem. - Eur. J.*, 2007, **11**, 6846-6858.

115 H. Li, C. Cheng, P. R. McGonigal, A.C. Fahrenbach, M. Frasconi, W.-G. Liu, Z. Zhu, Y. Zhao, C. Ke, J. Lei, R. M. Young, S. M. Dyar, D. T. Co, Y.-W. Yang, Y. Y. Botros, W. A. Goddard, III, M. R. Wasielewski, R. D. Astumian, and J. F. Stoddart, *J. Am. Chem. Soc.*, 2013**, 135**, 18609-18620.

116 S. Chia, J. Cao, J. F. Stoddart and J. I. Zink, *Angew. Chem. Int. Ed.*, 2001, **40**, 2447-2451.

117 B. C. Bunker, D. L. Huber, J. G. Kushmerick, T. Dunbar, M. Kelly, C. Matzke, J. Cao, J. O. Jeppesen, J. Perkins, A. H. Flood, and J. F. Stoddart, *Langmuir*, 2007, **23**, 31-34.

118 R. Hernandez, H.-R. Tseng, J. W. Wong, J. F. Stoddart, and J. I. Zink, *J. Am. Chem. Soc.*, 2004, **126**, 3370-3371.

119 T. D. Nguyen, K. C.-F. Leung, M. Liong, Y. Liu, J. F. Stoddart, and J. I. Zink, *Adv. Funct. Mater.*, 2007, **17**, 2101-2110.

120 A. Trabolsi, N. Khashab, A. C. Fahrenbach, D. C. Friedman, M. T. Colvin, K. K. Cotí, D. Benítez, E. Tkatchouk, J.-C. Olsen, M. E. Belowich, R. Carmielli, H. A. Khatib, W. A. Goddard, III, M. R. Wasielewski, and J. F. Stoddart, *Nat. Chem.*, 2010, **2**, 42-49.

121 Y. Wang, M. Frasconi, and J. F. Stoddart, *ACS Cent. Sci.*, 2017, **3**, 927-935.

122 C. Cheng, P. R. McGonigal, W.-G. Liu, H. Li, N. A. Vermeulen, C. Ke, M. Frasconi, C. L. Stern, W. A. Goddard, III, and J. F. Stoddart, *J. Am. Chem. Soc.* 2014, **136**, 14702-14705.

123 C. Cheng, P. R. McGonigal, S. T. Schneebeli, H. Li, N. A. Vermeulen, C. Ke and J. F. Stoddart, *Nat. Nanotechnol.*, 2015, *10*, 547-553.

124 Y. Qiu, L. Zhang, C. Pezzato, Y. Feng, W. Li, M.T. Nguyen, C. Cheng, D. Shen, Q.-H. Guo, Y. Shi, K. Cai, F. M. Alsubaie, R. D. Astumian and J. F. Stoddart, *J. Am. Chem. Soc.* 2019, **141**, 17472-17476.

125 A. Ueno, H. Yoshimura, R. Saka and T. Osa, *J. Am. Chem. Soc.*, 1979, **101**, 2779-2780.

126 A. Ueno, K. Takahashi and T. Osa, *J. Chem. Soc., Chem. Commun.*, 1981, 94-96.

127 S. Shinkai, *Pure Appl. Chem.*, 1987, **59**, 425-430.

128 S. Shinkai, T. Ogawa, T. Nakaji, Y. Kusano and O. Manabe, *Tetrahedron Lett.*, 1979, 4569.

129 S. Shinkai, T. Nakaji, Y. Nishida, T. Ogawa and O. Manabe, *J. Am. Chem. Soc.*, 1980, **102**, 5860-5865.

130 P. T. Glink, C. Schiavo, J. F. Stoddart and D. J. Williams, *Chem. Commun.*, 1996, 1483-1490.

131 M. Liu, X. Yan, M. Hu, X. Chen, M. Zhang, B. Zheng, X. Hu, S. Shao and F. Huang, *Org. Lett.*, 2010, **12**, 2558-2561.

