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Toward supramolecular polymers incorporating double cavity cucurbituril hosts

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ABSTRACT

We describe the synthesis of a series of guests (**1**–**6**) containing two adamantylammonium ions separated by xylylene spacing groups and their complexation properties toward double cavity cucurbituril host bis-*ns*-CB[10]. We observed the preferential formation of 1:1, 2:2, and oligomeric complexes rather than the desired *n*:*n* supramolecular polymers. Guest **7**, which contains a longer biphenyl spacer successfully precludes the formation of the 1:1 complex but results in the formation of the 2:2 complex (bis-*ns*-CB[10]$_2$·**7**$_2$) rather than supramolecular polymer. Guest **8**, which contains adamantylammonium, *p*-xylylene diammonium, and hexanediammonium ion binding regions is shown to reversibly form 2:2 and 1:2 complexes (bis-*ns*-CB[10]$_2$·**8**$_2$ and bis-*ns*-CB[10]·**8**$_2$) in response to changes in host:guest stoichiometry. Lastly, this equilibrium can be manipulated by the addition of exogenous CB[6], which selectively targets the hexanediammonium ion binding region of **8** and delivers the penta-molecular complex bis-*ns*-CB[10]·**8**$_2$·CB[6]$_2$.

1. Introduction

The synthetic and supramolecular chemistry of the cucurbit [*n*]uril family (CB[*n*]) of macrocycles has undergone extensive development since the pioneering work of Mock on CB[6] during the 1980s.[1,2] For example, the large values of K_a and high selectivities based on guest size, shape, and functional group preferences of CB[6] have been shown to transfer to the larger homologues CB[7] and CB[8].[3] In turn these large values of K_a, the associated free energy ($\Delta\Delta G$), and the inherent stimuli responsiveness of CB[*n*]·guest complexes (e.g., pH, photochemical, electrochemical, chemical) have led to their use in the development of a variety of molecular machines and biomimetic systems.[4–6] Our research group has been involved in studies of the mechanism of CB[*n*] formation, which has resulted in the preparation of new CB[*n*] type molecular containers (bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6]) with exciting properties (homotropic allosterism, chiral recognition, and folding).[7,8]

The use of supramolecular chemistry as a means to create and modify the properties of polymers has been the subject of active investigation over the past decade.[9] For example, a number of groups have demonstrated the oligo- and polymerization of suitable dimeric systems based on reversible hydrogen bonding and metal–ligand interactions.[10] Most relevant to the work described in this paper is the work of Harada who has investigated the use of cyclodextrin molecular containers as building blocks for supramolecular polymers by hydrophobically driven host–guest complexation in water.[11] In supramolecular polymeric systems, the degree of polymerization is controlled by the strength of the noncovalent interactions between monomers with higher values of K_a leading to longer polymers. As such, the use of members of the CB[*n*] family—with their exceedingly large values of K_a (up to 10^{15} M^{-1}),[3,12,13] —in the preparation or modification of polymeric and macromolecular species holds great promise. Accordingly, several groups have decorated the main chain or side chains of linear polymers[14] or dendrimers[15] with CB[*n*] binding groups and were therefore able to modify the properties of the polymer by addition of CB[*n*]. Kim's group even used a CB[6] derivative as the monomer to form covalent polymeric nanocapsules.[16] Lastly, the groups of Kim, Kaifer, and Scherman have used the ability of CB[8] to form homo-ternary or hetero-ternary complexes[4] to drive the formation of self-assembly dendrimers and a self-assembled diblock copolymer.[6,17]

In 2006, we reported the isolation and recognition capacity of bis-*ns*-CB[10].[7] Bis-*ns*-CB[10] contains two cavities that are able to bind to two guests simultaneously to form ternary complexes. In this process, the binding of the first guest preorganizes the second binding site for binding of the second guest, which is known as allostery. Even more interesting was the ability of bis-*ns*-CB[10] to distinguish between small and large guests within a mixture and

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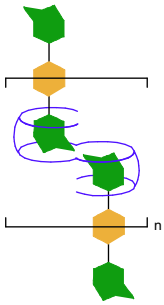


Figure 1. Hypothetical linear polymer comprising bis-*ns*-CB[10] and **1**.

form ternary complexes with two identical guests. This latter process is known as *homotropic allostery*. This ability is due to the flexibility of the central CH_2 bridges, which adjust their nonbonded $CH_2\cdots CH_2$ distance to accommodate the size of the guest. We envisioned that bis-*ns*-CB[10] with its ability to form tight ternary complexes under positive homotropic allosteric control would render bis-*ns*-CB[10] as an ideal component of supramolecular polymers in combination with suitable guests containing two binding epitopes. Figure 1 depicts the mode of polymerization that might result from the combination of bis-*ns*-CB[10] and suitable guests. Given the fact that such supramolecular polymers would be composed of two components we expected the behavior of the system to be sensitively dependent on host:guest stoichiometry. In addition, we expected the system to be responsive to the addition of exogenous host or guest by the formation of competitive host·guest complexes. This paper reports our initial studies in this research direction.

2. Results and discussion

This section is subdivided into several parts. We start with a discussion of the design of the guests (**1**–**8**, Chart 1) and their synthesis. Next, we discuss the characterization of the supramolecular species formed in the presence of bis-*ns*-CB[10] with a particular emphasis on absolute host:guest stoichiometry. Finally, we discuss the application of stimuli in the form of additional CB[*n*] hosts to control absolute binding stoichiometry in this system.

2.1. Design of guests 1–6

Chart 1 shows the structures of hosts CB[6], CB[7], and bis-*ns*-CB[10] and guests **1**–**9** used in this study. We were attracted to the possibility of preparing supramolecular polymers using the double cavity host bis-*ns*-CB[10] in combination with suitable guests (e.g., **1**–**8**) containing two binding domains (e.g., bis-*ns*-CB[10]$_n$·guest$_n$). Figure 1 depicts the desired *n*:*n* interaction between bis-*ns*-CB[10] and divalent guests. Although this proposed supramolecular polymerization appears straightforward, in reality the situation is more complex. For example, although linear supramolecular polymers can be formed from solutions comprising *n* hosts and *n* guests, the formation of discrete (cyclic) 1:1, 2:2, 3:3, or *n*:*n* aggregates can also be readily envisioned.[18] Compounding the situation is the reality that smaller discrete assemblies are likely to be favored on entropic grounds. Therefore, we decided to start simple and targeted guests **1**–**6** (Chart 1), which contain two adamantylammonium binding domains linked together by *o*-, *m*-, and *p*-xylylene units for several reasons. First, we envisioned that **1**–**6** would be straightforward to synthesize by substitution reactions. Second, we hoped that the different substitution patterns of **1**–**6** would result in the formation of different discrete or polymeric assemblies. Lastly, we hoped that the xylylene spacer between the adamantylammonium binding domains would be rigid enough to prevent the formation of a 1:1 host:guest inclusion complex. Upon closer inspection post facto, we realized that guests **1**, **2**, and **4**–**6** are more complex than we anticipated and actually contain one xylenediamine and two adamantylammonium binding domains (Fig. 2). In the discussion below we abbreviate these domains as PXDA and Ad, respectively.

2.2. Synthesis of guests 1, 2, and 4–6

The synthesis of **1** and **2** was achieved by twofold S_N2 reaction of the corresponding bis-(bromomethyl)benzenes (**12** and **13**) with adamantylamine (**10**) using Ag_2O in THF (Scheme 1). The free-base amines were then converted to the hydrochloride salts (**1** and **2**) by treatment with anhydrous HCl. All attempts to synthesize *ortho*-substituted **3** were unsuccessful due to competing intramolecular five-membered ring formation. Accordingly, we decided to prepare the tetramethylated series (**4**–**6**) of compounds to complete the substitution pattern series. Compounds **4**–**6** were prepared by reacting bis-(bromomethyl)benzenes (**12**–**14**) with *N*,*N*-dimethyladamantylamine **11** in refluxing CH_3CN.

