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REVIEW

Cucurbituril chemistry: a tale of supramolecular success

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This review highlights the past six year advances in the blossoming field of cucurbit[n]uril chemistry. Because of their exceptional recognition properties in aqueous medium, these pumpkin-shaped macrocycles have been generating some tremendous interest in the supramolecular community. They have also become key units in various self-organizing and stimulus-controlled assemblies, as well as in advanced materials and drug carriers. The scope of this review is limited to the main family of cucurbit[n]urils (n = 5, 6, 7, 8, 10). The reader will find an overview of their preparation, their physicochemical and biological properties, as well as their recognition abilities towards various organic and inorganic guests. Detailed thermodynamic and kinetic considerations, as well as multiple applications including supramolecular catalysis are also discussed.

1. Introduction

In 1905, Behrend and coworkers characterized the condensation products of glycoluril (**1**) and formaldehyde under strongly acidic conditions as "white, amorphous compounds, which are weakly soluble in dilute acid and base, and absorb large quantities of water without losing their dusty powdery character".[1] One of those products was found to contain "at least three molecules of glycoluril", condensed with twice as many formaldehyde units, thereby corresponding to the formula $C_{18}H_{18}N_{12}O_6$.[1] More than a century later, this characterization of what was likely a mixture of cucurbit[n]urils (CB[n]), is still remarkably valid. In 1981, Mock and coworkers revisited Behrend's experiments and, upon complexation with calcium sulfate, successfully crystallized a hydrated macrocycle bearing six glycoluril units linked by twelve methylene bridges, and interacting with the calcium cations *via* its two carbonylated rims. The authors named the structure "cucurbituril" for its resemblance to "a gourd or [a] pumpkin" (which belong to the Cucurbitaceae family), and to a cucurbit, a vessel connected to an alembic used by alchemists for distillations;[2] it is now known as curcurbit[6]uril (commonly abbreviated CB[6], or in some cases CB6, Q[6], Q6 or Cuc6, '6' representing the number of glycoluril units in the macrocycle). In the same study, CB[6] was already found to encapsulate alkylammonium cations.[2] Although other CB[n] analogs must have been formed together with CB[6] under the conditions reported by Mock,[3] one had to wait until 2000 for the isolation and X-ray characterization of three new members of the CB[n] family by Kim and coworkers

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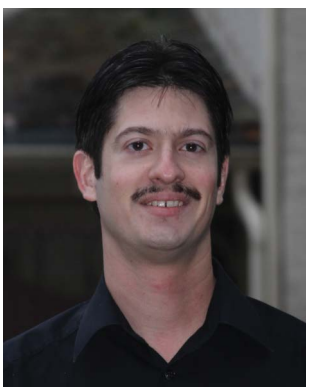

Eric Masson

Eric Masson was born in Lausanne, Switzerland. In 2001, he obtained a Master's degree in chemistry from the University of Lausanne, and in 2005, a Ph. D. in organic chemistry from the Swiss Federal Institute of Technology Lausanne (EPFL) under the guidance of Prof. Manfred Schlosser. He then spent two years as a post-doctoral associate at Yale University under the supervision of Prof. Andrew D. Hamilton, and joined Ohio University as an Assistant Professor in 2007. His research interests revolve around supramolecular and recognition chemistry, with a particular affinity for the cucurbituril family of macrocycles.

Xiaoxi Ling

Xiaoxi Ling was born in Shanghai, China. He obtained a Bachelor of Engineering degree in Applied Chemistry from East China University of Science and Technology in 2007. In September of the same year, he joined Ohio University, and became the first graduate student pursuing a Ph. D. degree under the guidance of Prof. Eric Masson. His current research is focused on the kinetics and thermodynamics of cucurbituril recognition, as well as on the preparation and applications of cucurbituril-containing molecular switches and advanced materials.

(CB[5], CB[7] and CB[8]; see Fig. 1 for the structure of CB[7]).[4] Less than two years later, Day *et al.* eventually identified[3] and crystallized[5] the interlocked complex CB[5] ⊂ CB[10] (as much as 65 g isolated from 1 kg glycoluril!).[3]

Thanks in part to these exciting developments, CB[n] chemistry has been blossoming at a remarkable rate since the beginning of our millennium, with a growth rate that does not pale in comparison to resorcinarenes and calixarenes, approximately seven and twelve years earlier: since 1997, the number of articles, reviews and patents related to CB[n]s has grown from less than 10 per year to 124 in 2010 (an average yearly growth rate of 10 documents, *vs.* 28 and 5.8 in the case of calixarenes and resorcinarenes, respectively; see Fig. 2). These numerical data support Kim's wish expressed during the last evening of the 1st International Conference on Cucurbiturils (July 10–11, 2009) held at POSTECH in Pohang, Korea, that CB[n]s would be to the next decade what calixarenes have been to the previous one.

2. Scope and limitations of this review

Several reviews describing the amazing recognition properties and applications of CB[n]s have been published in the past few years.[6–15] Yet the functionalization of CB[6][13,16–18] and the

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Xiaoyong Lu was born in Shanxi, China, studied chemistry in Xinzhou Teachers University from 1999 to 2002, and completed his undergraduate studies after a final evaluation from Shanxi University in 2003. He received a Master's degree in organic chemistry from Shanghai University in 2007, and worked in the pharmaceutical company Shanghai Chempartner before joining Ohio University as a graduate student. Xiaoyong has been an active member of the Masson group since 2008. His research interests include the recognition and catalytic properties of cucurbiturils, and the synthesis and evaluation of cucurbituril-based rotaxanes and nanomaterials.

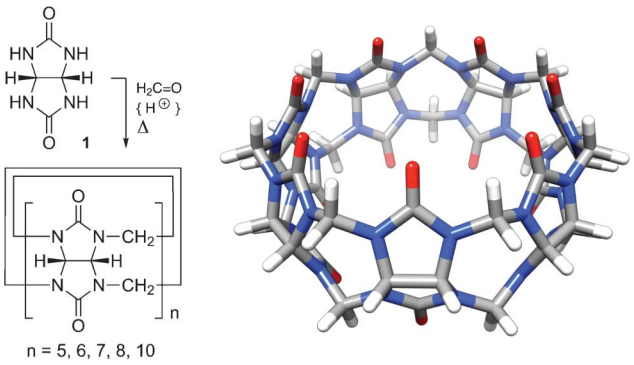


Fig. 1 Preparation of CB[n]s from glycoluril (**1**) and formaldehyde under acidic conditions. Structure of CB[7] from X-ray diffraction (carbon atoms in grey, hydrogens in white, nitrogens in blue and oxygens in red).

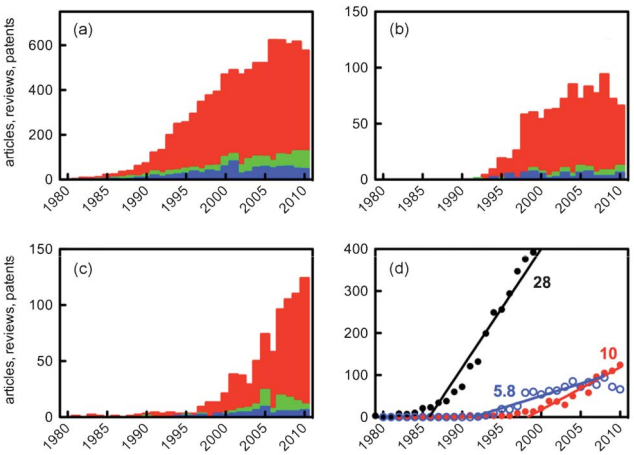
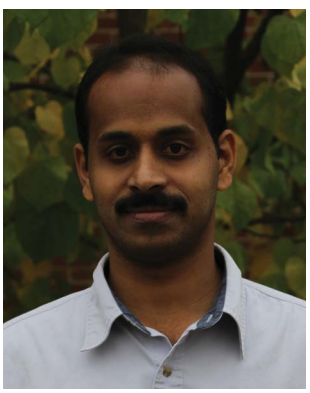


Fig. 2 Histograms representing the number of reviews (blue), patents (green) and articles (red) published each year, in the case of (a) calixarenes, (b) resorcinarenes and (c) CB[n]s. (d) Total number of published documents y *vs.* time t [year] for calixarenes (black), resorcinarenes (blue) and CB[n]s (red); the yearly growth rate k is determined by fitting the data with the discontinuous equation $y = k(t–t_0)$ when $t > t_0$, and $y = 0$ when $t \leqslant t_0$.



Roymon Joseph

Roymon Joseph was born in Kerala, India, and received his Bachelor's and Master's degrees from St. Berchmans College Changanacherry affiliated to Mahatma Gandhi University, Kerala. He obtained his Ph. D. degree from the Indian Institute of Technology Bombay in 2010 under the supervision of Prof. C. P. Rao, and continued to work there as a research associate for another year. He is currently a postdoctoral researcher with Prof. Eric Masson at Ohio University. His research interests include supramolecular chemistry, ion and molecular recognition, as well as bioorganic and bioinorganic chemistry.

Lawrence Kyeremeh-Mensah

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remarkable synthesis of new CB[n] analogues (inverted *i*CB[n]s,[19,20] *nor-seco*-CB[n]s[21–23] and various cyclic[24–27] and acyclic[28–30] congeners) have inevitably shrunk the review space solely dedicated to the theoretical studies and applications of the main family of CB[n]s (n = 5, 6, 7, 8 and 10). Therefore, the aim of the present review is to provide the reader with an overview of those studies carried out during the past six years, approximately since the publication of Isaacs' landmark article "The Cucurbit[n]uril Family".[12] For more in-depth information about selected aspects of CB[n] chemistry, we also recommend the very recent series of articles published in the *Israel Journal of Chemistry* on the occasion of the 2nd International Conference on Cucurbiturils held at the University of Cambridge, UK (June 29–July 2, 2011).[31]

3. Synthesis and characterization of CB[n]s

3.1 Preparation

Various procedures have been proposed for the preparation of mixtures of CB[n]s, all based on general protocols developed by Day,[3] Kim[4] and Isaacs.[14] Generally, a mixture of glycoluril, aqueous formaldehyde or paraformaldehyde, and hydrochloric or sulfuric acid (concentrated, or diluted to approximately 5 M) is heated to 80–100 °C during 10–100 h. Evaporation and consecutive precipitations in water and methanol afford a mixture of CB[n]s (n = 5–8, CB[6] being the major component of the mixture), as well as traces of CB[5] ⊂ CB[10], *i*CB[6] and other oligomers. Separation of each component is based on their differential solubility in water, water/methanol and diluted hydrochloric acid solutions, according to Fig. 3a.[14] A useful variation was proposed by Day,[3] and repeated by Halterman[32] and Leventis,[33] in which the authors use a hot 20% aqueous solution of glycerol to extract CB[7] from the mixture of CB[n]s with good selectivity. Recently, Scherman reported an alternate environmentally friendly separation of CB[5] and CB[7] (see Fig. 3b): CB[7] could be precipitated selectively upon complexation with 1-alkyl-3-methylimidazolium

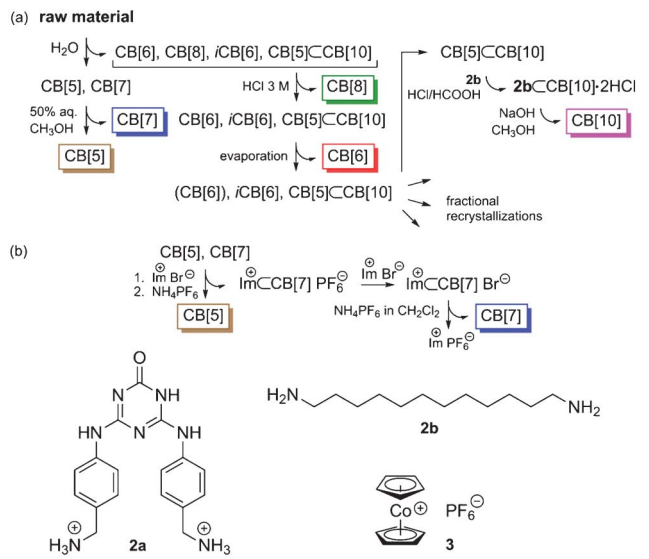
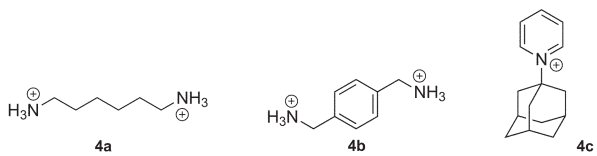


Fig. 3 Purification of CB[n]s: (a) General procedure;[14] (b) alternate method for the separation of CB[5] and CB[7].[34] Curved arrows indicate precipitation.

bromides (Im^+Br^- in Fig. 3b) and anion exchange with ammonium hexafluorophosphate ($NH_4^+PF_6^-$), and CB[5] was recrystallized from the aqueous phase. The imidazolium/CB[7] complex was subjected to Br^-/PF_6^- anion exchange, and CB[7] was released from the Im^+Br^-/CB[7] complex upon reverse anion exchange with $NH_4^+PF_6^-$ in dichloromethane under heterogeneous conditions.[34]

Free CB[10] was obtained in 2005 by Isaacs upon treatment of CB[5] ⊂ CB[10] with an excess amount of melamine derivative **2a** (yielding the ternary complex CB[10]·$\mathbf{2a}_2$), followed by the ejection of the first guest with methanol, and of the second one after reaction with acetic anhydride.[35] The crystal structure of free CB[10] was reported in 2009 by the same group.[15] A more recent procedure indicates that CB[5] can be ejected from CB[10] using commercially available 1,12-dodecanediamine (**2b**) at low pH; free CB[10] is obtained upon repetitive washing with a hot ethanolic solution of sodium hydroxide, and subsequent recrystallization in concentrated hydrochloric acid.[36]

In addition to elementary analysis, the purity of the macrocycles can be assessed by ^{1}H nuclear magnetic resonance spectroscopy (NMR), since the chemical shifts of the methylene hydrogens differ along the CB[n] series.[4,14] CB[n]s are hygroscopic, and may still interact with some water molecules even after several drying cycles; they may also be contaminated with hydrochloric acid and various cations and anions. Therefore, we recommend that the molecular weight of the isolated CB[n] (*e.g.*, the molecular weight of a CB[n]·xH_2O·yHCl complex) be determined by titration with a high affinity guest. For example, the Kaifer group uses UV-Vis titration with a solution of cobaltocenium hexafluorophosphate (**3**; 15 μM) and varying concentrations of CB[7] and CB[8],[37] while the Masson group usually opts for ^{1}H NMR titration with solutions containing a known concentration of 1,6-hexanediammonium (**4a**), *p*-xylylene diammonium (**4b**) or 1-adamantylpyridinium (**4c**) cations, in the case of CB[6], CB[7] and CB[8], respectively. The concentration of CB[n]-bound species can be obtained from the signals of free and bound guests, or by comparison and calibration with an inert standard present at a known concentration (*N*,*N*-dimethylformamide, dimethyl sulfoxide, sodium methanesulfonate, *etc.*). One should finally note that CB[n]s can be detected at concentrations as low as 10 ppb using surface enhanced Raman scattering (SERS) on Klarite™ nanostructured surfaces.[38]



3.2 Physical properties

CB[n]s bear two hydrophilic carbonylated rims and a hydrophobic cavity. Their total depth is 9.1 Å if one includes the van der Waals radii of the oxygen atoms, and the depth of the cavity is 7.4–7.8 Å if one considers the separation between the two planes of local electrostatic potential minima at both portals.[15,39–41] The width of the CB[5]–CB[8] cavities vary between 4.4 and 8.8 Å, and the ellipsoidal CB[5] ⊂ CB[10] complex has transverse and conjugate diameters of 10.7 and 12.6 Å,

respectively;[8,41] free CB[10] is also ellipsoidal, with transverse and conjugate diameters of 11.3 and 12.4 Å.[15] The diameter of the CB[n] portal is approximately 2 Å narrower than the cavity of the macrocycle (see Table 1). Depending on their size, the inner cavity of CB[n]s can host between 2 and 22 "high-energy" water molecules ("high-energy" relative to their stability in the aqueous environment), as calculated using a 55% packing coefficient[42] (*i.e.* a 55% ratio between the volume of the combined water guests and the volume of the CB[n] cavity; values are in excellent agreement with those extracted from X-ray crystal structures).[43] The water content of CB[5] and CB[8] parallels α- and γ-cyclodextrins (CD), respectively, while β-CD accommodates 6–7 water molecules, *vs.* 4 and 8 in the case of CB[6] and CB[7].[43] It is of course much more difficult to evaluate the number of water units at the carbonylated portals of CB[n]s, because of the complex network of possible dipole–dipole interactions in this region. As the reader will appreciate in the next sections, ejection of water from CB[n]s plays a critical role in the recognition properties of these macrocycles.

The cavity of CB[n]s is a remarkably unpolar and unpolarizable environment: based on the bathochromic shift observed when rhodamine 6G is encapsulated within CB[7], Nau determined that the dielectric constant in the cavity is equal or lower than 10.[44] CB[7] was also found to have an extremely low polarizability, even lower than perfluorohexane![45,46] This is not totally surprising if one remembers that no bonds or lone pairs are present inside the cavity of the macrocycle. Using the density functional method (DFT) at the B3LYP/6-311G(d,p) level, Nau also reported extremely high negative quadrupole moments for CB[n]s.[43]

CB[5], CB[6] and CB[8] form stable crystals with well-organized 1D channels. Two different polymorphs of CB[6] could be obtained, both revealing a honeycomb-like structure (the orientation of CB[6] differs in the two cases)[47,48] with large channels filled with water. CB[8] units can be located at the center and vertex of a perfectly square parallelepiped,[48] or adopt a distorted honeycomb structure with partially self-closed cavities.[49] CB[5], among other arrangements, forms a distorted honeycomb structure with water-filled channels, which transforms to a more stable layered phase upon heating.[50] This honeycomb organization, which maximizes interactions between the outer methylene and methine hydrogens and the carbonylated portal of the neighboring macrocycle, is a general characteristic of CB[n]s in the solid state. Although such CH/O interactions are very weak, their sheer number is responsible for the remarkable thermal stability of CB[n] crystals.[49] Nau also mentions that the orientation of the CB[n] units maximizes quadrupolar interactions between the macrocycles.[43] In the case of CB[5], CB/water interactions significantly compete against weak CB/CB interactions, while CB[7]/CB[7] interactions are strong, but outnumbered by the CB[7]/water interactions. To the contrary, CB[6] crystals are stabilized by strong CB/CB interactions, with limited CB[6]/water competition.[49] CB[8]/CB[8] contacts are weaker than CB[6]/CB[6] ones, but CB[8]/water interactions are also limited. Both CB[6] and CB[8] remain crystalline upon drying, while CB[5] and CB[7] become amorphous. These structural considerations likely explain why CB[5] and CB[7] are much more water-soluble than CB[6] and CB[8] (20–30 mM *vs.* less than 0.01 mM in pure water, see Table 1).[8] Fortunately, the solubility dramatically improves as the ionic strength of the medium is increased, or upon encapsulation with amphiphilic guests (see Table 1).

Table 1 Some physicochemical properties of CB[n]s

	a^a	b^b	c^c	S^d	n^g	$K_a{}^h$
CB[5]	2.4	4.4 (3.9)	7.4	20–30 (60)	2	
CB[6]	3.9	5.8 (5.5)	7.5	0.018 (60)^e	4	5.4×10^{10} ^{i}
CB[7]	5.4	7.3 (7.1)	7.6	20–30 (700)	8	5.0×10^{15} ^{j}
CB[8]	6.9	8.8 (8.6)	7.7	< 0.01 (1.5)	12	4.3×10^{11} ^{k}
CB[10]	9.5–10.6	11.3–12.4	7.8	< 0.05^f	22	

^{a} Portal diameter [Å].[8,12,15] ^{b} Cavity diameter calculated from the X-ray crystal structures,[8,12,15] and in parentheses, diameter corresponding to the distance between electrostatic potential minima [Å].[41] ^{c} Cavity depth determined from electrostatic potential minima [Å];[41] the total CB[n] depth, which includes the van der Waals radii of oxygen atoms, is 9.1 Å in all cases.[8,12,15] ^{d} Solubility in water [mM],[8,12,35] and in parentheses, in hydrochloric acid (3 M).[12] ^{e} In a 1 : 1 mixture of water and formic acid, instead of hydrochloric acid. ^{f} From ref. 35. ^{g} Number of water molecules in the CB[n] inner cavity, calculated using a 55% packing coefficient.[43] ^{h} Highest reported binding affinity towards organic guests [M^{-1}]. ^{i} in LiCl 0.20 M.[56] ^{j} in pure water.[57] ^{k} in acetate buffer (pD 4.74, 50 mM).[58]

Finally, we note that CB[6] and CB[8] crystals grown from acidic solutions display excellent proton conductivities, with very high anisotropicities (up to 8.6×10^3-fold higher conductivities were measured along the channels, than perpendicular to those).[55]

CB[n]s are virtually insoluble in all organic solvents, with a few exceptions. Kaifer is the first investigator to have reported a CB[7]-based rotaxane that is soluble in acetonitrile and dimethyl sulfoxide; the central station was *p*-xylylene dipyridinium, its counteranion hexafluorophosphate, and the unit was decorated with bulky hydrophobic stoppers.[51] The same group published several additional examples in a recent past, with millimolar solubilities in dimethyl sulfoxide, acetonitrile and *N*,*N*-dimethylformamide; in all cases, hexafluorophosphate was the counteranion to the positively charged guests.[52] Our group also recently determined that the solubility of CB[7]-bound *p*-xylylene diammonium (**4b**; trifluoromethanesulfonate as the counteranion) reaches 60 mM in dimethyl sulfoxide.[53] To the best of our knowledge, there has been only one example of a CB[8] interlocked assembly partially soluble in a non-aqueous solvent (a viologen unit linked to two tris(2,2′-bipyridine)ruthenium substituents in acetonitrile).[54]

3.3 Biological properties

CB[n]s are remarkably inert *in vitro* and *in vivo*: Nau and Day determined that the IC_{50} value of CB[7] towards Chinese hamster ovary CHO-K1 cells after 48 h is 0.53 mM.[59] At shorter incubation times (3 h), concentrations as high as 1.0 mM were found viable, and no cytotoxic effects were detected at concentrations of 0.50 mM or less. CB[7] is also inert at 1.0 mM towards human kidney HEK293, human hepatocyte HepG2 and murine macrophage RAW264.7 cells after 48 h of incubation.[60] A similar result was obtained with CB[5]. At concentrations greater than 0.10 mM, CB[7] is equally inert towards human A549 non-small lung cells, SKOV-3 ovarian cells, SKMEL-2 melanoma, XF-498 brain cells and HCT-15 human colon cells.[61] Intravenous injections into mice of a single dose of a CB[7] solution at 250 mg kg^{-1} showed little sign of toxicity, with a body weight loss of 5% 4 days after injection and

subsequent recovery.[59] Single oral doses of 600 mg kg^{-1} of a 1 : 1 mixture of CB[7] and CB[8] led to no adverse effect; the even lower toxicity of CB[7] *via* the oral route is probably due to the low absorption of CB[7] across the gastrointestinal system.[59] Monitoring the toxicity of CB[8] is more problematic due to its very low solubility in aqueous medium, yet at 20 μM, no sign of *in vitro* toxicity was observed. Unfortunately, we haven't found any toxicological information related to CB[6].

