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Host–Guest Systems

The Cucurbit[*n*]uril Family

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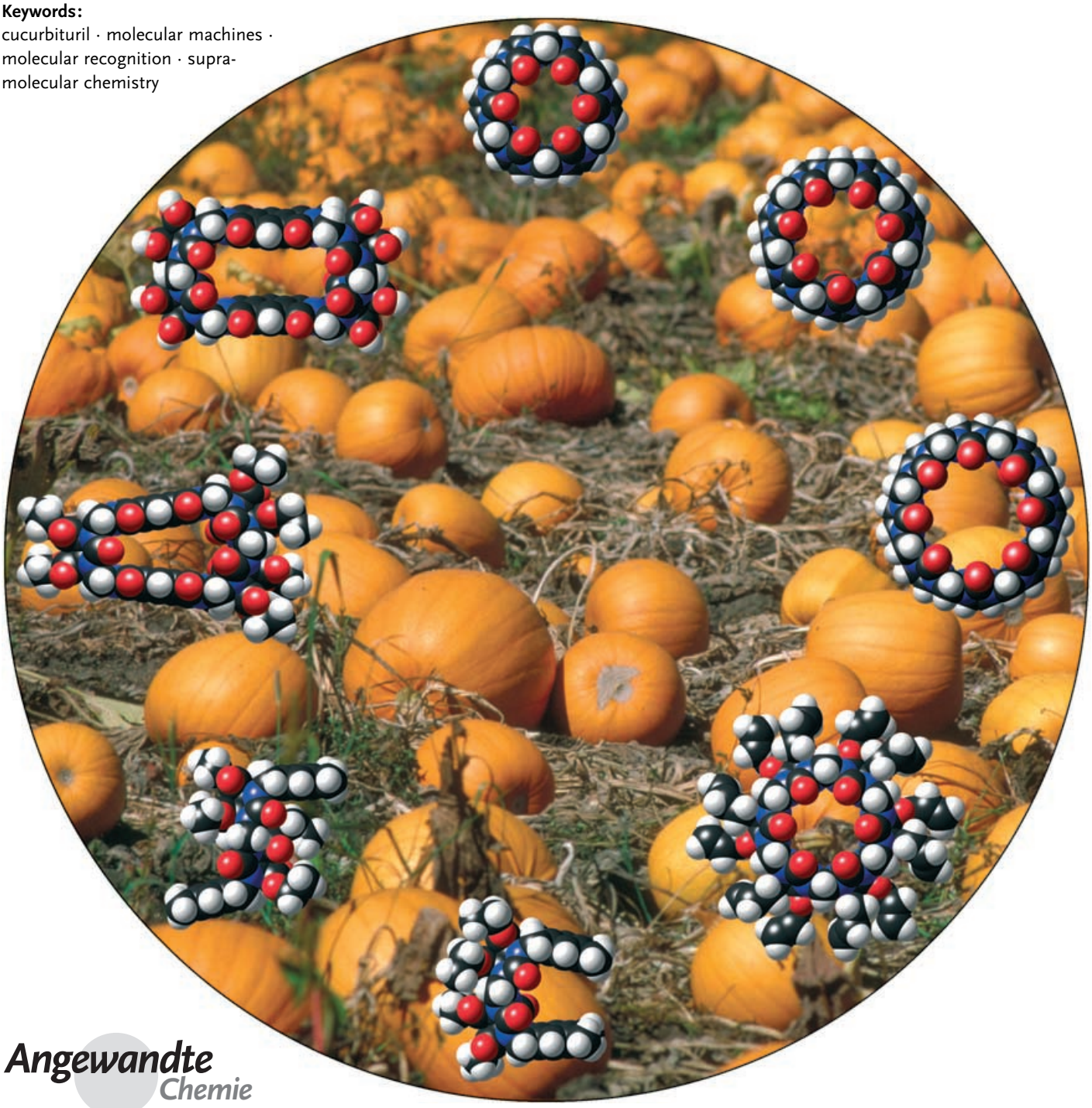

In 1981, the macrocyclic methylene-bridged glycoluril hexamer (CB[6]) was dubbed "cucurbituril" by Mock and co-workers because of its resemblance to the most prominent member of the cucurbitaceae *family of plants—the pumpkin. In the intervening years, the fundamental binding properties of CB[6]—high affinity, highly selective, and constrictive binding interactions—have been delineated by the pioneering work of the research groups of Mock, Kim, and Buschmann, and has led to their applications in wastewater remediation, as artificial enzymes, and as molecular switches. More recently, the cucurbit[n]uril family has grown to include homologues (CB[5]–CB[10]), derivatives, congeners, and analogues whose sizes span and exceed the range available with the α-, β-, and γ-cyclodextrins. Their shapes, solubility, and chemical functionality may now be tailored by synthetic chemistry to play a central role in molecular recognition, self-assembly, and nanotechnology. This Review focuses on the synthesis, recognition properties, and applications of these unique macrocycles.*

From the Contents

1. Introduction

In 1905—contemporaneous with the pioneering work of Schardinger on the cyclodextrins—Behrend et al. reported that the condensation of glycoluril (acetyleneurea) and formaldehyde in concentrated HCl yields an insoluble polymeric substance now known as Behrend's polymer.[1] Behrend et al. were able to obtain a crystalline substance in good yield (40–70%) by recrystallization of the product from concentrated H_2SO_4 and demonstrated its ability to form cocrystals (complexes) with a variety of substances including $KMnO_4$, $AgNO_3$, H_2PtCl_6, $NaAuCl_4$, congo red, and methylene blue. The constitution of this substance remained unclear until 1981 when Mock reinvestigated the report by Behrend et al., and disclosed the remarkable macrocyclic structure comprising six glycoluril units and twelve methylene bridges; they dubbed the compound cucurbituril in recognition of its resemblance to a pumpkin, the most prominent member of the *cucurbitaceae* family (Figure 1).[2] In this Review we refer to cucurbituril as cucurbit[6]uril and abbreviate this as CB[6] to distinguish it from cucurbit[*n*]uril (CB[*n*]) homologues containing a different number of glycoluril units.

In contrast to the host–guest chemistry of α-, β-, and γ-cyclodextrin which has developed steadily over the past century, the supramolecular chemistry of CB[6] only began to develop in the 1980s and 1990s as a result of the pioneering work of Mock,[3] Buschmann and co-workers,[4] and Kim and co-workers.[5,6] Interest in the CB[*n*] family has increased dramatically in the new millennium following the preparation of four new CB[*n*] homologues (CB[5], CB[7], CB[8], and CB[10]·CB[5]) by the research groups of Kim and Day.[7–9] CB[5]–CB[8] are now even available commercially. This increase in interest in the CB[*n*] family correlates with the great advances in many areas of fundamental and applied science—chemistry, biology, materials science, and nanotechnology—that rely on the ability to employ and control noncovalent interactions between molecules. Consequently, CB[6] and the CB[*n*] family have been the focus of numerous reviews[3,5,6,10–30] and patents.[30–48]

The pioneering work of Lehn, Cram, and Pedersen brought host–guest and supramolecular chemistry to the forefront of contemporary science.[49] The scientific insights gained from fundamental studies of noncovalent interactions have been of practical value in a wide range of applications including chromatographic stationary phases, sequestration of contaminants from solution, and the development of catalysts, chemical sensors, and new drugs. All of these applications require the availability of low-molecular-weight receptors,[50–52] natural or non-natural oligomers and polymers,[53,54] or solid-state materials[55–57] that interact with their analytes in high affinity, highly selective binding processes. In response, supramolecular chemists have designed, synthesized, and evaluated the recognition properties of a wide variety of non-

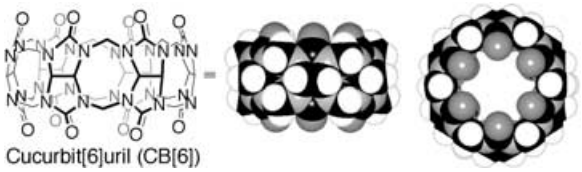

Figure 1. Structural formula of CB[6] as well as the side and top views of a space-filling model.

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natural receptors—including cyclodextrins, calixarenes, cyclophanes, crown ethers, and many others—that display remarkable affinity and selectivity (Figure 2).[50–52] Amongst these non-natural receptors, α-, β-, and γ-cyclodextrin remain the

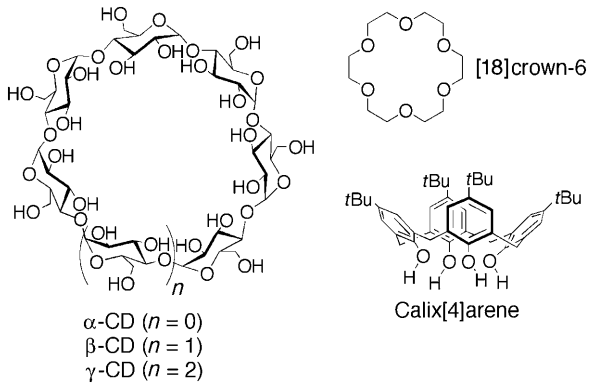

Figure 2. Structural formulas of α-, β-, and γ-cyclodextrin, [18]crown-6, and a calix[4]arene.

receptors of choice for industrial applications—despite a range of potential limitations which include low affinity, low selectivity, and challenges in their selective functionalization—because they are commercially available and inexpensive.

In this Review we trace the development of the supramolecular chemistry of CB[6] from its early days when it was plagued by issues—including poor solubility in aqueous and organic media, a lack of a homologous series of different sized hosts (for example, CB[*n*]), and an inability to access CB[*n*] derivatives and analogues by tailor-made synthetic procedures—to the present day when the CB[*n*] family is emerging as an outstanding platform for fundamental and applied molecular recognition and self-assembly studies. We, and others, believe that the CB[*n*] family is even poised to compete with the cyclodextrins as the platform of choice in industrial-scale applications. Today, the CB[*n*] family has overcome all of these early issues and currently possesses a confluence of properties that suggest their high potential in nanotechnology as components of molecular machines. These properties now include: 1) commercial availability in four different sizes, 2) binding interactions of high affinity, 3) high selectivity of binding, 4) synthetic control over size, shape, and functional-group placement, 5) high structural integrity, 6) solubility in both organic and aqueous solution, 7) association and dissociation with controlled kinetics, and 8) control of the molecular recognition processes by suitable electrochemical, photochemical, and chemical stimuli.

First, we begin with a discussion of the synthesis of CB[*n*] as well as their fundamental chemical and physical properties. Second, we present the recognition properties of the CB[*n*] family. In this section we emphasize the behavior of the most widely studied cucurbit[*n*]uril, CB[6], with an emphasis on those aspects of its recognition behavior—protonation, metal binding, selectivity based on size, shape, and charge, and the mechanism of binding—that are likely to apply universally to the CB[*n*] family. Third, we discuss the use of chemical, photochemical, and electrochemical stimuli to control recognition processes within CB[*n*]. Fourth, we discuss some applications of the CB[*n*] family in areas including catalysis,

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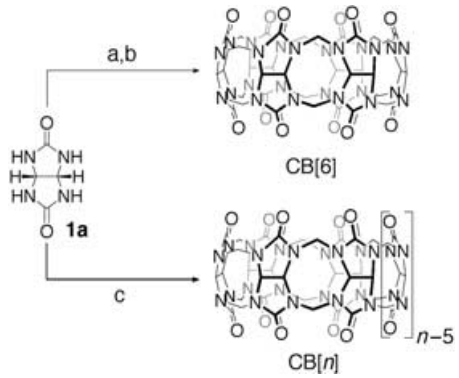
self-assembled monolayers, waste-stream remediation, DNA binding, gene transfection, and ion channels. Next, we discuss the use of the various CB[*n*] as components of molecular necklaces, rotaxanes and psuedorotaxanes, supramolecular amphiphiles, and self-sorting systems generated by self-assembly processes in solution and by crystal engineering in the solid state. Lastly, we discuss some mechanistic aspects of CB[*n*] synthesis based on our studies of the methylene-bridged glycoluril dimer as a model system and show how these insights lead to the synthesis of CB[*n*] derivatives, analogues, and congeners.

2. Synthesis of CB[n]

In the condensation of glycoluril (**1a**) and formaldehyde, neither Behrend et al. nor Mock detected any macrocyclic compounds (homologues) composed of a different number of glycoluril rings (for example, CB[5], CB[7], and CB[8]). It was not until nearly 20 years later when this reaction was conducted under milder, kinetically controlled conditions by the research groups of Kim and Day that CB[5]–CB[8] and CB[5]@CB[10] were detected and isolated (Scheme 1).[7–9,58]



Scheme 1. Synthesis of CB[6] from **1a** under forcing conditions and a mixture of CB[n] under milder conditions. a) CH_2O, HCl, heat; b) H_2SO_4; c) CH_2O, HCl, 100 °C, 18 h.

3. Fundamental Properties of CB[n]

3.1. Dimensions

CB[*n*] are cyclic methylene-bridged glycoluril oligomers whose shape resembles a pumpkin. Figure 3 shows the X-ray crystal structures for CB[5]–CB[8] and CB[5]@CB[10]. The cavity of CB[6] in the solid state contains three H-bonded H_2O molecules which can be released upon guest binding. The defining features of CB[5]–CB[10] are their two portals lined by ureido carbonyl groups that provide entry to their hydrophobic cavity.[59] Similar to the cyclodextrins, the various CB[*n*] have a common depth (9.1 Å), but their equatorial widths, annular widths *a*, and volumes vary systematically with ring size (Table 1). The portals guarding the entry to CB[*n*] are approximately 2 Å narrower than the cavity itself which results in constrictive binding that produces significant steric barriers to guest association and dissociation.[60] The cavity sizes available in the CB[*n*] family span and exceed those available with the cyclodextrins.