2.3. Characterization of bis-*ns*-CB[10] complexes with guests 1, 2, and 4–6

After we had synthesized guests **1**, **2**, and **4**–**6** we decided to investigate their use in the preparation of supramolecular

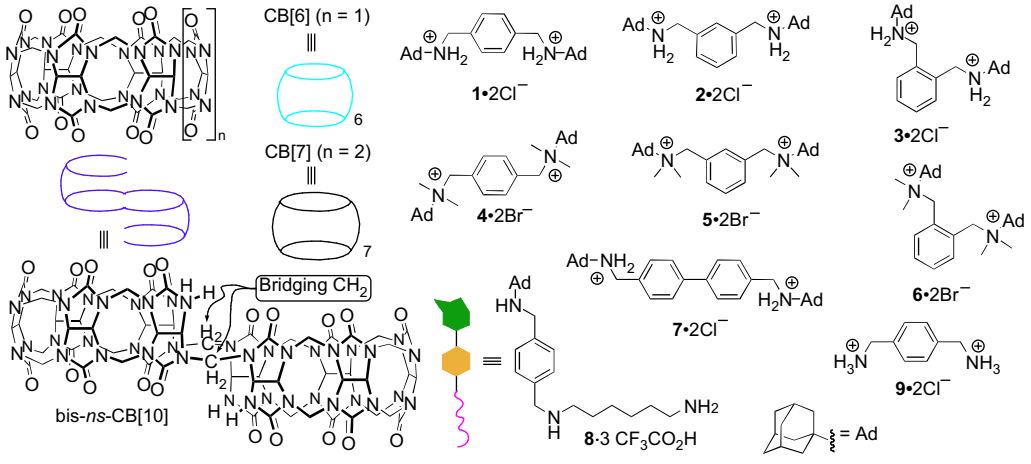


Chart 1. Compounds used in this study.

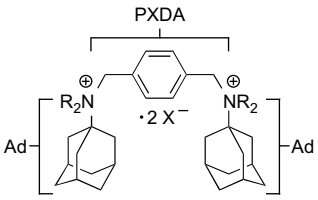
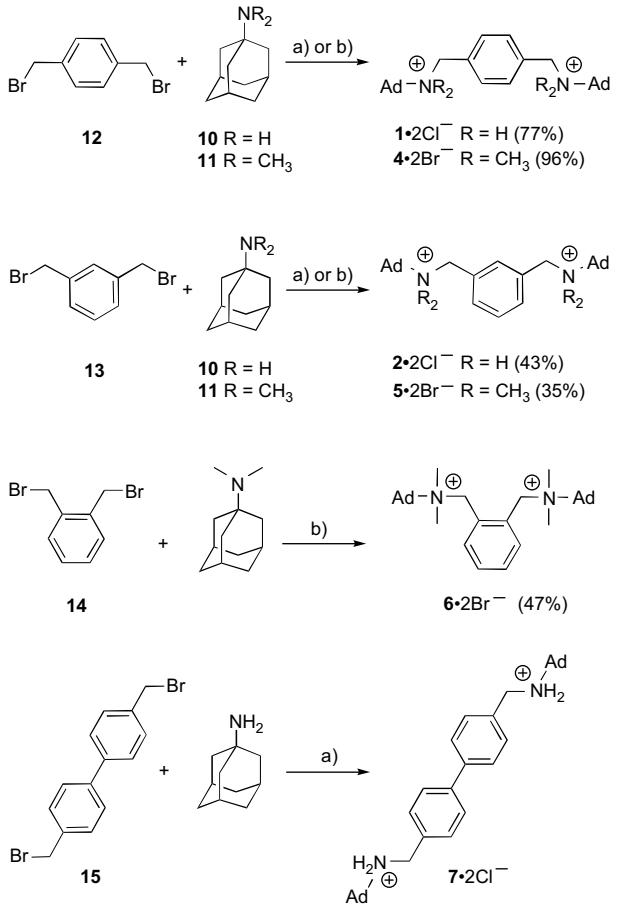


Figure 2. Depiction of the two different binding domains of the xylylene derived guests (**1**, **2**, and **4**–**6**) along with their abbreviations used in this paper.



Scheme 1. Synthesis of guest compounds **1**, **2**, and **4**–**7**. Conditions: (a) Ag_2O, THF; (b) CH_3CN, reflux.

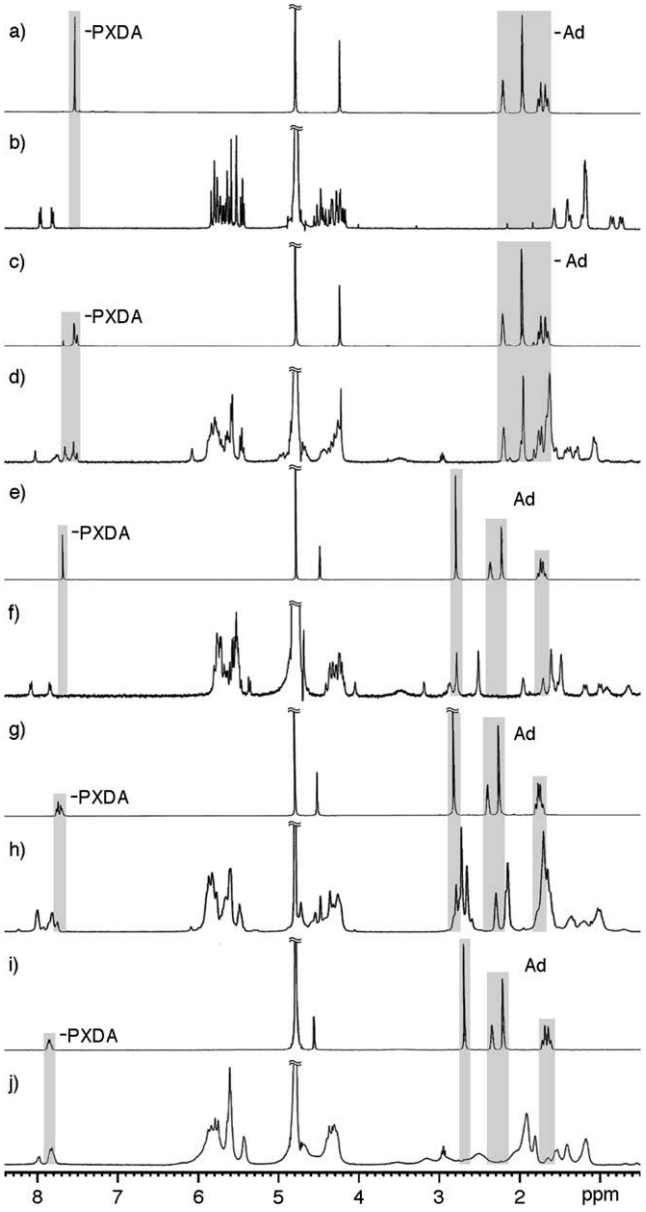


Figure 3. ^{1}H NMR spectra (400 MHz, D_2O, rt) recorded for solutions of: (a) **1**, (b) bis-*ns*-CB[10]·**1**, (c) **2**, (d) a mixture of **2** and bis-*ns*-CB[10]·**2**, (e) **4**, (f) a mixture of **4** and bis-*ns*-CB[10]·**4**, (g) **5**, (h) a mixture of **5** and bis-*ns*-CB[10]·**5**, (i) **6**, (j) bis-*ns*-CB[10]·**6**.

polymers. Figure 3 shows the ^{1}H NMR spectra recorded for guests **1**, **2**, and **4**–**6** alone and in the presence of bis-*ns*-CB[10]. The ^{1}H NMR spectra for the complexes between *p*-xylylene diamine derivatives **1** and **4** and bis-*ns*-CB[10] (Fig. 3b and f) are sharp and dispersed, which is indicative of a single, well-defined geometry. In contrast, the spectra obtained for the bis-*ns*-CB[10] complexes of *m*-xylylene diamine derivatives **2** and **5** (Fig. 3d and h) and *o*-xylylene diamine derivative **6** are broader and less well defined, which suggested the possibility of oligomeric or polymeric assemblies. Comparison of the ^{1}H NMR spectra for *para*-substituted **1** before (Fig. 3a) and after the addition of bis-*ns*-CB[10] (Fig. 3b) reveals that the protons corresponding to the Ad binding domain are shifted upfield whereas those of the PXDA binding domain are shifted downfield. It is well known that the cavity region of CB[*n*] compounds constitutes an NMR shielding region whereas the regions just outside the C=O lined portals are deshielding.[2] Accordingly, within the bis-*ns*-CB[10]·**1** complex, both Ad binding domains are inside the cavities of bis-*ns*-CB[10] whereas the PXDA group is outside the portal. Similar observations were made for the complex between *p*-substituted **4** and bis-*ns*-CB[10]. In contrast, the ^{1}H NMR spectra recorded for the complexes between bis-*ns*-CB[10] and **2**, **5**, and **6** show two classes of resonances for the PXDA (unshifted and downfield shifted) and Ad groups (unshifted and upfield shifted), which suggested that some of the Ad and PXDA domains are unbound and remote from the cavities of bis-*ns*-CB[10]. The integration of the resonances present in the ^{1}H NMR spectra of each of the bis-*ns*-CB[10] complexes with **1**, **2**, and **4**–**6** suggests that host and guest are present in equimolar amounts.[19] This observed relative stoichiometry is consistent with 1:1, 2:2, or the desired *n*:*n* complexes (Fig. 4).

