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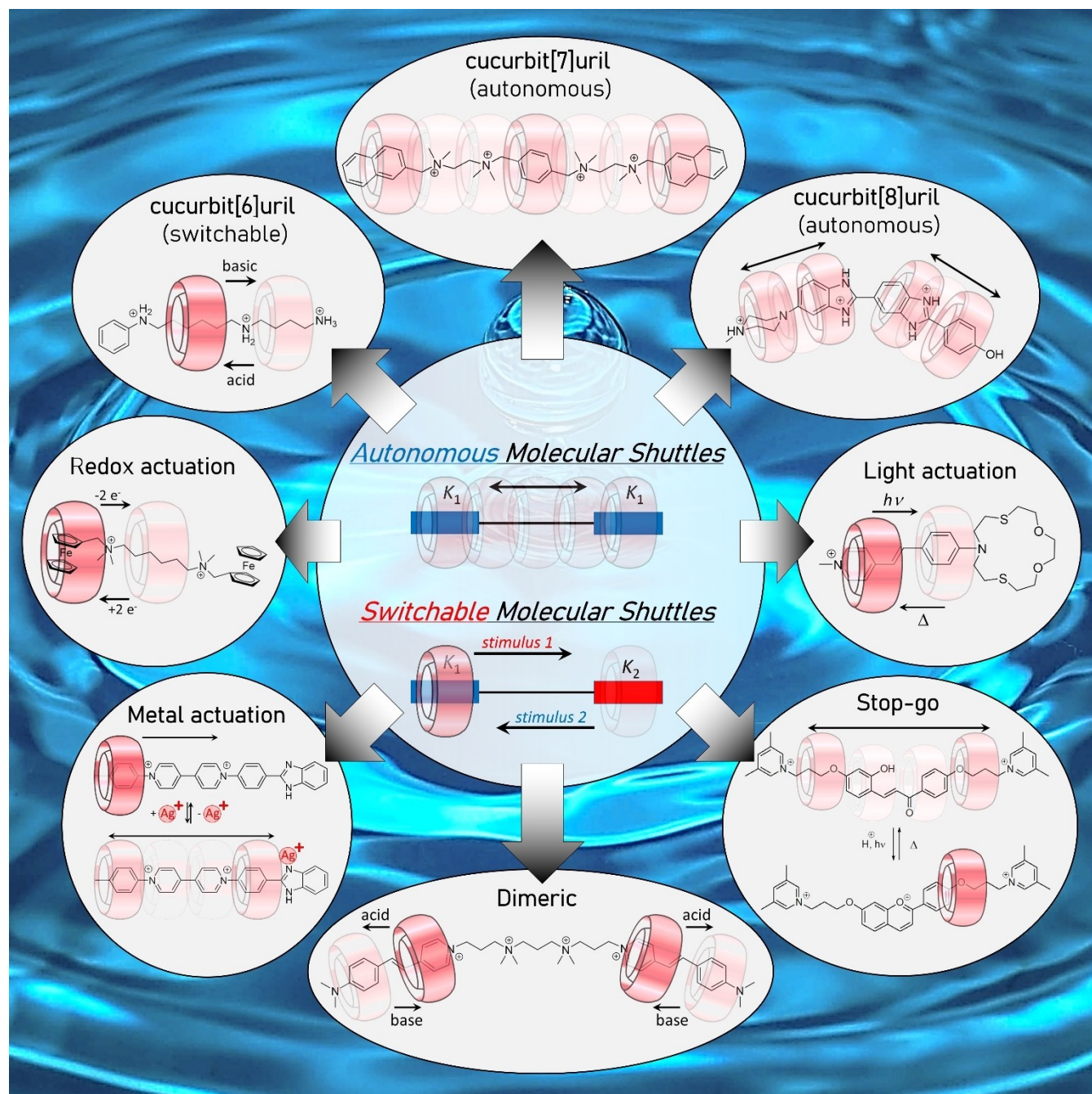


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# The Diversity of Cucurbituril Molecular Switches and Shuttles

Anthony Kermagoret\*<sup>[a]</sup> and David Bardelang\*<sup>[b]</sup>



Ring translocation switches and shuttles featuring a macrocycle (or a ring molecule) navigating between two or more stations continue to attract attention. While the vast majority of these systems are developed in organic solvents, the cucurbituril (CB) macrocycles are ideally suited to prepare such systems in water. Indeed, their stability and their relatively high affinity for

relevant guest molecules are key attributes toward translating the progresses made in organic solvents, into water. This concept article summarizes the findings, key advances and multiple possibilities offered by CBs toward advanced molecular switches and shuttles in water.

## 1. Introduction

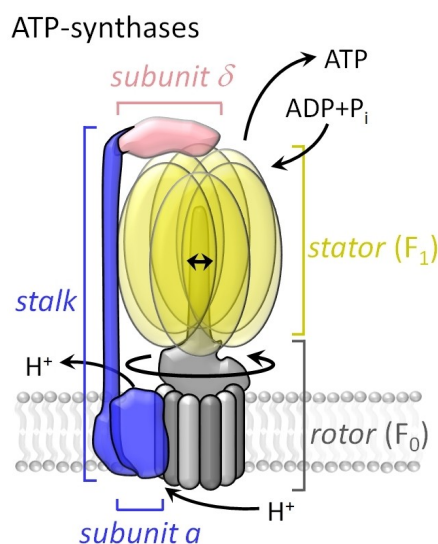
One of the most fascinating aspects of proteins is the capacity, for some of them, to self-organize into discrete assemblies, and produce controlled movements enabling access to advanced functions.<sup>[1]</sup> One typical example is the family of ATP-synthases that can reversibly produce ATP from ADP and P<sub>i</sub> by using the energy provided by a proton gradient (Figure 1).<sup>[2]</sup>

This natural molecular machine consists of a stator, a stalk and a mobile rotor whose directional, ratcheted motion is controlled by a nearby subunit, and is actuated by a directional flow of protons.<sup>[3]</sup> This fascinating assembly working either way (one direction or the other depending on whether ATP is consumed or produced), has probably inspired advanced molecular machines featured by controlled ring rotation.<sup>[4]</sup> On the other hand, "linear" molecule transport is also of crucial importance for cells. For example, DNA helicases are proteins, most often oligomerized as ring-shape hexamers, which translate in a biased (directional) motion along DNA strands for double-stranded (ds)-DNA unwinding (Figure 2).<sup>[5]</sup>

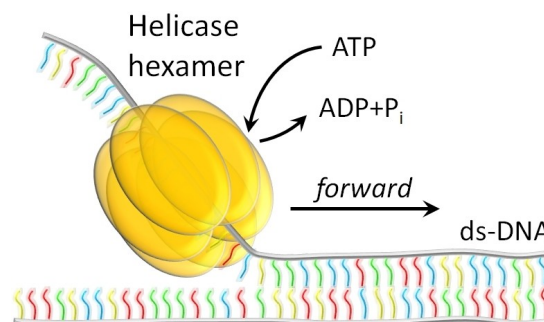
This shuttling step, crucial for cell machinery to access the genetic information, is dependent on ATP binding and hydrolysis, assumed to trigger helicase conformational changes linked to binding and release events along the track. While most require a single-stranded (ss)-DNA tail to engage in the process, the actual mechanism of unwinding which is composed of unidirectional translocation and base pair (bp) dissociation, was a time debated between a passive one (waiting for the neighboring bp to dissociate before moving forward), and an active one (the helicase promoting bp dissociation before, or by moving forward).<sup>[6]</sup> Today, there appears to be a continuum between these two non-mutually exclusive extrema, so that most helicases are featured by a certain extent of active and passive involvement.<sup>[7]</sup> Beside the similarity between the F<sub>1</sub> stator of ATPases and hexameric helicases regarding ATP binding and hydrolysis, it appears that

DNA unwinding is made possible by a chemically activated (unidirectional), supramolecular shuttle.

Beside these discoveries of natural molecular machines pervading biological systems, chemists have attempted to create similar artificial molecular systems in which a molecule could navigate along another molecule.<sup>[8]</sup> The first example, featuring a molecular string, a navigating macrocyclic ring and two stoppers, was a rotaxane reported in 1991 by the team of Fraser Stoddart.<sup>[9]</sup> The function of the stoppers was to prevent ring escape from the molecular track, and the ring was shuttling autonomously between two degenerate hydroquinol stations in the molecular axle. Three years later in 1994, the same group reported the first example of switchable ring shuttling con-



**Figure 1.** Scheme illustrating the directional flow of protons enabling the unidirectional rotation of the F<sub>0</sub> rotor of ATP synthases for the synthesis of ATP.



**Figure 2.** Scheme illustrating the directional transport of a helicase hexamer to unwind ds-DNA.

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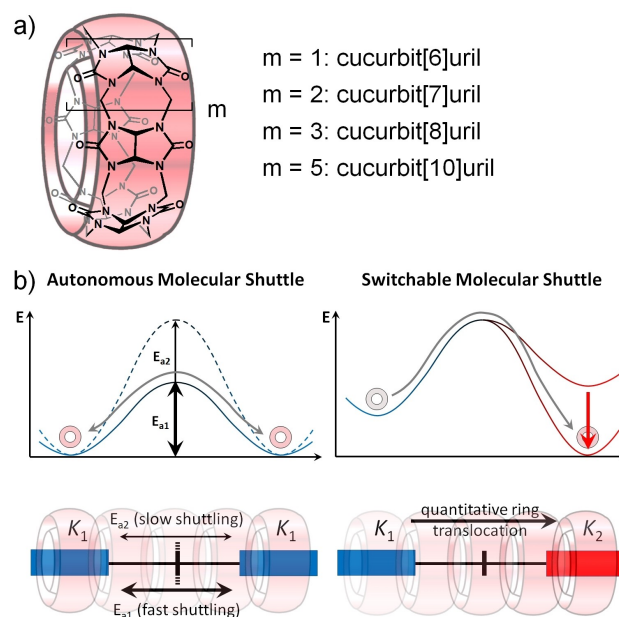
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trolled by an external stimulus.<sup>[10]</sup> By adding a chemical stimulus (here an acid or electro-oxidation), the initial station affinity (the benzidine station) changed, leading the ring to navigate controllably and reversibly (addition of base or reduction as inverse stimulus), from one station to the other. The external stimuli modified the nature of the stations to get a control of their affinities toward the studied macrocycle, eventually shuttling between the designed stations.<sup>[11]</sup> After these seminal reports, numerous examples were published varying the designs of the rings, threads and stoppers as well as the manners to prepare these rotaxanes.<sup>[12]</sup> Later, Jiang, Huc and coworkers showed that molecule shuttling can occur on a molecular track faster than disassembly.<sup>[13]</sup> Without stoppers, host-guest systems can so be featured by similar attributes.

Beside all these examples developed in organic solvents, few equivalent systems have been done in water.<sup>[14]</sup> Yet, solvents were shown to be important contributors of rings shuttling<sup>[15]</sup> and water is an important, available, non-toxic solvent, already used by natural molecular machines. Cyclodextrins have started to be used for the construction of molecular shuttles.<sup>[16]</sup> But systems based on cyclodextrins seem constrained to rotaxanes or similar entangled structures,<sup>[17]</sup> perhaps due to their limited binding constants toward molecular axles requiring a mechanical bond (stoppers), for the ring to remain close to the axle.

