CB[8]-Based Supramolecular Switches

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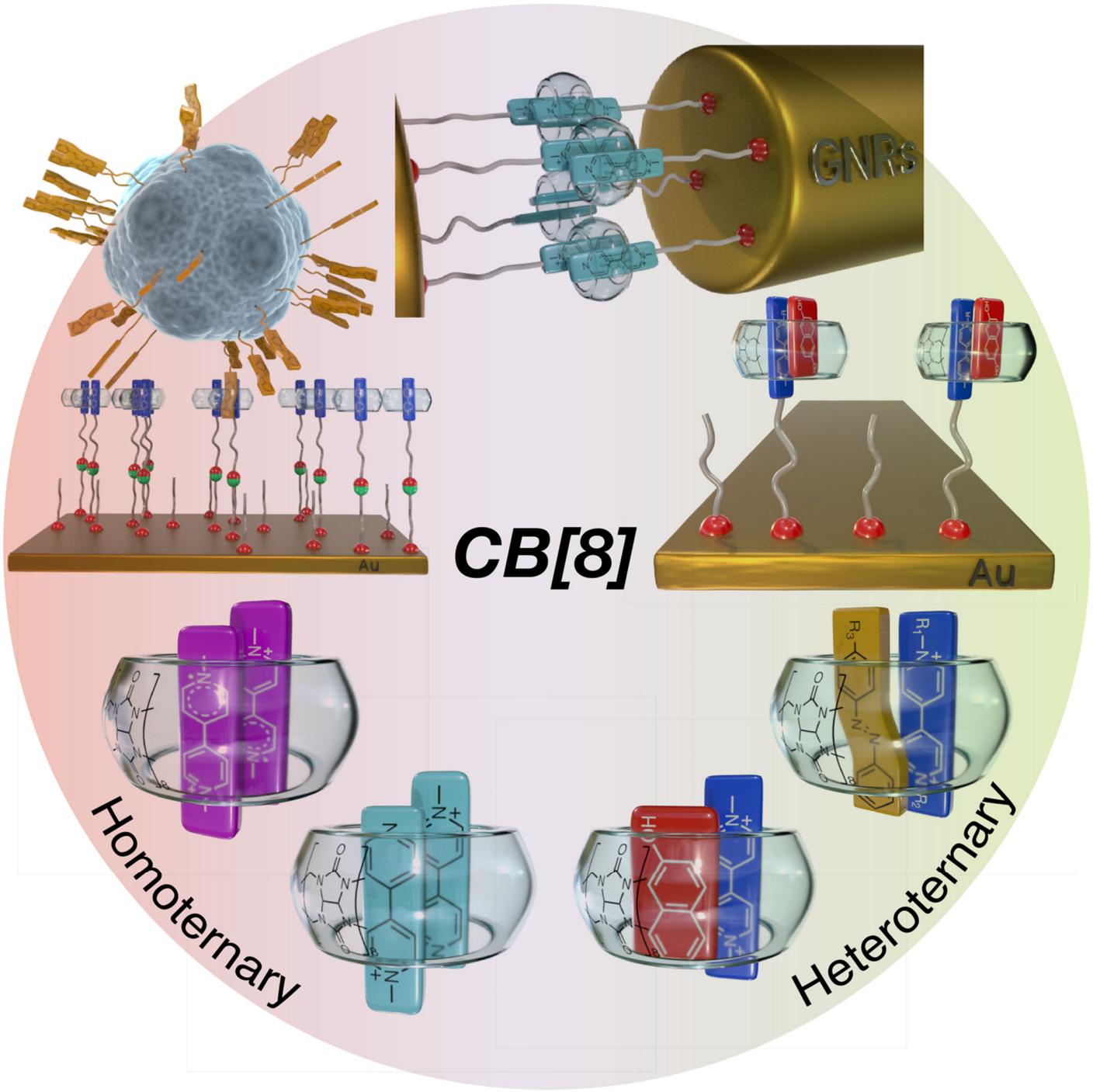


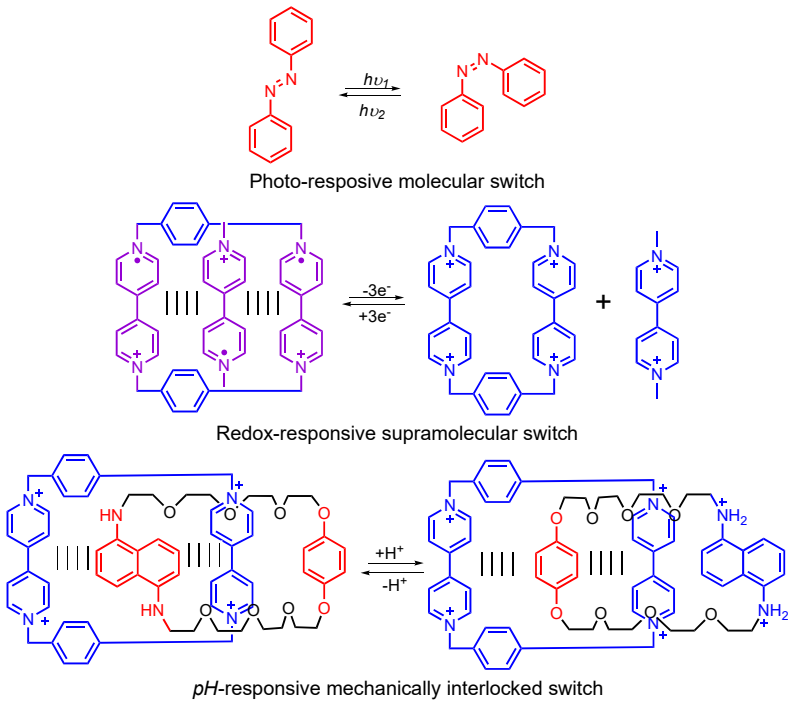
Abstract: The use of cucurbit[8]uril as molecular host has emerged in the chemical literature as a reliable strategy for the creation of dynamic chemical systems, due to its ability to form homo- and heteroternary complexes in aqueous media with appropriate molecular switches as guests. In that manner, CB[8]-based supramolecular switches can be designed in a predictable and modular fashion, through the election of appropriate guests able to condition the redox, photochemical or pH-triggered behaviour of tailored multicomponent systems. Furthermore, CB[8] allows the implementation of dual/triple and linear/orthogonal stimuli-dependent properties into these molecular devices by a careful election of the guests. This versatility on their design endows these supramolecular switches a huge potential for the rational development of new materials, where their function is not only determined by the custom-made stimuli-responsiveness, but also by the transient aggregation/disaggregation of homo- or heteromeric building blocks.

1. Introduction

Chemistry is increasingly moving its attention from the preparation and study of isolated static structures to the development of multicomponent responsive systems,[1] inspired by Nature's infinite talent to create complex functional matter by controlling the structural and dynamic features on the self-assembly of a handful of building blocks.[2]

In order to gain the desired spatiotemporal control over these abiotic ensembles, molecular switches have become the weapon of choice among chemists.[3] According to Grzybowski et al,[4] these devices can be defined and classified as "molecular, supramolecular, or mechanically interlocked entities capable of reversibly changing its shape in response to an external stimulus" (**Scheme 1**).

Specifically, a supramolecular switch is defined as a molecular device comprised of two or more self-assembled units, whose association can be transiently promoted or disrupted by the application of an external stimuli such as light, electrical potentials or chemical effectors. Crucially, in order to perform their function interconverting between structurally different equilibrium states, (supra)molecular switches sequentially use divergent energy inputs (a fuel and an antifuel). By doing so, the net mechanical work produced is null, a fact that certainly hampers the use of these devices on their own as artificial molecular machines.[5] Nevertheless, if we need those nanomachines to perform autonomous processes we will certainly require means to rule them.[6] (Supra)molecular switches are intrinsically well-suited for performing not only those controlling tasks, but for allowing a myriad of other man-operated multifaceted functions, such as those required on chemically-mediated digital processing,[7] smart molecular receptors and sensors,[8] supramolecular drug delivery systems,[9] controllable catalysis,[10] and other complex stimuli-responsive materials.[11]



Scheme 1. Examples of reversible photo-, redox-, and pH-driven molecular, supramolecular, and mechanically interlocked switches, respectively.[4]

In the present review, we will try to illustrate how the unique host-guest chemistry of cucurbit[8]uril has revolutionized the field of the design of supramolecular switches, allowing for the rational and modular development of dynamic multicomponent self-assembled aggregates, where the reversible temporal linking of homomeric or heteromeric building blocks is translated into functional chemical systems.

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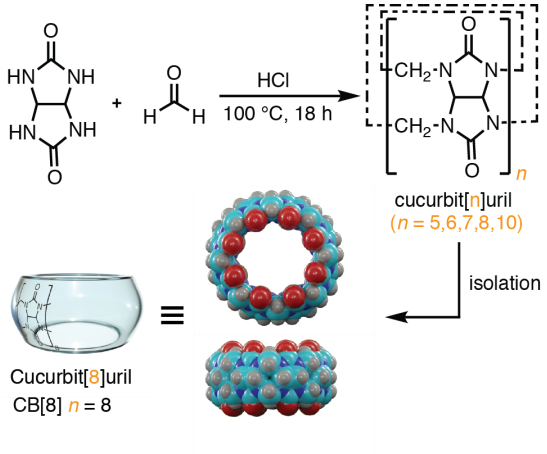
1.1. Cucurbit[8]uril: a unique molecular receptor

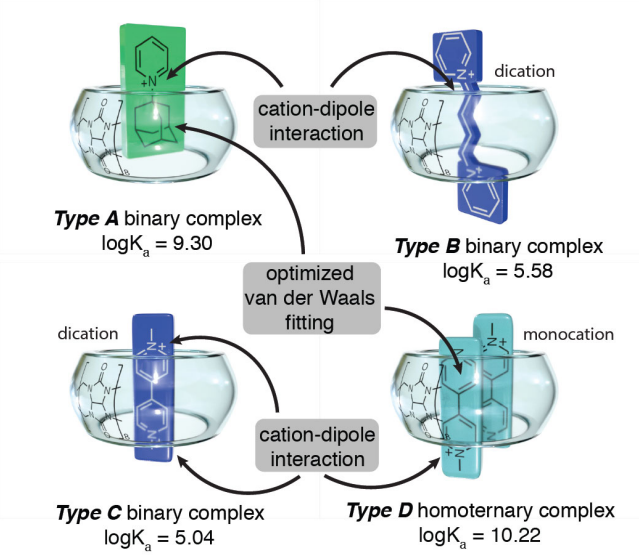
Cucurbit[n]urils (CB[n]s, n = 5–8, 10, 13–15, **Scheme 2**), constitute a well-suited family of building blocks for the construction of supramolecular switches, which are able to act in aqueous media as hosts of a huge variety of static and stimuli-responsive guests.[12] Structurally, CB[n]s are shaped by n glycoluril units joined together by 2n methylene bridges, producing pumpkin-shaped hollow molecules with an inner hydrophobic cavity accessible through two identical carbonyl-laced portals. CB[n]s exert their function as molecular receptors on the basis of these structural features, resulting in hosts capable of forming inclusion complexes with neutral or cationic organic guests by cation-dipole interactions,[13] hydrophobic forces,[14] and optimization of host-guest packing coefficients.[15] Furthermore, CB[n]s share among them some optimal characteristics for the development of potential applications, as they are commercially available, fairly non-reactive,[16] non-toxic,[17] and adequately soluble in aqueous media.[18]



Scheme 2. Synthesis of CB[n]s by the reaction between glycoluril and formaldehyde (top). Space filling model and schematic depiction of CB[8] (bottom).

