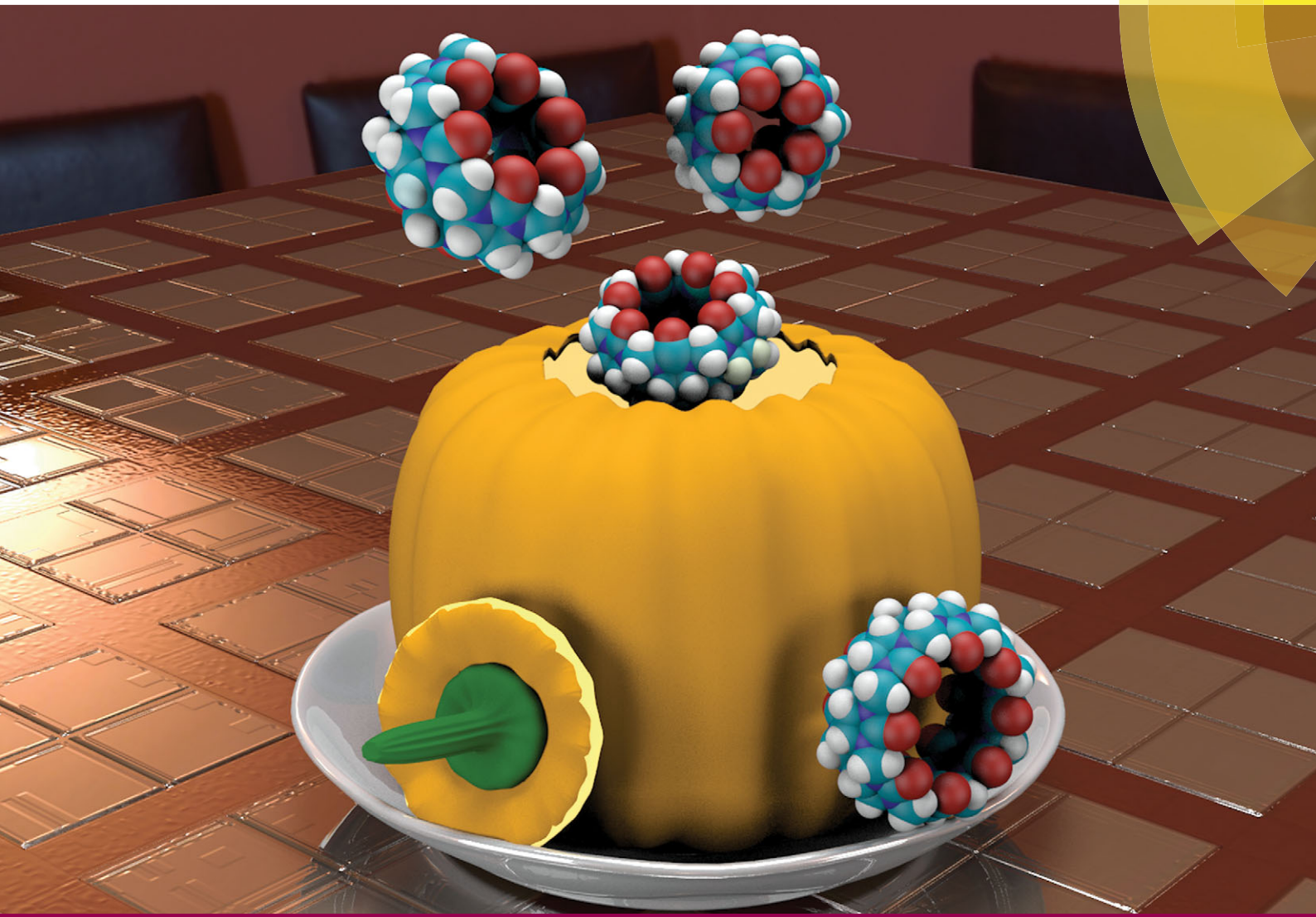
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# Cucurbiturils: from synthesis to high-affinity binding and catalysis

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In the wide area of supramolecular chemistry, cucurbit[*n*]urils (CB*n*) present themselves as a young family of molecular containers, able to form stable complexes with various guests, including drug molecules, amino acids and peptides, saccharides, dyes, hydrocarbons, perfluorinated hydrocarbons, and even high molecular weight guests such as proteins (*e.g.*, human insulin). Since the discovery of the first CB*n*, CB6, the field has seen tremendous growth with respect to the synthesis of new homologues and derivatives, the discovery of record binding affinities of guest molecules in their hydrophobic cavity, and associated applications ranging from sensing to drug delivery. In this review, we discuss in detail the fundamental properties of CB*n* homologues and their cyclic derivatives with a focus on their synthesis and their applications in catalysis.

## 1. Introduction

The chemistry of cucurbit[*n*]urils (CB*n*) is a rapidly developing field (Fig. 1), which has been regularly reviewed from different perspectives.[1–7] Most recently, the synthesis of functionalized derivatives has progressed, and among the manifold applications, cucurbituril-catalyzed reactions are receiving increasing attention, which defines two focus areas of this review. The factors which govern their molecular recognition and high-affinity binding properties are continuously unfolding, such that we also update information pertinent in this

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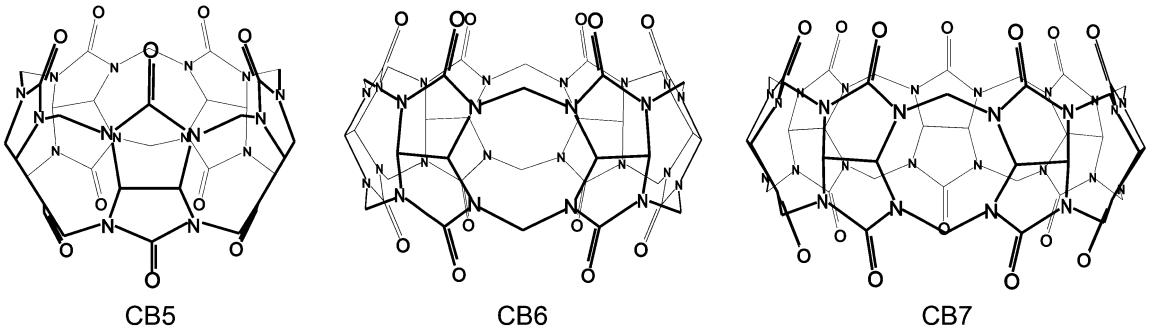



Fig. 1 Molecular structures of the three smallest CB*n* homologues.

fundamental area.[8–11] Biochemical and medicinal-chemical aspects[12–32] are excluded from this review, as are applications in chemosensing,[33–48] which in part have been recently reviewed elsewhere.[49]

## 2. Synthesis

### Synthesis of cucurbituril homologues

In 1905, the parent cucurbituril (CB6) was synthesized by Behrend and coworkers as a sparingly soluble "condensation product".[50] Until today, cucurbiturils are produced by variations of the old synthesis, which involves acid-catalyzed condensation of glycoluril (**1**) and formaldehyde (Fig. 2). The molecular structure of CB6 was uncovered by Mock and coworkers in 1981; Mock also coined the name "cucurbituril", due to the resemblance of its structure to a pumpkin, which in turn belongs to the botanical family *cucurbitaceae*.[51] The group of Kim as well as that of Day varied the reaction conditions (*e.g.*, 80–100 °C, HCl or 9 M $H_2SO_4$, 10–100 h), which proved to be essential to successfully isolate other homologues, including CB5, CB6, CB7, CB8, and CB10·CB5; CB6 remained the major product.[52–54] The precise reaction mechanism of CB*n* was investigated in great detail by the group of Isaacs.[55–58]

Recently, the structure of the yet largest CB*n* member (CB14) has been reported with 14 normal glycoluril units linked by 28 methylene bridges (Fig. 3).[59] The twisted CB14 provided important information that larger CB*n* are actually being formed in the course of CB*n* synthesis.

It should be noted that CB*n* preparation and purification often introduces various impurities, always water and acid, frequently acetone and methanol, and, depending on the isolated homologue, ammonium and alkali metal salts.[53] A number of techniques have been used to assess the purity (specifically the CB*n* content) of CB*n* samples, such as NMR, ITC, and TGA. Kaifer and coworkers have described a practical method to assay the purity of CB7 and CB8 based on UV-Vis titrations with cobaltocenium, which forms highly stable complexes with CB7 and CB8.[60]

### Synthesis of cucurbituril derivatives

Functionalized CB*n*, inverted-CB*n*, nor-*sec*-CB*n*, and various congeners have also been discovered (Table 1 and Fig. 4), with

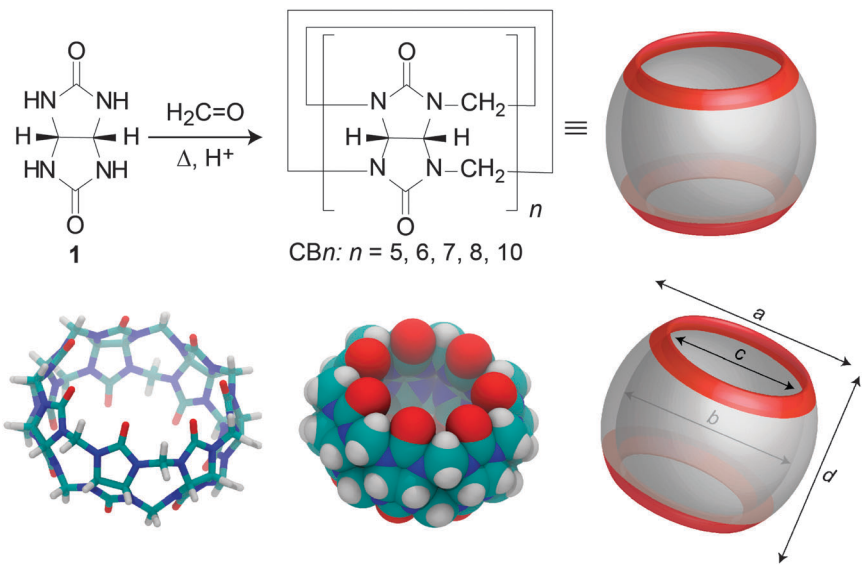



Fig. 2 (Top) Synthesis of CB*n* homologues by condensation of glycoluril (**1**) and formaldehyde under acidic conditions. (Bottom) Different representations of the CB7 structure.

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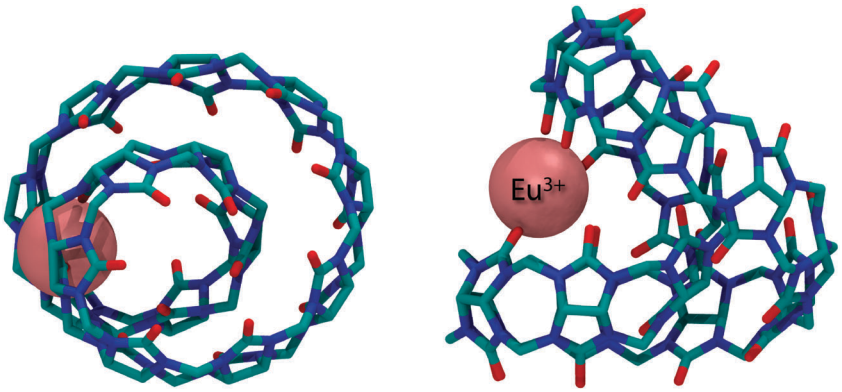



Fig. 3 Top (left) and side (right) view of the X-ray crystal structure of the $Eu^{3+}$ CB14 complex; hydrogen atoms removed for clarity.

Table 1 Timeline of the development of cucurbit[*n*]urils and related cyclic macrocycles

| Year | Compound name | Research group |
|---|---|---|
| 1905 | CB6 (not structurally identified) | Behrend[50] |
| 1981 | CB6 | Mock[51] |
| 1992 | $Me_{10}$CB5 | Stoddart[66] |
| 2000 | CB5,7,8 | Kim[52] |
| 2001 | $CycH_5$CB5, $CycH_6$CB6 | Kim[67] |
| 2002 | $Ph_2$CB6, CB10·CB5 | Nakamura, Day[54,68] |
| 2003 | $(HO)_{2n}$CB*n*, cucurbituril analogues, and partially substituted CB*n* | Isaacs, Kim, Day[69–72] |
| 2004 | $Me_4$CB6, $Me_6$CB6, hemicucurbit[*n*]uril (*n* = 6 and 12) | Day, Tao, Keinan, Miyahara[73–75] |
| 2005 | CB10, iCB*n* (*n* = 6 and 7), hemicucurbit[6]uril | Isaacs, Kim, Buschmann[76–79] |
| 2006 | *ns*-CB10 | Isaacs[80] |
| 2007 | (±)-Bis-*ns*-CB6, $Me_{12}$CB6 | Isaacs, Tao[81,82] |
| 2008 | Partially substituted CB*n*: $Me_n$CB*n* (*n* = 5 and 6), and $CycH_n$CB6 | Tao[83–86] |
| 2009 | Partially substituted $CycP_n$CB6 | Tao[87] |
| 2010 | Bambus[6]uril (Bu6) | Sindelar[88] |
| 2011 | (No new member reported) | |
| 2012 | Monofunctionalized CB6, monofunctionalized CB7 | Scherman, Isaacs[89–91] |
| 2013 | CB14, norbornahemicucurbiturils, dimeric cucurbit[6]uril, and cyclohexylhemicucurbit[6]uril | Tao, Sindelar, Isaacs, Aav[59,92–94] |
| 2014 | Monosubstituted CB6 at methylene bridge (mPhCB6) | Sindelar[95] |

essentially a new member reported in every year since 2000. Due to their enhanced cavity size and solubility, the new members display a range of novel applications, including their use for supramolecular vesicles, fluorescence sensing, drug delivery, catalysis, *etc.*[22,25,31,44,48,61–65]

The first modified CB*n* was reported by Stoddart in 1992, who synthesized the fully equatorially methylated CB5 ($Me_{10}$CB5).[66] Later, the group of Kim isolated the fully substituted cyclohexanecucurbit[*n*]urils ($CycH_5$CB5 and $CycH_6$CB6), that are soluble in organic solvents and, surprisingly, also 170 times better soluble in water than parent CB6.[67,96] Many partially substituted CB*n* and mixtures thereof have been obtained (Scheme 1 and Fig. 5).[53,68–73,82,84,85,87,96–101] The reactions of substituted glycolurils so far reported favor invariably the formation of the smaller CB*n* homologues, CB5 and CB6. In fact, no fully substituted CB7 or CB8 have been isolated. Since alkylation of CB*n* does not enable functionalization, Kim introduced in 2003 a direct method to produce fully hydroxylated CB*n* by oxidation of unsubstituted CB*n* under harsh conditions (hot $K_2S_2O_8$). The resulting prehydroxyl–CB*n* could be easily modified to provide tailored CB*n* derivatives with different functional groups, frequently accompanied by an enhanced solubility in common organic solvents.[72]

Isaacs *et al.* reported the isolation of inverted cucurbit[*n*]urils (iCB*n*, Fig. 6), which contain a single inverted glycoluril unit directed towards the inside of the CB cavity.[78] iCB6 and iCB7 were isolated either by gel permeation chromatography or by fractional crystallization. Heating of iCB6 or iCB7 in concentrated HCl resulted in the conversion into mixtures of (regular) CB*n*.[102] An indication for the reverse process, interconversion of CB7 to iCB7, has recently been obtained in the gas phase.[103] Until now, the inverted derivatives have not found any specific application.