3.2. Solubility, Acidity, and Stability

One of the potential limitations of the CB[*n*] family is their relatively poor solubility in water: CB[6] and CB[8] are essentially insoluble, whereas CB[5] and CB[7] possess modest solubility in water (Table 1). The solubility of the CB[*n*] family is generally lower than the cyclodextrins. Like urea itself, however, the carbonyl groups lining the portals of CB[*n*] are weak bases: the pK_a value of the conjugate acid of CB[6] is 3.02. Although the pK_a values for CB[5], CB[7], and CB[8] have not been measured, they are likely to be similar to that of CB[6]. Accordingly, the solubility of CB[5]–CB[8] increase dramatically in concentrated aqueous acid (for example, 61 mM for CB[6] in HCO_2H/H_2O (1:1), about

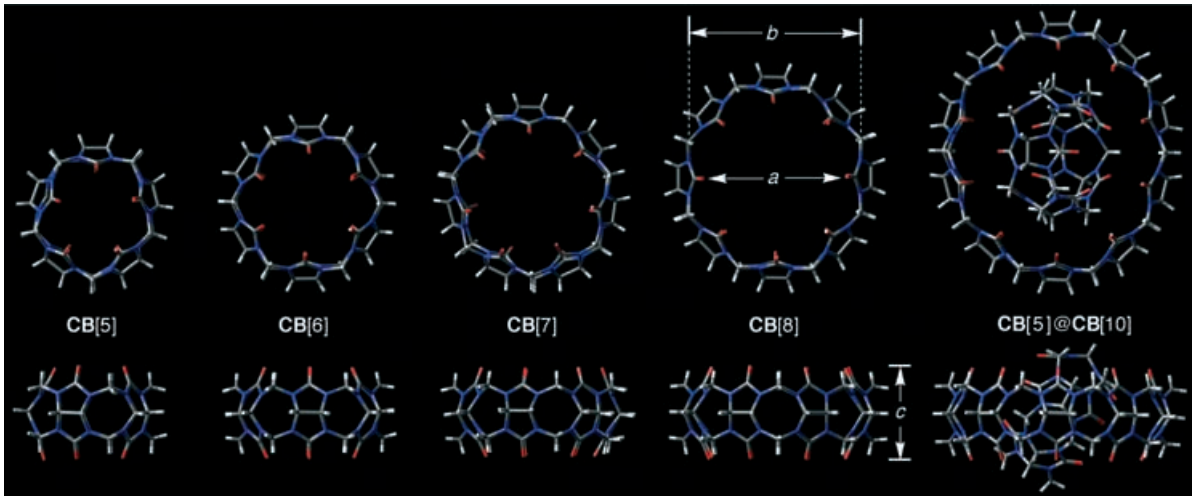


Figure 3. Top and side views of the X-ray crystal structures of CB[5],[7] CB[6],[2] CB[7],[7] CB[8],[7] and CB[5]@CB[10].[9] The various compounds are drawn to scale.

Table 1: Dimensions and physical properties of CB[*n*] and the cyclodextrins.

	M_r	a [Å][a]	b [Å][a]	c [Å][a]	V [Å^3]	s_{H_2O} [mM]	Stability [°C]	pK_a
CB[5]	830	2.4[5]	4.4[5]	9.1[5]	82[5]	20–30[5]	>420[5]	
CB[6]	996	3.9[5]	5.8[5]	9.1[5]	164[5]	0.018[61]	425[62]	3.02[63]
CB[7]	1163	5.4[5]	7.3[5]	9.1[5]	279[5]	20–30[5]	370[5]	
CB[8]	1329	6.9[5]	8.8[5]	9.1[5]	479[5]	<0.01[5]	>420[5]	
CB[10][b]	1661	9.0–11.0	10.7–12.6	9.1	–	–	–	–
α-CD	972	4.7[64]	5.3[64]	7.9[64]	174[64]	149[64]	297[65]	12.332[64]
β-CD	1135	6.0[64]	6.5[64]	7.9[64]	262[64]	16[64]	314[65]	12.202[64]
γ-CD	1297	7.5[64]	8.3[64]	7.9[64]	427[64]	178[64]	293[65]	12.081[64]

[a] The values quoted for a, b, and c for CB[*n*] take into account the van der Waals radii of the relevant atoms. [b] Determined from the X-ray structure of the CB[5]@CB[10] complex.[9]

60 mM for CB[5], about 700 mM for CB[7], and about 1.5 mM for CB[8] in 3 M HCl).[66–68] One of the outstanding features of CB[5]–CB[8] is their high thermal stability: thermal gravimetric analysis shows this to exceed 370 °C in all cases.

3.3. Electrostatic Potential

Electrostatic effects can play a crucial role in molecular recognition events in both aqueous and organic solution.[69] Figure 4 shows the electrostatic potentials of β-CD and CB[7]. Clearly, the electrostatic potential at the portals and within the cavity of CB[7] is significantly more negative than for β-CD. This difference in electrostatic potential has significant consequences for their recognition behavior: CB[*n*] exhibit a pronounced preference to interact with cationic guests whereas β-CD prefers to bind to neutral or anionic guests.

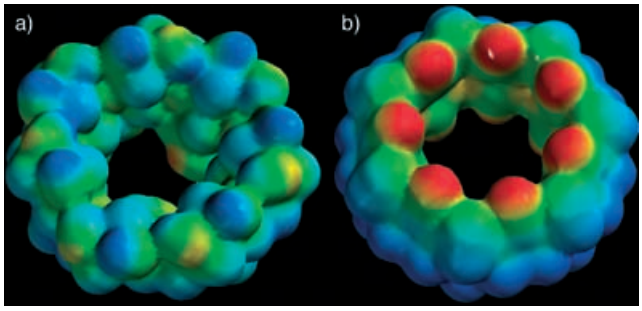


Figure 4. Electrostatic potential maps for a) β-CD and b) CB[7]. The red to blue color range spans −80 to 40 kcal mol^{-1}. Adapted from Kim and co-workers.[5]

4. Host–Guest Chemistry of CB[n]

The recognition properties of CB[6] are compared with those of α-CD and [18]crown-6 in this section. Many of the lessons learned from the chemistry of CB[6] can be generalized to the whole CB[*n*] family.

4.1 Comparison of the Thermodynamics of Complexation

Houk et al. recently reviewed the binding affinities for a wide variety of systems including synthetic host–guest, antibody–antigen, receptor–drug, and enzyme–substrate complexes.[70] The average binding affinity for 1257 α-, β-, and γ-CD complexes[71] ($K_a = 10^{2.5\pm1.1}$ M^{-1}) is an order of magnitude smaller and more narrowly distributed than the corresponding value for 973 synthetic host–guest pairs in water ($K_a = 10^{3.4\pm1.6}$ M^{-1}). A similar analysis using the 56 CB[6]·guest pairs reported by Mock and Shih[72] yields $K_a = 10^{3.8\pm1.5}$ M^{-1}. Table 2 compares the affinity of α-CD and CB[6] toward a series of alcohols, which are modest guests for both hosts. Despite its preference to interact with positively charged guests, CB[6] binds more tightly to the alcohols (except hexanol) than does α-CD although it does so in a nonselective manner. In general, CB[6] binds with higher affinity and higher selectivity toward its guest than do the cyclodextrins. A similar comparison between the affinity of CB[6] and [18]crown-6 toward several monovalent and divalent cations is given in Table 3. CB[6] shows higher affinity than [18]crown-6 toward all cations except Ba^{2+}, whose radius is a good match for the cavity of [18]crown-6. These examples are intended to illustrate that the binding ability of CB[6] generally equals or exceeds those of other well-known host molecules such as cyclodextrins and crown ethers.

Table 2: Calorimetrically determined log *K* values for the complexation of alcohols with CB[6] in HCO_2H/H_2O (1:1) at 25 °C and with α-CD in H_2O.[73,74]

	CH_3CH_2OH	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_3OH$	$CH_3(CH_2)_4OH$	$CH_3(CH_2)_5OH$
CB[6]	2.64	2.61	2.53	2.73	2.71
α-CD	0.99	1.46	1.91	2.51	2.90

Table 3: Calorimetrically determined log *K* values for the complexation of monovalent and divalent cations with CB[6] in HCO_2H/H_2O (1:1) at 25 °C and with [18]crown-6 in water.[66,75]

	Li^+	Na^+	K^+	Rb^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
CB[6]	2.38	3.23	2.79	2.68	2.80	3.18	2.83
[18]crown-6	–	0.80	2.03	1.56	<0.5	2.72	3.87

4.2 Lessons Learned from CB[6]

Compared to CB[6], which recently celebrated its 100th birthday, the supramolecular chemistry of CB[5], CB[7], CB[8], and CB[10], which were isolated only 5 years ago, is relatively undeveloped. While these CB[*n*] homologues promise much new chemistry, many of the basic lessons learned from the studies of CB[6] can, we hypothesize, be transferred to CB[*n*]. This section presents those lessons from a largely mechanistic viewpoint: Scheme 2 depicts a comprehensive mechanism for the interaction of CB[6] with protons, metal ions, amines, and ammonium ions.

4.2.1. Protonation of CB[6] at the Carbonyl Groups Lining the Portals

CB[6] is a weak base ($pK_a = 3.02$) that can be protonated in moderately acidic media. Accordingly, when binding studies are conducted with CB[6] in strongly acidic media (for example, HCO_2H/H_2O (1:1)) H^+ competes with guest binding (Scheme 2, red equilibria). Comparisons between binding constants measured in different media must, therefore, be treated with caution.

4.2.2. Binding of Metal Ions by CB[6]

Given that CB[6] binds H^+ at the ureido carbonyl groups of the portals, it is perhaps unsurprising that CB[6] also binds alkali-metal, alkaline-earth, transition-metal, and lanthanide cations in homogenous solution (Scheme 2, blue equilibria).[4,63,66,67,76–79] Table 3 shows the binding constants determined by Buschmann et al. for CB[6] with a variety of monovalent and divalent cations. The selectivity between the different cations is less than tenfold. The low selectivity observed and the lack of a simple trend in $\log K$ values is attributed to a mismatch between the ionic radii of the cations and the annular radius of the relatively rigid CB[6] ionophore (1.95 Å). The metal-binding equilibria (Scheme 2, blue equilibria) are in competition with protonation (red equilibrium); thus, as the acidity of the solution is increased the observed $\log K$ values for metal binding should decrease. Table 4 documents the decrease in the $\log K$ value of 2.4 units observed for CB[6]·Ba^{2+} upon changing the medium from water to water/HCO_2H (1:1).

Table 4: Calorimetrically determined log *K* values for the complexation of Ba^{2+} with CB[6] in HCO_2H/H_2O mixtures at 25 °C.[66,75]

HCO_2H/H_2O	50:50	40:60	30:70	25:75	0:100
log *K*	2.83	3.50	4.13	4.39	5.23

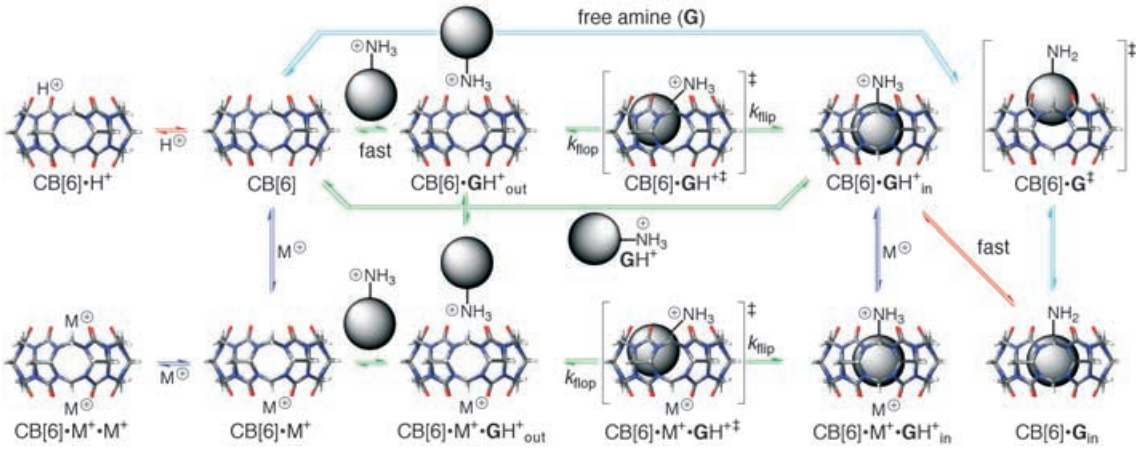
4.2.3. Preference of CB[6] for Positively Charged Organic Guests—Ion–Dipole Interactions

In their pioneering work, Mock and co-workers observed by a series of ^1H NMR competition experiments that alkylammonium ions bind tightly to CB[6] in HCO_2H/H_2O (1:1) and measured binding constants of 10^1–$10^7\ M^{-1}$. A selection of the results are given in Table 5.[2,72,80–82] Buschmann and coworkers have measured the corresponding thermodynamic parameters (ΔH and ΔS).[83] The experiments carried out by Mock and Shih were facilitated by two unusual characteristics

Table 5: Association constants measured for CB[6] with a variety of amines in H_2O/HCO_2H (1:1) at 40 °C.

Entry	Amine	K_a [M^{-1}]
1	NH_3	83
2	$H_2N(CH_2)_6H$ (**2**)	2300
3	$H_2N(CH_2)_6OH$ (**3**)	1200
4	$H_2N(CH_2)_6NH_2$ (**4**)	2800000
5	c-$(CH_2)_2CHCH_2NH_2$ (**5**)	15000
6	c-$(CH_2)_3CHCH_2NH_2$ (**6**)	370000
7	c-$(CH_2)_4CHCH_2NH_2$ (**7**)	330000
8	c-$(CH_2)_5CHCH_2NH_2$ (**8**)	80[a], 110000[b]
9	4-$MeC_6H_4CH_2NH_2$ (**9**)	320
10	3-$MeC_6H_4CH_2NH_2$ (**10**)	n.d.[c]
11	2-$MeC_6H_4CH_2NH_2$ (**11**)	n.d.[c]
12	$H_2N(CH_2)_5NH_2$ (**12**)	2400000
13	$H_2N(CH_2)_2S(CH_2)_2NH_2$ (**13**)	420000
14	$H_2N(CH_2)_2O(CH_2)_2NH_2$ (**14**)	5300

[a] Ref. [85]. [b] Measured for the hydrochloride salt in D_2O.[60] [c] n.d. = no binding detected.



Scheme 2. Comprehensive mechanistic scheme for molecular recognition by CB[6]. Red arrow: protonation; Blue arrow: cation binding, green arrow: ammonium ion binding, light blue arrow: amine binding.

of the host–guest complexes of CB[6]. First, the interior of CB[6] constitutes a ^{1}H NMR shielding region and upfield shifts of 1 ppm are common. The regions just outside the portals lined with carbonyl groups are weakly deshielding. Second, dynamic exchange processes between free and bound guest are often slow on the NMR time scale, thus allowing a direct observation of the free and bound guest simultaneously. To establish the importance of ion–dipole interactions relative to hydrogen bonds in the formation of CB[6] complexes (Figure 5), Mock and Shih considered the relative

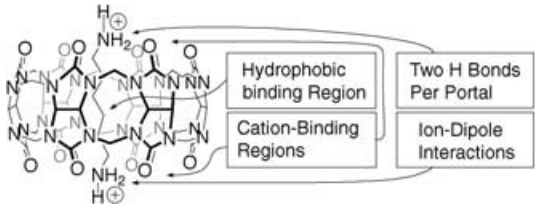


Figure 5. Representation of the different binding regions of CB[6] and the geometry of the complex between CB[6] and the hexanediammonium ion.

binding affinities of **2**–**4** (Table 4, entries 2–4). "Formal replacement of the terminal hydrogen of *n*-hexylamine with another amino group enhances binding 1200-fold. […] However, replacement of this hydrogen by a *hydroxyl* group contributes nothing to the stabilization of the complex. […] While the alcohol (and ammonium ions) may be hydrogen bonded in the complex, in the absence of CB[6] they would also be fully hydrogen bonded. […] The consequential feature of ammonium ions is that they are *charged*. […] Hence, it is our understanding that the high specificity for ammonium ions is largely an electrostatic *ion–dipole attraction*."[72] The preference of CB[6] for charged guests will transfer to the other members of the CB[*n*] family, but the relative importance of electrostatic interactions versus the hydrophobic effect may change as the cavity size increases. Blatov and coworkers recently developed a computational technique based on crystallographic data to identify suitable guests for each member of the CB[*n*] family.[84]

4.2.4. *Binding Selectivity of CB[6]*

The relative rigidity of CB[6] and the close juxtaposition of two binding regions that favor positively charged groups with one that favors hydrophobic residues imparts high selectivity to the binding of CB[6] (Figure 5). For example, Mock found that alkyl amines and alkane diamines exhibit length-dependent selectivity for CB[6]. Figure 6 shows a plot of the log K_a value versus chain length. CB[6] prefers butylamine relative to propylamine (8-fold) and pentylamine (4-fold) whereas pentanediamine and hexanediamine are preferentially bound relative to butanediamine (15-fold) and heptanediamine (64-fold). These high selectivities have been used to construct molecular switches (see Section 5.1). CB[6] is also size-selective: for example, it forms stable complexes with **6** and **7** whereas the three- and six-membered ring analogues **5** and **8** are rejected by CB[6] (Table 4, entries 5–8).