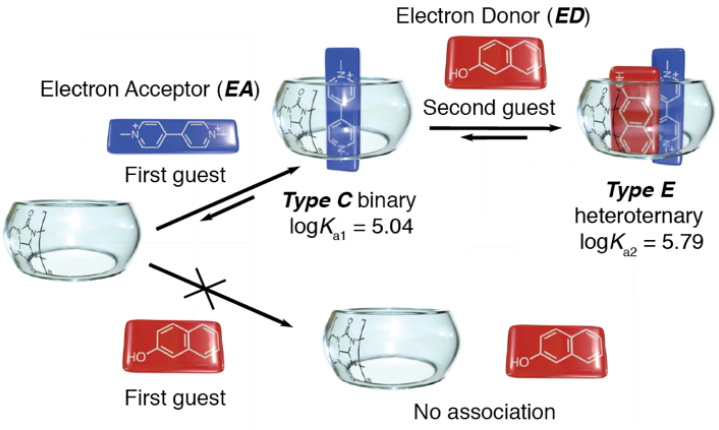
In particular, CB[8] was first synthesized, isolated and characterized by Kim *et al* nearly two decades ago.[19] Having a cavity of 493 Å^3 and 1.7 times the volume of CB[7], CB[8] was identified as the first member of the cucurbituril family able to form 1:2 complexes with appropriate guests. Considering the potential intermolecular interactions described above for the CB[n] family, the host-guest chemistry of CB[8] is somehow predictable (**Scheme 3**).

Thus, CB[8] was found to form **type A** binary complexes with monocationic guests owning bulky hydrophobic moieties, which establish cation-dipole interactions with one of the two portals and at the same time optimize the packing coefficient (e.g. 1-(adamantan-1-yl)pyridin-1-ium cation).[15b] **Type B** and **C** binary complexes are formed by dicationic guests that establish cation-dipole interactions with both portals, and differ only on the nature of the aliphatic or electron-acceptor aromatic regions introduced into the cavity of the host (e.g. butyl vs bipyridyl moieties within 1,1'-(butane-1,4-diyl)bis(pyridin-1-ium) and dimethyl-viologen cations, MV^{2+}, respectively). Furthermore, due to the large cavity of the receptor, **type D** homoternary 1:2 host:guest (HG_2) complexes can be as well anticipated, rendering aggregates in which two identical monocationic guests of appropriate size are able to maximize both the packing coefficient and two cation-dipole interactions, by positioning themselves into a complementary antiparallel fashion (e.g. two 1-methyl-[4,4'-bipyridin]-1-ium cations). In most cases, the cation-dipole interactions have been found to be crucial for the formation of these complexes, since the molecular receptor is not able to bind neutral substrates based only on hydrophobic interactions.[13,14]



Scheme 3. Expected **type A-D** CB[8]-guest complexes, based on the maximization of cation-dipole interactions,[13] hydrophobic effect[14] and optimization of packing coefficients.[15]

Despite the rich host-guest chemistry just described for CB[8], and related to the increased volume of its cavity compared with other CB[n]s, the uniqueness of CB[8] as molecular receptor is expanded by the very nature of its hollow structure. As analyzed by Scherman *et al*,[20] CB[8] displays a largely negative but rather uniform electrostatic potential inside its cavity, which shows regions of concentrated electron density more constrained to the portal areas than smaller homologues. This fact makes CB[8] a unique molecular receptor with a hydrophobic but polar cavity capable of stabilizing charge-transfer interactions between two guests of complementary nature, such as aromatic electron acceptors and donors.[21] Consequently, **type E** 1:1:1 heteroternary (HGG') complexes can be effectively developed but, first, an adequate **type C** binary aggregate should be obtained. In this case, the electron acceptor guest would have the ability to act as signal molecule, thus facilitating the binding of an otherwise non-associable electron donor as guest (**Scheme 4**).
It should be noted that this ability to form heteroternary complexes is quite rare among molecular receptors and, in most of the cases, the designed strategy for the formation of such aggregates makes use of host-guest van der Waals matching, where the host is too small or too big for the potential homodimers, but ideal for the dimensional fitting of the heterodimer.[22] Only few examples of hosts different than CB[8] make use of enhanced intermolecular interactions between guest pairs,[22,23] therefore making CB[8] an exceptional receptor as it facilitates the systematization on the election of heteropairs included on its cavity on the basis of foreseeable charge transfer interactions.[20]

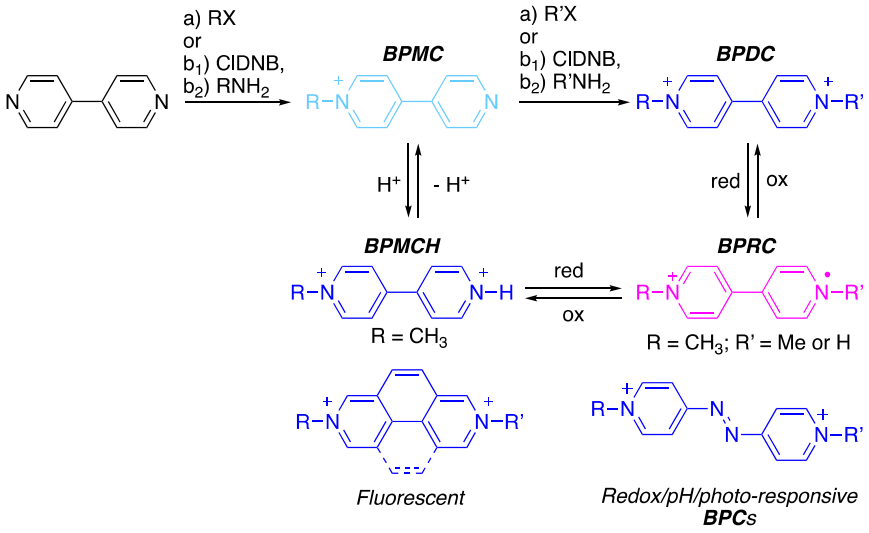


Scheme 4. Example of the sequential self-assembly of a **type E** heteroternary complex, *via* the initial formation of a **type C** intermediate with an aromatic bipyridine-based cation as first guest.

This host-guest chemistry of CB[8] has been extensively developed over the last two decades,[12] and incorporated into the toolbox of supramolecular chemistry as a powerful instrument for the construction of static aggregates, enabling the permanent linking of appropriately-functionalized homomeric and heteromeric building blocks. For example, following the pioneering discovery made by Urbach *et al*,[24] describing the CB[8]-mediated *N*-terminal recognition and dimerization of Phe-Gly-Gly peptides (Log$K_{1:2}$ = 11.17), such processes have found success for the supramolecular dimerization[25] or oligomerization[26] of appropriately-modified proteins.
Nevertheless, and as we would try to illustrate in this review, the true potential of CB[8]-based host-guest systems resides on the use of stimuli-responsive guests, since their activation/deactivation would lead to metastable states of the corresponding supramolecular systems, which can be controlled to produce reversible functions by supramolecular switching.

1.2. 4,4'-bipyridine-based cations as appropriate guests for CB[8]

The predictability of the requisites explained for the formation of CB[8]-based aggregates, at least one monocationic species on the system and a desirable dimensional matching between host and guests, immediately unlocked the use of 4,4'-bipyridine-based cations (BPCs) as substrates. These stable organic salts are a well-known class of redox-responsive electron acceptor molecules, which have been extensively used in the development of electrochromic[27] and other functional materials,[28] or as building blocks in supramolecular chemistry,[29] on the basis of their reversible one or two-electron reduction.[30]
As shown in **Scheme 5**, mono/di quaternization of the nitrogen atoms of 4,4'-bipyridine, leading to the corresponding mono/di cations, can be easily done by sequential nucleophilic substitution with an appropriate electrophile, Zincke reaction *via* activation of the pyridine rings,[30] or a combination of both synthetic protocols,[31] which allows the fine-tuning of the substitution pattern on the 4,4'-bipyridine scaffold. In the case of the bipyridine monocations, the non-alkylated nitrogen can be easily protonated, resulting therefore in acid-base responsive BPCs. Furthermore, the protonated derivative would have similar redox responsiveness compared with bipyridine dications,[32] based on the one-electron reduction of those that produces the corresponding radical monocation. In general, bipyridine-based cations can be easily fine-tuned, modifying their electron-acceptor capabilities and redox potentials, introducing convenient absorption/emission properties, or implementing fully reversible dual or triple redox/pH/photochemical-responsiveness.[30-33]

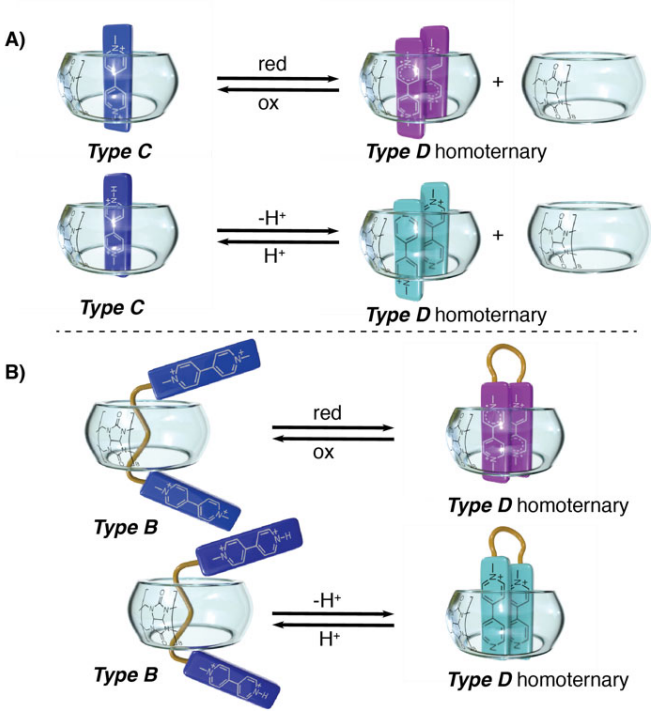


Scheme 5. Synthesis and stimuli-responsive behaviour of bipyridine-based cations (BPCs): bipyridine monocations (BPMCs), bipyridine dications (BPDCs and BPDCHs), and bipyridine radical monocations (BPRCs).