Recently, different monofunctionalized CB7 derivatives have been synthesized by Isaacs[91] through reaction of the acyclic glycoluril hexamer with a glycoluril bis(cyclic ether) (Scheme 2b). Further, the monofunctionalized CB7 with a chloroalkyl tether can be transformed into the azide functional group, such that other substrates can be conveniently conjugated *via* click chemistry (Scheme 2b). The high water solubility of the monofunctionalized CB7 (>250 mM) and their host–guest recognition properties will render them solubilization agents for poorly soluble drug molecules and promising candidates for labeling and chemosensing applications as well as surface modification.

A new related macrocycle, prepared by the acid-catalyzed condensation of 2,4-dimethylglycoluril and formaldehyde, was named bambus[6]uril (Fig. 7), Bu6, which combines the

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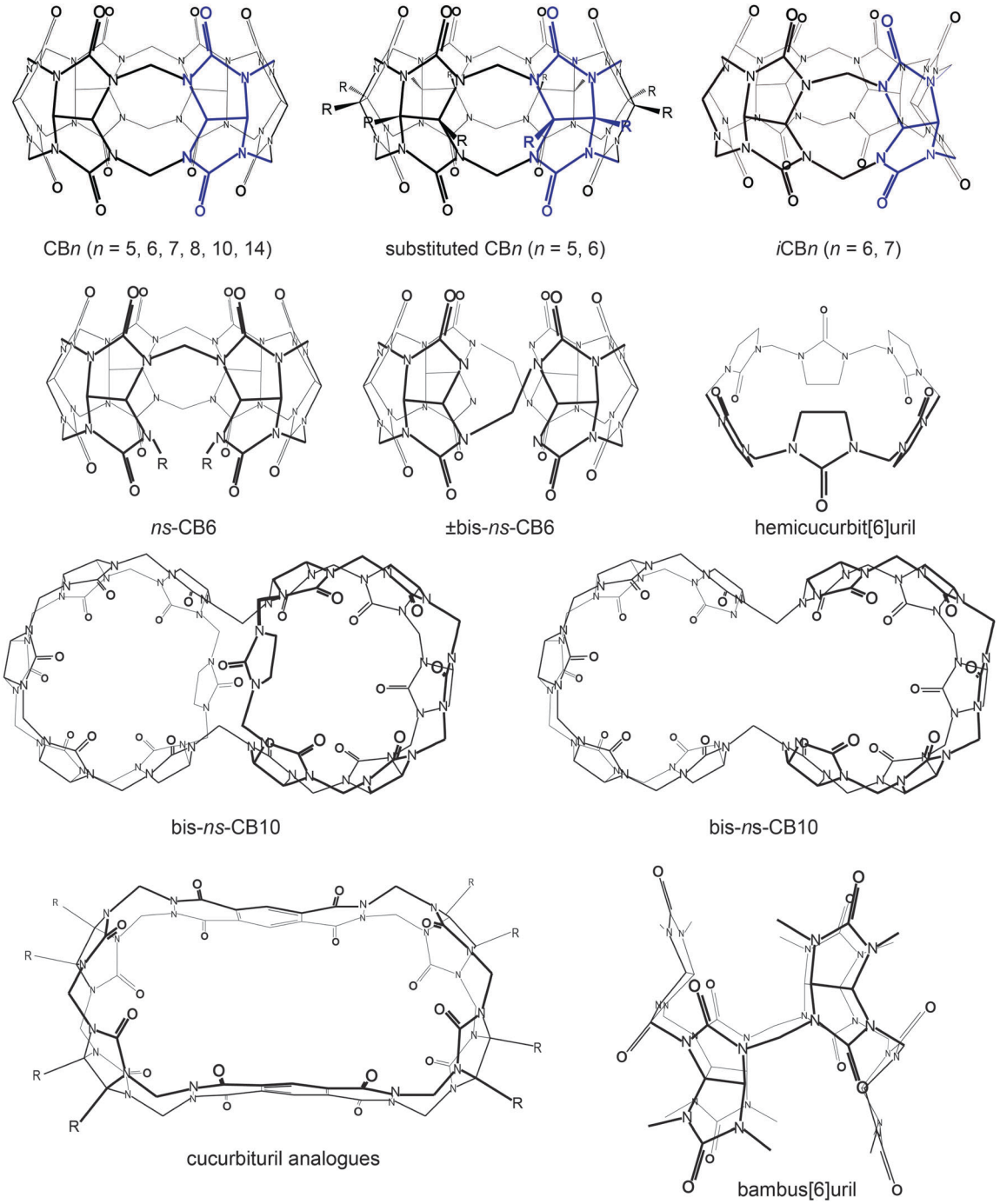


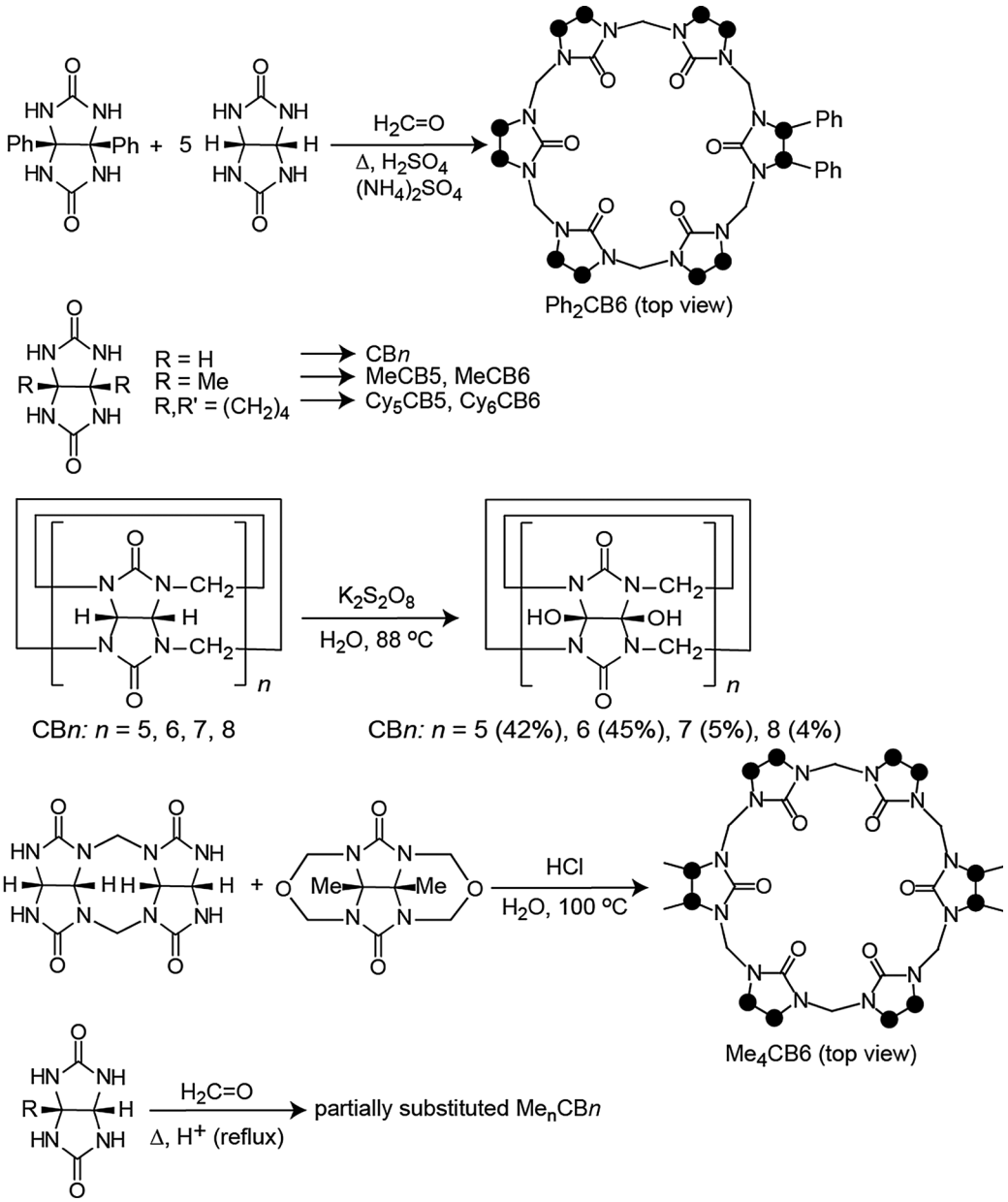

Fig. 4 Molecular structures of different cucurbit[*n*]urils and related cyclic macrocycles; blue parts indicate repetition units varying with *n*.

structural features of both, cucurbiturils and hemicucurbiturils. Bu6 acts, however, as an anion receptor, *e.g.*, it was shown to bind halide anions through C–H···$X^-$ interactions.[88,104,105]

By introducing new aldehydes to the reaction mixture of glycoluril and formaldehyde, Sindelar and coworkers have also synthesized the first example for a monosubstituted cucurbituril on the methylene-bridged position (Scheme 3). The most promising result was obtained with 3-phenylpropionaldehyde: (2-phenylethyl)-CB6 was isolated from the crude mixture in 0.2% yield.[95]

Other prominent derivatives include bis-nor-*sec*-CB10[80] and nor-*sec*-CB6,[81] which were synthesized by the group of Isaacs. Bis-nor-*sec*-CB10 has a similar structure as CB10, but lacks two methylene bridges which results in two symmetrically interconnected cavities (Fig. 8). Nor-*sec*-CB6 (Fig. 4) is structurally comparable to CB6 but lacks a single methylene bridge. The removal of another methylene bridge results in (±)-bis-nor-*sec*-CB6 (Fig. 4), the first reported chiral member of the CB*n* family.

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Scheme 1 Representative synthetic procedures for different cucurbituril derivatives; see Table 1 for references; dots mark connection points to the second identical half of the symmetric structures.

## 3. Physical properties and peculiarities of the cucurbituril cavity

The defining structural features of the CB*n* family are their highly symmetric structure, with negatively charged carbonyl rims and a hydrophobic cavity. The electrostatic potential map of CB*n* visualizes the high electron density at the carbonyl oxygens (Fig. 9) and clearly illustrates their cation-receptor functionality. Their inner cavity, however, has neither functional groups nor electron pairs pointing towards the inside. It therefore cannot engage in hydrogen-bonding interactions, which – along with the non-dipolar nature of the macrocycle itself – provides an intuitive rationale for the high hydrophobicity of the cavity.

### Polarity and polarizability

Understanding the unique binding of cucurbiturils requires an understanding of the physical microenvironment of the inner cavity. When a guest is encapsulated within the inner cavity of CB, its absorption, fluorescence, and NMR spectra usually change. Such complexation-induced spectral shifts suggest changes in the surrounding electronic and/or magnetic environment. Several solvatochromic dyes have been utilized to probe the cavity of CB*n*.[36,106] These probes are well known to display characteristic changes in their absorption, fluorescence, or phosphorescence spectra as the polarity of the (solvent) environment varies. For example, for CB7, the absorption spectra of rhodamine 6G signal the immersion in a less polar