2.4. Determination of absolute host:guest stoichiometry by diffusion ordered spectroscopy

In order to determine the absolute stoichiometry of complexes between bis-*ns*-CB[10] and guests **1**, **2**, and **4**–**6** we performed diffusion ordered NMR spectroscopy (DOSY).[20] DOSY spectroscopy

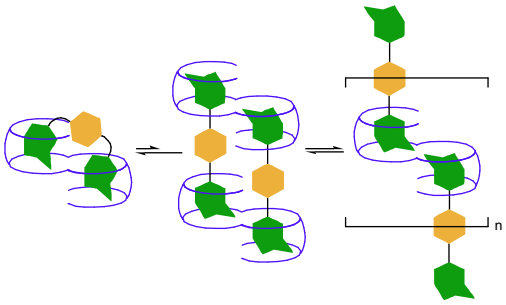


Figure 4. Potential equilibrium between bis-*ns*-CB[10]·**1**, bis-*ns*-CB[10]$_2$·**1**$_2$, and bis-*ns*-CB[10]$_n$·**1**$_n$ complexes.

allows a determination of the diffusion coefficients (D_s) of a given species in solution. From this knowledge of the values of D_s it is possible to infer the size of the species and therefore the absolute stoichiometry of the supramolecular complexes. Diffusion NMR was performed on samples prepared from equimolar amounts of host and guest for compounds **1**, **2**, and **4**–**6** with bis-*ns*-CB[10]. The bis-*ns*-CB[10]·**9**$_2$ complex—which does not undergo exchange processes with assemblies formed from bis-*ns*-CB[10] and guests **1**, **2**, and **4**–**6**—was used as an internal standard of known molecular size.[7] The diffusion coefficients for these complexes were determined in the standard manner by fitting a plot of field strength versus intensity using Eq. 1. In Eq. 1, I and I_0 are signal intensities, D is the diffusion coefficient measured in $m^2\,s^{-1}$, γ is the gyromagnetic ratio measured in $s^{-1}\,T^{-1}$, g is the gradient strength measured in $G\,cm^{-1}$, δ is the length of the gradient measured in milliseconds, and Δ is the diffusion time measured in milliseconds.[20,21] Table 1 summarizes the results of the DOSY measurements. The diffusion coefficients measured for the complex between bis-*ns*-CB[10] and *p*-xylylene diamine derivative **1** were nearly identical to that measured for bis-*ns*-CB[10]·**9**$_2$, which indicates this complex is best formulated as the 1:1 complex (bis-*ns*-CB[10]·**1**). Figure 5a shows an MMFF minimized model of the bis-*ns*-CB[10]·**1** complex. In contrast, the diffusion coefficient measured for the complex between *p*-substituted quaternary ammonium guest **4** is only 61% of that of bis-*ns*-CB[10]·**9**$_2$. For *perfect spheres*, theory predicts that increasing the molecular weight n-fold should lead to a decreased diffusion coefficient by a factor of $n^{-1/3}$; dimers (trimers) are therefore expected to have diffusion coefficients 79% (69%) those of the corresponding monomers. For the rod-like oligomers expected for assemblies based on bis-*ns*-CB[10] we have previously shown that dimers should have diffusion coefficients roughly 67–72% those of monomers.[22] We, therefore, formulate the complex between bis-*ns*-CB[10] and **4** as bis-*ns*-CB[10]$_2$·**4**$_2$. Examination of an MMFF model of bis-*ns*-CB[10]$_2$·**4**$_2$ (Fig. 5b) illustrates the 2:2

Table 1
Diffusion coefficients ($10^{-10}\,m^2\,s^{-1}$) measured for the complexes between bis-*ns*-CB[10] and guests **1**–**8** (D_2O, 400 MHz, 25 °C) and the corresponding dimensionless ratio of diffusion coefficients relative to internal standard bis-*ns*-CB[10]·**9**$_2$

Guest	D_s complex	D_s bis-*ns*-CB[10]·**9**$_2$	Ratio ($D_s/D_{s(\text{bis-}ns\text{-CB[10]}\cdot\mathbf{9}\cdot\mathbf{9})}$)
1	2.47	2.45	1.01
2	1.10	2.24	0.49
4	1.40	2.27	0.61
5	1.04	2.18	0.48
6	1.08	2.31	0.47
7	1.61	2.42	0.67
8 (10 °C)	1.22	1.54	0.79

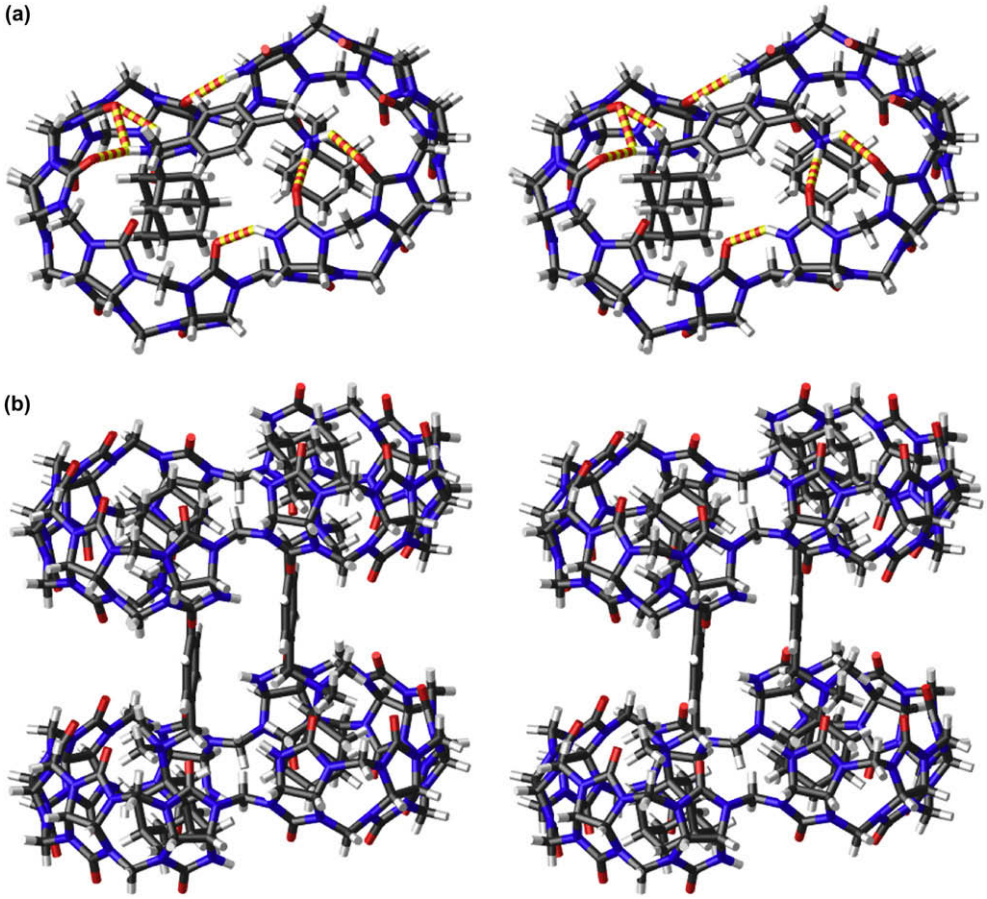


Figure 5. Stereoviews of the MMFF minimized geometries of: (a) bis-*ns*-CB[10]·**1** and (b) bis-*ns*-CB[10]$_2$·**4**$_2$. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow stripped.

stoichiometry.[23] For the complexes between **2**, **5**, **6**, and bis-*ns*-CB[10] the diffusion coefficients are significantly smaller and clustered in the range 0.47–0.49. This clearly suggests an absolute stoichiometry greater than 2:2. Unfortunately, in the absence of well-defined ^{1}H NMR spectra, X-ray crystallographic results, or electrospray mass spectrometric data assignment of an absolute stoichiometry to these aggregates is speculative.[24] Disappointed by these results, we decided to investigate some of the structural variables that might circumvent 1:1 or 2:2 complex formation and promote the formation of higher order linear oligomers or polymers.

$$I = I_0 e^{-D\gamma^2 g^2 \delta^2 (\Delta - \delta/3)} \quad (1)$$

2.5. Increased linker length between Ad binding domains

First, we decided to investigate the influence of the length of the linker between the Ad binding domains. For this purpose we targeted compound **7**, which connects two Ad binding domains with a biphenyl linker. We surmised that the length and rigidity of the biphenyl linking group would preclude the formation of a 1:1 complex and promote the formation of *n*:*n* oligomeric or polymeric structures. The synthesis of **7** was achieved by treatment of **15** with adamantylamine in the presence of Ag_2O in THF (Scheme 1).