2. Reversible switching of homoternary CB[8]-based complexes

By exploiting both the characteristics of CB[8] as host and bipyridine-based cations as appropriate stimuli-responsive guests, Kim *et al* reported an influential work of a **type C** 1:1 complex between CB[8] and dimethyl-viologen (MV^{2+}) as prototypic bipyridine dication (K_a = 1.1 x 10^5 M^{-1}) in aqueous media. This aggregate was found to convert completely and reversibly upon reduction of the guest to the **type D** 1:2 homoternary aggregate CB[8]:$(MV^{+\bullet})_2$ (**Scheme 6A**).[34] Remarkably, the apparent dimerization constant of the later process in presence of CB[8] was estimated to be as high as K_{dim} = 2 x 10^7 M^{-1}, five orders of magnitude larger than without the host, accounting for the ability of CB[8] to provide the dimer with an appropriate hydrophobic but polarized environment. In a later work by Sun *et al*, it was demonstrated that the discussed redox-controlled switch can be triggered by a photochemical stimulus using a covalently-linked Ru(II)complex-MV^{2+} hybrid.[35]

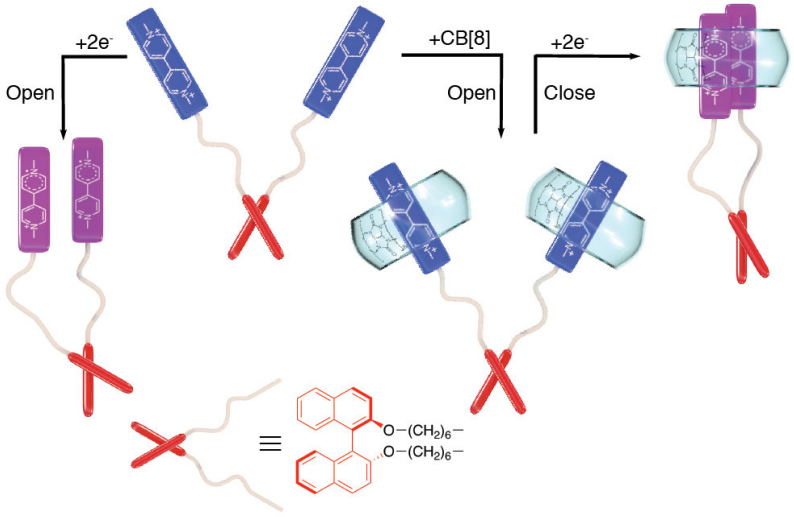
Similar to the redox-controlled dimerization of bipyridine dications, Urbach *et al* reported how the same type of conversion between binary and homoternary complexes can be reversibly achieved by an acid-base stimulus.[36] In this case, a fully reversible interconversion of **type C-D** aggregates can be simply accomplished by the protonation/deprotonation of the 1-methyl-[4,4'-bipyridin]-1-ium monocation used as guest (**Scheme 6A**).



Scheme 6. Schematic representations of inter (A) and intramolecular (B) redox or acid-base **type C-D** or **B-D** switches between binary and homoternary CB[8]-BPC complexes.

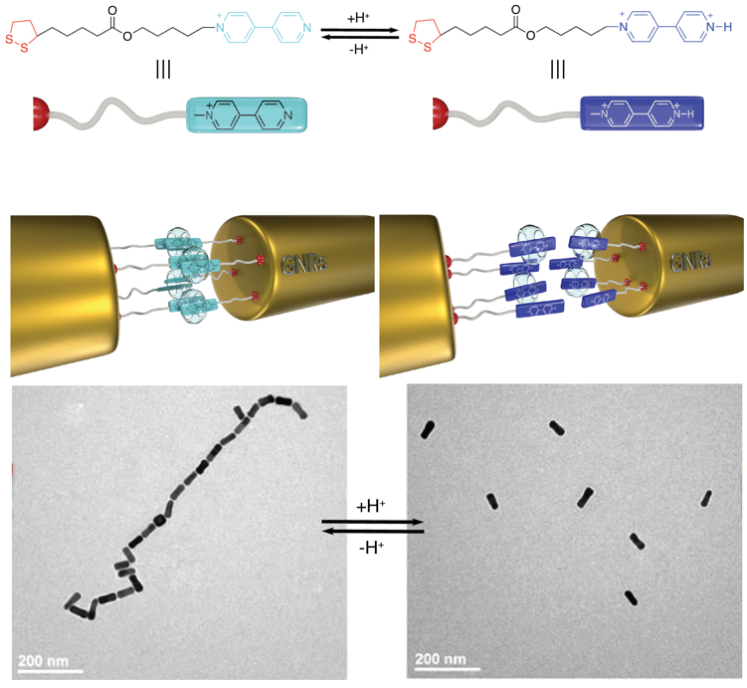
The reversible switching between monomeric and dimeric homoaggregates demonstrated in these seminal works, coupled with the ease of functionalization of 4,4'-bipyridine, quickly facilitated the development of functional applications involving the reversible linking of homomeric building blocks. In this manner, the first examples of implementation of these switches were on the development of supramolecular actuators, with two very similar works demonstrating the interconversion between pseudorotaxanes and molecular loops by means of redox[37] or acid-base[38] stimulus (**Scheme 6B**). In both cases, a kinetically-stable [2]pseudorotaxane-based aggregate owning a **type B** structure, with CB[8] acting as bead and a hexamethylene-bridged *bis*-bipyridine-based cation as thread, can be reversibly transformed into a **type D** molecular loop after the application of the corresponding stimuli.

Following this trend, and applying the reversible CB[8]-based **type C-D** redox-switching in flexible covalently-connected *bis*-bipyridine dications, Credi *et al* reported a series of supramolecular actuators based on tweezer-like molecules, implementing two 4,4'-bipyridinium arms attached to a chiral 1,1'-binaphthyl unit as a hinge. In aqueous media, the twist angle of the chiral aromatic moiety, and therefore the helicity of the system, can be reversibly modulated by reduction of the bipyridinium moieties, and/or addition of CB[8], showing non-trivial XNOR logic gate behaviors (**Scheme 7**).[39]



Scheme 7. Implementation of a CB[8]-based **type C-D** redox switch into a chemical logic gate.[39]

Interestingly, Kathiresan *et al* have reported the use of rigid instead of flexible linkers in *bis*/*tris*-bipyridine dications, avoiding in this manner the intramolecular ($MV^{+\bullet}$) pairing inside the cucurbituril, to produce reversible and redox-controlled polymerizations through **type C-D** interconversions.[40] In the same context, this redox-switch has been utilized as well for the reversible homodimerization of MV^{2+}-containing dendrimers,[41] as well as in the UV-triggered transient aggregation of TiO_2 nanoparticles functionalized with bipyridine dications.[42]



Scheme 8. Reversible pH-controlled oligomerization of MV^{2+}-functionalized gold nanorods through a **type C-D** complex interconversion.[45]

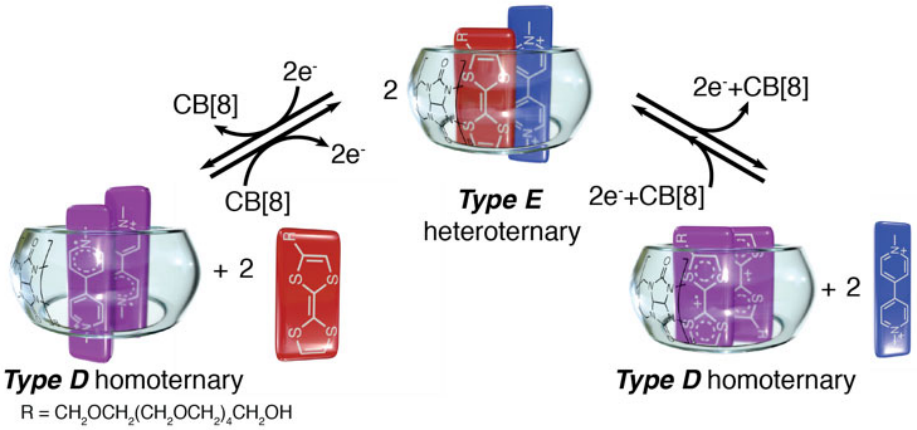
Finally, following the initial work on the pH-controlled intra/intermolecular dimerization of bipyridine monocations by CB[8], several reports have demonstrated its utility for the reversible supramolecular macrocyclization of rigid covalently-linked *bis*-bipyridine monocations,[43] the controlled intercrossing of the linear covalent polymer poly(*N*-(4-vinylbenzyl)-4,4′-bipyridinium dichloride-co-acrylamide into three-dimensional hydrogels,[44] or the controlled aggregation of BPC-functionalized gold nanorods (**Scheme 8**).[45]

3. Reversible switching of heteroternary CB[8]-complexes

Despite the potential of the redox or pH-driven binary-homoternary switches described in the previous section, most of the efforts on the development of CB[8]:BPCs-based supramolecular switches have made use of the unique capability of CB[8] to form heteroternary complexes with aromatic electron donors as second guests.[20] Having this in mind, and prior to introduce the different types of dynamic CB[8]-based heteroternary systems, the design principles for the creation of static CB[8]-based heteroternary aggregates will be briefly discussed.