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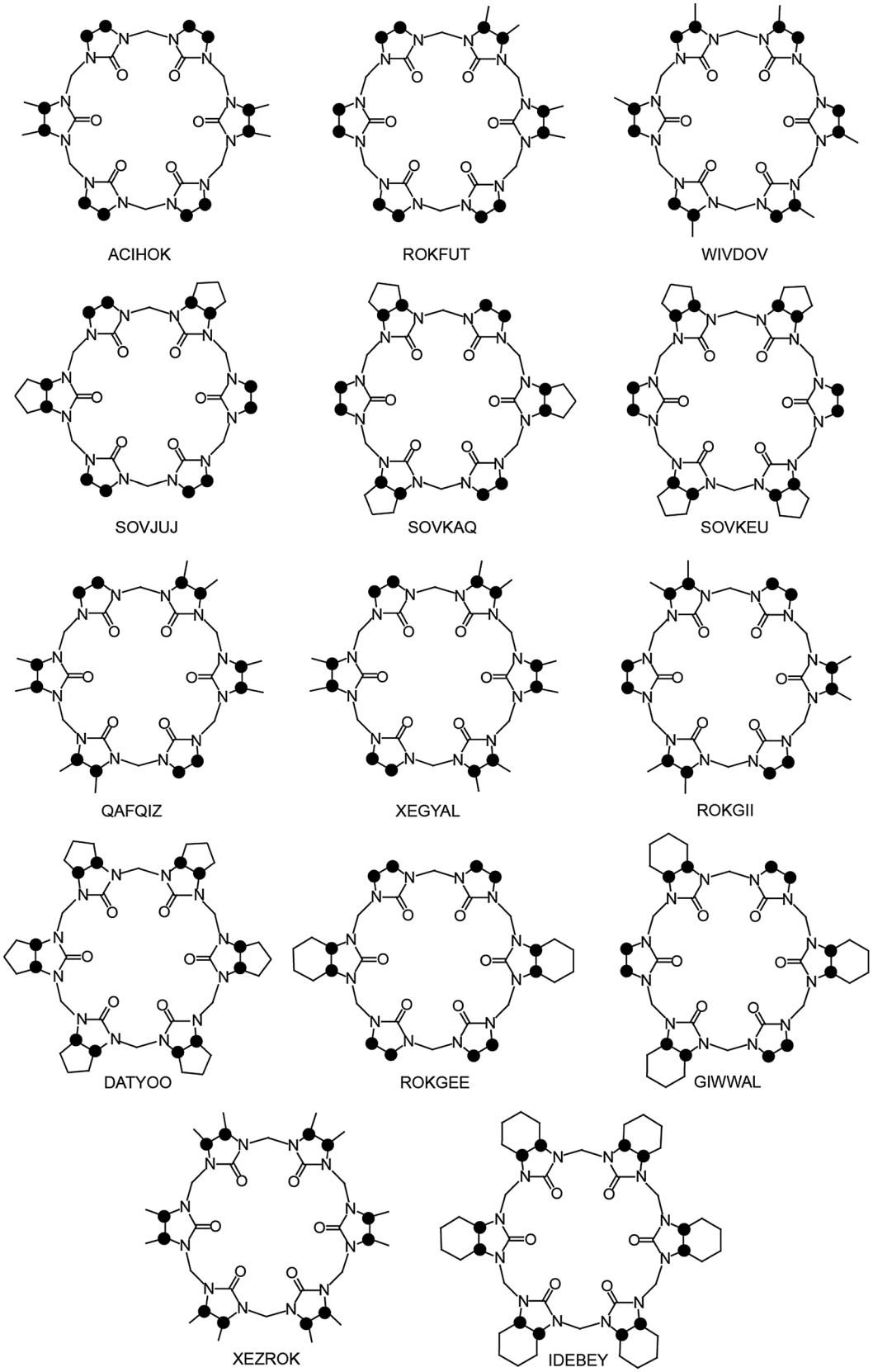



Fig. 5 Top views of the reported XRD molecular structures of substituted CB6 derivatives (codes taken from the CCDC data base); see Table 1 for references; dots mark connection points to the second identical half of the symmetric structures.

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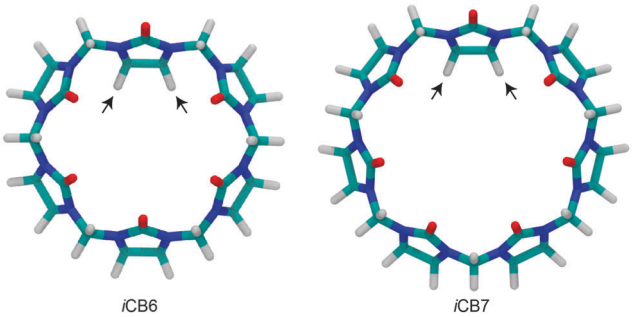



Fig. 6 Inverted cucurbiturils, iCB*n* (*n* = 6 and 7); arrows indicate inverted glycoluril units; see Fig. 4 for the molecular structure.

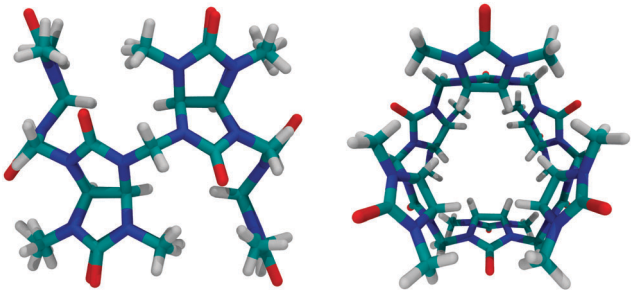
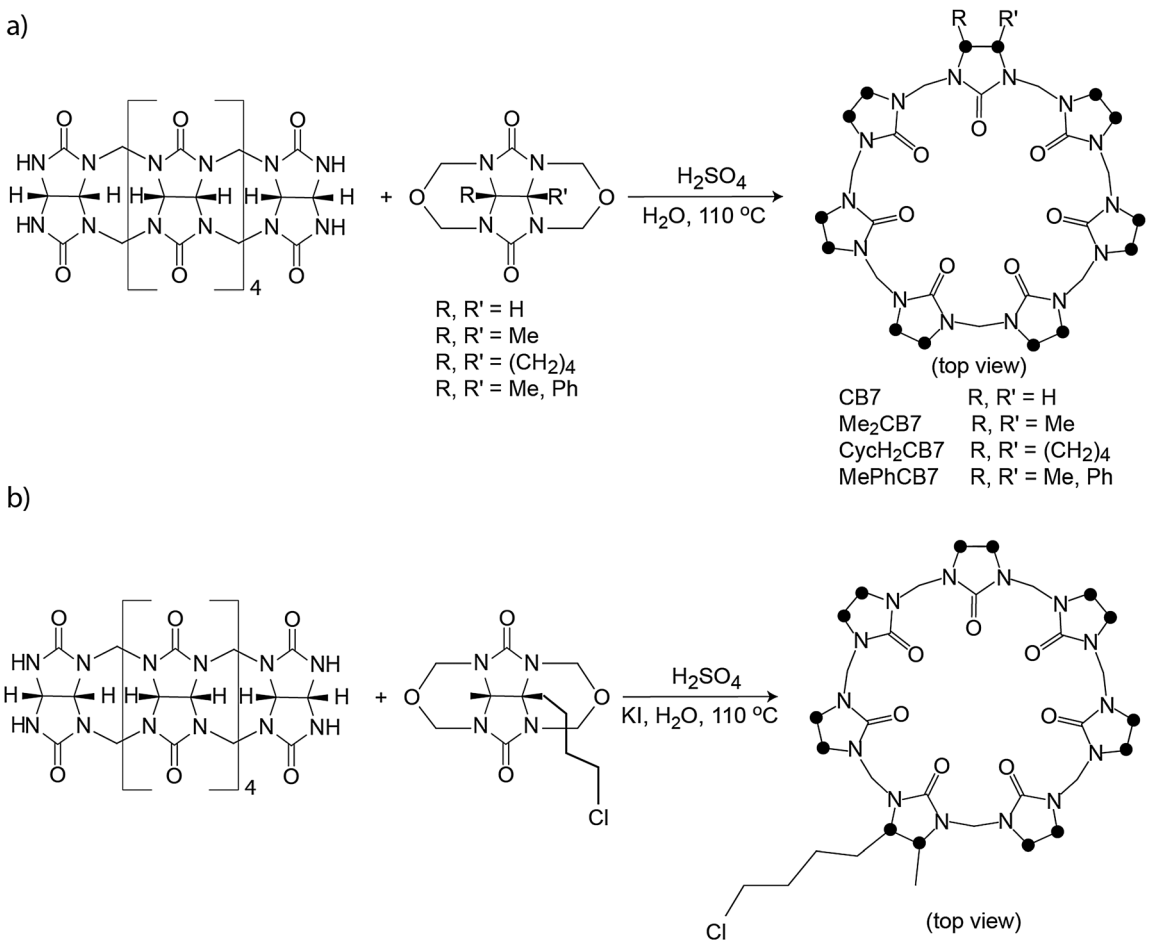


Fig. 7 Side and top views of bambus[6]uril; see Fig. 4 for the molecular structure.

environment when the dye is encapsulated. A polarity similar to that of alcohols (*n*-octanol, $\varepsilon = 10.3$) has been reported for CB7,[107] similar to the polarity determined for the cavities of other water-soluble macrocycles such as cyclodextrins or calixarenes. However, while CB*n* hosts have a nonpolar inner cavity and are themselves not dipolar, they display a very high quadrupole moment,[8] which allows higher-order electrostatic interactions. These have been implicated to account for the equatorial orientation of dipolar guests, such as ketones, in their cavity to achieve optimal quadrupole interactions.[8,108] In contrast to the low polarity of the inner cavity of CB*n*, the portal regions of CB*n* have expectedly a more polar microenvironment.[109]

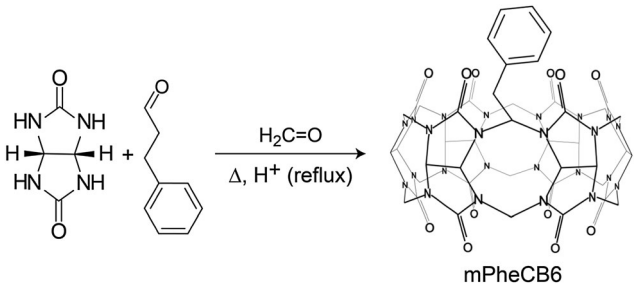
Beyond the relatively low polarity, we have shown that the inner cavity of CB*n* macrocycles has an extremely low polarizability/refractive index, which is closer to the gas-phase than to that of any other known solvent.[110,111] The polarizability was initially detected using DBO (2,3-diazabicyclo[2.2.2]oct-2-ene),




Scheme 2 (a) Synthesis of $Me_2CB7$, $CycH_2CB7$, and MePhCB7. (b) Synthesis of a monofunctionalized CB7 derivative; dots mark connection points to the second identical half of the symmetric structures.


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Scheme 3 Synthesis of the methylene bridge-monosubstituted cucurbituril mPheCB6.

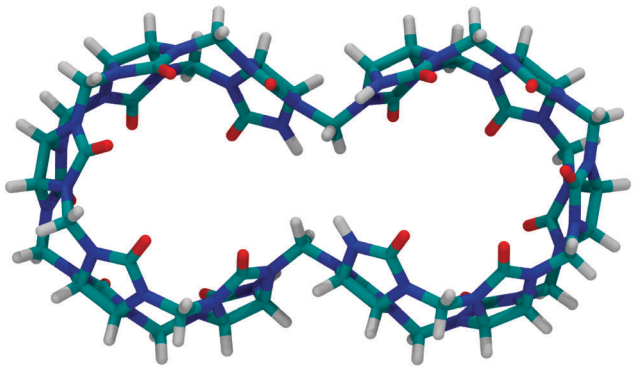


Fig. 8 Top view of bis-nor-*sec*-CB10; see Fig. 4 for the molecular structure.

a neutral azoalkane, as a spectrophotometric probe.[110] Its spherical shape and small size (111 Å$^3$) allow it to be fully immersed inside the size-complementary cavity of CB7 (242 Å$^3$) as well as that of other, similarly sized, water-soluble macrocycles, in particular β-cyclodextrin and *p*-sulfonatocalix[4]arene. A linear correlation between the inverse oscillator strength of the near-UV absorption band of DBO and the polarizability of different solvents was established, which could be subsequently used to interpolate or extrapolate the polarizability of several macrocyclic cavities, including CB7, cyclodextrins, and calixarenes (Table 2). The results showed that the CB7 interior has an extremely low polarizability (0.12), far below that of the two other macrocycles, which showed polarizabilities between those of water and benzene. The low polarizability of the CB*n* cavity can be rationalized along several lines: (i) there are no bonds or lone electron pairs pointing to the inside, (ii) the hosts are non-aromatic, (iii) any residual electron density at the nitrogens is mesomerically delocalized to the carbonyl oxygens, and, potentially, (iv) the packing is sufficiently loose to avoid close guest-to-wall contacts, *e.g.*, the packing coefficient (PC) of DBO in CB7 is only 46% and therefore relatively loose, leaving some "vacuum". For further discussion on PC arguments, see below and ref. 8.

Table 2 Refractive index and polarizability inside macrocyclic host molecules and different supramolecular environments, relative to those in selected solvents and the gas phase, taken from ref. 111

| Environment | Refractive index ($n$)[a] | Polarizability ($P$)[b] |
|---|---|---|
| Gas phase | 1.000 | 0.000 |
| CB7[c] | 1.17 | 0.11 |
| Perfluorohexane | 1.252 | 0.159 |
| β-Cyclodextrin | 1.33 | 0.20 |
| $H_2O$ | 1.333 | 0.206 |
| SDS micelles | 1.34 | 0.21 |
| *n*-Hexane | 1.375 | 0.229 |
| Triton XR-100 micelles | 1.38 | 0.23 |
| POPC liposomes | 1.38 | 0.23 |
| DMe-β-CD (2 : 1 complex)[d] | 1.39 | 0.24 |
| Calixarene[e] | 1.41 | 0.25 |
| Benzene | 1.501 | 0.295 |
| Diiodomethane | 1.742 | 0.404 |
| Hemicarcerand[f] | 1.86 | 0.45 |

[a] Refractive index, converted using the formula $P = (n^2 - 1)/(n^2 + 2)$. [b] From the empirical relationship ($1/f = 3020–8320P$) by using the oscillator strength ($f$) of DBO chromophore as a solvatochromic probe. [c] For equatorial chromophore orientation; values for axial chromophore alignment are $n = 1.19$ and $P = 0.12$. [d] Heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin. [e] *p*-Sulfonatocalix[4]arene, for equatorial chromophore orientation; values for axial chromophore alignment are $n = 1.43$ and $P = 0.26$. [f] Value determined using biacetyl as solvatochromic probe, *cf.* ref. 110.

By exploiting DBO as a fluorescent probe, the low polarizability inside CB7 could be independently confirmed through very long radiative lifetimes, which are theoretically expected to increase as the refractive index of the environment, that is, its polarizability, decreases. Further independent evidence for the unique electronic environment offered by the interior of CB7 has recently been reported by Czar and Jockusch.[112] The authors used acridine orange ($AOH^+$) as a probe to compare the gas-phase fluorescent properties of the free dye and its CB7 complex with that in aqueous solution. The excitation maxima of the dye in vacuum and in CB7 were the same, regardless of whether the CB7·$AOH^+$ complex is itself in the gas phase or in aqueous solution. This result supports the finding that the cucurbituril interior is indeed "gas-phase-like".

