Self-Assembly

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Supramolecular Ladders from Dimeric Cucurbit[6]uril**

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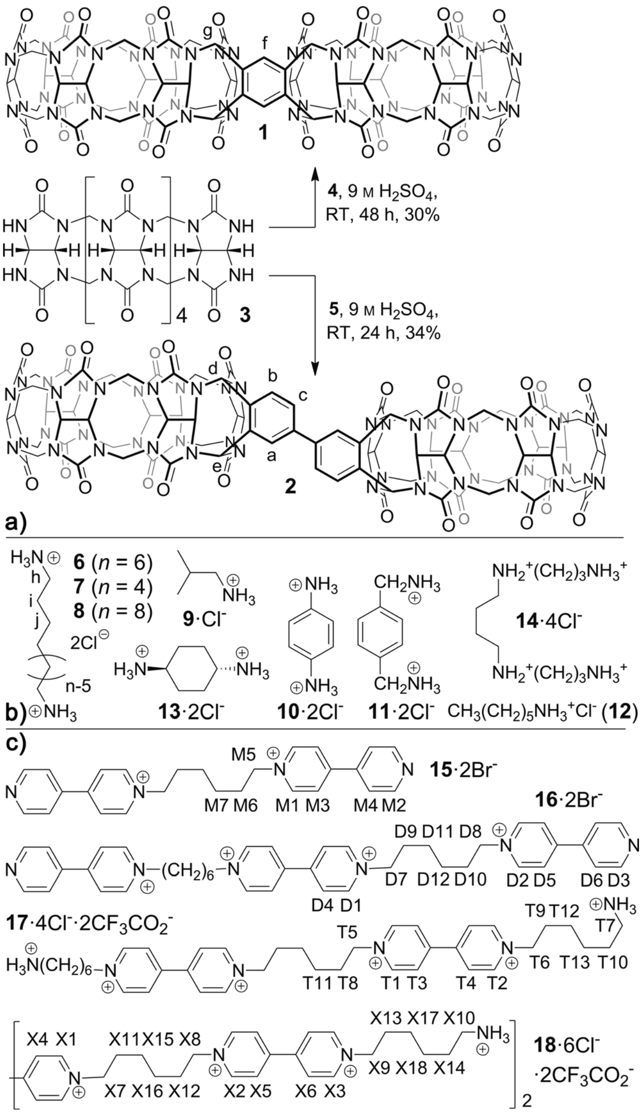
The cucurbit[*n*]uril (CB[*n*]; $n = 5$, 6, 7, 8, 10) family[1] of molecular containers have become the object of intense focus in the field of supramolecular chemistry over the past decade.[2] This surge in interest is due to the ability of CB[*n*] compounds to bind to suitable cationic guests with both high affinity (K_a up to $10^{15}\,\text{M}^{-1}$) and high selectivity in water[3] and the stimuli responsiveness (e.g. pH, chemical, photochemical, electrochemical) of the corresponding CB[*n*]·guest complexes. The remarkable recognition properties of CB[*n*]·guest complexes have been used as the basis for numerous applications of CB[*n*] compounds including chemical-sensing ensembles,[4] membrane-protein fishing,[5] drug solubilization and delivery,[6] and supramolecular catalysis.[7] Of highest utility for the construction of functional CB[*n*] derived systems is the ability of CB[8] to form CB[8]·guest$_2$ ternary complexes—generally with heteropairs of electron-deficient and electron-rich aromatic guests—which has been exploited by the Kim, Urbach, Scherman, and Brunsveld research groups to construct molecular machines, sensing systems, promotors of protein dimerization, and complex macromolecular and nanoparticle architectures.[8] Over the years, our research group has investigated the related ability of CB[10] and bis-ns-CB[10] to form ternary complexes that perform biomimetic functions (e.g. homotropic allostery, metalloporphyrin sensing) or form supramolecular polymers.[1e,9] Recently, we and others have developed routes to prepare monofunctionalized derivatives of CB[6][10] and CB[7].[11] We envisioned that it would be possible to adapt this chemistry toward the construction of CB[*n*] dimers containing two covalently connected, fully formed CB[*n*] groups. Because each CB[*n*] cavity of such CB[*n*] dimers would separately retain the ability to bind to a wide array of guests with high affinity and selectivity, we surmised that dimeric CB[*n*] would extend the range of appropriate (hetero) guest pairs and thereby complement the use of CB[8] in biomolecular derivatization and dimerization events, the formation of supramolecular polymers, and the assembly of nanoscale systems. Herein, we demonstrate the synthesis of dimeric CB[6] compounds **1** and **2** and the ability of **1** to form supramolecular ladders[12] when combined with oligomeric viologen-containing guests.