3.1. Design principles for the preparation of CB[8]-based heteroternary complexes

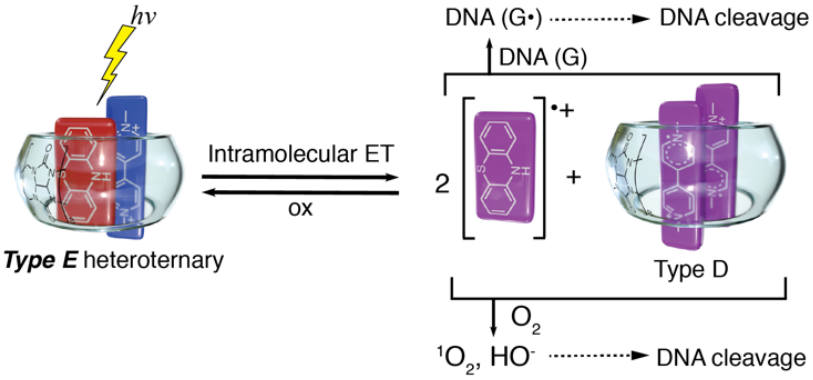
Since the discovery of the ability of CB[8] to produce heteroternary (HGG') complexes by host-enhanced charge transfer, the strategy has been extensively used for the permanent linking of extended architectures by using complementary BPCs and electron donor moieties as building blocks. In that fashion, it has been reported the preparation of a large number of static aggregates, such as small-molecule-based supramolecular polymers, polymer-based supramolecular polymers, peptides, proteins, micro/nanoparticles, etc.[12]
In 2008, Scherman *et al* envisioned for the first time the potential of the strategy in the context of the synthesis of supramolecular block copolymers, using the term "*supramolecular handcuff*" to describe the CB[8]-conditioned attachment.[46] In further works, this research group explored the requirements for the optimization of the charge transfer aggregate founded on the structural features of both the bipyridine-based cations[20] and electron donors.[47] Concerning the bipyridine dications, and as it would be expected, the higher its electron-acceptor ability the larger the stabilization of the charge transfer heteropair on the cavity of the receptor. Consequently, the association constants for a series of bipyridine dications and 2,6-dihydroxinaphthalene as prototypical electron donor nicely illustrates this trend, with values ranging from K_{a2} = 2.9 × 10^3 - 3.0 × 10^5 M^{-1}, depending on the pattern of the functionalization on the BPC.[20] On the other hand, binding constants ranging from 10^2-10^6 M^{-1} have been also reported for a wide variety of electron donors as second guests complexing to preformed CB[8]:MV^{2+}. In this case, although hydrophobic aromatic compounds are the best second guests for this system, polar electron-rich aromatic compounds with multiple hydroxyl functionalities bind with higher affinity to viologen derivatives with strong electron-accepting groups.[47]
Scherman *et al* have also studied the kinetics of the inclusion complexes between a series of electron donor guests to form **type E** heteroternary complexes, starting from the archetypical CB[8]:·MV^{2+} 1:1 aggregate.[48] In all cases, the association of the second guest proceeds with a very high rate constant (k_{a2} ≥ 10^7 M^{-1} s^{-1}) regardless of the nature of the second guest. Conversely, on the case of the dissociative rate constant, k_{d2} values were found to be 4−6 orders of magnitude lower than the corresponding k_{a2} values, showing also a strong correlation with the structure of the second guest and its thermodynamic binding constants K_{a2}. These results imply an impressive degree of flexibility on the design of the dynamics of CB[8]-based heteroternary systems.
These thoughtful reports by the Cambridge-based group are of great value for the rationalization of the design of CB[8]-based supramolecular switches, offering robust design principles grounded on the flexible thermodynamics and kinetics found for the heteroternary aggregates.



Scheme 9. Dual orthogonal reversible redox responsiveness of a **type D-E-D** complex.[51]

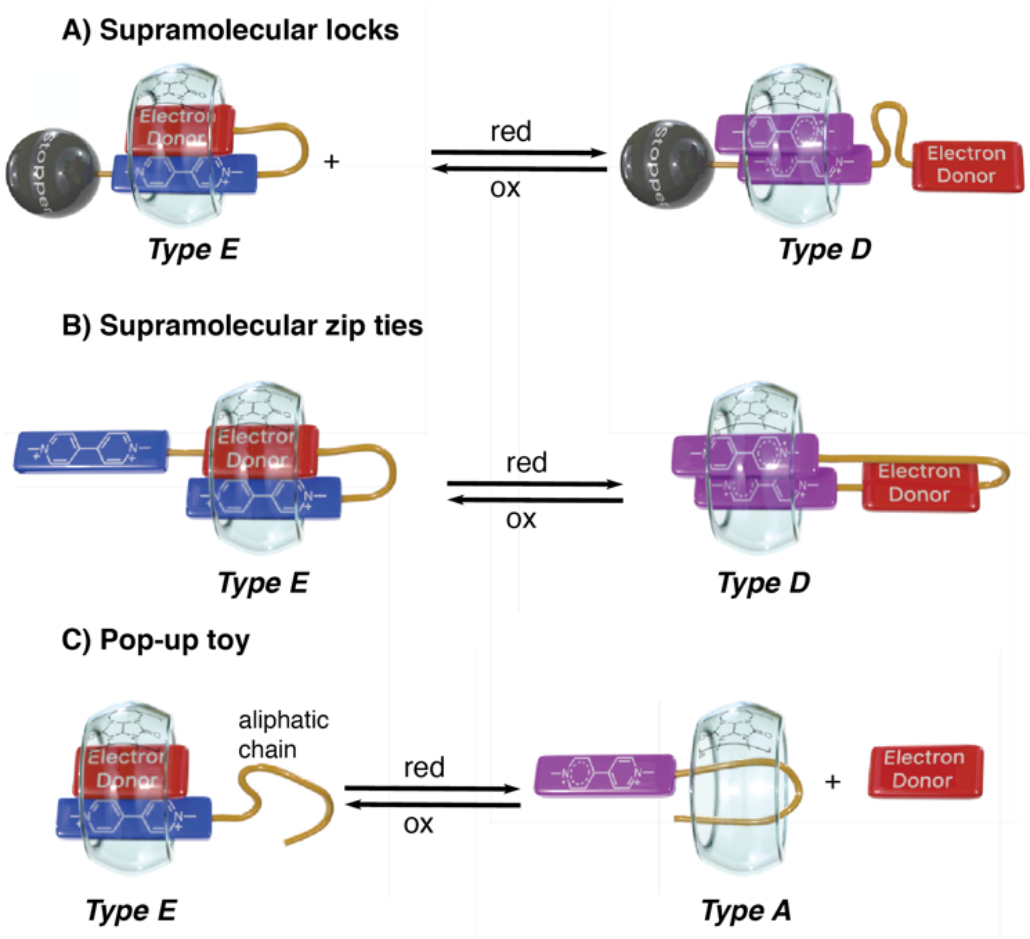
3.2. Reversible redox-switching of heteroternary CB[8]-based complexes

The use of BPCs as stimuli-responsive guests in heteroternary complexes with CB[8] was first reported by Kim *et al*, who described the interconversion of hetero- and homo-guest pairs triggered by the redox-responsiveness of MV^{2+}.[49] The reduction of the CB[8]:MV^{2+}:ED complex (ED = electron donor) generates the one-electron-reduced species CB[8]:$MV^{+\bullet}$:ED, which in turn reacts with free $MV^{+\bullet}$ in solution undergoing a rapid guest exchange that leads to the homoternary aggregate CB[8]:$(MV^{+\bullet})_2$, expelling in that manner the electron donor out of the receptor. The same principle can be applied to BPCs and *p*-dialkoxybenzene aromatic donors after functionalization with dendrons. The resulting heteroternary (HGG') complex can be reversibly switched to the homoternary [$H(G_r)_2$] complex, where G_r represents the one-electron reduced form of the dendronized BPC guest (G). By selecting suitable dendron sizes for guests G and G', this reversible redox conversion affords control of the size of the predominant ternary complexes.[50]
Following the same train of thought, Kim *et al* have also reported later a heteroternary complex showing dual orthogonal redox responsiveness (**Scheme 9**).[51] By using again MV^{2+} as electron acceptor and a redox-responsive tetrathiafulvalene derivative (TTFD) as non-passive ED, the reduction of the heteroternary complex CB[8]:MV^{2+}:TTFD reversibly led to the homoternary aggregate CB[8]:$(MV^{+\bullet})_2$, whilst the oxidation produced CB[8]:$(TTFD^{+\bullet})_2$, releasing a molecule of MV^{2+} out of the complex. More recently, Schalley *et al* have also demonstrated a dual orthogonal redox/pH-controlled **type E-D** switching of CB[8]:BPDC:ED complexes, by combining the characteristics of the MV^{2+} moiety as redox-responsive electron acceptor, and a phenylpyridine derivative as pH-sensitive electron donor.[52]
Another remarkable example of discrete redox-responsive charge transfer complex was reported by Peng *et al*,[53] who demonstrates that a careful design of the donor-acceptor pair can lead by itself to interesting applications. In their work, the authors characterize a heteroternary CB[8]:MV^{2+}:phenothiazine (PTZ) complex with NIR absorption. Under irradiation, the PTZ donor is excited and transfers an electron within the ternary complex, consequently generating $PTZ^{+\bullet}$ and $MV^{+\bullet}$ radicals. This photo-reduction pushes the system to the homoternary complex CB[8]:$(MV^{+\bullet})_2$, leading to the exclusion of the $PTZ^{+\bullet}$ from the cavity of the receptor and enabling its ability as photo-cleaver of a supercoiled plasmid DNA (pBR322), suggesting a potential application of this switch in photodynamic therapy (**Scheme 10**).