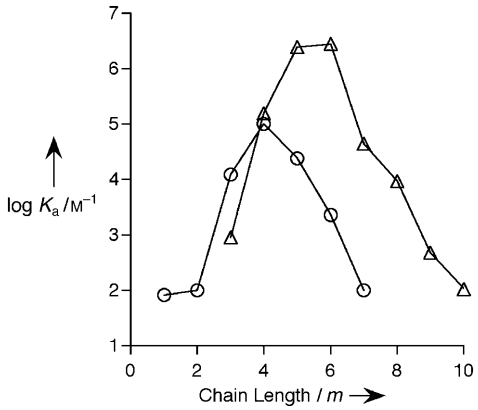


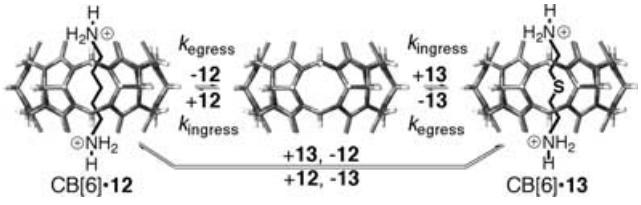
Figure 6. Relationship between the binding constant (log K_a) versus chain length m for $H(CH_2)_mNH_3^+$ (○) and $^+H_3N(CH_2)_mNH_3^+$ (△).

Similarly, CB[6] selects guests based on shape. For example, even though **7** and **9** have similar included volumes (86 versus 89 Å^3), the former binds 1000-fold more strongly (Table 4, entries 7 and 9).[60] Similarly, **9** is included within CB[6] whereas the *ortho* and *meta* isomers **10** and **11** are not bound (Table 4, entries 9–11). Lastly, CB[6] displays functional-group selectivity. For example, **12** binds 6-fold more tightly than **13**, which in turn binds 79-fold more tightly than **14** (Table 4, entries 12–14). Mock and Shih attribute this trend "to a solvation effect operating primarily on the uncomplexed guest; oxygen has greater intrinsic hydrophilicity than does sulfur, and a methylene group is more hydrophobic than is a thioether linkage."[72]

4.2.5. *Mechanistic Aspects of Association, Dissociation, and Exchange of Guests*

If CB[6] and other members of the CB[*n*] family are to become important components of molecular machines, it is critical that the factors controlling the kinetic and mechanistic aspects of their recognition behavior be thoroughly understood. In contrast to the behavior of most synthetic receptors in aqueous solution, CB[6] commonly displays slow kinetics of guest association, dissociation, and exchange on the NMR time scale. As discussed in Sections 4.2.1 and 4.2.2, CB[6] readily binds protons and metal ions at its portals that are lined with carbonyl groups. These equilibria compete with guest binding and lower the K_a value for guest binding accordingly (Scheme 2, red and blue equilibria).

Mock and Shih initially investigated the kinetics of guest exchange[72,82] according to the two limiting mechanisms shown in Scheme 3: 1) an associative mechanism that resem-



Scheme 3. Associative and dissociative mechanisms for guest exchange.

bles an S_N2 reaction, and 2) a dissociative S_N1-like mechanism. The kinetics of displacement, which can be followed by ^{1}H NMR spectroscopy, are first order in the CB[6]·**12** complex and independent of the concentration of the displacing guest which implies that the dissociative S_N1-like mechanism is followed. Values of k_{egress} range from $1.6\times10^{-5}\ s^{-1}$ (CB[6]·**7**) to $>10^2\ s^{-1}$ (CB[6]·**5**), which allowed the calculation of $k_{ingress}$ values of CB[6]·**7**: $5.5\ M^{-1}\ s^{-1}$; CB[6]·**5**: $>10^6\ M^{-1}\ s^{-1}$ based on a knowledge of the K_a value ($K_a = k_{ingress}/k_{egress}$). Interestingly, the rates of ingression *do not* correlate with values of K_a. Instead, the rates of ingression are influenced by the width of the guest (**7**: 5.7 Å) when that width exceeds the diameter of the portal of CB[6] lined with carbonyl groups (3.9 Å). Accordingly, significant deformation of the portals of CB[6] must occur in the transition state for ingression to allow access to its interior which raises its free energy and reduces the $k_{ingress}$ value. Although CB[6] is commonly regarded as being a rigid host, it is subject to deformation in the transition states during ingression and egression of the guests and even in the ground state of its complexes. For example, the X-ray crystal structure of CB[6]·4-Me$C_5H_4NH^+$ shows an ellipsoidal-shaped macrocycle that is elongated by 1.31 Å along the plane defined by the guest molecule.[86] Even larger deformations can be observed during molecular mechanics calculations of larger CB[*n*] complexes and even in the X-ray crystal structure of CB[5]@CB[10] which shows an ellipsoidal deformation of 2.1 Å.[9]

4.2.6. *Association and Dissociation Proceed via a Transiently Formed Exclusion Complex*

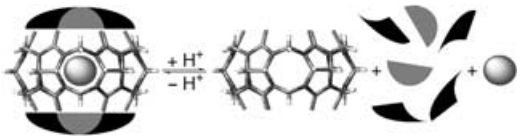
Mock and Shih recognized the possibility of two different modes of binding for an ammonium ion guest: the formation of an inclusion complex and an exclusion complex (for example, Scheme 2, CB[6]·**G**H^+_{in} and CB[6]·**G**H^+_{out}).[72] The equilibrium between those two isomeric complexes depends mainly on the size and shape of the attached alkyl groups. In a seminal study Knoche, Buschmann, and co-workers monitored the binding of **9**H^+ to CB[6] by UV/Vis measurements and found that the observed kinetic behavior could not be adequately explained by a simple equilibrium between CB[6], **9**H^+, and CB[6]·**9**H^+. Adequate modeling of the data requires the existence of two complexes: one in a fast pre-equilibrium with CB[6] and a second representing the spectroscopically observed inclusion complex CB[6]·**9**H^+_{in}.[4] Knoche, Buschmann, and co-workers proposed that the exclusion complex CB[6]·**9**H^+_{out} (shown in Scheme 2 as the general form CB[6]·**G**H^+_{out}) is the intermediate in fast pre-equilibrium. Nau and co-workers recently suggested that the transition state connecting the exclusion complex to the inclusion complex can be described by a flip-flop process (for example, Scheme 2, [CB[6]·**G**H^+]‡) in which the appended alkyl group pivots into the cavity without breaking its N-H···O hydrogen bonds.[60,85]

4.2.7. *pH-Dependency of the Transition States*

Although Mock and Shih showed early on that the rate of guest exchange does not respond to changes in pH in acidic solution (pH 1–4) they were unable to work at higher values of pH because of the limitations of the solvent mixture employed (HCO_2H/D_2O (1:1)). In important contributions, Nau and co-workers have studied the complexation of CB[6] with **8** as a function of pH (1–12), temperature (25–72 °C), cation identity, and cation concentration.[60,85] Most interestingly, the value of K_a is nearly constant in the region between the pK_a of CB[6] (3.02) and the pK_a of **8**H^+ (10.50); at lower and higher pH values, the value of K_a decreases as either H^+ competes with **8**H^+ for CB[6] (Scheme 2, red equilbria) or as the complex CB[6]·**8**H^+ is deprotonated to yield amine complex CB[6]·**8**. The rate constants for ingression and egression undergo dramatic increases near the pK_a of **8** and CB[6]·**8**H^+ (11.75), respectively. These dramatic changes can be explained by the involvement of the free amine **8** in the ingression and egression process (Scheme 2, **G**). Accordingly, Nau and co-workers included a new set of equilibria involving CB[6] and **8** into our general mechanistic understanding of CB[6] complexation (Scheme 2, light blue arrows). The free amine undergoes egression ($k_{egress}(\mathbf{8}) = 4.7\times10^{-6}\ s^{-1}$, $k_{egress}(\mathbf{8}H^+) = 1.45\times10^{-3}\ s^{-1}$) over 300-fold faster than its ammonium ion form. Similarly, the ingression rate constant ($k_{ingress}(\mathbf{8}) = 0.0145\ M^{-1}s^{-1}$, $k_{ingress}(\mathbf{8}H^+) = 8.0\times10^{-4}\ M^{-1}s^{-1}$) was 18-fold larger for the free amine. These results are extremely important for the development of molecular machines based on CB[*n*] since they indicate that not only can complexation be turned on and off by changes in pH, but also that the operational speed can be changed (up or down) by more than an order of magnitude.

4.2.8. *Studies on CB[6] in Saline Solution*

One of the major challenges that has faced the study of the CB[*n*] family is their poor solubility in aqueous and organic solution. For this reason, the majority of quantitative studies of binding with CB[6] have used HCO_2H/H_2O (1:1) as the solvent. It was known as early as 1992 that CB[6] binds to alkali and alkaline-earth cations in pure water and reaches a higher saturation concentration.[63] For example, the solubility of CB[6] increases dramatically in 0.2 M Na_2SO_4 (66 mM), LiCl (0.94 mM), KCl (37 mM), CsCl (59 mM), and $CaCl_2$ (70 mM). It was not until 1996, however, when Kim and co-workers reported that the solubilization of CB[6] in aqueous saline solution allows the study of guest binding in neutral water that the full importance of this discovery was realized.[87] The X-ray crystal structure of CB[6]·Na_4·$(H_2O)_{17}$·$(SO_4)_2$·THF revealed that the sodium ions act as lids that result in the encapsulation of THF (Scheme 4). Even more remarkably, the addition of CF_3CO_2H releases THF from this CB[6]·THF complex ($K_a = 510\ M^{-1}$) by competitive binding;[88] the process can be reversed by the addition of Na_2CO_3. In a related paper,



Scheme 4. Adding a lid to CB[6] and its removal. Sphere: THF, hemispheres: Na^+, wedges: H_2O.

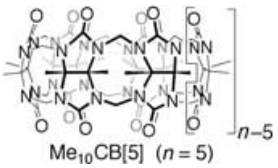
Kim and co-workers showed that the lids are not merely innocent by-standers, they actively participate in the binding of THF through formation of cesium–oxygen bonds.[89] Despite the reduced binding constants arising from competition with metal ions in solution, these pioneering studies showed that the supramolecular chemistry of CB[*n*] would not be limited to strongly acidic conditions. Currently, hydrochloride salts of suitable guests are often employed for the investigations since the resulting complexes are rendered water soluble in the absence of competing H^+ or M^+ ions.

4.3. Host–Guest Properties of the Homologues

We have focused on selected examples to illustrate the general principles and applications of CB[*n*] chemistry. There are, of course, a wealth of elegant contributions from numerous research groups that we have not been able to cover. This section highlights those examples that are not presented elsewhere in this Review.

4.3.1. CB[5] and Me_{10}CB[5]

The supramolecular chemistry of CB[5] and Me_{10}CB[5][90] (see Section 8.4) is controlled by the narrow portals lined with carbonyl groups which provide entry to a cavity of low



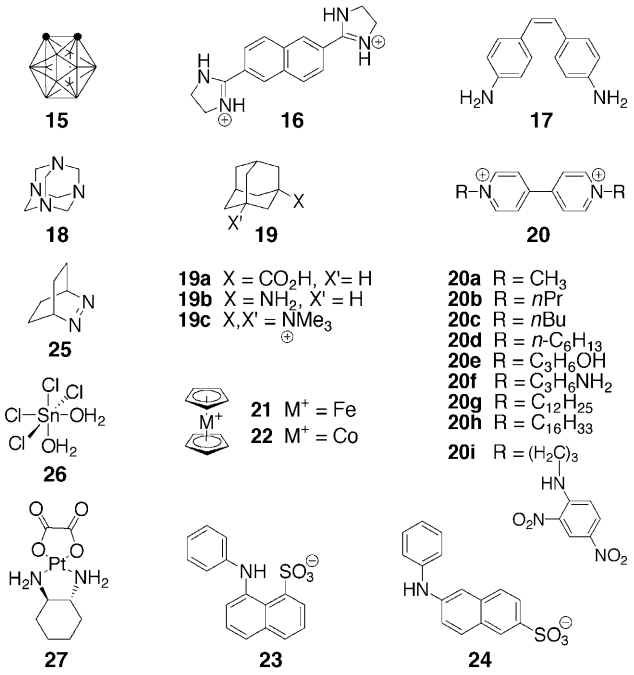
volume. Consequently, much of the supramolecular chemistry of CB[5] has been limited to the binding of protons as well as metal and ammonium ions at their portals.[67,68,76,77,79,91] Bradshaw, Izatt, and co-workers studied the ability of Me_{10}CB[5] to bind monovalent and divalent cations in HCO_2H/H_2O (1:1) and found a remarkably high selectivity toward Pb^{2+} ions ($> 10^{5.5}$ relative to alkali cations).[79] Somewhat surprisingly, CB[5] itself does not display a similar selectivity for Pb^{2+} ions.[76] CB[5] and Me_{10}CB[5] form weak host–guest complexes with α-, β-, and γ-cyclodextrins ($K_a \approx 10$).[61] Recently, Tao and co-workers reported that hexamethylenetetramine is capable of forming a lid on CB[5].[92] The most remarkable property of CB[5] and Me_{10}CB[5] is their ability to bind gases[93] (for example, Kr, Xe, N_2, O_2, Ar, N_2O, NO, CO, CO_2, and CH_4) and small solvents (for example, CH_3OH and CH_3CN). Such complexes were observed by Dearden and co-workers[91,94,95] by mass spectrometric investigations, by Miyahara et al.[96] in aqueous solution and the solid state, and discussed by Day[34,41] and Miyahara[45] in the patent literature. Miyahara demonstrated the reversible sorption and desorption of gas by solid Me_{10}CB[5], with capacities up to 40 $mL\,g^{-1}$ (N_2O). These results suggest that Me_{10}CB[5] and CB[5] may be of practical utility in reducing the level of NO_x gases from air.