132 J.-F. Xu, Y.-Z. Chen, L.-Z. Wu, C.-H. Tung and Q.-Z. Yang, *Org. Lett.*, **2014**, *16*, 684-687.

133 F. Huang, K. A. Switek and H. W. Gibson, *Chem. Commun.*, 2005, 3655–3657.

134 X. Ji, M. Zhang, X. Yan, J. Li and F. Huang, *Chem. Commun.*, 2013, **49**, 1178−1180.

135 M. Zhang, B. Zheng, B. Xia, K. Zhu, C. Wu and F. Huang, *Eur. J. Org. Chem.*, 2010, 6804-6809.

136 M. Zhang, B. Zheng and F. Huang, *Chem. Commun.*, 2011, **47**, 10103-10105.

137 X. Yan, M. Zhang, P. Wei, B. Zheng, X. Chi, X. Jia and F. Huang, *Chem. Commun.*, 2011, **47**, 9840-9842.

138 Z. Niu, C. Slebodnick, F. Huang, H. Azurmendi and H. W. Gibson, *Tetrahedron Lett.*, 2011, **52**, 6379-6382.

139 Q. Wang, M. Cheng, Y. Zhao, Z. Yang, J. Jiang, L. Wang and Y. Pan, *Chem. Commun.*, 2014, **50**, 15585-15588.

140 R. Rojanathanes, T. Tuntulani, W. Bhanthumnavin and M. Sukwattanasinitt, *Org. Lett.*, 2005, **7**, 3401-3404.

141 A. Lascaux, G. De Leener, L. Fusaro, F. Topić, K. Rissanen, M. Luhmerc and I. Jabin, *Org. Biomol. Chem.*, 2016, **14**, 738-746.

142 A. Lascaux, S. Le Gac, J. Wouters, M. Luhmerd and I. Jabin, *Org. Biomol. Chem.*, 2010, **8**, 4607–4610.

143 M. Ménand and I. Jabin, *Chem. - Eur. J.*, 2010, **16**, 2159-2169.

144 S. Le Gac, X. Zeng, C. Girardot and I. Jabin, *J. Org. Chem.* 2006, **71**, 9233-9236.

145 B. Tomapatanaget, T. Tuntulani and O. Chailapakul, *Org. Lett.*, 2003, **5**, 1539-1542.

146 P. D. Beer, D. Hesek and K. C. Nam, *Organometallics*, 1999, **18**, 3933-3943.

147 M. Muraoka, M. Ohta, Y. Mizutani, M. Takezawa, A. Matsumoto and Y. Nakatsuji, *J. Inclusion Phenom. Macrocyclic Chem.*, 2014, **78**, 137-144.

148 L. Luo, X. Zhang, N. Feng, D. Tian, H. Deng and H. Li, *Sci. Rep.*, 2015, **5**, 8982.

149 T. Haino, Y. Katsutani, H. Akii and Y. Fukazawa, *Tetrahedron Lett.*, 1998, **39**, 8133-8136.

150 J. Mendez-Arroyo, J. Barroso-Flores, A. M. Lifschitz, A. A. Sarjeant, C. L. Stern and C. A. Mirkin, *J. Am. Chem. Soc.*, 2014, **136**, 10340-10348.

151 See, for instance: L. Yang, X. Tan, Z. Wang and X. Zhang, *Chem. Rev.*, 2015, **115**, 7196-7239.

152 For a recent example, see: A. Saura-Sanmartin, A. Martinez-Cuezva, A. Pastor, D. Bautista and J. Berna, *Org. Biomol. Chem.*, 2018, **16**, 6980-6987.

153 J. Rotzler and M. Mayor, *Chem. Soc. Rev.*, 2013, **42**, 44-62.

154 See, for instance, the examples compiled on the review: R. N. Dsouza, U. Pischel and W. M. Nau, *Chem. Rev.*, 2011, **111**, 7941–7980.

155 P. R. Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M. Gómez-López, S. Iqbal, D. Philp, J. A. Preece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White and D. J. Williams, *Chem. - Eur. J.*, 1997, *3*, 152-170.