Scheme 10. Activation of a DNA photocleaver by a reversible redox **type E-D** switch.[53]

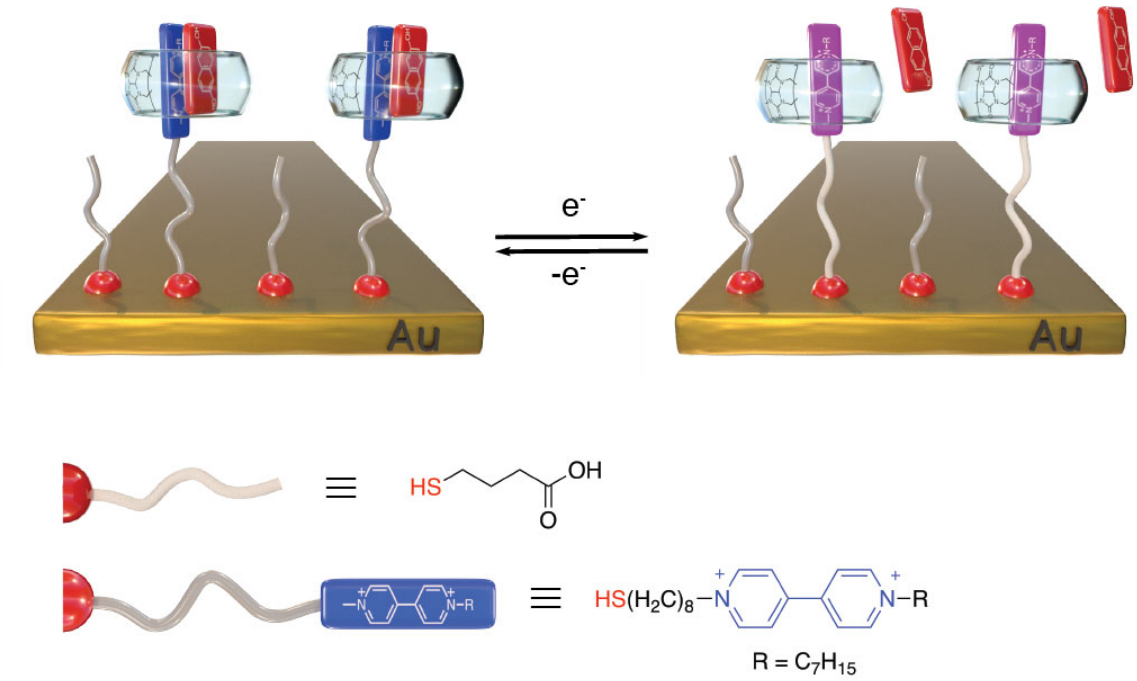
As in the case of the **type C-D** redox/pH-driven switch, some of the most obvious applications of the redox **type E-D** switches involving CB[8]:BPC:ED complexes can be obtained from the covalent linking of the guests, deriving into the development of appropriate functional threads with stimuli-responsiveness that modulates the attachment of the CB[8] to different stations, therefore producing the physical morphing of the obtained supramolecule. In this fashion, a series of works have applied the redox-responsive intramolecular switching in a variety of ways (**Scheme 11**), resulting on supramolecular actuators such as locks[49] or zip ties.[54]



Scheme 11. Redox-responsive heteroternary supramolecular actuators: lock (A),[49] zip tie (B),[54] and "pop-up toy" (C).[55]

A related, but much simpler example of this type of supramolecular actuators is the molecular "pop-up toy" developed by Ko,[55] which elegantly takes advantage of the different modes of interaction of a MV^{2+} unit owning a long alkyl chain as bipyridine dication component (**Scheme 11**). This salt and its radical cation form very stable 1:1 complexes with CB[8], where the aliphatic tail of the guest is in a folded conformation inside the receptor. On the other hand, the introduction of dihydroxynaphthalene as electron donor on the system substantially changes the mode of interaction of the bipyridine dication. In this case, the formation of the CB[8]:BPDC:ED ternary complex pushes the alkyl chain out of the host's cavity and, conversely, the one-electron reduction shoves the electron donor out of the receptor, leading to the binary CB[8]:BPRC complex (BPRC: bipyridine radical monocation), which restores the alkyl chain into its folded conformation inside CB[8].

Moving to more complex systems, the redox-controlled **type E-D** switch has found its utility on the development of functional surfaces with catch and release abilities. As many of the applications found for this type of CB[8]-based systems, its origin can be traced back to a ground-breaking paper by Kim *et al*,[56] who prepared a mixed self-assembled monolayer (SAM) of an appropriately functionalized bipyridine dication and 3-mercaptopropionic acid on gold (**Scheme 12**). The formation and disruption of the expected charge transfer complex with CB[8] on this surface was investigated by cyclic voltammetry, with the self-assembled monolayer working as electrode in a supporting electrolyte solution containing 2,6-dihydroxynaphthalene as electron donor. The reversible supramolecular switch works nicely under these conditions, with the electrochemical reduction destroying the charge transfer complex, consequently releasing the electron donor from the surface to the solution. Conversely, re-oxidation of the bipyridine radical monocation unit re-forms the heteroternary aggregate.

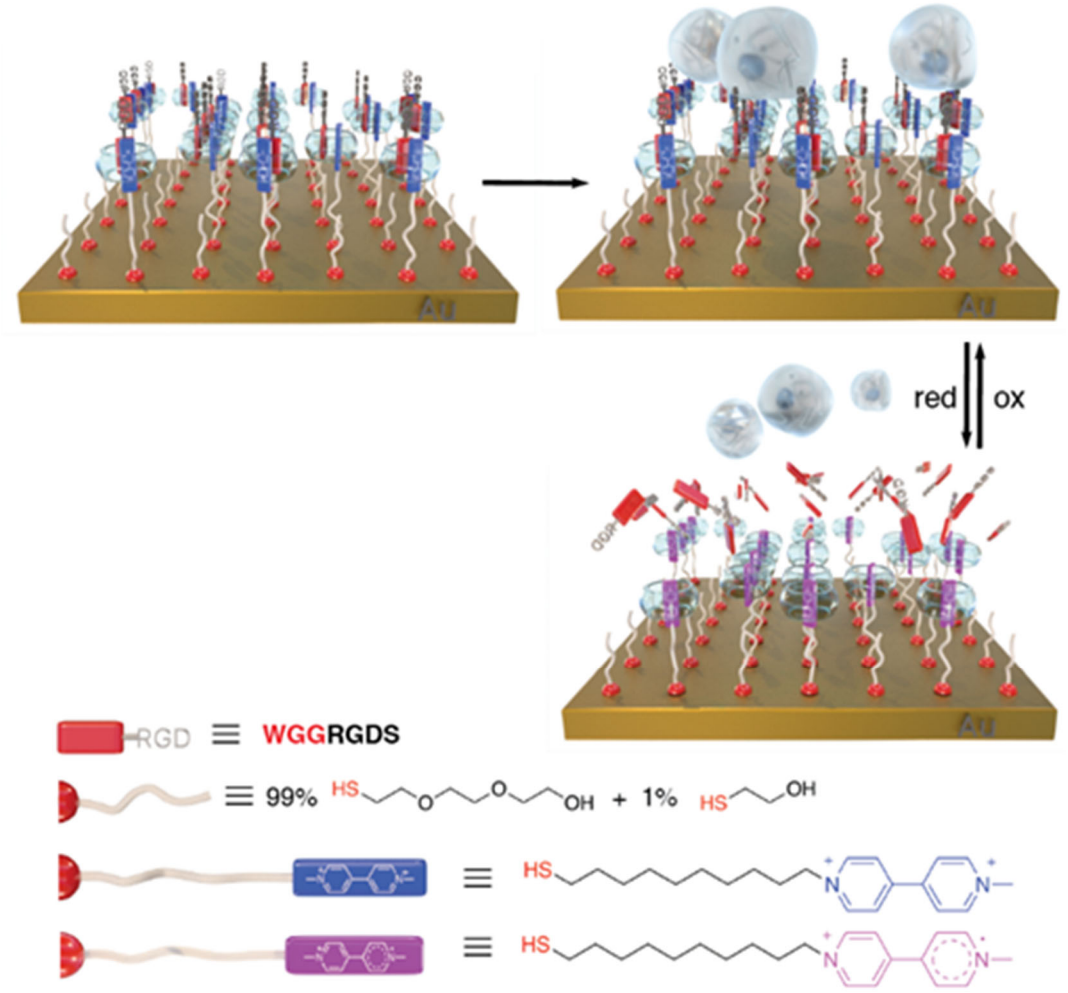


Scheme 12. Redox-responsive CB[8]:BPDC:ED complex supported on a SAM onto a Au surface.[56]

This result soon opened the door for the development of redox-controllable CB[8]-based supramolecular switches for the temporal attachment of a variety of building blocks on surfaces, since the only prerequisite to get trapped on the materials would be the introduction of an adequate electron donor moiety in their structure. In this manner, Scherman *et al* have reported a selective immobilization strategy for peptides bearing an *N*-terminal tryptophan, which acts as electron donor and forms complexes with CB[8]:MV^{2+}-functionalized gold surfaces[57] or silica nanoparticles.[58] This approach has been successfully implemented for the separation of peptide mixtures by the immobilization of the target peptides over the surfaces, followed by their release after an electrochemical stimulus. The same research group have also exploited this strategy for the reversible modification of CB[8]:MV^{2+}-functionalized gold surfaces[59] or nanoparticles[60] with naphthol-containing polymers. Similarly, Yuan *et al* reported a biosensor for the detection of a microRNA (miRNA-182-5p, a prostate cancer biomarker), based on tryptophan-modified single-stranded DNA fragments, with a complementary sequence to that of the target RNA, reversibly trapped onto a CB[8]:MV^{2+}-modified electrode.[61]

Finally, Jonkheijm *et al* described the trapping of a naphthol-modified yellow fluorescent protein onto the surface of MV^{2+}-functionalized nanoparticles and glass chips,[62] by the formation of the charge transfer complex between the naphthol and viologen moieties inside the CB[8] cavity. This research group also developed a system for the indirect fixation and release of cells onto gold surfaces.[63] In this approach, the CB[8]-mediated immobilization anchors the WGGRGDS peptide onto a viologen-modified gold surface (**Scheme 13**), with the *N*-terminal tryptophan acting as electron donor within the CB[8]: MV^{2+}:ED complex and the RGDS fragment as cell-adhesion point, producing stable and specific surfaces where (single) cell experiments can be performed.

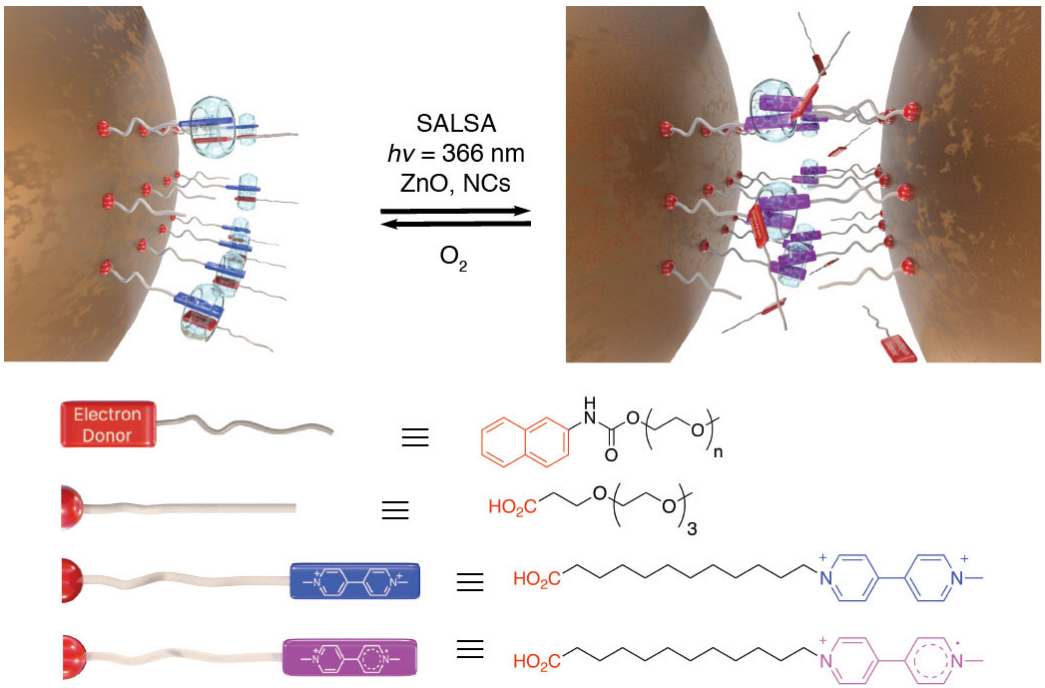
Crucially, in all these examples, the release of the peptide/oligonucleotide/polymer/protein-electron donor conjugate was efficiently achieved by the reversible one-electron reduction of the bipyridine dication functionalities, demonstrating the versatility of this redox-responsive supramolecular switch for the reversible attachment of complex highly-functionalized building blocks on to surfaces.



