Cucurbituril Homologues and Derivatives: New Opportunities in Supramolecular Chemistry

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ABSTRACT

The supramolecular chemistry of cucurbituril, a synthetic receptor, is fascinating because of the remarkable guest binding behavior of the host. Studies in the field, however, have met with limitations, since the only species known was the hexameric macrocyclic compound, cucurbit[6]uril. Recently we synthesized its homologues, cucurbit[*n*]uril ($n = 5, 7, 8$), and derivatives. These new members of the cucurbituril family have expanded the scope further, and interest in them has grown enormously. This Account is a compilation of recent literature covering the syntheses of the homologues and derivatives, and their supramolecular chemistry.

1. Introduction

Cucurbituril (cucurbit[6]uril, or CB[6]) is a hexameric macrocyclic compound self-assembled from an acid-catalyzed condensation reaction of glycoluril and formaldehyde. Although its synthesis first appeared in the literature in 1905,[1] its chemical nature and structure had been unknown until 1981, when full characterization was reported by Mock and co-workers.[2] The pumpkin-shaped molecule CB[6] has a cavity of ∼5.5 Å diameter, accessible from the exterior by two carbonyl-laced portals of ∼4 Å diameter. Although it resembles α-cyclodextrin (α-CD) in terms of cavity size, the highly symmetrical structure with two identical openings distinguishes it from α-CD. The guest binding properties of CB[6] as a synthetic receptor have been studied extensively by Mock.[3] In a similar way to CDs, the hydrophobic interior of CB[6] provides a potential site for inclusion of hydrocarbon molecules. Unlike CDs, however, it forms stable inclusion complexes with various protonated alkyl and arylamines.

The rigid structure and capability of forming stable complexes with molecules and ions also make CB[6] attractive as a building block for the construction of supramolecular architectures. Over the past decade, we synthesized a wide variety of supramolecular species such as polyrotaxanes,[4−7] molecular necklaces,[8−10] rotaxane dendrimers,[11] and rotaxane-based molecular switches[12] using CB[6] as a molecular bead. We also carried out DNA binding studies of pseudorotaxanes comprising CB[6] and polyamines[13] and investigated the potential utility of rotaxane dendrimers as gene carriers.[14] Our work in this area has been summarized in recent review articles.[15] In addition, several other applications of CB[6] have been demonstrated. For example, CB[6] can facilitate cycloaddition reactions with large rate acceleration inside the cavity.[16] Due to its strong affinity toward organic dye molecules, CB[6] is considered suitable for treatment of effluents from dye industries.[17]

As illustrated above, CB[6] is potentially as useful as crown ethers, CDs, and calixarenes in many applications, but it suffers from several shortcomings, which may explain why its chemistry has been developed so slowly until recently. First, its solubility in common solvents except for strongly acidic aqueous solution is extremely low. Most host−guest chemistry of CB[6] has been therefore studied in a 1:1 mixture of formic acid and water. Some years ago, we discovered that it dissolves appreciably in aqueous solution of alkali metal salts, presumably due to coordination of the metal ions to the portal carbonyl oxygens.[18] Nevertheless, its poor solubility in common solvents poses serious problems in expanding its applications. Second, no method to introduce any functional groups to the molecule was known. For example, glycoluril derivatives carrying substituents at the "bridging" positions fail to produce cyclization products upon condensation with formaldehyde. The lone exception was dimethylglycoluril, which yields decamethylcucurbit[5]uril as the only cyclization product.[19] Furthermore, no method has been reported to achieve direct functionalization of CB[6]. Third, homologues containing greater or fewer glycoluril units were not available. This is quite a contrast to the fact that several homologues were available in calixarenes, which are obtained from a base-catalyzed condensation of a phenol and formaldehyde.

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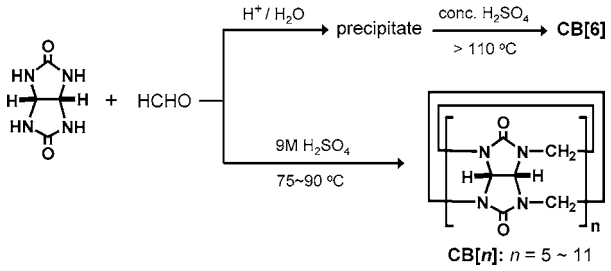
Scheme 1



Since they severely limit the scope of cucurbituril chemistry, we decided to tackle these problems when we initiated our work on CB[6] in early 1990s. After numerous unsuccessful attempts over several years, we finally succeeded in synthesis, isolation, and full characterization of cucurbituril homologues containing different number of glycoluril units, and cucurbituril derivatives soluble in common solvents. These new synthetic receptors with cavities smaller or larger than CB[6] and with good solubility have created a fresh wave of interest. Within a few years, many elegant studies have been reported. This article is a documentation of these recent developments, mainly based on the work performed in our laboratory.

2. Cucurbituril Homologues: Synthesis and Structures

2.1. Synthesis. The synthetic protocol of CB homologues is similar to the conventional CB[6] synthesis. Reaction of glycoluril with formaldehyde in 9 M sulfuric acid at ~75−90 °C for 24 h yields a mixture of CB[*n*] family. The key is the lower reaction temperature than that employed in the conventional CB[6] synthesis (>110 °C), which allows formation of significant amounts of CB homologues in addition to CB[6] (Scheme 1).[20] NMR and ESI mass studies confirmed that the reaction mixture contains a family of CB homologues, mostly from pentamer to octamer, with typical contents being ~10−15% CB[5], ~50−60% CB[6], ~20−25% CB[7], and ~10−15% CB[8]. Trace amounts of higher homologues (CB[*n*], $n = 9-11$) were also detected by mass spectrometry. Synthesis of the homologues under hydrothermal conditions yields a mixture of CB[*n*] with slightly higher CB[7] and CB[8] content.

CB homologues are separated in pure form using fractional crystallization and dissolution.[20] On standing, the reaction mixture first yields crystals of CB[8]. CB[6] is then separated by fractional dissolution of other CB homologues with acetone/water. From the soluble portion, CB[5] and CB[7] are isolated and further separated by fractional crystallization. It should be noted that the separation of the homologues is affected by traces of acid present in the mixture as well as by the NH_4^+ ion, which may be formed from thermal decomposition of glycoluril. Recently, Day and co-workers examined a wide range of reaction conditions in an attempt to optimize the yield of individual CB homologues and discussed the mechanism of cyclization.[21]

The mechanism of the CB[*n*] formation is not clearly known. Apparently, the reaction of glycoluril and formaldehyde first generates linear oligomeric products which then cyclize to produce a library of CBs. The conformations of the dimers and trimers and their implication for CB[*n*] formation have been discussed.[22] The template effects of various species including metal ions on the CB[*n*] synthesis have been explored,[23] but the exact role of the templates is not known.