156 P. R. Ashton, M. Gómez-López, S. Iqbal, J. A. Preece and J. F. Stoddart, *Tetrahedron Lett.*, 1997, **38**, 3635-3638.

157 Y. Liu, A. H. Flood, R. M. Moskowitz, and J. F. Stoddart, *Chem. - Eur. J.* 2005, **11**,369-385.

158 Y. Liu, A. H. Flood, and J. F. Stoddart, *J. Am. Chem. Soc.*, 2004, **126**, 9150-9151.

159 G. Cooke, P. Woisel, M. Bria, F. Delattre, J. F. Garety, S. G. Hewage, G. Rabani and G. M. Rosair, *Org. Lett.*, 2006, **8,** 1423-1426.

160 M. B. Nielsen, S. B. Nielsen and J. Becher, *Chem. Commun.*, 1998, 475-476.

161 M. B. Nielsen, J. G. Hansen and J. Becher, *Eur. J. Org. Chem.*, 1999, 2807-2815.

162 V. Balzani, P. Ceroni, A. Credi, M. Gómez-López, C. Hamers, J. F. Stoddart and R. Wolf, *New J. Chem.*, 2001, **25**, 25-31.

163 F. Jiang, M. Chen, J. Liang, Z. Gao, M. Tang, Z. Xu, B. Peng, S. Zhu and L. Jiang, *Eur. J. Org. Chem.*, 2016, 3310-3315.

164 B. Ferrer, G. Rogez, A. Credi, R. Ballardini, M. T. Gandolfi, V. Balzani, Y. Liu, H.-R. Tseng and J. F. Stoddart, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 18411-18416.

165 G. Rogez, B. Ferrer Ribera, A. Credi, R. Ballardini, M. T. Gandolfi, V.Balzani, Y. Liu, B. H. Northrop and J. F. Stoddart, *J. Am. Chem. Soc.*, 2007, **129**, 4633-4642.

166 A. Ueno, M. Fukushima and T. Osa, *J. Chem. Soc. Perkin Trans. 2*, 1990, 1067-1072.

167 J. Cao, X. Ma, M. Min, T. Cao, S. Wua and H. Tiana, *Chem. Commun.*, 2014, **50**, 3224-3226.

168 M. Fukushima, T. Osa and A. Ueno, *Chem. Lett.*, 1991, 709-712.

169 A. Ueno, Y. Tomita and T. Osa, *Tetrahedron Lett.*, 1983, **24**, 5245-5248.

170 T. Nakagama, K. Hirasawa, K. Uchiyama and T. Hobo, *Anal. Sci.*, 2001, **17**, 119-124.

171 W.-S. Lee and A. Ueno, *Macromol. Rapid Commun.*, 2001, **22**, 448–450.

172 R. J. Coulston, H. Onagi, S. F. Lincoln and C. J. Easton, *J. Am. Chem. Soc.*, 2006, **128**, 14750-14751.

173 P. Liu, C. Chipot, W. Cai and X. Shao, *J. Phys. Chem. C*, 2014, **118**, 12562-12567.

174 P. Liu, X. Shao and W. Cai, *Chin. J. Chem.*, 2015, **33**, 1199-1205.

175 Z.-B. Wang, Y. Takashima, H. Yamaguchi and A. Harada, *Org. Lett.*, 2011, **13**, 4356-4359.

176 K. Omori, Y. Takashima, H. Yamaguchi and A. Harada, *Chem. Lett.*, 2011, **40**, 758-759.

177 H. F. M. Nelissen, F. Venema, R. M. Uittenbogaard, M. C. Feiters and R. J. M. Nolte, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2045-2053.

178 T. Wang, M. D. Wang, C. D. Ding and J. J. Fu, *Chem. Commun.*, 2014, **50**, 12469-12472.

179 T. Wang, C. Wang, S. Zhou, J. H. Xu, W. Jiang, L. H. Tan and J. J. Fu. *Chem. Mater.*, 2017, **29**, 8325-8337.

180 T. Wang, G. P. Sun, M. D. Wang, B. J. Zhou and J. J. Fu, *ACS Appl. Mater. Interfaces*, 2015, **7**, 21295-21304.

181 T. Wang, L. H. Tan, C. D. Ding, M. D. Wang, J. H. Xu and J. J. Fu, *J. Mater. Chem. A*, 2017, **5**, 1756-1768.

182 J. M. Casas-Solvas, E. Ortiz-Salmer, I. Fernández, L. García-Fuentes, F. Santoyo-González and A. Vargas-Berenguel, *Chem. - Eur. J.*, 2009, **15**, 8146-8162.