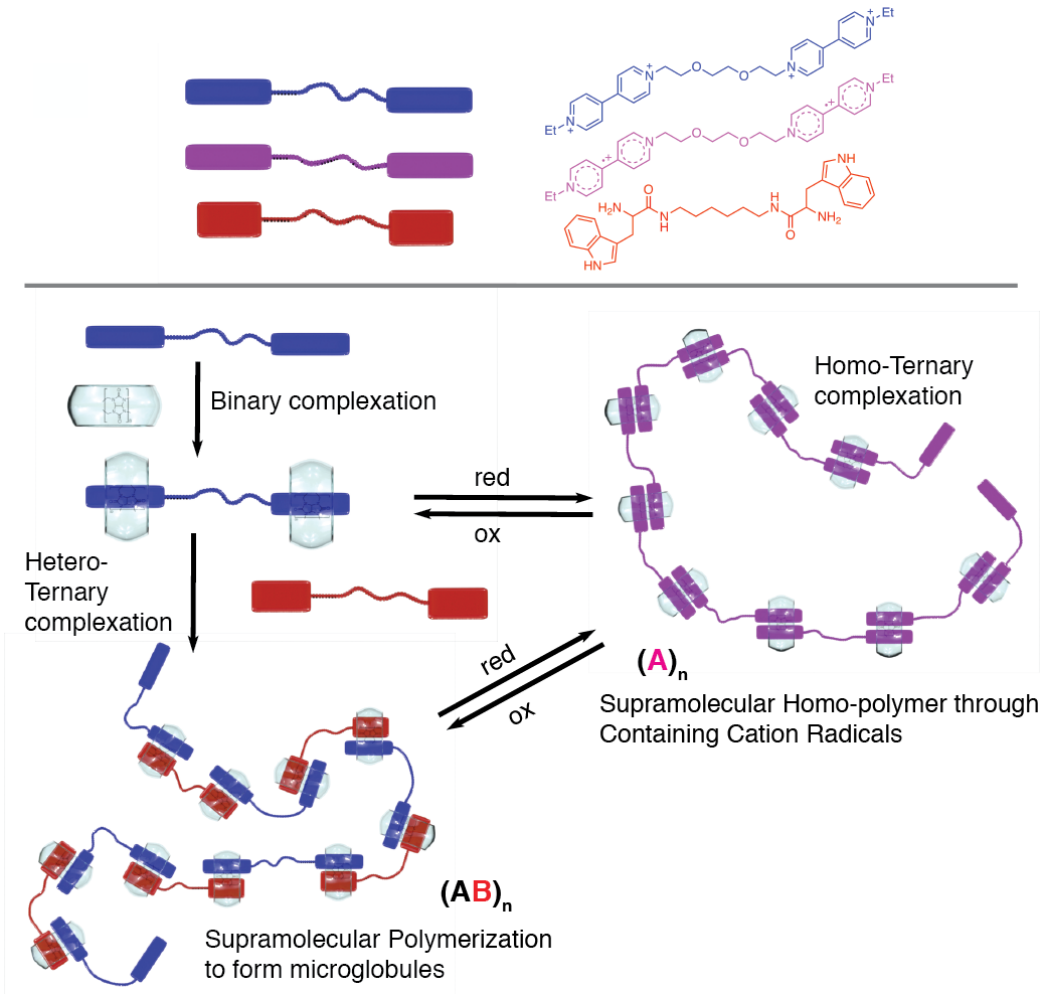
Scheme 13. Redox-responsive adhesion and release of cells into viologen-modified Au surfaces.[63]

An interesting twist of the described approach, reported by Lewiński *et al*,[64] shows its implementation in the semiconductor-assisted light modulation of supramolecular assemblies (SALSA strategy), using **type C** binary complexes with photoactive MV^{2+}-functionalized ZnO nanocrystals as the bipyridine dication part of the CB[8]:BPDC ensemble (**Scheme 14**). It was found that the aggregation of those multivalent nanoparticles can be modulated employing the reversible redox-controlled **type C-D** switch, with the reduction being triggered by the photoirradiation of the semiconducting nanocrystals and the corresponding electron transfer that induces the formation of $(MV^{+\bullet})_2$ within CB[8]. Furthermore, it was shown that the luminescent nature of the semiconductor nanocrystals provided an interesting possibility to visually monitor the capture and release of guest molecules from the surface-bound CB[8]-based assemblies. In that manner, redox-responsive heteroternary **type E** complexes were prepared by complexation of naphthalene-terminated poly(ethylene glycol) as second guest. As in the case of the **type C-D** interconversion, reversible switching between **type E-D** complexes could be achieved by applying the appropriate potential, demonstrating therefore a reversible catch and release mechanism for the designed system.

A similar methodology has been also reported for the synthesis of redox-responsive supramolecular polymers, which have a huge potential in the development of drug delivery, sensing or catalytic systems.[65] In this occasion, a covalently-linked *bis*-bipyridine dication was found to form a **type C** complex with CB[8]. By using the **type C-D** complex interconversion, a reversible supramolecular polymerization is achieved by reduction of the *bis*-bipyridine dication. Additionally, the authors demonstrated the reversible interconversion of this homopolymer into a supramolecular block copolymer of $(AB)_n$ nature by employing a covalently-bonded *bis*-tryptophan as electron donor on a CB[8]:*bis*-BPDC:*bis*-ED ensemble, enabling in that manner the homo-heteropolymer transformation by a **type E-D** interconversion (**Scheme 15**).

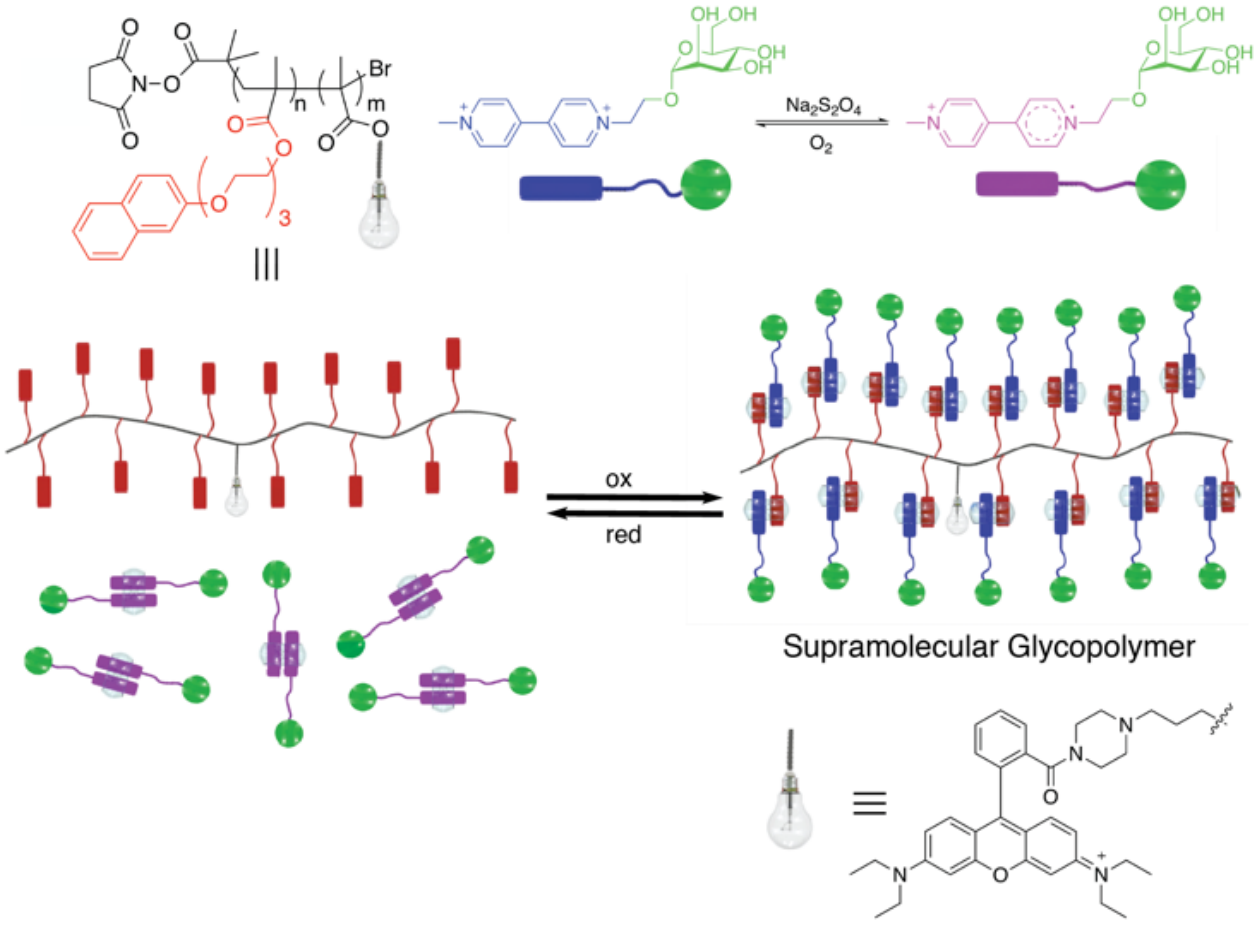


Scheme 14. Light-triggered redox-based **type E-D** reversible switch producing the controlled aggregation of ZnO nanocrystals.[64]



Scheme 15. Reversible homo- to heteropolymer transformation induced by a **type D-E** redox switch.[65]

A nice example of the power of this reversible switching mechanism for the design and synthesis of functional polymers has been reported by Scherman and co-workers,[66] accounting for the redox-based post-functionalization of linear 2-naphthol-appended methacrylate covalent copolymers with CB[8]:monosaccharide-functionalized BPDCs complexes**.** This work included the first example of a reversible switching between monovalent (CB[8]-mannoside-viologen hybrids) and multivalent ligands (a supramolecular glycopolymer), and their potential on the rational design of lectin binders (**Scheme 16**). Zhang *et al*,[67] have also reported the redox-conditioned preparation of a related supramolecular glycolipid, formed by CB[8] ternary complexation of naphthylglucosamine as the polar head and a bipyridine dication with an octyl chain as hydrophobic tail. These supramolecular glycolipids self-assemble in water to form vesicles that interact specifically with Concanavalin A, thus demonstrating that the carbohydrate moieties are available at the surface of the aggregates for target recognition.