Our recent reports of the templated synthesis of gram-scale quantities of glycoluril hexamer **3** and its subsequent conversion into CB[6] derivatives by condensation with phthalaldehyde derivatives under acidic conditions[10a,c] provided an entry to the preparation of CB[6] dimers. Accordingly, we prepared benzene-1,2,4,5-tetracarbaldehyde (**4**) and biphenyl-3,3′,4,4′-tetracarbaldehyde (**5**) following reports in the literature (see Supporting Information).[13] When a 1:2 mixture of tetraaldehyde **4** and glycoluril hexamer **3** was stirred in 9 M H_2SO_4 at room temperature for 48 hours, we observed the formation of **1** (Scheme 1) as an insoluble



Scheme 1. a) Synthesis of CB[6] dimers **1** and **2**, and b) structures of guests **6**–**14**, and c) guests **15**–**18**.

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precipitate, which was isolated in pure form in 30% yield after washing with MeOH. Conversely, condensation of a 1:2 mixture of **5** and **3** in 9 M H_2SO_4 at room temperature remained homogenous; pure **2** was isolated in 34% yield after Dowex ion-exchange chromatography and recrystallization from aqueous CF_3CO_2H (Scheme 1). The structures of **1** and **2** were elucidated by the standard spectroscopic methods (^{1}H NMR, ^{13}C NMR, ESI-MS). The ^{1}H NMR spectra of **1** and **2**, recorded as their ternary complexes with hexanediammonium ion **6** (Figure 1), confirmed their D_{2h}- and time-averaged C_s-symmetry, respectively. For example, all four methine (H_g) and both aromatic (H_f) resonances of **1**·**6**$_2$ appear as singlets in a 2:1 ratio (Figure 1 c) whereas the methine (H_d and H_e) and aromatic (H_a–H_c) resonances of **2**·**6**$_2$ appear as distinct resonances in a 1:1:1:1:1 ratio (Figure 1 b). We formed ternary complexes between **1** and **2** and a variety of mono- and diammonium guests (**6**–**14**; Supporting Information), which confirmed that the recognition properties of each cavity of **1** and **2** displays recognition properties similar to those of CB[6].

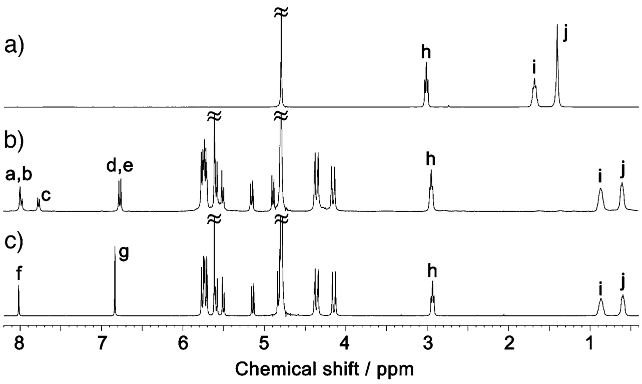

Figure 1. ^{1}H NMR spectra (400 MHz, D_2O, 298 K) recorded for: a) **6**, b) **2**·**6**$_2$, and c) **1**·**6**$_2$. Proton assignments are found in Scheme 1 a.

Crystallization of **2** from aqueous CF_3CO_2H gave crystals of **2** as its CF_3CO_2H solvate, which were suitable for structure determination by single-crystal X-ray diffraction.[14] Figure 2 a shows a stereoscopic representation of **2** from the crystal structure. Compound **2**—with its biphenyl unit—exhibits a torsional angle of 36° in the crystal structure comprising a racemic mixture of both enantiomeric forms. The structure of **2** displays a significant ellipsoidal deformation of the cavity ($a = 10.8$ Å, $b = 9.3$ Å, $c = 9.2$ Å) owing to the attached *o*-xylylene substituent, as expected.[10a] Figure 2 b illustrates the packing of molecules of **2** into tapes along the *z*-axis in the crystal. These tapes are held together by four C–H···O hydrogen bonds[15] (distance = 2.421 Å, angle = 155°; distance = 2.474 Å, angle = 114°) between molecules of **2** of the opposite handedness. C–H···O hydrogen bonds are well known to be important in determining the crystal structure and solubility of CB[*n*] compounds.[16] These H-bonded tapes pack with their long axes parallel into sheets in the *xz* plane; these sheets stack upon one another along the *y*-axis.