183 K. A. Nielsen, S. Bähring and J. O. Jeppesen, *Chem. - Eur. J.*, 2011, **17**, 11001-11007.

184 S. Shinkai, M. Ishihara, K. Ueda and O. Manabe, *J. Chem. Soc., Perkin Trans. 2*, 1985, 511-518.

185 D.-H. Qu and B. L. Feringa, *Angew. Chem. Int. Ed.*, 2010, **49**, 1107-1110.

186 O. B. Berryman, A. C. Sather and J. Rebek Jr., *Chem. Commun.*, 2011, **47**, 656–658.

187 O. B. Berryman, A. C. Sather, A. Lledó and J. Rebek, *Angew. Chem. Int. Ed.*, 2011, **50**, 9400-9403.

188 S. Bähring, G. Olsen, P. C. Stein, J. Kongsted and K. A. Nielsen, *Chem. - Eur. J.*, 2013, **19**, 2768-2775.

189 F. Durola and J. Rebek Jr., *Angew. Chem. Int. Ed.*, 2010, **49**, 3189-3191.

190 M. H. Al-Sayah and N. R. Branda, *Org. Lett.*, 2002, **4**, 881-884.

191 D. J. Cram and J. M. Cram, *Container Molecules and their Guests*, The Royal Society of Chemistry, Cambridge, 1994.

192 A. Kikuzawa, T. Kida and M. Akashi, *Org. Lett.*, 2007, **9**, 3909-3912.

193 Y. Molard, D. M. Bassani, J.-P. Desvergne, P. N. Horton, M. B. Hursthouse and J. H. R. Tucker, *Angew. Chem. Int. Ed.*, 2005, **44,** 1072-1075.

194 Y. Molard, D. M. Bassani, J.-P. Desvergne, N. Moran and J. H. R. Tucker, *J. Org. Chem.*, 2006, **71**, 8523-8531.

195 S.-K. Chang and A. D. Hamilton, *J. Am. Chem. Soc.*, 1988, **110**, 1318-1319.

196 C.-K. Liang, G. V. Dubacheva, T. Buffeteau, D. Cavagnat, P. Hapiot, B. Fabre, J. H. R. Tucker and D. M. Bassani, *Chem. - Eur. J.*, 2013, **19**, 12748-12758.

197 A. Tron, P. J. Thornton, C. Lincheneau, J.-P. Desvergne, N. Spencer, J. H. R. Tucker and N. D. McClenaghan, *J. Org. Chem.*, 2015, **80**, 988−996

198 A. Tron, I. Pianet, A. Martinez-Cuezva, J. H. R. Tucker, L. Pisciottani, M. Alajarin, J. Berna and N. D. McClenaghan, *Org. Lett.*, 2017, **19**, 154-157.

199 S. Shinkai, K. Inuzuka and O. Manabe, *Chem. Lett.*, 1983, 747-750.

200 S. Shinkai, K. Inuzuka, K. Hara, T. Sone and O. Manabe, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2150-2155.

201 T. Nabeshima, D. Nishida and T. Saiki, *Tetrahedron*, 2003, **59**, 639-647.

202 C. Schaefer, R. Eckel, R. Ros, J. Mattay and D. Anselmetti, *J. Am. Chem. Soc.*, 2007, **129**, 1488-1489.

203 S. Fery-Forgues and F. Al-Ali, *J. Photochem. Photobiol. C,* 2004, **5**, 139-153.

204 S. Shinkai, T. Nakaji, T. Ogawa, K. Shigematsu and O. Manabe, *J. Am. Chem. Soc.*, 1981, **103**, 111-115.

205 T. Nabeshima, A. Sakiyama, A. Yagyu and N. Furukawa, *Tetrahedron Lett.*, 1989, **30**, 5287-5288.

206 A. Mulder, A. Jukovic, L. N. Lucas, J. van Esch, B. L. Feringa, J. Huskensa and D. N. Reinhoudt, *Chem. Commun.*, 2002, 2734-2735.