4.3.2. CB[6]

The pioneering work of Buschmann et al. has established equilibrium constants and in many cases the enthalpic (ΔH) and entropic (ΔS) contributions to ΔG for the binding of CB[6] to ω-amino acids and ω-amino alcohols,[97] aliphatic alcohols, acids, and nitriles,[73] bipyridine derivatives,[98] aromatic compounds,[99,100] non-ionic surfactants and poly(ethylene glycols),[101] cyclodextrins,[61] diamides,[102] and α-amino acids and dipeptides.[103] Analogous to CB[6]·M^+ complexes, the values of K_a measured for the complexation of organic guests with CB[6] increase as the percentage of HCO_2H decreases as a result of reduced competitive protonation of CB[6].[104] Knoche and co-workers studied the complexation of azobenzenes with CB[6],[4,105] Bartik and co-workers the binding of neutral guests such as Xe, THF, and CF_3CO_2H in CB[6] by ^{129}Xe, ^{19}F, and ^1H NMR spectroscopy,[88,106] and Dearden and co-workers the formation and dissociation of CB[6] pseudorotaxanes and the corresponding exclusion complexes in the gas phase.[91] The research groups of Wagner and Buschmann have shown that CB[6] enhances the fluorescence of 1,6- and 2,8-anilinonaphthalene sulfonates in solution and the solid state,[107–109] while Wu and co-workers shown recently that CB[6] also binds diazonium compounds.[110]

4.3.3. CB[7]

CB[7] is slightly more voluminous than β-CD (Table 1), and thus can bind a wider range of guests than CB[6] or CB[5]. CB[7] binds a variety of positively charged aromatic compounds including adamantanes and bicyclooctanes,[5,92,111,112] naphthalene,[7,113,114] stilbene,[115] viologen,[116–120] *o*-carborane,[121] ferrocene,[5,122] and cobaltocene[122] derivatives (**15**–**25**). CB[7] also binds the metal complexes



26[123] and **27**[5,41] as well as related compounds[124,125] which suggests the use of CB[7] to reduce toxicity in cancer treatment.

A number of elegant studies by Kaifer and co-workers have demonstrated that many of the unusual properties of CB[6] are retained by CB[7]. For example, Ong and Kaifer determined the values of K_a for CB[7]·**20a** in 0–0.2 M NaCl and 0–0.2 M $CaCl_2$ and demonstrated that Na^+ and Ca^{2+} ions compete with **20a** for binding to CB[7] which reduces the K_a value by a factor of 9–40.[119] In two elegant studies, the research group of Kaifer showed that the CB[7] bead can reside in different locations along guests containing multiple binding sites (for examplw, CB[7]·**20a**–CB[7]·**20g**).[120,126] CB[7] resides on the longer butyl and hexyl chains of **20c** and **20d** whereas it resides on the viologen nucleus of derivatives that contain shorter (**20a** and **20b**) or hydrophilic residues (**20e** and **20f**). These results imply that CB[7] retains the highly selective binding properties noted above for CB[6]. CB[7] forms a pseudorotaxane with **20i**. Nau and co-workers have used CB[7]·2,3-diazabicyclo[2.2.2]oct-2-ene to show that the polarizability of the CB[7] cavity is extremely low[127,128] and to distinguish between alternative mechanisms in fluorescence-quenching studies.[58,129] Wagner et al. have studied the enhancement in fluorescence observed upon binding of anilinonaphthalene sulfonates by CB[7].[113] CB[7] was recently reported to form a weak 1:2 exclusion complex with C_{60} by high-speed vibration milling,[130] and more recently CB[7] has been used as an additive to separate positional isomers by capillary electrophoresis.[131]

4.3.4. *CB[8]*

The cavity of CB[8] is similar in terms of volume to γ-CD, but is less conformationally flexible. CB[8] behaves like a larger version of CB[5]–CB[7] in many ways, but also exhibits more complex recognition behavior. Just like CB[5]–CB[7], CB[8] prefers to bind to positively charged guests by ion–dipole interactions.[7,132] CB[8] readily binds single guest molecules that partially (CB[8]·**20a**, $K_a = 1.1 \times 10^5\ M^{-1}$) or completely (CB[8]·**19b**) fill its cavity. In contrast to CB[5]–CB[7], the voluminous cavity of CB[8] is capable of simultaneously binding two aromatic rings (Figure 7), as shown by the ready formation of the termolecular complex CB[8]·**16**·**16**.[7,133] Even more strikingly, a mixture of CB[8] and CB[8]·$\mathbf{16}_2$ is formed when CB[8] and **16** are mixed in a 1:1 ratio. This result demonstrates there is cooperativity between the binding of the first and second aromatic rings. Kim and co-workers have also demonstrated the selective formation of a hetero-termolecular complex CB[8]·**20a**·**28** which results in

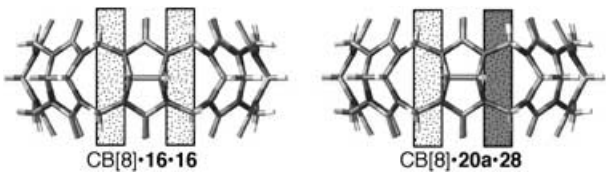
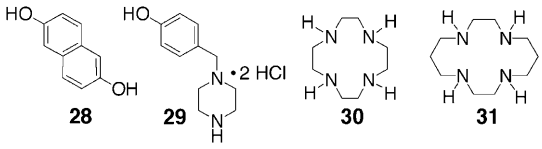


Figure 7. Schematic representations of the termolecular complexes CB[8]·**16**·**16** and CB[8]·**20a**·**28**.

enhanced charge-transfer interactions between **20a** and **28** in the complex.[134] This recognition motif has been used to



control intramolecular folding processes[135] and the formation of vesicles.[136] More recently, Tao and co-workers have shown that aromatic piperazine derivatives form a mixture of 1:1 and 1:2 complexes with CB[8] (for example, CB[8]·**29** and CB[8]·$\mathbf{29}_2$).[137] Similarly, Fedin and co-workers recently reported the crystal structure of the CB[8]·$PhPO(OH)_2$·$PhPO(OH)_2$ complex.[138] CB[8] is even capable of encapsulating cyclen (**30**) or cyclam (**31**). Even more remarkably, CB[8]·**30** and CB[8]·**31** can coordinate with Cu^{II} or Zn^{II} ions which results in macrocycle within macrocycle complexes that resemble the Russian Matrioshka dolls.[139]

4.3.5. *CB[10]*

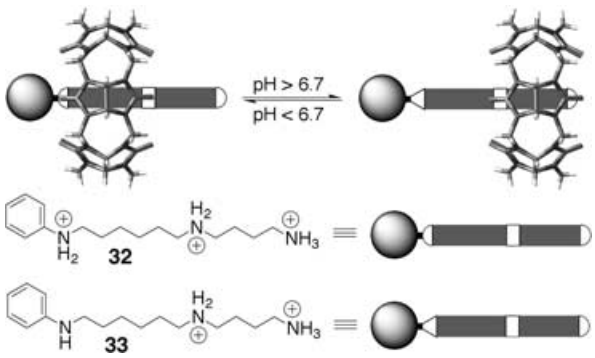
Day et al. successfully isolated CB[10] as its CB[5]@CB[10] complex (Figure 3). The structure of this remarkable complex was established by X-ray crystallography to resemble a gyroscope.[9] Despite the fact that it was not possible to isolate free CB[10] by removal of CB[5], chemical exchange between free and bound CB[5] was demonstrated through the use of ^{13}C-labeled CB[5]. Such molecular gyroscopes and the related molecular ball bearing[121] CB[7]·**15** are potential components of future molecular machines.

5. Control over the Recognition Processes

The creation of molecular machines[140] by self-assembly processes is currently of great interest. One of the most fundamental molecular machines is a molecular switch that can toggle between two different states by appropriate environmental stimuli (chemical, electrochemical, or photochemical). The CB[*n*] family is ideally suited for such applications because of the high affinity and high selectivity of their binding processes.

5.1. Chemical Control—Molecular Switches

An early example of a molecular switch was published by Mock and Pierpont in 1990. In this study, CB[6] was induced to shuttle along a triamine string by changing the pH value (which resulted in changes in the protonation state of the aniline N atom; Scheme 5).[141] At pH values below the pK_a value of the anilinium group (6.73), the CB[6] bead resides in the hexanediammonium region with its higher binding constant (CB[6]·**32**, left); above the pK_a value, the bead moves to the still fully protonated butanediammonium region (CB[6]·**33**, right). Kim and co-workers have reported



Scheme 5. CB[6]-based molecular switch.

molecular switches based on CB[6] rotaxanes with UV/Vis and fluorescence outputs[142] that can be actuated by changes in the pH value, but requires both the correct pH value and heat for the switch to be turned off,[143] and that a slow transformation occurs from the kinetic to the thermodynamically more-stable rotaxane.[144]

5.2. Photochemical Control

The ability of the two portals lined with carbonyl groups in the CB[*n*] family to orient two guests within their cavity (see Section 4.3.4) results in opportunities to accelerate and control chemical reactions. Kim and co-workers found that CB[8] binds two equivalents of (*E*)-**34** to form CB[8]·**34**·**34**.[145] Irradiation of this complex (300 nm, 30 min) results in the formation of CB[8]·*syn*-**35** and only a trace of CB[8]·*anti*-**35** (Scheme 6). Free **36** is released upon addition of base. The dimerization of (*E*)-**34** within γ-CD is slower (72 h) and less stereoselective (*syn*:*anti* = 80:20). CB[8] accelerates and controls the stereochemistry of the [2+2] photoreaction.

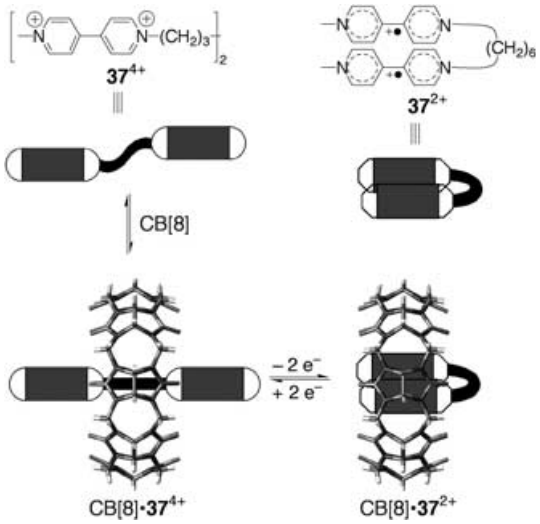
A solution of CB[7] and (*E*)-**34** forms the complex CB[7]·(*E*)-**34** which, upon irradiation (350 nm) converts nearly quantitatively into CB[7]·(*Z*)-**34**. Remarkably, CB[7]·(*Z*)-**34** is stable at room temperature for 30 days.[115] This result demonstrates that CB[7] is able to control the otherwise unfavorable equilibrium between CB[7]·(*E*)-**34** and CB[7]·(*Z*)-**34**.

5.3. Electrochemical Control

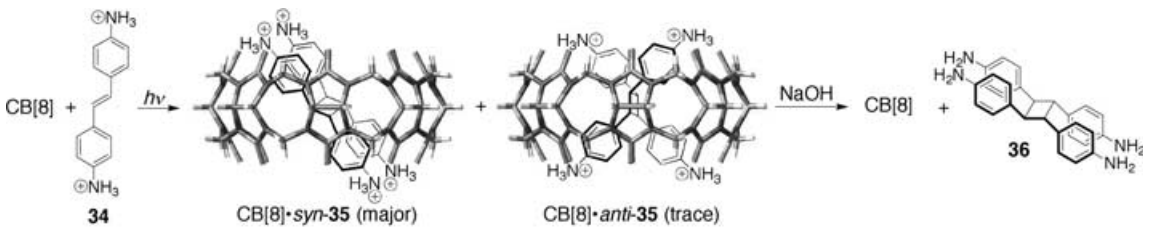
The CB[*n*] family displays a marked preference to interact with positively charged guest species. For example, the research groups of Kim[116] and Kaifer,[117] studied the interaction of CB[7] with $\mathbf{20a}^{2+}$ ($K_a = 2\times10^5\,\text{M}^{-1}$) and its reduced forms $\mathbf{20a}^{\bullet+}$ ($K_a = 8.5\times10^4\,\text{M}^{-1}$) and $\mathbf{20a}^{0}$ ($K_a = 2.5\times10^2\,\text{M}^{-1}$) by electrochemical measurements. Two unusual observations were made: 1) the presence of CB[7] prevents the dimerization of $\mathbf{20a}^{\bullet+}$ and 2) the reduction of $\mathbf{20a}^{\bullet+}$ occurs by a direct electron-transfer pathway. Related observations were made by Ong and Kaifer for the CB[7]·**21** and CB[7]·**22** complexes ($K \geq 10^6\,\text{M}^{-1}$).[122]

The cavity of CB[8] is large enough to accommodate two flat aromatic ring systems, provided they possess complementary electrostatic profiles (such as in the charge-transfer complex CB[8]·**20a**·**28**). Very interestingly, Kim and co-workers found that CB[8] binds a single molecule of $\mathbf{20a}^{2+}$ (CB[8]·$\mathbf{20a}^{2+}$, $K_a = 1.1\times10^5\,\text{M}^{-1}$); upon electrochemical reduction, however, the complex undergoes disproportionation to form a mixture of CB[8] and the termolecular complex CB[8]·$\mathbf{20a}^{\bullet+}$·$\mathbf{20a}^{\bullet+}$.[132a] The presence of CB[8] enhances the dimerization of $\mathbf{20a}^{\bullet+}$ by a factor of 10^5. Thus, electrochemistry allows quantitative control of the stoichiometry of the host–guest complex within CB[8]!

The dimerization of the tetrathiafulvalene radical cation is also promoted by CB[8].[146] Armed with this knowledge, Kim and co-workers prepared dimeric viologen $\mathbf{37}^{4+}$.[132b] This compound forms a stable 1:1 complex with CB[8] (CB[8]·$\mathbf{37}^{4+}$, $K_a = 2.3\times10^5\,\text{M}^{-1}$) where the CB[8] bead resides mainly on the hexamethylene spacer (Scheme 7). Electrochemical reduction (or light-induced chemical reduction with $[\text{Ru}^{\text{II}}(\text{bpy})_3]$) effects a folding process which results in the formation of molecular loop CB[8]·$\mathbf{37}^{2+}$ which displays dramatically reduced dimensions relative to CB[8]·$\mathbf{37}^{4+}$ (28 × 18 versus



Scheme 7. A [2]pseudorotaxane-based molecular machine.