2.6. Characterization of the complex between bis-*ns*-CB[10] and guest 7

The ^{1}H NMR spectrum of a sample containing equimolar amounts of bis-*ns*-CB[10] and **7** shows a single set of resonances, which is consistent with a single well-defined host·guest complex (Fig. 6). The bis-*ns*-CB[10]:**7** ratio was determined to be 1:1 based on integration of the ^{1}H NMR spectrum. The protons of the Ad domain in Figure 6b are shifted upfield relative to the adamantyl protons of uncomplexed **7** in Figure 6a, which suggests that the Ad domain of **7** is bound inside the bis-*ns*-CB[10] cavity. Also of interest were the resonances for the biphenyl group, which split into one upfield and one downfield shifted set of resonances in the complex. To differentiate between the multitude of possible *n*:*n* complexes formed, we performed diffusion NMR experiments. Figure 7 shows a plot of intensity versus field strength for an equimolar mixture of (bis-*ns*-CB[10]·**7**)$_n$ and bis-*ns*-CB[10]·**9**$_2$ as an internal monomeric standard. Fitting these curves to the theoretical equation (Eq. 1) allowed us to extract diffusion coefficients for (bis-*ns*-CB[10]·**7**)$_n$ (D_s=1.61×10^{-10} m^2 s^{-1}) and bis-*ns*-CB[10]·**9**$_2$ (D_s=2.42×10^{-10} m^2 s^{-1}) as an internal standard. The ratio of the values of D_s for (bis-*ns*-CB[10]·**7**)$_n$ and bis-*ns*-CB[10]·**9**$_2$ is 0.67. This diffusion constant ratio falls in the lower end of the range expected (0.67–0.72) for rod-shaped dimers.[22,25] On the basis of the DOSY measurements we formulate the complex as bis-*ns*-CB[10]$_2$·**7**$_2$. In contrast to the 1:1 complex observed between bis-*ns*-CB[10] and guest **1**, which contained a short *p*-xylylene linking group, guest **7** did form a higher order complex but with a 2:2 absolute stoichiometry. Although the longer biphenyl linker present in **7** did preclude 1:1 complex formation as designed, we believe that the rigidity of the linking group resulted in a preference for 2:2 complex formation (e.g., cyclization) rather than oligomerization. This result highlights one of the main challenges in the formation of supramolecular polymers from pairs of monomers containing two binding groups.

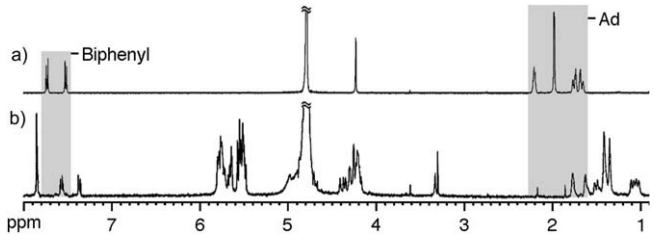


Figure 6. ^{1}H NMR spectra (400 MHz, D_2O, rt) recorded for solutions of: (a) **7**, (b) bis-*ns*-CB[10]$_2$·**7**$_2$.

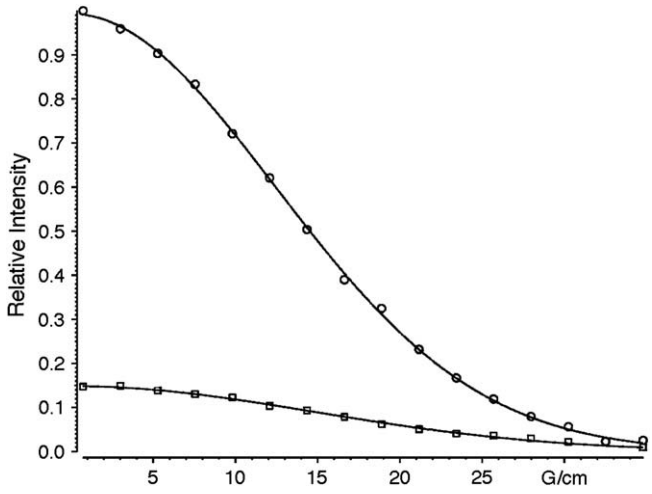


Figure 7. Plot of signal intensity versus gradient strength and the best fit of the data to Eq. 1. Symbols: o, bis-*ns*-CB[10]$_2$·**7**$_2$; □, bis-*ns*-CB[10]·**9**$_2$.

2.7. Design of heterovalent guest 8

Although we were disappointed that guest **7** with a rigid linker did not result in supramolecular polymers when combined with bis-*ns*-CB[10] we hypothesized that the presence of two identical Ad binding domains was to blame. Given that bis-*ns*-CB[10] exhibits homotropic allosterism we wondered what would happen if we synthesized **8**, which contains Ad and hexanediammonium (HDA) binding domains connected by a *p*-xylylene linker (Fig. 8). Would bis-*ns*-CB[10] choose to form the 1:1 complex bis-*ns*-

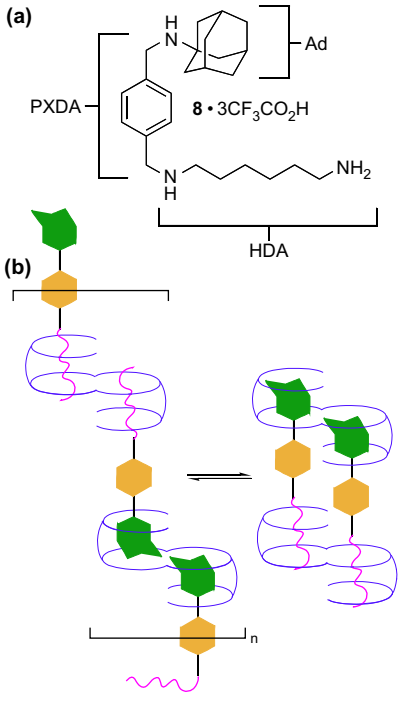
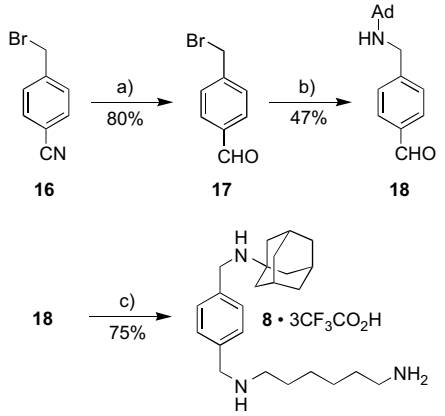


Figure 8. (a) Depiction of the three binding domains of **8** along with their abbreviations used in this paper. (b) Theoretical equilibrium between a linear polymer comprising bis-*ns*-CB[10] and **8** and bis-*ns*-CB[10]$_2$·**8**$_2$.

CB[10]·**8** in which the two cavities are filled by different sized binding groups (e.g., Ad and HDA) and violate homotropic allostery? Would bis-*ns*-CB[10] choose to form the 2:2 complex bis-*ns*-CB[10]$_2$·**8**$_2$ (Fig. 8)? We hypothesized that homotropic allostery might destabilize the cyclic aggregate bis-*ns*-CB[10]$_2$·**8**$_2$ that contains two molecules of bis-*ns*-CB[10] of different non-bonded $CH_2\cdots CH_2$ distance (e.g., steric mismatch). When both of those hypotheses are true we might expect the formation of a supramolecular polymer bis-*ns*-CB[10]$_n$·**8**$_n$.