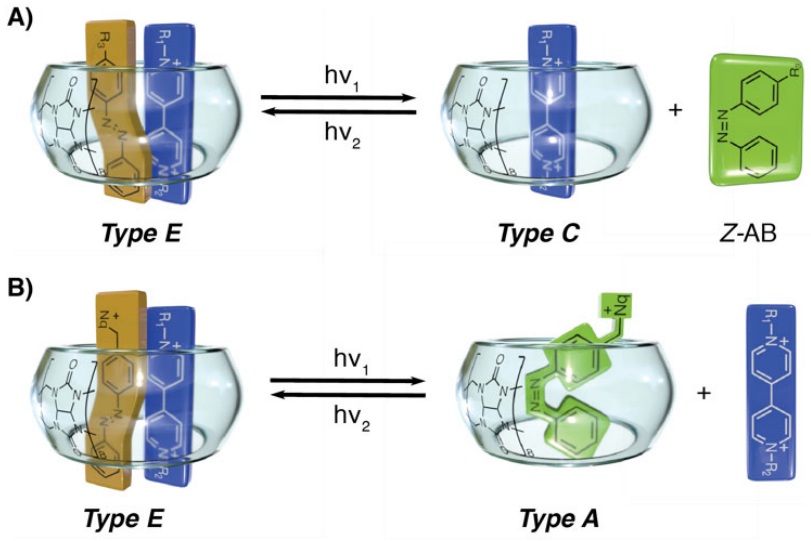


Scheme 16. Reversible redox-guided post-functionalization of a napththol-containing polymer by a **type D-E** switching.[66]

3.3. Reversible photoswitching of CB[8]:BPC:ED complexes

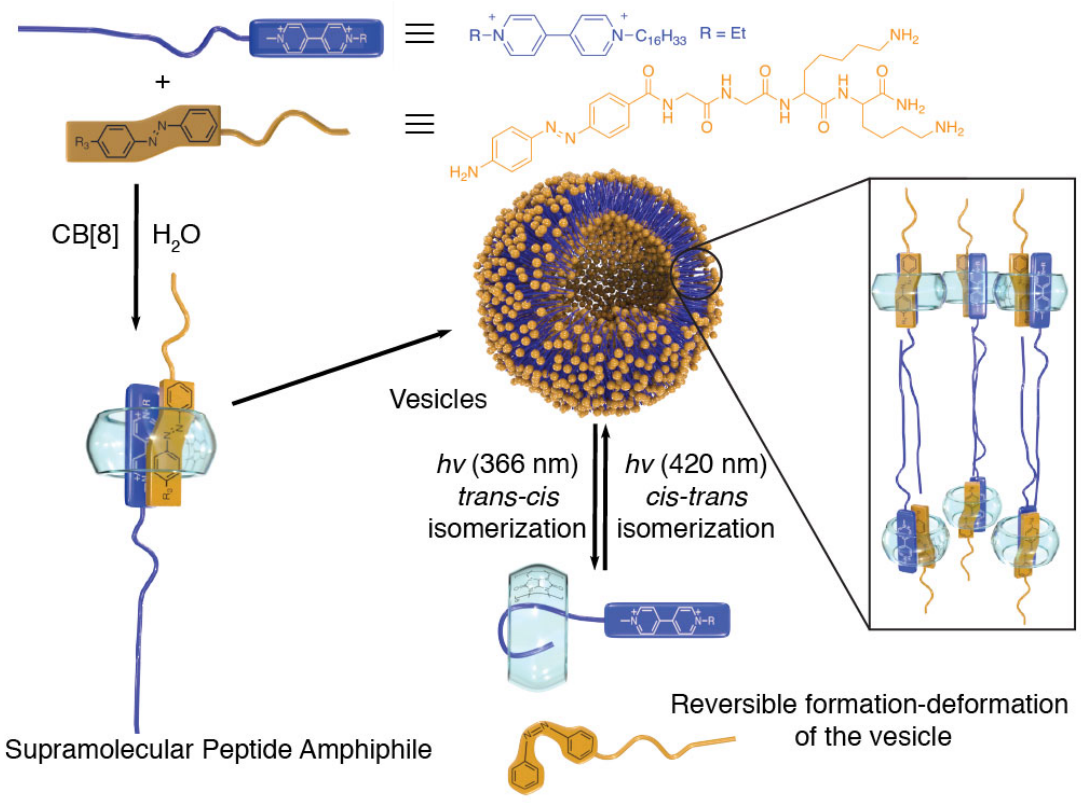
Despite the possibility of designing photoresponsive ternary complexes, simply by modification of the bipyridine-based dications structure as light-reactive electron acceptor first guests (for instance, by introducing an isomerizable double bond connecting the two pyridinium units, **Scheme 5**),[33] most of the reported cases on CB[8]-based heteroternary reversible photoswitches make use of *E*/*Z*-isomerizations of azo bonds, with those installed into azobenzene subunits (*E*/*Z*-AB) acting as electron donors within the corresponding triad. In consequence, isomerization produces an obvious change on the shape of the azobenzene component, with the receptor being now too small to allocate the two guests.

This being said, we can find two different situations depending on the nature of the sort of complex interconversion taking place (**Scheme 17**). In the most obvious case, a **type E-C** photoswitching is achieved by using a bipyridine dication as passive first guest, and a neutral electron-rich *E*-AB derivative as second electron donor guest, with the isomerization expelling *Z*-AB out of the CB[8], which prefers to complex the bipyridine dication as charge-optimized substrate. On the contrary, monocationic *E*-AB derivatives with a benzylic quaternized nitrogen, as positively-charged recognition site for CB[8], can be used as electron donor first guests with the BPC introduced as second. In this case, complexation of the second guest moves the cucurbituril from its initial position to optimize the charge transfer on the heteroternary complex. Then, the **type E-A** interconversion is produced upon light-triggered isomerization, with the bipyridine dication being pushed out of the receptor. This anomalous behavior can be associated to an optimized packing coefficient for the *Z*-AB monocation.



Scheme 17. CB[8]:BPDC-based reversible photoswitches showing **type E-C** or **E-A** interconversions. N⁺q stands for a quaternized nitrogen atom.

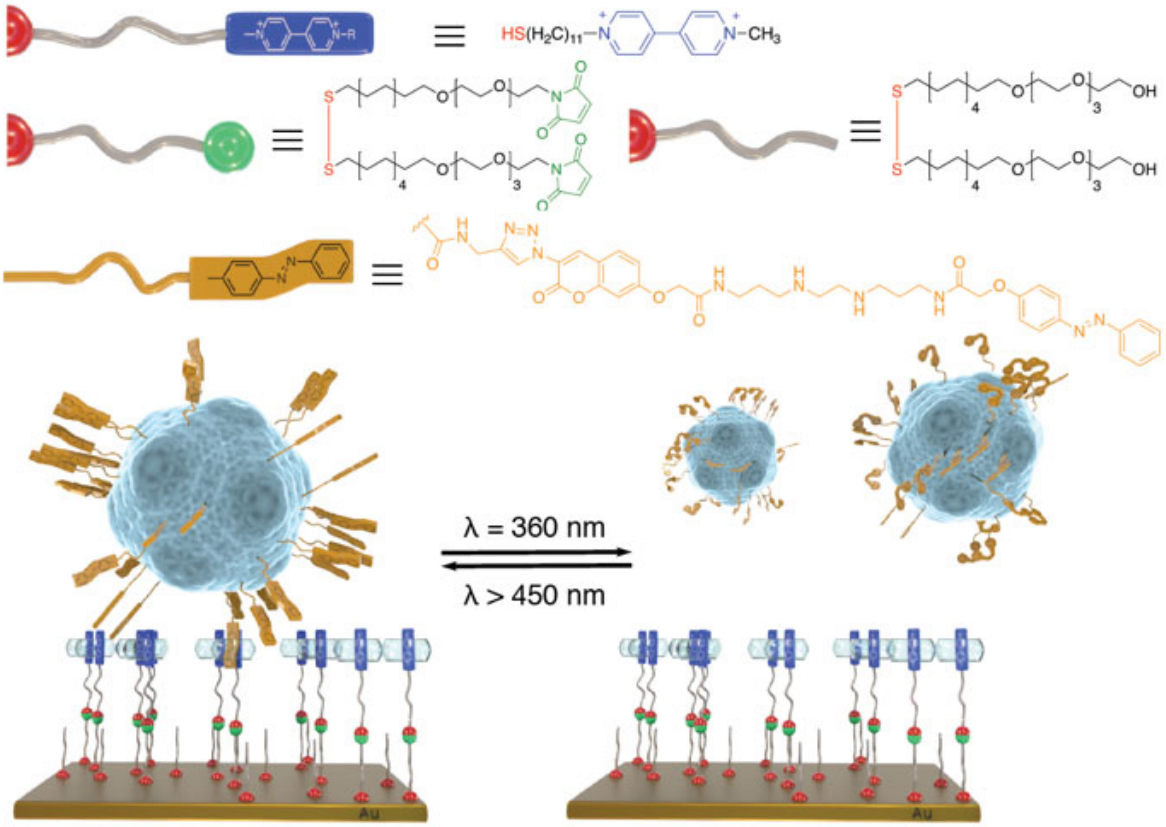
As a prototypical example of the **type E-C** process, Das *et al*, have reported the reversible photo-controlled assembly and disassembly of a supramolecular peptide amphiphile into a vesicle (**Scheme 18**).[68] The amphiphile is constructed by CB[8] complexation of a bipyridine dication containing a hexadecyl unit as the hydrophobic tail, and an *E*-AB-modified peptide as the hydrophilic electron donor head. Vesicles were efficiently self-assembled in aqueous media using this strategy, and assembled/disassembled through the UV irradiation-mediated *E*-*Z* isomerization of the azo group, which produces the expulsion of the neutral *Z*-AB out of the molecular receptor. Furthermore, accounting for the potential of light as external reversible stimuli, the authors show how this switchable system can be used for the spatiotemporal controlled photo-release of the fluorescent dye (6)-carboxyfluorescein out of the vesicle, demonstrating its potential as drug delivery vehicle. In fact, this strategy has been recently exploited for the targeted photo-controlled delivery of doxorubicin from supramolecular vesicles.[69]