207 A. Mulder, A. Jukovic´, J. Huskens and D. N. Reinhoudt, *Org. Biomol. Chem.*, 2004, **2**, 1748-1755.

208 A. Mulder, A. Juković, F. W. B. van Leeuwen, H. Kooijman, A. L. Spek, J. Huskens and D. N. Reinhoudt, *Chem. - Eur. J.*, 2004, **10**, 1114-1123.

209 H.-L. Sun, Y. Chen, J. Zhao and Y. Liu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9376-9380.

210 R. Anand, F. Manoli, A. Vargas-Berenguel and S. Monti, *J. Drug Delivery Sci. Technol.*, 2012, **22**, 266-269.

211 P. D. Beer and A. S. Rothin, *J. Chem. Soc., Chem. Commun.*, 1988, 52-54.

212 A. Lützen, O. Haß and T. Bruhn, *Tetrahedron Lett.*, 2002, **43**, 1807-1811.

213 S. Zahn, W. Reckien, B. Kirchner, H. Staats, J. Matthey and A. Lützen, *Chem. - Eur. J.*, 2009, **15**, 2572-2580.

214 H. Staats, F. Eggers, O. Haß, F. Fahrenkrug, J. Matthey, U. Lüning and A. Lützen, *Eur. J. Org. Chem.*, 2009, 4777–4792.

215 C. Kremer, G. Schnakenburg and A. Lützen, *Beilstein J. Org. Chem.*, 2014, **10**, 814–824.

216 C. Kremer and A. Lützen, *Chem. - Eur. J.*, 2014, **20**, 8852-8855.

217 S. Shinkai, A. Yoshioka, H. Nakayama and O. Manabe, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1905-1909.

218 E. Seward and F. Diederich, *Tetrahedron Lett.*, 1987, **28**, 5111-5114.

219 E. M. Seward, R. B. Hopkins, W. Sauerer, S.-W. Tam and F. Diederich, *J. Am. Chem. Soc.*, 1990, **112**, 1783-1790.

220 H. Kanazawa, M. Higuchi and K. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 16404-16405.

221 B. Masci, S. Pasquale and P. Thuéry, *Org. Lett.*, 2008, **10**, 4835-4838.

222 B. Daly, T. S. Moody, A. J. M. Huxley, C. Yao, B. Schazmann, A. Alves-Areias, J. F. Malone, H. Q. N. Gunaratne, P. Nockemann and A. P. de Silva. *Nat. Commun.*, 2019, **10**, 1-7.

223 Z. Ye, Z. Yang, L. Wang, L. Chen, Y. Cai, P. Deng, W. Feng, X. Li and L. Yuan, *Angew. Chem. Int. Ed.*, 2019, **58**, 12519-12523.

224 S. Li , G.-H. Weng, B. Zheng, X. Yan, J. Wu, W. Lin, H.-X. Chen and X.-C. Zhang, *Eur. J. Org. Chem.*, 2012, 6570-6575.

225 X. Ji, J. Li, J. Chen, X. Chi, K. Zhu, X. Yan, M. Zhang and F. Huang, *Macromolecules*, 2012, **45**, 6457-6463.

226 R. Ballardini, V. Balzani, A. Di Fabio, M. T. Gandolfi, J. Becher, J. Lau, M. B. Nielsen and J. F. Stoddart, *New J. Chem.*, 2001, **25**, 293-298.

227 I. Pochorovski and F. Diederich, *Acc. Chem. Res.*, 2014, **47**, 2096-2105.

228 C. Gropp, B. L. Quigley and F. Diederich, *J. Am. Chem. Soc.*, 2018, **140**, 2705-2717.

229 J. V. Milic and F. Diederich, *Chem. - Eur. J.*, 2019, **25**, 8440-8452.

230 I. Pochorovski, J. Milić, D. Kolarski, C. Gropp, W. B. Schweizer and F. Diederich, *J. Am. Chem. Soc.*, 2014, **136**, 3852−3858.