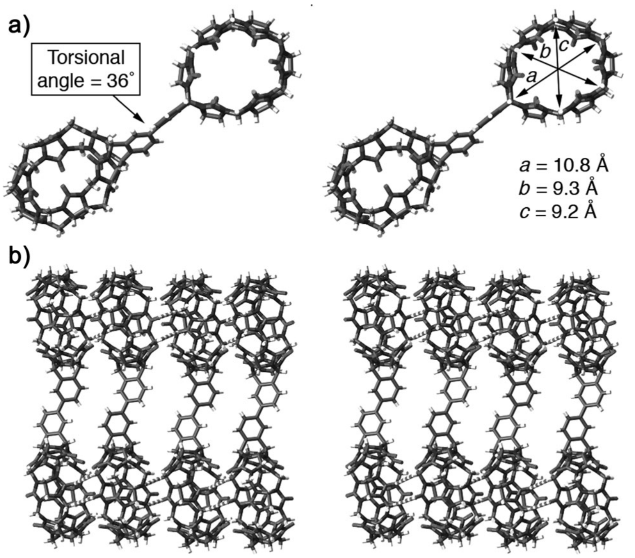

Figure 2. Stereoviews of the crystal structure of **2**: a) an individual molecule of **2**, and b) the observed crystal packing motif. Solvating CF_3CO_2H molecules have been removed for clarity.

After elucidating the structure and basic recognition properties of double-cavity CB[6] dimers **1** and **2**, we decided to investigate the use of **1** in the preparation of supramolecular ladders. For this purpose, we designed and synthesized compounds **15**–**18** (Scheme 1 c, Supporting Information) which contain one, two, three, and four hexanediammonium units connected by viologen units.[17] The hexanediammonium units constitute strong binding sites for each CB[6]-sized cavity of **1**, whereas the larger viologens are weaker binders; the viologens are not so large, however, as to prevent shuttling through each CB[6]-sized cavity. We envisioned that **16**–**18** would undergo self-assembly in the presence of **1** to generate supramolecular ladders **1**$_2$·**16**$_2$, **1**$_3$·**17**$_2$, and **1**$_4$·**18**$_2$ (Figure 3).[18] As an initial control experiment, we prepared a mixture of **1** (1 equiv) and monomeric guest **15** (2 equiv) in D_2O and stirred at 50 °C for one hour which gave the **1**·**15**$_2$ assembly (Figure 3). The ^{1}H NMR spectra recorded for **15** alone and

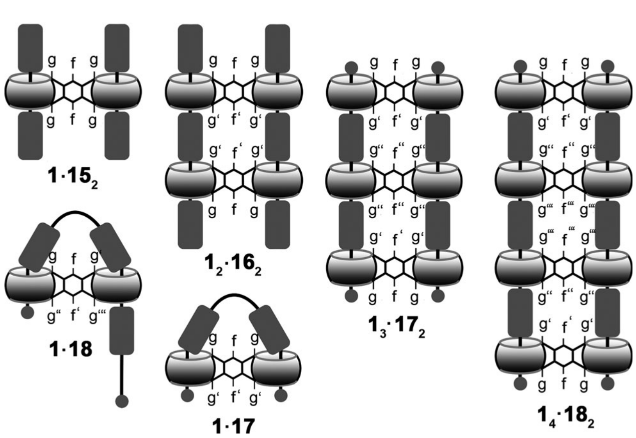

Figure 3. Representation of the geometry of **1**·**15**$_2$, **1**$_2$·**16**$_2$, **1**$_3$·**17**$_2$, **1**$_4$·**18**$_2$, **1**·**17**, and **1**·**18**. Viologens = filled rectangles; NH_3^+ = filled circles.