3.4 Growth mechanism

The mechanism of CB[n] formation, a step growth *cyclo*-oligomerization, has been studied in detail by Isaacs and coworkers.[20,62,63] The first step is the dimerization of glycoluril (**1**) in the presence of formaldehyde under acidic conditions, which can afford the pair of diastereomers **5a** and **5b**, the "curved" isomer **5b** being more stable than the S-shaped analog **5a** by at least 2 kcal mol^{-1}.[62] Isaacs then managed to isolate further intermediates of the oligomerization process (glycoluril trimer to hexamer), which all adopt the "curved" conformation. Since (1) CB[n] can only be formed with a fully curved oligomer, and (2) the probability for one or more "S-shaped" mismatches increases during oligomerization, an intramolecular "S-to-curved shape correction" isomerization must be operational. The same authors propose the fragmentation of S-isomer **5a** to iminium **5c**, which undergoes S-to-curved isomerization *via* the spiro intermediate **5d** (see Fig. 4).[20] The mixture of CB[n]s thus obtained results from a subtle interplay between kinetics and thermodynamics. Day[3] and Isaacs[62] clearly showed that, while CB[8] can undergo reorganization to smaller analogs, CB[5]–CB[7] are more stable, or behave as kinetic traps (*i.e.* their respective formation is irreversible under all experimental conditions tested so far): cyclization attempts with glycoluril dimers and trimers afford a high ratio of CB[6] ($2 \times 3 = 3 \times 2 = 6$), and a high yield of CB[8] is obtained with glycoluril tetramers ($2 \times 4 = 8$); also, a high ratio of CB[5] is obtained with glycoluril pentamer, and

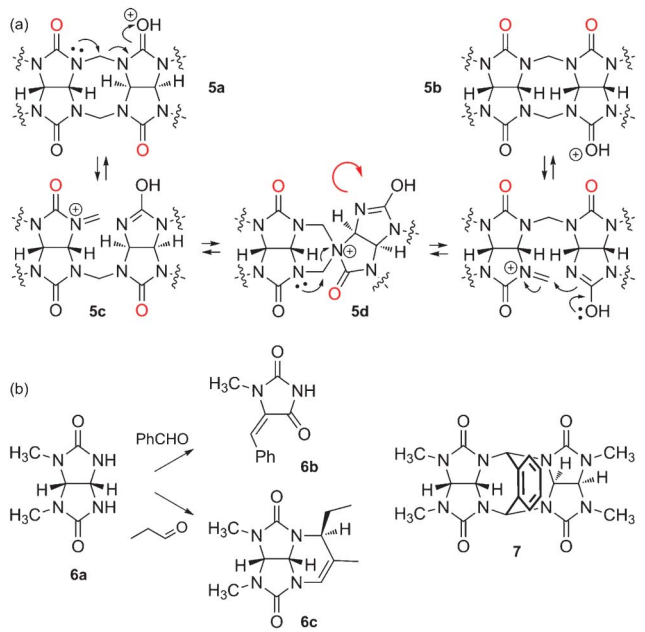


Fig. 4 (a) "S-to-curved shape" correction mechanism, operational during the cyclooligomerization of glycoluril (**1**) and formaldehyde. (b) Undesired reactions between glycoluril derivatives and aldehydes.

CB[6] is the only cyclization product from the glycoluril hexamer. Yet, the formation of small amounts of size-mismatched CB[n]s (such as CB[5] when condensing glycoluril trimers, for example), indicates that oligomers can undergo concomitant fragmentation and recombination before cyclization.[62] When discussing the ratios of CB[n] formed during the oligomerization process, one should also consider plausible template effects[3] caused by other components of the reaction mixture, such as glycoluril oligomers, CB[n]s, cations and anions, and especially water!

Although it would be tempting to prepare CB[n] derivatives bearing functionalized methylene bridges from glycoluril and various aldehydes in a one-pot reaction, Isaacs recently showed that failure is very likely. Indeed, methylated glycoluril **6a** did not afford any dimer in the presence of various aldehydes, and small amounts of hydantoin **6b** were detected instead. Performing the reaction in anhydrous trifluoroacetic acid (in an attempt to favor condensation) was equally unsuccessful, and in the case of propanal, compound **6c** was isolated in a 67% yield (see Fig. 4). While condensation of glycoluril derivative **6a** in the presence of phthalaldehyde was successful, the thermodynamically more stable S-shaped conformation of dimer **7** precludes any incorporation into CB[n]s.[63] Yet, Isaacs and coworkers have just proposed a very elegant two-step procedure that circumvents those functionalization obstacles: the authors described the gram-scale preparation of the fully curved open glycoluril hexamer (similar to structure **5b**, with six glycoluril units instead of two), and showed that it readily undergoes ring closure with *o*-phthalaldehydes and naphthalene-2,3-dicarbaldehyde in 9 M sulfuric acid or concentrated hydrochloric acid to afford the corresponding monofunctionalized CB[6] hosts in excellent yields (up to 83%).[64]

4. Recognition properties of CB[n]s

We divide this chapter into three sections, which describe the recognition properties of CB[n]s towards (1) inorganic species, such as metallic cations, their counteranions and various clusters, (2) organic guests in solution, and (3) organic guests in the gas phase.

4.1 Inorganic cations, counteranions and clusters

An impressive number of crystal structures depicting interactions between CB[n]s, metallic cations, metal clusters and their corresponding counteranions, have been published during the past decade, in particular by Fedin and coworkers.[7] CB[n]s bind to metallic cations *via* their two carbonylated portals; however, most metals interact with only a fraction of the oxygen atoms at the CB[n] rim (*i.e.* the metal does not usually sit at the center of the portal, with the notable exception of cesium).[65–67] In the case of alkali and alkali-earth metals, several cations may occupy the same portal.[9,68–71] Transition and group 13 metal ions do not usually interact directly with the oxygens of the CB[n] rim, and binding takes place between the carbonyl groups and the coordinated water molecules of the metal aqua complexes (CB[n] behaves as an outer-sphere ligand).[66,72,73] In the case of lanthanides, both direct metal–portal and metal–water–portal interactions have been observed.[67,74] Large metallic clusters also interact with CB[n]s *via* their coordinated water molecules, with the cluster often sitting right above the center of the portal (see Fig. 5 for an example).[9,71,75–83] Contrary to clusters involving CB[5] and CB[6], crystal structures of CB[7] complexes are still

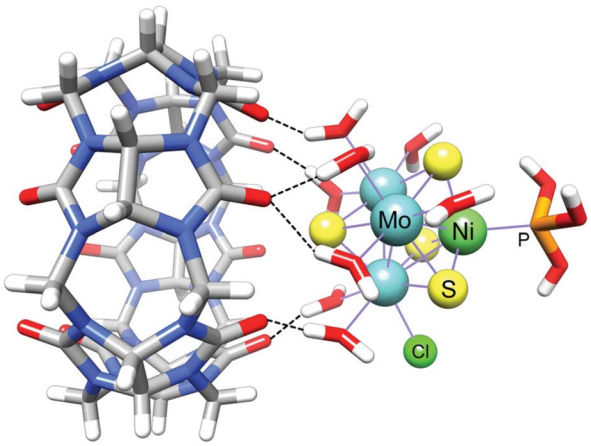


Fig. 5 Clusters interacting with CB[n]s *via* their coordinated water molecules: structure of the CB[6]/$\{[Mo_3(Ni(P(OH)_3)S_4(H_2O)_8Cl]^{3+}\}_2$ adduct (only one cluster shown; a second complex interacts with the opposite CB[6] portal). Violet lines represent metal–ligand and metal–metal bonds, and dashed black lines hydrogen bonding interactions between water and the CB[6] rim.[78]

rare, with a few uranyl/CB[7] assemblies[84–86] and one rubidium/hydroquinone ⊂ CB[7] complex[87] representing the only examples published so far. Finally, we want to stress that CB[7] and CB[8] can even encapsulate metallic cations and organometals such as metallocenes (from iron,[88,89] cobalt,[90] molybdenum[91] and titanium),[91] as well as several complexes of tin, nickel, cobalt, copper, iron and palladium.[92–97]

Binding affinities of metallic cations towards CB[n]s are highly dependent on the composition of the solvent (pure water, 50% formic acid, *etc.*), and the stoichiometry of the interaction is unclear (Kim and Inoue suggest that alkali metal ions probably form 2 : 1 complexes with CB[6],[56] while Buschmann and Schollmeyer indicate the formation of 1 : 1 complexes;[98] also, metal/CB stoichiometries of up to 5 : 1 have been reported with some transition metals).[99] If one applies a 1 : 1 binding model, affinities of alkali metal ions towards CB[6] range from 3.3×10^2 to 3.1×10^3 M^{-1} in pure water,[100] and binding constants of up to 1.7×10^5 M^{-1} have been reported in the case of barium.[101] We also note that affinities of alkali and alkaline earth metal ions towards CB[5] are much lower (7.9–70 M^{-1} only), and that data related to CB[7] and CB[8] are almost inexistent; in fact, our group recently had to measure the binding affinity of sodium towards CB[7] and CB[8] (7.7×10^2 and 4.2×10^2 M^{-1}, respectively, in deuterium oxide).[102]

Anions and anionic clusters can occupy the void between stacks of CB[n]s,[103,104] or may be encapsulated inside the cavity of the macrocycle. The anionic unit may even affect the recognition properties of the CB[n] cavity: in a recent example, a large electron-rich polyoxovanadate cluster interacting with the equatorial periphery of CB[8] was found to enable the reduction and encapsulation of two viologen radical cations.[105] As mentioned before, several crystal structures show the encapsulation of anions into the cavity of CB[n]s; recent examples include chloride and nitrate inclusion within CB[5],[106–110] as well as perrhenate ReO_4^- within CB[6] and CB[7].[111,112] Yet, to the best of our knowledge, evidence of anion encapsulation in solution has been reported on only one occasion: the affinity of chloride and nitrate anions towards CB[5] was monitored by fluorescence spectroscopy (λ_{ex} = 240 nm, λ_{em} = 340 nm), and a 1 : 1 binding model could be used to fit the interaction with the nitrate anion (binding affinity 1.7×10^2 M^{-1} in 4.0 M sulfuric acid).[108]

4.2 Organic guests

CB[n]s can encapsulate numerous organic guests, and in most cases, thermodynamic parameters can be determined by UV-Visible spectroscopy, isothermal titration calorimetry, and ^{1}H NMR spectroscopy. In the latter case, hydrogen atoms sitting near the center of the CB[n] cavity undergo a strong upfield shift (up to 1.6 ppm),[113] decentered hydrogens are affected by a more moderate upfield shift,[114] and hydrogen atoms located outside the cavity undergo a significant downfield shift (up to 0.7 ppm), that weakens as the distance between the hydrogens and the portal increases.[115] Although less frequently evaluated, kinetic parameters can also be measured in some instances, and can be used to assess plausible mechanisms for the formation, threading and dethreading of CB[n] complexes. Therefore, we split this section into the thermodynamic and kinetic components of the recognition mechanisms.

4.2.1 Thermodynamics of the CB[n]–guest interaction. (*a*) *Generalities.* Supramolecular chemists would certainly agree that one of the most striking features of CB[n]s is their extreme affinity towards selected organic guests (see Table 1). Indeed, the Isaacs group measured affinities exceeding 10^{12} M^{-1} as early as 2005,[58] and two years later, Kaifer, Isaacs, Gilson, Kim and Inoue reported the record-breaking affinity of 3.0×10^{15} M^{-1} with CB[7] and ferrocene derivative **8c**.[116] Very recently, a 5.0×10^{15} M^{-1} binding constant[57] was measured by Kim, Inoue and Gilson between guest **9c**[117] and CB[7]. These affinities, which reach or slightly surpass the benchmark avidin–biotin interaction (approximately 10^{15} M^{-1}),[118,119] represent the strongest non-covalent interactions ever measured, if one excludes the few systems relying on polyvalency[120] (the interaction per binding unit being lower), and of course interactions between enzymes and transition states.[121] As described by Mock a quarter century ago, CB[n]s are ideal hosts for positively charged amphiphilic guests, with the positive charges interacting with the carbonylated rims through ion-dipole stabilization, and the hydrophobic moiety sitting inside the CB[n] cavity; affinities as high as 1.3×10^7 M^{-1} were measured at that time in the case of spermine and CB[6] in a 50% formic acid solution.[114]

Binding enthalpy. We now realize that the nature of the CB[n]–guest interaction is much more subtle, especially since Kaifer and Kim have shown that the affinity between CB[7] and the *neutral* hydroxymethylferrocene **8a** reaches 3.0×10^9 M^{-1}![88] In a landmark article,[116] Kaifer, Isaacs, Gilson, Kim and Inoue reported that the enthalpies of the interaction between ferrocene derivatives **8a**–**8c** and CB[7] are virtually identical (−21.5 kcal mol^{-1}), although their total charges are radically different (see Fig. 6)! Very recently, some of these authors observed a similar behavior with substituted adamantanes **9** and bicyclo[2.2.2]octanes **10** (binding enthalpies −19.0 to −20.1, and −15.6 to −16.3 kcal mol^{-1}, respectively; see Fig. 6).[57] A very likely explanation is that the strong coulombic attractions between positively charged substituents and the partially negative CB[7] rim (approximately 60 kcal mol^{-1} per positive unit) are perfectly counterbalanced by the dramatic losses in solvation

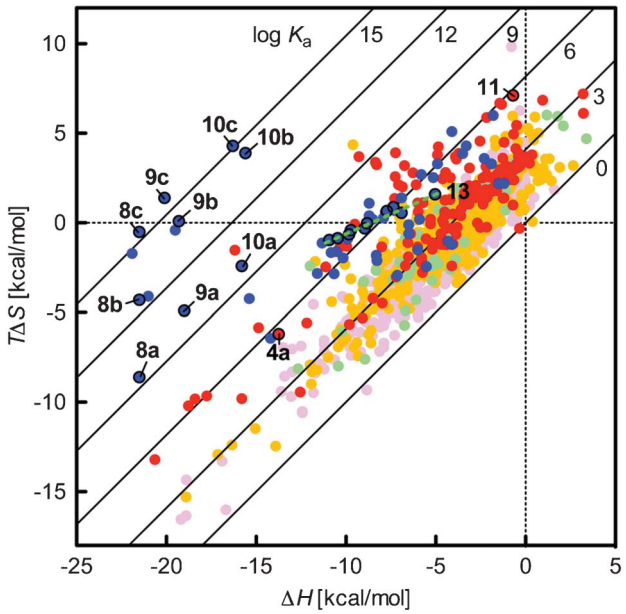
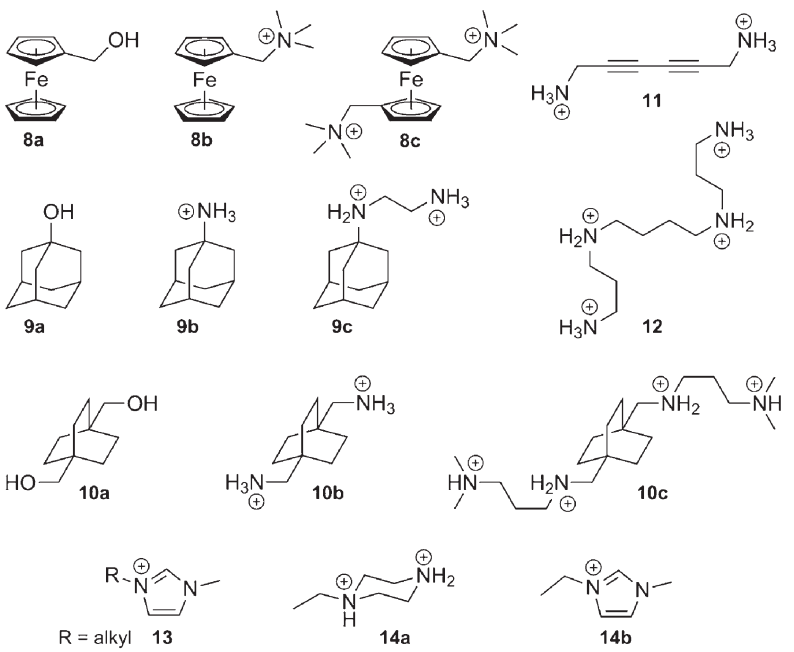


Fig. 6 Enthalpy–entropy compensation plot for the complexation of α-CD (pale pink dots), β-CD (pale orange dots), γ-CD (pale green dots),[128,130] CB[6] (red dots)[56,65,101,124,132–148] and CB[7] (blue dots)[57,141,142,149–156] with various guests. The dashed green line connects the 1-alkyl-3-methylimidazolium **13** data points (length of the alkyl chain: 1, 2, 3, 4, 6, 8, 9, 10, 12, 14 carbons atoms).[149]

enthalpy upon binding; therefore, ion-dipole interactions in water are not the main driving force of the CB[n]–guest interaction *per se*, and the loss of solvation may or may not surpass the coulombic attraction (in the case of guests **8**–**10**, the sum of the coulombic and solvation energies varies between −7.0 and +7.2 kcal mol^{-1},[57] according to the empirical Mining Minima algorithm M2).[122,123] The complementarity between the size and shape of the CB[n] cavity and its guest, possibly leading to favorable van der Waals interactions (−27 to −39 kcal mol^{-1}[157] in the **8**–**10** series, still according to M2 calculations), has a much stronger impact on the binding affinity. However, one should remember that CB[n]s have an extremely low polarizability, therefore (1) interactions between hydrophobic guests and the bulk should be slightly more favorable compared to interactions with the CB[n] cavity, and (2) dispersion interactions between the guest and the cavity should be weak. Nau even suggests that the driving force of the cavity–guest interaction is solely caused by the ejection of high-energy water molecules from the cavity, a non-classical enthalpic hydrophobic effect![43] The significantly negative average binding enthalpy of selected guests towards CB[7] compared to CDs (see Fig. 6) seems to corroborate this model. Accordingly, Keinan reported the remarkable thermodynamic differences between the interaction of 1,6-hexanediammonium **4a** and a series of diyne dications such as 1,6-hexa-2,4-diynediammonium (**11**) with CB[6]:[124] the binding enthalpy of diammonium **4a** was found to be −14 kcal mol^{-1}, but only −0.70 kcal mol^{-1} in the case of dication **11**; the authors suggested that the interaction between the electron-rich diyne rod and the macrocycle walls may even be repulsive![124] This effect can be justified since, due to the low polarizability of the cavity, the cavity-to-bulk enthalpic *gain* in dispersion interaction between unsaturated systems like dication **11** and water is greater than the one between saturated dication **4a** and water. Macartney proposed that quadrupole–dipole interactions play a role in the stability of CB[n]–neutral guest complexes and in their orientation within the cavity of the macrocycle.[125] The optimum geometry is reached when the dipole of the guest is perpendicular to the quadrupole moment of CB[n]. For example, acetone, pentan-3-one and 3,3-dimethylbutan-2-one, albeit much less hydrophobic than common CB[n] guests, display unexpectedly significant binding affinities towards CB[7] (5.8×10^2, 2.1×10^3 and 6.7×10^3 M^{-1}, respectively), and according to the force-field MM2 model, their carbonyl units are likely to be located within the equatorial plane of the macrocycle and perpendicular to the CB[7] quadrupole.[125] As far as other neutral guests are concerned, alcohols and carboxylic acids bind weakly to CB[n]s (binding constants in the 10^1–10^2 M^{-1} range). The



length of the alkyl chain in the aliphatic alcohol and carboxylic acid series does not have a significant effect on binding affinities towards CB[6] (4.1–5.4 $\times$ 10^2 M^{-1} in the propanol to heptanol series, and 5.0–6.2 $\times$ 10^2 M^{-1} in the propanoic to nonanoic acid group, both measured in 50% formic acid).[126] Binding enthalpies and entropies are also remarkably constant among both series (ΔH = -0.49 $\pm$ 0.22 and -0.32 $\pm$ 0.08 kcal mol^{-1}; $T\Delta S$ = + 3.1 $\pm$ 0.2 and 3.4 $\pm$ 0.1 kcal mol^{-1}, respectively). These values suggest that the encapsulation of these guests triggers the ejection of the same number of water molecules from the host cavity, and that dispersion interactions are insignificant.

Binding entropy. The changes in configurational entropy upon binding (*i.e.* the loss of mobility of both CB[n] and its guest after complexation) do not significantly depend on the charge of the guest, and rigid CB[n]s interacting with constrained guests afford high affinities.[57,116] For example, the more flexible dication **4a** suffers from a 6.1 kcal mol^{-1} entropic penalty (at 25 °C) upon binding to CB[6], while the encapsulation of diyne **11** is entropically favorable by 7.0 kcal mol^{-1} (Fig. 6).[124] However, the *total* binding entropy, as measured by isothermal titration calorimetry, becomes less and less unfavorable as positively charged units are added to the guests (for example, $T\Delta S$ = $-8.6 \rightarrow -0.5$, $-4.9 \rightarrow +$ 1.4 and $-2.4 \rightarrow +$ 4.3 kcal mol^{-1}, in the case of series **8**, **9** and **10**, respectively; see Fig. 6);[57] therefore, since the effect of the configurational entropy can be neglected, the parameter that has the most dramatic effect on the variations in binding affinities is the difference in solvation entropies, caused by the hydration water molecules being ejected from the host and guest upon binding. This observation is in stark contrast to the common enthalpy–entropy compensation model valid for most supramolecular systems, where binding entropies and enthalpies are closely linked.[121,127–129] For example, large sets of thermodynamic data corresponding to the interactions between guests and α-, β- or γ-CD indicate that in general, gains in binding enthalpies are approximately compensated by losses in binding entropies (see Fig. 6),[128,130] leading to a narrower range of binding affinities ($10^{2.1\pm0.9}$, $10^{2.6\pm1.0}$ and $10^{2.8\pm1.1}$ M^{-1};[131] Pearson product–moment correlation coefficients r of the enthalpy–entropy compensation: 0.91, 0.88 and 0.91, respectively). However, in the case of CB[6] and especially CB[7], deviations from the enthalpy–entropy correlation are significant, with broader ranges of binding affinities ($10^{3.6\pm1.5}$ and $10^{7.1\pm3.5}$ M^{-1}, respectively, corresponding to correlation coefficients r equal to 0.83 and 0.56; see Fig. 6). Even if the combined sets of thermodynamic data pertaining to CB[n]s are approximately 15 times smaller than the combined CD sets, and therefore create a bias towards lower correlation coefficients, we think that the latter are not merely due to a statistical effect, but really indicate that variations in solvation entropy upon binding cause the deviations from the common enthalpy–entropy compensation model.

Summary. In short, extreme binding affinities observed with CB[n]s are mainly due to: (1) the ability of the guests and their substituents sitting close to the CB[n] portals, *in particular positively charged ones*, to return as many hydration water molecules as possible to the bulk upon binding (a process that is both enthalpically and entropically favorable), (2) the rigidity of the macrocycles and some selected guests, (3) a minimally penalizing loss of solvation energy upon encapsulation, and (4) favorable ion-dipole interactions between positively charged substituents and the CB[n] rims, as well as multiple hydrogen bonding (see sections 4.2.1(e) and (f) for a discussion about the impact of hydrogen bonding on the geometry of CB[8] and CB[10] assemblies).