2.8. Synthesis of heterovalent guest 8

The synthesis of **8** was achieved in three steps, starting with commercially available nitrile **16** as depicted in Scheme 2. Conversion of nitrile **16** to aldehyde **17** was carried out according to the literature procedure.[26] Benzyl bromide **17** was alkylated with **10** to afford compound **18** in 47% yield. Subsequent reaction of **18** with *N*-(*tert*-butoxycarbonyl)-1,6-hexanediamine (**19**) afforded the corresponding diamine, which was deprotected to yield **8** (75%) as a water-soluble trifluoroacetate salt.



Scheme 2. Synthesis of **8**. Reaction conditions: (a) (i) DIBAL, toluene, 0 °C, 1 h. (ii) 10% HCl, 1 h, rt. (b) **10**, Ag_2O, THF. (c) (i) *N*-(*tert*-butoxycarbonyl)-1,6-hexanediamine (**19**), toluene, reflux, 20 h. (ii) $NaBH_4$, MeOH, reflux (30 min), then stir at rt (15 h). (iii) TFA/CH_2Cl_2 (1:1), rt, 8 h.

2.9. Characterization of the complex between bis-*ns*-CB[10] and guest 8

We first prepared the complex between equimolar amounts of bis-*ns*-CB[10] and **8**. The ^{1}H NMR spectra of uncomplexed guest **8** and its complex are shown in Figure 9a,b. The ^{1}H NMR spectrum of the complex (Fig. 9b) is composed of a significant number of relatively sharp resonances, which suggested that the system is not polymeric. Integration of the ^{1}H NMR spectrum of the assembly confirmed that equal numbers of molecules of bis-*ns*-CB[10] and **8** were incorporated. The diffusion coefficient for the complex was 79% that of the monomeric standard bis-*ns*-CB[10]·**9**$_2$ (Table 1), which suggests that complex is best formulated as bis-*ns*-CB[10]$_2$·**8**$_2$.[27] Fortunately, we also observed a peak at m/z=1339 in the ESI-MS, which corresponds to [bis-*ns*-CB[10]$_2$·**8**$_2$]$^{3+}$, which confirms the assignment of 2:2 stoichiometry.[28]

It was possible to tease some information from the chemical shifts of the resonances for distinct regions of guest **8** within the bis-*ns*-CB[10]$_2$·**8**$_2$ complex. For example, when either the Ad or the HDA portion of guest **8** is bound within the interior of bis-*ns*-CB[10] the adjacent PXDA domain is positioned directly outside the host cavity. We refer to this situation as PXDA$_{out}$. The spectroscopic fingerprint for a PXDA$_{out}$ situation is a slight deshielding of the resonances for the PXDA domain. Conversely, when a PXDA binding

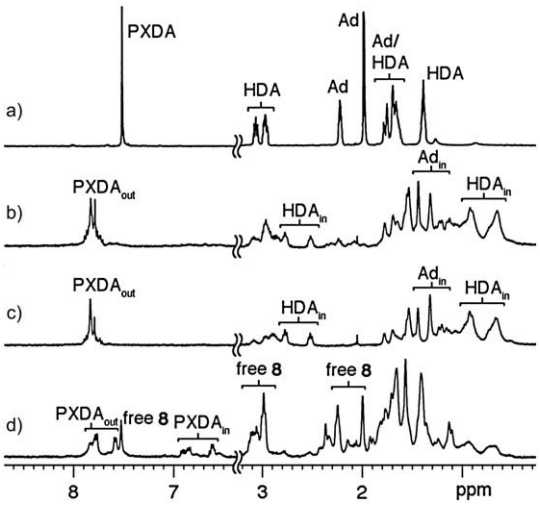
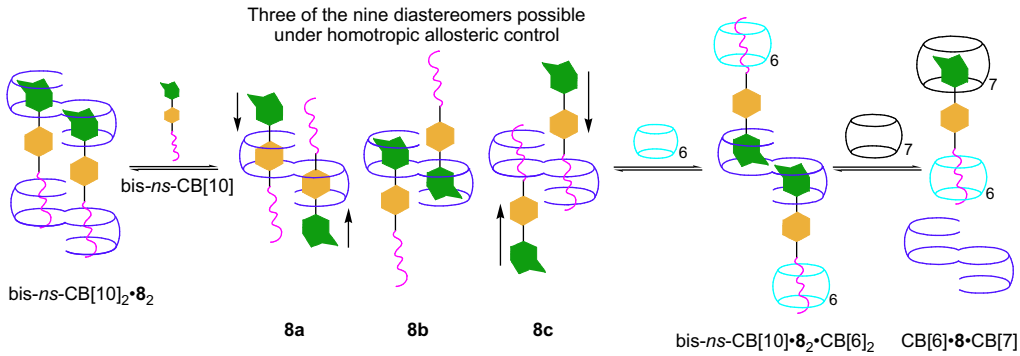


Figure 9. ^{1}H NMR spectra (400 MHz, D_2O, rt) recorded for: (a) **8**, and mixtures of bis-*ns*-CB[10] and **8** at different relative stoichiometries (b) 1:1, (c) 2:1, and (d) 1:2.

domain is inside the cavity of bis-*ns*-CB[10], we refer to the situation as PXDA$_{in}$. The spectroscopic fingerprint for a PXDA$_{in}$ situation is a shielding of the resonances for the PXDA domain. Figure 9b shows spectroscopic fingerprints for PXDA$_{out}$, Ad$_{in}$, and HDA$_{in}$ binding modes. Accordingly, we formulate the geometry of the bis-*ns*-CB[10]$_2$·**8**$_2$ complex as shown in Scheme 3. We depict the bis-*ns*-CB[10]$_2$·**8**$_2$ assembly, which displays homotropic allostery but we believe the alternate diastereomer where each molecule of bis-*ns*-CB[10] contains one HDA and one Ad binding domain is also formed.

Given the ability of bis-*ns*-CB[10] to display homotropic allosterism we wondered whether changing the relative stoichiometry of bis-*ns*-CB[10] to guest **8** would result in changes in the molecularity of the resulting complex or changes in the location of the host along guest **8** (e.g., PXDA$_{in}$ binding mode). Figure 9c shows the ^{1}H NMR spectrum obtained from a 2:1 mixture of bis-*ns*-CB[10] and **8**. This spectrum is nearly identical to that shown in Figure 9b, which indicates that an excess of host bis-*ns*-CB[10] is not sufficient to change the absolute molecularity of the assembly.[29] In contrast, Figure 9d shows the ^{1}H NMR obtained from a 1:2 mixture of bis-*ns*-CB[10] and **8**. At a 1:2 relative stoichiometry, the ^{1}H NMR spectrum shows a reduction in the intensity of the resonances corresponding to HDA$_{in}$ and Ad$_{in}$ geometries and the appearance of a new set of resonances corresponding to a PXDA$_{in}$ geometry. Scheme 3 depicts three possible diastereomers of the bis-*ns*-CB[10]·**8**$_2$ complex under homotropic allosteric control. The diastereomers with two PXDA$_{in}$, Ad$_{in}$, and HDA$_{in}$ binding modes are referred to as **8a**, **8b**, and **8c**, respectively. Because the cavity of bis-*ns*-CB[10] contains two distinct ureidyl C=O portals (e.g., top and center) there are three possible diastereomers (e.g., top–top, top–center, and center–center) for **8a**, **8b**, and **8c**.[30] The dominant formation of a 1:2 host:guest stoichiometry complex was further supported by the observation of a peak at m/z=794 in the ESI-MS, which corresponds to the [bis-*ns*-CB[10]·**8**$_2$]$^{3+}$ ion. We confirmed a spacing of 0.33 m/z units, which supports our formulation of a 3$^+$ ion. We also observed an ion of substantial intensity for the 4$^+$ state. The driving force for this stoichiometry induced change from bis-*ns*-CB[10]$_2$·**8**$_2$ to bis-*ns*-CB[10]·**8**$_2$ is interesting and informative. Bis-*ns*-CB[10] contains two cavities each of which contribute significant binding free energy upon complexation. In contrast, guest **8** contains three binding sites (Ad, PXDA, and HDA). Because the Ad, PXDA, and HDA binding regions are connected by common NH_2^+ groups, it is not possible for two adjacent binding regions (e.g., Ad and PXDA or PXDA and HDA) to be bound simultaneously. In contrast, the more widely spaced Ad



Scheme 3. Depiction of the equilibrium structures obtained upon treatment of bis-*ns*-CB[10]$_2$·**8**$_2$ with **8** then CB[6] then CB[7].