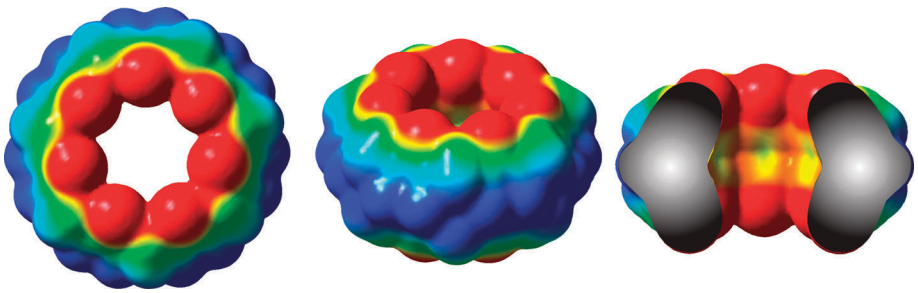


Fig. 9 Electrostatic potential map (top and side view) of CB7, revealing the negatively charged carbonyl portals (in red).

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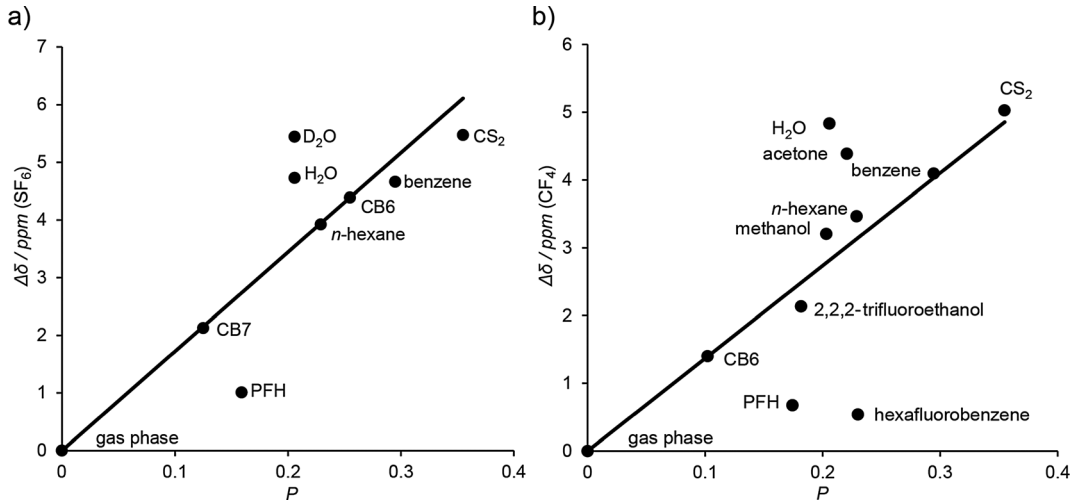



Fig. 10 Linear correlation of the $^{19}F$ chemical shift in the gas phase, different solvents, and in the complexes with CB6 and CB7 *versus* the polarizability (*P*) of the environment (a) for $SF_6$ and (b) for $CF_4$ as solvato-resonant polarizability probes. The chemical shifts (down-field) are relative to the gas phase. The polarizabilities of the CB6 and CB7 cavities were interpolated from the correlations, see text and ref. 45.

Most recently, we have involved NMR to further test the much debated hypothesis of a unique "phase of matter" inside cucurbiturils.[45] In detail, we took advantage of the fact that $^{19}F$ chemical shifts do not strongly depend on magnetic shielding effects (such as $^{1}H$ NMR shifts), but rather on the polarizability of the immediate surrounding of the F atoms.[113,114] In an unconventional approach, $SF_6$ and $CF_4$ were used as "solvato-resonant" probes for the polarizability (*P*) by establishing a linear empirical correlation between the $^{19}F$ chemical shift and the polarizability of different solvents as well as the gas phase (Fig. 10). The polarizability of the CB7 cavity, interpolated from the $^{19}F$ chemical shift of the CB7·$SF_6$ complex, was found to be higher ($P$ = 0.13) than that of the gas phase ($P \equiv 0.00$) but lower than that of water ($P$ = 0.21), a result which is well in line with previous results obtained by optical spectroscopy.[36,106,110,112] $CF_4$ did not bind to CB7, but could be used as a solvato-resonant probe for CB6; in this case, the interpolated polarizability ($P$ = 0.10) was found to be even somewhat lower than the value obtained for $SF_6$ inside CB7.[115]

## Structural features

Table 3 lists pertinent structural parameters of common CB*n* homologues and stereoisomers. In contrast to many other macrocyclic hosts, CB*n* have a very rigid structure (borne out, for example, by small distortions in various crystal structures)[116,117] which renders the definition of the cavity parameters particularly informative. In detail, all CB*n*, ($n$ = 5–8 and 10), have the same height ($d$ = 9.1 Å) but show large variations in cavity width (Table 3). It can be seen that the cavity width of CB10 is slightly too small to allow equatorial encapsulation of CB5. Indeed, the X-ray structure of the CB10·CB5 complex showed that CB5 sits diagonally to the axis of CB10.[54]

The key-and-lock principle for macrocyclic hosts requires a complementarity between the guest size and the volume of the binding site to allow the formation of an inclusion complex. It has been shown that the "inner" cavity of CB*n* (Fig. 11) is best suited to assess this complementarity and to evaluate binding strengths on grounds of PC arguments (see next Section).[8] As can be seen from Table 4, the sizes of the inner CB*n* cavities span a very large range from 68–691 Å$^3$, those of the inverted iCB*n* diastereoisomers are expectedly slightly smaller.

Table 3 Structural parameters of CB*n* and iCB*n*; see Fig. 2

| | Outer diameter | Inner cavity | | Height |
|---|---|---|---|---|
| | *a* | *b* | *c* | *d* |
| CB5 | 13.1 | 4.4 | 2.4 | 9.1 |
| CB6 | 14.4 | 5.8 | 3.9 | 9.1 |
| CB7 | 16.0 | 7.3 | 5.4 | 9.1 |
| CB8 | 17.5 | 8.8 | 6.9 | 9.1 |
| CB9[a] | 19.0 | 10.3 | 8.6 | 9.1 |
| CB10[b] | 20.0 | 11.7 | 10.0 | 9.1 |
| iCB6[c] | 10.7–14.4 | 3.8–5.8 | 4.3–3.9 | 9.1 |
| iCB7[c] | 11.2–16.0 | 5.4–7.3 | 6.7–5.4 | 9.1 |

[a] Values were calculated for the geometry of CB9 optimized by the B3LYP/6-311G** method. [b] Average determined from the crystal structure with the CCDC code COQWOV, ref. 55. [c] Range defined by the shortest and longest wall-to-wall distances; determined from the crystal structures of iCB6 and iCB7 with the CCDC codes NEBDII and NEBDEE, respectively, from ref. 78.

## Packing coefficient

Rebek and Mecozzi introduced the packing coefficient (PC), that is, the ratio of the guest size and the host cavity volume, as an estimator of the steric goodness of fit of host–guest inclusion complexes.[118] A value of *ca.* 55% was found to give the best binding affinities for the resulting host–guest complexes, while larger or smaller values were associated with lower affinities. Although the packing rule was originally derived for capsules as hosts, it has proven useful for several other macrocyclic receptors, particularly cucurbiturils.[8] It has not been written down yet that the number of 55% is actually a natural one as far as water-soluble host–guest systems are concerned: the packing coefficient of water in water, for example, is also 55%, meaning that each water molecule ($V$ = 17.0 Å$^3$) has on average 45% void

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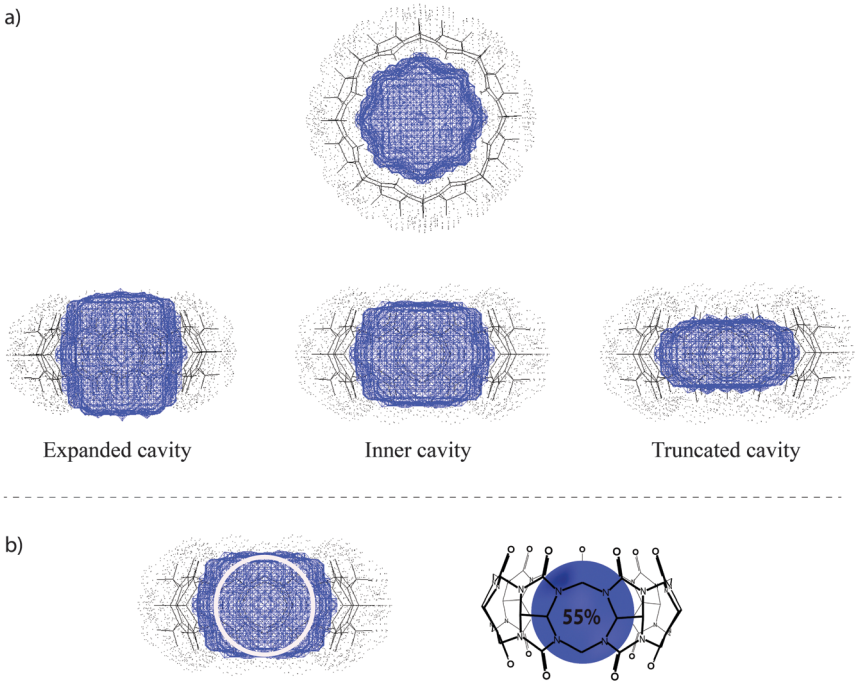



Fig. 11 (a) Top and side views of different cavity definitions, taken from ref. 8. Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) Schematic illustration of an ideal cavity filling of 55% by encapsulation of a spherical guest.

Table 4 Calculated volumes ($V$/Å$^3$) of the inner cavities of CB$n$ and iCB$n$[8]

| Host | $V$/Å$^3$ | Host | $V$/Å$^3$ |
|---|---|---|---|
| CB5 | 68 | CB7 | 242 |
| iCB6[a] | 121 | CB8 | 367 |
| CB6 | 142 | CB9 | 515 |
| iCB7[a] | 221 | CB10 | 691 |

[a] Values calculated in analogy to ref. 8.

Table 5 Occupancy of the inner cavity of CB$n$ with water molecules[8]

| | Number of water molecules in inner cavity | | |
|---|---|---|---|
| CB$n$ | MD simulation | PC analysis | $\Delta E_{pot}$[a] (kJ mol$^{-1}$) |
| CB5 | 2 [2.0][b] | 2 | −41.6 ± 28.8 |
| CB6 | 4 [3.3][b] | 4 | −51.1 ± 29.0 |
| CB7 | 7 [7.9][b] | 8 | −102.4 ± 31.3 |
| CB8 | 10 [13.1][b] | 12 | −66.2 ± 10.7 |
| CB9 | 14 | 16 | — |
| CB10 | 20 | 22 | — |

[a] Difference in potential energy for the removal of all cavity water molecules and transfer of those to a spherical cavity in the aqueous bulk, see ref. 120. [b] Values from ref. 120 are given in square brackets.

space at its disposition. The enthalpic minimum (estimated from the Lennard-Jones potential with $\varepsilon_0 = 1.12\sigma$), lies at 71% for a spherical cavity, which is higher because of the neglect of entropy, the consideration of which lowers the ideal PC value.

We have previously demonstrated that PC arguments can be successfully applied to predict the stability of CB$n$ complexes.[8] The analysis of packing coefficients for representative sets of known guests with clearly defined hydrophobic binding motifs revealed average values of 47% for CB5, 58% for CB6, 52% for CB7, and 53% for CB8, which are well in line with the ideal packing (55% solution). In general, guests with associated packing coefficients of higher than 75% do not form stable inclusion complexes as a consequence of the associated entropic penalty unless additional interactions (such as ion–dipole ones) are at work. On the other hand, guests with packing coefficients lower than 30% also do not form stable complexes. Therefore, while the absolute PC values are only an empirical estimator, stable inclusion complexes result within the PC range of 45–65%.

### Release of high-energy water molecules

The first guest molecules experimentally proven to be encapsulated in the hydrophobic cavity of a cucurbituril (CB6) were water molecules.[52] Depending on their cavity volume, CB$n$ can accommodate between 2 (for CB5) to 22 water molecules (for CB10). Estimates for the number of water molecules contained in the CB cavity are given in Table 5.[8] These water molecules are of high energy as a consequence of their greatly limited hydrogen bonding and due to weak dispersion interactions with the walls of the weakly polarizable CB cavity (see above).

In aqueous solution, the release of high-energy water from the cavity upon the complexation by a guest contributes a major part to the overall hydrophobic effect (Fig. 12).[8,119–121] Biedermann *et al.* used MD simulations to calculate the relative potential energy gain for the removal of all water molecules from CB$n$ cavities (Table 5).[120] The Results showed that the deficiency of hydrogen bonding of the encapsulated water molecules and their absolute number are the determinants for the overall gained energy. With increasing cavity size, the energy of each water molecule decreases due to improved hydrogen-bonding possibilities. The maximum calculated potential energy was obtained

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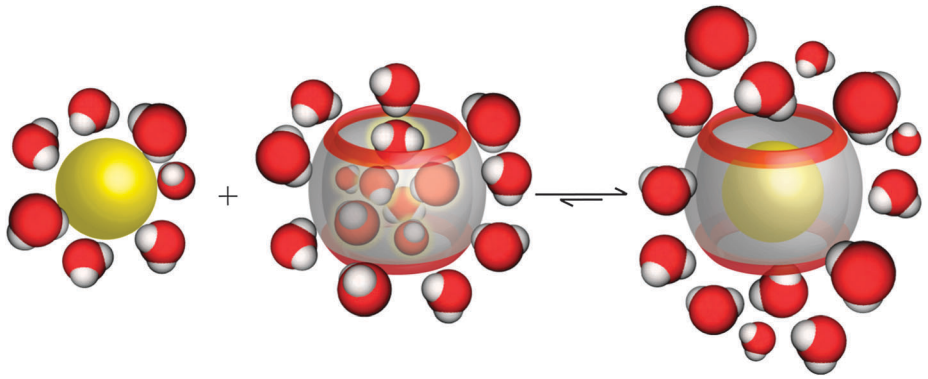


Fig. 12 Schematic illustration of the release of high-energy water molecules from the CB7 cavity upon binding of a hydrophobic guest.

for CB7. Indeed, the 242 Å$^3$ large CB7 cavity does not allow the internal water molecules to arrange in a structurally stable H-bond network.