2.2. Structures and Physical Properties. CB homologues CB[5], CB[7], and CB[8] have been fully characterized by various spectroscopic methods and X-ray crystallography (Figure 1).[20] Chart 1 compares some structural parameters of the CB homologues. On going from CB[5] to CB[8], the mean diameter of the internal cavity increases progressively from ~4.4 to ~8.8 Å. Likewise, the portal increases its mean diameter from ~2.4 to ~6.9 Å. In terms of cavity size, CB[6], CB[7], and CB[8] are analogous to α-, *β*-, and *γ*-CD, respectively. ^{1}H and ^{13}C NMR spectra are helpful in identifying the homologues.[20] The chemical shift difference between the two sets of methylene protons progressively increases from

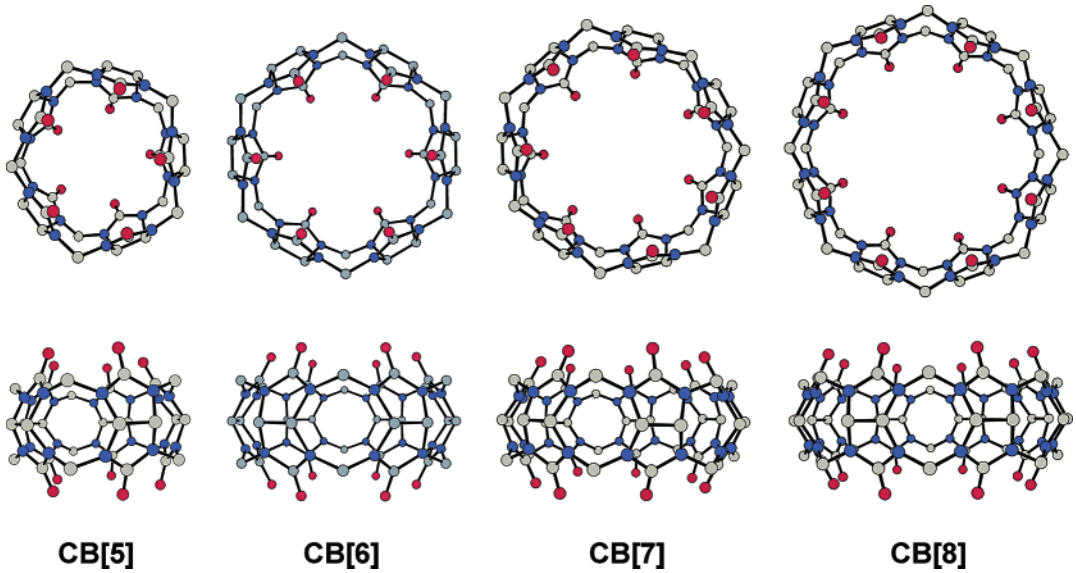


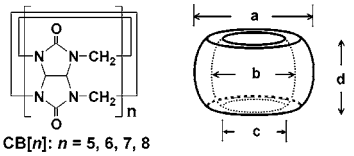
FIGURE 1. X-ray crystal structures of CB[*n*] ($n = 5-8$). Color codes: carbon, gray; nitrogen, blue; oxygen, red.

Table 1. Relative Strain Energy of CB[*n*][a]

	cucurbit[n]uril								
	CB[4]	CB[5]	CB[6]	CB[7]	CB[8]	CB[9]	CB[10]	CB[11]	CB[12]
ΔE (kcal/mol)	+23.03	+5.06	0.00	+1.14	+5.86	+12.87	+21.41	+31.03	+41.43

[a] Ab initio calculation at HF/3-21G* level.

Chart 1



CB[*n*]: *n* = 5, 6, 7, 8

		CB[5]	CB[6]	CB[7]	CB[8]
outer diameter (Å)	a	13.1	14.4	16.0	17.5
cavity (Å)	b	4.4	5.8	7.3	8.8
	c	2.4	3.9	5.4	6.9
height (Å)	d	9.1	9.1	9.1	9.1
cavity volume (Å^3)	-	82	164	279	479

1.42 to 1.65 ppm on going from CB[5] to CB[8]. The chemical shifts of the methylene and methine carbons move downfield on going up in the homologous series.

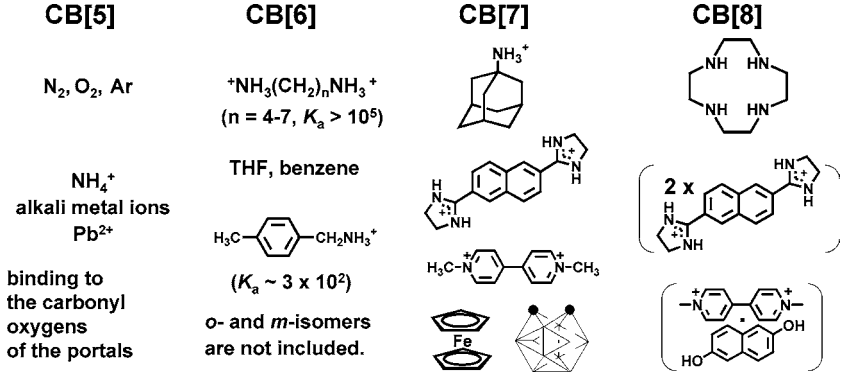
Solubility of CB homologues in common solvents is also low ($<10^{-5}$ M), except that CB[5] and CB[7] have a moderate solubility in water ($2-3 \times 10^{-2}$ M), which is comparable to that of β-CD (1.6×10^{-2} M). All the CB homologues are soluble in acidic water as well as in aqueous alkali metal ion solution. The homologues have high thermal stability in the solid states. No decomposition is observed up to 420 °C for CB[*n*] ($n = 5$, 6, and 8) although CB[7] starts decomposing at a somewhat lower temperature (370 °C). Prolonged heating of CB[8] in conc HCl at 100 °C produces the smaller homologues, while smaller CB homologues do not show either interconversion or detectable decomposition.[21]

The stability of CB homologues can be inferred from the relative strain energy upon cyclization. Ab initio calculations performed on the series of CB[*n*] homologues for $n = 4-12$ (Table 1)[24] revealed that the most stable homologue is CB[6], closely followed by CB[7] with relative strain energy ~1 kcal/mol. CB[5] and CB[8] have less than 6 kcal/mol relative strain energy, while this is significantly high for other homologues. These results nicely corroborate the experimental composition of the homologue mixture and may explain why only a trace amount of CB[*n*] for *n* higher than 8 is observed.

3. Supramolecular Chemistry of Cucurbituril Homologues

3.1. Host−Guest Chemistry. CB homologues share characteristic features of CB[6], hydrophobic cavity, and polar carbonyl groups surrounding the portals. However, their varying cavity and portal sizes lead to remarkable molecular recognition properties different from those of CB[6] (Chart 2). CB[6] forms very stable complexes with protonated diaminoalkanes ($^+NH_3(CH_2)_nNH_3^+$, $n = 4-7$, $K > 10^5$) and moderately stable complexes with protonated aromatic amines such as *p*-methylbenzylamine ($K \sim 3 \times 10^2$); the *o*- and *m*-isomers are not included. It can also encapsulate neutral molecules such as tetrahydrofuran and benzene in aqueous solution. On the other hand, CB[7] forms complexes with larger guest molecules that are not included in CB[6]. For example, CB[7] forms a 1:1 complex with 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene (**BDIN**). It binds protonated adamantylamine as well as methyl viologen dication (*N*,*N*′-dimethyl-4,4′-bipyridinium, $\mathbf{MV}^{2+}$) in a 1:1 ratio. Neutral molecules such as ferrocene and carborane get easily encapsulated in CB[7] in aqueous solution. The cavity of CB[8] is large enough to include two **BDIN** molecules to form a 1:2 complex, or two different guest molecules such as $\mathbf{MV}^{2+}$ and 2,6-dihydroxynathphalene (**HN**) to form a 1:1:1 complex (see below). It can encapsulate another macrocycle, such as cyclen and cyclam. The smallest homologue CB[5] can encapsulate small molecules such as N_2 in the cavity and binds cations such as NH_4^+ and Pb^{2+} strongly at the portals. Two NH_4^+ ions can completely seal both the openings of CB[5].