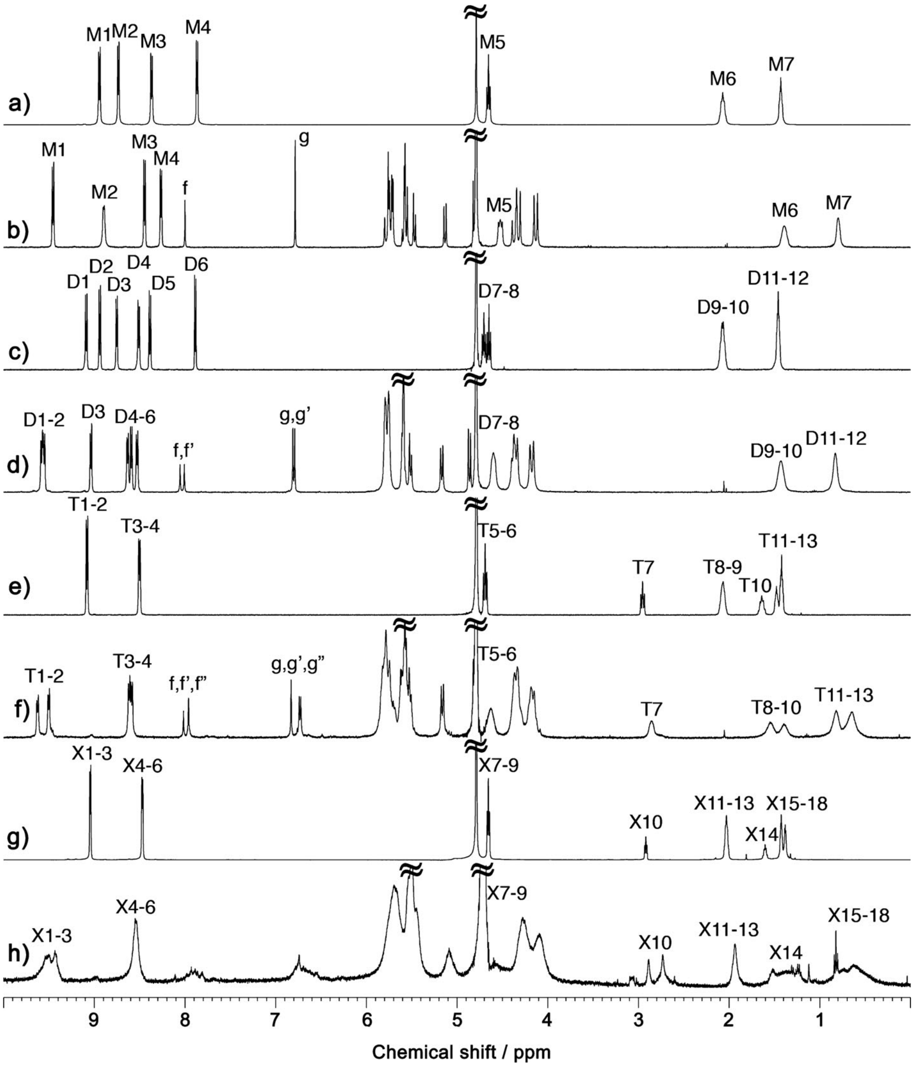

Figure 4. ^{1}H NMR spectra (400 MHz, D_2O, RT) recorded for: a) guest **15**, b) assembly **1**·**15**$_2$, c) guest **16**, d) assembly **1**$_2$·**16**$_2$, e) guest **17**, f) assembly **1**$_3$·**17**$_2$, g) guest **18**, and h) a 4:2 mixture of **1** and **18**. Proton assignments are found in Scheme 1a.

the **1**·**15**$_2$ assembly are shown in Figure 4a,b. As expected based on the geometry depicted in Figure 3, the four symmetically equivalent (H_g) protons resonate as a singlet at 6.78 ppm, which indicates that the **1**·**15**$_2$ complex maintains the D_{2h}-symmetry of the host **1**. The substantial changes in chemical shift observed for guest protons M6 and M7 (upfield) and M1 (downfield) upon formation of **1**·**15**$_2$ establish that the hexylene unit of **15** is bound within the cavity of **1** with the pyridinium N atom at each C=O lined portal. Similarly, heating a mixture of **1** (2 equiv) and **16** (2 equiv) for 24 hours in D_2O at 50 °C results in an assembly that we formulate as the two-rung supramolecular ladder **1**$_2$·**16**$_2$ (Figure 3). Figure 4c,d show the ^{1}H NMR spectra recorded for **16** alone and the **1**$_2$·**16**$_2$ ladder. As expected, the hexylene protons (D9–D12) of dimeric guest **16** undergo substantial upfield shifts, indicative of cavity binding whereas pyridinium protons D1 and D2, which are located just outside the ureidyl C=O portals, shift downfield. Interestingly, protons H_f and H_g, which are symmetrically equivalent and appear as two singlets in the ^{1}H NMR spectrum of host **1**, now appear as four singlets (H_f, $H_{f'}$, H_g, $H_{g'}$) in the **1**$_2$·**16**$_2$ supramolecular ladder. The increased number of resonances is consistent with the top–bottom dissymmetry of host **1** within the **1**$_2$·**16**$_2$ assembly (Figure 3). The absolute stoichiometry (e.g. 2:2) of the **1**$_2$·**16**$_2$ supramolecular ladder was further confirmed by the electrospray mass spectrum, which displayed the expected molecular ion $[\mathbf{1}_2\cdot\mathbf{16}_2+3\,Br]^{5+}$ at $m/z = 1107$, and by diffusion ordered spectroscopy (DOSY),[19] which yielded a diffusion coefficient for **1**$_2$·**16**$_2$ ($D = 147.9\times10^{-12}\,m^2\,s^{-1}$, Table 1) that is 78.7% of the monomeric control assembly **1**·**15**$_2$ ($D = 188.0\times10^{-12}\,m^2\,s^{-1}$, Table 1).[20]