On the other hand, cucurbiturils (CBs, Figure 3a), have rapidly been featured by acceptable to good water solubility, rather high binding constants,<sup>[18]</sup> and corresponding molecular switchable shuttles were described quite soon after their discovery so without need for rotaxation.<sup>[19]</sup>

Exploited in supramolecular chemistry since the 80's, cucurbit[n]uril (CB[n]) macrocycles combine a hydrophobic cavity with two electron rich carbonyl laced portals offering strong inclusion properties, especially for guest molecules combining hydrophobicity and a cationic group.<sup>[20]</sup> While guest molecules for CB[6] are mainly limited to aliphatic compounds, CB[7] and CB[8] can complex aromatic or polycyclic groups like adamantanes. The largest macrocycles in the series with a permanent open cavity (CB[8] or CB[10]) can also encapsulate larger guests, or two guests, potentially dramatically widening the scope of feasible molecular machines.<sup>[21]</sup> For CB[8] molecular switches, the reader can consult the excellent review by Peinador, Kaifer, Garcia and coworkers.<sup>[21b]</sup> In the following, host and guest molecules are considered concentrated enough so



**Figure 3.** (a) Molecular structure of cucurbit[n]urils ( $n = 6, 7, 8, 10$ ). (b) Energy profiles of autonomous and switchable molecular shuttles and related ring shuttlings.

that they can be considered dynamically associated. Coming back to the two seminal reports by Stoddart and coworkers, one can distinguish *autonomous molecular shuttles* (AMS, Figure 3b pictured with cucurbituril complexes) from *switchable molecular shuttles* (SMS, Figure 3b). AMS are featured by degenerate (i.e. identical) or quasi-degenerate (i.e. different) station binding, resulting in symmetrical (or palindromic) systems for the former and asymmetrical systems for the latter. The macrocycle exchange reflects the equilibrium of ring binding between two competitive sites driven by the Brownian motion. The speed of ring shuttling is linked to the kinetic barrier for the ring to move from the 1<sup>st</sup> to the 2<sup>nd</sup> station (energy of the transition state). Conversely, SMS are characterized by necessarily asymmetric designs relying on at least two different stations whose affinity for the ring is modulated by external stimuli (i.e. light, redox, pH, metal complexation, etc). In this case, the thermodynamics most often controls ring residence on relevant stations and defines the states of a supramolecular switch. However, high kinetic barriers can



Anthony Kermagoret received his PhD from the University of Strasbourg (France) in 2007 in metal complexation and catalysis. He then developed various research projects in organometallic and polymer chemistry at the University of Paris-Sud (France), RWTH (Germany), Lyon I University (France) and University of Liege (Belgium). In 2015, he became associate professor at Aix-Marseille University (France). His research focuses on supramolecular chemistry, macromolecular engineering and organometallics.



David Bardelang got his PhD in Marseille (France) in 2005 about the use of cyclodextrins in spin trapping experiments. He then moved to Birmingham (UK) working on helicates with Mike Hannon as a postdoc before moving to Canada for two years working on peptides, gels and cucurbiturils with Chris Ratcliffe and John Ripmeester at NRC. Since 2009, he is a researcher at CNRS in Marseille working on the supramolecular chemistry of cucurbiturils and other macrocycles.

impede ring oscillation or shuttling, and generate a kinetically trapped unfavored thermodynamic system.

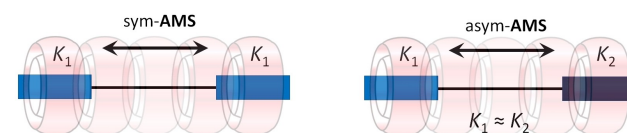
While molecular switches and shuttles are normally accepted, not producing work (contrary to molecular motors), the energy profiles of the *autonomous* and *switchable* molecular shuttles differ in that asymmetry is primordial for SMS. Furthermore, kinetic aspects and fuel consumption must also be considered for the construction of advanced molecular machines featuring molecular or information ratchets.<sup>[22]</sup> However, all these examples were developed in organic solvents, but water is desirable not only from a sustainable and environmental perspective, but also to better understand the principles at work in natural molecular machines. In 2017, Zhu, Zhu and Zhao proposed a review about host:guest systems involving controlled movements of cucurbiturils.<sup>[23]</sup> However, the concepts of autonomous, switchable autonomous, and stop-go molecular shuttles were not discussed and several important advances have been made since then. Here we summarize all the conceptual and experimental advances of cucurbituril molecular shuttles in water since their discovery, and propose several challenges to tackle in the future.

## 2. General Principles of Cucurbituril Molecular Shuttles

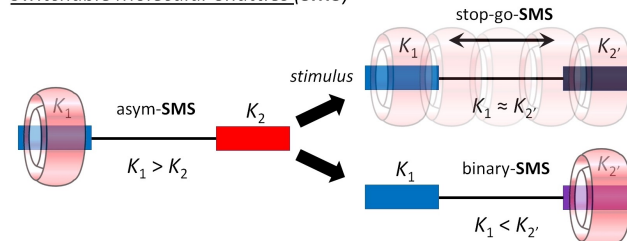
### 2.1. The structure of the axle dictates the outcome (autonomous or switchable)

First, all reported systems are described in water (with few exceptions in DMSO). Then, the cucurbituril shuttling (autonomous by Brownian motion), and the cucurbituril switch (each forward and backward step activated by one stimulus), both involve a host exchange between (at least) two sites. In principle, when two stations of a guest axle have an equivalent affinity for a host, ring shuttling is observed. While symmetric guests having identical chemical stations are the most obvious systems to create a shuttle (sym-AMS, Figure 4), asymmetric guest molecules featured by different but competitive stations are also possible (asym-AMS, Figure 4). In this case, the ring distribution on the two competitive stations is linked to their respective affinity for the host, but for the CB shuttling to remain autonomous, the affinities for the two different stations must remain the same order of magnitude. In these cases (autonomous shuttling), no external stimulus is required to actuate ring translocation and sym/asym-AMS present the same energetic profile (Figure 3b, left). Remarkably, the ability to modulate the host affinity for one station of a dissymmetric guest via various stimuli is a starting point for a controlled host translocation on the axle, and so molecular shuttling can be triggered from immobilized rings (SMS, Figure 4). Then two cases are possible. First, if the affinity for the second station reaches that of the 1<sup>st</sup>, or if the affinity of the 1<sup>st</sup> station is decreased to reach that of the 2<sup>nd</sup>, then the ring can enter the autonomous shuttling mode (stop-go-SMS).<sup>[24]</sup> Alternatively, the affinity of a ring for a station of an autonomous shuttle can be

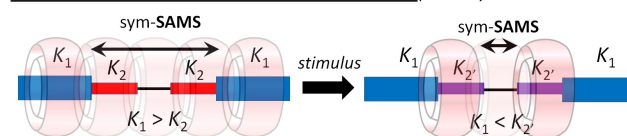
### Autonomous Molecular Shuttles (AMS)



### Switchable Molecular Shuttles (SMS)



### Switchable Autonomous Molecular Shuttles (SAMS)



**Figure 4.** Schematic structures of autonomous molecular shuttles (sym-AMS, asym-AMS) and of switchable molecular shuttles (asym-SMS, stop-go-SMS and binary-SMS) considering shuttling between two stations. At the bottom, concept of switchable molecular shuttles with remanence of macrocycle shuttling, before and after actuation.

changed resulting in the ring sitting on a precise station (go-stop-SMS). Second, the affinity for the 2<sup>nd</sup> station can become so high that triggering a unique ring shuttling on the newly preferred station (binary-SMS). Alternatively, the affinity of the 1<sup>st</sup> station can be decreased actuating ring translocation on the newly preferred 2<sup>nd</sup> station. Finally, relevant stimuli were observed to maintain CB shuttling on a molecular thread, but the stimulus changed the ring shuttling distance (Switchable Autonomous Molecular Shuttles, SAMS, Figure 4). Often, all these processes are reversible.

### 2.2. Stimuli for switchable molecular shuttles (SMS)

The characteristic interactions of CB[n] toward chemical functions of the molecular axle have allowed to test several external stimuli to achieve switchable ring shuttling. While encapsulation of hydrophobic fragments in the CB[n] cavity is now well-established, the carbonyl rims provide additional stabilization energies when facing cationic groups via dipole-cation interactions or charge-assisted hydrogen bonds, in particular for ammonium groups. As a consequence, the pH is often used to modulate the CB[n] affinity for amine-containing fragments. Conversely, since the carbonyl rims of CB[n] are repelled by anionic moieties (repulsive anion-dipole interactions), the affinity of a guest station can be dramatically impacted by a neighbouring, pH-controlled carboxylate function. Beside pH, appropriate irradiation of aqueous solutions of CB[n] complexes was observed to result, in some cases, in ring shuttling (or ring setting), because it can affect the charge

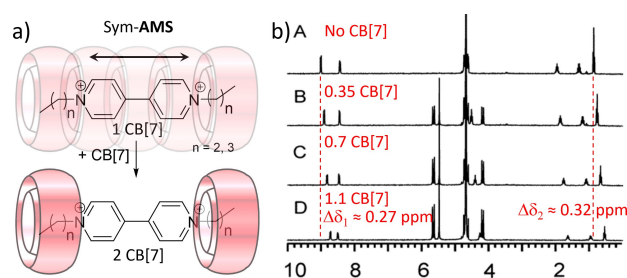
distribution along the guest structure, or can induce function isomerization generating deleterious steric hindrance for CB[n] binding. Apart from pH and light, RedOx actuation has also been investigated and proved to be a good stimulus to control the CB[n] affinity for relevant guest molecules, or fragments of molecular threads. For instance, the electron reduction of the pyridinium group erases its cationic charge thereby modulating ring position (and shuttling) on relevant axes. The introduction of macrocycles was also shown to result in CB[n] reorganization (place and dynamics), along relevant molecular threads. In these cases, unfavourable dipole-dipole interactions between the carbonyl rims of neighbouring CB[n] was sufficiently high to command (in part) those movements, generally considering that, when possible, a maximum number of CB[n] must be complexed on a molecular thread (release of high-energy water from the cavities of CB[n] in excess).<sup>[25]</sup> Conversely, cyclodextrins can be entitled to face CB[n], and multiple hydrogen bonds between two different host rims are expected to stabilise the hetero-host assembly.<sup>[26]</sup> Finally, metal cations have also been observed to trigger ring translocation or fixation. These five stimuli (macrocycle competition [impacting equilibria] and the four others: pH, light, redox, and metal complexation [impacting the nature of the guest]), proved to be efficient means to control ring shuttling in CB[n] supramolecular assemblies. These actuation strategies are summarized in the section dedicated to switchable molecular shuttles.