and HDA binding domains may be complexed simultaneously. Consequently, at a 1:1 bis-*ns*-CB[10]:**8** stoichiometry guest **8** is forced to use both the Ad and the HDA binding domains in order for both cavities of bis-*ns*-CB[10] to be filled. When the bis-*ns*-CB[10]:**8** stoichiometry is raised to 1:2 there is enough guest present so that the Ad, PXDA, and HDA binding domains compete for inclusion inside each cavity of bis-*ns*-CB[10] based on their individual binding affinities.[31]

2.10. Reversibility of host:guest molecularity

Understanding that the molecularity of the bis-*ns*-CB[10]·**8**$_2$ complex is responsive to host:guest stoichiometry, we wanted to demonstrate the reversibility of the switching process shown in Scheme 3 in a stimuli–responsive manner. Figure 10a shows the ^{1}H NMR spectrum of an initial sample containing bis-*ns*-CB[10]·**8**$_2$. Figure 10b shows the ^{1}H NMR spectrum recorded after the sample of Figure 10a was saturated with solid bis-*ns*-CB[10]. The spectrum shown in Figure 10b—which shows only peaks for a PXDA$_{out}$ binding mode—indicates the transformation from bis-*ns*-CB[10]·**8**$_2$ molecularity to bis-*ns*-CB[10]$_2$·**8**$_2$. Figure 10c shows the ^{1}H NMR spectrum recorded after the sample of Figure 10b was treated with 2 equiv of **8**. The ^{1}H NMR spectrum shows return of the equilibrium to favor the bis-*ns*-CB[10]·**8**$_2$ complex in the presence of excess guest. We find this reversible change in molecularity intriguing because it results, in principle, in a change in the overall length of the aggregate, which could be very useful in the construction of molecular muscles.[32]

2.11. Stimuli–responsive switching behavior

In the previous sections, we showed that a change in bis-*ns*-CB[10]:**8** stoichiometry resulted in a reversible change in the molecularity of the host·guest complex. We rationalized this behavior in terms of the binding constants of various binding domains of the guest toward bis-*ns*-CB[10]. Given the very high binding affinity and high selectivity exhibited by various members of the CB[*n*] family toward ammonium ion guests (e.g., K_a (CB[6]·hexanediammonium)=4.5×10^8 M^{-1} and K_a (CB[7]·adam antylammonium)=4.2×10^{12} M^{-1}) we wondered whether CB[6] and CB[7] could be used to selectively complex the HDA and Ad binding domains of **8** and thereby serve as an exogenous chemical stimulus to control the molecularity of the interaction of bis-*ns*-CB[10] with **8** and potentially reduce the number of diastereomers observed.

Figure 11b shows the ^{1}H NMR spectrum measured after the addition of 2 equiv of CB[6] to a solution containing the mixture of diastereomers of bis-*ns*-CB[10]·**8**$_2$, which is shown in Figure 11a. The addition of CB[6] results in the selective complexation of the HDA binding domain by CB[6] because of its high K_a value, which sterically precludes binding at the PXDA binding domain of **8** and leaves only the Ad binding domain open for complexation with bis-*ns*-CB[10]. There are three possible diastereomers of the pentamolecular complex bis-*ns*-CB[10]·**8**$_2$·CB[6]$_2$, which are shown in Figure 12. The ^{1}H NMR spectrum of the major diastereomer of bis-*ns*-CB[10]·**8**$_2$·CB[6]$_2$ shows a pair of doublets for the PXDA binding

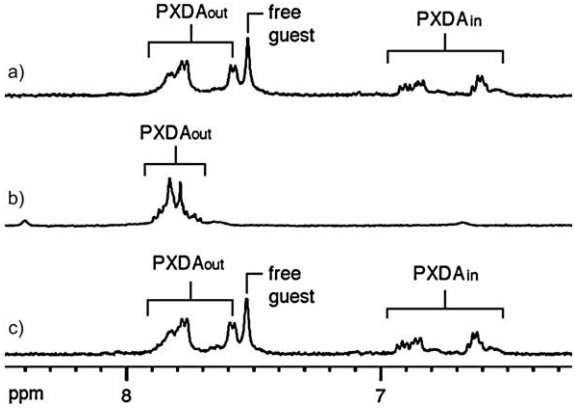


Figure 10. Aromatic region of the ^{1}H NMR spectra (400 MHz, D_2O, rt) of a sample undergoing alternate successive additions of bis-*ns*-CB[10] and **8**: (a) a 1:2 ratio of bis-*ns*-CB[10] to **8**, (b) after addition of excess bis-*ns*-CB[10], and (c) after addition of excess **8**.

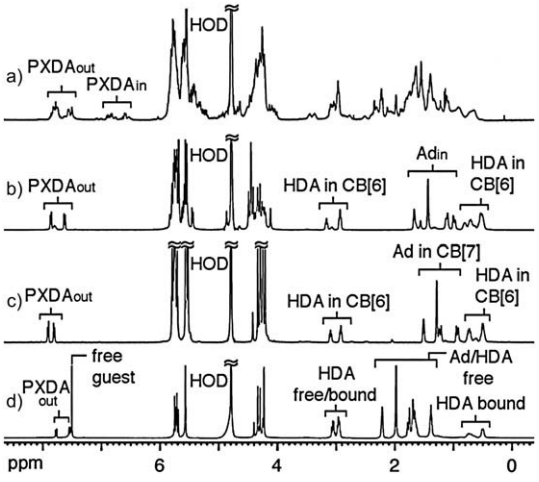


Figure 11. ^{1}H NMR spectra (400 MHz, D_2O, rt) recorded for solutions of: (a) bis-*ns*-CB[10]·**8**$_2$, (b) after addition of 2 equiv CB[6] to obtain CB[6]$_2$·**8**$_2$·bis-*ns*-CB[10], and (c) after addition of 2 equiv CB[7] to obtain CB[7]·**8**·CB[6] and solid bis-*ns*-CB[10]. (d) Control spectrum for a mixture of CB[6]·**8** and excess **8**.

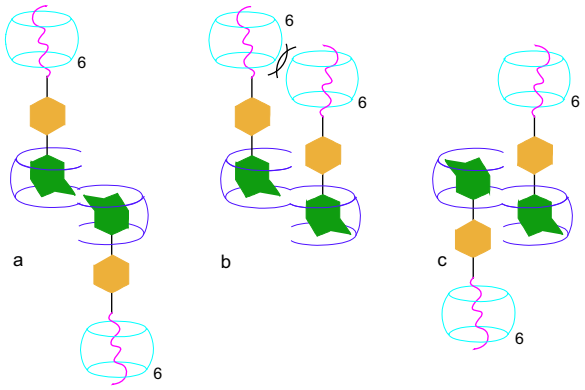


Figure 12. Three different diastereomers of the bis-*ns*-CB[10]·$\mathbf{8}_2$·CB[6]$_2$ complex.

domain in the PXDA$_{out}$ region along with a single set of resonances for the Ad and HDA binding domains in the Ad$_{in}$ and HDA$_{in}$ regions. The observation of a pair of doublets in the PXDA$_{out}$ region is consistent with the top–top and center–center diastereomers, but is inconsistent with the top–center diastereomer based on symmetry considerations.[33] Most interesting to us is the observation that bis-*ns*-CB[10]·$\mathbf{8}_2$·CB[6]$_2$ is on average longer than the precursor mixture of diastereomers of bis-*ns*-CB[10]·$\mathbf{8}_2$. The free energy associated with the complexation of the HDA binding region of **8** by CB[6] performs work and stretches the CB[10]·$\mathbf{8}_2$ complex. The reversible control of the extension and contraction of such supramolecular (polymeric) systems would be very interesting in the creation of molecular machines.

To control the subsequent contraction of the bis-*ns*-CB[10]·$\mathbf{8}_2$·CB[6]$_2$ complex we decided to take advantage of the remarkably high binding affinity of CB[7] toward adamantylammonium ions. Figure 11c shows the ^{1}H NMR spectrum recorded for a solution containing bis-*ns*-CB[10]·$\mathbf{8}_2$·CB[6]$_2$ that was treated with 2 equiv of CB[7]. The resonances for the PXDA and Ad domains exhibit new patterns but remain in the PXDA$_{out}$ and Ad$_{in}$ regions indicative of the formation of CB[7]·**8**·CB[6]. Free bis-*ns*-CB[10] precipitates. In this process, the binding free energy of CB[7] toward the Ad domain of **8** and the precipitation of bis-*ns*-CB[10] provide the driving force for the reduction in the overall dimensions of the supramolecular complex.