The impact of positively charged substituents can be appreciated when the binding affinity of various ammonium cations is compared to their corresponding neutral amines; several studies carried out by Nau[153,157–160] and Macartney[161,162] indicate that affinity ratios between both forms towards various CB[n]s range from 16 to 32 000;[159] the decimal logarithm of these values correspond to the pK_a shift of the ammonium cation upon encapsulation by CB[n]s (1.2–4.5 pK_a units). The latter value is one of the highest ever reported for both synthetic and natural systems.[163]

One should finally note that attempts to predict binding affinities *in silico*, using the M2 algorithm for example,[57,116,123] remain unpractical, with errors usually greater than 2 kcal mol^{-1}; considering the subtlety of the CB[n]–guest interaction as far as solvation is concerned, this error is in fact remarkably low. Nau also rightfully notes that a precise evaluation of the possible, albeit very minor dispersion interactions between guests and the inner wall of the CB[n] cavity should be evaluated using the second order Møller–Plesset theory (MP2) with extended basis sets.[43]

(*b*) *CB[5].* As discussed on numerous occasions, the CB[n] series displays remarkable and selective recognition properties, yet CB[5] is too small to accommodate many organic guests, and the richness of its chemistry is mostly inorganic, as described in section 4.1. We note, however, that CB[5] can encapsulate xenon (approximate binding affinity 1.3 $\times$ 10^3 M^{-1}),[164] as well as methane, ethylene and ethane (binding constants in the 10^3, 10^2 and 10^1 M^{-1} range, respectively).[165]

(*c*) *CB[6].* The recognition properties of CB[6] have been studied during the past thirty years, and numerous guests have been identified.[12] Among those, the positively charged form of spermine **12** displays the strongest interaction (5.4 $\times$ 10^{10} M^{-1} in 0.20 M LiCl, and 3.3 $\times$ 10^9 M^{-1} in 50 mM NaCl), followed closely by 1,6-hexane- and 1,5-pentanediammonium (2.9 and 1.5 $\times$ 10^8 M^{-1}, respectively, in 50 mM NaCl).[56] We note that the shortest 1,ω-alkanediammonium dication to strongly interact with CB[6] is 1,4-butanediammonium, which binds 6.0 $\times$ 10^4 times stronger than its 1,3-analog (2.0 $\times$ 10^7 M^{-1} *vs.* 3.3 $\times$ 10^2 M^{-1} in 50 mM NaCl); according to Kim and Inoue, this per-methylene difference is the highest ever measured in supramolecular chemistry.[56] In fact, 1,3-propanediammonium does not form an inclusion complex with CB[6], but interacts with its rim externally.[166] As the alkyl chain gets longer ($\omega \geqslant 7$), the binding affinity decreases due to a subtle interplay between enthalpic losses and entropic gains. Those incremental entropic gains may suggest that long 1,ω-alkyldiammoniums interact with CB[6] *via* only one of their portals, and do not adopt a much more constrained S-shape which would have allowed CB[6] contact at both ammonium groups. Enthalpic losses suggest that in this series, coulombic attractions between the CB[6] portal and the ammonium groups compete advantageously against losses in solvation energy. Similar trends are observed with 1-alkyl-3-methylimidazolium **13**[149] and alkylammonium cations,[56] with a marked drop in binding affinity between hexyl- and heptylammonium (1.7 $\times$ 10^5 *vs.* 5.8 $\times$ 10^3 M^{-1}), most probably because longer alkyl chains dislodge coordinated alkali metals from the CB[6] rim opposite to the ammonium group. In those cases, binding affinities

follow the classical enthalpy–entropy compensation model (see green dashed line in Fig. 6). Although curling of alkyl chains inside the CB[6] cavity has never been reported, we found four cases where two guests form ternary complexes with CB[6]: the first example is the well-known encapsulation of a terminal alkyne together with an organic azide, which leads to a dramatic rate enhancement of their [3 + 2] cycloaddition, affording the corresponding 1,2,3-triazole.[167] This CB[6]-catalyzed reaction has been exploited on several occasions, in particular by Tuncel and coworkers,[168–170] for the design of CB[6]-based self-organizing systems and molecular switches (see sections 5.1 and 5.2). The second and third cases of double encapsulation are the formation of 1 : 2 complexes between CB[6] and *N*-ethylpiperazines (**14a**)[166] or the ionic liquid 1-ethyl-3-methylimidazolium (**14b**),[171] with the two ethyl groups co-existing within the cavity of the macrocycle; the last example is the capture of two molecules of carbon dioxide by solid CB[6] exposed to the gas[172] (as a matter of fact, a similar sorption has been recently reported with CB[7]).[173] In addition to the impossibility for alkyl chains to curl inside CB[6], the formation of stable ternary complexes with two CB[n] units thread consecutively along the same 1,ω-alkyldiammonium chain has never observed upon combination of the three individual components; however, in a unique example, Tuncel and coworkers managed to lock two CB[6] units along a polyaminated axle **15**, and subsequently force the two macrocycles to shuttle and share the same 1,12-dodecanediamine station upon full deprotonation of the axle and subsequent reprotonation (see Fig. 7a).[169] Also, to the best of our knowledge, there has been only one report where a disubstituted ammonium could share two CB[n] units (a transient, unstable complex between a polyaminated axle, CB[6] and CB[8];[174] see section 5.1), and 1 : 1 complexes are always the most stable configurations.[175,176] For example, Kim and Inoue showed that the dihexylammonium cation (**16**) forms a 1 : 1 assembly in the presence of an excess amount of CB[6], with one hexyl chain encapsulated, and the other one sitting at the periphery of the

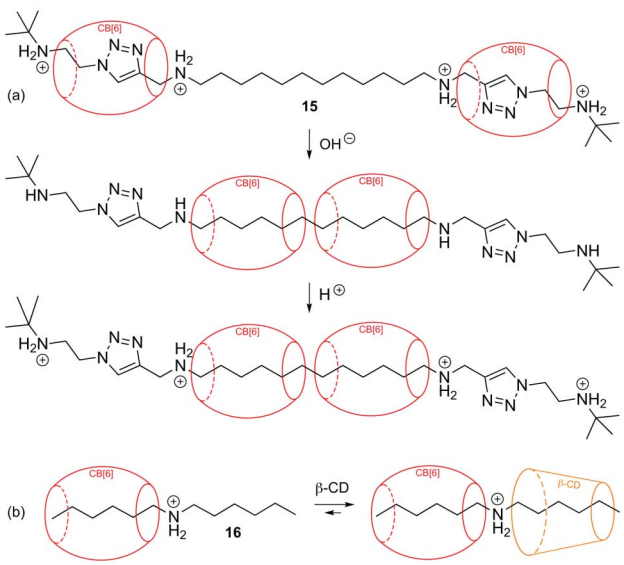


Fig. 7 (a) Two CB[6] units locked along the 1,12-dodecanediammonium station of axle **15**.[169] (b) Formation of a 1 : 1 complex between dihexylammonium (**16**) and CB[6], and of a ternary assembly with β-CD.[177]

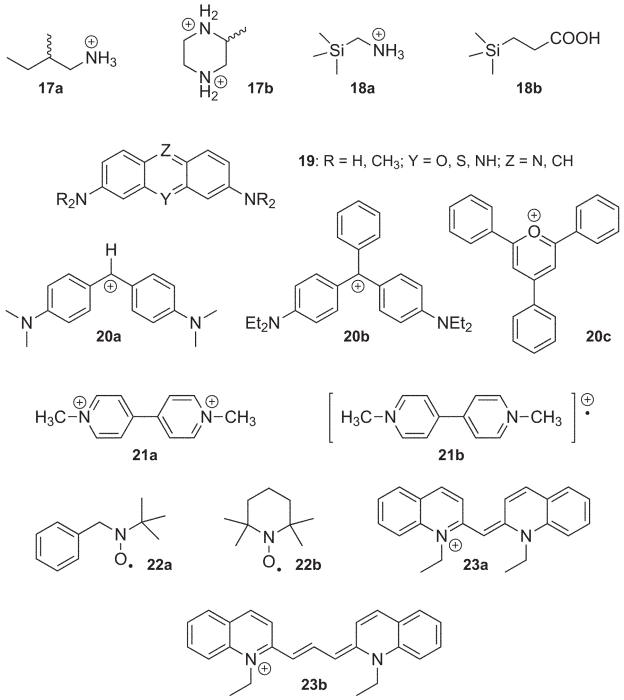
macrocycle.[177] However, the outer hexyl chain can be encapsulated within β-CD, whose rim interacts with CB[6] *via* multiple hydrogen bonds, and benefits from the weakened positive charge of the ammonium group at the CB[6] portal; the presence of CB[6] actually improves the binding affinity of β-CD towards the hexylammonium moiety by 33 times, a remarkable case of supramolecular positive cooperativity (see Fig. 7b).[177]

As far as neutral guests are concerned, Luhmer and coworkers showed that gases such as sulfur hexafluoride,[132] and to a lesser extent xenon,[178,179] form adducts with CB[6] (binding affinities 3.1×10^4 and 2.1×10^2 M^{-1} in a 0.20 M sodium sulfate solution). Nau and coworkers recently identified 15 hydrocarbons capable of interacting with CB[6] with affinities greater than 3×10^3 M^{-1}; binding constants of propane, butane, isobutane and cyclopentane reach 1.5×10^5, 2.8×10^5, 8.5×10^5 and 1.3×10^6 M^{-1}, respectively, in a 1.0 mM hydrochloric acid solution![165] Scherman also reported that a 1 : 1 complex of CB[6] and diethyl ether, with no cation or anion attached, could be precipitated upon vapor diffusion of the organic solvent into a solution of CB[6] interacting with a positively charged imidazolium ionic liquid.[180]

Finally, we note the unique case of CB[6]-mediated chiral recognition described by Kim and Inoue,[142] a phenomenon nicknamed by the authors as "assembled enantiorecognition": the binding affinity of CB[6] towards (*S*)-2-methylbutylammonium ((*S*)-**17a**) is 19 times higher when one of the CB[6] portals interacts with an excess of (*R*)-2-methylpiperazine ((*R*)-**17b**) compared to its (*S*)-enantiomer (1.5×10^4 *vs.* 8.0×10^2 M^{-1}, a 95% enantioselectivity, the highest discrimination ever reported in supramolecular chemistry using an achiral macrocyclic mediator!).[142] In other terms, the CB[6]/(*S*,*R*)-**17a/17b** ternary complex is 1.7 kcal mol^{-1} more stable than its corresponding CB[6]/(*S*,*S*)-**17a/17b** diastereoisomer.

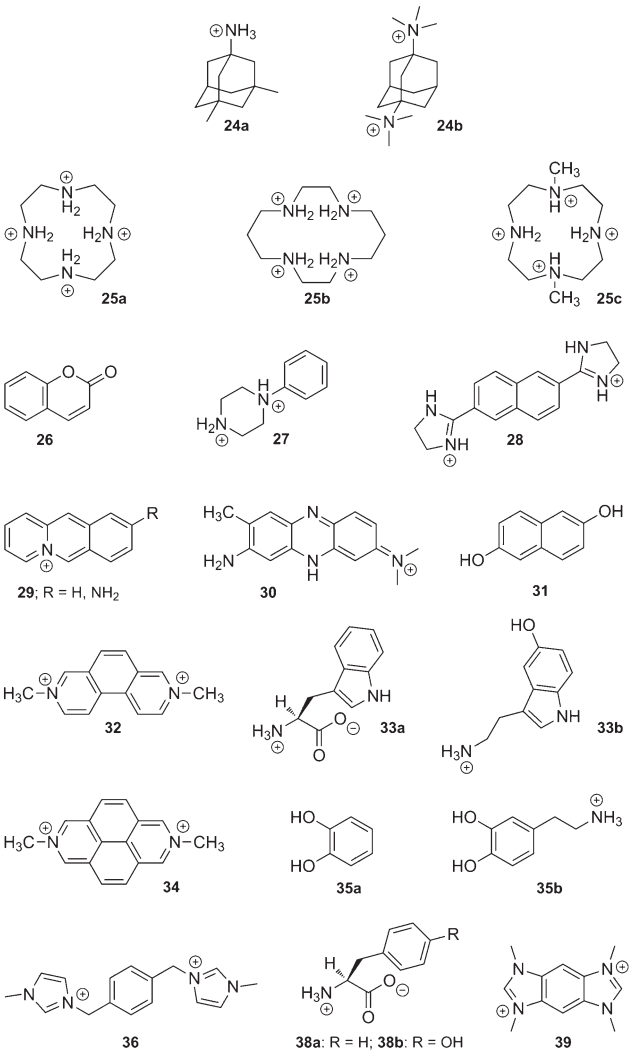
(*d*) *CB[7].* Among all the members of the CB[n] family, CB[7] displays the strongest interactions towards positively charged amphiphilic guests, with affinities greater than 10^{15} M^{-1}.[57,116] Unlike all other synthetic hosts, CB[7] displays common affinities between 10^7 and 10^{12} M^{-1}, with adamantyl-, ferrocenyl-, *p*-xylylenyl- and trimethylsilyl-containing guests forming the tightest complexes.[58] The affinity and selectivity of trimethylsilylmethylammonium (**18a**) and 3-(trimethysilyl)propionic acid (**18b**) towards CB[7] is unprecedented (8.9×10^8 and 1.8×10^7 M^{-1}, respectively, while no interaction is observed towards CB[6] and CB[8]!).[58] The interaction between CB[7] and the neutral silane **18b** illustrates again the importance of a good fit between guests and CB[n]s. Another outstanding feature of CB[7] is its ability to encapsulate positively charged units instead of interacting with them *via* its portals.[181] Examples of such guests include a series of tetraalkylammonium, tetraalkylphosphonium and trialkyl-sulfonium cations, with tetraethylammonium, tetramethyl-phosphonium and triethylsulfonium displaying the highest affinities (1.0, 2.2 and 5.2×10^6 M^{-1}, respectively, in pure water).[181] The fact that hydrophobic interactions and possibly favorable coulombic interactions between the alkyl substituents (where most of the positive charge is located) and the inner portion of the CB[7] rim can overcompensate the drastic loss in cation solvation energy is remarkable. CB[7] forms complexes with other guests bearing a diffuse positive charges, such as tricylic basic dyes **19** proflavine, pyronine, acridine, oxonine, thionine and

some of their derivatives (binding affinities 10^6–10^7 M^{-1}), yet it is unclear whether the heteroatom(s) of the tricylic units are located at the portal or inside the cavity of CB[7].[182–184]



We note that CB[7] has also been found to interact with diphenylmethane (**20a**), triphenylmethane (**20b**)[185,186] and triphenylpyrylium (**20c**)[187,188] carbocations (binding affinities 2.0×10^4, 1.7×10^4 and 7.5×10^5 M^{-1}, respectively), as well as several radicals. For example, Kaifer showed that methylviologen radical cations (**21b**; noted MV^+ thereafter), obtained upon reduction of dicationic viologen **21a** (noted MV^{2+} in the following sections), form stable inclusion complexes with CB[7] (binding affinity 5.0×10^4 M^{-1});[189] Anderson reported that CB[7] threading along an oligoaniline axle increased the thermodynamic and kinetic stability of its oxidized radical cation form, with a first oxidation potential reduced by 0.57 V![190] Similarly, Liu showed that the conductive doped form of polyaniline (*i.e.* its radical cation) is stabilized when surrounded by multiple CB[7] units.[191] Finally, Lucarini reported the CB[7] encapsulation of nitroxides **22a** and 2,2,6,6-tetramethyl piperidine-*N*-oxyl (TEMPO; **22b**)[192] as well as some derivatives,[193] and monitored the interaction by electron paramagnetic resonance; important changes in the nitrogen hyperfine splitting were observed upon encapsulation. We note that CB[7] has also been used to disrupt aggregates and other non-covalent interactions such as π–π stacking: Kaifer showed that CB[7] could efficiently break the *J*-aggregate formed upon stacking of the pseudoisocyanine dye **23a**, and the *H*-aggregate formed with the pinacyanol dye **23b**. In both cases, the absorption bands of *J*- and *H*-aggregates (575 and 473 nm, respectively) vanished upon addition of the macrocycle.[194,195]

(*e*) *CB[8]*. Like CB[7], CB[8] displays some remarkably strong binding affinities towards large amphiphilic positively charged guests, such as adamantane derivatives **24a** and **24b** (up to 4.3×10^{11} M^{-1}).[58] It can also encapsulate macrocycles such as fully protonated cyclen (**25a**) and cyclam (**25b**), as well as their Cu(II) and Zn complexes.[7]



Interestingly, while the protonated cyclam (**25b**) adopts the more stable *trans*-III configuration even while encapsulated,[196] subsequent complexation with Cu(II) affords a 7 : 3 mixture of the unusual *trans*-I and *trans*-II configurations in the solid state.[197] Incorporation of the partially methylated cyclen **25c** into the cavity of CB[8] has also been reported.[198] When set in the presence of CB[8], long alkylammonium chains (8–16 carbon atoms in the alkyl unit) curl inside the cavity of the macrocycle, and the entropic penalty caused by conformational restriction, which peaks at 12 carbon atoms, is overcompensated by enthalpic gains; affinities are remarkably similar along the C_8–C_{16} series (1.0–4.8×10^6 M^{-1}), and thus follow the classical enthalpy–entropy compensation model.[199,200] Van der Waals contact between the curled hydrophobic chain and the cavity has been proposed as the main cause of the enthalpic gain. One could also argue that curling maximizes the number of ejected high-energy water molecules from the cavity. Similarly to alkylammoniums, but also to 1,4-butylidene- and 1,10-decylidenedipyridinium cations,[201] this curling behavior is observed in the case of the 1,12-dodecanediammonium cation (binding affinity 1.1×10^6 M^{-1}), which adopts a U-shaped conformation within CB[8], with both ammonium heads located at the same portal and separated by a water molecule.[202] We note that the

CB[8] encapsulation of nitroxide radicals has also been reported on several occasions,[203–205] including by Kaifer and coworkers.[205]

Despite these findings, the richness of CB[8] chemistry is attributed without any doubt to its ability to encapsulate two guests into its cavity, and to form highly stable ternary complexes. A series of applications, including supramolecular catalysis and the design of new polymeric materials, have exploited this property, and will be described in sections 5.3.2 and 5.5.1. Several guests have been found to undergo double encapsulation into CB[8], such as two equivalents of coumarin (**26**),[206] *N*-phenylpiperazine (**27**),[207] naphthyl derivative **28**,[4] aminoacridiziniums **29**,[208] and neutral red **30** under acidic conditions.[209] Hetero-ternary complexes are particularly stable when favorable interactions between both guests add to the stability of the assembly. For example, the charge-transfer complex between electron-deficient MV^{2+} (**21a**) and electron-rich 2,6-dihydroxynaphthalene (**31**) is readily encapsulated by CB[8].[210] An elegant variation of this interaction is the formation of a ternary complex between CB[8], an MV^{2+} unit linked to yellow fluorescent proteins, and a dihydroxynaphthalene unit linked to cyan fluorescent proteins, as published by Brunsveld and coworkers very recently.[211] Two other examples reported by Kaifer are the CB[8] encapsulation of 2,7-dimethyldiazaphenanthrenium (**32**) and indole derivatives such as tryptophan (Trp; **33a**) and serotonin (**33b**),[212] as well as the formation of ternary CB[8]/dimethyldiazapyrenium (**34**) complexes with catechol (**35a**) and dopamine (**35b**).[213] Recently, Scherman reported the encapsulation of bisimidazolium salt **36** and various small guests, such as phenol, acetone, diethyl ether and tetrahydrofuran, which fill the small void left by the large bisimidazolium in the CB[8] cavity.[214] Looped structures can be readily obtained when both electron-poor and electron-rich units are linked; several examples based on the viologen/naphthol motif have been reported (see axle **37** in Fig. 8).[215–220] Another interesting feature of CB[8] is its ability to encapsulate two MV^{+} radical cations (**21b**), while the dicationic MV^{2+} (**21a**) forms a binary complex with CB[8]; electrochemical or light-induced reduction of the latter affords the corresponding radical cation.[220–226]

Finally, we describe the remarkable recognition properties of the $MV^{2+} \subset$ CB[8] [2]pseudorotaxane towards selected amino acids, as unveiled by Urbach and coworkers. $MV^{2+} \subset$ CB[8] forms ternary complexes with Trp (**30a**), phenylalanine (Phe; **38a**) and tyrosine (Tyr; **38b**), with a marked preference for Trp (**30a**; binding affinity 4.3×10^4 *vs.* 5.3 and 2.2×10^3 M^{-1} in the case of Phe (**38a**) and Tyr (**38b**), respectively);[227,228] moreover, in a peptide sequence, $MV^{2+} \subset$ CB[8] targets *N*-terminal Trp with very good selectivity over internal or *C*-terminal Trp residues

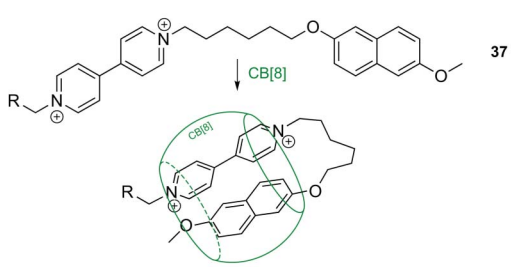


Fig. 8 Formation of a looped structure triggered by CB[8], and stabilized by charge transfer interactions.[218]

(up to a 40-fold specificity). Formation of the ternary complex leads to the emergence of a charge-transfer band (λ_{max} 420–450 nm) and to the quenching of Trp fluorescence.[227] CB[8] alone was also found to interact with two short peptides bearing *N*-terminal Trp or Phe residues with high affinity (3.6×10^9 and 1.5×10^{11} M^{-2}, respectively).[229]

In a subsequent study, Urbach studied the CB[8]-mediated pairing of peptides containing one or more Trp residues with a series of synthetic analogs bearing one or more MV^{2+} side-units (see Fig. 9), thereby affording discrete "peptide duplexes".[230] Peptide and small molecule recognition experiments were also carried out using benzobis(imidazolium) **39** instead of MV^{2+}; binding affinities were found to parallel those of MV^{2+}-containing assemblies.[150] Brunsveld showed that the yellow fluorescent protein, once linked to a Phe-glycine-glycine peptide (Phe-Gly-Gly) dimerizes in the presence of CB[8], since the latter can encapsulate two Phe units; dimerization caused a decrease of the fluorescence anisotropy by intermolecular energy transfer (homo-FRET). A similar interaction between Phe-Gly-Gly-labeled yellow and green fluorescent proteins was monitored by hetero-FRET.[231] Finally, we note that Urbach recently prepared the first example of a CB[8]-containing rotaxane, by "clicking" extremely bulky alkyne-substituted tetraphenylmethane stoppers to a CB[8]-bound MV unit substituted with azide-terminated linkers.[232]

(*f*) *CB[10]*. Not much of the chemistry of CB[10] has been unveiled since its isolation by Isaacs and coworkers in 2005.[35] In the same article, the authors described the remarkable formation of an inclusion complex between calix[4]arene derivative **40** and CB[10], as well as ternary assemblies between a selection of adamantyl derivatives and assembly **40** $\subset$ CB[10] (see Fig. 10 for a force-field minimized structure of ternary complex **9b**·**40**·CB[10]).[35] Besides the isolation of a potassium-coordinated water $\subset$ CB[5] $\subset$ CB[10] complex,[233] there has been only three new reports of CB[10] recognition: Isaacs described the conformational behavior of some triazene-arylene units in the presence of CB[n] hosts (including guest **41**), and showed it exclusively adopted the quadruple *anti* conformation inside the

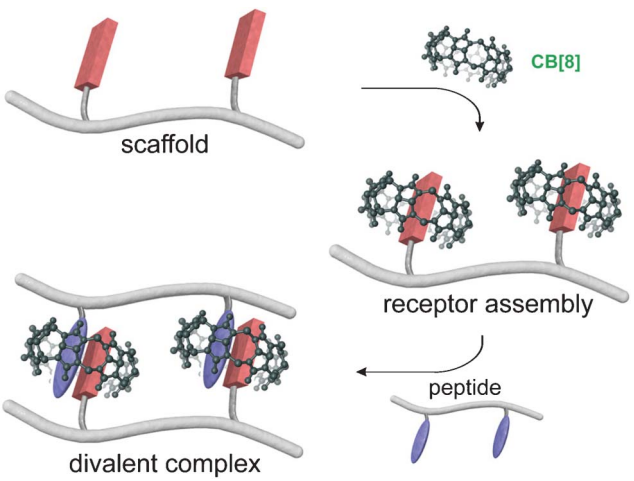


Fig. 9 Formation of "peptide duplexes" upon CB[8] interaction with Trp-rich (residues in blue) and MV^{2+}-decorated peptides (MV^{2+} units in red). Reprinted with permission from ref. 230. Copyright 2009 American Chemical Society.