Chart 2



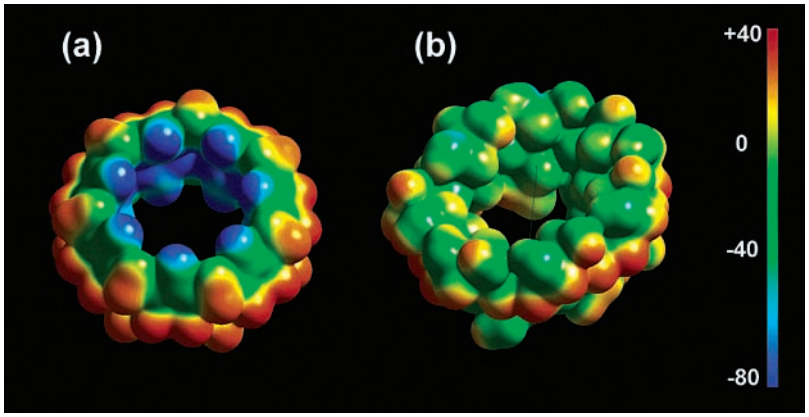


FIGURE 2. Electrostatic potential surfaces of (a) CB[7] and (b) β-CD.

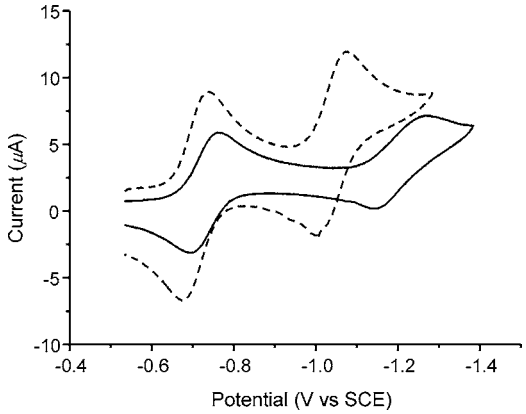
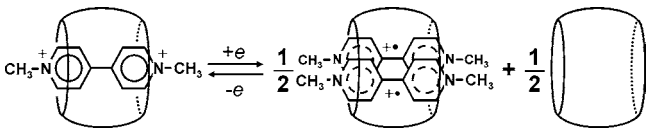


FIGURE 3. Cyclic voltammograms of MV^{2+} in the presence of 3 equiv of CB[7] (solid line) and absence of CB[7] (dashed line).

As seen above, CBs bind guests of varying sizes similar to CDs, but the two host families have fundamental differences in host−guest interactions originated from the different functional groups decorating the cavity entrances. The OH groups encircling the cavity entrances of CDs can contribute to guest binding mainly through hydrogen bonding, whereas the carbonyl groups at the portals of CBs allow charge−dipole interaction as well as hydrogen bonding with guests, and are capable of coordination to metal ions. Such differences can be easily visualized by the electrostatic potential (ESP) profiles of CBs and CDs. Figure 2 compares calculated ESP surfaces of CB[7] and β-CD.[24] In CBs the regions around carbonyl oxygens are found to be significantly negative (blue-colored) as expected. Note that the inner surface of the cavity is also quite negative while the outer surface is somewhat positive. On the other hand, the portal and cavity of CDs are almost neutral. Consequently, CBs preferentially bind guests with positive charge whereas CDs prefer neutral guest molecules. It should also be pointed out that the high structural rigidity of CBs in comparison to CDs allows highly selective recognition processes.

The different inclusion behavior between CBs and CDs is nicely illustrated by the electrochemical behavior of $\mathbf{MV^{2+}}$ in the presence of CB[7][25,26] and β-CD.[27] First of all, CB[7] binds $\mathbf{MV^{2+}}$ strongly ($K_{2+} = \sim 2 \times 10^5$ M^{-1}). One-electron reduction of $\mathbf{MV^{2+}}$ leads to $\mathbf{MV^{+\bullet}}$, which still binds

Scheme 2



tightly to CB[7] with a slightly lower binding affinity ($K_+ = \sim 1 \times 10^5$ M^{-1}), as indicated by a small negative shift (∼−20 mV) in the first half-wave potential ($E_{1/2}$) in the presence of CB[7] (Figure 3). However, the large negative shift (∼−110 mV) in the second $E_{1/2}$ in the presence of CB[7] indicates that further reduction of the guest to $\mathbf{MV^0}$ substantially decreases its binding affinity to CB[7] ($K_0 = \sim 2 \times 10^2$ M^{-1}). Therefore, the complex formation constants of CB[7] toward the three species ($\mathbf{MV^{2+}}$, $\mathbf{MV^{+\bullet}}$, $\mathbf{MV^0}$) follow the order $K_{2+} > K_+ \gg K_0$, which is exactly opposite to that for β-CD. In other words, β-CD does not bind $\mathbf{MV^{2+}}$ appreciably but has a higher affinity toward $\mathbf{MV^{+\bullet}}$ although the binding constant is still small (∼30 M^{-1}), as indicated by a small positive shift in the first $E_{1/2}$ in the presence of large excess β-CD.[27] The large positive shift in the second $E_{1/2}$ in the presence of β-CD indicates that $\mathbf{MV^0}$ binds to β-CD relatively strongly ($K_0 = \sim 1400$ M^{-1}), leading to the order $K_{2+} < K_+ \ll K_0$.

The cation radical $\mathbf{MV^{+\bullet}}$ has a strong tendency to dimerize and therefore exists as a monomer and a dimer in equilibrium in aqueous solution. However, the dimerization of the radical cation is effectively suppressed in the presence of equimolar CB[7] by forming a stable 1:1 CB[7]/$\mathbf{MV^{+\bullet}}$ complex, as confirmed by spectroelectrochemical studies. Similar to CB[7], CB[8] also forms an exclusive 1:1 host−guest complex with $\mathbf{MV^{2+}}$ with a formation constant of 1.1×10^5 M^{-1}.[28] However, one-electron reduction of $\mathbf{MV^{2+}}$/CB[8] complex leads to rapid generation of the 2:1 inclusion complex $(\mathbf{MV^{+\bullet}})_2$/CB[8] (Scheme 2). The mechanism of this fast process is not clear. The dimerization constant of $\mathbf{MV^{+\bullet}}$ in the presence of equimolar CB[8] is estimated to be 2×10^7 M^{-1}, which is about 10^5 times larger than that of $\mathbf{MV^{+\bullet}}$ alone in aqueous media.[28] Such redox control of the stoichiometry in host−guest complexation may provide a working principle for electrochemically controllable molecular machines.

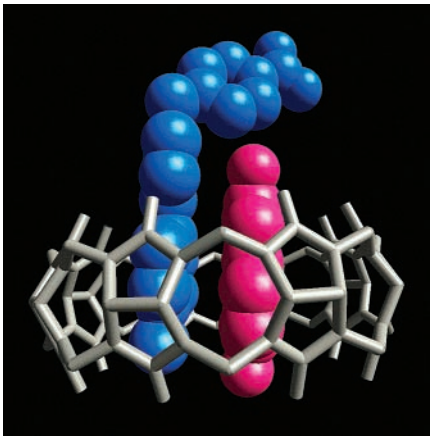


FIGURE 4. X-ray crystal structure of a charge-transfer complex stabilized inside CB[8].