However, the energy of each individual internal water molecule is highest for small CB*n*, such as CB5 and CB6, but the total energy for releasing all water from the inner cavity of CB7 is higher due to the larger number of water molecules (more than twice) that are released upon the complexation process. On the other hand, the large cavity of CB8 allows the optimization of the H-bond network to a degree that is structurally similar to bulk water, with the result that the energy contribution for water release is less from CB8 than from CB7, despite its larger cavity. Kim and coworkers have reported another essential role for water molecules on host–guest recognition.[122] After the transfer of the CB*n*–alkyldiammonium complexes from aqueous solution to the gas phase, it was found that the complex stabilities in the gas phase are different from those in aqueous solutions. The results were attributed to the fact that water molecules affect the ion–dipole interactions between the host and the guest. Indeed, in the absence of solvent, ion–dipole interactions are the main driving force for complexation. In contrast, in solution, the hydrophobic effect, and in particular the release of high-energy water, become dominant.

## 4. Host–guest Chemistry

The host–guest chemistry of CB*n* has already been reviewed extensively.[1,4,8,9,24,98,123–125] The hydrophobic effect, with emphasis on the release of the high-energy water, as well as ion–dipole and dipole–dipole interactions have been addressed as the main driving forces for the binding of different guests by CB*n*. In 1983, Mock and coworkers were the first to study the complexation of alkylammonium and alkyldiammonium ions with CB6 in aqueous formic acid and to determine their binding affinities.[126] Two years later, Freeman reported the first X-ray diffraction structure of a host–guest complex of a CB*n*, that of the *p*-xylylenediammonium ion encapsulated by CB6 (Fig. 13).[127]

The first structure-selectivity relationships between various alkyl- and aryl-substituted ammonium ions and CB6 were also established by Mock.[128,129] The extensive studies revealed that

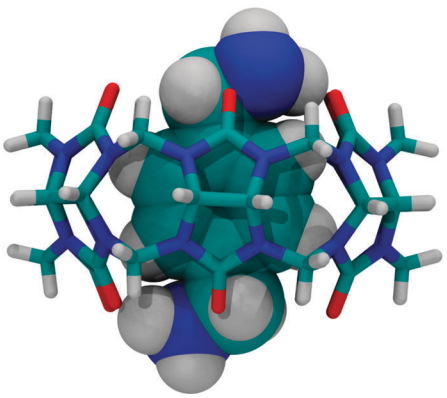


Fig. 13 X-ray structure of the *p*-xylylenediammonium ion encapsulated by CB6, the first X-ray diffraction structure of a CB*n* complex.[127]

CB6 shows a chain length-dependent selectivity (Fig. 14). Diammonium ions with a pentano or hexano bridge bind significantly stronger to CB6 than those with shorter or longer lengths. For 1,6-diammoniumhexane, the alkyl chain contracts to adopt a slightly folded conformation in order to optimize cavity filling and to additionally maximize ion–dipole interactions.[130] It was also found that CB6, with a cavity volume of 142 Å$^3$, exhibits size and shape complementarity.[44,128,129,131–134] For example, CB6 can form an inclusion complex with *p*-tolylmethanamine, but not with its *ortho* or *meta* isomers. Similarly, we have shown that even though *n*-pentane, isopentane, and neopentane are equally large (all 96 Å$^3$, PC = 68%), only the first two guests showed sizable binding with CB6, while neopentane does not form an inclusion complex with CB6, likely for kinetic reasons (slow ingression through the tighter portals).[44] A consistent result had been obtained by Mock for the neopentylammonium ion.[126,128] Moreover, CB6 differentiates between saturated and unsaturated hydrocarbons, with the latter displaying a weaker binding for the same carbon framework.[44]

As is the case for all macrocycles that possess a hydrophobic cavity, the guest hydrophobicity plays also an important role in the stability of CB complexes. For example, an alkylamine with a thioether linkage was found to bind more strongly than its oxygen counterpart, but less than the alkylamine itself. This result has been attributed to the hydrophobicity of an alkyl

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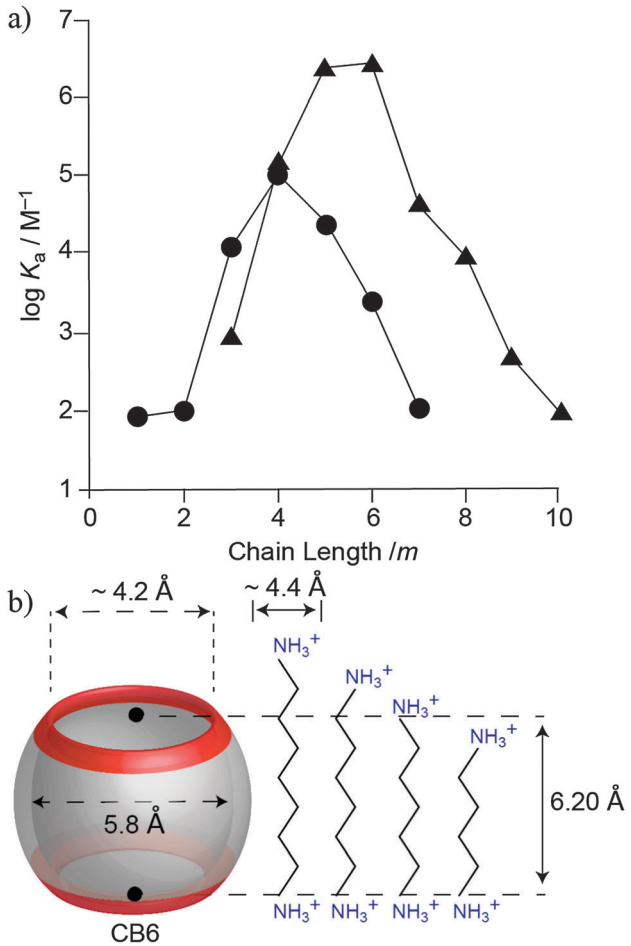



Fig. 14 (a) Relationship between the binding constant (log $K_a$) *versus* chain length *m* for $H(CH_2)_mNH_3^+$ (●) and $^+H_3N(CH_2)_mNH_3^+$ (▲). (b) Dimensional comparison between CB6 and various α,ω-alkane diammonium ions.

group being highest, that of an alkoxy group being lowest, and that of an alkylthio group being in between.[128] It should be noted that the driving force due to desolvation of convex guests is mainly related to their surface area. It produces a "classical" hydrophobic effect with a favorable entropic component, which is different from the "nonclassical" effect due to the removal of high-energy water from concave cavities, which has a favorable enthalpic signature.[121]

Recently, we have reported a size-selective binding of alkyl *versus* perfluoroalkyl chains by CB*n*.[45] CB7 shows preferential binding of perfluoroalkyl residues over normal alkyl groups, which characterizes this macrocycle as being at least as fluorophilic as lipophilic in nature. The $^1H$ and $^{19}F$ NMR of the *ditopic* guest 1-(perfluorobutyl)pentane clearly expose this binding preference (Fig. 15). The preferential binding of the fluorinated residue can be reconciled in terms of the sufficiently large cavity size of CB7 (242 $Å^3$), which snugly fits the perfluoroalkyl tail and results in an ideal packing of 55%. In contrast, the smaller CB6 homologue (cavity size 142 $Å^3$) showed a preferential complexation of the alkyl chain of the same guest, because the volume of the perfluoroalkyl group is slightly too large to be accommodated by the smaller host cavity.

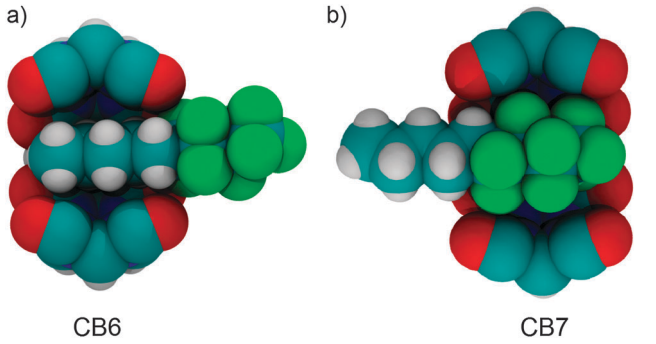



Fig. 15 Representative structures illustrating the residue-selective binding of 1-(perfluorobutyl)pentane with (a) CB6 and (b) CB7.

## High-affinity binding

CB*n* bind many size/shape complementary guests with very high affinity ($10^3$–$10^{10}$ $M^{-1}$). CB7, for example, forms stable 1 : 1 inclusion complexes with adamantanes[135,136] and diamantanes,[137,138] with bicyclooctanes,[110,135,136] and with ferrocene[98,139–143] as well as with cobaltocene[143–145] derivatives (Table 6). The reported affinities of such residues can approach[146,147] or even exceed[137] those of the strongest non-covalent interactions found in nature, in the biotin–avidin pair. The ferrocene–CB7 complex was first reported by Kaifer[143] and Kim[98] in 2003. Fig. 16 shows two crystallographically independent ferrocene/CB7 complexes that differ in their co-conformation, *i.e.*, the relative alignment of the guest inside the host.[148] DFT calculations in the gas phase (B3LYP/6-31G*) predict that the complex with perpendicular orientation should be favored.[149] We have attributed this to quadrupole interactions resulting from the high (negative) quadrapole moment of both, CB7 and ferrocene.[8] Further studies on ferrocene derivatives led to an extremely high affinity of $10^{15}$ $M^{-1}$ by introducing an ammonium unit (Table 6).[150]

Adamantylammonium was also found to form a very stable complex with CB7 ($K_a = 4.2 \times 10^{12}$ $M^{-1}$).[136] Most recently, Isaacs and coworkers have reported the tightest binding that was ever measured for a monovalent molecular recognition event in water, between CB7 and diamantane diammonium ion, with $K_a = 7.2 \times 10^{17}$ $M^{-1}$ in $D_2O$ and $1.9 \times 10^{15}$ $M^{-1}$ in 50 mM

Table 6 Binding constants for the complexation of adamantane (**A**), bicyclo[2.2.2]octane (**B**), ferrocene (**C**), and diamantane (**D**) derivatives with CB7 (see Fig. 17 for molecular structures)

| Guest | $K$/$M^{-1}$ | Guest | $K$/$M^{-1}$ |
|---|---|---|---|
| **A1**[a] | $7 \times 10^9$ | **C1**[d] | $>10^6$ |
| **A2**[b] | $2 \times 10^{10}$ | **C2**[e] | $3 \times 10^9$ |
| **A3**[b] | $2 \times 10^{14}$ | **C3**[b] | $2 \times 10^{12}$ |
| **A4**[b] | $1 \times 10^{14}$ | **C4**[e] | $4 \times 10^{12}$ |
| **A5**[b] | $8 \times 10^{14}$ | **C5**[e] | $3 \times 10^{15}$ |
| **A6**[c] | $2 \times 10^{12}$ | **D1**[a] | $4 \times 10^9$ |
| **A7**[b] | $5 \times 10^{15}$ | **D2**[f] | $3 \times 10^{11}$ |
| **B1**[b] | $6 \times 10^9$ | **D3**[f] | $2 \times 10^{15}$ |
| **B2**[b] | $2 \times 10^{14}$ | **D3**[f] | $7 \times 10^{17}$[g] |
| **B3**[b] | $1 \times 10^{15}$ | | |

[a] Unpublished results, by fluorescent indicator displacement. [b] From ref. 135. [c] From ref. 136. [d] From ref. 143. [e] From ref. 150. [f] From ref. 137. [g] Measured in pure $D_2O$.

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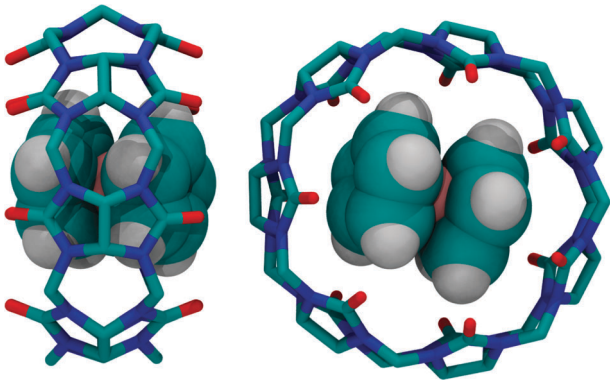
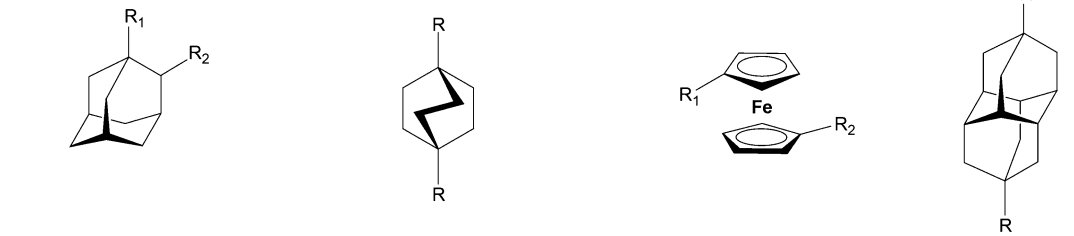


Fig. 16 Two different X-ray crystal structures of the complex between ferrocene and CB7 (side view for co-axial co-conformation and top view for orthogonal co-conformation), see ref. 139.

$NaO_2CCD_3$ by using $^1H$ NMR competition experiments.[137] The crystal structure of the CB7 complex, Fig. 18, shows the complete inclusion of the diamantane residue in the CB7 cavity. The near perfect size as well as shape complementarity between the rigid CB7 cavity and the diamantane core led to an attomolar dissociation constant.

The combined binding constants for CB7 in Table 6 can be approximately understood – considering only the composite hydrophobic effect and ion–dipole interactions, but ignoring differential dispersion interactions for the known reasons[8] – as follows: (1) the removal of all high-energy water molecules alone can account for a binding constant as high as $10^8$ $M^{-1}$. (2) The desolvation of the guest contributes another factor of $10^2$–$10^4$, depending on its hydrophobic surface area. (3) Up to two suitably, ideally centro-symmetrically, placed trimethylammonium groups add another factor of $10^3$ each. This results in the observed range from $10^{10}$–$10^{18}$. Incidentally, the fact that a quaternary trimethylammonium group presents (when measured under identical conditions) a better binding motif than a ternary or primary ammonium group (Table 6) demonstrates nicely that hydrogen bonding interactions present no dominant driving force in the binding of guests to CB*n* hosts. In fact, hydrogen bonding of guests with a host is in general unlikely to outperform hydrogen bonding with water molecules in aqueous solution.