Scheme 6. [2+2] photoaddition reaction mediated by CB[8].

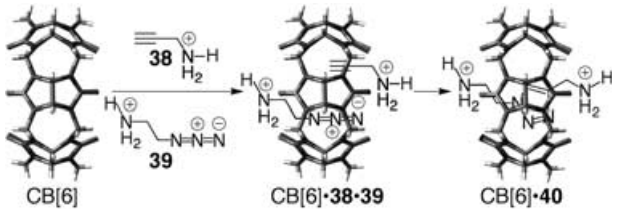
15 × 18 Å). The observed large changes in size and shape may be useful in the design of molecular actuators.[132c]

6. Applications of the CB[n] Family

The outstanding recognition properties of the CB[*n*] family have led to their use in numerous applications, some of which are highlighted in this section.

6.1. Catalysis

A long-standing challenge in supramolecular chemistry has been the design of catalysts. Mock et al. recognized that CB[6] was ideally suited for this purpose because of the presence of two portals lined with carbonyl groups that can potentially recognize two ammonium ions, thus forming a termolecular complex that orients and compresses those substrates for chemical reaction.[147,148] Mock et al. studied the dipolar cycloaddition between azide **38** and alkyne **39** catalyzed by CB[6] in an elegant example of click chemistry

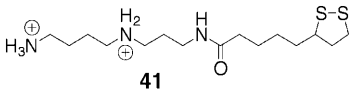


Scheme 8. Catalysis of a [3+2] dipolar cycloaddition inside CB[6].

(Scheme 8).[149] They found that the CB[6]-catalyzed reaction of **38** and **39** is a rare example of what is known as the Pauling principle of catalysis, which states that "the complementarity between an enzyme and the *transition state* for its conducted reaction ought to be greater than that between enzyme and the reactants".[147] Remarkably, CB[6] accelerates this reaction by a factor of 5.5×10^4 compared to the bimolecular reaction and renders it highly regioselective. The reaction also displays several features that are commonly observed in enzymatic reactions, namely: 1) reaching a limit in the reaction rate at high concentrations of **38** and **39**, 2) product release from CB[6]·**40** is rate-limiting, 3) inhibition of the substrate through formation of nonproductive termolecular complex CB[6]·**38**·**38**, and 4) competitive inhibition by nonreactive substrate analogues. Steinke's research group has used the CB[6]-promoted dipolar cycloadditon of azides and terminal acetylenes for the preparation of catalytically self-threading rotaxanes,[150,151] [2]-, [3]-, and [4]-rotaxanes and pseudorotaxanes,[152] as well as oligotriazoles.[153]

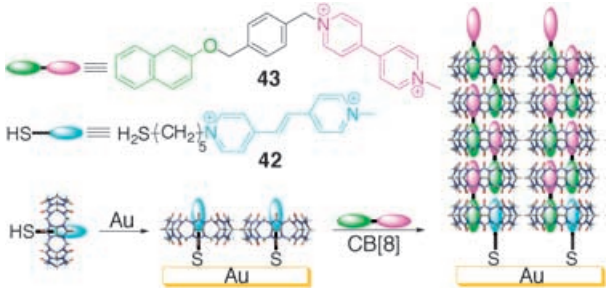
6.2. Self-Assembled Monolayers (SAMs)

To realize the full potential of pseudorotaxanes as components of molecular machines it is necessary to develop methods for their immobilization on solid substrates. Kim and co-workers have reported the functionalization of a gold surface with the pseudorotaxane CB[6]·**41**.[154] Surface plas-



mon resonance (SPR) studies have shown that SAMs comprising CB[6]·**41** undergo reversible dethreading and rethreading of the CB[6] beads upon treatment with 0.1 M NaOH followed by CB[6]. Cyclic voltametry measurements indicate that the SAM formed by pseudorotaxane CB[6]·**41** constitutes an effective barrier to redox processes involving $[Fe(CN)_6]^{3-}$: a quasireversible redox wave is observed after dethreading. This reversible gating behavior may have application in the design of surface-bound molecular machines.

More recently, Kim and co-workers have reported a surface-initiated supramolecular polymer based on CB[8]-stabilized charge-transfer interactions (Scheme 9). An aque-



Scheme 9. Formation of pseudorotaxane CB[8]·**42** on a gold substrate and formation of a surface-bound supramolecular polymer based on CB[8]-stabilized charge-transfer interactions.

ous solution containing CB[8] and thiol **42** results in the formation of pseudorotaxane CB[8]·**42**; dipping a gold substrate into this solution results in the formation of a self-assembled monolayer. Supramolecular polymerization from the CB[8]·**42** SAM was initiated by immersing the substrate in a solution containing CB[8] and **43**. The course of the reversible supramolecular polymerization could be monitored by FT-IR, SPR, and AFM and controlled by changing the conditions (time and concentration). The polymer consists of four CB[8] beads per chain on average.[155]

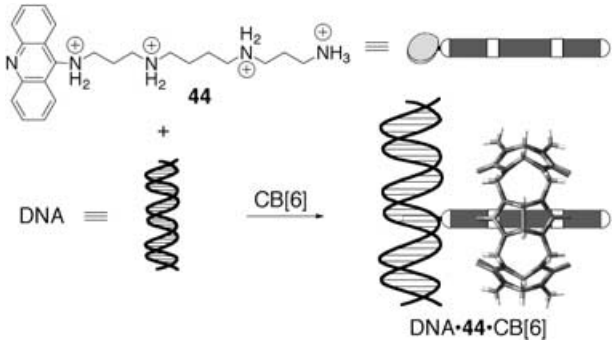
6.3. Waste-Stream Remediation of the Textile Industry

The application of CB[6] toward the complexation of indicator dyes such as congo red and methylene blue was published by Behrend et al. in 1905. Since then, the research groups of Buschmann[30,31,104,156–171] and Karcher[172–176] have studied the ability of CB[6] to effectively remove heavy metals, chromates and dichromate, aromatic substances, acid dyes, direct dyes, and reactive dyes from textile waste streams, quantified the influence of key parameters such as pH, temperature, salts, and surfactants on the process, and studied methods for regeneration of the solid phase. Taketsuji and

Tomioka found that Behrend's polymer was more efficient in these applications than CB[6].[35,177,178] Major issues that need to be resolved include loading levels, the covalent attachment of CB[6] to solid phases suitable for use in fixed-bed filters, and cost. The area has been reviewed previously.[14,19]

6.4. DNA Binding and Gene Transfection

Nakamura, Kim, and co-workers investigated a noncovalent approach to selectively deliver CB[6] to DNA.[179] The concept is illustrated in Scheme 10. Compound **44** contains



Scheme 10. Intercalation of acridine–spermine rotaxane CB[6]·**44** into DNA. The components are not drawn to scale.

acridine and tetramine regions which function as DNA intercalator and CB[6] binding elements, respectively. Mixing DNA, CB[6], and **44** results in formation of a termolecular complex (DNA·**44**·CB[6]) as monitored by gel electrophoresis. The DNA·**44**·CB[6] complex partially protects supercoiled DNA against cleavage by the restriction enzyme *Ban*II. In a complementary study, Kim and co-workers demonstrated that G3, G4, and G5 poly(propyleneimine) dendrimers bearing diaminobutane moieties (PPI-DAB) for binding CB[6] functions as a gene-delivery carrier.[180] The PPI-DAB·CB[6] conjugates have low cytotoxicity and successfully transfect Vero 76 and 293 cells with efficiencies only tenfold lower than poly(ethyleneimine), which is one of the most potent gene-transfer carriers.

7. Self-Assembly Processes Using CB[n]

This section describes the use of CB[*n*] in multicomponent self-assembly processes in solution and the solid state. The formation of CB[*n*] complexes with high affinity for binding a guest as well as their well-defined geometrical features make them particularly well-suited for these studies.

7.1. Molecular Necklaces

Interlocked structures such as rotaxanes and catenanes are the subject of intense investigation in supramolecular chemistry because of their potential use as molecular machines in nanotechnological applications.[140] Kim and co-workers have demonstrated the utility of the CB[*n*] family as a molecular bead in the formation of molecular necklaces ([*n*]MN) which contain $n-1$ rings threaded onto a single ring.[181–184] The members of the [*n*]MN family are topological isomers of the linear oligocatenanes exemplified by olympiadane (Figure 8).[185]

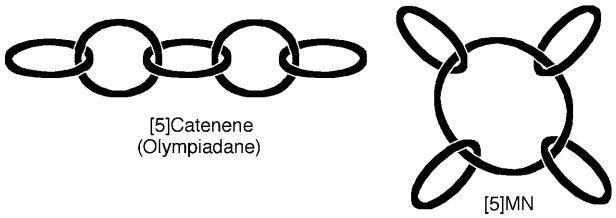
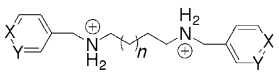
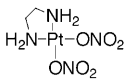


Figure 8. Oligocatenanes and molecular necklaces are topological isomers.

The interaction of **45** with CB[6] results in pseudorotaxane CB[6]·**45**. During this process the butanediammonium



45 $n = 1$, X = N, Y = CH
46 $n = 2$, X = CH, Y = N

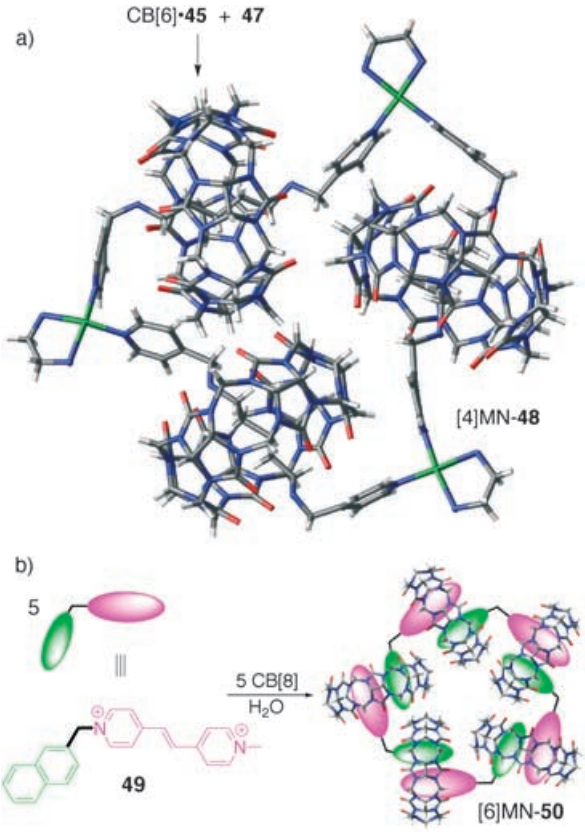


47

linker is rigidified in its all *trans* conformation, with the pyridyl groups displayed in roughly opposite directions. Heating CB[6]·**45** and **47** at reflux in water results in the formation of [4]MN-**48** through coordination of the pyridyl groups to the platinum centers (Scheme 11).[181] In a thorough study, the length of the alkanediammonium linker, the position of the pyridyl N atom (**45** versus **46**), and the temperature of the self-assembly process were found to control the equilibrium between [4]MN and [5]MN. Recently, Kim and co-workers demonstrated that their pseudorotaxane approach could be extended to different CB[*n*] and different noncovalent interactions. For example, **49** contains both electron-rich naphthalene rings and electron-poor dipyridylethylene units; these separate moieties are known to form a charge-transfer complex within CB[8]. To achieve formation of [6]MN, Kim and co-workers connected these two units by a methylene bridge whose angle of approximately 109° should favor the formation of a pentameric macrocycle. Indeed, the self-assembly process between CB[8] and **49** results in the formation of [6]MN-**50** as deduced by NMR spectroscopy, ESI mass spectrometry, and X-ray crystallographic analysis. Changing the length and angle of the linking groups should make it possible to synthesize molecular necklaces of different sizes, shapes, and number of CB[*n*] beads.

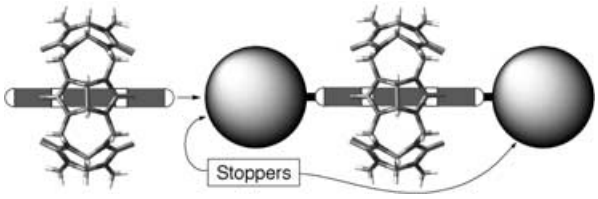
7.2. Pseudorotaxanes, Rotaxanes, and their Oligomeric Analogues

Rotaxanes—mechanically interlocked wheel and axle complexes—have assumed important roles in supramolecular



Scheme 11. Formation of molecular necklaces using: a) CB[6] and b) CB[8] as beads.

chemistry and nanotechnology because of their ability to undergo controlled motions with respect to one another in response to environmental stimuli. Most commonly, rotaxanes are prepared from pseudorotaxanes—non-interlocked wheel and axle complexes—through the addition of bulky stoppers by reactions that result in the formation of covalent bonds (Scheme 12). The circular shape and outstanding



Scheme 12. The stoppering approach to rotaxane formation.

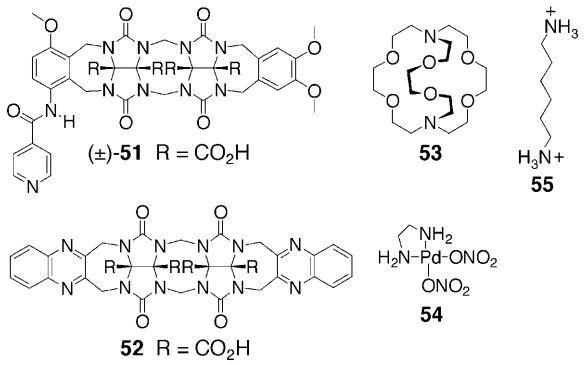
binding properties of CB[6] suggested its use as the wheel in rotaxane formation. Indeed, any CB[*n*] complex which extends past the rim of the cavity can be considered a pseudorotaxane starting material for reactions leading to the formation of rotaxane, polyrotaxane, and polypseudorotaxanes.[186] CB[6]-based rotaxanes have been prepared in solution by dipolar cycloadditions,[147,150–152,187] stoppering with dinitrophenyl groups,[188] amide-bond formation,[189–193] ionic interactions,[194] and coordination of alkylcobaloximes.[195,196] A variety of polymer backbones and side chains have been threaded with CB[6] beads including polyacrylamides and polystyrenes,[197] poly(hexamethyleneimine),[151,198] di- and polyviologen,[98,199] and poly(propyleneimine) dendrimers.[200] A rotaxane derived from Ph_2CB[6] (see Section 8.4) was stoppered with dinitrophenyl groups,[201] the CB[5]·spermine pseudorotaxane has been stoppered with benzoyl and furoyl groups,[202] and Newkome-type dendritic wedges containing viologen focal point functionality have been threaded with CB[7].[118]

7.3. Supramolecular Amphiphiles

Kim and co-workers reported the formation of a charge-transfer complex within CB[8] that triggered the assembly of vesicles.[136] Sonication of an equimolar mixture of CB[8], **28**, and **20g** or **20h** results in the formation of a turbid violet solution. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and dynamic light scattering measurements showed that the vesicles based on CB[8]·**20g**·**28** were nearly monodisperse with a diameter of 20 nm, whereas those based on CB[8]·**20h**·**28** had an average diameter of 870 nm. Remarkably, the vesicles are quite robust and retain their shape when allowed to dry on a substrate. Addition of cerium(IV) ammonium nitrate oxidizes **28** to the quinone which disrupts the charge-transfer complex and results in the collapse of the vesicles.