Scheme 18. Reversible photo-controlled assembly and disassembly of a supramolecular peptide amphiphile into a vesicle.[68]

Other examples of the light-driven **type E-C** interconversion have been reported, showing the versatility of the approach for the light-controlled self-assembly of new functional materials, including hybrid raspberry-like colloids,[70] supramolecular polymeric nanoparticles[71] or polymeric networks.[72] Furthermore, in a recent work, Jonkheijm and coworkers have used the **type E-C** photoswitch for the reversible immobilization of cowpea chlorotic mottle virus nanocages on surfaces (**Scheme 19**).[73] By covalently attaching *E*-AB functionalities to the viral capsids, the authors were able to bind those through heteroternary complexation to a CB[8]:MV^{2+}-modified self-assembled monolayer onto Au. As expected, the *E*-*Z* isomerization by UV light irradiation, even of small localized regions of the material, produces the release of the AB-modified viral particles from the CB[8]:MV^{2+}-containing surface. The research group have also reported a modification of this method for the catch and release of eukaryotic cells, based on a **type E-C** photoswitch involving MV^{2+} motifs as electron acceptors and arylazopyrazoles as *E*-*Z* isomerizable electron donors.[74]

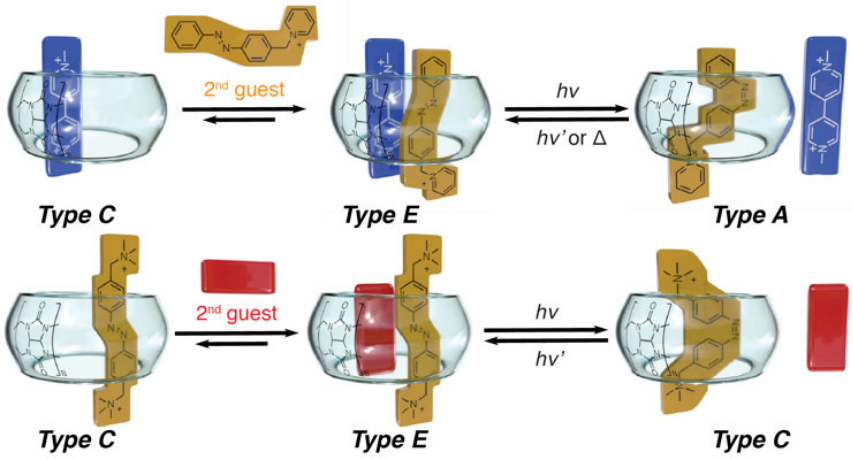
Regarding the reversible **type E-A** photoswitches (**Scheme 17**), those were first studied by using an *E*-AB derivative with a pyridinium group attached to the benzylic position of the chromophore. This compound acts as electron donor component in the heteroternary complex CB[8]:MV^{2+}:*E*-AB^{+} and, as commented before, its *E*−*Z* isomerism enables the supramolecular photo-switching by expulsion of the MV^{2+} electron acceptor, on the basis of a better binding of the *Z*-AB^{+} moiety to CB[8] compared to the viologen.[75] The use of similar CB[8]:MV^{2+}:*E*-AB^{+} **type E-A** switches have been recently reported for the development of photoresponsive polyelectrolyte multilayer films,[76] photocontrolled supramolecular polymers,[77] as well as for the synthesis of photo-rheological fluids.[78]



Scheme 19. Redox-responsive catch and release of viral nanoparticles into viologen-modified SAMs.[73]

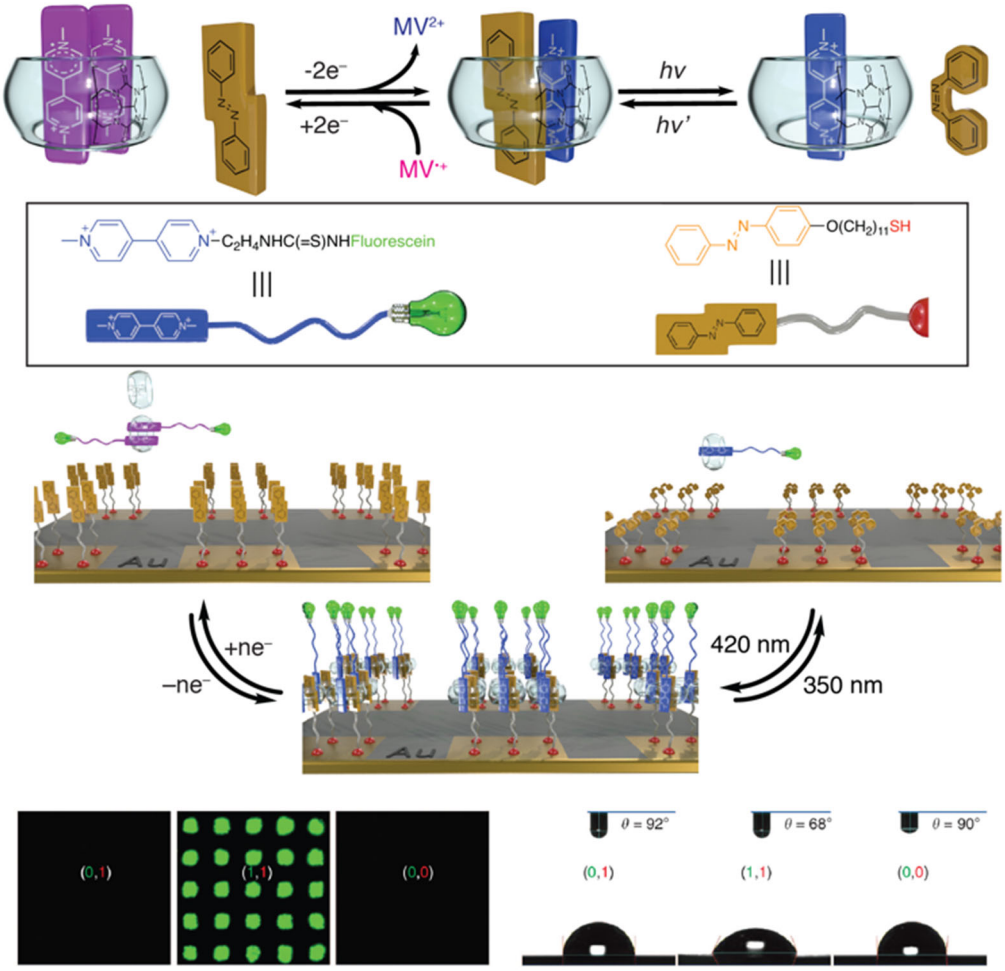
Interestingly, it should be noted that the introduction of a second benzylic quaternized nitrogen on the azobenzene moiety produces an umpolung on the behavior of the dicationic AB (**Scheme 20**).[79] Here, the *E*-AB^{2+} derivative acts as first guest, with association constants for the CB[8]:*E*-AB^{2+} complex with a series of prototypic electron donors on the range of $K_{a2} = 10^{3}–10^{5}\ M^{-1}$. Under these circumstances, *E*-*Z* isomerization pushes the electron donor component out of the complex rendering the **type C** aggregate CB[8]:*Z*-AB^{2+}.

Finally, *E*/*Z*-isomerization-driven **type E-A** interconversion has found its utility on the development of supramolecular actuators. Clearly inspired by the pioneering work of Kim *et al.* on the construction of CB[8]-mediated molecular loop locks (**Scheme 6** and **Scheme 11**),[37],[54],[55] Liu *et al* have reported two supramolecular complexes that can be converted into stable [2]pseudorotaxanes, based on flexible threads containing a MV^{2+} moiety covalently attached to *E*-AB or *E*-AB^{+} derivatives. In both cases, the azo-group isomerization could be modulated in a reversible manner controlling the interconversion of ‘locked’ and ‘unlocked’ states, that also acted as efficient DNA regulators.[80]



Scheme 20. CB[8]-based **Type E-A** and **E-C** reversible photo-switches.

Finally, the use of AB moieties as light-responsive electron donors on heteroternary complexes with redox-responsive bipyridine dications, opens the door for the design of dual-responsiveness within heteroternary CB[8] complexes, yielding aggregates that would be potentially able of being independently perturbed by a chemical potential and light. In fact, this possibility has been demonstrated by Scherman *et al*,[81] reporting a CB[8]:BPC:*E*-AB heteroternary complex constructed with a fluorogenic redox-responsive bipyridine dication (MVF^{2+}) and a *E*-azobenzene derivative as photo-responsive electron donor. As designed, the aggregate responds in aqueous media to both redox potentials and light in a controlled and fully reversible manner, generating a **type D-E-C** multifunctional switch. Furthermore, the authors exploited this unique double switch to amplify the applied stimuli into macroscopic properties, by tuning the surface wettability of a functional self-assembled monolayer of **type E** heteroternary complex CB[8]:MVF^{2+}:*E*-AB on a gold surface, therefore providing suitable systems for the development of memory devices (**Scheme 21**).



Scheme 21. Dual orthogonal reversible redox/photo-responsiveness of a **type D-E-C** switch.[81]

4. Summary and outlook

Since the isolation and characterization of CB[8] two decades ago, a number of research groups have studied its extraordinary properties as molecular receptor, associated with its ability to form homo- and heteroternary complexes with appropriate guests. In this review, we have tried to illustrate the enormous potential of the conjunction of CB[8] and stimuli-responsive guests, such as bipyridine-based cations, for the development of functional supramolecular switches. The use of those dynamic systems is especially interesting since they can be reversibly transformed by the application of external stimuli such as light, redox potential, or pH, and even allowing the implementation of orthogonal stimuli responsiveness. Furthermore, these exceptional properties of CB[8]-based supramolecular switches can be applied for the rational design of responsive materials, whose final function is also controlled by the assembly/disassembly of the modified building blocks. Future developments in this field could afford new materials that mimic the properties of the dynamic supramolecular systems found in Nature, and therefore have an enormous potential impact in the development of smart sensors, catalytic, or drug delivery systems, among many other applications.

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Keywords: cucurbit[8]uril • host-guest systems • heteroternary complexes • self-assembly • supramolecular chemistry

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