Interestingly, diamantane in CB7 presents a more densely packed complex (PC = 79%) than adamantane in CB7 (61%). The latter has an essentially perfect packing. Indeed, the binding constant of the diamantane derivative D2 is less than that of the adamantane derivative A3. The tight packing of D3 is structurally reflected in a significantly expanded cavity (increase in the diameter by ~0.3 Å and increase in the volume from 242 to 258 Å$^3$).[137] The fact that D3 shows nevertheless the




| | $R_1$ | $R_2$ |
|---|---|---|
| **A1** | –H | –H |
| **A2** | –OH | –H |
| **A3** | $–NH_3^+$ | –H |
| **A4** | –H | $–NH_3^+$ |
| **A5** | $–CH_2NH_3^+$ | –H |
| **A6** | $–NMe_3^+$ | –H |
| **A7** | $–^+NH_2(CH_2)_2NH_3^+$ | –H |

| | R |
|---|---|
| **B1** | $–CH_2OH$ |
| **B2** | $–CH_2NH_3^+$ |
| **B3** | $–CH_2^+NH_2(CH_2)_3NHMe_2^+$ |

| | $R_1$ | $R_2$ |
|---|---|---|
| **C1** | –H | –H |
| **C2** | $–CH_2OH$ | –H |
| **C3** | $–CH_2NHMe_2^+$ | –H |
| **C4** | $–CH_2NMe_3^+$ | –H |
| **C5** | $–CH_2NMe_3^+$ | $–CH_2NMe_3^+$ |

| | R |
|---|---|
| **D1** | –H |
| **D2** | $–NH_3^+$ |
| **D3** | $–NMe_3^+$ |

Fig. 17 Molecular structures of high-affinity binders to CB7.

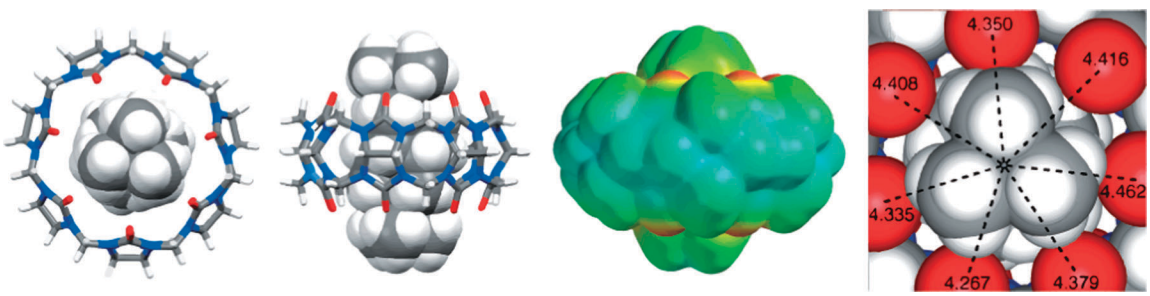



Fig. 18 Representations of the X-ray crystal structure of the CB7·diamantane diammonium complex. Taken from ref. 137. Copyright © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

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highest binding constant suggest that the PC value is overcompensated by the positive effect caused by the methylation of both amino groups; the latter causes a central positioning of the positive charge and, presumably, increased Coulombic interactions due to a drop in the apparent dielectric permittivity between the interacting (partial) charges.

In contrast to other supramolecular recognition systems, the thermodynamic data for the complexation of CB*n* with a variety of guest molecules overcome the enthalpy–entropy compensation trend.[135,139,150] The cancellation of enthalpic gain by commensurate entropic changes of opposite sign in the course of binding is common for tight non-covalent complexes, like protein–ligand binding; other macrocycles, *e.g.*, cyclodextrins, also obey the enthalpy–entropy compensation principle.[150–155] This establishes a stand-alone feature of CB*n* macrocycles, which can be attributed, among others, to the dominant role of the release of high-energy water as the enthalpic driving force for complexation.

Most recently, Vàzquez *et al.* have reported a new method for identifying the quality of high affinity binders to CB7 and CB8 by indicator displacement, in which dyes with a macrocycle-specific optical fingerprint upon encapsulation by CB7 and CB8 were used. This method allows a rapid screening of strongly and selectively binding guest molecules at micromolar concentrations.[156]

## 5. Catalysis inside CB*n* cavities

The potential of CB*n* to control and catalyze chemical reactions through their distinctive inner cavity[4,64,103,125,157–166] has been explored to a considerably lesser extent than that of cyclodextrins as alternative macrocycles.[167–173] Nevertheless, several successful examples of CB*n*-catalyzed or CB*n*-promoted unimolecular and bimolecular reactions are nowadays available, and have been previously reviewed by Sivaguru.[64] Herein, we summarize chemical reactions catalyzed by CB*n*, and highlight recent achievements (Table 7). Physical phenomena induced by complexation, such as the modulation of photoinduced electron transfer,[174] photostabilization,[36] complexation-induced p$K_a$ shifts,[16,18,175–177] solubility enhancements of guests,[14,178–182] and adverse effects on chemical reactions, that is inhibition,[183–187] are not in the focus in this review, because they have been covered elsewhere.

### CB6-catalyzed 1,3-dipolar cycloadditions

The dipolar [3+2] cycloaddition between azides (**2**) and acetylenes (**3**) was the first reaction reported to be happening inside the CB cavity, particularly inside CB6.[157] In fact, it paved the way to a type of catalytic reactions which have later become famous as *in situ* "click chemistry".[210,211] As can be seen from Scheme 4, the formation of the [1,2,3]-triazole heterocycle **4** was accelerated by a factor of $6 \times 10^4$ with regiospecificity. Unambiguously, the strong ion–dipole interactions between the ammonium ions and the CB6 carbonyl rims stabilize the ternary complex. Mock explained the observed rate enhancement in terms of: (1) overcoming of entropic constraints and (2) a strain activation of the bound substrate.[157] Carlqvist and Maseras have used quantum-calculations (DFT, B3LYP/6-31G(d)) to provide more details on 1,3-dipolar cycloaddition inside CB6. The calculations, which lack consideration of dispersion interactions, showed no evidence for a transition state stabilization, which was interpreted in favour of the entropy constraints argument.[212] Be this as it may, the CB6-catalyzed click reaction has been subsequently extensively used for synthesis of rotaxanes, pseudorotaxanes, and polyrotaxanes.[160,213–218]

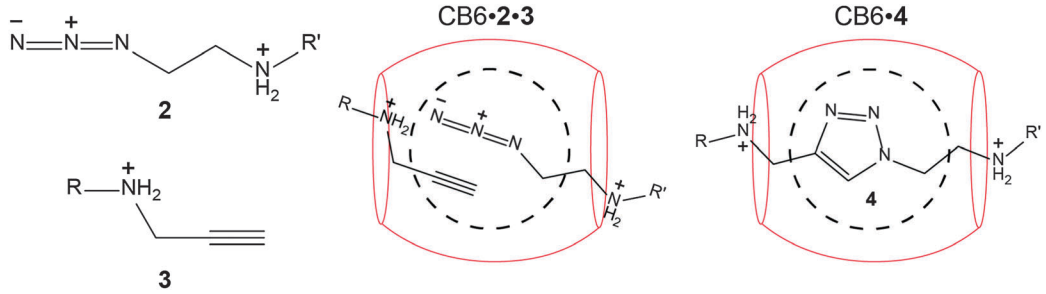
### Oxidation reactions catalyzed by CB*n*

The oxidation of alcohols into their corresponding aldehydes by *o*-iodoxylbenzoic acid (IBX) was investigated in the presence of CB8. The conversion of aryl and allyl alcohols was increased by 30–50% in the presence of CB8.[162,203] The pH effect on the conversion was also addressed; maximum conversion was obtained at neutral pH.[203] A similar catalytic effect was obtained when the same reaction was conducted in the presence of acetic acid.[219] The catalytic role of CB8 is not entirely understood in this case.

Table 7 Timeline for reports on chemical reactions mediated by CB*n*

| Year | Reaction | Host (catalyst) | Guest (reactant) | Ref. | Reaction conditions |
|---|---|---|---|---|---|
| 1983 | 1,3-Dipolar cycloaddition | CB6 | **2** and **3** | 157 | Aq. formic acid, 40 °C |
| 2001 | Photodimerization | CB8 | **10** | 188 | $h\nu$ (300 nm) |
| 2005, 2006 | Photodimerization | CB8 | **20** | 189 and 190 | $h\nu$ (Hg lamp) |
| 2005, 2007, 2014 | Photodimerization | CB8 | **13–15** | 191–193 | $h\nu$ (Hg lamp) |
| 2006 | Photodimerization | CB7 | **33** | 194 | $h\nu$ (365 nm) |
| 2008 | Photodimerization | CB8 | **29**, **31** | 195 and 196 | $h\nu$ (Hg lamp) |
| 2008, 2010, 2011 | Photodimerization | CB8 | **23** | 197–200 | $h\nu$ (>300 nm) |
| 2008, 2014 | Photodimerization | CB8 | **25** | 201 and 202 | $h\nu$ (>300 nm) |
| 2009 | Hydrolysis | CB6, CB7 | **7–9** | 166 | |
| 2009, 2011 | Oxidation | CB8 | Alcohols | 162 and 203 | IBX |
| 2010 | Oxidation | CB6 | Alkanes | 204 | Oxovanadium(IV) |
| 2010 | Desilylation | CB7 | **44** | 205 | Ag(I) salts |
| 2010 | Hydrolysis | CB7 | ArCOCl | 184 | |
| 2011 | Photolysis | CB7 | **47** and **50** | 206 | Transition metal ions |
| 2013 | Oxidation | HemiCB6 | **5** | 207 | |
| 2013 | Oxidation | HemiCB6 | Phenols | 208 | IBX |
| 2013 | Retro-Diels–Alder | CB6, CB7, CB8 | Azoalkanes, *e.g.*, **47**, **50** | 103 | Gas phase |
| 2014 | Photofragmentation | CB8 | **35** and **39** | 209 | $h\nu$ (Xe lamp) |

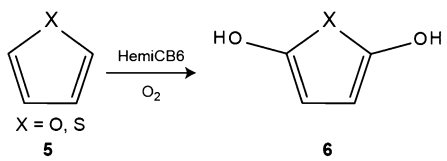
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Scheme 4 Click reaction of azide (**2**) and alkyne (**3**) to form a [1,2,3]-triazole (**4**) catalyzed by CB6.

Reddy *et al.* studied a series of known reactions mediated by molecular halogens (iodine and bromine) and their solid-state CB6 complexes.[220] The solid state complexes were prepared by diffusing the halogen vapors through solid CB6. For example, the iodine-catalyzed Prins cyclization reaction was investigated by using free iodine *versus* the CB6·$I_2$ solid-state complex. The results revealed that, in the presence of the pre-complexed iodine, the cyclization proceeded in higher yields. It should be noted that the structures of the CB6·$I_2$ and CB6·$Br_2$ inclusion complexes are known,[221] while their use as reagents presents a novel application.[220]

Tao and coworker reported the aerobic oxidation of furan and thiophene (Scheme 5). In aqueous solution, the oxidation was found to take place in the presence of HemiCB6, while no reaction happened in the absence of the host. The protonation of HemiCB6 appears to play a major role, because the oxidation was accelerated at low pH.[207] The IBX oxidation of hydroxylbenzyl alcohols was investigated in the absence and presence of HemiCB6. The IBX oxidation of phenols is known to produces a mixture of aldehydes and *o*-quinones, while the presence of HemiCB6 directed the IBX oxidation towards the phenolic hydroxyl groups to produce aldehydes.[208]




Scheme 5 Aerobic oxidation of heterocyclic substrates (**5**) mediated by hemicucurbit[6]uril.

## Hydrolysis reactions catalyzed by CB*n*

García-Río and coworkers studied the hydrolysis of different substituted benzoyl chlorides in the presence of CB7 and DM-β-CD (methylated β-cyclodextrin).[184] The reaction was catalyzed by CB7 and inhibited by DM-β-CD when the benzoyl chloride was carrying electron-donating substituents. For the substrates with electron-withdrawing groups, the reaction was catalyzed by DM-β-CD and inhibited by CB7. For example, the hydrolysis of 4-nitrobenzoyl chloride was inhibited in the presence of CB7 by a factor of 100, while for 4-methoxybenzoyl chloride the hydrolysis was accelerated 5-fold. The results were explained in terms of a differential stabilization of the acylium ion intermediate (in the transition state) by the CB7 carbonyl rim.[184]

Klöck *et al.* reported the hydrolysis of amides (**7**), carbamates (**8**), and oximes (**9**) in acidic aqueous solutions mediated by CBs (Fig. 19).[166] In the presence of CB6 and CB7, the reaction showed a catalytic effect. The hydrolysis of carbamates with a cadaverine moiety, which is known to bind very strongly to CB6 and CB7, was accelerated by a factor of ~5 ($k_{cat}/k_{uncat}$) for CB6 and CB7 at pD 0.9 and by a factor of 11.6 for CB7 at pD 1.4. In the case of the mono-*N*-(*tert*-butoxy)carbonyl derivative (**8**), the deprotection rate constant was found to be ~30 times faster with CB6 than the uncatalysed reaction. Furthermore, the

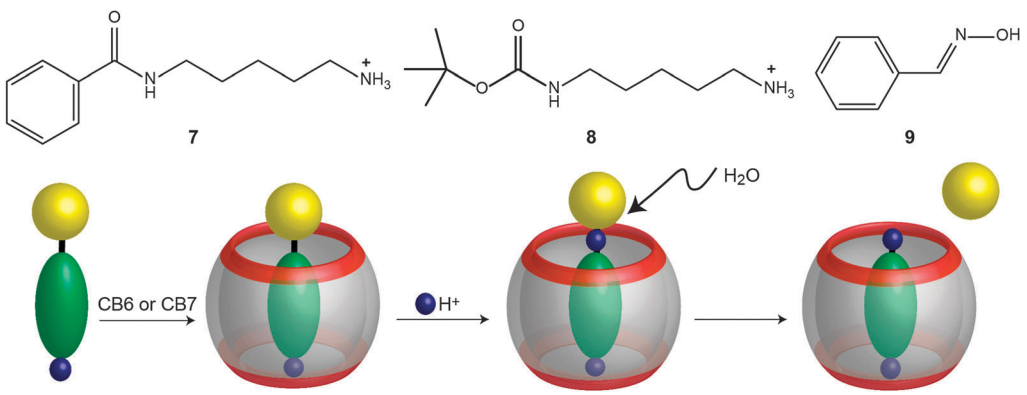



Fig. 19 Acidic hydrolysis of an amide (*N*-benzoyl-cadaverine, **7**), a carbamate (mono-*N*-(*tert*-butoxy)carbonyl cadaverine, **8**), and an oxime (benzaldoxime, **9**) mediated by CB*n*.[166]

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oxime (**9**) hydrolysis in the presence of CB7 was studied. At high pD values (*e.g.* pD 5.8), the catalyzed reaction was very fast, with a peak acceleration factor of 285. The catalytic effect was attributed to a complexation-induced p$K_a$ shift,[15,17,159,160,181,182] which assists the required protonation of the substrate.[16,18,176,177,222,223] Unfortunately, since the reaction product binds more strongly than the reactant (*e.g.*, benzaldehyde binds 6 times better than benzaldoxime), product inhibition was observed.