### 3. Autonomous Molecular Shuttles (AMS)

#### 3.1. Threads with distant stations (degenerate or not)

Symmetrical guest axles having two identical stations are the simplest structures for host shuttling. Kaifer and coworkers prepared a multi-station guest molecule by grafting two alkyl chains on a viologen.<sup>[27]</sup> In case of propyl or butyl groups, addition of CB[7] led to a shift to higher fields of <sup>1</sup>H NMR signals of the alkyl groups, which is characteristic of their CB[n] inclusion, the signals corresponding to the viologen remaining almost unchanged. Remarkably, the <sup>1</sup>H NMR titration with CB[7] only showed one set of signals corresponding to alkyl chain inclusion, even at one equivalent of host. Yet, the capture of one CB[7] on one alkyl chain (1:1 host:guest ratio), necessarily leads to an unsymmetrical complex, and so two sets of signals for a mixture of free and included groups should have been observed.<sup>[27]</sup> This unique set of NMR signals (alkyl stations occupancy confirmed when considering 2 equivalents of CB[7]), is an evidence of a fast CB[7] exchange between the two alkyl stations at one equivalent of host (Figure 5).

The same behavior has been reported with ditolyl-viologen,<sup>[28]</sup> or diphenyl-viologen as guest molecules, confirming that a CB[7] shuttling is generated when small hydrophobic groups are grafted on the two sides of a viologen.<sup>[29]</sup> Moreover, the positive charges along these rigid viologen axles seem traversable for the host, even if generating unfavorable transition states with the hydrophobic cavity during host shuttling. This raises the question of possible release followed



**Figure 5.** (a) Shuttling of CB[7] on two distant alkyl stations of a viologen. (b) <sup>1</sup>H NMR confirmed ring shuttling at one equivalent of host and CB[7] sitting on the two alkyl chains (with almost identical spectra), at two equivalents of host (Adapted with permission from: Ref. [27] >. Copyright 2004 American Chemical Society).

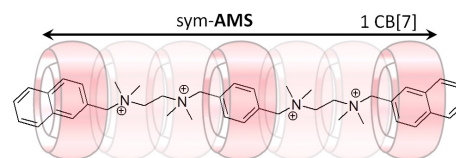
by host re-capture.<sup>[25]</sup> by the other hydrophobic group. However, viologen itself is a good guest for CB[7],<sup>[30]</sup> and host sitting on the center as a transition state seems much more favorable (enthalpically and entropically), than host release and re-capture.

The shuttling of CB[n] also appeared possible on guest molecules presenting competitive stations of different natures, provided the respective affinities for the host remain the same order of magnitude. For instance, Zhang et al. assessed the CB[7] binding properties of a tris-station guest thread having a central p-xylene-diammonium site, in competition with two terminal ammonium-naphthalene stations (Figure 6).<sup>[31]</sup>

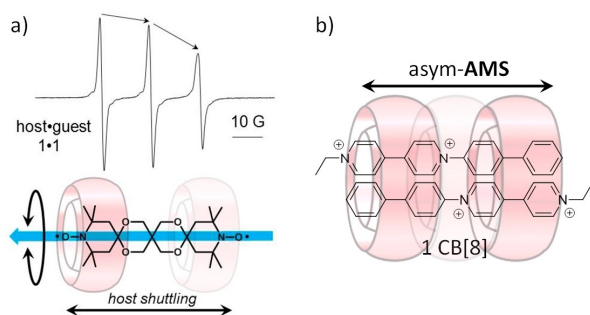
Since CB[7] is characterized by a high affinity for the three stations, the authors hypothesized a dynamic host:guest equilibrium the whole length of the guest axle.<sup>[31]</sup>

Besides, we have reported a paramagnetic symmetric compound also able to make CB[8] shuttling over it. The dinitroxide biradical **tBtk** was shown by EPR spectroscopy to capture one CB[8], shuttling over the two attached TEMPO units (Figure 7a).<sup>[32]</sup> Results were confirmed by <sup>1</sup>H NMR of the bishydroxylamine reduced analogue of **tBtk**.

Finally, Schalley and coworkers discovered a series of 2:2 complexes featured by strong emission enhancement caused by the controlled chromophore oligomerization.<sup>[33]</sup> In this work, they noticed the CB[7] shuttling on a 4,4'-biphenyl-pyridinium pyridine guest, and the CB[8] shuttling over two guest molecules stacked in a head-to-tail manner (Figure 7b). This shows that cucurbituril shuttling may be a largely encountered phenomenon provided guest molecules are sufficiently long, sterically adapted to thread through the macrocycle cavity and possess stations of comparable affinities.



**Figure 6.** Autonomous CB[7] shuttling on a symmetric three-station molecular thread.



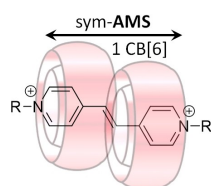
**Figure 7.** (a) Ring shuttling of one CB[8] in water along the dinitroxide biradical **bTbk** (Sym-AMS) and presenting a characteristic EPR signal (reproduced from Ref. [32]). (b) Ring shuttling of one CB[8] in water along two stacked viologens (asym-AMS) as deduced from NMR.

### 3.2. Threads with proximate stations (degenerate or not)

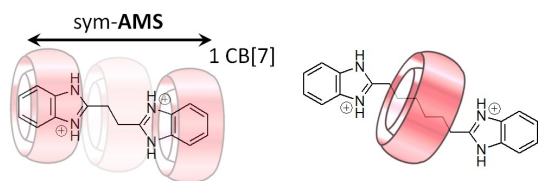
When the thread structure is built so that two stations are very close, CB[*n*] shuttling can be observed between two adjacent stations, as reported when a short spacer is introduced between two pyridinium stations (Figure 8).

Studies of inclusion complexes of CB[*n*] with bispyridinium ethylene compounds shown a dynamic character at room temperature in water. Even if only one ring can sit between the two cationic charges, the ethylene spacer makes the station too large for a single CB[6] accommodation making the ring shuttling in the whole space available (on the most favorable sites).<sup>[34]</sup> A slow exchange between free and complexed pyridinium sites was observable by <sup>1</sup>H NMR on a CB[6]/bispyridinium ethylene rotaxane and shuttling was also observed in DMSO-*d*<sub>6</sub>.<sup>[34]</sup>

In another example, Ni, Tao and coworkers prepared a series of alkyl-bridged dibenzimidazolium guest molecules, and showed for short alkyl spacers (i.e. ethyl chain), a fast CB[7] exchange between the two benzimidazolium sites as observed on <sup>1</sup>H NMR spectra (Figure 9).<sup>[35]</sup>



**Figure 8.** Autonomous molecular CB[6] shuttling between two adjacent stations of a symmetric stilbenic bipyridinium molecular thread.



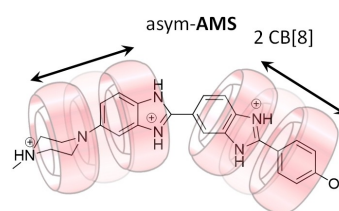
**Figure 9.** Autonomous CB[7] ring shuttling on a symmetrical bis-benzimidazolium cation connected by a two-carbon linker, compared to a "static" 1:1 complex for a longer six-carbon linker.

The authors also observed a significant impact of the CB[7] complexation on the fluorescent intensities of the assemblies, and single complexation without shuttling for a hexyl linker. In 2012, Zhao and coworkers reported the dynamic behavior of several CB[7] rotaxanes prepared by slippage at 100 °C in water,<sup>[36]</sup> one of which featured by autonomous shuttling on a symmetric scaffold and another on an asymmetric thread. However, autonomous shuttling is not limited to CB[6] or CB[7]. The asymmetric molecule H33258, a well-known bioreagent dye, presents two central benzimidazoles linked in a head-to-tail fashion, and a methylpiperazinium and a phenol in periphery. While photophysical properties were noticed to be modified after CB[7] binding,<sup>[37]</sup> at acidic pH, protonation of the imidazole groups made H33258 to recruit two CB[8]. <sup>1</sup>H NMR spectra of the resulting 2:1 complex were in line with CB[8] captured on both benzimidazoliums and the two terminal functions (phenol and piperazinium), making the shuttling hypothesis for each ring, the most likely (Figure 10).<sup>[38]</sup>

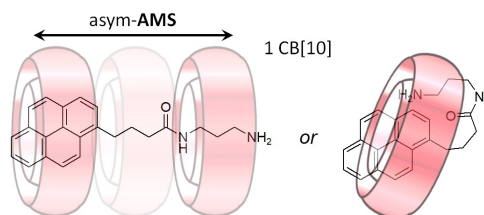
While this 2:1 complex is an efficient fluorescent sensor for metal cations like Al<sup>3+</sup>, Hg<sup>2+</sup>, Fe<sup>3+</sup>, Fe<sup>2+</sup>, Cr<sup>3+</sup>, Eu<sup>3+</sup>, Tm<sup>3+</sup> and Yb<sup>3+</sup> under neutral conditions, the sensor ability was lost at acid pH, maybe due to the shuttling phenomenon.<sup>[38]</sup> Finally, ring shuttling is also suspected with the largest cucurbituril member: CB[10]. A competition for the inclusion in CB[10] of two moieties of aminopropyl-1-pyrenebutanamide has been proposed to produce ring shuttling between the two stations (Figure 11), according to <sup>1</sup>H NMR;<sup>[39]</sup> unless both fragments are included in a folded conformation in CB[10].

### 4. Switchable Molecular Shuttles (SMS)

This part details the various stimuli applied to control CB[*n*] translocation along multistation guest molecules. Importantly, it seems that SMS inherently have to be *asymmetrical*, in the sense of carrying at least two different stations for cucurbiturils,



**Figure 10.** Autonomous ring shuttling of two CB[8] on the asymmetric structure of H33258 in water.



**Figure 11.** Proposed CB[10] shuttling between the pyrene and aminopropyl moieties or 1:1 complex featuring a folded guest conformation.

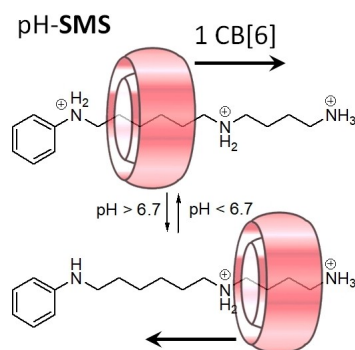
to enable controlled ring translocation. While the pH activation is the most popular strategy to control CB[*n*] switches, other interesting stimuli including Redox or cation coordination have been reported.