The formation of a three-rung supramolecular ladder **1**$_3$·**17**$_2$ required heating a heterogenous mixture of **1** (3 equiv) with **17** (2 equiv) in D_2O at 60 °C for a period of five days. Figure 4e,f show the ^{1}H NMR spectra recorded for **17** alone and the **1**$_3$·**17**$_2$ ladder. The hexylene protons T8–T13 undergo upfield shifts upon complex formation, whereas pyridinium protons T1 and T2 undergo downfield shifts (Figure 4e,f) consistent with cavity binding of the hexylene units. Three resonances are observed for H_f (H_f, $H_{f'}$, $H_{f''}$) and H_g (H_g, $H_{g'}$, $H_{g''}$) in a 1:1:1 integral ratio, which is in agreement with expectations based on symmetry considerations for the geometry of **1**$_3$·**17**$_2$ shown in Figure 3. Although we were

Table 1: Diffusion coefficients obtained by DOSY NMR spectroscopy.[a]

Species	$D_{complex}$ [10^{-12} $m^2\,s^{-1}$]	$D_{free\,guest}$ [10^{-12} $m^2\,s^{-1}$]
2·**6**	223.6	–
1·**6**	224.8	–
15	–	386.9
1·**15**$_2$	188.0	–
16	–	290.2
1$_2$·**16**$_2$	147.9	–
17	–	269.4
1$_3$·**17**$_2$	137.7	–
1·**17**	190.6	
18	–	206.9
1+**18** (4:2)	98.0	–
1·**18**	168.3	–

[a] 600 MHz, D_2O, 298 K.

unable to obtain ESI-MS data for this dodecacationic complex, the diffusion coefficient obtained from DOSY spectroscopy for $\mathbf{1}_3{\cdot}\mathbf{17}_2$ ($D = 137.7\times10^{-12}\,\mathrm{m^2\,s^{-1}}$, Table 1) is 73.2 % of that for $\mathbf{1}{\cdot}\mathbf{15}_2$, which is in excellent accord with theoretical considerations.[20]

Finally, we mixed **1** (4 equiv) with **18** (2 equiv) and stirred at 80 °C in D_2O for ten days to reach equilibrium. The ^{1}H NMR spectra for **18** alone and for the resultant assembly are shown in Figure 4 g,h. Based on the complexity of the ^{1}H NMR spectrum it is clear that a mixture of assemblies was formed. The upfield shifts observed for the hexylene protons (X11–X18) and the downfield shifts for pyridinium protons X1–X3 suggest that the same basic recognition motif (e.g. hexylene cavity encapsulation) is operative for assemblies based on **1** and **18**. However, the observation of several resonances for X10 in the 3.1–2.6 ppm range suggests that some of the $^+N(CH_2)_6N^+$ units of guest **18** may remain uncomplexed. The DOSY spectrum of the mixture of assemblies formed from **1** + **18** (4:2) yielded $D = 98.0\times10^{-12}\,\mathrm{m^2\,s^{-1}}$, which is significantly smaller than that expected for $\mathbf{1}_4{\cdot}\mathbf{18}_2$ (MW = 9923; $D_{\text{theory}} = 124.1\times10^{-12}\,\mathrm{m^2\,s^{-1}}$).[20] We estimate that, on average, the mixture of self-assembled species formed from a 4:2 mixture of **1** and **18** is composed of eight molecules of **1** and four molecules of **18** with a molecular weight around 20000.