7.4. Self-Sorting Systems

Self-sorting—the ability to distinguish between identical and other molecules even within complex mixtures—is commonplace in natural and biological systems but is still rare in designed supramolecular systems.[203] The CB[*n*] family, with their high binding affinities, high selectivities, and reduced rates of chemical exchange are ideal components for self-sorting systems. Isaacs and co-workers demonstrated that a 12-component mixture comprising **51**$_2$·**54**$_2$, **52**$_2$, **53**·K^+, CB[6]·**55**, CB[8]·**20a**·**28**, and β-CD·**19a** undergoes a "social self-sorting" in aqueous solution.[111]



7.5. Crystal Engineering

The CB[*n*] family has been used extensively in crystal-engineering studies.

7.5.1. Polyrotaxanes

The use of CB[6] as a bead in the formation of polyrotaxanes in the solid state was the subject of an excellent review by Kim.[6] Kim's strategy uses the highly symmetrical CB[6] as a molecular bead to complex and conformationally order alkanediammonium ions containing pyridyl ligands at their termini. These pyridyl ligands subsequently coordinate to a variety of metal ions (for example, Cu^{II}, Co^{II}, Ni^{II}, Ag^{I}, and Cd^{II}). The X-ray structure of a polycatenated two-dimensional polyrotaxane net is illustrated in Figure 9.

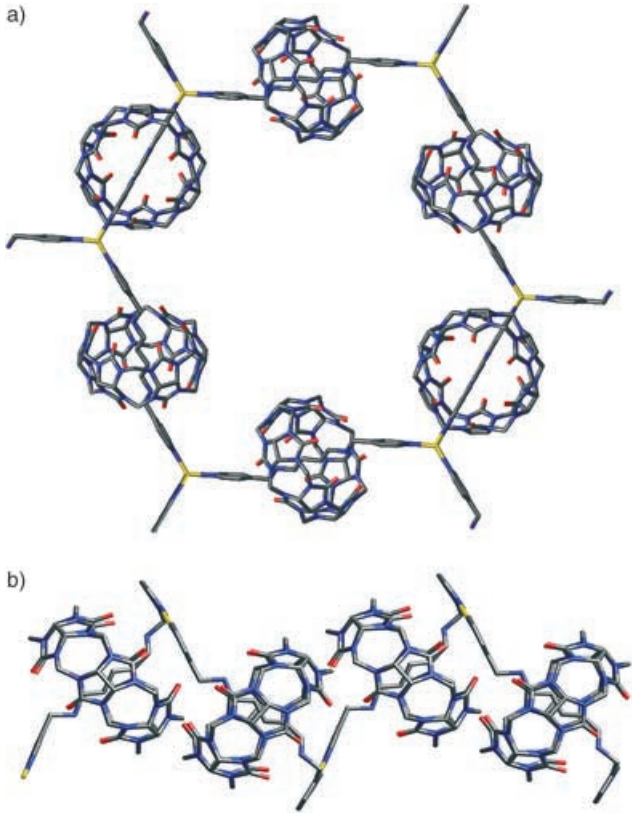


Figure 9. a) A portion of the polycatenated two-dimensional polyrotaxane network **56**, and b) the helical polyrotaxane **57** formed from CB[6], **46**, and $AgNO_3$. C: gray; N: blue; O: red; Ag: yellow.

Pseudorotaxane CB[6]·**45** is formed by threading CB[6] with **45**.[204] The CB[6] bead is held in position by ion–dipole interactions between the ammonium centers of the string (**45**) and the oxygen atoms of CB[6]. The addition of $AgNO_3$ results in a polyrotaxane (**56**) in which CB[6] is threaded on a 2D coordination polymer network (Figure 9a). The effects of structural variation of the components on the supramolecular structure are subtle: for example, the use of $Ag(O_3SC_6H_4CH_3)$ instead of $AgNO_3$ leads to the formation of a one-dimensional polyrotaxane coordination polymer whereas the use of **46** as the thread with $AgNO_3$ leads to helical polyrotaxane **57** (Figure 9b).[205] Other examples include zig-zag, square-wave, and linear one-dimensional polyrotaxanes, square-grid-shaped two-dimensional, and even three-dimensional polyrotaxane networks.[21,206–210]

7.5.2. CB[n] as a Ligand in Metal Complexes

The carbonyl groups lining the portals of CB[*n*] bind metal ions with high affinity and selectivity in solution and the solid state. Consequently, many X-ray crystal structures of CB[6] beads linked by various metal ions have been reported; we present three examples here that illustrate the approach. Fedin, Sykes, Clegg, and co-workers reported the crystal structure of an unusual trimetallic double cube cluster of $[Mo_6HgSe_8(H_2O)_{14}Cl_4]^{4+}$ which becomes sandwiched between adjacent CB[6] molecules and extends to form an infinite chain in the crystal (Figure 10a).[211,212] A triple-decker sandwich-type structure that forms upon crystallization of CB[6] and gadolinium bromide from water ($\{(CB[6])[Gd(H_2O)_4](CB[6])[Gd(H_2O)_4](CB[6])\}^{6+}$ Figure 10b) was reported by Fedin and co-workers.[213] An unusual aspect of this structure is that discrete structural units are formed containing only three CB[6] molecules connected by two Gd^{3+} ions and four hydrogen bonds. Such lanthanide-containing materials may be important in a variety of applications

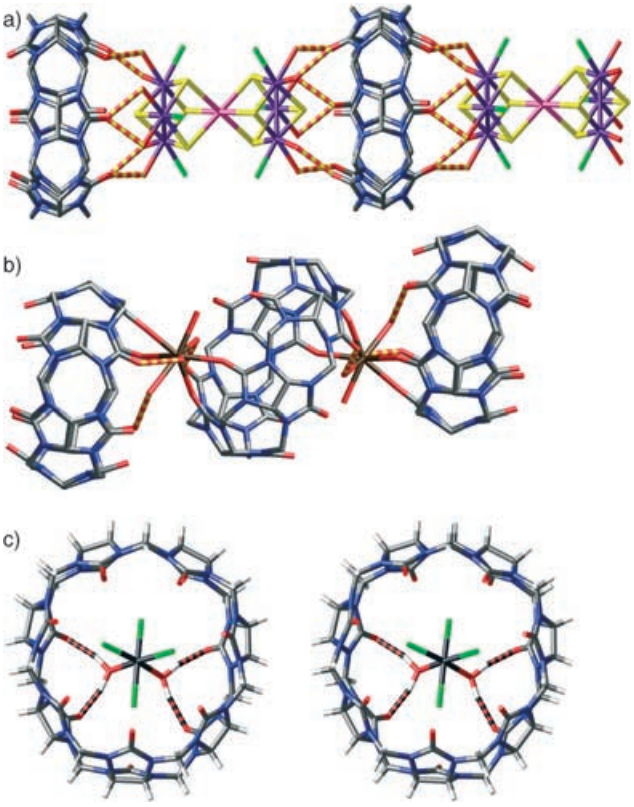


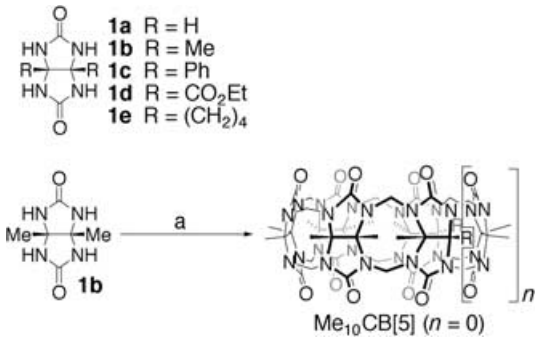
Figure 10. X-ray crystal structures of: a) $[Mo_6HgSe_8(H_2O)_{14}Cl_4]^{4+}$CB[6], b) $\{CB[6]\{Gd(H_2O)_4\}CB[6]\{Gd(H_2O)_4\}CB[6]\}^{6+}$, and c) a stereoview of *cis*-$[SnCl_4(OH_2)_2]$@CB[7]. C: gray; H: white; N: blue; O: red; Cl: green; Gd: brown; Se: yellow; Mo: purple; Hg: pink; Sn: gray; H bonds: striped.

including relaxation agents for magnetic resonance imaging, luminescent probes, and catalysts for the cleavage of DNA and RNA. The first endoannular metal halide complex of CB[7] was realized by Day and co-workers with the X-ray structure of *cis*-$[SnCl_4(OH_2)_2]$@CB[7] (**26**@CB[7], Figure 10c).[123] A CB[8] metal–aqua complex was recently realized by Fedin and co-workers with the structure of $Sr_2(H_2O)_{12}\cdot[Sr(H_2O)_3(NO_3)_2]_2CB[8]\cdot(NO_3)_4\cdot(H_2O)_8$ and a related complex.[214,215] Wu and co-workers recently reported a similar Cu(II) complex of CB[5].[216] Structures containing CB[6] complexed with a previously unknown tautomer of $HP(OH)_2$,[217] Rb^+,[218] Sm^{III},[219,220] Na^+,[87] Cs^+,[89] K^+,[221] Ca^{2+},[222,223] molybdenumselenide and tungstenselenide aqua complexes and related structures,[224–226] $[W_3S_4(H_2O)_9]^{4+}$ and related structures,[227–229] $[Nb_2(\mu\text{-}S_2)_2(H_2O)_8]^{4+}$,[230] $[ClPdMo_3Se_4(H_2O)_7Cl_2]^+$ and related structures,[231–233] $[W_3S_7Cl_6]_2$,[234] $[Mo_3S_4Ni(H_2O)_7Cl_3]^+$ and related structures,[235–237] *trans*-$[InCl_2(H_2O)_4]^+$ and *trans*-$[InCl_4(H_2O)_2]^-$,[238] $(H_7O_3)_4[FeCl_4]_2Cl_2(H_2O)_2$,[239] $(H_7O_3)_4[GaCl_4]_2Cl_2(H_2O)_2$,[240] $[(UO_2)_4O_2Cl_4(H_2O)_{11}]$,[241] $[Cl_3InW_3S_4(H_2O)_9]^{2+}$,[242] $[Cr(H_2O)_6(NO_3)_3(H_2O)_{13}]$,[243] and $[Zr_4(OH)_8(H_2O)_{16}]Cl_8\cdot(H_2O)_{16}$ are also known.[244]

8. Derivatives, Analogues, and Congeners of the CB[n] Family

The preceding sections have demonstrated the great potential of the CB[*n*] family in molecular recognition, self-assembly, and nanotechnology. Potential limitations of the CB[*n*] family include their poor solubility in water, which necessitates the use of high salt concentrations (for example, 0.2 M NaCl), and their insolubility in polar or nonpolar organic solvents. A second potential limitation of CB[*n*] when we began our research in this area in 1998 was an inability to modify the internal or external molecular surfaces of the CB[*n*] molecule. It seemed likely that if the CB[*n*] family could be modified to improve their solubility in organic media, to alter the size and shape of the cavity, and to provide different functional groups that interact directly with guests then the range of potential applications of the CB[*n*] family would be dramatically expanded. The following sections describe the approaches that we,[245–249] and others,[8,90,201,250–254] have taken toward alleviating these potential limitations.

Over the years there have been numerous attempts to prepare CB[*n*] derivatives by the use of substituted glycoluril derivatives in CB[*n*]-forming reactions. Nolte and co-workers were the first to pursue this line of inquiry, which led to the development of molecular clips based on diphenylglycoluril (**1c**).[255] The first fully characterized CB[*n*] derivative was reported by Stoddart and co-workers in 1992 with the synthesis of Me_{10}CB[5] from dimethylglycoluril (**1b**) and formaldehyde under acidic conditions (Scheme 13).[90,256] These studies led to more questions than they answered. Why was the CB[*n*]-forming reaction of **1b** successful whereas the corresponding reaction with **1c** failed? What is the scope of glycoluril monomers that can be used in CB[*n*]-forming reactions? Why did the original cyclization of **1a** lead



Scheme 13. Synthesis of Me_{10}CB[5]. a) Conc. HCl, CH_2O, reflux, 16% yield.

to CB[6] exclusively, whereas **1b** led to a pentameric macrocyclic Me_{10}CB[5] exclusively? What factors are responsible for the remarkably high yield observed for CB[6] formation given that the formation of a pair of methylene bridges between two glycoluril rings can result in either C- or S-shaped diastereomers (for example, **58C** and **58S**, respectively, Figure 11)?

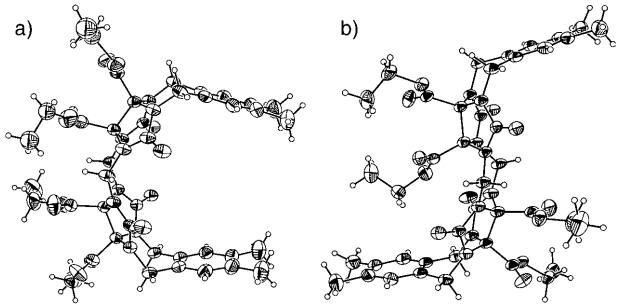
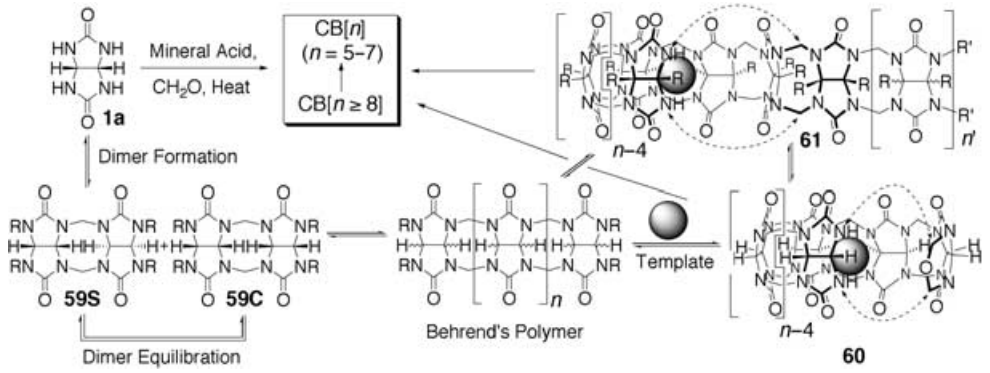


Figure 11. X-ray crystal structures of methylene-bridged glycoluril dimers: a) C-shaped **58C** and b) S-shaped **58S**.