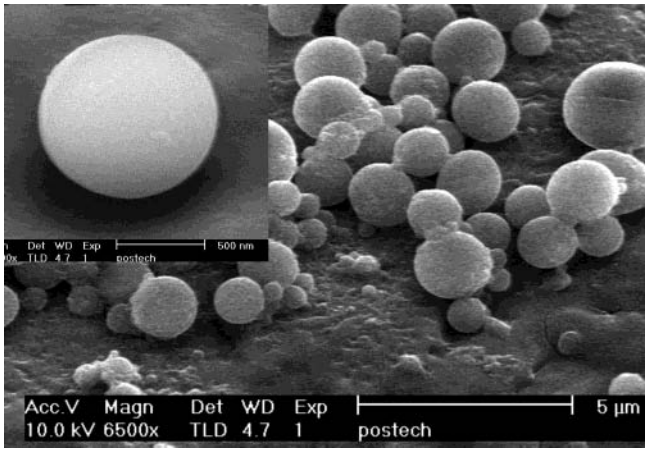
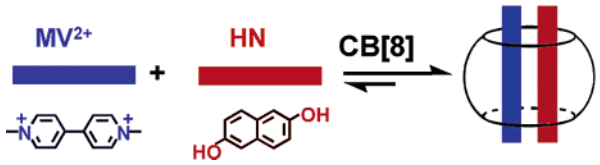


FIGURE 5. SEM image of vesicles formed with a charge-transfer complex in CB[8].

3.2. Charge-Transfer Complex Formation in Cucurbit-[8]uril. Instantaneous and quantitative formation of an inclusion complex containing a hetero-guest pair is observed upon addition of 1 equiv of **HN** to the 1:1 complex of $\mathbf{MV}^{2+}$ and CB[8].[29] The ternary complex is also formed exclusively when their components are mixed in a 1:1:1 ratio (Scheme 3). The major driving force for the ternary

Scheme 3



complex formation appears to be strong charge-transfer (CT) interaction between **HN** and $\mathbf{MV}^{2+}$ inside the host cavity. The 1:1:1 ternary complex exhibits a CT absorption band at 580 nm which is largely red-shifted ($\Delta\lambda = 120$ nm) with concomitant high increase in intensity compared to that of a 1:1 mixture of $\mathbf{MV}^{2+}$ and **HN** in the absence of CB[8]. Strong fluorescence quenching is also observed upon formation of the CT complex inside CB[8]. Without CB[8], the CT interaction is very weak. The highly enhanced CT interaction between the two guests is probably due to their close contact within the cavity of CB[8], which has been confirmed by X-ray crystallography (Figure 4). Spectroscopic and electrochemical properties of the ternary complex are currently being investigated.

This unique phenomenon can be utilized for the detection of biologically important molecules containing aromatic side chains. For example, tyrosine, tryptophane, and dopamine form stable CT complexes ($K = \sim 10^3 - 10^5$) with $\mathbf{MV}^{2+}$ inside CB[8],[30] as indicated by color, UV–visible, emission, and ^{1}H NMR spectral changes. In particular, noticeable color changes allow the naked-eye detection of these molecules.

3.3. Vesicle Formation. The stable CT complex formation inside a host provides new opportunities in creating elaborate supramolecular assemblies. For example, we recently studied the spontaneous formation of giant vesicles triggered by the formation of a CT complex inside CB[8].[31] Sonication of an equimolar mixture of CB[8], viologen with a long alkyl chain ($\mathbf{C_1VC_{16}}^{2+}$), and **HN** in water results in a violet turbid solution with a broad absorption band centered at ~550 nm, indicating the formation of a CT complex inside CB[8], which was further confirmed by NMR and ESI mass measurements. The SEM images of the complex show relatively large vesicles with

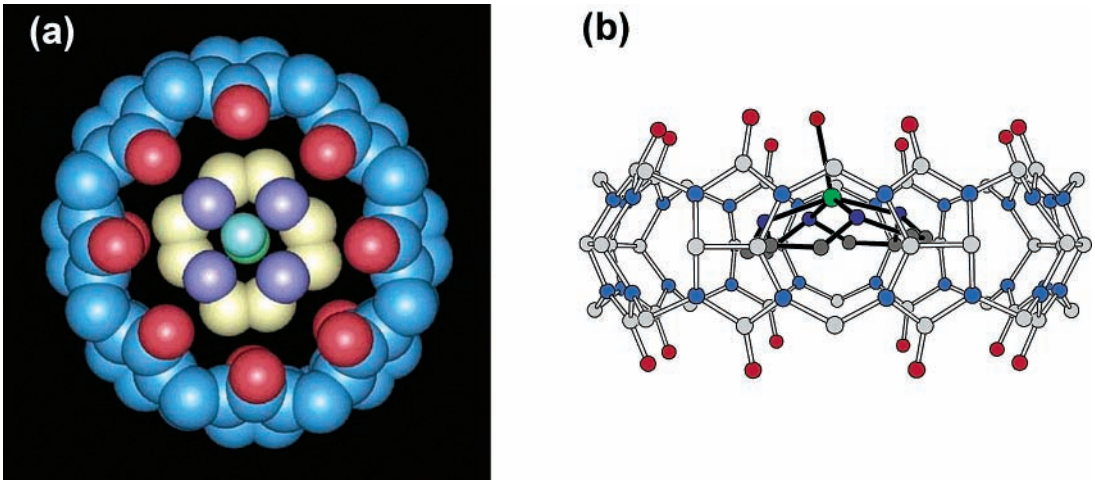
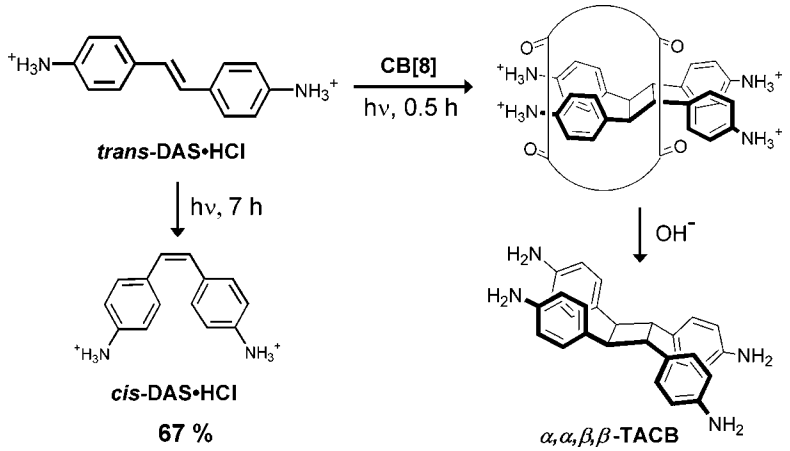


FIGURE 6. X-ray crystal structure of [Cu(cyclen)(H_2O)] encapsulated in CB[8]: (a) space-filling model and (b) ball-and-stick model. Color code: copper, green; oxygen, red; nitrogen, blue; carbon, gray.