#### 4.1. pH activated SMS: amine protonation

The first molecular switch based on a CB complex was described by Mock et al. in 1990 and consisted of a phenyl-terminated linear triamine guest encapsulated by CB[6] (Figure 12).<sup>[19]</sup> Under acidic conditions, the three amine groups are protonated and CB[6] occupies the hexyl moiety between two ammoniums because it presents a more favorable binding ( $K_a = 2.8 \times 10^6 \text{ M}^{-1}$ ), compared to the butyl moiety ( $K_a = 2.7 \times 10^5 \text{ M}^{-1}$ ). One order of magnitude in affinity difference thus appears sufficient to trigger ring translocation. At pH higher than 6.7, the less basic hexylamine moiety lost his proton, and a CB[6] translation to the most favorable butyl site was induced. Mock et al. confirmed the reversibility of the switch by pH decrease.<sup>[19]</sup>

Next, Kim et al. explored the supramolecular assemblies of a linear six-pyridinium guest having a central  $-\text{NH}-(\text{CH}_2)_4-\text{NH}-$  site and CB[6].<sup>[40]</sup> Under acidic conditions, the butyl site was occupied by CB[6] but basic conditions led a CB[6] to switch to one of the two hexyl chains placed between two pyridiniums. Interestingly, increasing the pH did not show the immediate reversibility of the switch. The researchers had to heat the solution at 80 °C to observe a CB[6] back to the initial butyl position, and estimated to 26 kcal/mol the corresponding activation barrier. Indeed, while two hexyl sites are accessible for CB[6] under basic conditions, this strong energy barrier hampers the immediate exchange shuttling on the guest axle.<sup>[40]</sup>

A few examples of dimeric pH-SMS have been reported showing interesting directional ring translations, due to the thread design and to the presence of two rings respectively behaving as stoppers for one another. In 2008, Tuncel et al. synthesized via CuAAC chemistry a linear guest presenting two bis-amine triazole groups separated by a linear alkyl spacer.<sup>[41]</sup> Protonation of the amines permitted the two CB[6] macrocycles to complex the two triazole groups, however their deprotona-



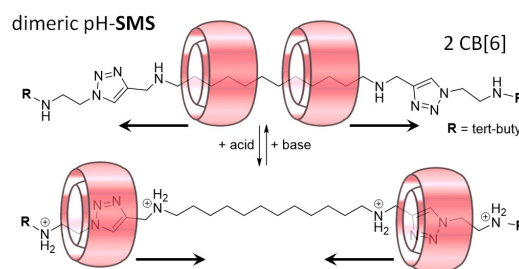
**Figure 12.** First example of a CB[6] molecular switch, the ring shuttling quantitatively from the hexyldiammonium to the butyldiammonium station by careful pH tuning.

tion seemed to lead to CB[6] dethreading from the neutral guest, probably due to the presence of sodium cations competing for interactions with the carbonyl crowns of CB[6]. To prepare a rotaxane analogue (Figure 13), the researchers used a tBu-amine-azide reactant and performed the click reaction on the di-alkyne precursor in the presence of CB[6].

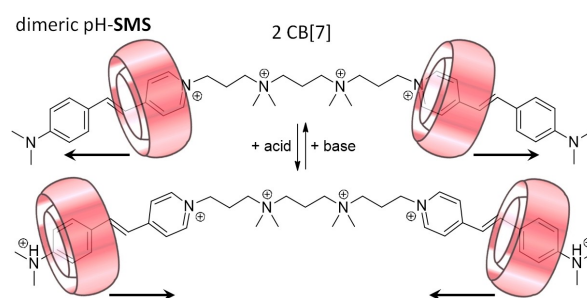
The resulting CB[6] rotaxane showed ring complexation on the triazole sites at acidic pH, and on the long alkyl spacer at basic pH. Similarly to Kim et al.,<sup>[40]</sup> the group of Tuncel observed that the acidic switch was featured by an activation barrier of around 100 kJ/mol by variable temperature NMR.<sup>[41]</sup> To determine the Gibbs activation free energy of the slippage process of CB[6] on linear threads carrying two bulky stoppers, Masson et al. studied di-amine linear guests bearing various organic end-groups such as isobutyl, methylcyclopropyl, methylallyl and trifluoromethyl.<sup>[42]</sup> Kinetic experiments of CB[6] complexation and <sup>1</sup>H NMR studies allowed to provide an estimation of corresponding activation barriers in the range 23.7 to 28.9 kcal/mol. Interestingly, modeling of the inclusion pathways suggested that an ammonium deprotonation step is required to enable CB[6] translocation.<sup>[42]</sup>

Spectrophotometric titrations, accompanied by <sup>1</sup>H NMR spectra were of prime importance to study the CB[7] inclusion on a bis-styrylpyridinium dye having a propyl-diammonium spacer and donor dimethylamine end-groups. Chernikova et al. observed, under neutral conditions using a phosphate buffer, a moderate bathochromic shift of 38 nm due to the pyridinium complexation by CB[7] which generated a less polar environment around the dye (Figure 14).<sup>[43]</sup>

In contrast without buffer, the CB[7] inclusion on the dimethylamine end-group induced a  $pK_a$  shift and led to the protonation of the two amines. In the hexa-ammonium form,



**Figure 13.** Reversible double quantitative ring shuttling in a CB[6] [3]-rotaxane controlled by pH.



**Figure 14.** Reversible quantitative CB[7] shuttling on a [3]-pseudorotaxane.

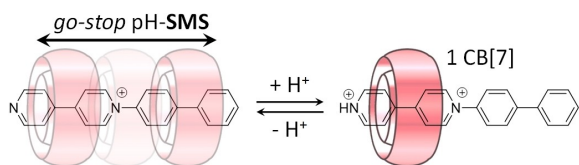
the donor-acceptor charge transfer of the dye was interrupted and a remarkable blue-shift from 482 to 336 nm was characterized by UV-Vis spectroscopy.<sup>[43]</sup> In the previously mentioned paper featuring a CB[8] shuttling on two stacked guest molecules, a *go-stop* pH SMS was reported.<sup>[33]</sup> A CB[7], autonomously shuttling on a 4,4'-biphenyl-pyridine can be set on one hand of the molecule by protonation of the pyridine (Figure 15).

This is another example of a switchable mode of shuttling between autonomous and static.

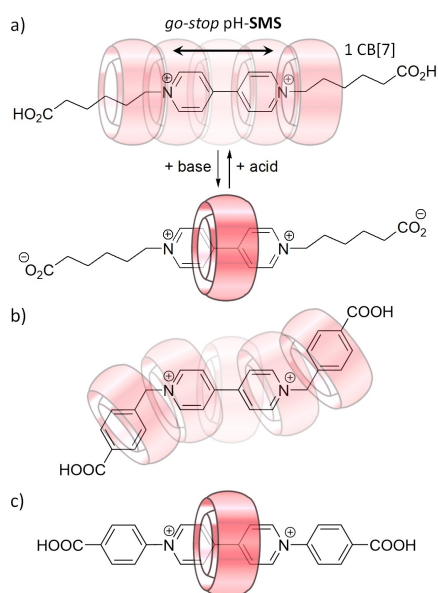
#### 4.2. pH activated SMS: carboxylic acid deprotonation

Kaifer and coworkers reported a dialkyl-viologen guest molecule with two carboxylic acid terminal functions.<sup>[44]</sup> The presence of 1.2 equiv of CB[7] led to one set of <sup>1</sup>H NMR signals and, by varying the host:guest stoichiometry, the authors confirmed that this phenomenon was caused by a fast intramolecular CB[7] exchange between two stations, in other words by a CB[7] shuttling (Figure 16a).

More interestingly, deprotonation of the terminal acids made the alkyl stations unfavored and localized the CB[7] on



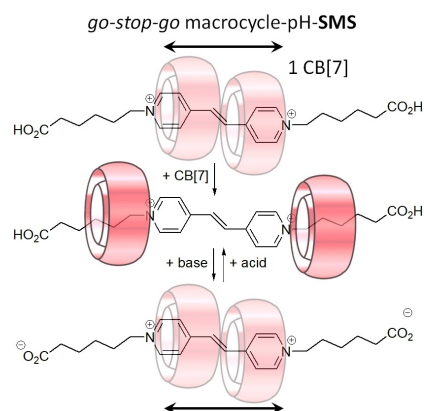
**Figure 15.** An example of a *go-stop* shuttling mode, starting from autonomous shuttling and ending by the CB[7] macrocycle residing on the viologen station upon protonation.



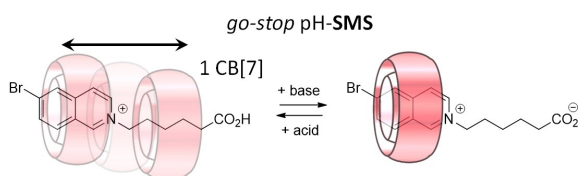
**Figure 16.** (a and b) Reversible access to autonomous CB[7] ring shuttling by pH modulation of the charged state of terminal carboxylic acid groups. (c) While shuttling is observed in alkyl and benzyl viologens, this is not so for para-benzoic acid viologen.

the central viologen thereby producing a *go-stop*-SMS.<sup>[44]</sup> Similar results were obtained for an aromatic analogue (Figure 16b).<sup>[45]</sup> However, the absence of COOH groups leads to CB[7] shuttling between benzyl groups,<sup>[46]</sup> but the absence of methylene groups (connecting the viologen to benzoic acid groups, Figure 16c) resulted in the absence of shuttling and host localization on the viologen, whatever pH.<sup>[47]</sup> These properties were next expanded considering a bispyridinium ethylene bearing two pentyl chains terminated by two carboxylic acid groups.<sup>[48]</sup> While the shuttling phenomenon has been identified between the two pyridinium stations in the presence of 1 equiv. of CB[7] (Figure 17), excess host led to a switch of the CB[7] position to occupy the two pentyl chains, without shuttling.

Moreover, basic conditions induced the deprotonation of the terminal acid groups, and the generated anionic charges triggered the elimination of one CB[7], the remaining ring shuttling back over the bispyridinium ethylene station. The shuttling behavior was so recovered on the resulting zwitterionic rotaxane.<sup>[48]</sup> This original system combines a CB[7] shuttling, a stoichiometric switch and a pH actuation. This pH tunable 1:1 or 2:1 host:guest complexation was also featured by interesting photophysical properties and, notably, a twisted intramolecular charge transfer leading to a low fluorescence emission intensity when the bispyridinium ethylene station was occupied. The bispyridinium spacer expansion by a bisethylene-phenylene group allowed to observe another CB[7] shuttling between the cationic charges.<sup>[49]</sup> This 1:1: complexation mode favored intramolecular charge transfers leading to red-shifted emissions.<sup>[49]</sup> Similarly, Ma et al. clearly observed a shuttling of CB[7] along an axle constituted of a 6-bromoisoquinoline and an alkyl chain (propyl, butyl or pentyl), terminated by a carboxylic acid group (Figure 18).<sup>[50]</sup> Under neutral conditions, this assembly presented a low phosphorescence, but under basic conditions, the generated carboxylate suppressed the shuttling, forcing the ring to remain on the quinoline, and resulting in a strong phosphorescence.<sup>[50]</sup>



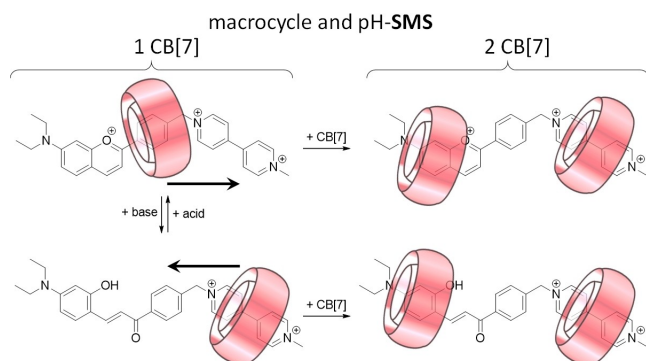
**Figure 17.** Autonomous ring shuttling followed by ring fixation upon CB[7] binding and ring shuttling after pH change (*go-stop-go*-SMS).