8.1. Mechanistic Hypothesis for CB[n] Formation

Control over the tailor-made synthesis of CB[*n*] homologues, derivatives, and analogues was hampered by an inadequate understanding of the mechanism of CB[*n*] formation. A mechanistic framework advanced by Day et al.[8] and Isaacs and co-workers[247] is shown in Scheme 14. In brief, glycoluril (**1a**) undergoes condensation with H_2CO to yield a mixture of methylene-bridged glycoluril dimers **59C** and **59S** which can undergo further oligomerization to yield Behrend's polymer as a mixture of diastereomers. Further growth and isomerization of the S- to C-shaped structures in Behrend's polymer yields **60** and **61** under the potential control of suitable templating agents. Both **60** and **61** may undergo cyclization by end-to-end condensation (for example **60**→CB[*n*]) or by back-biting (for example, **61**→CB[*n*]) to enter the CB[*n*] manifold. Interconversions between the various CB[*n*] may then occur within the CB[*n*] manifold.



Scheme 14. Proposed mechanism for the formation of CB[*n*].

8.2. Effect of Acid, Salts, and Templates on the Product Distribution

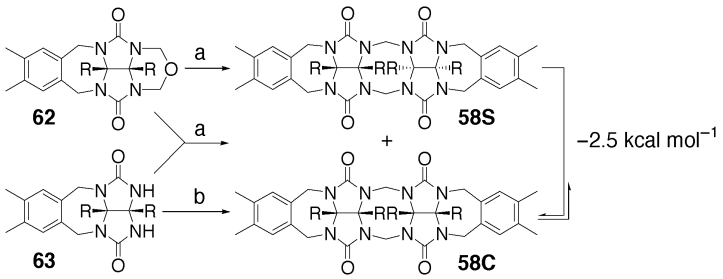
Day and co-workers performed a series of elegant experiments to determine the effect of acid type, acid and reactant concentration, salts, and templates on the distribution of CB[5]–CB[8] in the product mixture.[8,121,250] They surveyed a variety of acids for CB[*n*] formation (for example, HCl, H_2SO_4, HBF_4, CH_3SO_3H, PTSA, and trifluoroacetic acid (TFA)) and determined that a high concentration of strong acid, such as >5 M HCl, is necessary for conversion of oligomers **60** and **61** into CB[*n*]; weak acids such as TFA are insufficient. Decreasing the concentration of **1a** from 155 mg mL^{-1} to 0.125 mg mL^{-1} in concentrated HCl enhanced the combined yield of CB[5] and CB[6] from 67% to 100%, as would be predicted if the length of the oligomer **60** or **61** controls the size of the CB[*n*] formed. To address the fate of the formed CB[*n*] once it has entered the CB[*n*] manifold, Day and co-workers performed product resubmission experiments. CB[5], CB[6], and CB[7] are stable to the reaction conditions (conc. HCl, 100 °C, 24 h) whereas CB[8] contracted to give a mixture of CB[5]–CB[8] (4:13:38:45). These experiments suggest that the low abundance of the higher homologues ($n>8$) may be a consequence of their destruction under the reaction conditions. These experiments also suggest that fragmentation of the methylene-bridged glycoluril oligomers such as **61** to **60** are possible under aqueous acidic conditions.

Day et al. also found that salts such as LiCl, NaCl, KCl, RbCl, CsCl, and NH_4Cl have modest effects on the relative yields of CB[5]–CB[8].[250] For example, K^+ favors formation of CB[5] whereas Li^+ favors the formation of higher homologues; these salts are posited to exert their influence during the transformation of Behrend's polymer to **60** and **61**. Similarly, the addition of *o*-carborane as a potential template for the formation of CB[7] in CB[*n*]-forming reactions had a small but discernible effect on the CB[5]–CB[8] product distribution.[121] Theoretical studies suggest that H_3O^+ may act as a template during CB[*n*] synthesis.[257]

8.3. The Methylene-Bridged Glycoluril Dimer as a Model System

In contrast to the work of Day et al., which focused on the latter stages of the mechanism of CB[*n*] formation, we decided in 1998 to focus on the simplest building block of the CB[*n*] family, namely, the methylene-bridged glycoluril dimer substructure (**59C** and **59S**, Scheme 14). This section focuses on the insights that we gained from these model studies that led to the synthesis of CB[*n*] analogues.

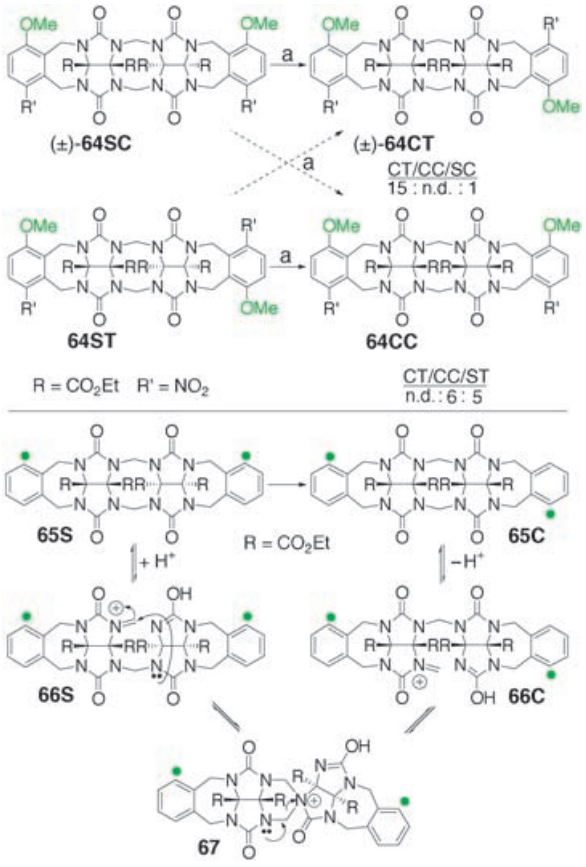
We developed three related synthetic methods (two homodimerization and one heterodimerization) from **62** and **63** that provided efficient access to methylene-bridged glycoluril dimers, such as **58C** and **58S**, with *o*-xylylene "walls" and a variety of substituents (Scheme 15).[247,249] We found that substituted dimers bearing electron-withdrawing groups (for example, R = CO_2Et) form readily whereas those bearing groups such as R = Ph that stabilize adjacent positive charge form slowly and with significant formation of by-product. These experiments provide a rationale for the observed scope of CB[*n*]-forming reactions.[249] Since the equilibrium between **59S** and **59C** is of fundamental importance to CB[*n*] synthesis, we decided to investigate the equilibrium between the S-shaped and the C-shaped forms by following the separate isomerization of diasteromerically pure samples of **58S** and **58C** to yield equilibrium mixtures (**58C**:**58S** = 97:3, Scheme 15) of the two diastereomers.[247] The C-shaped form is about 2.5 kcal mol^{-1} more stable than



Scheme 15. Formation and isomerization of methylene-bridged glycoluril dimers. a) $ClCH_2CH_2Cl$, PTSA, reflux; b) $ClCH_2CH_2Cl$, CH_2O, PTSA, reflux. R = CO_2Et, PTSA = *para*-toluenesulfonic acid.

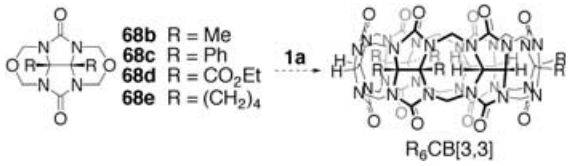
the S-shaped form, which provides a rationale for the high yields observed in the formation of the CB[*n*] family in which all the dimeric units adopt the C-shaped form.

During our studies of the model system with the methylene-bridged glycoluril dimer we also observed that the isomerization from the S-shaped to C-shaped dimer was highly diastereoselective. The isomerization of **64ST** (S-shaped, *trans*) and **64SC** (S-shaped, *cis*) under anhydrous acidic conditions ($ClCH_2CH_2Cl$, PTSA, reflux) gave **64CC** (C-shaped, *cis*) and **64CT** (C-shaped, *trans*), respectively (Scheme 16). In principle at least three different outcomes



Scheme 16. Isomerizations and a suggested mechanism.[258] a) PTSA, $ClCH_2CH_2Cl$, reflux. n.d. = not detected.

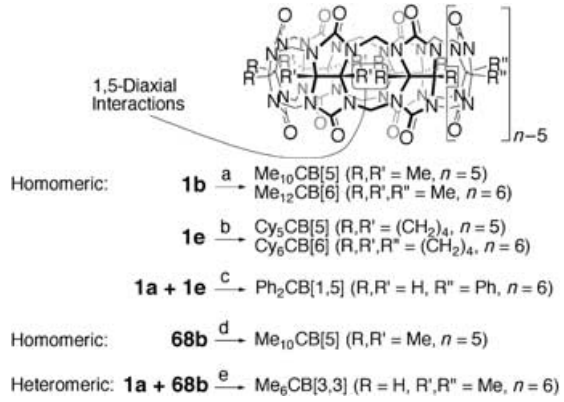
were conceivable: 1) scrambling, 2) retention, or 3) transposition of the relative position of the "methoxy labels" (green dots) as might occur during intermolecular (scrambling) or intramolecular (retention or trnscription) S- to C-shaped isomerization. Scheme 16 (bottom section) also shows our suggested mechanism for this *intramolecular* isomerization which proceeds by the intermediacy of a spirocyclic N-acylammonium intermediate (**67**). The implications of this result toward the synthesis of CB[*n*] derivatives and analogues are twofold: Under the anhydrous acidic conditions used, the methylene-bridged glycoluril dimer subunits do not undergo the fragmentation reactions observed during CB[*n*] synthesis (see Scheme 14, **61**→**60**). This result suggests that CB[8] and the higher homologues might display enhanced stability if synthesized under anhydrous acidic conditions. Since the methylene-bridged glycoluril dimer substructure does not become disconnected during isomerization, it should be possible to exploit the selective heterodimerization reactions between glycoluril NH compounds such as **1** and glycoluril cyclic ethers such as **68** to prepare CB[*n*] derivatives with control over their functionalization pattern and potentially their size. For example, we predicted that it might be possible to prepare CB[*n*] derivatives from two different glycoluril derivatives (for example, **1a** and **68**) and that those derivatives might alternate in the formed CB[*n*] derivative (for example, R_6CB[3,3]; Scheme 17).



Scheme 17. Proposed synthesis of CB[*n*] derivatives.

8.4. Preparation of CB[n] Derivatives

There are three potential pathways for the synthesis of CB[*n*] derivatives from glycolurils (**1**) and glycoluril cyclic ethers (**68**)—two homomeric cyclzations and one heteromeric cyclization. Examples of all three have now been demonstrated in the literature (Scheme 18). In 1992, Stoddart and

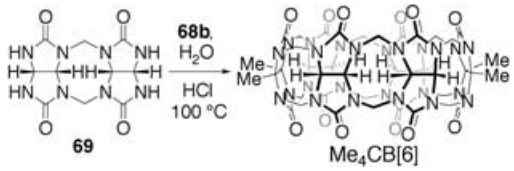


Scheme 18. Synthesis of CB[*n*] derivatives. a) CH_2O, HCl, heat; b) CH_2O, HCl, heat; then H_2SO_4, H_2O, heat; c) CH_2O, $(NH_4)_2SO_4$, H_2SO_4; then H_2O, 70–95 °C; d) HCl, H_2O, heat; e) HCl, LiCl, heat.

co-workers showed that the homomeric cyclization of **68b** yields the pentameric macrocycle Me_{10}CB[5] in low yield (Scheme 13).[90,256] Miyahara et al. reported an improved procedure to access Me_{10}CB[5] with a NH_4^+ lid (36%) and removal of the lid using Amberlite IRA410.[96] Keinan and co-workers recently reported a novel pentanediamine-derivatized polystyrene resin that allowed the isolation of Me_{12}CB[6].[259] Similarly, Kim and co-workers were able to isolate Cy_5CB[5] (16%) and Cy_6CB[6] (2%) by the cyclization of **1e**.[253] The distinguishing feature of Cy_5CB[5] and

$Cy_6CB[6]$ is their enhanced solubility in water (200 mM) and organic solvents (up to 30 mM in MeOH, DMSO, DMF, and CH_3CN). This enhanced solubility of $Cy_5CB[5]$ and $Cy_6CB[6]$ allowed the preparation of ion-selective electrodes which displayed a high selectivity for Pb^{2+} ions and acetylcholine, respectively, relative to potentially interfering cations (K^+, NH_4^+, Na^+, Cu^{2+}, and choline). Nakamura and co-workers demonstrated that mixtures of **1a** and **1c** gave a CB[6] derivative containing a single diphenylglycoluril unit (Ph_2CB-[1,5]) in a remarkable 30% yield. $Ph_2CB[1,5]$ even forms a rotaxane with a spermine axle.[201] Day et al. showed that **68b** is transformed into $Me_{10}CB[5]$ in high yield (85%).[8]

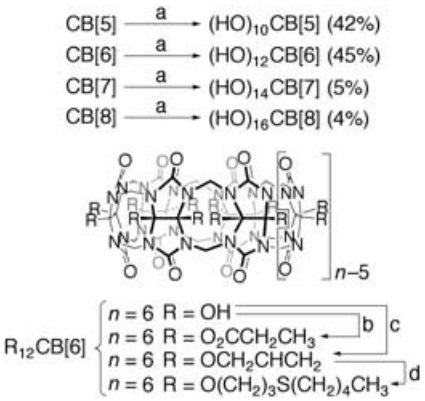
One potential drawback of the use of glycoluril derivatives in CB[*n*]-forming reactions is that derivatives of the smaller homologues CB[5] and CB[6] form preferentially. This result is attributed to 1,5-diaxial interactions between substituents on adjacent glycoluril rings that comprise the CH_2-bridged eight-membered rings; such interactions are postulated to increase as the size of the CB[*n*] increases.[33,34] To alleviate this problem, Day et al. studied CB[*n*]-forming reactions between substituted and unsubstituted glycoluril derivatives, with the reasoning that the presence of unsubstituted glycoluril would relieve the 1,5-diaxial interactions. The heteromeric cyclization reaction of **1a** and **68b** gave the D_{3h}-symmetrical $Me_6CB[3,3]$ in which substituted glycoluril units alternate with unsubstituted ones in 10% yield.[247,251] CB[5] and CB[7] derivatives were also present in the reaction mixture, but were not isolated in pure form. A related heteromeric cyclization reaction between **68b** and **69** delivers $Me_4CB[6]$ in 30% yield on multigram scale (Scheme 19).[260] Interestingly, the cavity of $Me_4CB[6]$ is ellipsoidal and binds 2,2′-bipyridine with its aromatic rings parallel to the long axis of the cavity.



Scheme 19. Synthesis of $Me_4CB[6]$.