3. Conclusions

In summary, we have studied the complexation between double cavity host bis-*ns*-CB[10] and divalent guests **1**–**8** with the goal of forming stimuli–responsive supramolecular polymeric systems of *n*:*n* absolute stoichiometry. In practice, we found that guests **1**, **2**, and **4**–**6**, which contain two adamantylammonium ion binding domains separated by *p*-, *m*-, and *o*-xylylene groups preferentially form 1:1 (bis-*ns*-CB[10]·**1**), 2:2 (bis-*ns*-CB[10]$_2$·$\mathbf{4}_2$), and short potentially cyclic oligomeric complexes (with **2**, **5**, and **6**). We found that a longer spacer between the adamantyl binding groups (e.g., biphenyl spacer in **7**) successfully prevents 1:1 complex formation but promotes 2:2 complex formation (bis-*ns*-CB[10]$_2$·$\mathbf{7}_2$) at the expense of supramolecular polymers. Finally, we investigated the interaction between bis-*ns*-CB[10] and guest **8**, which contains Ad, PXDA, and HDA binding domains with a particular emphasis on bis-*ns*-CB[10]:**8** stoichiometry. At 1:1 bis-*ns*-CB[10]:**8** stoichiometry the Ad and HDA binding domains are complexed to satisfy the ability of bis-*ns*-CB[10] to complex two binding groups simultaneously. At 1:2 stoichiometry all three binding domains become complexed during formation of a mixture of diastereomers of bis-*ns*-CB[10]·$\mathbf{8}_2$. Lastly, we showed that the addition of CB[6] and CB[7] molecular containers substantially simplifies the composition of this mixture by selective complexation of the HDA and Ad binding domains of **8**, respectively.

In conclusion, this work highlights some of the challenges that need to be overcome in the formation of supramolecular polymers from divalent hosts and divalent guests, namely the preferential formation of lower molecularity (cyclic) complexes (e.g., 1:1, 2:2), which are favored from an entropic viewpoint in the absence of enthalpic penalties for formation of 1:1 and 2:2 complex formation. In ongoing work we are targeting the preparation of trivalent guests that contain a central CB[7] binding region and terminal adamantylammonium binding groups that will prevent 1:1 and 2:2 complex formation by steric interaction between CB[7] groups. An aspect of the work with potentially broad impact is the recognition of the special behavior of guests (e.g., **8**) that contain multiple *overlapping binding regions*. In such systems, binding at one domain sterically prevents binding at an adjacent domain. The addition of CB[*n*] molecular containers that selectively complex a given portion of guest **8** (e.g., CB[6] and CB[7]) can control the reversible extension and contraction of this system, which is of potential use in the formation of stimuli–responsive molecular machines (e.g., molecular muscles). Lastly, we would like to highlight the successful formation of the penta-molecular complex bis-*ns*-CB[10]·$\mathbf{8}_2$·CB[6]$_2$, which is enabled by the extremely high affinity of CB[*n*] hosts for their ammonium ion targets (K_a up to 10^{15} M^{-1}) in water.[12] The formation of high molecularity complexes where multiple different components occupy a predetermined location on the basis of simple binding affinities[34] in water suggests methods for the construction of even higher molecularity functional systems.

4. Experimental section

4.1. General

Starting materials were purchased from commercial suppliers and used without further purification. Compound **17** was prepared according to a literature procedure.[26] THF and toluene were distilled from sodium benzophenone ketyl before use. TLC analysis was performed using precoated plates from EMD Chemicals Inc. Column chromatography was performed using silica gel (230–400 mesh, 0.040–0.063 μm) from Sorbent Technologies using eluents in the indicated v/v ratio. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer and are reported in cm^{-1}. NMR spectra were measured on Bruker AM-400, DRX-400, and DRX-500 instruments operating at 400 MHz or 500 MHz for ^{1}H and 100 MHz or 125 MHz for ^{13}C. The chemical shift for 1,4-dioxane in the ^{13}C NMR spectra was referenced at 67.19 ppm. Mass spectrometry was performed using a VG Autospec instrument by fast atom bombardment (FAB) using the indicated matrix or a JEOL AccuTOF instrument by electrospray ionization (ESI) using solutions of the complexes in 50:50 MeOH/H$_2$O (v/v).

4.2. Compound 1

To a solution of **12** (117 mg, 0.442 mmol) in anhyd THF (10 mL) was added Ag_2O (205 mg, 0.884 mmol). After 5 min, **10** (200 mg, 1.32 mmol) was added and the reaction mixture was sonicated for 8 h. The silver salts were removed by filtration and the filtrate was concentrated by rotary evaporation. The residue was chromatographed (SiO_2, $CHCl_3$/MeOH 40:1+2% NH_4OH) giving **1** as a white solid. The free base was dissolved in $CHCl_3$ (25 mL) and HCl gas was bubbled through the solution to deliver **1**·(HCl)$_2$ (162 mg, 0.339 mmol) in 77% yield. Mp>300 °C (dec). TLC ($CHCl_3$/MeOH 20:1+1% NH_4OH) R_f 0.25. IR (cm^{-1}): 3415m, 2913s, 2852m, 1616w, 1454m, 1080m, 836m. ^{1}H NMR (400 MHz, D_2O): 7.52 (s, 4H), 4.25 (s, 4H), 2.24 (br s, 6H), 2.00 (br s, 12H), 1.78 (d, J=12.6, 6H), 1.70 (d, J=12.2, 6H). ^{13}C NMR (100 MHz, D_2O, 1,4-

dioxane as reference): 133.3, 131.0, 59.0, 43.5, 38.6, 35.5, 29.5. MS (FAB, glycerol): *m/z* 405 (100, $[M+H]^+$). HRMS (FAB, glycerol): *m/z* 405.3269 ($[M+H]^+$, $C_{28}H_{41}N_2$, calcd 405.3270).

4.3. Compound 2

To a solution of **13** (175 mg, 0.662 mmol) in anhyd THF (12 mL) was added Ag_2O (307 mg, 1.32 mmol). After 5 min, **10** was added (300 mg, 1.987 mmol) and the reaction mixture was sonicated for 8 h. The silver salts were removed by filtration and the filtrate was concentrated by rotary evaporation. The residue was chromatographed (SiO_2, $CHCl_3$/MeOH 35:1+1% NH_4OH) giving **2** as a white solid. The free base was dissolved in $CHCl_3$ (25 mL) and HCl gas was bubbled through the solution to deliver **2**·$(HCl)_2$ (136 mg, 0.284 mmol) in 43% yield. Mp>300 °C (dec). TLC ($CHCl_3$/MeOH 30:1+1% NH_4OH) R_f 0.20. IR (cm^{-1}): 3419w, 2906s, 2761s, 1571m, 1452m, 1366m, 1078s, 803m, 699s. ^1H NMR (400 MHz, D_2O): 7.67 (s, 1H), 7.60–7.45 (m, 3H), 4.25 (s, 4H), 2.24 (br s, 6H), 2.00 (br s, 12H), 1.78 (d, *J*=12.6, 6H), 1.70 (d, *J*=12.4, 6H). ^{13}C NMR (125 MHz, D_2O, 1,4-dioxane as reference): 132.6, 130.9, 130.7, 130.2, 58.5, 43.1, 38.1, 35.0, 29.0. MS (FAB, glycerol): *m/z* 405 (100, $[M+H]^+$). HRMS (FAB, glycerol): *m/z* 405.3285 ($[M+H]^+$, $C_{28}H_{41}N_2$, calcd 405.3270).

4.4. Compound 4

A solution of **12** (100 mg, 0.379 mmol) and **11** (204 mg, 1.14 mmol) in CH_3CN (5 mL) was heated to reflux for 12 h and then cooled to rt. The resulting precipitate was filtered and washed with CH_3CN (3 mL). The white solid was dried under high vacuum to afford **4** (110 mg, 0.177 mmol) in 96% yield. Mp 273–277 °C. IR (cm^{-1}): 2914s, 2854m, 1475m, 1387m, 1306m, 1034m, 854s, 748m. ^1H NMR (400 MHz, D_2O): 7.55 (s, 4H), 4.37 (s, 4H), 2.68 (s, 12H), 2.26 (br s, 6H), 2.12 (br s, 12H), 1.65 (d, *J*=12.4, 6H), 1.59 (d, *J*=12.4, 6H). ^{13}C NMR (125 MHz, D_2O, 1,4-dioxane as reference): 134.8, 131.1, 76.9, 60.6, 43.7, 35.4, 31.2 (only seven of the eight expected resonances were observed). MS (FAB, glycerol): *m/z* 541 (100, $[M-Br]^+$). HRMS (FAB, glycerol): *m/z* 541.3160 ($[M-Br]^+$ $C_{32}H_{50}N_2Br$, calcd 541.3157).