**Figure 18.** A bromoisquinoliniumalkyl carboxylic acid with CB[7] shuttling on both sides of the cationic charge. The shuttling is suppressed upon basification and restored after acidification.

### 4.3. pH activated SMS: chemical reaction

In a very interesting example of a CB[7] SMS featured by a pH switch, Basilio, Parola and coworkers explored the effect of pH on an amino-flavylium-viologen guest molecule in the presence of CB[7] (Figure 19).<sup>[51]</sup> Under acidic conditions, the phenyl-spacer between the cationic charge localized on the oxygen atom of the flavylium and the viologen, is the most favorable site for CB[7] inclusion. Moreover, excess of CB[7] induced a switch in the initial CB[7] position, the viologen site being occupied together with the flavylium site (2:1 host:guest complex, Figure 19). However in basic conditions, the flavylium function evolved to a neutral chalcone function and made the viologen the most favorable inclusion site for CB[7], while a second host could complex the phenol group. The researchers confirmed the pH reversibility of the supramolecular switch, but they noticed that the slow kinetics of the flavylium/chalcone rearrangement permitted to observe the signature of metastable intermediate complexes on UV-Vis spectra.<sup>[51]</sup> Finally, Kaifer, Lubal, Sindelar and coworkers used pH to control the inclusion of CB[7] on a ferrocene guest bearing an amine group and a carboxylic acid.<sup>[52]</sup> In an acid solution, the CB[7] strongly complexed the ferrocene, but a higher pH generated the carboxylate, repelling the CB[7] but the cationic charge of the ammonium maintained a host-guest interaction. The presence of a bispyridinium-ethylene competitor guest allowed to monitor by UV-vis spectroscopy, the pH controlled CB[7]-ferrocene complexation/release.<sup>[52]</sup>

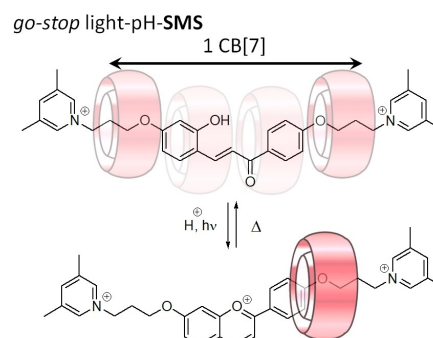


**Figure 19.** An amino-flavylium viologen conjugate featured by CB[7] binding on the central station, and quantitative ring shuttling upon either CB[7] addition or pH changes.

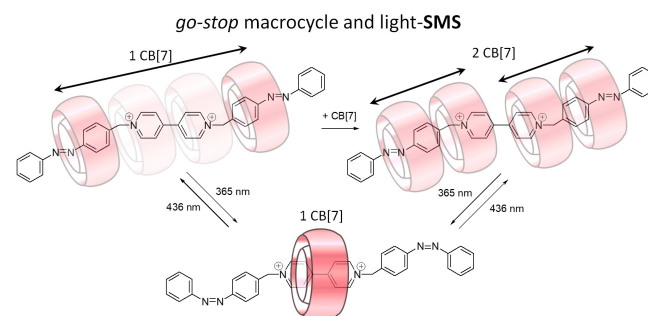
### 4.4. Light activated SMS

Today, there are few instances of light-controlled cucurbituril molecular switches and shuttles. While CB[*n*] shuttling has been observed to impact the photophysical properties of host:guest complexes, the opposite is true and appropriate photo-irradiation can govern the shuttling properties of CB[*n*] complexes. An elegant activation/deactivation mode of ring shuttling was attained with a CB[7] complex of a trans-chalcone functionalized with two terminal propyl-pyridinium groups, creating two CB[7] stations (Figure 20).<sup>[53]</sup> Since the two terminal stations had similar affinities for CB[7], a shuttling was observed by <sup>1</sup>H NMR in water. However in the presence of acid, the UV irradiation of the 1:1 complex solution led to the transformation of the trans-chalcone into a cationic, flavylium function making a station more favorable to accommodate the CB[7] ring, and thus inhibiting the shuttling behavior.<sup>[53]</sup> Since the reaction is fully reversible, appropriate conditions enabled regeneration of the trans-chalcone and reactivated ring shuttling.

Another elegant strategy to control CB shuttling consisted of grafting two photosensitive azobenzene groups on the extremities of a viologen (Figure 21).<sup>[54]</sup> The viologen and the benzyl part of the two azobenzene (AZB) groups showed high affinity for CB[7], and the <sup>1</sup>H NMR spectrum of a 1:1 complex was in agreement with fast shuttling along the guest axle between the two cationic benzyl groups. In the presence of two



**Figure 20.** Reversible entry-exit of autonomous ring shuttling for CB[7] driven by a flavylium-chalcone exchange controlled by light and temperature.



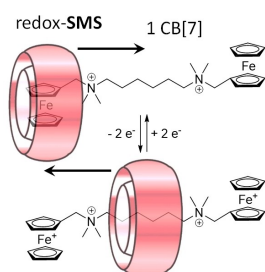
**Figure 21.** Autonomous ring shuttling on a diazobenzene-viologen guest molecule, and shuttling (i) modulation (distance) by capture of another CB[7] or (ii) arrest triggered by light.

equiv. of CB[7], the authors observed double ring shuttling, the two CB[7] mainly residing around the charges of the viologen. However, UV irradiation induced trans-cis isomerization of the azobenzenes, making these stations inaccessible for CB[7], so dramatically reducing the space available for binding. This resulted in a ring expulsion, the remaining CB[7] sitting on the central, viologen station.<sup>[54]</sup> This example could also have been classified as a SAMS as the ring shuttling distance can be controlled, the initial and final steps featured by autonomous ring shuttling.

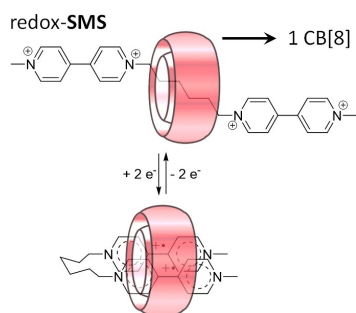
Finally, Sashuk and coworkers reported a CB[7] complex where the host sited preferentially on a heptane spacer, separating a merocyanine and a dimethylammonium-benzaldehyde group.<sup>[55]</sup> Its UV light irradiation induced conversion of the merocyanine into a spirocyan and forced CB[7] to occupy the dimethylammonium-benzaldehyde position, which enhanced the benzaldehyde reactivity and selectivity toward various hydrazides. This original light activated SMS system allows the control of the CB[7] catalytic activity.

#### 4.5. Redox activated SMS

To our knowledge, the high affinity of CB[7] to ferrocene-ammonium guests has been established in 2005.<sup>[56]</sup> The year after, Kaifer and co-workers exploited this property to build a covalent ferrocene dimer linked by a diammonium spacer.<sup>[57]</sup> With one CB[7] sitting on a ferrocene group, the researchers showed that ferrocene oxidoreduction dramatically impacted its affinity to CB[7], eventually resulting in ring translocation on



**Figure 22.** Reversible quantitative CB[7] ring translocation (switch) on a bis-ferrocene diammonium guest molecule triggered by electron exchange.



**Figure 23.** Reversible ring translocation triggered by redox stimulated viologen reduction evolving to a CB[8]-stabilized  $\pi$ -dimer.

the central hexamethylene station, between the cationic charges of the two ammonium groups (Figure 22).<sup>[57]</sup>

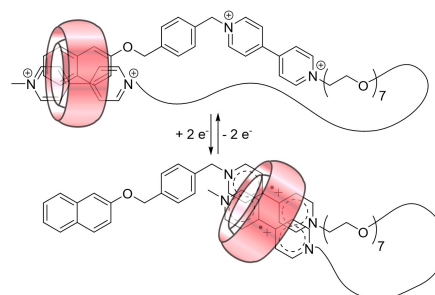
It now seems probable that more sophisticated systems based on CB[7], ferrocene guests and this redox actuation will be developed in the future.

Beside ferrocene as an electron-responsive fragment, Kim and coworkers exploited the dimerization of viologen radical cations in CB[8] cavities,<sup>[58]</sup> to prepare CB molecular switches.<sup>[21b]</sup> They took advantage of the propensity of viologen groups to  $\pi$ -dimerize upon reduction, to fold a viologen dimer connected by an alkyl chain (Figure 23).<sup>[59]</sup>

The CB[8] ring preliminarily sitting on the hexamethylene station reversibly switched its position upon reduction onto the folded  $\pi$ -dimer, forming a RedOx triggered molecular loop. A similar approach has been developed by Garcia, Peinador et al. on a naphthalene-viologen guest bearing a second viologen on poly(ethylene glycol) spacer and CB[8].<sup>[60]</sup> The short PEG chain (3 units) occupied the CB[8] cavity, while a long chain (7 units) allowed the terminal viologen-naphthalene CB[8] complexation stabilized by acceptor-donor interactions (Figure 24). This system, reminding a molecular lasso could inspire researchers toward more advanced systems transiently capturing compounds, with proper design.

In both cases, upon viologen reduction, CB[8]-stabilized  $\pi$ -dimers were obtained,<sup>[21b,61]</sup> like a zip tie.<sup>[60]</sup> An interesting extension of this strategy was the use of a reductive photocatalyst able to trigger viologen pairing in CB[8], a dioxygen atmosphere oxidizing the two reduced viologens, back to their initial state.<sup>[59]</sup>

Finally, Schalley and coworkers reported a cascade of supramolecular events involving several host:guest complexes with cucurbiturils and host translocations, mediated by macrocycle addition or redox stimuli.<sup>[62]</sup> The successive reductive/oxidative steps achieved a dynamic ring shuttling far from equilibrium. This strategy has clearly the potential to be far much exploited for advanced molecular machines since it combines with these building blocks (CB[8] and viologens): (i) ring shuttling, (ii) RedOx activation and (iii) out-of-equilibrium conditions (fuel consumption) to potentially drive components unidirectionally.



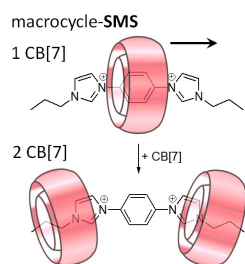
**Figure 24.** Zip tie strategy exploiting viologen-naphthalene CB[8] complexation and viologen radical cation dimerization in CB[8] upon reduction.