231 S. Ruiz-Botella, P. Vidossich, G. Ujaque, C. Vicent and E. Peris, *Chem. - Eur. J.*, 2015, **21**, 10558-10565.

232 T. Ogoshi, T. Akutsu, Y. Shimada and T. Yamagishi, *Chem. Commun.*, 2016, **52**, 6479-6481.

233 W.-B. Hu, W.-J. Hu, X.-L. Zhao, Y. A. Liu, J.-S. Li, B. Jiang and K. Wen, *J. Org. Chem.*, 2016, **81**, 3877-3881.

234 G. Yu, X. Zhou, Z. Zhang, C. Han, Z. Mao, C. Gao and F. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 19489-19497.

235 Z. Li, J. Yang, G. Yu, J. He, Z. Abliz and F. Huang, *Chem. Commun.*, 2014, **50**, 2841-2843.

236 Z. Li, J. Yang, G. Yu, J. He, Z. Abliz and F. Huang, *Org. Lett.*, 2014, **16**, 2066-2069.

237 J. Yang, X. Chi, Z. Li, G. Yu, J. He, Z. Abliz, N. Lia and F. Huang, *Org. Chem. Front.*, 2014, **1**, 630-633.

238 Z. Li, J. Yang, and F. Huang, *Chin. J. Chem.* 2018, **36**, 59-62.

239 Z. Li, G. Yu and J. Yang, *Org. Chem. Front.*, 2017, **4**, 115-118.

240 Y. Liu, F. Zhou, F. Yang and D. Ma, *Org. Biomol. Chem.*, 2019, **17**, 5106-5111.

241 X. Wu, L. Gao, X.-Y. Hu and L. Wang, *Chem. Rec.*, 2016, **16**, 1216–1227.

242 T. Xiao, W. Zhong, L. Xu, X.-Q. Sun, X.-Y. Hu and L. Wang, *Org. Biomol. Chem.*, 2019, **17**, 1336-1350.

243 Q. Duan, Y. Cao, Y. Li, X.-Y. Hu, T. Xiao, C. Lin, Y. Pan and L. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 10542-10549.

244 J. Zhou, G. Yu, L. Shao, B. Hua and F. Huang, *Chem. Commun.*, 2015, **51**, 4188-4191.

245 J. Ma, Q. Meng, X. Hu, B. Li, S. Ma, B. Hu, J. Li, X. Jia and C. Li, *Org. Lett.*, 2016, **18**, 5740-5743.

246 Y. Zhou, K. Jie and Y. Yao, *New J. Chem.*, 2017, **41**, 916-919.

247 G.-W. Zhang, Y. Han, Y. Han, Y. Wang and C.-F. Chen, *Chem. Commun.*, 2017, **53**, 10433-10436.

248 D. Xia, Y. Li, K. Jie, B. Shi and Y. Yao, *Org. Lett.*, 2016, **18**, 2910-2913.

249 K. Jie, Y. Zhou, Y. Yao, B. Shi and F. Huang, *J. Am. Chem. Soc.*, 2015, **137**, 10472-10475.

250 K. Jie, Y. Yao, X. Chi and F. Huang, *Chem. Commun.*, 2014, **50**, 5503-5505.

251 Y. Yao, P. Wei, S. Yue, J. Li and M. Xue, *RSC Adv.*, 2014, **4**, 6042-6047.

252 T. Ogoshi, S. Takashima and T. Yamagishi, *J. Am. Chem. Soc.*, 2015, **137**, 10962-10964.

253 T. Ogoshi, S. Takashima and T. Yamagishi, *J. Am. Chem. Soc.*, 2018, **140**, 1544-1548.

254 D. Kaizerman-Kane, M. Hadar, N. Tal, R. Dobrovetsky, Y. Zafrani and Y. Cohen, *Angew. Chem. Int. Ed.*, 2019, **58**, 5302.