Scheme 4

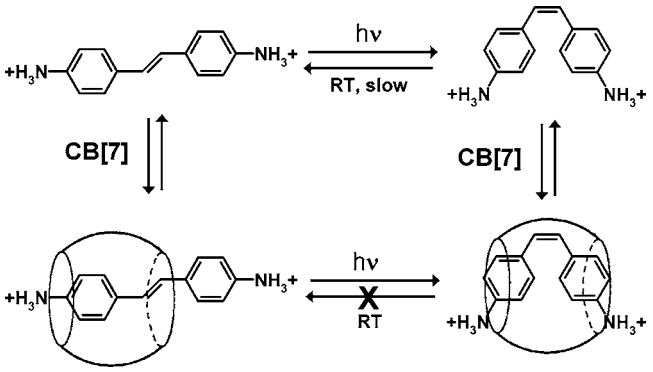


diameters of 0.02−1.2 μm (Figure 5). A high-resolution TEM image of the vesicles reveals their hollow structures. The vesicles are robust as they maintain the spherical shape even under the SEM experiment conditions. Further evidence for the formation of vesicle is provided by encapsulation of a fluorescent dye within the interior of the vesicles. Here the ternary complex behaves as a supramolecular amphiphile with a large polar headgroup and a hydrophobic tail. Since the ternary complex is stabilized by CT interaction, redox chemistry can be used to trigger the collapse of the vesicles. On treating the complex with cerium (IV) ammonium nitrate, which oxidizes **HN** to naphthoquinone, the band at 550 nm disappears, indicating the destruction of the CT complex. Collapse of the vesicles was subsequently confirmed by SEM. Useful applications of this novel, supramolecular, redox-controllable vesicle system can be envisaged in many areas including development of smart materials.

3.4. Macrocycle within a Macrocycle. The inclusion of a macrocycle guest in a macrocycle host, reminiscent of the famous Russian Matrioshka dolls, is fascinating, as such supramolecular architectures are not only aesthetically pleasing, but also potentially useful as biomimetic systems. We reported such a macrocycle within macrocycle by encapsulating cyclen (or cyclam) in CB[8].[32] The smaller macrocycles can form transition metal complexes with Cu^{II} or Zn^{II} ions while still encapsulated in the CB[8] cavity (Figure 6). These are the first examples of transition metal macrocyclic complexes encapsulated in molecular or supramolecular hosts. An electrochemical study revealed that the encapsulation of Cu(cyclen) in CB[8] causes a large positive shift of the $Cu^{II/I}$ redox potential and a substantial decrease in the electron-transfer rates. This supramolecular system thus mimics redox-active metalloproteins in which redox centers are embedded in protein coats and may also serve as biomimetic systems for the binding, activation, and catalytic transformation of specific substrates.

Day and co-workers reported an interesting macrocycle within a macrocycle in which CB[5] is located inside the larger homologue CB[10].[33] Free motion of CB[5] within CB[10], reminiscent of a gyroscope, suggested the name gyroscane. The isolation of free CB[10] by removal of CB-

Scheme 5



[5] from the cavity has not been successful. This work however suggests possibility of a template synthesis of higher CB homologues.

3.5. Cucurbit[*n*]uril-Mediated Chemical Reactions. The cavity of CB[*n*] can be used as a reaction chamber to mediate chemical reactions, as illustrated by the classic cycloaddition work of Mock et al.[16] We demonstrated a facile, highly stereoselective [2 + 2] photoreaction of *trans*-diaminostilbene dihydrochloride (DAS) in the cavity of CB[8] in solution (Scheme 4).[34] UV irradiation of an aqueous solution containing CB[8] and *trans*-DAS in a 1:2 ratio followed by a base treatment affords α,α,*β*,*β*-tetrakis-(4-aminophenyl)cyclobutane almost exclusively with a small amount of the α*β*α*β* isomer. In the absence of CB-[8], however, the main reaction pathway for *trans*-DAS upon UV irradiation is the isomerization to *cis*-DAS. The origin of the high stereoselectivity of the photodimerization mediated by CB[8] has been proposed on the basis of a theoretical study. Before the photoreaction occurs, CB[8] and *trans*-DAS form a 1:2 host−guest complex in aqueous solution. Although both syn and anti orientations are possible when the two guest molecules are included in CB[8], the syn conformation is more favored for the photocyclization to give the αα*ββ* product. This work illustrates that bimolecular reactions between appropriately designed guest molecules can be facilitated with high regio- and stereoselectivity.

By encapsulation, CB[*n*] can stabilize otherwise unstable species. For example, *cis*-DAS, which can be gener-

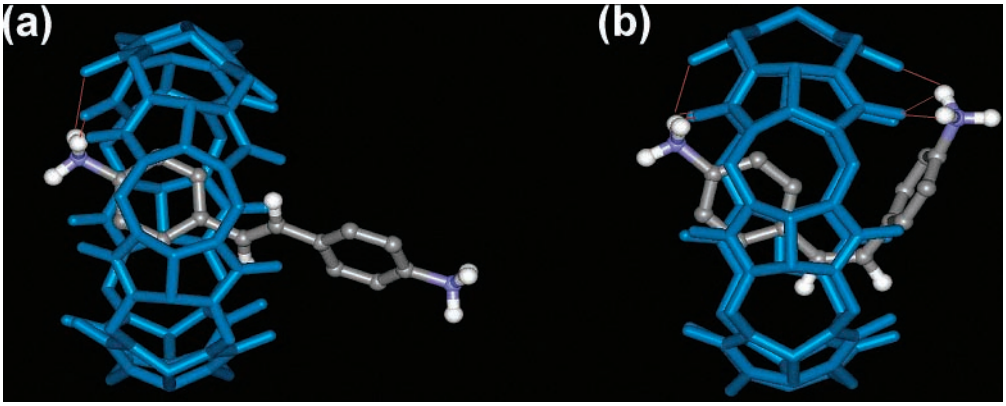


FIGURE 7. Energy-minimized structures of (a) *trans*-DAS/CB[7] and (b) *cis*-DAS/CB[7] complexes.

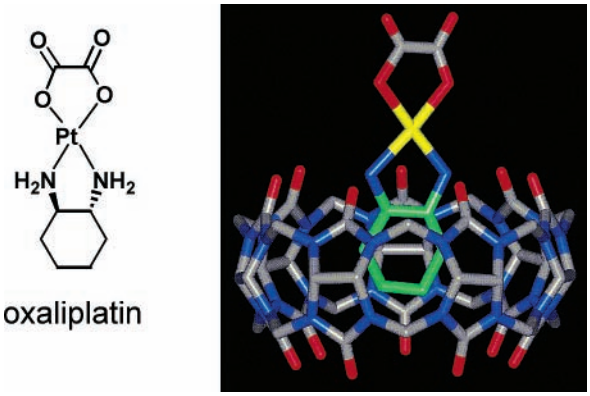
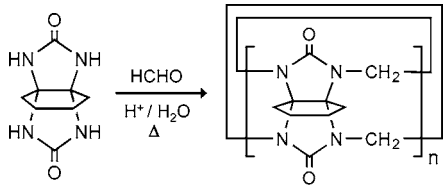


FIGURE 8. X-ray crystal structure of oxaliplatin/CB[7] complex.

ated from *trans*-DAS by UV light irradiation, slowly converts to the trans form in the dark. However, once it forms a 1:1 host−guest complex with CB[7], the guest does not undergo isomerization to the trans form at an appreciable rate at room temperature (Scheme 5).[30] Ab initio calculations revealed that, although free *cis*-DAS is less stable than the trans by 9 kcal mol^{-1}, the former has larger binding energy (by ∼23 kcal mol^{-1}) than the latter in forming a 1:1 inclusion complex with CB[7] because both terminal amine units of the cis isomer can form hydrogen bonds with the portal oxygens of CB[7] whereas only one terminal amine unit of the trans isomer can form such bonds (Figure 7). Consequently, the inclusion complex of the cis isomer is more stable than that of the trans isomer at least in the gas phase.