## 4.6. Macrocyclic activated SMS

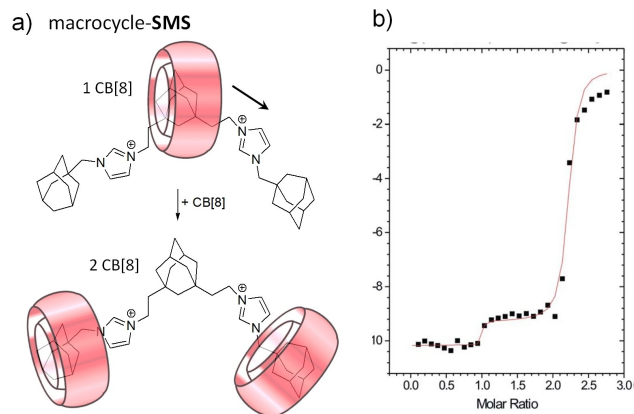
Intramolecular competition for CB[n] accommodation can be observed on tris-station guest molecules. The station presenting the highest affinity for CB[n] is the one occupied, but to optimize further CB[n] complexation, a reorganization of the complex is frequently observed for example when two CB[n] cannot sit on vicinal stations due to repulsive dipole-dipole interactions between carbonyl rims. This phenomenon is at the origin of a CB[n] triggered, CB[n] translocation even on a less favorable station, the energy loss being compensated by the newly captured CB[n] for which the release of intracavity high-energy water molecules is an essential driving force.<sup>[25]</sup>

In this vein, Schmitzer et al. synthesized a series of symmetrical bis(alkylimidazolium) guests with a phenyl spacer, and observed CB[7] binding on the central phenylene.<sup>[63]</sup> When long alkyl chains (more than 3 carbon atoms) were present, an excess of CB[7] triggered translocation of the initially bound CB[7] on the phenylene, to allow complexing lateral alkyl chains (Figure 25).<sup>[63]</sup>

Similarly, Macartney et al. observed a CB[7]-triggered CB[7] switch from the alkyl spacer of two pyridiniums, to a lateral dimethylamine group in the presence of excess host.<sup>[64]</sup> In another article, they observed CB[7] translocation after additional CB[7] binding on succinylcholine, BW284c51, and  $\alpha,\omega$ -bis(trialkylammonium)alkane dications (or their phosphonium analogues).<sup>[65]</sup> García-Río et al. explored the CB[7] complexation on tetradecyltrialkylammonium and noticed its translocation from the center of the C14 chain to the ammonium head, upon complexation of a second CB[7].<sup>[66]</sup> Wang and coworkers linked two (4-pyridyl)phenyl units using a viologen spacer and confirmed by <sup>1</sup>H NMR the CB[7] translocation on the linear rigid guest to the lateral groups, with increasing amounts of host.<sup>[67]</sup> This behavior has also been observed with CB[8]. Indeed, a sequential formation of 1:1 and 2:1 host:guest complexes was characterized by Vícha and coworkers through the addition of CB[8] on a solution of a bis-imidazolium guest featured by a central adamantane site, and two terminal adamantane groups (Figure 26).<sup>[68]</sup> Initially, the central adamantane is occupied by one CB[8], but upon addition of more host, the first macrocycle is translocated on a peripheral adamantane. This behavior is in stark contrast with the sequential binding of CB[7] on this tris-adamantane guest, and has been studied by isothermal titration calorimetry (ITC), for which corresponding thermogram showed



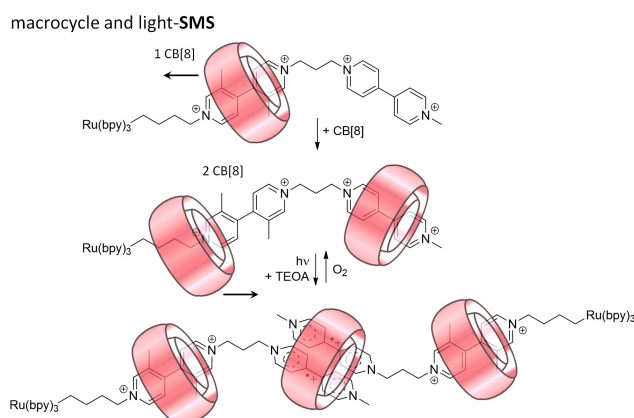
**Figure 25.** Quantitative ring translocation from the central position of a symmetric bis-imidazolium guest molecule to one of the alkyl chains in periphery upon addition of more CB[7].



**Figure 26.** (a) Quantitative CB[8] translocation (switch) from the central adamantane position of a triadamantane-bis-imidazolium guest molecule upon addition of more CB[8]. (b) ITC thermogram corresponding to the titration of this guest with CB[8] in water (Reproduced from Ref. [68] (<https://pubs.rsc.org/en/content/articlelanding/2016/ra/c6ra23524g>) with permission from the Royal Society of Chemistry).

an unexpected break that could be due to the host translocation (Figure 26b).<sup>[68]</sup> The authors confirmed these results by measurements of binding constants which revealed a larger affinity of CB[8] for the central adamantane. However, to enable a second CB[8] to be bound, the 1:1 complex reorganized (ring translocation), to make enough room for optimized second CB[8] binding.

In another example, the sequential CB[8] inclusion on a 3,3'-dimethyl-4,4'-bipyridinium-4,4'-bipyridinium chain grafted on a tris(bipyridine)ruthenium complex has been studied by Sun et al.<sup>[69]</sup> The first CB[8] complexed the 3,3'-dimethyl-4,4'-bipyridinium, but it was pushed toward the ruthenium complex tail after a second CB[8] binding event on the other viologen fragment (Figure 27). Finally the authors exploited the photocatalytic properties of the Ru center to induce the reduction of the 4,4'-bipyridinium (using triethanolamine TEOA as sacrificial electron donor), into a radical cation, which dimerized inter-



**Figure 27.** Quantitative CB[8] shuttling on an asymmetric viologen guest molecule triggered by host displacement due to another incoming CB[8], and viologen reduction triggering  $\pi$ -dimerization of the viologen end-group and restoration of initial CB[8] binding on the "central" 3,3'-dimethyl viologen.

molecularly by forming a  $\pi$ -dimer complex<sup>[70]</sup> stabilized in the CB[8] cavity.<sup>[69]</sup> Dioxygen allowed re-oxidation of the  $\pi$ -dimer to recover the initial complex. Thus, the competitive reduction/oxidation reactions under light and O<sub>2</sub> atmosphere enabled to do an out-of-equilibrium, dynamic multimodal switch. Fedorova et al. reported a sequential reorganization of CB[7] complexes from a 1:2 CB[7]:guest complex to a 2:1 complex with increasing amounts of CB[7].<sup>[71]</sup> This original evolution has been observed using a bis(styrylpyridinium)-propyl guest having two terminal methoxy groups, while the same guest but having terminal dimethylamine groups could receive one to three CB[7] hosts. These evolutions were accompanied by strong changes in fluorescence spectra.<sup>[71]</sup>

Cyclodextrins have also been used to cause cucurbituril translocation on appropriate axle molecules. Liu and coworkers reported the CB[7] translocation from an octyl appended group of a viologen, to the viologen station upon addition of  $\alpha$ -cyclodextrin in deuterated water (Figure 28).<sup>[72]</sup>

Similar movements were noted when using dioctyl-viologen, CB[7] and  $\alpha$ -cyclodextrin. Later, Vicha and coworkers reported the CB[7] translocation by  $\beta$ -cyclodextrin on a ditopic imidazolium guest molecule.<sup>[73]</sup>

#### 4.7. Metal activated SMS

**Sodium ion activated.** Then, Bohne et al. showed that cation coordination is an elegant way to control a host translocation, always in water.<sup>[74]</sup> The authors studied a naphthalene-phenylene ammonium guest and showed that, at high concentrations of sodium cations, a competition between the CB[7] inclusion on the naphthalene and on the phenyl group was generated (Figure 29).<sup>[74]</sup>

Phenyl station allowed the two carbonyl rims of CB[7] to independently interact with the guest ammonium group and a sodium cation.

**Silver ion activated.** The linear VPI guest molecule containing a viologen, a phenylene and an imidazole fragment (a

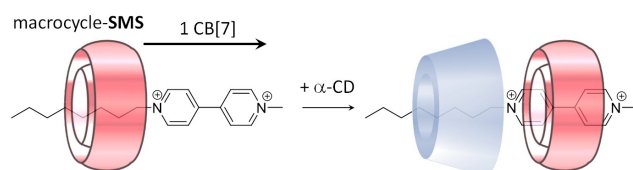


Figure 28. CB[7] shuttling induced by  $\alpha$ -cyclodextrin complexation.

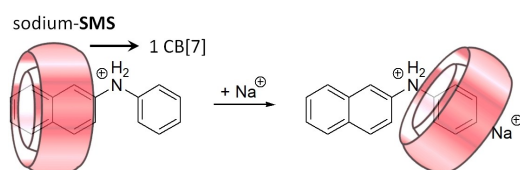


Figure 29. Shuttling of CB[7] from the naphthyl to the phenyl station upon Na<sup>+</sup> ion addition.

benzimidazole), inherently presents three potential CB[7] inclusion sites (Figure 30).<sup>[75]</sup>

Firstly, Wang, Kermagoret, Bardelang and coworkers showed that the viologen was the most favorable station for CB[7].<sup>[75a]</sup> Increasing the concentration of CB[7] did not change the 1:1 host:guest assembly. However acidic conditions led to the imidazole protonation, which remarkably made the phenylene station more favorable for CB[7], thereby triggering a quantitative ring translocation from the viologen to the phenylene station (pH-SMS). As a consequence of the phenylene inclusion, the carbonyl rim of CB[7] close to the imidazole stabilized it in its protonated form via hydrogen bonds and led to a pK<sub>a</sub> shift of the imidazole function from 4.0 (free VPI) to 6.8 (CB[7]·VPI).<sup>[75a]</sup> The authors exploited the pH controlled switch of CB[7]·VPI to expose the toxic viologen group to cancer cells (featured by a pH  $\approx$  6.8), while the viologen is masked by its CB[7] inclusion for non-cancerous cells (pH  $\approx$  7.4).<sup>[75a]</sup> Furthermore, this complex can also be activated by silver ions in water (Figure 30) resulting in a complex where the Ag<sup>+</sup> ion is stabilized by interactions both with the imidazole nitrogen atom of VPI and by two oxygen atoms of the nearest carbonyl rim of CB[7].<sup>[75b]</sup> Addition of chloride salts demonstrated the reversibility of the metal-actuated switch via AgCl precipitation. Moreover, a second ring translocation was observed when large excesses of CB[7] were added onto solutions of CB[7]·VPI-H<sup>+</sup> and CB[7]·VPI-Ag<sup>+</sup> since a second CB[7] could be stabilized on the benzimidazole station, therefore inciting the first CB[7] to sit back on the viologen station. Changing the benzimidazole station to the more hydrophobic naphthimidazole group in VPI-N afforded similar results, except that stoichiometric amounts of hosts enabled ring translocation for the CB[7]<sub>2</sub>·VPI-N-H<sup>+</sup> and CB[7]<sub>2</sub>·VPI-N-Ag<sup>+</sup> complexes.<sup>[76]</sup> On the other hand, increasing hydrophobic contribution by grafting a tolyl group on the other end of VPI (T-VPI) resulted in marked