255 Y. Zhou, K. Jie and F. Huang, *Chem. Commun.*, 2018, **54**, 12856-12859.

256 Y. Zhou, K. Jie and F. Huang, *Org. Chem. Front.*, 2017, **4**, 2387-2391.

257 Y. Zhou, K. Jie and F. Huang, *Chem. Commun.*, 2017, **53**, 8364-8367.

258 K. Cai, Y. Shi, C. Cao, S. Vemuri, B. Cui, D. Shen, H. Wu, L. Zhang, Y. Qiu, H. Chen, Y. Jiao, C. L. Stern, F. M. Alsubaie, H. Xiao, J. Li and J. F. Stoddart, *Chem. Sci.*, 2020, **11**, 107-112.

259 M. Berville, L. Karmazin, J. A. Wytko and J. Weiss, *Chem. Commun.*, 2015, **51**, 15772-15775.

260 P. R. Ashton, V. Balzani, O. Kocian, L. Prodi, N. Spencer and J. F. Stoddart, *J. Am. Chem. Soc.*, 1998, **120**, 11190-11191.

261 H. Wu, Y. Chen, L. Zhang, O. Anamimoghadam, D. Shen, Z. Liu, K. Cai, C. Pezzato, C. L. Stern, Y. Liu and J. F. Stoddart, *J. Am. Chem. Soc.*, 2019, **141**, 1280-1289.

262 B. M. Rambo, H.-Y. Gong, M. Oh and J. L. Sessler, *Acc. Chem. Res.*, 2012, **45**, 1390-1401.

263 X. Chi, W. Cen, J. A. Queenan, L. Long, V. M. Lynch, N. M. Khashab and J. L. Sessler, *J. Am. Chem. Soc.*, 2019, **141**, 6468-6472.

264 S. T. J. Ryan, J. del Barrio, R. Suardíaz, D. F. Ryan, E. Rosta and O. A. Scherman, *Angew. Chem. Int. Ed.*, 2016, **55**, 16096-16100.

265 J. Wei, T.-T. Jin, J.-X. Yang, X.-M. Jiang, L.-J. Liu, T.-G. Zhan and K.-D. Zhang, *Tetrahedron Lett.*, 2020, **61**, 151389.

266 A. Blanco-Gómez, A. Fernández-Blanco, V. Blanco, J. Rodríguez, C. Peinador and M. D. García, *J. Am. Chem. Soc.*, 2019, **141**, 3959-3964.

267 A. Blanco-Gómez, I. Neira, J. L. Barriada, M. Melle-Franco, C. Peinador and M. D. García, *Chem. Sci.*, 2019, **10**, 10680-10686.

268 K. Kurihara, K. Yazaki, M. Akita and M. Yoshizawa, *Angew. Chem. Int. Ed.*, 2017, **56**, 11360-11364.

269 M. J. Langton and Paul D. Beer, *Acc. Chem. Res.*, 2014, **47**, 1935-1949.

270 K. M. Mullen, J. J. Davis and P. D. Beer, *New J. Chem.*, 2009, **33**, 769-776.

271 M.-L. Yen, W.-S. Li, C.-C. Lai, I. Chao and S.-H. Chiu, *Org. Lett.*, 2006, **8**, 3223-3226.

272 Y. Han, Z. Meng, Y.-X. Ma and C.-F. Chen, *Acc. Chem. Res.*, 2014, **47,** 2026-2040.

273 T. Han, Q.-S. Zong and C.-F. Chen, *J. Org. Chem*., 2007, **72**, 3108-3111.

274 Y. Han, J. Guo and C.-F. Chen, *Chin. J. Chem.*, 2014, **32**, 721-726.

275 J.-M. Lehn, *Chem. - Eur. J.*, 1999, **5**, 2455-2463.

276 P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652-3711.

277 M. Mondala and A. K. H. Hirsch, *Chem. Soc. Rev.*, 2015, **44**, 2455-2488.

278 L. Catti, N. Kishida, T. Kai, M. Akita and M. Yoshizawa, *Nat. Commun.*, 2019, **10**, 1.