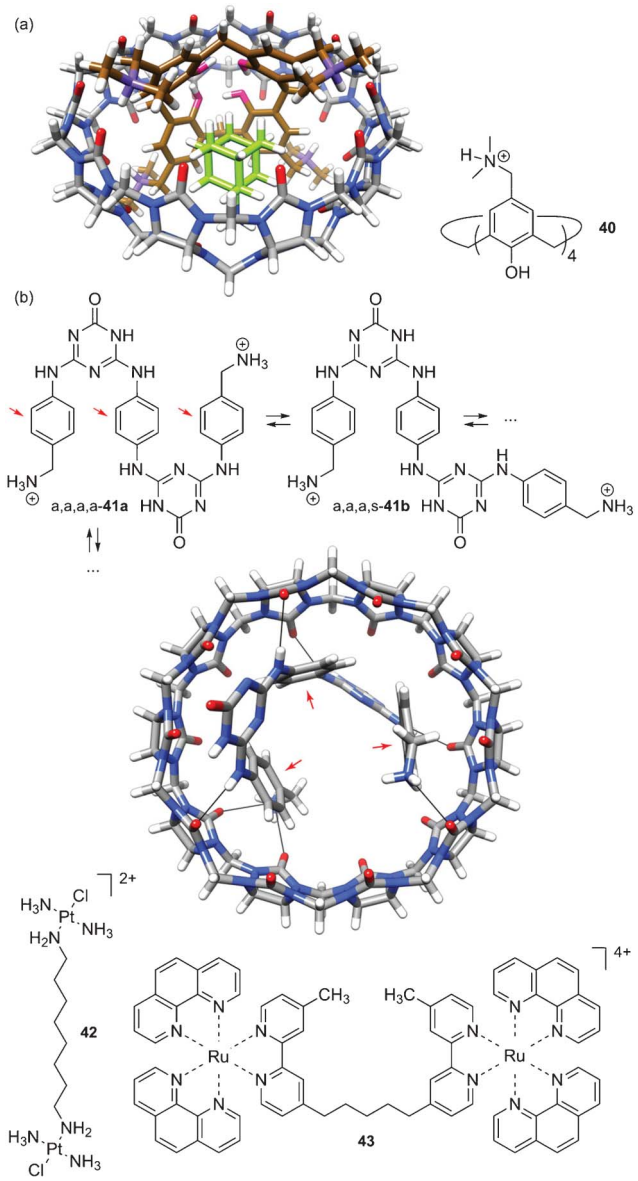


Fig. 10 (a) MMFF-optimized structure of ternary complex **9b**·**40**·CB[10] (1-adamantylammonium (**9b**) in bright green and calixarene **40** in brown and violet).[35] (b) Conformers of triazene-arylene **41** and X-ray structure of complex a,a,a,a-**41a** ⊂ CB[10].[234] Red arrows point towards the three phenylene units. Structures of Pt(II) and Ru(II) complexes **42** and **43**; both can be encapsulated by CB[10].[36]

cavity of CB[10] (see guest a,a,a,a-**41a** in Fig. 10).[234] In agreement with Urbach's discussion about the structure of CB[8]–peptide complexes,[229] the a,a,a,a conformation maximizes N–H/O=C and NH_3^+/O=C interactions, while no intramolecular π–π interaction between aromatic rings is observed (see the red arrows in Fig. 10, which point towards the three phenylene units). The authors judiciously show that the CB[10]–guest interaction modes parallel the three-dimensional folding of proteins: ejection of solvating water molecules to the bulk is a critical driving force of both protein folding and CB[n] encapsulation, and hydrogen bonds and coulombic interactions are responsible for the exact geometry of the folded (or interlocked) structures.[234]

Wagner, Kaifer and Isaacs also showed that porphyrins (metal free, or coordinated to Zn(II), Fe(III) and Mn(III)), bearing four methylpyridinium substituents, form an inclusion complex with CB[10].[235] According to force-field MMFF optimization, the plane of the porphyrin macrocycle is perpendicular to the equatorial plane of CB[10], and two positively charged pyridinium units interact with each CB[10] portal, while CB[10] is significantly distorted into an oval shape. The electrochemical and spectroscopic properties of the porphyrin derivative were barely affected by the surrounding CB[10]. Interestingly, ternary complexes could be obtained upon addition of pyridine derivatives, MV^{2+} (**21a**), quinoline and isoquinoline, and affinities were surprisingly high (up to 4.8×10^5 M^{-1}); yet, those guests did not coordinate to the metallic center, but merely interacted with the porphyrin ring *via* π–π stacking.[235]

Keene, Day and Collins showed that Pt(II) and Ru(II) complexes **42** and **43** could slip through CB[10], and interact with the macrocycle *via* their alkyl central station.[36] In the case of guest **43**, part of the bipyridyl ligands were also located in the CB[10] cavity. A fast exchange on the NMR time scale was observed with platinum guest **42**, while the very bulky ruthenium/bipyridyl head groups caused guest **43** to exchange slowly; despite the complexity of the **43** ⊂ CB[10] pseudorotaxane geometry, remarkably clear ^{1}H NMR spectra could be recorded for the free guest and the CB[10]-bound assembly.[36]

4.2.2 Kinetics of CB[n]–guest interactions. The kinetics of ingression and egression of alkylammonium cations in and out of CB[n]s have been unveiled by Mock and Shih,[114] and studied in detail by Nau and coworkers.[236,237] Although it is trivial to demonstrate that the binding affinity of a guest towards CB[n], a thermodynamic parameter, is equal to the ratio of its ingression and egression rates (both kinetic parameters), there is virtually no correlation between ingression rates and binding affinities. Within the large pool of CB[n] guests, narrow units tend to display fast exchange kinetics on the NMR time scale (*i.e.* a single resonance is detected, with the chemical shift corresponding to the weight average of those of the free and bound guests), wide guests favor slow exchanges (*i.e.* separate signals are detected for the free and bound guests), and a significant number of guests adopt intermediate exchange rates, sometimes leading to dreadful signal broadening, which prevents a precise assessment of the geometry of the complex, and compromises most attempts to quantify the binding affinities by NMR titration. Based on ingression and egression rates at various pH, Nau proposed a mechanism involving first an association complex between the ammonium and the carbonylated portal, with the alkyl chain still dangling in the aqueous phase, followed by a "flip-flop" mechanism of the alkyl unit into the CB[6] cavity, using the ion–dipole interaction between the ammonium and the macrocycle rim as an anchor (see Fig. 11).[236,237] At high pH, the hydrophobic chain of the neutral amine directly penetrates into CB[6]. The extra stabilization of the exclusion complex coupled to the necessary distortion of the CB[6] portal during the flip-flop process leads to a much slower ingression of ammonium guests compared to their

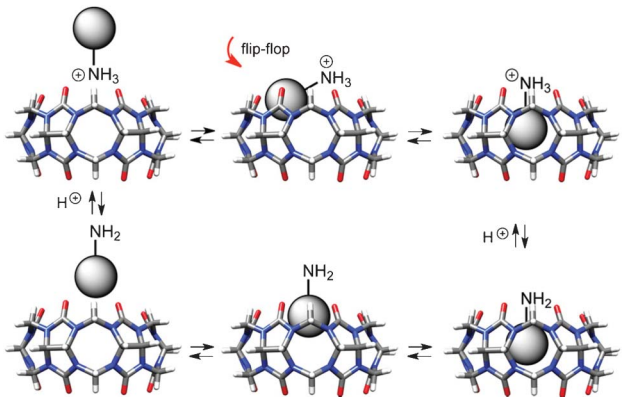


Fig. 11 Plausible ingression mechanism of alkylamines into CB[n]s.[236,237]

corresponding neutral amine. This mechanism, although very likely, may need to be slightly refined for large and rigid guests such as ferrocenyl derivative **8b**, which may be too large to undergo the flip-flop mechanism. We also note that CB[7] and CB[8] are quite flexible, and can slip over remarkably large guests, especially if those can undergo significant distortion; for example, CB[7] can slip over 15-crown-5[238] and even 21-crown-7.[239]

We have recently studied the kinetics of CB[6] slippage along polyaminated axles **44**, and have identified two mechanisms for the CB[6] translation from station 1 to station 2 (see Fig. 12).[240] Although the threading of the protonated ammonium guest through CB[6] first comes to mind, we favor an alternate process, involving (1) the "intra-rotaxanic" deprotonation of the ammonium cation by the carbonyl portal of CB[6], followed by acid–base equilibrium with the aqueous medium, (2) the slippage of the neutral amine through the CB[6] cavity, and (3) the fast protonation of the opposite CB[6] carbonyl followed by the reprotonation of the amine guest (see Fig. 12). Since we have shown that incorporation of water molecules within the cavity of CB[6] during the slippage process is unlikely,[240] CB[6] could have to overcome a penalty as high as 60 kcal mol^{-1} (which corresponds to the loss of solvation of the cation) when slipping

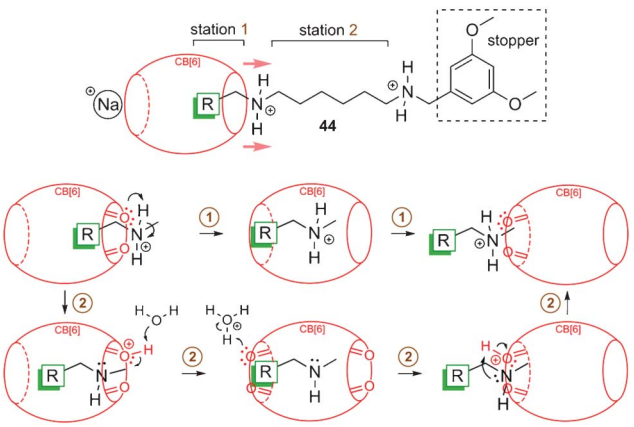
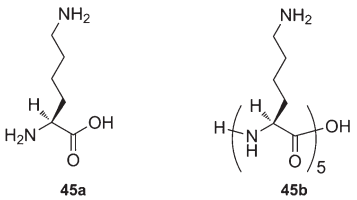


Fig. 12 CB[6] slippage along a polyaminated axle, between station 1 and station 2 of guest **44**. A deprotonation–reprotonation mechanism of the ammonium unit is favored (pathway 2) over direct CB[6] translation along the positively charged group (pathway 1).[240]

over the ammonium group. When threading takes place over the neutral amine, the loss of solvation is limited to 4 kcal mol^{-1}.[241] We also found the slippage rates to be highly dependent on even minor sterical alterations of the *N*-terminal substituent R, with free Gibbs energies of activation ranging from 24 to 29 kcal mol^{-1} (which correspond to half-lives of [2]pseudorotaxanes **44** ⊂ CB[6] at 100 °C ranging from 2 s to 3 h). Similar barriers of 24 and 26 kcal mol^{-1} were determined in two other cases of CB[6] threading over a nitrogen atom.[170,242]

4.3 CB[n] recognition in the gas phase

Much of the gas phase chemistry of CB[n]s has been studied by Dearden and coworkers.[243] Several features of the host–guest interaction, such as the formation of inclusion or exclusion complexes in the gas phase, can be readily determined: Dearden showed that inclusion complexes of CB[6] undergo guest exchange with *tert*-butylamine much slower than exclusion complexes (we note that *tert*-butylamine does not penetrate into the cavity of CB[6]).[244] Sustained off-resonance irradiation-collision-induced dissociation experiments (SORI-CID) afford similar information, since exclusion complexes readily dissociate, and inclusion complexes require higher energies that may even trigger the fragmentation of the macrocycle.[244,245] 1,4-Butanediammonium was found to form 2 : 1 doubly charged exclusion complexes with CB[5], with the two singly charged 1,4-butanediamines interacting with each CB[5] portal. To the contrary, CB[6] encapsulates the guest, and the doubly charged 1 : 1 complex is virtually the only product (a trace of a doubly charged 2 : 1 adduct was detected).[245] Exchange and SORI-CID experiments confirmed the structure of both inclusion and exclusion complexes. Interestingly, the optimum length of 1, ω-alkyldiammonium cations for binding to CB[6] is ω = 4, as determined by SORI-CID, and not ω = 6 like in solution. This difference is most likely due to the greater energy penalty for additional loss of cation solvation when 1,4-butanediammonium interacts with CB[6] in solution, since the two ammonium units sit deeper in the macrocycle and are less exposed to water.[246] The interaction between lysine (Lys; **45a**), CB[5] and CB[6] was also studied: Lys forms a singly charged exclusion complex with CB[5] and a doubly charged pseudorotaxane with CB[6]. The authors also propose that pentalysine **45b** interacts with both portals of CB[6] in a "clamp"- or "forceps"-like conformation without slipping through the macrocycle.[247] *Ortho*- and *meta*-phenylenediamine were found to form exclusion complexes with CB[6], while the *para*-isomer inserted into the macrocycle cavity.[244] Dearden showed that CB[7] could encapsulate benzene, fluorobenzene and toluene, while having its portals covered with two guanidinium units. According to DFT calculations at the B3LYP/6-31+G(d) level, those complexes are not thermodynamically stable in the gas phase, and result from their formation in solution.[248] Scherman showed that complexes of CB[8], a MV dimer and some naphthol derivatives were stable in the gas phase and could be readily assessed by mass spectrometry.[249] Finally, Da Silva recently reported that aggregation of CB[n]s as dimers, trimers or tetramers in the gas phase is a general phenomenon, as long as the portals are available for interactions with neighboring CB[n] units.[250]



5. Applications of CB[n] chemistry: a progress report

The outstanding recognition properties of CB[n]s have prompted the rapid development of exciting applications in the supramolecular, synthetic, medicinal and material science fields. In this chapter, we highlight the recent progress in the design of new self-organizing systems and stimulus-responsive switches (sections 5.1 and 5.2), in the development of CB[n]-promoted and CB[n]-catalyzed organic reactions (section 5.3), and in the exploitation of CB[n]s as key units in novel drug carriers (section 5.4), and advanced materials (section 5.5).

5.1 Self-organizing systems

The supramolecular community identifies self-sorting or self-organizing systems, as one or several hosts that can discriminate between a set of guests, and form well-defined assemblies. Nuances about self-sorting have been carefully described by Isaacs,[251,252] who pioneered self-sorting with CB[n]s[252] and invented the notion of "social self-sorting" (*i.e.* heteromeric complex formation)[251] as the counterpart to Anderson's "narcissistic self-sorting" (*i.e.* homomeric aggregation).[253] Schalley clearly summarized these notions in a recent article.[219]

A series of examples involving CB[n]s have been published during the past six years. Isaacs and coworkers showed that CB[6] and CB[7] respectively target adamantanebutylammonium (**46a**) at its butyl moiety and cyclohexanediammonium (**46b**); yet this self-organizing is only kinetically favored, and the macrocycles exchange their respective guest in the course of 56 days to afford the thermodynamically favored combination, with the adamantyl unit encapsulated inside CB[7] and the cyclohexyl unit in CB[6] (see Fig. 13a).[254] The driving force of the reaction is the 4.3 × 10^3-fold gain in binding affinity when CB[7] is displaced from the cyclohexane to the adamantane unit; this largely overcompensates the 14-fold loss of affinity suffered by CB[6] after the exchange. The rate-limiting steps are the egression of guest **46a** and the ingression of guest **46b** from and into CB[6] (2.2 × 10^{-3} and 1.2 × 10^{-3} M^{-1} s^{-1}, respectively, at room temperature).[254] The relatively strong affinity of cyclohexanediammonium (**46b**) towards CB[6] (1.4 × 10^6 M^{-1}) and the bulkiness of the guest were found to cause an extremely slow egression of this guest from CB[6], with a rate as low as 8.5 × 10^{-10} M^{-1} s^{-1}, two orders of magnitude slower than the dissociation of the benchmark avidin–biotin pair![118]

Kim and Inoue showed that CB[7] binds to the aromatic residue of dipeptide Phe-Gly, and efficiently discriminates between Phe-Gly and Gly-Phe (binding affinities of 3.0 × 10^7 and 1.3 × 10^3 M^{-1}, respectively, a 2.3 × 10^4-fold difference!); CB[7] can also recognize dipeptides Tyr-Gly and Trp-Gly over Gly-Tyr and Gly-Trp with 1.8 × 10^4 and 2.0 × 10^3 fold

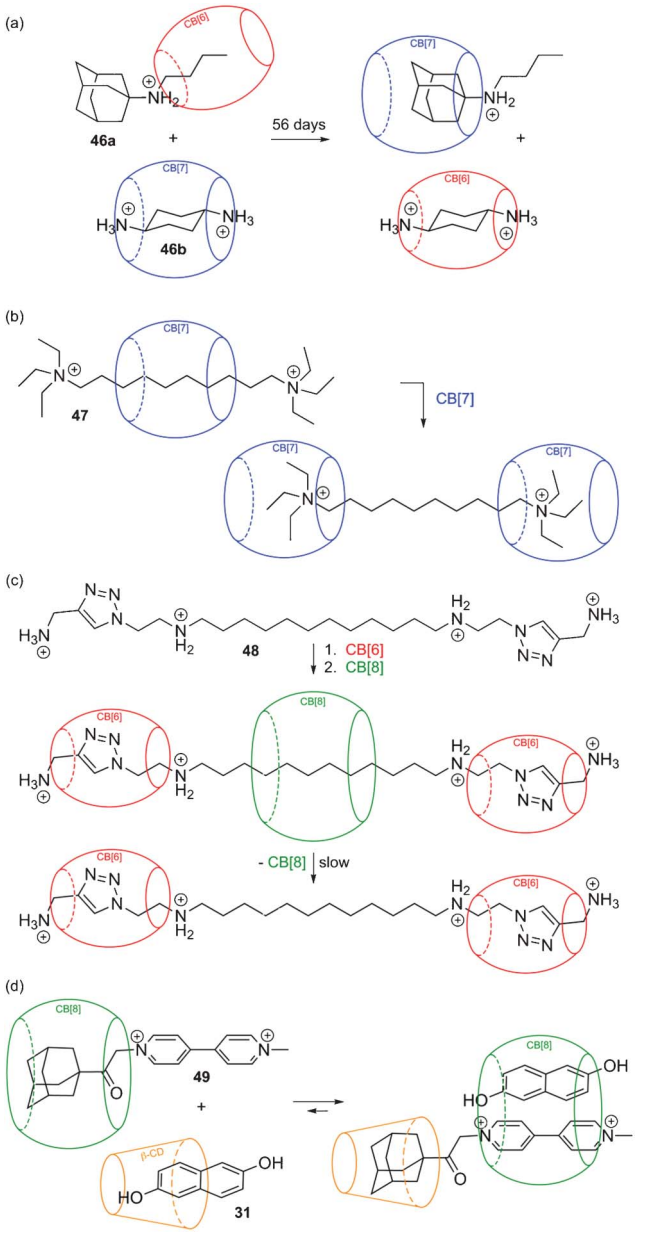


Fig. 13 (a) Kinetic *vs.* thermodynamic self-sorting of CB[6] and CB[7] towards guests **46a** and **46b**.[254] (b) Interaction between acetylcholinesterase inhibitor **47** and CB[7] (1.0 and 2.0 equiv., respectively).[256] (c) Self-assembly between axle **48**, CB[6] and CB[8].[174] (d) Self-organization between adamantyl/MV derivative **49**, 2,6-dihydroxynaphthalene (**31**), CB[8] and β-CD.[260]

selectivities, respectively.[156] Very recently, Urbach showed that CB[7] targets selectively the N-terminal Phe residue of the human insulin B-chain against all other surface-exposed residues, and forms a 1 : 1 complex with the protein (binding affinity 1.5 × 10^6 M^{-1})![255] For additional recognition mechanisms involving peptides and CB[8], we recommend the other publications from the Urbach group (see section 4.2.1(e)). Macartney showed that some α,ω-bis(trialkylammonium)alkane bolaamphiphilic acetylcholinesterase inhibitors **47** (or their phosphonium analogs) interact with 1.0 equivalent CB[7] *via* their alkyl central station; however, upon addition of more than 2.0 equivalents CB[7], the

macrocycles bind to the terminal ammonium stations and leave the central alkyl unit exposed to the solvent (see Fig. 13b).[256] A similar scenario was observed with a series of α,ω-bis(pyridinium)alkane dications.[257] For these reorganization mechanisms to take place, the strength of CB[7] binding to the central station must be (1) greater than the affinity towards one terminal station, and (2) weaker than the combined CB[7] affinities towards both terminal stations (*i.e.* lower than the product of the binding constants). Tuncel described the self-sorting properties of polyaminated axle **48** towards CB[6], CB[7] and CB[8]: CB[6] interacts exclusively with the terminal triazole stations, while CB[7] and CB[8] bind to the central 1,12-dodecanediammonium station. Remarkably, upon addition of 2.0 equivalents CB[6] to [2]pseudorotaxane **48** ⊂ CB[8], unstable [4]pseudorotaxane **48**·$(CB[6])_2$·CB[8] is initially formed (the only example where two CB units share the same ammonium cation, see section 4.2.1(a)), and CB[8] is then slowly ejected, with the dethreading rate obviously depending on the exchange kinetics of the two CB[6] 'valves' sitting at the terminal stations (see Fig. 13c).[174] In a recent study,[219] Schalley discussed the self-sorting processes taking place between CB[7], CB[8], 2,6-dihydroxynaphthalene (**31**), MV^{2+} (**21a**), and several guests bearing the latter electron-withdrawing and electron-donating units on a single axle, a process called integrative self-sorting.[258,259] Also this year, Liu and coworkers described a very elegant self-organizing system involving both CB[8] and β-CD; upon combination of CB[8]-bound adamantyl/MV derivative **49** with β-CD-bound 2,6-dihydroxynaphthalene (**31**), quaternary complex 31 49 CB[8] β-CD was formed, with β-CD now encapsulating the adamantyl unit, and CB[8] the charge transfer complex between MV and 2,6-dihydroxynaphthalene (see Fig. 13d)![260]

Isaacs reported a remarkable hybrid natural/synthetic self-sorting system involving CB[7], an enzyme (bovine carbonic anhydrase (BCA) or acetylcholinesterase (AChE)), and inhibitors bearing both enzyme- and CB[7]-binding units (see compounds **50** and **51** in Fig. 14). CB[7] can efficiently disrupt the interaction between BCA and inhibitor **50** *via* the transient formation of a ternary BCA **50** ⊂ CB[7] assembly (this interaction actually enhances the rate of dissociation of BCA and inhibitor **50**); after disruption, the catalytic activity of the enzyme is restored (Fig. 14a). In the case of AChE, the AChE (**51** ⊂ $CB[7])_4$ assembly is stable, and CB[7] does not dislodge the inhibitor from the more open sites of the enzyme, which remains inactive (Fig. 14b).[117]

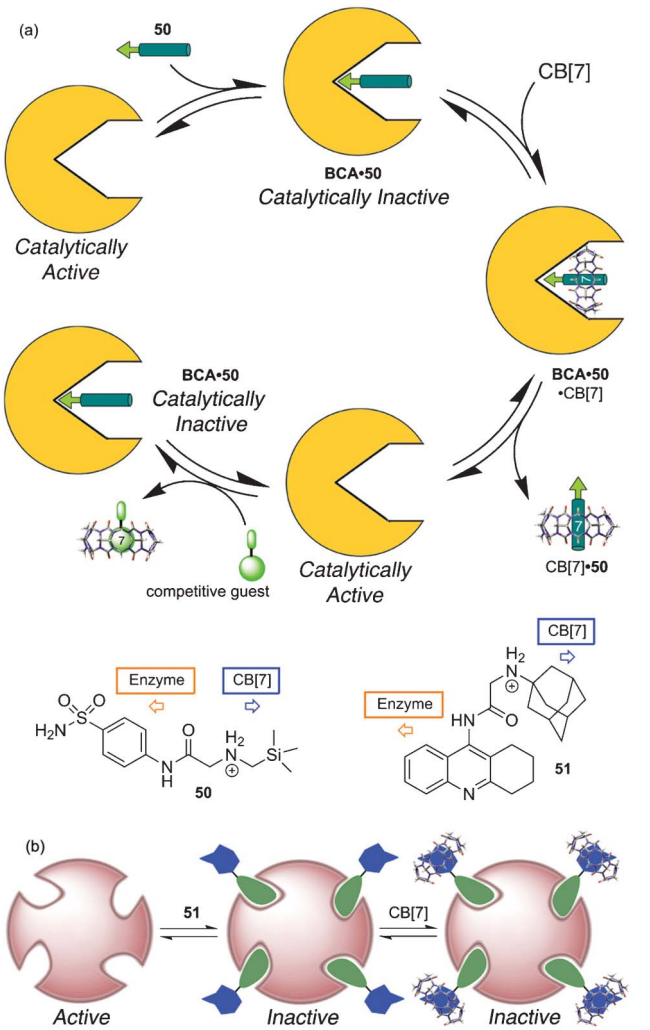


Fig. 14 (a) Successful CB[7]-mediated control of inhibitor activity towards the BCA enzyme. (b) Unsuccessful control of AChE activity. Reprinted with permission from ref. 117. Copyright 2010 American Chemical Society.