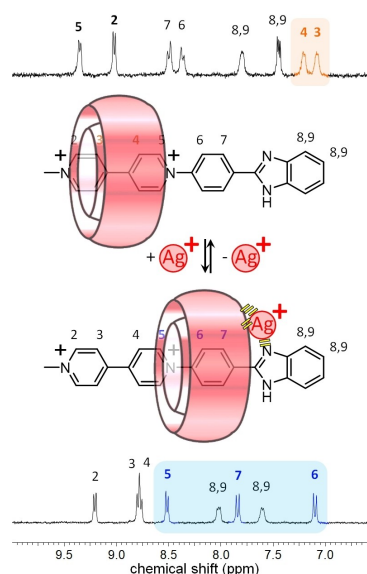
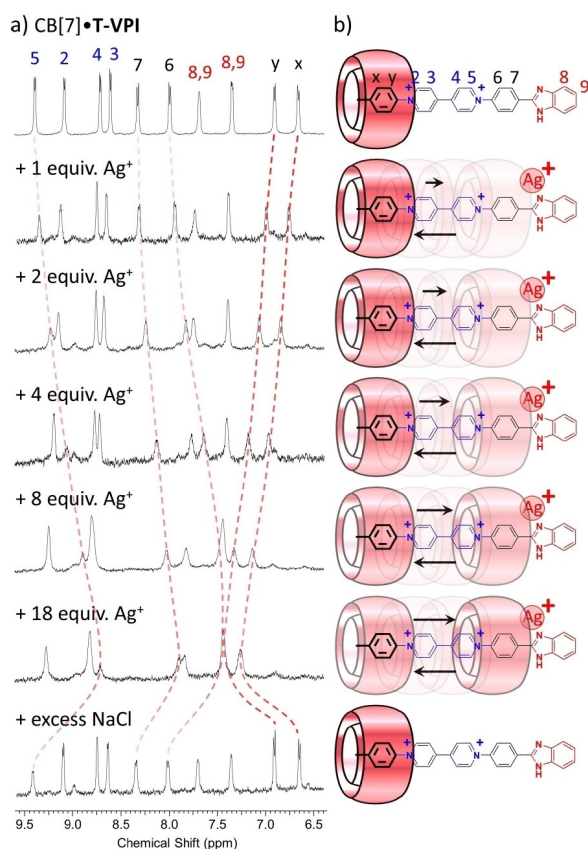


Figure 30. Reversible silver-actuated quantitative CB[7] ring translocation (switch), from the viologen to the phenylene station of VPI (Adapted with permission from: Ref. [75b]). Copyright 2018 American Chemical Society).

changes in CB[7] binding behavior (Figure 31). In this case, the tolyl group is the most favored station for CB[7] at neutral pH or in the absence of  $\text{Ag}^+$ . However, the imidazole station can again interact with  $\text{H}^+$  or  $\text{Ag}^+$  ions, increasing the CB[7] binding affinity on the phenylene station, not sufficiently to make the ring quantitatively switching, but enough for the ring to compete for tolyl and phenylene accommodation. Further addition of CB[7] permitted to occupy both tolyl and phenylene stations, thereby stopping the autonomous shuttling process.<sup>[76]</sup> To summarize, metal-coordination as a stimulus allowed for ring translocation or autonomous ring shuttling but the systems remain at thermodynamic equilibrium. Nevertheless, metal cations introduced a new way to modulate the structure of cucurbituril supramolecular complexes and dynamics of ring shuttling. Especially, since the silver cations have a reasonably low affinity for the imidazole station in the presence of CB[7] ( $K_d$  mM range),<sup>[75b]</sup> one can easily and gradually (in principle even continuously) tune the magnitude of ring shuttling by simply changing the concentration of  $\text{Ag}^+$  in the medium.



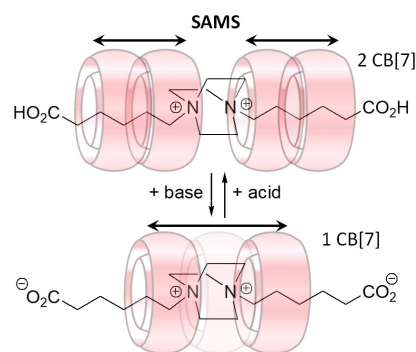
**Figure 31.** Reversible silver-actuated entry in an autonomous CB[7] shuttling mode in T-VPI between the tolyl and phenylene stations (Reproduced from: Ref. [76]).

## 5. Switchable Autonomous Molecular Shuttles (SAMS)

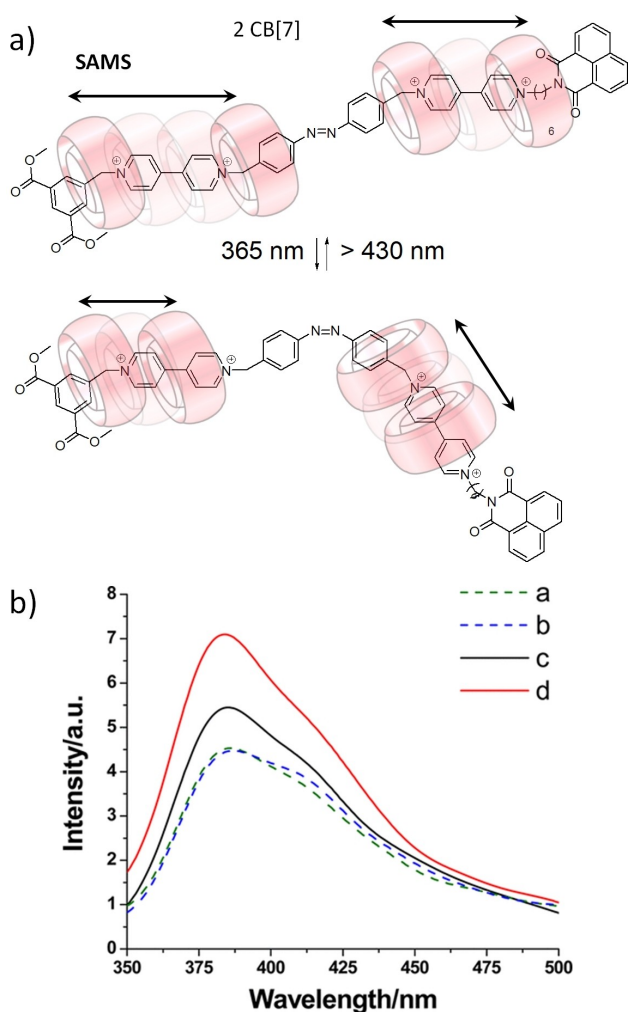
Among the variety of CB molecular shuttles, many are autonomous (AMS) and many are triggered by an external stimulus (SMS). However, one class of molecular shuttles stands between AMS and SMS. These combine the attributes of the two classes, remaining autonomous, but an external trigger actuates a significant change in the ring navigation, thereby modulating the ring shuttling distance. For example, a viologen bearing two p-toluic acid or a guest molecule presenting a central triethylenediammonium and two long alkyl chains terminated by a carboxylic acid (Figure 32), pH changes triggered CB[7] shuttling over two different domains.<sup>[45]</sup>

In this last example under neutral conditions, the authors observed CB[7] shuttling along each pentyl chain in the presence of 2 equiv. of host. However basic conditions restricted the shuttling to only one CB[7] travelling over the triethylenediammonium core which is otherwise unoccupied by CB[7]; maybe due to the too short distance between the cationic charges which cannot interact well at the same time with the two carbonyl rims of CB[7]. The same team explored the CB[7] capture by dialkylviologen guest molecules bearing terminal benzimidazoliums and noticed the same CB[7] shuttling along the axle. However, when two tetramethyl-CB[6] were added to complex the terminal benzimidazoliums, the CB[7] was fixed on the central viologen station.<sup>[77]</sup> Compounds from Figures 16, 17 and 32 can be compared as they are all featured by a central dication (of a different nature), and of identical side-arms. When the central linker is short, there is shuttling, when it is of intermediate size (viologen), the CB7 sits there, and when it is longer, there is CB[7] shuttling again. This illustrates well the subtleties in addressing CB[7] shuttling and predict shuttling behavior depending on guest molecular design. In another example, Liu and coworkers described a CB[7] [3]-rotaxane featured by two shuttling rings navigating over given distances that can be controllably changed by appropriate light irradiation (Figure 33).<sup>[36]</sup>

Indeed, the presence of an azobenzene switch in the center of the rotaxane allowed the thread to switch from trans to cis



**Figure 32.** The travelling site and travelling distance of CB[7] can be modulated on this guest affording an example of a switchable autonomous molecular shuttle (SAMS).



**Figure 33.** (a) The shuttling distance of two CB[7] along the molecular thread can be changed on this light-responsive rotaxane. (b) Fluorescence spectra assigned to the trans-SAMS (black curve) and to the cis-SAMS (red curve, reproduced with permission from: Ref. [36]. Copyright 2012 American Chemical Society).

isomers reversibly, inducing enough changes to constrain each ring to shuttle on reduced domains.<sup>[36]</sup>

## 6. Key Advances

Since the first example of a quantitative CB[6] translocation in water in 1990,<sup>[19]</sup> researchers have described more than 40 examples of cucurbituril complexes featured by ring shuttling. While the simplest systems are characterized by a CB ring autonomously shuttling between two identical stations separated by a flexible or rigid linker, the most sophisticated ones rely on various stimuli to (i) quantitatively and reversibly translocate a CB ring, (ii) change the shuttling distance, or (iii) control the entry or the exit, to or from autonomous shuttling. Several of these systems can be accompanied by large structural or conformational changes impacting shuttling entry, exit or distances. Several of them also possess inherent features that make them belong to several categories at once. For

example, some systems are sensitive to pH but also to light or chemicals. Some others possess autonomous and switchable features. Hence, the proposed classification tried to account for the inherent characteristics of each system and to list coherent ensembles characterized by common features.