### Photochemical reactions catalyzed or templated by CB*n*

Complexation by CB*n* greatly influences the photophysical properties of encapsulated guests[34,36,42,175,224] and their excited state processes[4,53,183–187] which can be used, in combination with their ability to control the spatial arrangement of two components in their ternary complexes, to design more efficient and more selective photochemical reactions.[4,42,64,188,197,198,201] Photochemical applications are facilitated by the fact that CB*n* are optically transparent in the near UV and the visible region, with the exception of some chromophore-modified derivatives.[225–227] In fact, other macrocyclic hosts (*e.g.*, cyclodextrins,[168–171] calixarenes,[228,229] and the octaacid host[230,231]) have also been widely used as molecular containers for intermolecular photochemical reactions. Of interest in this context are particularly the larger CB*n* homologues, CB7 and CB8, which are sufficiently large to accommodate two guests and, thus, to form ternary complexes, but which have only been reported in 2001.[52] An overview of the corresponding photocyclization reactions templated by CB*n* is shown in Scheme 6.

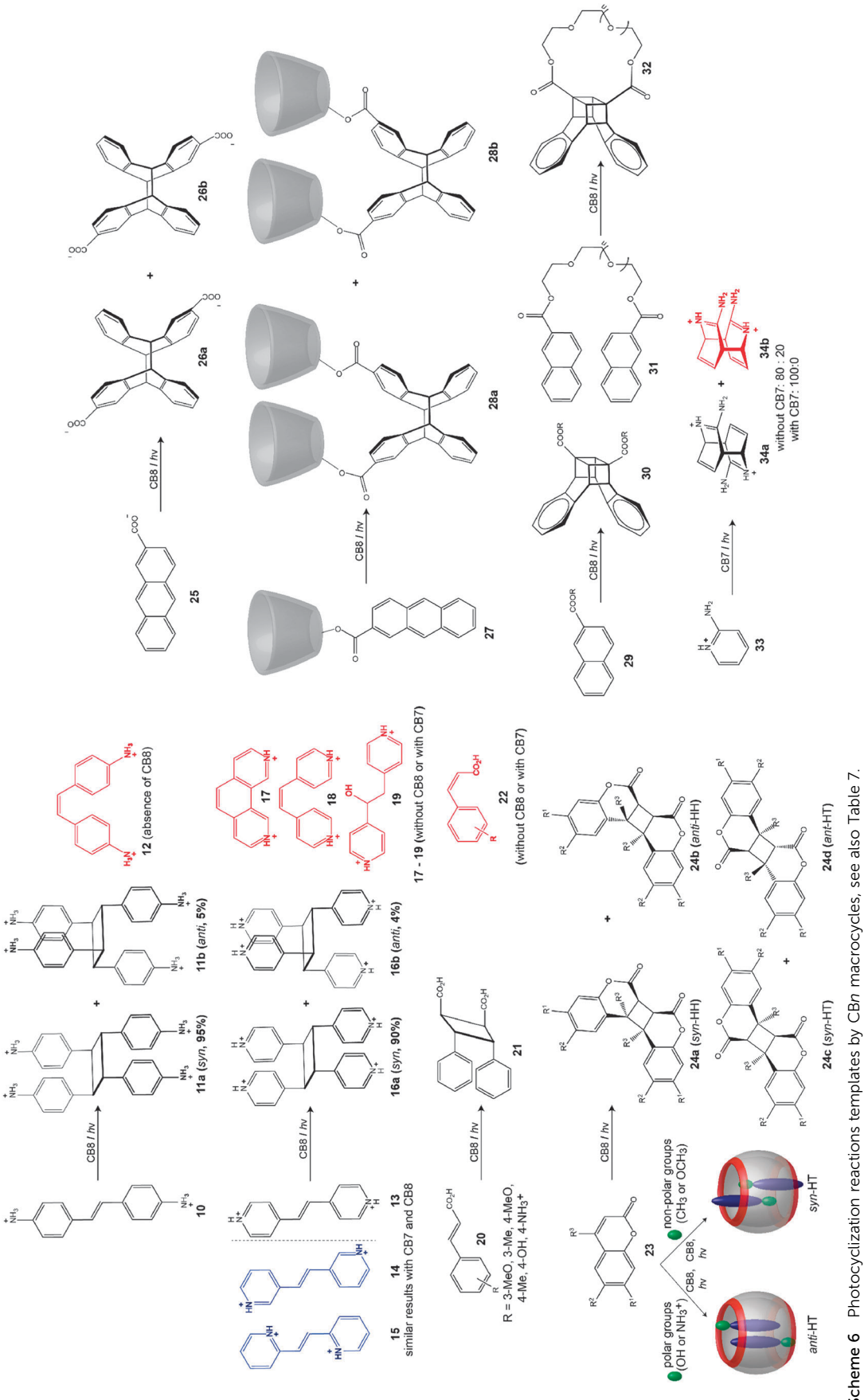
The first case of CB-catalyzed photoreactions with high stereoselectivity was reported by Kim and coworkers.[188] Two equivalents of (*E*)-diaminostilbene (**10**) were shown to form a stable 1 : 2 complex with CB8 in aqueous solution, and upon UV-irradiation (at 300 nm, 30 min) the ternary complex underwent a [2+2] cycloaddition to yield the *syn*-adduct (**11a**) as major product and only a trace amount of the *anti*-adduct (**11b**). Interestingly, in the presence of CB8, no formation of the (*Z*)-isomer (**12**) was observed, while in the absence of CB8 the (*Z*)-isomer (**12**) was the main product.[232] Other advantages offered by CB*n* were their ability to release the product from the cavity by increasing the pH (~9) and to be recycled after precipitation with excess methanol.[188]

Ramamurthy and coworkers carried out another impressive set of experiments.[189–192] By irradiation of different olefins (**13–15**) encapsulated in CB8 in aqueous solution, the *syn* dimer was obtained in 90% yield (**16a**), while irradiation of the 1 : 2 host–guest complex in the solid state showed no dimerization even after two days.[191,192] When these reactions were carried out without CB8, phenanthroline (**17**), the *cis*-isomer (**18**), and the hydration product (**19**, major product) were formed instead. Although photodimerization did not happen in the presence of CB7, the formation of **18** was promoted by this smaller host in higher yield (>67%) than in the absence of CB7.[191] Symmetrical and unsymmetrical bispyridyl ethylenes, as well as stilbazole derivatives were employed in related photocycloaddition reactions; through a combination of best fit and a minimization of electrostatic repulsion within the CB8 cavity, new reactions could be designed.[192] Ramamurthy further extended this chemistry to include the photodimerization of neutral guests, such as *trans*-cinnamic acid (**20**).[189,190] Upon irradiation of **20** encapsulated by CB8 (in aqueous solution as well as in the solid state), the reaction afforded the *syn* head-to-head dimer (**21**), along with the corresponding *cis* isomer (**22**).[189] The latter was formed as dominant product in the presence of the smaller CB7. Zhang and coworkers have employed the same reaction type to construct covalently attached hyperbranched polymers, which present photosensitive supramolecular polymers with high molecular weight.[193]

Sivaguru reported the [2+2] cycloaddition of coumarin derivatives (**23**), both cationic and neutral, in the presence of CB8.[197–199,233] It was shown that upon UV excitation (>300 nm) of the 1 : 2 complex of CB8 and two coumarins, the head-to-tail (HT) adduct was formed as the major product. The type of HT adduct (*syn* or *anti*) depended on the nature of substituents; coumarins with polar functional groups led to the *anti* photoadduct and those with nonpolar groups to the *syn* counterpart. Later, Sivaguru and coworkers showed that the formation of the 1 : 2 complex (ternary complex) is the rate determining step for the cycloaddition, in which the formation of the 1 : 1 complex is kinetically fast and that of the 1 : 2 complex is actually slow.[200] In the case of methylated coumarin (6-methylcoumarin), photodimerization led exclusively to the *syn* dimer (>99%) with a *syn*-HH/*syn*-HT ratio of about 70 : 30.[233] The research groups of Inoue and Kim reported the effect of CB8 on the [4+4] cross-photodimerization of 2-anthracene carboxylate (**25**) and another 2-anthracene carboxylate linked to α-CD (**27**).[201] In the case of the self-photodimerization of **25**, no significant effect on the *syn*/*anti* ratio or the head-to-head/head-to-tail ratio was observed in the presence and absence of CB8, *e.g.*, the head-to-tail product remained the major isomer (**26a** and **26b**). In contrast, the cross-photodimerization of **27** inverted the HT/HH ratio form 98 : 2 to 1 : 99 by changing the templating host from γ-CD to CB8; accordingly, the products of the reaction with CB8 were **38a** and **38b**. The [4+4] photodimerization of anthracene in the presence of CB8 has recently been applied to polymer ligation and covalent network formation.[202] Another example, for the photodimerization of alkyl-2-naphthoate (**29**), was reported by Wu and coworkers, which afforded the cubane-type products **30**.[195,196] The photodimerization of methyl-2-naphthoate occurred efficiently in the presence of CB8 (60% conversion after 2 h), whereas in the free form methyl-2-naphthoate does not react. Similar results were obtained for 2-naphthalene-labeled poly(ethyl glycol) (**31**); the 1 : 1 complex was irradiated (>280 nm) for 12 min, sufficient to obtain more than 96% of the dimer (**32**); no product was formed in the absence of CB8.[196]

Macartney and coworkers demonstrated that photocycloadditions are not limited to the larger CB8 host, but that they can also be conducted with the intermediary sized CB7.[194] In the presence of 50 mol% of CB7, 2-aminopyridine (**33**, as hydrochloride salt) underwent a [4+4] photodimerization and afforded exclusively the *anti–trans* isomers (**34a**) in 90% yield after irradiation for 21 h. In the absence of CB7, a mixture of

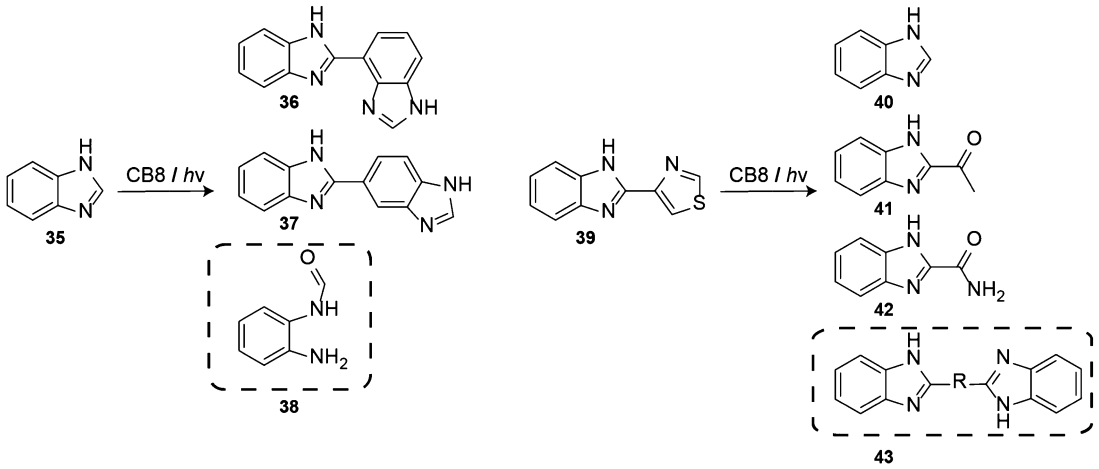
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Scheme 6 Photocyclization reactions templates by CB*n* macrocycles, see also Table 7.


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Scheme 7 CB8 modulates the phototransformation of (a) benzimidazole (**35**) and (b) thiabendazole (**39**); marked products were observed only in the presence of CB8.

*anti–trans* (**34a**) and *syn–trans* (**34b**) was obtained in a 4 : 1 ratio. Importantly, CB7 was also found to stabilize the photoproduct and, thus, to protect it from thermal re-aromatization. Packing arguments suggest a stronger binding of the photoproduct in this case,[8] that is, product inhibition is expected, but actually desirable in this special case.

The pre-assembled 1 : 2 host–guest complexes of CB8 and benzimidazole (**35**) underwent photohydrolysis to form a new major photoproduct, 2-aminoformanilide (**38**) (Scheme 7). When the reaction was carried out in the absence of CB8, the photoreaction of **35** led to dehydrodimerization products (**36**) and (**37**). The phototransformation of free thiabendazole (**39**) also leads to the formation of **40**, **41**, and **42**, while in the presence of CB8 the coupling product **43** was formed as an additional product.[209]

## Catalysis assisted by metal ions

Due to their electronegative carbonyl rims, CB*n* macrocycles are well known to bind metal cations at the portal regions.[234–242] This property has recently been employed to promote or catalyze organometallic reactions.[204–206] Demets and coworkers reported the oxidation of short unbranched alkanes, *e.g.* *n*-pentane, in the presence of CB6/oxovanadium(IV) (Fig. 20).[204] Upon treatment of the complex with hydrogen peroxide or iodosylbenzene, a mixture of 2-pentanol, 2-pentanone, and 3-pentanone was obtained.