3.6. Miscellaneous Supramolecular Systems. CB[7] may be used as a host for drugs of appropriate size since its aqueous solubility and internal dimensions are comparable to those of β-CD. For example, CB[7] forms a stable 1:1 complex ($K = \sim 2 \times 10^5\ M^{-1}$) with the anticancer drug oxaliplatin by encapsulating the cyclohexyl ring of the guest inside the cavity, which has been confirmed by X-ray analysis (Figure 8).[35] The high stability of the complex suggests the potential use of such complexes in controlled release of drugs. We also observed that CB[7] readily forms highly stable inclusion complexes ($K > 10^7$) with ferrocene derivatives such as ferrocene substituted amine and alcohol.[30] Nau and Marquez examined the spectroscopic properties of 2,3-diazabicyclo-[2,2,2]oct-2-

Scheme 6



ene (DBO) encapsulated in CB[7] to characterize the chemical environment of the CB[7] cavity.[36] Surprisingly, the polarizability inside CB[7] cavity is very low, even lower than that in perfluorohexane, and therefore the photophysical properties of DBO inside CB[7] are closer to those in the gas phase than to those in solution. Entrapment of *cis*-$SnCl_4(OH_2)_2$[37] and *o*-carborane[38] inside the CB[7] cavity has been reported.

4. Cucurbituril Derivatives

4.1. Decamethylcucurbit[5]uril (Me_{10}CB[5]). The only cucurbit[n]uril derivative reported in the literature was decamethylcucurbit[n]uril (Me_{10}CB[5]) until very recently. Although the possible formation of Me_{10}CB[5] from dimethylglycoluril-formaldehyde condensation was hinted earlier,[39] the isolation and full characterization of the compound was first reported by Stoddart et al. in 1992.[19] X-ray crystal structure of Me_{10}CB[5] is nearly identical to that of CB[5] with a cavity of diameter 4 Å and portals of diameter ∼2.5 Å. Bradshaw, Izatt, and co-workers studied complexation of Me_{10}CB[5] with various metal ions[40] in formic acid/water (1:1) by calorimetric and potentiometric methods and observed that the macrocycle binds most metal ions in a 1:1 stoichiometry in the acidic solution. Interestingly, Me_{10}CB[5] shows exceptionally high affinity for Pb^{2+} ion (log $K > 9$), which may be due to the size match between Pb^{2+} and Me_{10}CB[5] portals. Recently, Buschmann et al. reported stability constants of the complexes formed between Me_{10}CB[5] and alkali, alkaline earth, and ammonium ions in aqueous solution,[41] but the data should be reexamined as the Me_{10}CB[5] used in this study turned out to be its diammonium complex.[42]

Dearden et al. observed the encapsulation of small guest molecules such as N_2, O_2, methanol, or acetonitrile in Me_{10}CB[5] in the gas phase using electrospray ionization

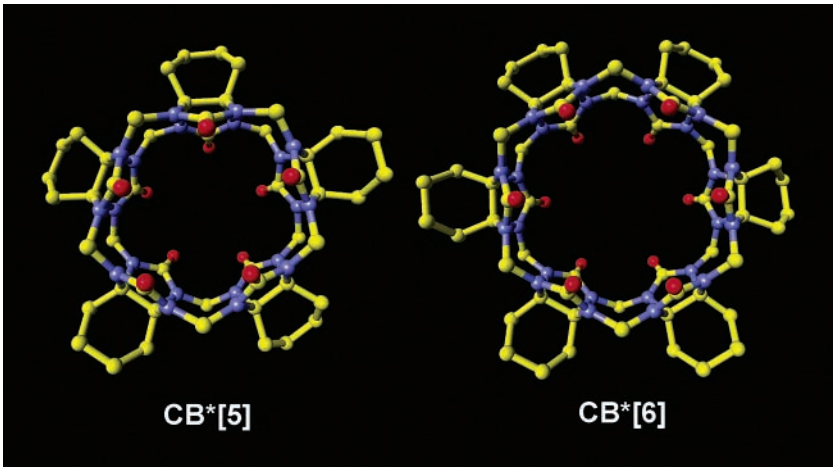


FIGURE 9. X-ray crystal structures of CB*[5] and CB*[6].

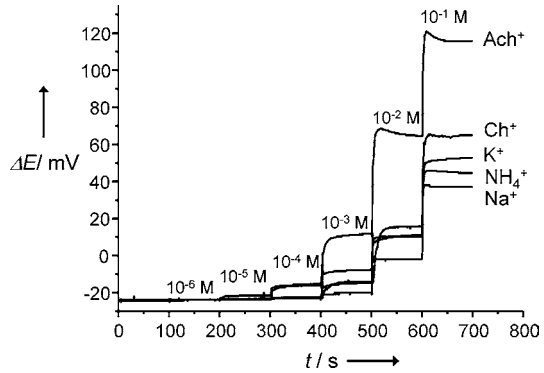
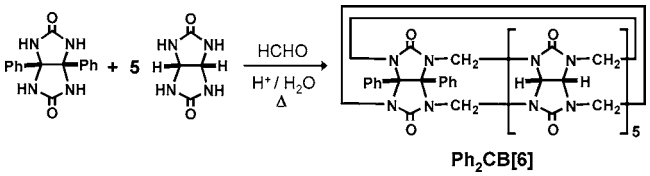


FIGURE 10. Responses of an ISE based on CB*[6] to acetylcholine (Ach^+) and other interfering ions including choline (Ch^+).

FT mass spectrometry.[43] The trapped gas molecules fail to escape as the portals are capped with ammonium ions. If an ionophore such as 18-crown-6 is present in the gas phase, the ammonium ion "lid" can be removed, and the guest gets released. The rate of guest release depends on its size. Recently, Miyahara and co-workers reported the synthesis of ammonium ion "lid" free Me_{10}CB[5], and its gas absorption and desorption properties.[44] Gases of small (such as He, Ne, and H_2) or large diameters (such as Kr, Xe, and CH_4) compared to the portal size are not absorbed significantly. However, gases of intermediate sizes (N_2, O_2, Ar, N_2O, NO, CO, and CO_2) are absorbed and released in cycles indicating the possible use of Me_{10}CB[5] in the solid state as a molecular sieve.

4.2. Soluble Cucurbiturils (CB*[*n*]). Most CB homologues and Me_{10}CB[5] are practically insoluble in common solvents limiting their use. Recently we succeeded in synthesizing new soluble CB[n] derivatives, CB*[*n*] (n = 5, 6), by the reaction of cyclohexanoglycoluril and formaldehyde (Scheme 6).[45] The NMR data revealed cyclic pentamer and hexamer as major products in a 8:1 ratio, with a small amount of unidentified homologues. After a series of dissolutions and fractional crystallizations, CB*-[5] and CB*[6] were isolated in 16% and 2% yields, respectively. Their X-ray analyses revealed the expected structures with cyclohexane rings outside decorating the "equators" reminiscent of the ringed planet Saturn (Figure 9). The portal and cavity sizes of CB*[5] and CB*[6] are essentially the same as those of the CB counterparts. Both CB*[5] and CB*[6] are soluble in common solvents such as water, methanol, DMF, and DMSO. Interestingly, both are more soluble in water ($\sim 2 \times 10^{-1}$ M) than in organic solvents ($\sim 3 \times 10^{-2}$ M or less). The origin of their high solubility in water is not clearly understood.