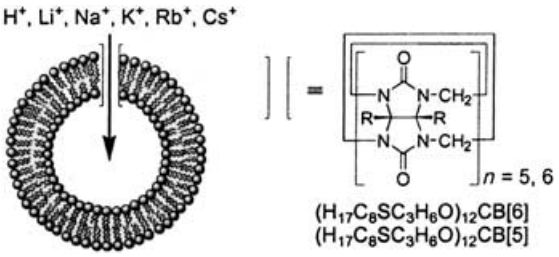
8.5. Direct Functionalization of CB[n]

Kim and co-workers recently made a major breakthrough in the synthesis of CB[*n*] derivatives by the direct functionalization of CB[5]–CB[8].[254] Scheme 20 shows the direct oxidation of CB[5]–CB[8] with $K_2S_2O_8$ in water to yield the perhydroxylated species $(HO)_{2n}CB[n]$. The reaction is efficient for CB[5] and CB[6] (yields of 42 and 45%, respectively); optimization of the reaction conditions is needed to improve the yields in the derivatization of CB[7] and CB[8] (ca. 5%). The cause of the low yields in these reactions is still unclear, but may be related to selective formation of CB[5] and CB[6] derivatives in the direct cyclization of glycoluril derivatives. $(HO)_{12}CB[6]$ has good solubility in DMSO and DMF which allows its subsequent derivatization. $(HO)_{2n}CB[6]$ can be acylated by treatment with propionic anhydride to yield $(CH_3CH_2CO_2)_{12}CB[6]$ and treated with allyl bromide to yield $(CH_2CHCH_2O)_{12}CB[6]$. The allylated compound $(CH_2CHCH_2O)_{12}CB[6]$ undergoes photochemical reaction with pentanethiol to afford $\{CH_3(CH_2)_4S$-$(CH_2)_3O\}_{12}CB[6]$. These landmark reactions represent the first covalent derivatization reactions of CB[*n*] derivatives. $(CH_2CHCH_2O)_{12}CB[6]$ can even be covalently attached to slides derivatized with (3-sulfanylpropyl)triethoxysilane and can also be covalently attached to silica gel and used in chromatographic applications.[46,261]



Scheme 20. Direct functionalization of CB[*n*]. a) $K_2S_2O_8$, H_2O, 85 °C; b) Et_3N, $(CH_3CH_2CO)_2O$, DMSO; c) NaH, DMSO, allyl bromide; d) $CH_3(CH_2)_4SH$, *hν*.

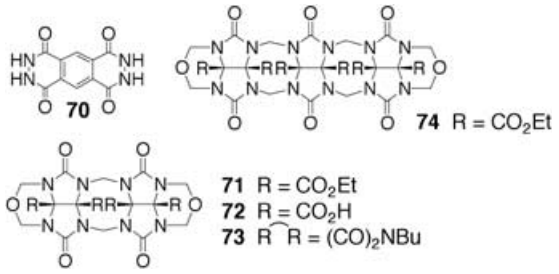
Kim and co-workers have also demonstrated that these lipophilic CB[*n*] derivatives possess new properties. $\{CH_3$-$(CH_2)_7S(CH_2)_3O\}_{12}CB[6]$ forms nanospheres with diameters of 50–150 nm when emulsified.[254] They also demonstrated recently that $\{CH_3(CH_2)_7S(CH_2)_3O\}_{12}CB[6]$ and $\{CH_3$-$(CH_2)_7S(CH_2)_3O\}_{12}CB[5]$ become incorporated in large unilamellar vesicles and function as ion channels (Scheme 21).[262] The CB[6] derivative $(CH_3(CH_2)_7S$-$(CH_2)_3O)_{12}CB[6]$ shows ion selectivity ($Li^+ > Cs^+ \approx Rb^+ > K^+ > Na^+$) which is opposite to the binding affinities of CB[6]. Remarkably, $\{CH_3(CH_2)_7S(CH_2)_3O\}_{12}CB[6]$ shows an ion flux of 5 pA (ca. 3×10^7 ions s^{-1}) which is comparable to that of gramicidin! In contrast, $\{CH_3(CH_2)_7S(CH_2)_3O\}_{10}CB[5]$ with its smaller portals (2.4 Å) only allows the smaller Li^+ and Na^+ ions to pass. Such lipophilic CB[*n*] derivatives show much promise for applications as sensors, in ion separations, and as components of molecular devices.



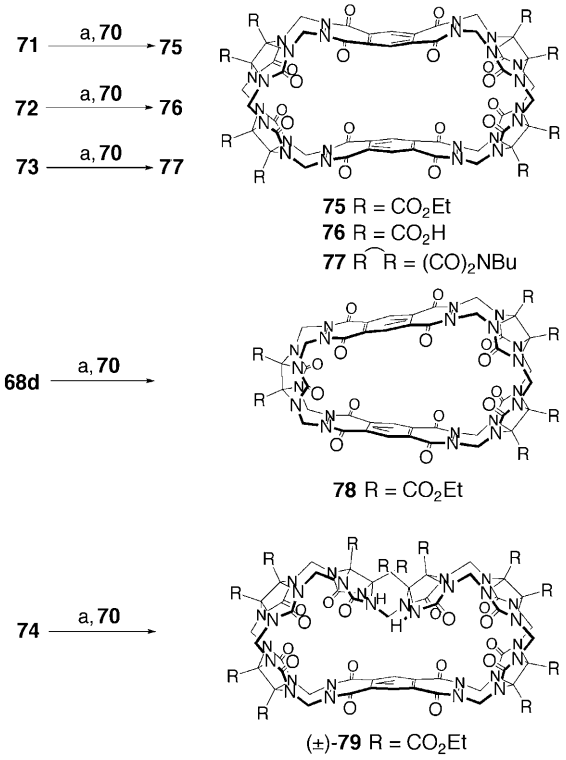
Scheme 21. Lipophilic CB[5] and CB[6] derivatives as ion channels.

8.6. Preparation of Cucurbit[n]uril Analogues

We discovered that phthalhydrazides function as nucleophilic glycoluril surrogates in typical methylene-bridge-forming reactions. On the basis of the mechanistic reasoning described above, we hypothesized that combinations of bis(phthalhydrazide) **70** and glycoluril ether building blocks **68**, **71**–**74** would yield CB[*n*] analogues with predetermined size, shape, and functionalization patterns.[246,248,263]



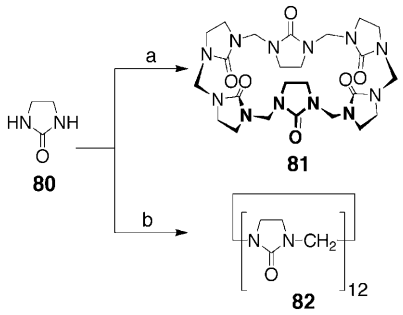
In accord with these expectations, cyclization reactions of **70** with **71**–**73** proceeded smoothly and delivered CB[6] analogues **75**–**77** in high yield (Scheme 22). Similarly, **70** reacts with **68d** to yield CB[5] analogue **78** in relatively low yield (6%). Remarkably, methylene-bridged glycoluril trimer **74** reacts with **70** to yield CB[7] analogue (±)-**79** incorporating a single bis(phthalhydrazide) unit rather than a CB[8] analogue with two such units. Several features of these cucurbit[*n*]uril analogues are noteworthy: 1) they contain electrochemically, UV/Vis, and fluorescently active "walls"; 2) their elongated shapes (**75**: 5.9 × 11.2 × 6.9 Å; **78**: 5.6 × 9.8 × 6.2 Å; (±)-**79**: 5.7 × 11.3 × 4.3 Å differ from those of the circular CB[*n*]; 3) the C_2-symmetric (±)-**79** is chiral and contains only a single bridging CH_2 group which points directly into the cavity; and 4) the analogues are soluble in both organic and aqueous media depending on the substituents. CB[6] analogue **77** retains the binding capacity of the parent macrocycles, as demonstrated by the complexation of the *p*-xylylenediammonium ion.[248]



Scheme 22. CB[*n*] analogues. a) $MeSO_3H$, 80°C.

8.7. Hemicucurbit[6]uril and Hemicucurbit[12]uril

Miyahara et al. recently further expanded the CB[*n*] family with the preparation of hemicucurbiturils by the acid-catalyzed condensation of ethyleneurea (**80**, Scheme 23).[264] Remarkably, hemicucurbit[6]uril (**81**) is formed in 94% yield when the reaction is conducted at RT in 4N HCl, whereas hemicucurbit[12]uril (**82**) is formed in 93% yield in 1N HCl at 55°C. The X-ray crystal structure of **81** shows that it assumes the alternate conformation depicted in Scheme 23. Unlike CB[*n*], **81** does not bind metal cations, but does retain the ability to bind small organic molecules such as $HCONH_2$ and $HOCH_2CCH$. Interestingly, **82** gelates ethyleneglycol in the 0.5 to 5.0 wt% range. The detailed recognition properties and practical applications of **81** and **82** remain to be explored.

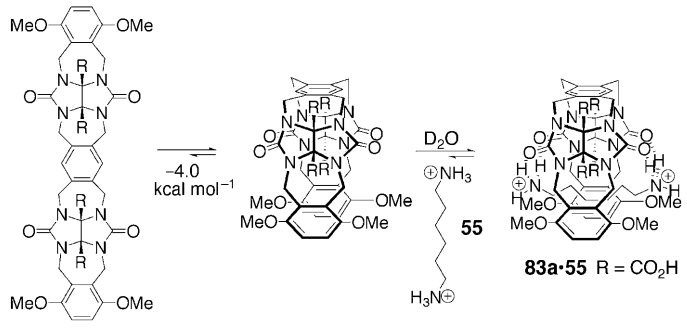


Scheme 23. Synthesis of **80** and **81**. a) CH_2O, 4N HCl, RT; b) CH_2O, 1N HCl, 55°C.

8.8. Preparation of Acyclic Cucurbit[n]uril Congeners

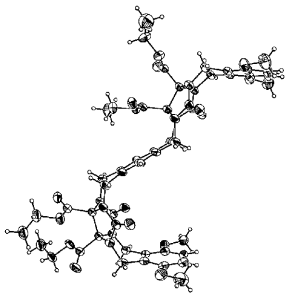
Issues associated with macrocyclization and stereochemistry (for example, S- versus C-shaped diastereomers) complicate the preparation of CB[*n*] derivatives and analogues that are poised to dramatically expand the scope of applications of the CB[*n*] family. Recently, we described an approach to acyclic CB[*n*] congeners (**83a**, Scheme 24) that circumvents these issues while maintaining the binding profile of CB[6] itself.[245,263b] Based on the precedent of Nolte,[265] we hypothesized that employing alternating glycoluril and aromatic rings would preorganize **83a** into the a,a,a,a conformation required

a)



83a R = CO_2H
83b R = CO_2Et

b)



Scheme 24. a) Structures of **83a** and **83b** as well as a schematic illustration of **83a·55**. b) X-ray crystal structure of the a,a,s,a conformer of **83b**.

to act as an acyclic CB[*n*] congener. Indeed, **83a** displays several of the features characteristic of the CB[*n*] family, namely: 1) high affinity and selectivity for positively charged guests, 2) length-dependent affinity for alkanediammonium ions, 3) guest discrimination on the basis of size and shape, and 4) competitive binding with alkali metals present in solution. The use of longer aromatic spacers may result in CB[*n*] congeners whose recognition properties parallel those of the higher homologues.

9. Summary and Outlook

Cucurbit[6]uril is celebrating its 100th birthday this year! It was only in 1981 at age 76, that the structure of this unusual macrocycle was elucidated by Mock and co-workers. In their early pioneering work they demonstrated that CB[6] displays: 1) remarkably high affinity for alkanediammonium ions as a consequence of ion–dipole and hydrophobic interactions, 2) size, shape, and functional-group selectivity, 3) unusually slow kinetics of association and dissociation, and 4) behavior of an enzyme mimic. CB[6] was clearly a talented host, but a series of perceived problems limited the scope of applications to which it could be applied. Compared to α-, β-, and γ-cyclodextrin with their good solubility in aqueous solution, their commercial availability in a variety of sizes, their well-known chemical functionalization, and their affinity toward a wide variety of species, CB[6] was not in a position to challenge the cyclodextrins as the recognition platform of choice for studies of molecular recognition in aqueous solution.

In the intervening time, all of these perceived issues have been either partially or fully resolved, which has dramatically expanded the range of applications to which the CB[*n*] family can be applied. The solubility of CB[6] increases dramatically in the presence of salts which allows their recognition and self-assembly processes to be studied in neutral aqueous solution. It was not until the turn of the millennium, however, that the CB[*n*] family expanded dramatically with the preparation of CB[5], CB[7], CB[8], and CB[10]·CB[5] by the research groups of Kim and Day. The recognition properties of these new CB[*n*] homologues—which are now commercially available—parallel and exceed those of CB[6]. Recognition processes within CB[6], CB[7], and CB[8] are subject to efficient chemical, electrochemical, and photochemical control. These attributes along with the detailed knowledge of the mechanism of formation and dissociation of CB[6] complexes has led to the application of the CB[*n*] family in areas as diverse as gas purification, catalysis, molecular machines, waste-stream remediation, supramolecular polymers, self-assembling and self-sorting systems, crystal engineering, self-assembled monolayers, and even gene transfection.

The remaining issue—the tailor-made preparation of CB[*n*] derivatives, analogues, and congeners—has been tackled by several research groups including ours. Fully and partially substituted CB[5] and CB[6] derivatives can be prepared by the use of substituted glycoluril derivatives in CB[*n*]-forming reactions. More recently, the direct perhydroxylation of CB[5]–CB[8] was achieved by Kim and co-workers. We have prepared CB[*n*] analogues and congeners by mechanistically guided building-block approaches. These CB[*n*] derivatives possess enhanced solubility in aqueous and organic media and largely retain the binding profile of the parent CB[*n*]. CB[*n*] derivatives have already been used as molecular "molecular sieves", in the preparation of ion-selective electrodes, as amphiphiles for vesicle formation, for the functionalization of glass substrates, and as artificial ion channels.

Many of the major issues confronting CB[*n*] supramolecular chemistry—enhanced aqueous and organic solubility, the (commercial) availability of a range of different-sized CB[*n*] homologues, and the development of tailor-made synthetic procedures for the synthesis of CB[*n*] derivatives, analogues, and congeners—have now been partially or fully addressed. We, and others, believe that the CB[*n*] family is now in a position to challenge the cyclodextrins as the recognition platform of choice for studies of molecular recognition in water. The unusual recognition properties of the CB[*n*] family—strong binding, high selectivity, tunable kinetics of association and dissociation, and efficient methods for chemical, electrochemical, and photochemical control of binding—suggest that the CB[*n*] family will become important components in molecular machines and nanotechnology. The groundwork has been laid for a second century of CB[*n*] chemistry that promises advances even more dramatic than the first!

Addendum (6. July 2005)

Since submission of the final version of this review a number of papers,[266–299] reviews,[300–304] and patents[305–313] related to the CB[n] family have appeared in the literature.

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