5.2 Molecular switches

When an external stimulus, such as a pH or a temperature change, light irradiation, *etc.* triggers self-sorting, allows some re-organization towards a new well-defined system, or induces a change in detectable output, the overall mechanism becomes a switch. A series of examples involving CB[n]s have been reported during the past few years.

5.2.1 Temperature-driven switches. Our group has published the preparation of spermine derivative **52**, and its recognition properties towards CB[6] and CB[7].[261] This axle, which bears three stations, and can be targeted by both macrocycles, may adopt up to 18 different configurations (configurations 000, 006, 060, 066, 606, 666, 007, 070, 077, 707, 777, 076, 706, 776, 067, 767, 766 and 676, if the occupancy of the three stations is listed consecutively, '0' represents a free station, and '6' or '7' a station complexed by CB[6] or CB[7]). Upon careful optimization of the experimental conditions (such as buffer composition, concentrations of hosts and guests, and in particular, temperature), the intricate interplay between multiple equilibria and complexation rates could be controlled, and configurations '676' and '666' obtained selectively (see Fig. 15): the kinetically favored configuration '676' was obtained at 25 °C, and underwent a reorganization towards the thermodynamically preferred '666' assembly upon heating (a case of thermally induced host/guest scrambling).[261] In several recent studies, we[240] and others[170,242] have also shown that CB[6] shuttling between two stations over a nitrogen atom required an activation energy of 24–29 kcal mol^{-1}, and therefore some heating to overcome the barrier (section 4.2.2).

5.2.2 pH-driven switches. In addition to the switch developed by Tuncel and already described in section 4.2.1(c),[170] several pH-controlled systems have been reported during the past few

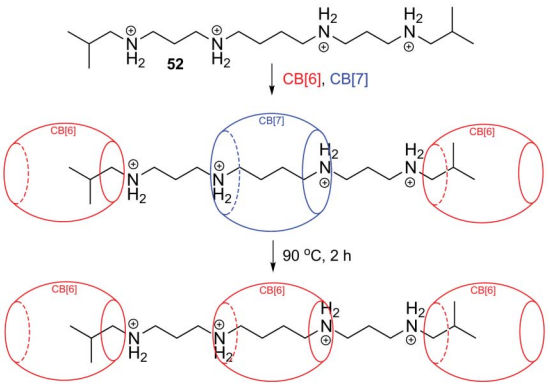


Fig. 15 Kinetic *vs.* thermodynamic self-sorting of polyaminated axle **52** in the presence of CB[6] and CB[7].[261]

years. For example, Kaifer showed that CB[7] interacts preferentially with the carboxyalkyl substituent of MV derivative **53** at low pH, and shuttles to the central bipyridine station at higher pH, due to adverse interactions between the negative carboxylate unit and the CB[7] rim (see Fig. 16a).[262,263] Very recently, Sindelar showed that carboxylic acids could actually be encapsulated within CB[7] if connected to two positive pyridinium units; when the pH was raised from 3.5 to 12, deprotonation of the acid triggered the ejection of CB[7] and the formation of a very loose complex with the terminal pyridinium substituents.[264] Tian and coworkers designed V-shaped cyanine dye **54** and monitored its interaction with CB[7] as a function of the pH; CB[7] interacts with the protonated aniline branch at pH 4–6, and switches to the neutral dimethylaniline at pH 8–11 (see Fig. 16b). Remarkably, the absorption spectra of both neutral and protonated forms of the dye in the absence of CB[7] are virtually identical (λ_{max} 445 nm), yet when CB[7] binds to the protonated aniline unit, a 17 nm hypsochromic shift is observed (λ_{max} 428 nm), and when it interacts with the dimethylaniline substituent, a 14 nm bathochromic shift is detected (λ_{max} 459 nm). The pH-dependent switch can thus be readily monitored by color change (yellow under acidic conditions, red at high pH).[265] Liu recently reported the pH-driven formation of a loop upon encapsulation of bipyridinium **55** into CB[8] (Fig. 16c); after protonation, CB[8] interacts preferentially with the alkyl central station, and the guest adopts a straight shape.[266]

Although the following example by Nau does not involve the displacement of CB from one station to another, the controlled on/off fluorescence output of this system makes it pertinent to this section: benzimidazole derivative **56** is barely fluorescent at high pH, due to a photoinduced electron transfer between the benzimidazole unit and the excited naphthalimide fluorophore; at lower pH, protonation of benzimidazole prevents the electron transfer, and fluorescence increases. Upon addition of CB[7], which encapsulates the benzimidazole moiety, an additional increase in fluorescence is observed, probably due to constraints in rotational and vibrational freedom, and to the proximity between the naphthalimide fluorophore and the CB[7] portal. Therefore, the system behaves as an AND logic gate, with the two inputs being CB[7] and the concentration of protons: both protons (lower pH) and CB[7] are needed in order to generate a high fluorescence output (see Fig. 16d).[267]

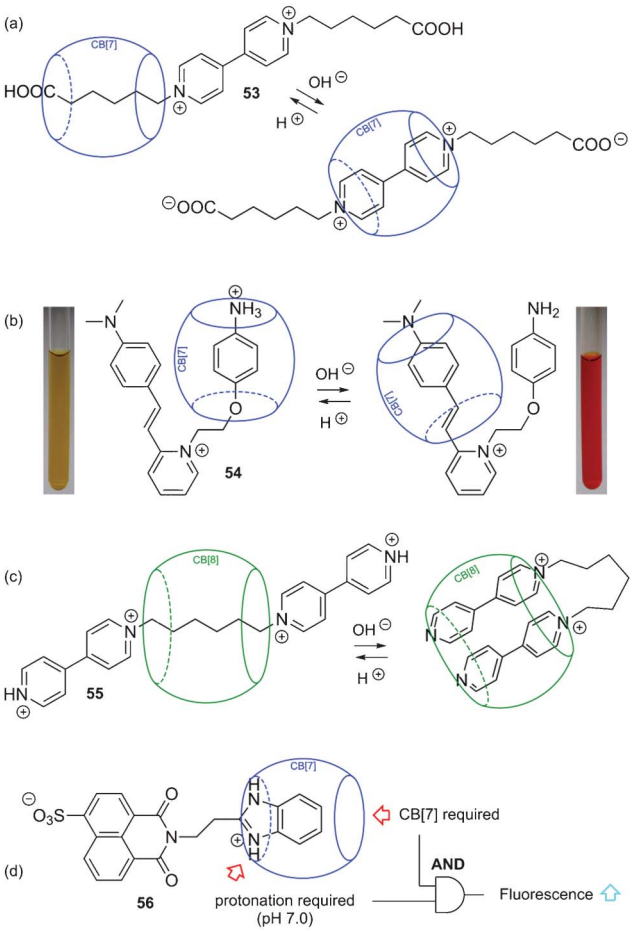


Fig. 16 pH-controlled CB[n] switches.

Finally, we report two pH-driven switches involving both CB[n]s and β-CD. Isaacs showed that disubstituted ammonium **57** interacts with CB[6] *via* its alkyl substituent, and quaternary ammonium **58** with β-CD *via* its adamantyl unit, when all four components are combined at pH < 7; however, under basic conditions (pH > 13), disubstituted ammonium **57** gets deprotonated, interacts now preferentially with β-CD (*via* its adamantyl unit), and leads CB[6] to interact with the alkyl substituent of quaternary ammonium **58** (see Fig. 17a)![268] Thompson, Kim and Yui prepared mixed CB[7]/β-CD polypseudorotaxane **61**·CB[7] β-CD by "clicking" alkyne-substituted pseudorotaxane **59** ⊂ CB[7] with azide-substituted adduct **60** ⊂ β-CD. CB[6] could then be shuttled from the xylylene to the triazole/propylene glycol units by varying the pH from 2 to 11 without any concomitant dethreading, thanks to the steady position of the β-CD macrocycle along the polymer (see Fig. 17b).[269]

5.2.3 Electrochemically-driven switches. We first note the elegant system developed by Kaifer and coworkers, in which CB[7] shuttles from the ferrocenyl station of axle **62** to the central xylylene (or hexylene) station upon electrochemical oxidation of ferrocene to the corresponding ferrocenium cation (the latter displays a much weaker affinity towards CB[7] than its reduced analogue); the process is fully reversible (see Fig. 18).[270]

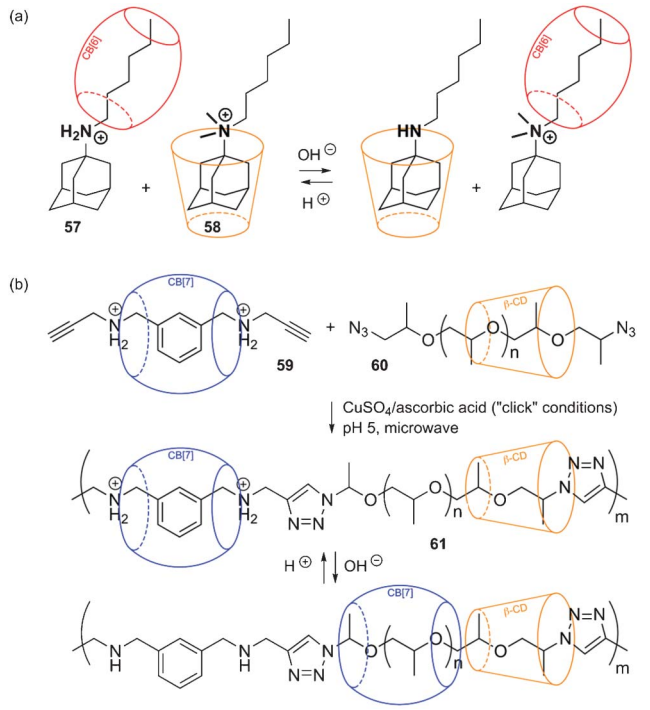


Fig. 17 (a) pH-mediated selective host/guest pairing between secondary and quaternary ammonium cations **57** and **58**, CB[8] and β-CD.[268] (b) CB[7]-shuttling along a β-CD-shielded polymer.[269]

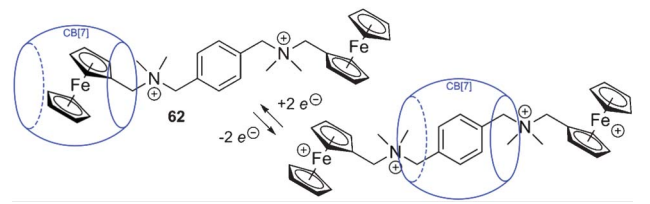


Fig. 18 Redox-controlled shuttling of CB[7] along a ferrocene derivative.[270]

We also take the opportunity to recommend two recent reviews by the same author, summarizing the properties of redox active guests encapsulated by CB[n] and CD hosts.[271,272]

Most redox-controlled switches involve CB[8], and exploit its ability to encapsulate two MV^+ radical cations, obtained upon reduction of the corresponding dications MV^{2+}. For example, Kim showed that axle **63** forms loop **63**·CB[8] upon interaction with CB[8] (the two possible donor–acceptor combinations are present in solution), and undergoes a reorganization to loop **64**·CB[8] upon electrochemical reduction (see Fig. 19a);[216] similarly, Sun and Peng showed that guest **65** adopts a looped conformation inside CB[8], and forms 2 : 1 complex $\mathbf{66}_2$·CB[8] upon reduction (Fig. 19b). The authors also noted the presence of looped radical cation **66**·CB[8].[220] In another report, Sun described the shuttling of CB[8] from the 3,3′-dimethylviologen station to the neighboring MV station of axle **67** upon reduction, with concomitant formation of dimer $\mathbf{68}_2$·CB[8] (Fig. 19c).[225] We note that reductions have also been carried out by light irradiation on axles linked to a photo-sensitizer (a Ru(II)-tris(bipyridine) unit for example), in the presence of a sacrificial electron donor such as triethanolamine.[218,224]

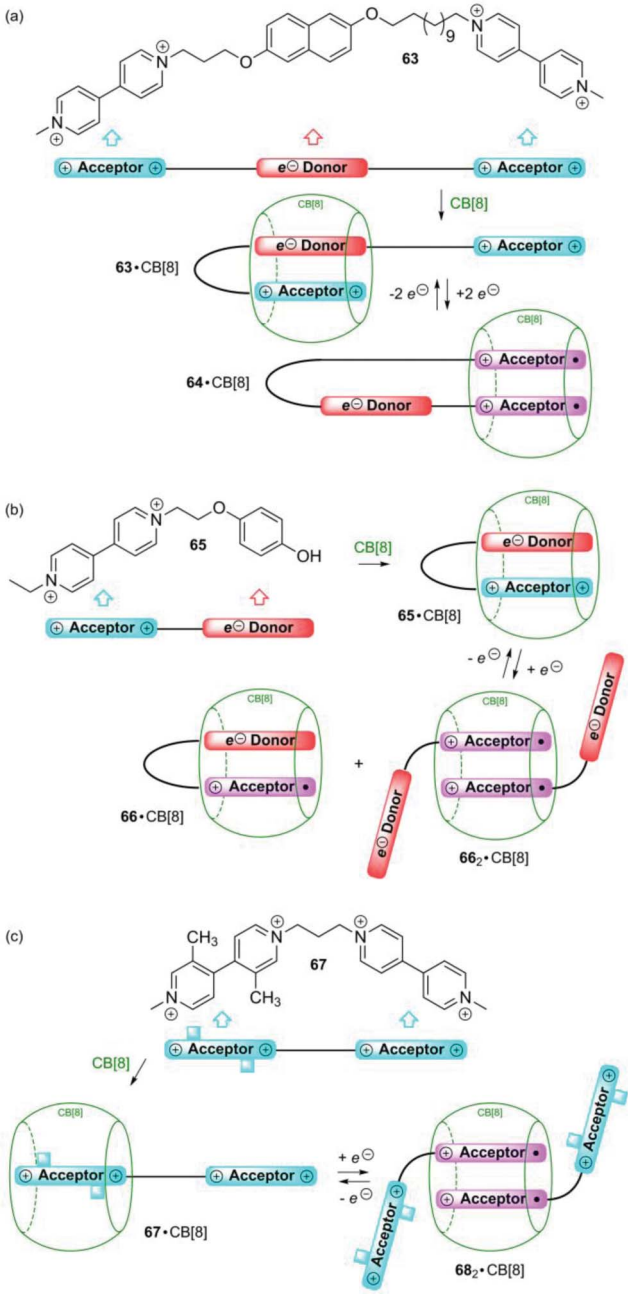


Fig. 19 Redox-controlled switches, exploiting the contrasted recognition properties of CB[8] towards MV^{2+} cations and MV^+ radical cations.

Finally, we describe a remarkable redox-controlled self-sorting switch recently reported by Kim and coworkers. CB[8] readily encapsulates MV^{2+} (**21a**) and electron-donating tetrathiafulvalene (**69**); upon reduction with sodium dithionite, CB[8] frees tetrathiafulvalene (**69**), and forms a ternary complex with the dimer of the MV^+ radical cation (**21b**); the ternary adduct **21a**·**69**·CB[8] is regenerated upon treatment with oxygen. The donor–acceptor complex can also be oxidized with Fe(III); CB[8] then liberates MV^{2+} (**21a**) and forms a ternary complex with the dimer of radical cation **69**; reduction with sodium metabisulfite regenerates the original ternary assembly **21a**·**69**·CB[8] (see Fig. 20)![273]

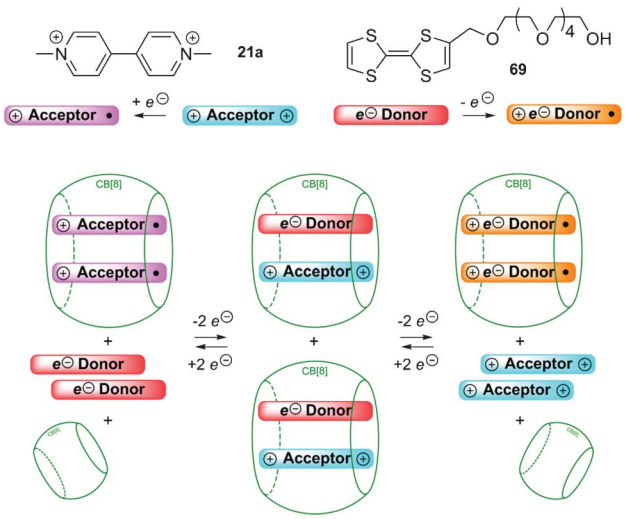


Fig. 20 A redox-controlled three-position switch, involving CB[8], MV^{2+} (**21a**), tetrathiafulvalene (**69**)and their respective radical cations.[273]

5.2.4 Enzyme-controlled switches. The following tandem assay has been developed by Nau and coworkers.[154,274] CB[7] and the fluorescent dye Dapoxyl, which undergoes a 200-fold fluorescence enhancement upon encapsulation with CB[7] (an effect also observed with several other dyes),[45,275] were first combined with a selected amino acid (histidine, arginine, Tyr or Lys); upon subsequent addition of the specific decarboxylase, the amino acid was converted to the corresponding decarboxylated species (histamine, agmatine, tyramine or cadaverine (**70**), respectively). Since the decarboxylated ammoniums display a much stronger affinity than their corresponding amino acids towards CB[7], and are thus more prone to competing with the fluorescent dye, a decrease in fluorescence takes place upon decarboxylation. The authors used this tandem assay to show the selectivity of the decarboxylases towards their corresponding L-amino acids, and to measure the enantiomeric purity of D-Lys; the method is remarkably precise and accurate, and enantiomeric excesses as high as 99.98% could be determined.[274] The reverse process, with the substrate displaying a higher affinity towards CB[7] compared to the product of the enzymatic reaction, could be similarly monitored; for example, the tandem assay was applied to the oxidation of cadaverine (**70**) to 5-aminopentanal (**71**) with diamine oxidase (see Fig. 21). The effect of oxidase inhibitors, such as the cyanide anion, could be probed using this method. One should also note that the concentration of CB[7] is low enough not to significantly affect the enzyme kinetics, since only a fraction of the substrate is bound to the macrocycle.[276]

Very recently, Urbach and Nau adapted this tandem assay to the continuous monitoring of the enzymatic cleavage of enkephalin-type peptides by metallopeptidase thermolysin, using acridine orange as the fluorescent probe.[277] As noted by the authors, thermolysin metallopeptidases play critical roles in reproduction and cardiovascular homeostasis mechanisms, and enkephalin-type peptides are involved in pain perception, emotional behavior, and play a role in dementia caused by the Alzheimer's disease. The affinity of the reacting peptide towards CB[7] is only moderate (approximately 10^4 M^{-1}) compared to the cleaved peptide (affinity greater than 10^6 M^{-1}), which

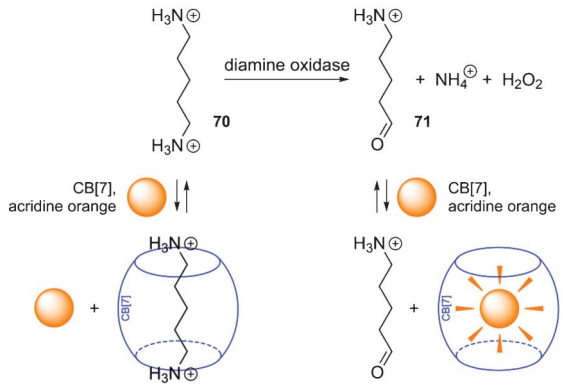


Fig. 21 Tandem assay for diamine oxidase monitored by CB[n] and a fluorescent dye.[276]

competes with acridine orange for CB[7] binding. Therefore, upon enzymatic cleavage, the dye is released from CB[7] and the fluorescence decreases. The kinetics of the cleavage can be readily monitored, and can be used to assess peptide sequence specificity, the effect of terminal charges (neutral amide *vs.* carboxylate units) on the degradation rates, stereospecificity, as well as *endo-vs.* exopeptidase activity. The tandem assay was also used to determine the inhibition constant of the protease inhibitor phosphoramidon (17.8 ± 0.4 nM).[277]

5.3 Impact of CB[n]s on organic reactivity

CB[n]s impact the distribution of reactants and products at equilibrium (a thermodynamic effect, section 5.3.1), as well as reaction rates (see section 5.3.2 for kinetic effects); both inhibition and rate enhancement are discussed below.