4.5. Compound 5

A solution of **13** (100 mg, 0.379 mmol) and **11** (204 mg, 1.14 mmol) in CH_3CN (5 mL) was heated to reflux for 12 h and then cooled to rt. The resulting precipitate was filtered and washed with CH_3CN (3 mL). The white solid was dried under high vacuum to afford **5** (83 mg, 0.134 mmol) in 35% yield. Mp 206–210 °C. IR (cm^{-1}): 2907s, 2851m, 1470s, 1378m, 1305m, 1035s, 817s, 756s. ^1H NMR (400 MHz, D_2O): 7.65–7.50 (m, 4H), 4.38 (s, 4H), 2.69 (s, 12H), 2.27 (br s, 6H), 2.13 (br s, 12H), 1.66 (d, *J*=12.6, 6H), 1.60 (d, *J*=12.6, 6H). ^{13}C NMR (125 MHz, D_2O, 1,4-dioxane as reference): 139.0, 136.3, 130.5, 129.8, 76.9, 60.8, 43.6, 35.4, 35.4, 31.3. MS (FAB, glycerol): *m/z* 541 (100, $[M-Br]^+$). HRMS (FAB, glycerol): *m/z* 541.3168 ($[M-Br]^+$, $C_{32}H_{50}N_2Br$, calcd 541.3157).

4.6. Compound 6

A solution of **14** (100 mg, 0.379 mmol) and **11** (204 mg, 1.14 mmol) in CH_3CN (5 mL) was heated to reflux for 12 h and then cooled to rt. The resulting precipitate was filtered and washed with CH_3CN (3 mL). The white solid was dried under high vacuum to afford **6** (110 mg, 0.177 mmol) in 47% yield. Mp 155–158 °C. IR (cm^{-1}): 3477m, 3380, 3044w, 2915s, 2880s, 2853m, 1478s, 1372m, 1303m, 1033s, 827m, 752s. ^1H NMR (400 MHz, D_2O): 7.70–7.60 (m, 4H), 4.44 (s, 4H), 2.63 (s, 12H), 2.30 (br s, 6H), 2.17 (br s, 12H), 1.68 (d, *J*=12.6, 6H), 1.61 (d, *J*=12.6, 6H). ^{13}C NMR (100 MHz, D_2O, 1,4-dioxane as reference): 136.5, 132.0, 130.0, 78.1, 57.0, 43.4, 35.3, 35.1, 31.2. MS (FAB, glycerol): *m/z* 541 (100, $[M-Br]^+$). HRMS (FAB, glycerol): *m/z* 541.3184 ($[M-Br]^+$, $C_{32}H_{50}N_2Br$, calcd 541.3157).

4.7. Compound 7

To a solution of **15** (225 mg, 0.662 mmol) in anhyd THF (12 mL) was added Ag_2O (307 mg, 1.33 mmol). After 5 min, **10** (300 mg, 1.99 mmol) was added and the reaction mixture was sonicated for 8 h. The silver salts were removed by filtration and the filtrate was concentrated by rotary evaporation. The residue was chromatographed (SiO_2, $CHCl_3$/MeOH 35:1+1% NH_4OH) giving **7** as a white solid. The free base was dissolved in $CHCl_3$ (25 mL) and HCl gas was bubbled through the solution to deliver **7**·$(HCl)_2$ (153 mg, 0.318 mmol) in 48% yield. Mp>330 °C (dec). TLC ($CHCl_3$/MeOH 30:1+1% NH_4OH) R_f 0.10. IR (cm^{-1}): 2918s, 2851w, 2757w, 1456m, 1309m, 1099m, 794s. ^1H NMR (400 MHz, D_2O): 7.68 (d, *J*=7.8, 4H), 7.47 (d, *J*=7.8, 4H), 4.17 (s, 4H), 2.14 (br s, 6H), 1.92 (br s, 12H), 1.69 (d, *J*=12.5, 6H), 1.60 (d, *J*=12.5, 6H). ^{13}C NMR (100 MHz, D_2O, 1,4-dioxane as reference): 141.3, 131.8, 131.0, 128.3, 58.9, 43.7, 38.7, 35.5, 29.6. MS (FAB, 3-NBA): *m/z* 481 (100, $[M+H]^+$). HRMS (FAB, 3-NBA): *m/z* 481.3583 ($[M+H]^+$, $C_{34}H_{45}N_2$, calcd 481.3583).

4.8. Compound 8

A 10 mL flask containing a solution of **17** (103 mg, 0.382 mmol) and **19** (99 mg, 0.458 mmol) in anhyd $PhCH_3$ (6 mL) was fitted with a Dean–Stark trap and reflux condenser. The reaction mixture was refluxed for 16 h and then cooled to rt. The solvent was removed by rotary evaporation and the residue dried at high vacuum. The residue was dissolved in MeOH (5 mL) and cooled to 0 °C. A solution of $NaBH_4$ (87 mg, 2.292 mmol) in MeOH (1 mL) was added dropwise and then the mixture was heated at reflux for 30 min before stirring at rt for 15 h. The solvent was concentrated by rotary evaporation and the residue dissolved in EtOAc (25 mL) and washed with brine (2×25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The resulting residue was taken up in a mixture of TFA (3 mL) and CH_2Cl_2 (3 mL) and stirred at rt overnight. Upon removal of the solvent under reduced pressure and high vacuum, **8** (135 mg, 287 mmol) was obtained in 75% yield. Mp 175–178 °C. IR (cm^{-1}): 2921w, 2855w, 1655s, 1459w, 1174s, 1129s, 830m, 798m, 720s. ^1H NMR (400 MHz, D_2O): 7.39 (s, 4H), 4.12 (s, 4H), 2.94 (t, *J*=7.9, 2H), 2.85 (t, *J*=7.4, 2H), 2.10 (br s, 3H), 1.87 (br s, 6H), 1.70–1.50 (m, 10H), 1.27 (br m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 133.7, 132.7, 131.2, 59.2, 51.2, 47.9, 43.7, 40.1, 38.8, 35.7, 29.7, 27.3, 26.0, 25.9. MS (FAB, 3-NBA): *m/z* 370 (100, $[M+H]^+$). HRMS (FAB, 3-NBA): *m/z* 370.3218 ($[M+H]^+$, $C_{24}H_{40}N_3$, calcd 370.3222).

4.9. Compound 18

To a solution of **17** (209 mg, 1.05 mmol) in anhyd THF (10 mL) was added Ag_2O (236 mg, 1.05 mmol). After 5 min, **10** (159 mg, 1.05 mmol) was added and the reaction mixture was sonicated for 8 h. The silver salts were removed by filtration and the filtrate was concentrated by rotary evaporation. The residue was chromatographed (SiO_2, $CHCl_3$/MeOH 20:1+1% NH_4OH) giving pure **18** (103 mg, 0.382 mmol) as a white solid in 47% yield. Mp 75–78 °C. IR (cm^{-1}): 2899m, 2845m, 1686s, 1606m, 1578m, 1141m, 1096m, 820s, 776s. ^1H NMR (400 MHz, $CDCl_3$): 9.95 (s, 1H), 7.79 (d, *J*=8.0, 2H), 7.49 (d, *J*=8.0, 2H), 3.82 (s, 2H), 2.07 (br s, 3H), 1.60–1.20 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 192.1, 149.3, 135.1, 129.9, 128.7, 51.0, 44.9, 42.9, 36.7, 29.6. MS (FAB, 3-NBA): *m/z* 270 (100, $[M+H]^+$).

HRMS (FAB, 3-NBA): m/z 270.1861 ($[M+H]^+$, $C_{18}H_{24}NO$, calcd 270.1858).

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Supplementary data

Supplementary data includes ^{1}H and ^{13}C NMR spectra for new compounds, DOSY results for selected complexes, and electrospray mass spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.055.

References and notes

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29. The NMR samples are prepared from solid host and a solution of guest. The excess unbound host bis-*ns*-CB[10] remains insoluble and is removed before transferring the solution to an NMR tube for analysis.
30. For a more complete description of this top–center isomerism and experimental observation of the diastereomers in simpler systems see Ref. 7. If homotropic allostery is not followed then an additional 12 diastereomers are possible.
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