The use of *Z*-cyclooctene, cyclohexane, and styrene as substrates showed no products formation, which was attributed to the fact that such guests do not form complexes with CB6, consistent with a detailed study of hydrocarbon binding to CB6.[44]

Masson and Lu have recently reported a novel catalytic cycle for the desilylation of a trimethylsilylalkynyl derivative (**44**) assisted by CB*n* in the presence of Ag(I) salts (Fig. 21).[205] The formation of a ternary complex, *e.g.*, $Ag^+$·CB7·trimethylsilylalkynyl, was postulated, which would first lead to trimethylsilanol (**46**) complexed inside CB7 and an alkynylsilver organometallic complex. It was assumed that the latter is subsequently hydrolyzed to the desilylated alkyne (**45**) and $Ag^+$.

Our group documented a phase-selective photolysis of bicyclic azoalkanes (2,3-diazabicyclo[2.2.1]hept-2-ene (**47**) and 2,3-diazabicyclo[2.2.2]octa-2-ene (**50**)) promoted by transition-metal ions coordinated to the CB7 rim (Fig. 22).[206] The reaction was selected to afford a photoproduct with a reduced affinity to the host and with a higher solubility in an organic phase than in water. In detail, irradiation of **47** and **50** in their near-UV n,π* absorption band in water is known to cause nitrogen extrusion under formation of bicyclo[2.1.0]pentane (housane) (**48**) as exclusive photoproduct of **47** and of a 70 : 30 mixture of 1,5-hexadiene

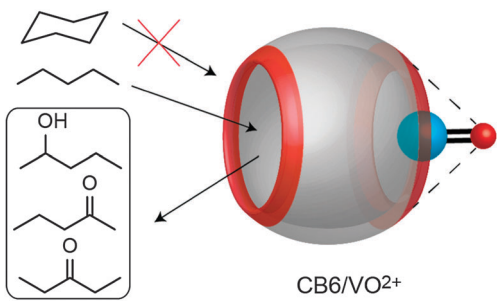



Fig. 20 The CB6/oxovanadium(IV) complex catalyzes *n*-pentane oxidation, but not that of larger alkanes.

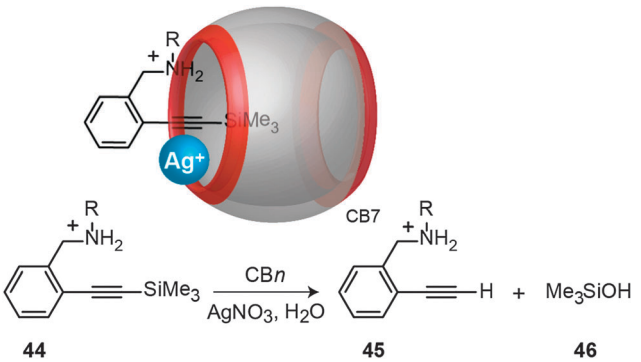



Fig. 21 CB*n*-catalyzed desilylation of trimethylsilylalkynyl derivatives (**44**) in the presence of Ag(I) salt; shown on top is the postulated ternary complex.

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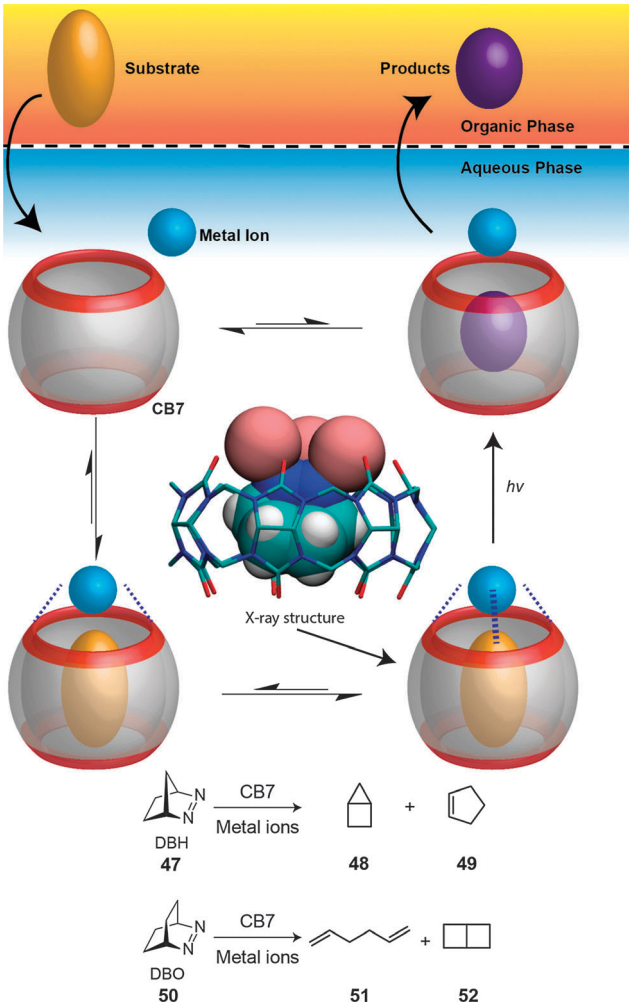



Fig. 22 Chemoselective photoreactions of bicyclic azoalkanes (**47** and **50**) mediated by CB7 in the presence of transition metal ions.[206]

(**51**) and bicyclo[2.2.0]hexane (**52**) as photoproducts of **55**; the conversion can be conveniently monitored by gas chromatography. In the presence of CB7 and of specific transition metal ions ($Fe^{3+}$, $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$, $Ag^{+}$, also $Tl^{+}$), the photolysis of DBO afforded a 5-fold to 10-fold excess of the diene product. The chemoselectivity was postulated to occur from the triplet-excited state, populated by heavy-atom-induced intersystem crossing. With the smaller azoalkane **47**, surprisingly, cyclopentene (**49**) was formed as a new photoproduct (41%), but only in the presence of both, CB7 and $Ag^{+}$. Because the formation of a ternary complex between CB7, $Ag^{+}$, and **50** could be crystallographically established, it is likely that a new mechanism, photoinduced electron-transfer, leads to cyclopentene. Such redox-active ternary complexes can be considered as metalloenzyme models.

### Catalysis and reactivity inside the inner phase of CB*n* in the gas phase

Lee *et al.* have investigated chemical reactions, retro-Diels–Alder reactions of bicyclic azoalkanes, inside CB*n* molecular containers in the gas phase by using a mass spectrometric study combined with quantum-chemical calculations.[103] Ion mobility experiments were first performed to prove that the formed complexes between CB*n* (CB6, CB7, and CB8) and the protonated azoalkanes (DBH, DBO, and DBN) are indeed inclusion complexes and not of the exclusion type. It was clearly shown that free CB7 exhibits the same drift time as the host–guest complex (Fig. 23a), which depends directly on the collisional cross section areas of the "empty" and the "filled" CB7. The fact that the cross sections are the same cannot be reconciled with an exclusion complex, because it would display a significantly larger cross section.

In a systematic approach, we have examined the fragmentation reaction of each viable complex of differently sized CB*n* and guests (for example CB7, Fig. 23b). After the mass selection, the protonated complexes, $[CBn{\cdot}guest{\cdot}H]^{+}$, were subject to collision-induced dissociation (CID) experiments. This thermal activation of the CB*n*–azoalkane complexes induced in some cases dominant chemical reactions of the encapsulated guests and the formation of $[CBn{\cdot}fragment{\cdot}H^{+}]$ product complexes as opposed to irreversible dissociation of the host–guest complexes; the latter was expected and is observed for many supramolecular assemblies, including cyclodextrin complexes. For example, protonated DBH inside CB7 afforded elimination of ethylene with subsequent dissociation of the intermediary pyrazole complex upon CID. In contrast, when DBH was more tightly packed (inside CB6) or more loosely packed (with CB8), the simple dissociation pathway into guest and host dominated over the inner-phase chemical reaction. Most interestingly, thermal activation of DBO complexed inside CB7 or CB8 (note that no complex was formed for DBO with CB6) led, predominantly, first to elimination of ethylene, followed by elimination of hydrogen cyanide, and, ultimately, dissociation of the protonated propenimine complex (Fig. 23c).

The chemical reactivity of the gas phase complexes was interpreted in terms of three contributing factors: (1) the intrinsic activation energies for chemical reaction of the guest, (2) the constrictive binding displayed by the particular host, and (3) the void space inside the host–guest complex. Modelled Lennard-Jones 12–6 potentials of a spherical guest expanding inside the inner cavity of a rigid host, which included attractive (dispersion) and repulsive van der Waals forces, showed that the chemical reaction is "switched on" when the packing coefficients of the complexed guest falls within the range of 30–50%. In these cases, as shown by DFT calculations, the transition state experiences a dispersive stabilization, because the substrate must expand towards the cavity walls in order to eliminate the nitrogen molecule. These gas-phase reactions do therefore provide a genuine and puristic case of an inner-phase "catalysis" of a chemical reaction.

## 6. Conclusions and outlook

Looking at only a single decade of active research on cucurbituril homologues, their potential in the areas of synthesis, high-affinity binding, and catalysis is still waiting to be fully explored. With respect to synthesis, several exciting developments have

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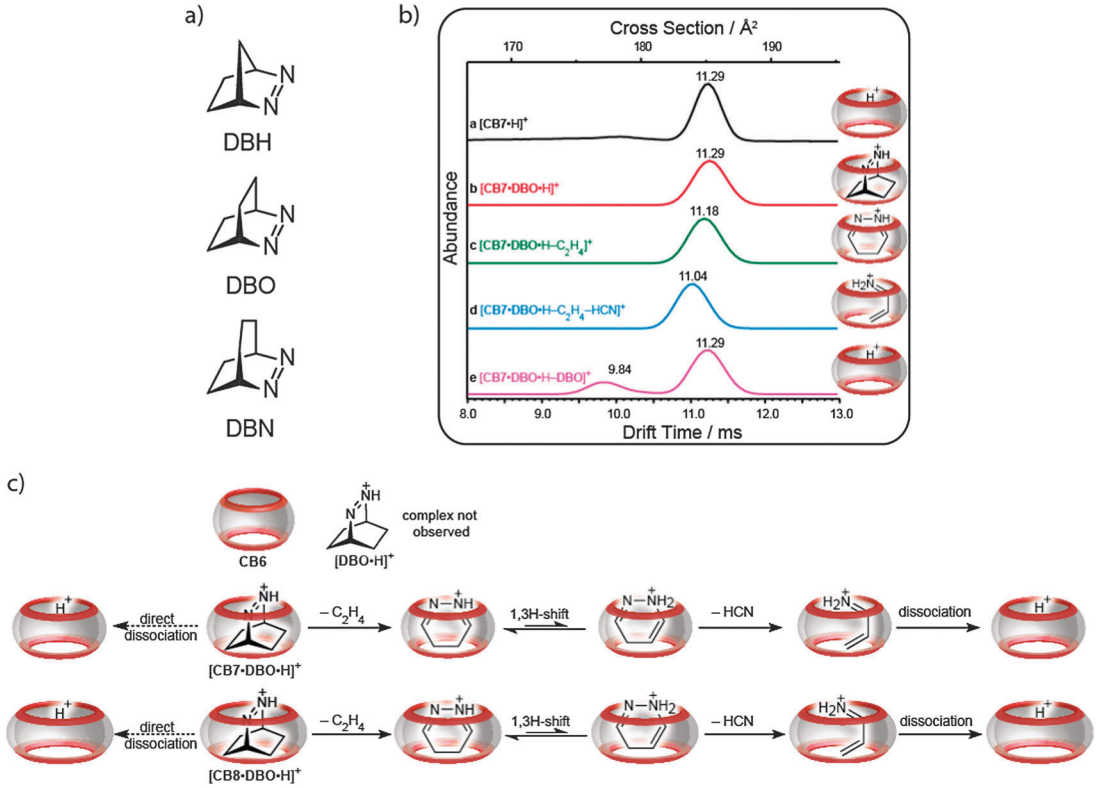



Fig. 23 (a) Chemical structures of the bicyclic azoalkanes. (b) Ion mobilograms of different CB7 complexes. (c) Reaction and dissociation pathways of the inclusion complex of DBO inside CB*n* in the gas phase.

taken place, which include the emergence of monofunctionalized derivatives,[90–92,96] also through convergent synthesis routes (Table 1).[87,95] The monofunctionalized derivatives offer much potential for the labeling of surfaces and for selective conjugation to biomolecules. Also new homologues are still being reported, such as the recently reported largest member, CB14.[59] With respect to high-affinity binding, new host–guest combinations are still pushing the limits, and the highest value, attomolar binding, has just recently been reached.[137] Cucurbiturils are, among macrocycles, the hosts with highest (commonly 6 orders of magnitude higher) affinity, paving the way for *hitherto* unprecedented applications in biology, medicine, and material science. While recent studies point to the importance of the extrusion of high-energy water as an important denominator,[119] the quantitative understanding of the underlying factors responsible for the high-affinity binding of cucurbituril homologues remains challenging.[243] In contrast, dispersion interactions appear to be of very minor importance for guest binding by cucurbiturils in aqueous solution, which renders these hosts as interesting experimental and theoretical models to dissect the contributions of intermolecular interactions to host–guest binding, for example in the binding of perfluorinated compounds. Another mechanistic trend in recent years involves the use of gas-phase studies to obtain fundamental information on the host–guest binding of cucurbiturils.[103,112,122] With respect to catalysis, to address the third thematic area of this review, several case studies are nowadays available (Table 7). Nevertheless, compelling application examples which fully exploit the high affinities of cucurbiturils, their peculiariar binding properties, or the availability of derivatives (including monofunctionalized ones to explore heterogeneous conditions) are still waiting to be uncovered.

## Acknowledgements

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