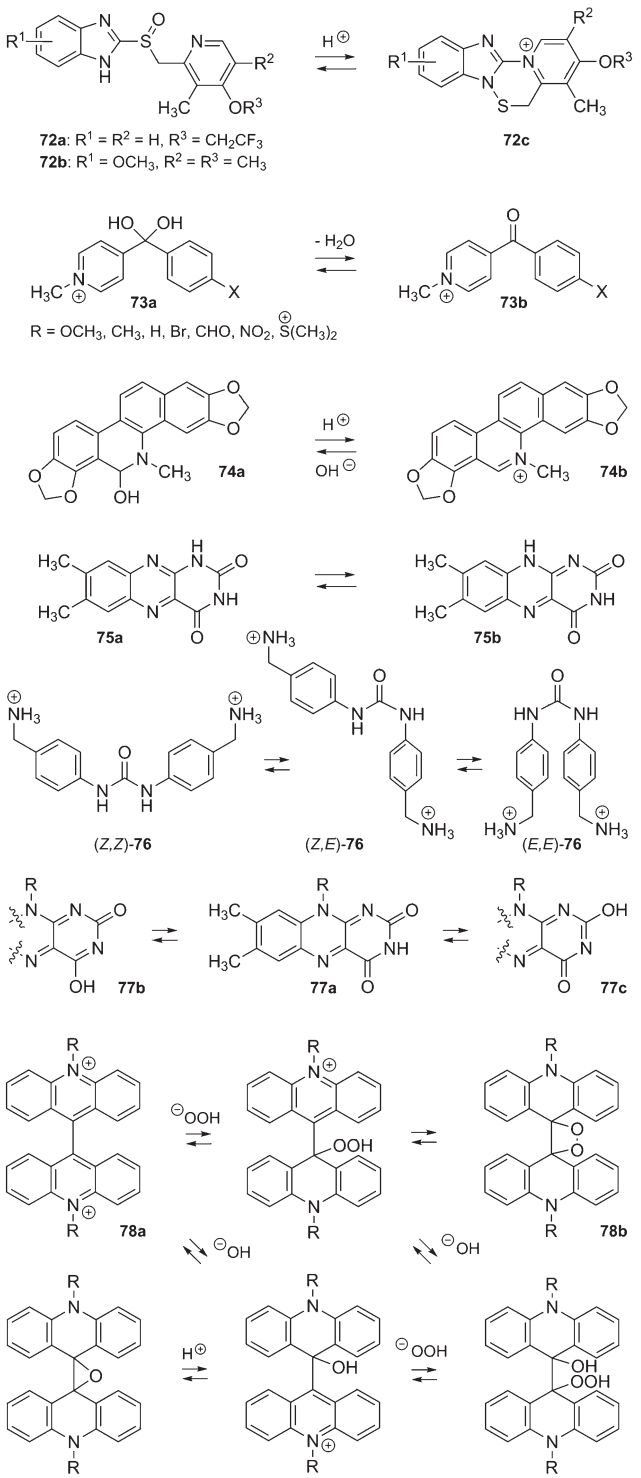
5.3.1 Thermodynamic effects. As already discussed, the geometry of guests can be profoundly altered upon interaction with CB[n]s; for example, straight axles can curl within the cavity of the macrocycle or adopt a looped shape. In addition to those conformational modifications, interaction with CB[n]s usually increases the pK_a of ammonium cations (by up to 4.5 units), or in other terms, the macrocycle affects the equilibrium between the ammonium cation, the neutral amine and the solvated proton. Although examples are still scarce, CB[n]s were recently found to affect the thermodynamics of more complex equilibria. For example, Nau and coworkers showed that CB[7] could stabilize the active form **72c** of proton-pump inhibitors lansoprazole (**72a**) and omeprazole (**72b**);[158] the macrocycle also protects sulfenamide **72c** from decomposition, and does not prevent it from reacting with sulfides, a key process for its bioactivity (gastric acid production is reduced upon reaction of sulfenamide **72c** with cysteine residues of the gastric enzyme (H^+-K^+)-ATPase).[278] Sotiriou-Leventis and Leventis showed that CB[7] could affect the equilibrium between ketones **73b** and their hydrated *gem*-diol analogs **73a**. In the presence of the macrocycle, the equilibrium is displaced further towards the keto form,[279] and the equilibrium constant is multiplied by approximately 4 (corresponding to an extra 0.80 kcal mol^{-1} stabilization of the keto form upon interaction with CB[7]). As mentioned before, Macartney also reported the stabilization of a diphenylmethane carbocation (**20a**) to the expense of the corresponding carbinol.[185] Biczók

showed that the equilibrium between the alkanolamine and the iminium forms of sanguinarine (**74a** and **74b**, respectively) could be shifted towards the iminium form in the presence of CB[7], due to extra stabilization of the pyridinium unit by the CB[7] rim.[280] We note that in the presence of an excess amount of CB[7], a 1 : 2 complex **74b**·(CB[7])$_2$ is detected; to the best of our knowledge, this is the only example where one pyridinium unit participates in the stabilization of two CB[7] macrocycles.[280] The same authors also reported that CB[7] could trigger the partial tautomerization of lumichrome **75a** to the corresponding isoalloxazine **75b**.[281] Isaacs and coworkers showed that CB[7] could promote the *trans*→*cis* isomerization of 4,4'-diaminoazobenzene by overcompensating the higher stability of the free *trans* isomer, at least between pH 3 and 6.[282] They also described the impact of CB[8] on the ratios of *N*-substituted ureas conformers, such as guest **76**, and note for example that in the presence of a stoichiometric amount of CB[8], the (*E*,*E*)-**76b**·CB[8] adduct is formed exclusively.[283] In addition, Isaacs and coworkers beautifully showed that triazene-arylene **41**, as well as a few analogs, exclusively adopt (1) the fully *anti* conformation in the cavity of CB[10] (see guest a,a,a,a-**41a** in Fig. 10, section 4.2.1(f)), (2) the *anti-anti-anti-syn* conformation inside CB[8] (guest a,a,a,s-**41b** in Fig. 10), and (3) the *anti-syn-syn-anti* conformation when interacting with two CB[7] units![234]

Choudhury and Pal showed that the equilibrium between lactam **77a** and lactims **77b** and **77c** was shifted towards the lactims in the presence of CB[7], despite all three species only forming exclusion complexes with CB[7]. Hydrogen bonding between the hydroxy groups of the lactims and the CB[7] rim may be responsible for this effect.[284] Finally, our group has just reported that CB[7] could stabilize positively charged lucigenin derivatives **78a** to the expense of the corresponding neutral 1,2-dioxetanes **78b** in a complex network of equilibria promoted by the addition of hydrogen peroxide. 1,2-Dioxetanes **78b** undergo a chemiluminescent degradation pathway, which can therefore be interrupted or dimmed in the presence of CB[7].[285]

5.3.2 Kinetic effects. Amazingly, the first case of CB[n]-assisted supramolecular catalysis was reported as early as 1983,[167] only two years after the isolation of CB[6].[2] Mock showed that the propargylammonium and 2-azidoethylammonium cations could form a ternary complex with CB[6], and that the encapsulated alkyne and azide could undergo 1,3-dipolar cycloaddition to yield the corresponding 1,2,3-triazole ring; an exceptional 55 000-fold rate increase was observed relative to the cycloaddition in the absence of CB[6].[167,286] This reaction, which allows the preparation of [2]rotaxanes with no possibility for CB[6] to escape as long as bulky stoppers are connected to the ammonium groups, has been applied on numerous occasions to the design of complex interlocked systems, in particular by Steinke and Tuncel.[11,168,170,174,287–291]

In 2001, Kim reported that two equivalents of (*E*)-diaminostilbene dihydrochloride **79** could be encapsulated by CB[8], and that irradiation at 300 nm during 30 min triggered [2 + 2] cycloaddition and the formation of cyclobutane derivative **80** (*syn*/*anti* ratio > 95 : 5);[292] the reaction was found to be much slower within γ-CD with a poorer stereoselectivity (72 h, *syn*/*anti* ratio 4 : 1),[293] and in the absence of any macrocycle, isomerization to (*Z*)-diaminostilbene was the main reaction.[294]

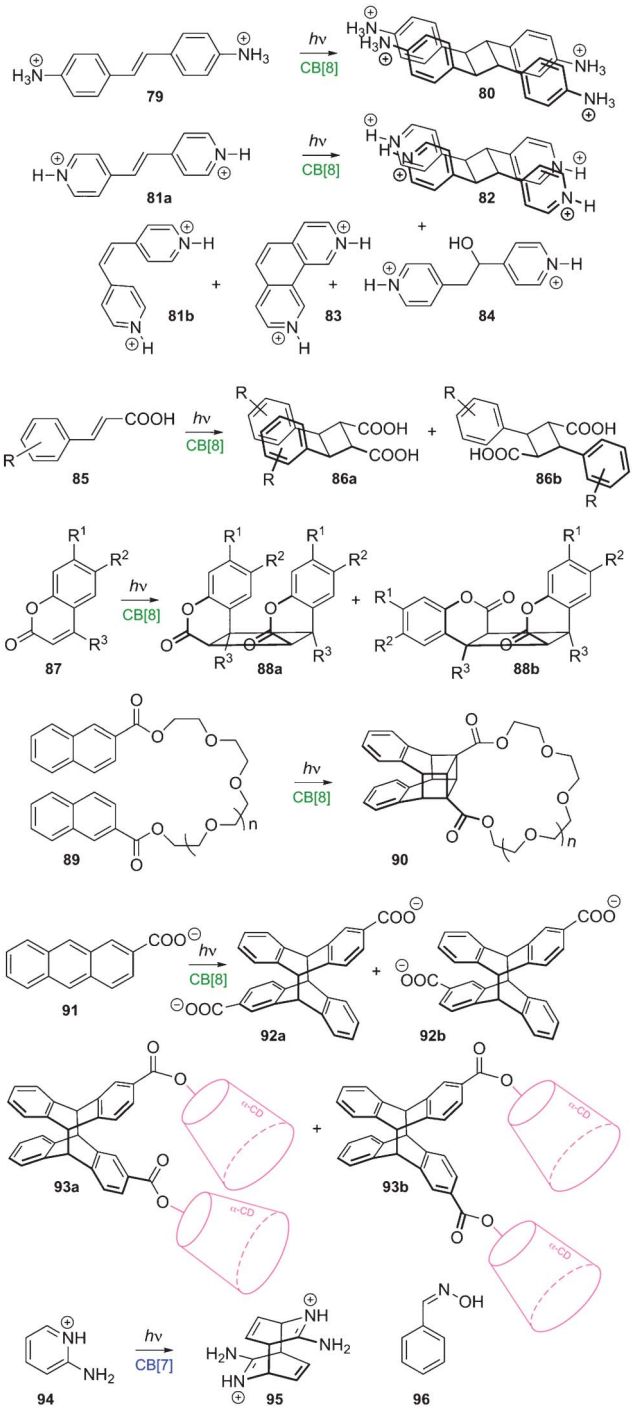


Ramamurthy reported a similar [2 + 2] cycloaddition with *trans*-1,2-bis(4-pyridyl)ethylenes **81a**, and in the presence of CB[8], cyclobutane derivative **82** was obtained in 90% yield. When the reaction was carried out with CB[7], *cis*-1,2-bis(4-pyridyl)ethylene **81b**, 2,9-phenanthroline **83** and hydration product **84** were obtained in a 67 : 12 : 21 ratio, while in the absence of macrocycle, the ratio was 17 : 5 : 78. 2- and 3-Pyridyl derivatives, as well as *trans*-n-stilbazoles afforded mostly the *syn* [2 + 2] cycloaddition products in the presence of CB[8] and the

cis-1,2-bis(pyridyl)ethylene or *cis*-stilbazoles without any macrocycle.[295] The product distributions of the [2 + 2] cycloaddition of unsymmetrical azastilbenes were later studied.[296] Ramamurthy also reported the dimerization of *trans*-cinnamic acids **85** in the absence and presence of CB[8], both in solution and in the solid state (*i.e.* upon grinding of the reaction partners). Irradiation of *trans*-cinnamic acids **85** in water without macrocycle, or with CB[7], triggered isomerization to their *cis* analog, while irradiation of their crystals afforded the *anti* head-to-tail dimer **86b**, if a reaction takes place at all. The same reaction carried out in the presence of CB[8] afforded a mixture of *cis*-cinnamic acid and *syn* head-to-head dimer **86a**. When the reaction was carried out in the solid state, the *anti* head-to-tail isomer **86b** could also be detected in some cases.[297,298] Sivaguru showed that coumarins **87** could undergo [2 + 2] cycloaddition when a pair is encapsulated into CB[8], and *syn* head-to-head and head-to-tail adducts **88a** and **88b** are usually the major products.[299,300] The formation of the ternary complex is likely the rate determining step of the reaction,[301] and excellent *syn*/*anti* ratios are obtained with only 10 mol% CB[8].[302] In pure water or other organic solvents, various *syn*/*anti* ratios were determined, and often, the yield was very poor.

Wu showed that 2-naphthoate **89** could form a 1 : 1 complex with CB[8] by adopting a looped shape, with both naphthyl units encapsulated. 500 W irradiation at $\lambda > 280$ nm for 12 min triggered a [4 + 4] cyclodimerization, which afforded cubane-like product **90** in a 96% yield, while no adduct was formed in a host-free environment.[303] Methyl and ethyl 2-naphthoate,[304] as well as 2-cyanonaphthalene,[305] could also be photodimerized upon encapsulation with CB[8], much faster than in the absence of the macrocycle (no reaction was observed with 2-cyanonaphthalene in pure water). Kim and Inoue reported the CB[8]-mediated [4 + 4] photocyclodimerization of 2-anthracene carboxylate **91**, linked (or not) to α-CD. While CB[8] encapsulation does not significantly effect the distribution of *syn*/*anti*, head-to-head/head-to-tail adducts with 2-anthracene carboxylate (head-to-tail isomers **92a** and **92b** are the major products), dimerization of the α-CD-linked derivative in the presence of CB[8] affords almost exclusively the head-to-head isomers **93a** and **93b**, while the corresponding head-to-tail products are obtained when the anthracene units are bound to γ-CD![306] This example illustrates how interactions remote from the reaction sites can dramatically affect the stereochemistry of photoreactions in confined spaces. A recent extension by Inoue shows that when the anthracene carboxylate units are connected to the same chiral anchor (α and β-CD), and the cycloaddition is promoted by double encapsulation of the aromatic units into CB[8], *syn*- and *anti* head-to-head dimers can be respectively obtained with excellent yields and enantioselectivity.[307] Finally, Macartney reported a unique example of a CB[7]-mediated [4 + 4] photodimerization of the 2-aminopyridinium cation (**94**), which affords exclusively the *anti-trans* adduct **95** in 90% after irradiation at 365 nm during 21 h. In a host-free medium, a 4 : 1 mixture of *anti-trans* and *syn-trans* isomers is obtained, and the conversion is twice slower.[308]

Compared to the number of reported CB[n]-promoted photoreactions, rationalized examples of CB[n]-catalyzed reactions that are not triggered by irradiation are still scarce, despite an early take-off with the [3 + 2] azide-alkyne cycloaddition described above. Nau recently showed that CB[n]s can catalyze



the hydrolysis of amides, carbamates and oximes with acceleration factors ranging from 4 to 285, as long as substituents are chosen judiciously, and the reactive units are positioned close to the CB[n] rim.[309] The macrocycle then facilitates the protonation of the reacting unit due to favorable interactions between the positively charged guest and the carbonylated rim of CB[n]s (another case of a CB[n]-mediated pK_a shift). In the case of benzaldoxime (**96**), a 10-fold acceleration was observed with only 10 mol% CB[7], at least at low conversion (< 30%); however, the hydrolysis product, benzaldehyde, displays a stronger binding affinity towards CB[7] than the oxime, and acts as a catalyst poison.[309] The same author also showed that the formation of sulfenamide **72c** (see previous section) from benzimidazoles **72a**

and **72b** can be catalyzed by CB[7], which enhances the basicity of the encapsulated benzimidazole units, increases the concentration of their protonated forms, and thereby accelerates the intramolecular nucleophilic attack by the neighboring pyridine ring.[158] García-Río reported the CB[7]-catalyzed hydrolysis of benzoyl chlorides, as long as those are substituted with electron-donating groups (acceleration factors up to 5.5-fold in the case of *p*-methoxybenzoyl chloride). Using Hammett plots, the authors determined that the mechanism was dissociative (*i.e.* S_N1-like; $\rho^+ = -3.1$), and that the favorable interaction between the partially negative CB[7] portal and the acylium cation developing at the transition state decreased the activation barrier of the reaction.[310] Finally, we note that rate enhancements of the oxidation of aryl and allyl alcohols to the corresponding aldehydes with hypervalent *o*-iodoxybenzoic acid (IBX) have also been reported in the presence of CB[8].[311]

A few organometallic reactions promoted or catalyzed by CB[n]s have been published recently. Demets showed that pentane, unlike cyclohexane, cyclooctene or styrene, could be oxidized to a mixture of 2-pentanol, 2-pentanone and 3-pentanone upon treatment with hydrogen peroxide or iodosylbenzene in the presence of an oxovanadium/CB[6] complex and various solvents; the author proposed that CB[6] was responsible for the selectivity, since only pentane could readily enter the cavity of the macrocycle.[312] The Ru(II)-catalyzed reduction of aldehydes to the corresponding alcohols was also reported to be facilitated in the presence of CB[6], but no mechanism was suggested.[313] Our group has recently published the first mechanistically rationalized case of an organometallic reaction catalyzed by CB[n]s.[314] We found that CB[6], CB[7] and CB[8] could catalyze the Ag(I)-promoted desilylation of trimethylsilylalkynyl derivative **97**, and proposed the following mechanism (see Fig. 22): (1) a fraction of guest **97** interacts with CB[n] (depending on the size of the macrocycle, different binding sites are targeted; in the case of CB[7], the trimethylsilyl unit is encapsulated, but the mechanism is valid for all CB[n]s); (2) Ag cations form π-complex Ag·**97** ⊂ CB[7], since favorable interactions between silver and the oxygen lone pairs of the CB[n] portal can stabilize the complex; (3) assembly Ag·**97** ⊂ CB[7] undergoes a nucleophilic substitution when water displaces the trimethylsilyl unit (water probably crosses the CB[7] portal and reaches the interior of the cavity before displacing the trimethylsilyl group); products of the substitution are CB[7]-bound trimethylsilanol-d^1, deuterium cations and presumably alkynylsilver **98**;[315] (4) alkynylsilver **98** is hydrolyzed in the presence of D^+, and phenylacetylene derivative **99** is obtained quantitatively, while CB[7] liberates trimethylsilanol-d^1, and can interact with guest **97** as a new cycle begins.[314]

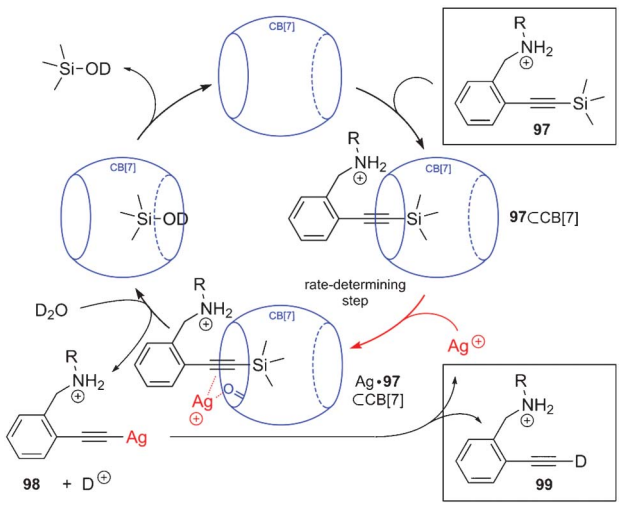
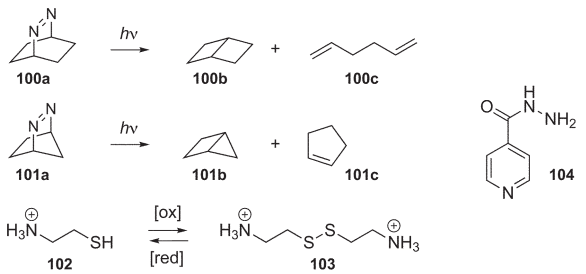


Fig. 22 Plausible cycle for CB[n]-catalyzed desilylations in the presence of Ag(I) salts.[314]

While not an organometallic reaction *per se*, the photolysis of azoalkanes **100a** and **101a** encapsulated within CB[7] was found to be significantly affected by metallic cations (the latter interact with the CB[7] portal and the nitrogen atoms of the azoalkanes).[316] The reactions, reported by Nau and coworkers, were carried out in a biphasic mixture of water and pentane, from which the products were collected and analyzed by gas chromatography. Remarkably, some metals had a significant effect on the product distribution: in the presence of Tl(I), Fe(III), Co(II), Ni(II), Cu(II) and Ag(I), photolysis of CB[7]-bound azoalkane **100a** afforded a mixture of bicyclo[2.2.0]hexane (**100b**) and 1,5-hexadiene (**100c**) in an averaged ratio of 13 : 87, while 30 : 70 ratios were obtained with free azoalkane **100a** (the products are formed after ring closure and opening of the 1,4-cyclohexadiyl biradical). CB[7] encapsulation thus tends to favor reactions from the triplet excited state by selective metal-induced intersystem crossing. In the case of azoalkane **101a**, all conditions afforded exclusively housane (**101b**), with one amazing exception: in the presence of Ag(I), a 59 : 41 mixture of housane (**101b**) and cyclopentene (**101c**) was obtained.[316] The authors proposed that CB[7]-bound Ag(I) triggers a one-electron oxidation of singlet azoalkane **101a**; the resulting radical cation would afford a 1,3-cyclopentanediyl radical cation upon nitrogen elimination, and cyclopentene would be formed after subsequent rearrangement.[317]



While catalysis with CB[n]s shows signs of a very promising future, the opposite effect, namely reaction inhibition or retardation by CB[n]s, should not be overlooked. Such reactions illustrate that CB[n]s may be used as "protecting groups" in organic synthesis. A remarkable example by Macartney is the inhibition of hydrogen/deuterium exchange at the C(2) positions of bis-imidazolium **36** upon interaction with CB[7]. Rate retardation reaches 1.3×10^3, which translates into a 3.1 pK_a shift at the C(2) position, from 22.3 to 25.4! The author attributes the extra basicity to C(2)–H/O=C hydrogen bonding interactions between the guest and the CB[7] portal.[318] García-Río reported that the solvolysis of 1-bromoadamantane and electron-poor benzoyl chlorides were slowed down by 10^3- and 10^2-fold, respectively, when bound to CB[7].[310] Kaifer showed

that CB[6] encapsulation of cysteamine (**102**) completely inhibits its oxidation to cystamine (**103**) with Fe(III) chloride; only trace amounts of cystamine (**103**) were detected when oxidation was carried out with oxygen or chloropicrin (in a host-free medium, reactions are complete after 7 h, 3 h and 40 min, respectively). CB[6] also totally inhibits the reduction of cystamine (**103**) to cysteamine (**102**) when treated with dithiothreitol, while the same reaction without CB[6] is completed in 1 h.[319] Tao and coworkers have recently reported that acylation of the anti-tuberculosis drug isoniazid (**104**), a hydrazide, could be slowed down by 5.5–77 times in the presence of CB[6] or CB[7] and various acetylating agents. Interestingly, the mode of interaction (exclusion complex in the case of CB[6] and encapsulation with CB[7]) does not have a significant effect on the inhibition.[320] Finally, Biczók showed that the alkanolamine form of sanguinarine **74a** could be protected against photooxidation with oxygen if surrounded by CB[7].[280]

5.4 CB[n]s as key units for drug delivery

The lack of target specificity and solubility of hydrophobic drugs in biological medium are serious impediments to the treatment of various pathologies, including cancer. These problems can be circumvented in part by using drug carriers such as nanoparticles, micelles, liposomes, carbon nanotubes, quantum dots, as well as amphiphilic macrocycles like cyclodextrins.[321–324] It is thus not surprising that CB[n]s have been considered as potent drug delivery vehicles during the past few years.