Scheme 7



The remarkable solubility in water at a neutral pH allowed us to study their host−guest chemistry in neutral water. In neutral water, CB*[6] forms a stable 1:1 host−guest complex with acetylcholine, an important neurotransmitter, whereas choline shows little interaction with CB*[6]. CB*[6] therefore behaves as an artificial receptor that can differentiate acetylcholine from choline in neutral water, which may find useful applications in neuroscience. Metal ion binding to CB*[5] has been also studied in neutral water. The good solubility of CB*[*n*] in organic solvents allows fabrication of membrane electrodes for ion sensing. The membrane electrode prepared from CB*[6] detects acetylcholine with high selectivity over choline and other interfering ions such as Na^+, K^+, and NH_4^+ (Figure 10). The membrane electrode made with CB*[5] behaves as an ion selective electrode for Pb^{2+}.

Recently, Nakamura and co-workers[46] reported the first unsymmetrically substituted cucurbituril, diphenylcucurbit-[6]uril, (Ph_2CB[6]). Reaction of a mixture of diphenylglycoluril and glycoluril (1:5) with formaldehyde produced a mixture of CB[6] and Ph_2CB[6] from which Ph_2CB[6] was isolated in 30% yield by gel permeation chromatography (Scheme 7). Comprehensive structural characterization of Ph_2CB[6] was provided by NMR studies of its soluble spermine complex. The synthesis of Ph_2CB[6] may be a route for further functionalization of the macrocycle via the phenyl rings.

5. Summary and Perspectives

In this Account we covered the new cucurbituril homologues and derivatives with specific reference to their synthesis, host−guest chemistry, and application prospects. A subtle interplay between the homologues of varying cavity dimensions and the size and nature of the guests has resulted in a broad spectrum of new host−guest systems. The diversity in guest binding behavior has led to several interesting studies such as redox control of guest binding, stabilization of charge-transfer complexes inside the host cavity, encapsulation of drug molecules, formation of redox-controllable vesicles, and so on. On the basis of these recent studies, numerous applications in broad disciplines can be envisaged including separation, transport, sensor, catalysis, drug/gene delivery, and controlled drug release. The field of CB-based functional materials and devices is also only in its infancy and prospects are enormous. In particular, CB-based molecular switches, memories, and machines may be developed leading to new nanotechnology.[47]

With the discovery of new CB homologues and derivatives, new opportunities emerge as well as challenges. The mechanism of cyclization and the template effects are issues to be more elaborately addressed. A major limitation has been direct functionalization of CB[6] or the homologues leading to their derivatives. Appending reactive functionalities directly on the CB surface resulting in derivatives with well-defined structures would further broaden the scope of CB chemistry. The covalent functionalization of CBs would pave the way to newer applications in the same manner as the upsurge in applications of CDs after they were functionalized. CBs with specialized functions, such as chiral CBs with enantioselective properties, may find many uses including chiral columns for chromatography. Finally, new CB analogues can be synthesized adopting diverse synthetic routes resulting in receptors with yet unknown properties. With a greater control over the synthesis strategy, discovery of such receptors is a distinct possibility.

Though CB[6] was discovered nearly a century ago, the addition of new CB homologues and derivatives has widened the scope further. The past two years have witnessed a heightened interest in CB chemistry. However, the real potential of these intriguing molecular receptors is only beginning to be defined.

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References

(1) Behrend, R.; Meyer, E.; Rusche, F. Condensation Products from Glycoluril and Formaldehyde. *Liebigs Ann. Chem.* **1905**, *339*, 1−37.
(2) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. Cucurbituril. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368.
(3) Mock, W. L. Cucurbituril. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2, pp 477−493.
(4) Whang, D.; Jeon, Y.-M.; Heo, J.; Kim, K. Self-Assembly of a Polyrotaxane Containing a Cyclic "Bead" in Every Structural Unit in the Solid State. *J. Am. Chem. Soc.* **1996**, *118*, 11333−11334.
(5) Whang, D.; Kim, K. Polycatenated Two-Dimensional Polyrotaxane Net. *J. Am. Chem. Soc.* **1997**, *119*, 451−452.
(6) Lee, E.; Heo J.; Kim, K. A Three-Dimensional Polyrotaxane Network. *Angew. Chem., Int. Ed.* **2000**, *39*, 2699−2701.
(7) Park, K.-M.; Whang, D.; Lee, E.; Heo, J.; Kim, K. Transition Metal Ion Directed Supramolecular Assembly of One- and Two-Dimensional Polyrotaxanes Incorporating Cucurbituril. *Chem. Eur. J.* **2002**, *8*, 498−508.
(8) Whang, D.; Park, K.-M.; Heo, J.; Ashton, P.; Kim, K. Molecular Necklace: Quantitative Self-Assembly of a Cyclic Oligorotaxane from Nine Molecules. *J. Am. Chem. Soc.* **1998**, *120*, 4899−4900.
(9) Roh, S.-G.; Park, K.-M.; Sakamoto, S.; Tamaguchi, K.; Kim, K. Synthesis of a Five-Membered Molecular Necklace. *Angew. Chem., Int. Ed.* **1999**, *38*, 637−641.
(10) Park, K.-M.; Kim, S.-Y.; Heo, J.; Whang, D.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Designed Self-Assembly of Molecular Necklaces. *J. Am. Chem. Soc.* **2002**, *124*, 2140−2147.
(11) Lee, J. W.; Ko, Y. H.; Park, S.-H.; Yamaguchi, K.; Kim, K. Novel Pseudorotaxane-Terminated Dendrimers. *Angew. Chem., Int. Ed.* **2001**, *40*, 746−749.
(12) Jun, S. I.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Rotaxane-Based Molecular Switch with Fluorescence Signaling. *Tetrahedron Lett.* **2000**, *41*, 471−475. Lee, J. W.; Kim, K.; Kim K. A Kinetically Controlled Molecular Switch Based on Bistable [2]-Rotaxane. *Chem. Commun.* **2001**, 1042−1043.
(13) Isobe, H.; Tomita, N.; Lee, J. W.; Kim, H.-J.; Kim, K.; Nakamura, E. Ternary Complexes Between DNA, Polyamine, and Cucurbituril. *Angew. Chem., Int. Ed.* **2000**, *39*, 4257−4260.
(14) Lim, Y.-b.; Kim,T.; Lee, J. W.; Kim, S.-m.; Kim, H.-J.; Kim, K.; Park, J.-s. Self-Assembled Ternary Complex of Cationic Dendrimer, Cucurbituril, and DNA: Noncovalent Strategy in Developing Gene Delivery Carrier. *Bioconjugate Chem.* **2002**, *13*, 1181−1185.
(15) Kim, K. Mechanically Interlocked Structures Incorporating Cucurbituril. *Chem. Soc. Rev.* **2002**, *31*, 96−107. Lee, J. W.; Kim, K. Rotaxane Dendrimers. *Top. Curr. Chem.* **2003**, *228*, 111−140.
(16) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. Catalysis by Cucurbituril. The Significance of Bound-Substrate Destabilization for Induced Triazole Formation. *J. Org. Chem.* **1989**, *54*, 5302−5308.
(17) Karcher, S.; Kornmüller, A.; Jekel, M. Cucurbituril for Water Treatment. Part I: Solubility of Cucurbituril and Sorption of Reactive Dyes. *Water Res.* **2001**, *35*, 3309−3316.
(18) Jeon, Y.-M.; Kim, J.; Whang, D.; Kim, K. A Molecular Container Assembly Capable of Controlling Binding and Release of Its Guest Molecules. *J. Am. Chem. Soc.* **1996**, *118*, 9790−9791.
(19) Flinn, A.; Hough, G. C.; Stoddart, J. F.; Williams, D. J. Decamethylcucurbit[5]uril. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1475−1477.
(20) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. New Cucurbituril Homologues: Syntheses, Isolation, Characterization, and X-ray Crystal Structures of Cucurbit[*n*]uril (n = 5, 7, and 8). *J. Am. Chem. Soc.* **2000**, *122*, 540−541.
(21) Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. Controlling Factors in the Synthesis of Cucurbituril and Its Homologues. *J. Org. Chem.* **2001**, *66*, 8094−8100.
(22) Chakraborty, A.; Wu, A.; Witt, D.; Lagona, J.; Fettinger, J. C.; Isaacs, L. Diastereoselective Formation of Glycoluril Dimers: Isomerization Mechanism and Implications for Cucurbit[n]uril Synthesis. *J. Am. Chem. Soc.* **2002**, *124*, 8297−8306.
(23) Day, A. I.; Blanch, R. J.; Coe, A.; Arnold, A. P. The Effects of Alkali Metal Cations on Product Distributions in Cucurbit[*n*]uril Synthesis, *J. Incl. Phenom. Macrocylic Chem.* **2002**, *43*, 247−250.
(24) Park, S.-H.; Kim, K., unpublished work.
(25) Kim, H.-J.; Jeon, W. S.; Ko, Y. H.; Kim, K. Inclusion of Methyl viologen in Cucurbit[7]uril. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5007−5011.
(26) Ong, W.; Gómez-Kaifer, M.; Kaifer, A. E. Cucurbit[7]uril: A Very Effective Host for Viologens and Their Cation Radicals. *Org. Lett.* **2002**, *4*, 1791−1794.
(27) Mirzoian, A.; Kaifer, A. E. Reactive Pseudorotaxanes: Inclusion Complexation of Reduced Viologens by the Host β-Cyclodextrin and Heptakis(2,6-di-O-methyl)-β-Cyclodextrin. *Chem. Eur. J.* **1997**, *3*, 1052−1058.
(28) Jeon, W. S.; Kim, H.-J.; Lee, C.; K. Kim, Control of the Stoichiometry in Host−guest Complexation by Redox Chemistry of Guests: Inclusion of Methyl-viologen in Cucurbit[8]uril. *Chem. Commun.* **2002**, 1828−1829.