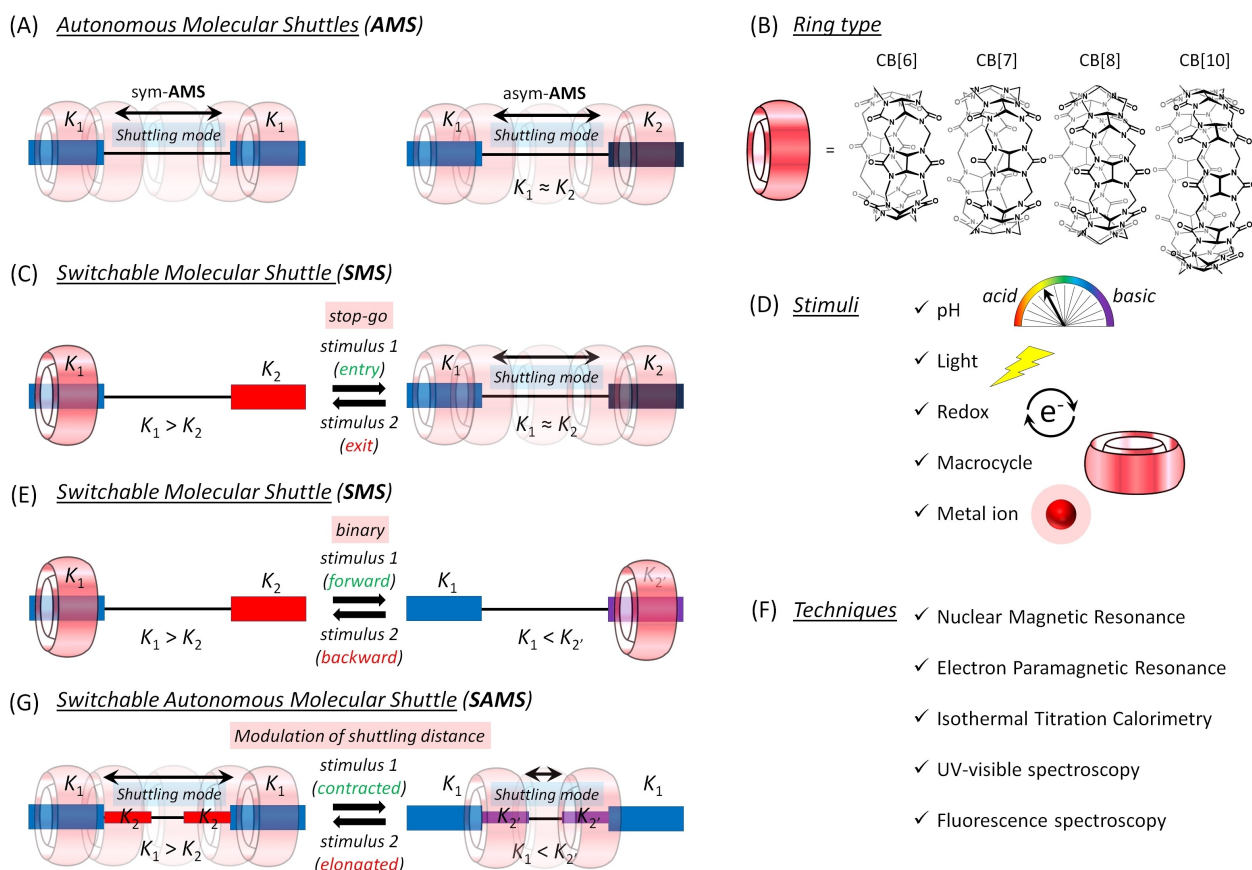
Major advances can be summarized as follows (Figure 34):

- Cucurbituril autonomous shuttling need not consist of navigating between two identical stations (degeneracy of CB[n] binding). Structurally different stations can be amenable for autonomous shuttling as long as the energetic difference in station binding remain weak.
- Demonstration of use of almost all cucurbiturils with large open cavity (CB[6], CB[7], CB[8], CB[10]) although more examples with, and definitive proof of, CB[10] shuttling are needed.
- Control of entry or exit of the autonomous shuttling mode, be it binary (i.e. H<sup>+</sup>) or continuous (i.e. Ag<sup>+</sup>).
- Besides pH long ago shown to be relevant to control CB shuttling, light, redox and chemical stimuli (macrocycles, metal ions) were shown to be excellent ways to control various shuttling behaviors.
- Initially designed monomeric switches have been extended to dimeric switches by palindromic threads and new stimuli have been progressively made relevant to switch cucurbituril positions on appropriate axle molecules (see D).
- <sup>1</sup>H NMR is the technique of choice to identify and study CB[n] molecular shuttles but other techniques like ITC, EPR, UV-vis and fluorescence spectroscopies have also started to be used to characterize complexes with shuttling behaviours. More in-depth characterizations are desirable, in part to identify specific signatures of shuttling when occurring in a system under investigation and help ascertain the shuttling behavior. Theoretical studies are also likely to play a key role in better understanding CB shuttling and effects like those of solvent, temperature and other stimuli.<sup>[78]</sup>
- Modulation of the (autonomous) shuttling distance by relevant stimuli.

Cucurbiturils have also started to be used in mechanized silica nanoparticles, as stopper rings to maintain a key compound in porous silica, before shuttling and ring escape to release the included molecules.<sup>[79]</sup> Besides, we can note that the most frequently used CB is CB[7], probably due to its better water solubility compared to CB[6] and unambiguous complex formation with respect to CB[8] which is featured by possible double-accommodation in its cavity. It also appears that, beside relevant stimuli, the structure of the guest molecule largely dictates the shuttling behaviour of the ring.

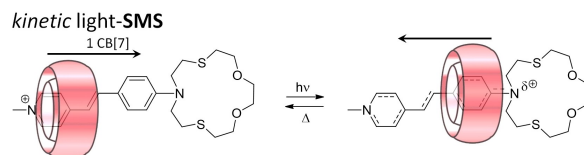
## 7. Conclusion and Next Challenges

This article highlights the high potential of CB[n] as ring compounds for the construction of molecular shuttles and machines. Their symmetrical circular structure, stability, water solubility, sensitivity to cations, and high affinity toward relatively simple molecular threads make them ideal compounds for artificial molecular machines in water. Since the



**Figure 34.** Key advances in the concepts, macrocycles, stimuli available and techniques used, about, or to study cucurbituril based molecular switches and shuttles.

discovery of the first CB molecular switch in 1990, the degree of complexity in this field is progressively rising over time. Today, there appears to be much possibilities to build advanced molecular shuttles, breakthroughs in organic solvents more generally leading the field. Up to now, several categories of CB molecular shuttles have been described (Figure 34), all characterized by ring navigation between two or more stations. However, a clear distinction must be made between CB rings navigating only once after actuation (quantitative ring translocation or supramolecular switches), and CB rings navigating autonomously between two stations. While supramolecular switches can be reset by appropriate stimuli (often opposite like reversed pH, cation sequestration or irradiation at different wavelengths), autonomous shuttles are characterized by dynamic equilibria and statistical features. Up to now and for CBs, the vast majority of these phenomena takes place at thermodynamic equilibrium. One critical next step stands in the exploration of conditions compatible in water with a functioning away from equilibrium.<sup>[80,47]</sup> In 2017, Chernikova and co-workers discovered that a CB[7] ring can be transiently translocated away from equilibrium by light on a (1,4-dioxo-7,13-dithia-10-azacyclopentadecan-10-yl)styryl-1-methylpyridinium guest (Figure 35).<sup>[78]</sup> Interestingly, UV irradiation induced an intramolecular charge transfer, relocating a part of the cationic charge from the pyridinium to the aza cycle and so leading to a



**Figure 35.** Ring translocation by light affording a kinetic product which can be reset back to its initial state.

quantitative CB[7] translocation to this newly formed cationic station. However, deexcitation of the guest re-localized the positive charge on the pyridinium and the CB[7] moved back to its initial position.<sup>[78]</sup> This phenomenon has been described for other pyridinium styryl dyes complexed by CB[7].<sup>[81]</sup> Conceptually, the system absorbs light energy and converts it into a ring movement, but no net transport can be done as the system returns to its fundamental state (reverse ring translocation). In such systems and as already outlined in organic solvents, one can benefit from the exploration of the potential energy surface of CB[n] binding on the thread which is made possible by the Brownian motion. Introducing a ratchet could certainly change the system in a molecular motor, the ratchet preventing back motion after first ring translocation and introducing the unidirectionality required, away from equilibrium for work production.

Furthermore, several points are still unexplored and would merit further attention:

- The shuttling speed in these systems has, to the best of our knowledge never been measured or estimated. Such knowledge would improve our understanding of CB[n] based molecular shuttling in water. The shuttling speed must be correlated to the time resolution of techniques used for measurements. Time-resolved techniques could thus be useful for the study of CB[n] molecular shuttles in water.
- New stimuli could broaden the palette of available means to actuate and control ring shuttling in water.
- Getting typical signatures of CB molecular shuttles other than by NMR would also be positive as definitive proof of their existence seems reluctant to other analyses which often suggest implication of host shuttling rather than providing a direct proof.
- The functionalization of CB[n] to make it responsive to various stimuli<sup>[82]</sup> could open new perspectives in host:guest shuttling systems.
- Most importantly and in the light of recent advances in the field of molecular machines,<sup>[83a–c,22c,83d]</sup> the demonstration of unidirectional CB transport in water should be reported. This would open the way to advanced molecular machines working away from equilibrium and producing work. Efforts toward such systems have recently been made with the setting of a partial energy ratchet using CB[7] in water by the use of a very efficient kinetic trap.<sup>[47]</sup> This allowed for a “directional” guest exchange but not for unidirectional ring transport on a thread.
- Likewise, out-of-equilibrium autonomous shuttling seems possible with supply of a relevant energy source like light (see section 4–4).
- A key challenge of the field consists of amplifying the movements or the speed of a CB on a track in a manner translating such movement to our scale.<sup>[84]</sup> This could in principle be done by imparting such movements (autonomous or quantitative) in a material.<sup>[8c,85]</sup>
- Energy harnessing or storage from molecular shuttling is another possibility for example with light-powered devices contracting or decontracting to large extents.<sup>[86]</sup>
- Another challenge could consist of using a CB molecular shuttle in biology where ring shuttling would bring a critical additional function to the molecular thread.<sup>[75a]</sup>
- A last challenge could consist of preparing a molecular Turing machine that could take the form of a CB macrocycle shuttling directionally over a thread while writing a message (building a molecule) according to information “read” by the macrocycle as a function of its travel along the molecular thread. The team of David Leigh has made a critical achievement in this direction recently in organic solvent.<sup>[22c]</sup>
- Finally, perhaps the most common way to envision a shuttle is to focus on an arbitrarily fixed thread and consider ring shuttling. However, it seems equally relevant to consider a fixed ring and focus on thread shuttling. This could open a new avenue not for ring shuttling but for thread shuttling, at least in the domain of cucurbiturils and is actually already found in nature, as pictured by proteins or protein oligomers

in charge of controlling the entry/exit of relevant compounds in cells or cell compartments. For example, proteins regulating monochain import or export from cell membrane,<sup>[87]</sup> or the ring-shape oligomerized viral nsP1 controlling the ingress of metabolites and proteins and the egress of viral RNA.<sup>[88]</sup>

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created in this study.

**Keywords:** cucurbituril · host:guest · macrocycle · shuttle · switch

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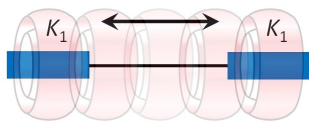
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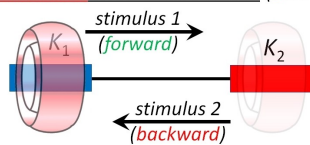
## CONCEPT

*Autonomous Molecular Shuttles (AMS)*



The enriching shuttling of cucurbiturils. The number and complexity of supramolecular systems featured by cucurbituril macrocycles shuttling over other molecules do not cease to

*Switchable Molecular Shuttle (SMS)*



increase. This concept article discusses the recent advances in the field and proposes challenges to tackle.

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1 – 19

The Diversity of Cucurbituril Molecular Switches and Shuttles