Although CB[n]s are virtually non-toxic, they readily cross cell membranes, as shown by Scaiano and García in the case of mouse embryonic 3T3 cells; cell penetration was monitored by fluorescence using CB[7]- and CB[8]-bound acridine orange and pyronine Y dyes.[183] Similarly, CB[7] is also internalized by murine macrophage RAW264.7 cells.[60] The effect of CB[n]s on a series of antitumoral platinum complexes has been studied on several occasions, in particular by Wheate, Day and Collins.[61,325–330] CB[n] encapsulation usually inhibit the degradation of the bioactive agents, and has a weak positive or negative effect on their cytotoxicity, depending on the size of the macrocycle and the nature of the platinum complex. Day and Collins also showed that CB[7] had little impact on the biological properties of albendazole, an anti-cancer agent plagued by its very low solubility in aqueous medium. However, CB[6]- or CB[7]-encapsulation enhanced its solubility by 2000-fold![331] Similar conclusions were reached with an albendazole derivative,[332] as well as the anti-cancer drug camptothecin.[333] Nakamura showed that CB[6] had a significant effect on selected enzymatic reactions of DNA. For example, the topoisomerization of a supercoiled plasmid catalyzed by calf thymus topoisomerase I is markedly accelerated in the presence of CB[6]-bound spermidine, compared to the free polyamine; to the contrary, the hydrolysis of the plasmid by the endonuclease *Ban*II is slower in the presence of CB[6]-bound spermine compared to the free axle.[334] Finally, in a recent article, Isaacs and Rotello showed for the first time that cytotoxicity of a bioactive agent could be regulated by CB[7] encapsulation.[335] Functionalized gold nanoparticles, which were decorated with a series of hexanediammonium units (AuNP-NH_2 in Fig. 23), readily interacted with CB[7] (approximately 40 macrocycles

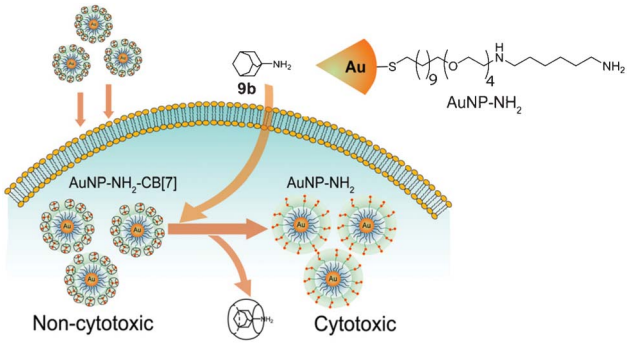


Fig. 23 CB[7]-controlled cytotoxicity of functionalized gold nanoparticles. Reprinted with permission from ref. 335. Copyright 2010 Nature Publishing Group.

around each nanoparticle, overall diameter 12 nm; see assemblies AuNP-NH_2-CB[7] in Fig. 23), and the large CB[n] units efficiently shielded the gold cores. After 3 h of incubation in the presence of human breast cancer cells MCF-7, the assemblies were internalized, and remained trapped within endosomes even after 24 h, with no toxicity observed at concentrations lower than 50 μM. To the contrary, CB[7]-free particles were released into the cytosol, causing apoptosis at a 1.3 μM IC_{50} value (34% cell survival at 2 μM after 24 h). Subsequent incubation of the cells containing the CB[7]-protected assemblies with adamantylammonium (**9b**; 0.40 mM) led to the capture of CB[7] by the competitive guest, to the disruption of the endosome membrane by the now CB[7]-free gold nanoparticles, and to cell death (40% cell survival at 2 μM, comparable to the 34% survival obtained in the control experiment)![335]

Du and coworkers,[336,337] as well as Zink and Stoddart,[338–344] showed a series of examples where mesoporous silica nanoparticles (MSNPs) act as drug containers, and CB[n]s as switchable lids that control the release of the bioactive agent. MSNPs MCM-41 (approximately 0.5 μm, containing hexagonally arranged pores with an average diameter of 2 nm) are readily prepared upon hydrolysis of tetraethyl orthosilicate in the presence of cetyltrimethylammonium bromide; they can then be functionalized with side-chains bearing a CB[n] binding site, soaked into a solution of a drug mimic (in these studies, it was replaced with fluorescent dyes such as rhodamine B or calcein for easy monitoring), capped with CB[n]s, and rinsed. The large macrocycles decorating the surface of the MSNPs efficiently prevent the release of the dye (see Fig. 24). Upon pH increase,[337,339–342] addition of a competitive guest,[336,337] reductive cleavage of a stopper,[338] or magnetically induced heating,[344] the CB[n] lids are ejected or shuttled away from the nanoreservoirs at a tunable rate, and the dye is released in solution. In two particularly remarkable examples, Zink and Stoddart described (1) MSNPs, which remain closed at pH 6.5–9, but can be opened at high (> 10) or low pH (< 5),[341] and (2) MSNPs interlaced with light-switchable *cis*/*trans* azobenzene units in their pores, and decorated with CB[6]-binding substituents at their periphery; the adsorbed dye can only be released upon light irradiation, which triggers the *trans*→*cis* isomerization of azobenzenes and opens the pores, coupled to a pH increase, which releases CB[6]; the system thus behaves as an AND logic gate.[343] Finally, Cheon and Zink prepared MSNPs containing

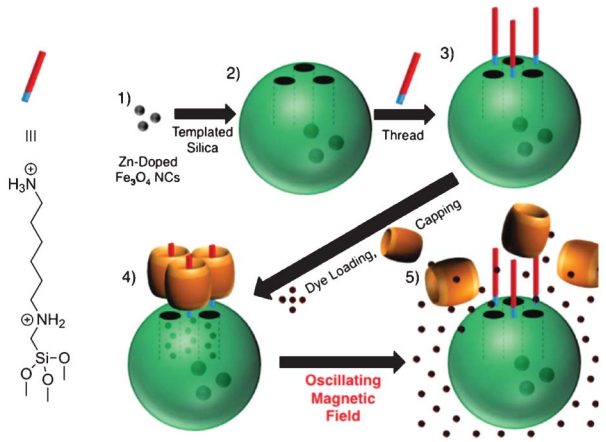


Fig. 24 Magnetic MSNPs filled with doxorubicine, linked to 1,6-hexanediammonium chains, and capped with CB[6]. Local heating by an oscillating magnetic field triggers the ejection of CB[6] and the subsequent release of the drug. Reprinted with permission from ref. 344. Copyright 2010 American Chemical Society.

zinc-doped iron oxide nanocrystals, and functionalized them with 1,6-hexanediammonium chains; the assemblies were then loaded with doxorubicine, capped with CB[6] and internalized into breast cancer cells MDA-MB-231.[344] Upon application of an oscillating magnetic field, the nanoparticles generated some local heat, which facilitated the ejection of CB[6] and the release of doxorubicine (see Fig. 24). A 37% cell death was observed after 5 min of magnetic field exposure when the particles were loaded with the cytotoxic agent, *vs.* 16% with unloaded assemblies, thereby indicating that both hyperthermia and drug release induced cell death.[344]

We finally note that the interactions between biologically relevant molecules and CB[n]s have been evaluated on various occasions. Examples include the common fluorescent stain 4',6-diamidino-2-phenylindole,[345] vitamin B12,[346] a series of fungicidal and anthelmintic benzimidazoles,[347] alkaloids palmatine,[348] dehydrocorydaline[348] and berberine,[349,350] antituberculosis drugs pyrazinamide and isoniazid,[351] β-blocker atenolol, antidiabetic glibenclamide, mydriatic tropicamide,[352] the Alzheimer's NMDA glutamate receptor drug memantine, the well-known analgesic paracetamol,[353] as well as the anesthetics procaine, prilocaine, tetracaine, procainamide and dibucaine.[162]

5.5 CB[n]s in nano and advanced materials

In addition to the medicinal applications described above, CB[n]s have been incorporated into promising novel materials. In the following section, we describe the preparation and properties of CB[n]-containing polymers (section 5.5.1), dendrimers (section 5.5.2), metallic nanoparticles (section 5.5.3), fullerenes (section 5.5.4), nanosheets, vesicles, films and surfaces (sections 5.5.5 and 5.5.6) and hydrogels (section 5.5.7).

5.5.1 Polymers. CB[n]s have been incorporated into polymers on several occasions. In this section, we divide those assemblies into three categories: CB[n]s are usually (1) thread along the main chain of the polymer, (2) connecting monomers, oligomers or polymers to form longer assemblies, or (3) bound to side branches. Examples from the first category can be prepared by consecutive slippage of a series of CB[n] units along the polymer chain; for example, Kim showed that CB[6] could be threaded along an axle bearing 10 repeating viologen units linked by decamethylene chains, and bound to all the decamethylene units if a stoichiometric amount of CB[6] was added.[354] Steinke reported a similar consecutive threading mechanism along poly(iminohexamethylene); after 400 h at 90 °C in the presence of an excess amount of CB[6], 45% of the 1,6-hexanediammonium stations could be surrounded by the macrocycle (very close to the 50% limit, since as mentioned in Section 5.1, an ammonium group cannot be shared by two CB[n] units).[355] An alternate preparation of polymers bearing CB[n]s along their main chain is the CB[n] encapsulation of monomers followed by polymerization: Buschmann showed that CB[6]-shielded polyamides could be formed upon reaction of CB[6]-bound 1,6-hexanediamine with adipoyl chloride,[356,357] and Liu recently reported that CB[7]-shielded polyanilines could be readily prepared by oxidation of aniline with ammonium persulfate under acidic conditions in the presence of CB[7]. The resulting polymer was found to be much more water soluble than its unshielded counterpart.[191]

CB[n]s can also be used to connect chains together either covalently or non-covalently, by exploiting two remarkable properties of the macrocycles: (1) CB[6] can catalyze the 1,3-dipolar addition between an alkyne and an azide, and (2) CB[8] can encapsulate two guests in its cavity. Steinke showed that polymer **107** could be obtained upon reaction of an equimolar mixture of dialkyne **105** and diazide **106** in the presence of an excess amount of CB[6].[287] Scherman reported that a 5000 g mol^{-1} MV-terminated poly(ethylene glycol) monomethyl ether chain could be "connected" to a 5000 g mol^{-1} 2-naphthoxy-terminated analog (or to 10 500 g mol^{-1} 2-naphthoxy-terminated *cis*-1,4-poly(isoprene)) by using CB[8], since the macrocycle encapsulates both the electron-deficient MV and the electron-rich naphthol. In the case of the poly(isoprene) derivative, micelles (approximately 250 nm) were likely formed upon connection to the MV unit, as assessed by dynamic light scattering experiments.[358] Using the same strategy, these authors could prepare an "ABA" triblock copolymer from two equivalents of a polymer linked to an electron-rich unit (fragment A), one equivalent of an MV dimer (the two MV units being linked *via* a short triethylene glycol spacer; fragment B), and two equivalents of CB[8]. The elongation process and the gain in molecular weight were monitored using diffusion ordered spectroscopy experiments, and by measuring solution viscosities.[359] Scherman also showed that the critical solution temperature of poly(*N*-isopropylacrylamide) linked to an electron-rich dibenzofuran end group could be increased by 5.7 °C (from 24.5 to 30.2 °C) upon addition of CB[8]-bound MV; the effect is due to an increase in hydrophilicity at the polymer terminus upon encapsulation with CB[8]. The process is fully reversible after addition of a competitive guest such as the adamantylammonium cation (**9b**).[360] Such thermoresponsive materials may be particularly appealing to the design of devices for stimulus-controlled drug delivery. The same author also reported the preparation of 3D viscoelastic polymeric networks from styrene/acrylamide copolymer **108a** decorated with MV units, 2-naphthoxy-substituted acrylamide copolymer **108b** and

CB[8] (see Fig. 25). A spectacular increase in viscosity (up to 10^3-fold) was observed at concentrations as low as 5% in water with a substoichiometric amount of CB[8] (0.50 equivalent), accompanied by the usual absorbance in the visible range due to charge transfer interactions between the electron-rich and electron-poor CB[8] guests (see Fig. 25, vial d and figures e and f).[361]

Zhang and coworkers described the formation of a polymer from CB[8] and axle **109**. Connections between monomers are reinforced with a double charge transfer interaction between anthracene and MV units surrounded by two CB[8] macrocycles (see Fig. 26)![362] The obtained polymer (hydrodynamic

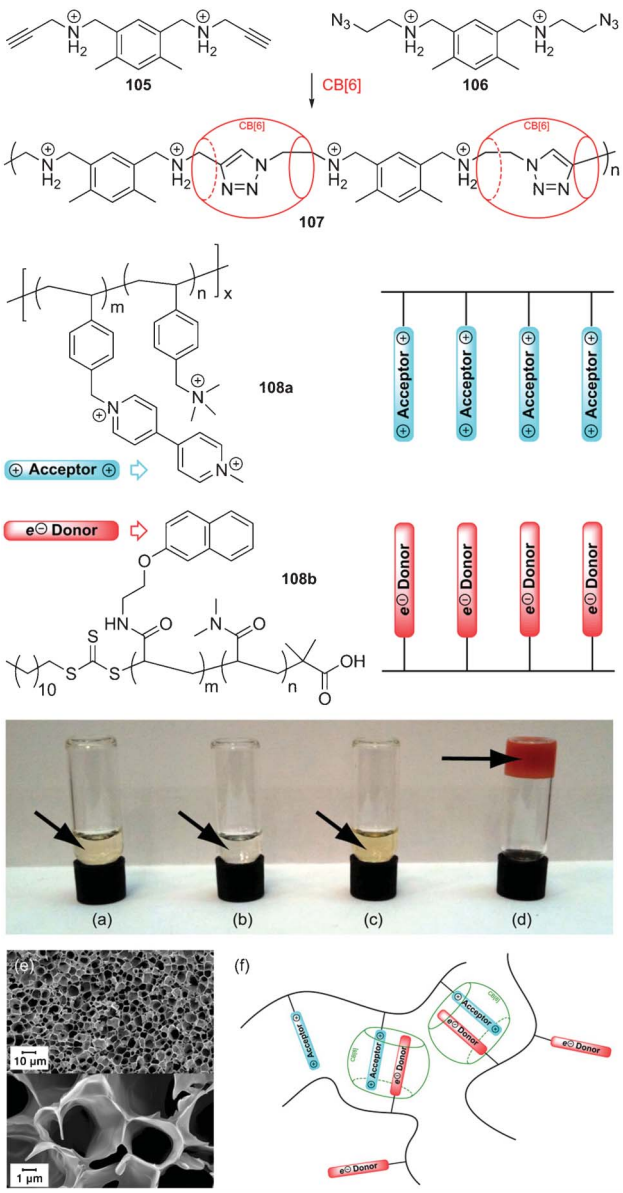


Fig. 25 CB[n]-assisted formation of polymers and 3D polymeric networks. Solutions (5 wt%) of (a) copolymer **108a**, (b) copolymer **108b**, (c) a 1 : 1 mixture of copolymers **108a** and **108b**; (d) hydrogel formed upon addition of 0.50 equivalent CB[8] (5% cross-linking) to solution (c). (e) Scanning electron microscopy (SEM) image of the cryo-dried hydrogel. (f) Cartoon illustrating the supramolecular structure of the 3D polymeric network. (a)–(f): Reprinted with permission from ref. 361. Copyright 2010 American Chemical Society.

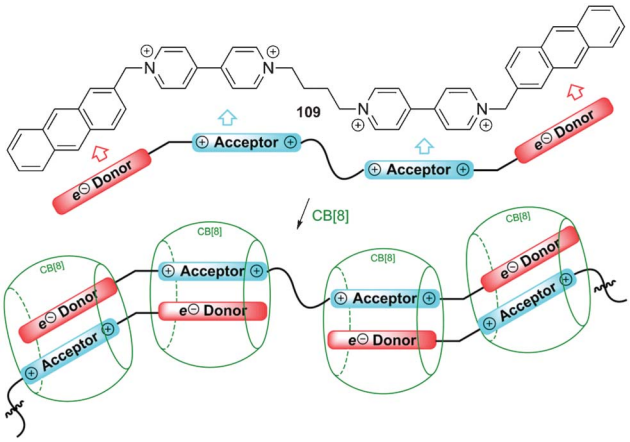


Fig. 26 Formation of a polymer from monomer **109**, stabilized by double charge transfer interaction and double CB[8] encapsulation.[362]

radius 30 nm) is not as flexible as traditional polymer chains; also the small segment elasticity shows that the chains are easily lengthened as springs. When the concentration of monomer **109** is increased to 4.0 mM, a deep purple gel is obtained upon CB[8]-assisted polymerization; addition of potassium cations disrupts the interactions between the polymer chains and the gel collapses.[362]

Finally, several polymeric systems bearing CB[n] units bound to side chains have been reported. For example, Kim described the preparation of a polyacrylamide derivative decorated with spermidine side chains that can interact with CB[6]. Complexation with the macrocycle caused a dramatic increase in the polymer thermal stability (330 °C *vs.* 150 °C).[363] Polyethylene derivatives decorated with CB[6]-bound 1, 6-bis(pyridyl)hexane units,[364] or CB[7]-bound MV groups,[365] as well as copolymers of acrylamide and CB[6]-bound butylammonium methacrylate[366] were also prepared. Scherman reported the preparation of a dynamic adduct between a methacrylate copolymer decorated with 2-naphthoxy groups, CB[8] and an α-mannoside viologen; the assembly could self-organize to target Concanavalin A, a tetrameric lectin that interacts specifically with mannose.[367] Kaifer showed that *p*-xylylene sulfonium salt **110** binds extremely strongly to CB[7] (binding affinity 4.0×10^{10} M^{-1}), and since it is a precursor to poly(phenylenevinylene) conducting polymers (PPV) *via* the Wessling route and intermediate **111** (see Fig. 27),[368] the authors were hoping to incorporate CB[7] rings along the polymeric chain. Attempts were fruitless, probably because CB[7] overstabilizes precursor **110** and prevents polymerization to intermediate **111**.[369] However, addition of CB[7] to axle **111** triggered the encapsulation of the diethylsulfonium substituents, and allowed the formation of PPV (**112**) upon heating as well as the release of CB[7]-bound diethyl sulfide, which remains close to the PPV main chain. CB[7] was also found to considerably enhance the rate of diethyl sulfide elimination.[369]

5.5.2 Dendrimers. During the past ten years, several CB[n]-containing dendrimers have been synthesized, mostly by the Kim[370,371] and Kaifer[217,372–376] groups. MV^{2+} (**21a**), followed by MV first, second and third generation Newkome-type dendrimers **113a**–**113c** were found to interact with CB[7] with

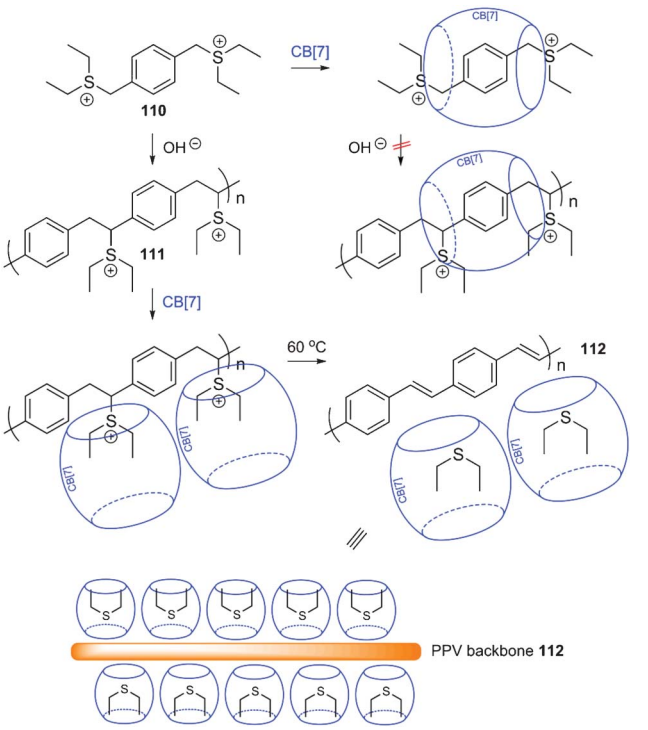
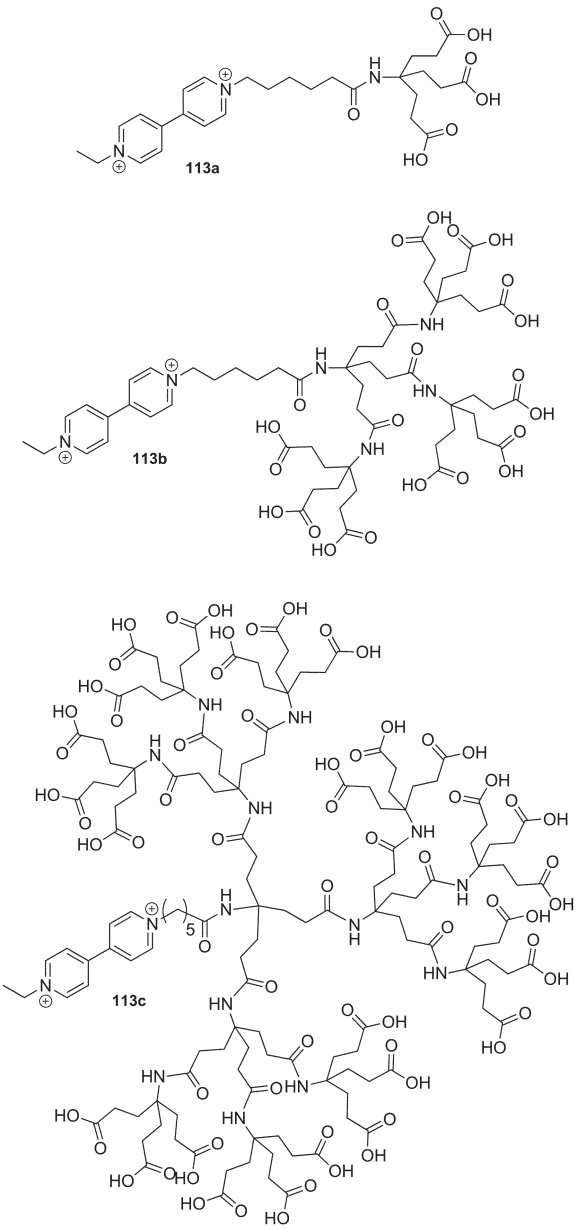


Fig. 27 Preparation of CB[7]-coated poly(phenylenevinylene) (PPV) *via* the Wessling route.[369]

increasingly tight affinities, at least until the third generation at pH 3.2 (2.9, 5.9, 6.2 and 3.4 × 10^5 M^{-1}, respectively); a plausible reason for this enhanced affinity is the modest loss of solvation of the MV unit due to the bulky substituents, leading to an increase in net coulombic interactions between the guest and the CB[7] portal. However, at neutral pH, the affinity markedly decreases as the dendrimer generation increases (2.2 × 10^5 M^{-1}, 5.5, 5.7, and 1.3 × 10^4 M^{-1} in the case of MV^{2+} (**21a**) and structures **113a**–**113c**), probably because of competitive interactions between the outer negative carboxylate units and MV.[372] The opposite effect was observed when MV was replaced with neutral ferrocene: ferrocenecarboxylic acid and the first generation dendrimer did not interact with CB[7], because of adverse interactions between the carboxylate units and the CB[7] rim, while second and third generation dendrimers displayed significant binding affinities (3.8 and 7.7 × 10^5 M^{-1}, respectively). Also, electrochemical kinetics slowed down markedly with larger dendrimers.[374] A similar binding enhancement was observed with a cobaltocene central station at least between the first and second generation (binding affinities are 1.0 × 10^4 and 3.4 × 10^6 M^{-1}, respectively); the third generation dendron displayed a weaker affinity (4.0 × 10^5 M^{-1}), probably due to sterical hindrance; cyclic voltammetry showed that CB[7] induced cathodic shifts in the half-wave potential value ($E_{1/2}$) corresponding to the reduction of cobaltocenium (23 and 110 mV in the case of first and second generations, respectively; this indicates that CB[7] interacts preferentially with cobaltocenium compared to cobaltocene); a decrease in the electron transfer rate was also detected upon interaction with CB[7], which widens the separation between the metal and the electrode.[375]



Kaifer also reported the formation of a binary complex between an MV^{2+}-linked dendrimer and CB[8], and of a ternary complex between two of these dendrimers and CB[8] upon reduction.[373] The same group later showed that a ternary complex could be formed between CB[8] and two dendrimers linked to MV^{2+} and *p*-dialkoxybenzene units, respectively. Reduction again induced a reorganization of the assembly, with both MV^{+} radical cations encapsulated into CB[8], and the two identical dendrons dangling at its periphery.[217] Finally, Li and coworkers showed that electron transfer from the outer naphthyl units of a dendrimer to a molecule of anthracenecarboxylic acid buried within the dendrimer is hampered by naphthyl-naphthyl interactions, which cause excimer formation and self-quenching; however, upon encapsulation (and isolation) of the naphthyl units by CB[7], the fluorescence quantum yield could be enhanced by up to 100%.[377]