(29) Kim, H.-J.; Heo, J.; Jeon, W. S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Selective Inclusion of a Hetero-Guest Pair in a Molecular Host: Formation of Stable Charge-Transfer Complexes in Cucurbit[8]uril. *Angew. Chem., Int. Ed.* **2001**, *40*, 1526−1529.
(30) Kim, K.; et al. Unpublished work.
(31) Jeon, Y. J.; Bharadwaj, P. K.; Choi, S.W.; Lee, J. W.; Kim, K. Supramolecular Amphiphiles: Spontaneous Formation of Vesicles Triggered by Formation of a Charge-Transfer Complex in a Host. *Angew. Chem., Int. Ed.* **2002**, *41*, 4474−4476.
(32) Kim, S.-Y.; Jung, I.-S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Macrocycles within Macrocycles: Cyclen, Cyclam, and Their Transition Metal Complexes Encapsulated in Cucurbit[8]uril. *Angew. Chem., Int. Ed.* **2001**, *40*, 2119−2121.
(33) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. A Cucurbituril-Based Gyroscane. *Angew. Chem., Int. Ed.* **2002**, *41*, 275−277.
(34) Jon, S. Y.; Ko, Y. H.; Park, S.-H.; Kim, H.-J.; Kim, K. A Facile, Stereoselective [2 + 2] Photoreaction Mediated by Cucurbit[8]uril. *Chem. Commun.* **2001**, 1938−1939.
(35) Kim, K.; Jeon, Y. J.; Kim, S.-Y.; Ko, Y. H. Inclusion Compound Comprising Cucurbituril Derivatives as Host Molecule and Pharmaceutical Composition Comprising the Same. *PCT Int. Appl.* **2003**, WO 0324978 A1 20030327.
(36) Marquez, C.; Nau, W. M. Polarizabilities Inside Molecular Containers. *Angew. Chem., Int. Ed.* **2001**, *40*, 4387−4390.
(37) Lorenzo, S.; Day, A. I.; Craig, D.; Blanch, R. J.; Arnold, A. P.; Dance, I. The First Endoannular Metal Halide-Cucurbituril: *cis*-$SnCl_4(OH_2)_2$@Cucurbit[7]uril. *CrystEngComm* **2001**, *49*, 1−7.
(38) Blanch, R. J.; Sleeman, A. J.; White, T. J.; Arnold, A. P.; Day, A. I. Cucurbit[7]uril and *o*-Carborane Self-Assemble to Form a Molecular Ball Bearing. *Nano Lett.* **2002**, *2*, 147−149.
(39) N.-Y. Shih, Ph.D. Thesis, University of Illinois at Chicago, Chicago, 1981.
(40) Zhang, X. X.; Krakowiak, K. E.; Xue, G.; Bradshaw, J. S.; Izatt, R. M. A Highly Selective Compound for Lead: Complexation Studies of Decamethylcucurbit[5]uril with Metal Ions. *Ind. Eng. Chem. Res.* **2000**, *39*, 3516−3520.
(41) Buschmann, H.-J.; Cleve, E.; Jansen, K.; K. Wego, A.; Schollmeyer, E. Complex Formation Between Cucurbit[n]urils and Alkali, Alkaline Earth and Ammonium Ions in Aqueous Solution. *J. Incl. Phenom. Macrocyclic Chem.* **2001**, *40*, 117−120.
(42) Jansen, K.; Buschmann, H.-J.; Wego, A.; Döpp, D.; Mayer, C.; Drexler, H.-J.; Holdt, H.-J.; Schollmeyer, E. Cucurbit[5]uril, Decamethylcucurbit[5]uril and Cucurbit[6]uril. Synthesis, Solubility and Amine Complex Formation. *J. Incl. Phenom. Macrocyclic Chem.* **2001**, *39*, 357−363.
(43) Kellersberger, K. A.; Anderson, J. D.; Ward, S. M.; Krakowiak, K. E.; Dearden, D. V. Encapsulation of N_2, O_2, Methanol, or Acetonitrile by Decamethylcucurbit[5]uril$(NH_4^+)_2$ Complexes in the Gas Phase: Influence of the Guest on "Lid" Tightness. *J. Am. Chem. Soc.* **2001**, *123*, 11316−11317.
(44) Miyahara, Y.; Abe, K.; Inazu, T. "Molecular" Molecular Sieves: Lid-Free Decamethylcucurbit[5]uril Absorbs and Desorbs Gases Selectively. *Angew. Chem., Int. Ed.* **2002**, *41*, 3020−3023.
(45) Zhao, J.; Kim, H.-J.; Oh, J.; Kim, S.-Y.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. Cucurbit[n]uril Derivatives Soluble in Water and Organic Solvents. *Angew. Chem., Int. Ed.* **2001**, *40*, 4233−4235.
(46) Isobe, H.; Sato, S.; Nakamura, E. Synthesis of Disubstituted Cucurbit[6]uril and Its Rotaxane Derivative. *Org. Lett.* **2002**, *4*, 1287−1289.
(47) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. Artificial Molecular Machines. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348−3391.

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