5.5.3 Metallic nanoparticles. In 2007, the García group was first to stabilize metal nanoparticles with CB[n]s.[378] In that study, the authors had reported the formation of gold nanoparticles (Au NPs) interacting with CB[5], CB[6] and CB[7], upon (1) reduction of tetrachloroauric acid with sodium borohydride in the presence of CB[n]s, and (2) gas phase adsorption of gold atoms on dry powders by vapor deposition using an equimolar ratio of gold and CB[7]. While CB[5] and CB[6] afforded significantly aggregated Au NPs with a diameter ranging from 3 to 10 nm, the size distribution of Au NPs prepared in the presence of CB[7] was bimodal, with diameters of 0.4–1.2 nm and 4–9 nm, respectively. The authors proposed that the smaller NPs were encapsulated within CB[7]. Au/CB[7] assemblies were found to be particularly stable, since unlike Au/CB[5] and Au/CB[6], (1) Au could not be extracted with toluene in the presence of a phase transfer agent, (2) Au/CB[7] remained almost unaltered in the presence of cyanide anions, and (3) it did not precipitate upon heating. Also, electron energy loss spectra showed a weak carbon K-edge signal, thereby indicating the presence of an organic layer around the small Au NPs.[378] García then used positron annihilation lifetime measurements to show that the free volume of CB[7] decreased when interacting with small Au NPs, in accordance with the assumption that the NPs can sit within the cavity of the macrocycle.[379] The same author also showed that photolysis of Au@CB[7] at 532 nm affords an intense transient spectrum generated upon electron ejection from excited Au clusters, which decays well past 1.6 ms; CB[7] hinders electron–hole recombination between the Au clusters, and no transient is detected with larger Au NPs, as expected.[380] Irradiated Au@CB[7] NPs were also found to enhance the rate of dimerization of phenylacetylene to 1,3-diphenylbutadiyne by a factor of 7, since light generates positively charged Au clusters that promote the reaction.[380] Scherman recently reported that the aggregation of Au NPs could be controlled by CB[5] (see Fig. 28).[381] In the absence of the macrocycle, reduction of tetrachloroauric acid with sodium borohydride afforded 8 nm Au NPs, which displayed the characteristic surface plasmon resonance signal (SPR) at 520 nm; however, when the reduction was carried out in the presence of 0.10 equivalent CB[5], a new SPR signal was observed at 620 nm, and was likely caused by the longitudinal plasmon resonance of 1D aggregates. Larger amounts of CB[5] disrupted aggregation, and caused a blue-shift of the SPR signal, with maxima still at higher wavelengths than the control experiment in the absence of macrocycle; this observation suggested that 3D aggregates were still present in solution. Dynamic light scattering experiments yielded the same conclusions, with Au NP average solvodynamic diameters of 8, 320, 70, 10 and 10 nm in the presence of 0.0, 0.10, 0.20, 0.50 and 1.0 equivalent CB[5], respectively. We note that the aggregation/deaggregation process is reversible and therefore thermodynamically driven, since it can be affected upon subsequent addition of CB[5] to a solution of Au/CB[5] NPs.[381] This phenomenon was exploited by Scherman, who used CB[5] as a "glue" for Au NPs, thereby allowing aggregation of Au NPs as a plasmonic substrate with repeatable, fixed and rigid interparticle separations of 0.9 nm. This concept was applied *in situ* by using CB[7] as a self-calibrated SERS reporter substrate which offered reproducible SERS performance, and could be used for the selective host–guest detection of rhodamine 6G.[382] The same group also described the preparation of Au NP/polymer/CB[8] composites using Au NPs tethered to MV units and an acrylamide-based copolymer linked to electron-rich 2-naphthoxy units. Addition of CB[8] linked the Au NPs to the copolymer upon formation of the ternary MV/naphthoxy/CB[8] complex. Aggregation of the MV-functionalized Au NPs could also be triggered upon reduction with sodium dithionite in the presence of CB[8], since the macrocycle encapsulates the dimers of the reduced MV^{+} radical cation, and thus forms a network of Au NPs.[383] Aggregation is only observed when both CB[8] and the reductant are present in solution. Geckeler reported that 10–16 nm Au NPs could be prepared after a 48 h treatment of potassium tetrachloroaurate with sodium hydroxide in the presence of CB[7], while virtually no reaction was observed after a month in the absence of the macrocycle. The role of CB[7] in the reduction process remains unknown.[384]

Silver nanoparticles (Ag NPs) can also be prepared and stabilized in the presence of CB[n]s, as our group has recently reported. We showed that 5.3 and 3.7 nm monocrystalline Ag NPs could be prepared upon reduction of silver nitrate with sodium borohydride in the presence of CB[7] and CB[8], respectively (see micrographs in Fig. 29c, e, f and i); solutions of these particles, which display a characteristic SPR band at approximately 415 nm (Fig. 29j), have remained stable during at least 10 months.[102] To the contrary, CB[5] and CB[6] induced rapid aggregation and sedimentation. Based on calculations, we proposed that CB[n]s interact with Ag NPs *via* their carbonylated portal, and that the entropically favorable macrocyclic effect (*i.e.* the greater affinity of a guest towards a cyclic host bearing *n* identical binding sites, compared to its affinity towards the *n* separate fragments)[385] enhances the Ag-carbonyl interactions. However, in the case of CB[5] and CB[6], the 5 (or 6) oxygen atoms may not be ideally positioned for Ag binding (an enthalpic impediment). Also, the proximity of the 5 (or 6) partially negative oxygen atoms may enhance partially positive mirror charges on several adjacent silver atoms at the metal surface; such a possible ligand-induced repulsive Ag–Ag interaction may in fact prevent the ligand from properly interacting with the NPs. When the larger and more flexible CB[7] and CB[8]

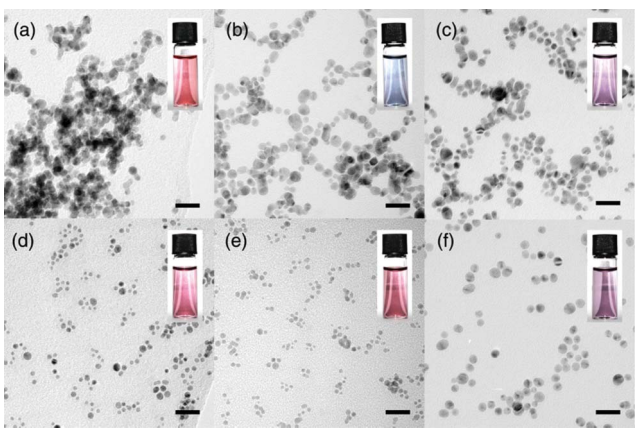


Fig. 28 Transition electron micrographs (TEM) of Au/CB[5] NPs with CB[5]/Au ratios of (a) 0.0, (b) 0.10, (c) 0.20, (d) 0.50, (e) 1.0 and (f) 1.0 with CB[5] being added after the reduction of tetrachloroauric acid (scale bar: 20 nm).[381]

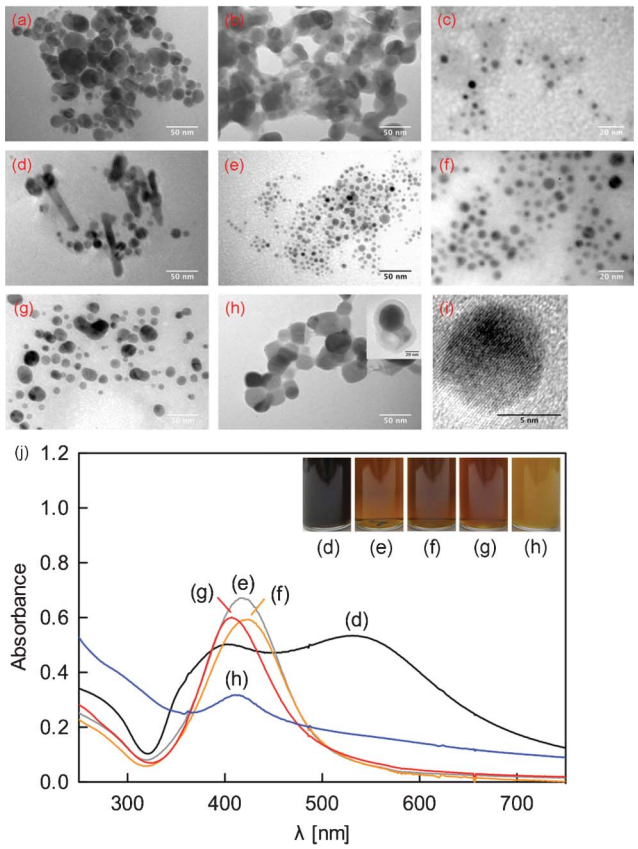


Fig. 29 TEM of (a) Ag/CB[5], (b) Ag/CB[6], (c) Ag/CB[8], (d) Ag/CB[7] (0.10 equiv. CB[7]), (e) Ag/CB[7] (0.50 equiv. CB[7]), (f) Ag/CB[7] (1.0 equiv. CB[7]), (g) Ag/CB[7] (2.0 equiv. CB[7]) and (h) Ag/CB[7] (5.0 equiv. CB[7]). (i) High-resolution TEM of Ag/CB[7] NPs (1.0 equiv. CB[7]). (j) UV-Vis spectra and photographs of Ag/CB[7] assemblies, as represented in TEM (d)–(h). Solutions and suspensions were diluted 10 times immediately before UV-Vis analysis, and suspension (d) was stirred. 1.0 equiv. CB[n] was used in samples (a)–(c). Reprinted with permission from ref. 102. Copyright 2011 American Chemical Society.

are used, their carbonyl oxygens may better adapt to the structural and electronic requirements of the Ag surface, and the entropic gain attributed to the macrocyclic effect would over-compensate the enthalpic penalty for a slight deformation of the CB[n] unit.

We also showed that the optimal silver nitrate/CB[7] ratio for the formation of stable Ag NPs (Ag concentration 1.0 mM) is 1 : 1 – 2 : 1, while large excesses or low substoichiometric amounts of CB[7] trigger aggregation (see Fig. 29). Surprisingly, masking the portals of CB[7] by encapsulating a guest substituted with bulky groups had only a minor effect on the stability of the Ag NPs; in this case, CB[7] probably interacts with Ag *via* a fraction of its carbonyl oxygen atoms.[102] Similarly to Au NPs, Geckeler showed that narrowly-dispersed Ag NPs (approximately 6 nm) could be prepared upon reaction of silver nitrate with sodium hydroxide in the presence of CB[7]; again the mechanism is unclear. These Ag NPs were cytotoxic towards two cancer cell lines (MCF-7 and NCI-H358) at approximately 10 μg mL^{-1} after a 24 h incubation period.[386]

De la Rica and Velders recently reported the formation of nanopore assemblies upon combination of silver nitrate (0.10 mM) with CB[7] (1.0 mM). Addition of thioacetamide as a sulfide source triggered the formation of silver sulfide nanoclusters (approximately 20 nm), whose size matches well the dimensions of the nanopore assemblies (*i.e.* the silver sulfide nanoclusters grow in the nanopores). Using high-resolution TEM, the authors showed that the nanoclusters were composed of perfectly aligned nanocrystals (< 1 nm)![387] Recently, Demets prepared lead iodide nanodisks (5–34 nm wide, 0.7 nm thick) upon reaction of potassium iodide (2.0 mM) with a 1 : 1 mixture of CB[7] and lead nitrate (1.0 mM) and sedimentation over two days.[388] Cao prepared 3 nm palladium NPs upon treatment of palladium chloride with sodium borohydride in the presence of CB[6]; depending on the Pd/CB[6] ratio, contamination with triangular and cubic assemblies took place. These Pd NPs were found to be efficient catalysts in the Suzuki–Miyaura coupling of aryl halides (including less reactive aryl chlorides) with arylboronic acids (0.50 mol% Pd/CB[6] in a 1 : 1 ethanol-water mixture); the catalyst could be recovered easily, afforded high yields even after 5 cycles, and could be stored under aerobic conditions.[389]

5.5.4 Fullerenes. Due to the enormous interest that these species have generated in the past quarter of a century, we devote a separate section to the intriguing interaction between carbon allotropes and CB[n]s. Geckeler showed that [60]fullerene (C_{60}) forms a 2 : 1 complex with CB[7] upon addition of C_{60} to an alkaline solution of CB[7] and stirring during 24 h; unlike C_{60} which is soluble in toluene, the dark brown complex was insoluble in all common organic solvents and acidic solutions. Alternatively, C_{60} and CB[7] can be grinded using a mixer mill during 4 h, and the resulting powder washed with water (pH 12) and toluene to eliminate the unreacted partners. Although the structure of the assembly remains unclear, CB[7] may interact with the two fullerenes *via* its carbonylated portals.[390–392] A similar 2 : 1 complex could also be prepared using CB[8] instead of CB[7].[393] Finally, Ogoshi reported that single-walled carbon nanotubes (SWCNTs) could interact with CB[7] upon addition of the macrocycle (3.5 mM) to a suspension of SWCNTs in water (0.20 mg mL^{-1}) and sonication during 3 h. Approximately 80% of the SWCNTs were then removed by centrifugation, leaving a homogeneous black supernatant that remained stable for over a month (while raw SWCNTs are insoluble in water)! Addition of 1-adamantylamine (**9b**), which binds strongly to CB[7], triggered aggregation, thereby confirming the interaction between the macrocycle and SWCNTs. Even more surprisingly, and contrary to CB[7], CB[5] did not improve the solubility of the SWCNTs.[394]

5.5.5 Nanosheets and vesicles. Li reported that upon a 1 min ultrasonic treatment of a mixture of CB[8] (0.10 mM) and quinoline (2.0 mM) followed by a 3 h standing period, square CB[8] nanosheets could be obtained, with edge lengths ranging from 0.2 to approximately 3 μm (see Fig. 30). Remarkably, two thirds of the nanosheets bear a rather uniform thickness (1.7–2.1 nm; average 1.8 nm), which corresponds to the outer diameter of CB[8]. Scanning tunneling microscopy (STM) shows that the CB[8] portals are perpendicular to the sidewalls of each of their neighbors, with a 1.66 nm square lattice measured by powder X-ray diffraction, in agreement with the binding

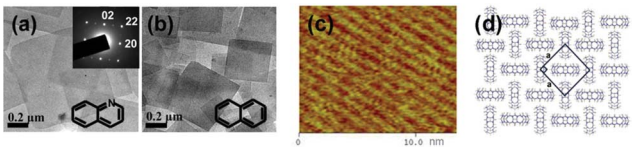


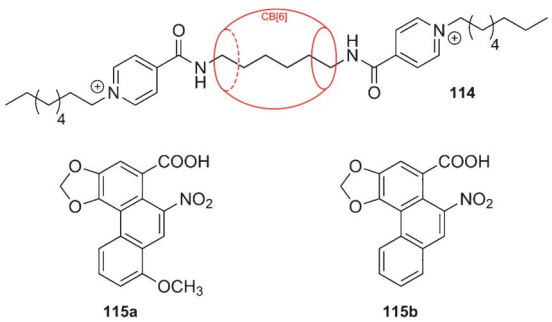
Fig. 30 TEM images of (a) CB[8]/quinoline and (b) CB[8]/naphthalene nanosheets. (c) STM image, and (d) proposed molecular packing of the nanosheets.[395]

model.[395] Similar results were obtained with naphthalene, styrene, carbazole and tetrahydronaphthalene, instead of quinoline.

Zhang and Zhou recently showed that the critical aggregation concentration of axle **114** is greatly reduced once surrounded by CB[6] (1.8×10^{-5} and 3.2×10^{-7} M^{-1}, respectively), and that the interlocked assembly could form vesicles (diameter 50–200 nm) that remained stable over a week in aqueous medium. Aggregates of the free guest were much smaller (1–4 nm).[396]

5.5.6 Films and functionalized surfaces. Linking CB[n]s to metal surfaces could lead to various exciting applications, especially in the biosensing field. Unfortunately, as noted by Li and coworkers,[397] the preparation of CB[n] monolayers on surfaces is limited, since they are usually obtained either by threading the macrocycles along surface-bound organic axles,[398–400] or by using functionalized CB[n]s after a difficult synthesis;[16] yet in 2008, the same author showed that a gold electrode could interact efficiently with CB[6], CB[7] and CB[8], once dipped into a 1.0 mM solution of CB[7] or into saturated solutions of the other two analogs during 24 h; rinsing with deionized water did not wash away the macrocycles. Moreover, upon dipping into a 5.0 mM ferrocene solution in acetonitrile, gold-bound CB[7] could trap the guest in its cavity while remaining anchored to the metallic surface; as expected, the CB[6]-functionalized surface did not interact with ferrocene.[397] Jonkheijm and Brunsveld applied this method to the immobilization of the yellow fluorescent protein YFP on a CB[7]-functionalized gold surface, by linking the protein to a ferrocene unit that could get anchored into CB[7].[401] A similar method was used by Gallopini to link a MV^{2+}/CB[7] pseudorotaxane to a titanium oxide nanoparticle film; without the macrocycle, MV could not be adsorbed on the metal oxide surface. MV^{2+} could also be electrochemically reduced to its radical cation, affording deep blue films.[402] Demets reported a method to form thin films of CB[6] on glass, fluorine doped tin oxide (FTO) glass electrodes and gold surfaces, by dipping those into a solution of CB[6] in aqueous ammonia, followed by heating to remove the excess ammonia. Successive horizontal layers of CB[6] could be deposited in this way.[403] In a recent study, Quintana and coworkers coated a glassy carbon electrode with a Nafion/CB[8] mixture, and applied it to the quantitative analysis of tryptophan in human serum.[404] CB[6] and CB[7] could also be intercalated into Zn_2Al layered double hydroxides, and released upon addition of a suitable cationic guest.[405] Finally, we note the straightforward method developed by Demets to characterize insoluble compounds by cyclic voltammetry: the author showed that a viscous paste of poly(vinyl chloride) and finely powdered CB[6] in tetrahydrofuran could be used to immobilize the insoluble analytes on FTO electrodes.[406]

CB[n]s are also promising tools in the separation and purification of high-value compounds, since they can interact with both the surface of stationary phases and the target molecule. As a proof of concept, Feng and Wu showed that the separation of the *ortho*, *meta* and *para*-isomers of nitrotoluene, nitrophenol, nitrophenolate and nitroaniline by capillary electrophoresis could be greatly improved if CB[7] (5.0 mM, 15% methanol in a phosphate buffer) were adsorbed onto the inner wall of the capillary.[407] Using the same method, the very similar aristolochic acids **115a** and **115b** could be separated with a CB[7]-enriched phosphate buffer (3.0 mM CB[7], 10% aqueous acetonitrile).[408] CB[n]s can also be applied to the separation of mixtures of peptides, as recently shown by Scherman and coworkers. In this case, a gold surface was decorated with CB[8]-bound viologen units linked to gold-anchored alkanethiol chains; the modified surface was found to selectively recognize a peptide bearing a Trp residue upon formation of the ternary MV Trp CB[8] complex. The peptide could then be released by electrochemical reduction of MV and isolated.[400]



5.5.7 Hydrogels. Stimuli-responsive hydrogels have generated a lot of interest in the past few years, due to their promising applications in material science and controlled drug release.[409–411] We have already shown that CB[8] is particularly attractive for the preparation of hydrogels, thanks to their ability to encapsulate two guests in their cavity, and to interconnect polymers[361] (see section 5.5.1 and Fig. 25). Kim found that the slow cooling of a warm solution of CB[7] (3–5 wt%) to room temperature in various diluted acids afforded a CB[7] gel.[412] This gelation is pH-dependent, with an optimum pH range 0–2. At lower pH, the solution remains transparent and, at higher pH, CB[7] precipitates. In 0.50 M sulfuric acid and 3% CB[7], sol-to-gel transition was observed at 42 °C, and gel-to-sol between 43 and 57 °C. Long fibers (> 10 μm), composed of bundles of fibrils, were observed by atomic force microscopy (AFM), with a diameter of the fibrils similar to the dimensions of CB[7] (approximately 1.2 nm). Subsequent X-ray structures unveiled the herringbone structure of the fibrils, with C–H/O hydrogen bonds between the CB[7] units and various contacts with water (see Fig. 31).[412]

Slow cooling of a mixture of CB[7], 1.0 M sulfuric acid and 0.10 equivalent *trans*-4,4′-diaminostilbene dihydrochloride also affords a white gel; yet upon irradiation, *trans*→*cis* isomerization triggers gel-to-sol transition. A subsequent heating/cooling cycle regenerates the gel.[412] Tan and coworkers also showed that hydrogels could be obtained upon cooling a 50 °C solution of butylammonium tosylate (1.8–2.5 M) and CB[6] (35–70 mM); gel-to-sol transitions ranged from 16–26 °C, and bundles of

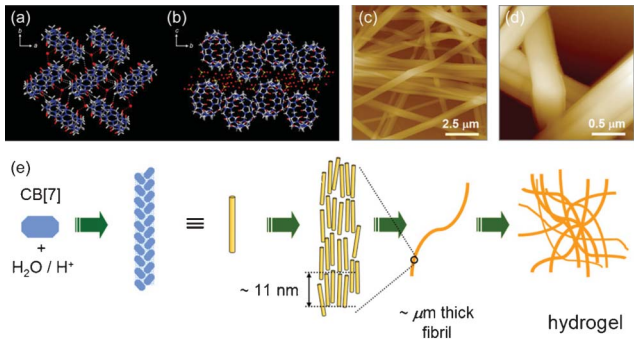


Fig. 31 X-Ray structure of CB[7]: organization on (a) the *ab* plane, and (b) the *bc* plane. Channels between the macrocycles are filled with water, hydronium cations and sulfate anions. (c) and (d) AFM images of the CB[7] gel on a mica substrate. (e) Structure of the CB[7] hydrogel: from macrocycles to bundles of fibrils. Reprinted with permission from ref. 412. Copyright 2007 John Wiley & Sons.

fibers were observed by scanning electron microscopy. Those fibers were also composed of fibrils, which were formed by stacking interactions between the tosylate units.[413]

6. Conclusion and outlook

Thirty years ago, Freeman, Mock and Shih unveiled the structure of CB[6], and noticed that this aesthetically appealing macrocycle could encapsulate alkylammonium cations with high affinity. Only two years later, they reported the remarkable 55 000-fold rate enhancement of the [3 + 2] cycloaddition between an alkyne and an azide inside the cavity of CB[6], paving the way for the design of various interlocked systems and molecular switches. However, the poor solubility of the macrocycle and its unwillingness to undergo chemical modification kept the field rather dormant until the beginning of our millennium. The successful preparation of CB[7] and CB[8], as well as the functionalization of CB[6] then triggered a dramatic increase in the number of articles, reviews and patents published every year.

The popularity of CB[n]s is largely due to their outstanding recognition properties, and to the exceptional strength of their interaction with various guests. In fact, CB[n]s should appear at a prominent position in any supramolecular or bioorganic chemistry textbook, since (1) they display the strongest non-covalent interaction ever measured between a host and a single stable guest (up to 5×10^{15} M^{-1}!), and (2) the affinity reaches or even slightly surpasses the strength of the landmark biotin–avidin interaction (10^{15} M^{-1}). These extreme values are due to a subtle combination of factors, such as (1) the ability of the guests and their substituents sitting close to the CB[n] portals to return as many water molecules as possible to the aqueous environment upon binding (this process is both enthalpically and entropically favorable), (2) the rigidity of the macrocycles coupled to restricted conformational mobility of the free guests, (3) a minimally penalizing loss of solvation energy upon binding, and (4) favorable coulombic interactions between positively charged substituents and the CB[n] rims, as well as multiple hydrogen bonding; we should however point out that the coulombic interaction, which is extreme in the gas phase, is negatively affected in solution by a dramatic loss of solvation energy of the positive guest upon encapsulation. Also, as noted by Nau, it is still unclear to what extent dispersion forces impact the interaction between the very weakly polarizable cavity of CB[n]s and their guests. This contribution is anticipated to be either insignificant or very minor at best.

These recognition properties have allowed the design of new self-organizing and stimulus-controlled supramolecular systems, the use of CB[n]s as removable shields for the controlled release of bioactive agents, and the incorporation of these macrocycles into a series of advanced materials, polymers, nanoparticles, films and hydrogels. The increasing focus on CB[n] applications has been welcomed by Scherman and Nau in a joint address during the 2nd International Conference on Cucurbiturils. Both organizers actually stressed that despite a very successful decade, long-term practical applications of CB[n] chemistry would have to be pursued in order to preserve its momentum; we firmly adhere to that statement.

Still, even thirty years after the elucidation of the CB[6] structure, we like to say that wherever CB[n]s are involved, unexpected and sometimes very unusual results will emerge. This has been true on several occasions during our past three years of excursion into CB[n] chemistry, when for instance, CB[n]s were found to catalyze a silver-promoted desilylation reaction, while we were expecting severe rate retardation (see section 5.3.2). As far as recent, yet to be published results are concerned, there is no end in sight for exciting surprises!

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