To gain insight into the failure to obtain the four-rung supramolecular ladder $\mathbf{1}_4{\cdot}\mathbf{18}_2$, we decided to study the interaction between host **1** and guest **16**–**18** under conditions of excess guest molecules where uncomplexed hexylene binding sites could be expected. For example, the ^{1}H NMR spectrum of a mixture of **1** (1 equiv) and **17** (2 equiv) results in the formation of the 1:1 complex **1·17** (Supporting Information) that features a back-folded geometry as depicted in Figure 3. The results of electrospray mass spectrometry (observation of $[\mathbf{1}{\cdot}\mathbf{17}\text{-}2H]^{4+}$ at $m/z = 666.7$) and DOSY ($D = 190.6\times10^{-12}\,\mathrm{m^2\,s^{-1}}$) provide strong support of the 1:1 nature of the **1·17** complex. In a similar way, an equimolar mixture of **1** and **18** results in the formation of the 1:1 complex **1·18** in which two hexylene units remain uncomplexed. We suggest that related looped structures—which feature uncomplexed hexylene units—may be competing during the assembly of the hypothetical $\mathbf{1}_4{\cdot}\mathbf{18}_2$ four-rung supramolecular ladder.

In summary, we have shown that the condensation of glycoluril hexamer **3** with tetraaldehydes **4** and **5** leads to dimeric cucurbit[6]uril compounds **1** and **2**. Each cavity of **1** and **2** retains the innate binding ability of CB[6] itself. Host **1** undergoes self-assembly with **16** and **17** to yield two- and three-rung supramolecular ladders $\mathbf{1}_2{\cdot}\mathbf{16}_2$ and $\mathbf{1}_3{\cdot}\mathbf{17}_2$ as established by ^{1}H NMR, DOSY, and electrospray mass spectrometric measurements. The three-rung supramolecular ladder $\mathbf{1}_3{\cdot}\mathbf{17}_2$ has nanoscale dimensions of 2.6 × 4.0 nm and a molecular weight of 7389, which is in the range of small proteins. We believe that the significance of this work goes beyond the system-specific details by further demonstrating that the syntheses of CB[*n*] compounds are sufficiently developed to produce CB[*n*]-based structures of high complexity. Furthermore, the availability of CB[6] dimers (**1** and **2**) and the potential for higher-order multivalent CB[*n*] scaffolds offers promise for expanding the range of binding epitopes that can be used to induce dimerization and higher-order assembly of appropriate nanoscale objects like proteins, polymers, and nanoparticles. We will report on the outcome of these and related studies in due course.

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Keywords: cucurbit[*n*]urils · DOSY NMR · self-assembly · supramolecular chemistry · viologen

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[14] CCDC 918840 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[17] Competitive binding experiments between **1**, **6**, and **15** (Supporting Information) establish that **6** and **15** bind with comparable strength to host **1**. Accordingly, we expect that the terminal pyridinium-$(CH_2)_6NH_3^+$ and internal pyridinium-$(CH_2)_6$-pyridinium binding sites of **17** and **18** will bind with comparable affinity to **1**.

[18] The design of **16**–**18** feature flexible $(CH_2)_6$ spacers connected by rigid viologens; upon complexation with CB[6] dimer **1** we expected that the $(CH_2)_6$ spacers would become rigidified, which would favor the formation of supramolecular ladders relative to supramolecular polymers. The insolubility of **1** and the poor solubility of the supramolecular ladders (approximately 10 mM) prevented an examination of the higher concentration regime where supramolecular polymers might be expected to become increasingly favorable.

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[20] If we use the common assumption that these assemblies can be treated as spheres of uniform density, then it is possible to equate the ratio of diffusion coefficients for two assemblies (D_A/D_B) to the ratio of the cube roots of the molecular weights of the species $(MW_B)^{1/3}/(MW_A)^{1/3}$. The Supporting Information contains a full derivation of this equation. Accordingly, for the case of assemblies $\mathbf{1}\cdot\mathbf{15}_2$ (MW = 2857) and $\mathbf{1}_2\cdot\mathbf{16}_2$ (MW = 5401) we predict $D_{\mathbf{1}_2\cdot\mathbf{16}_2}/D_{\mathbf{1}\cdot\mathbf{15}_2} = 0.809$, which is close to the experimental value of 0.787. Similarly, for the case of assemblies $\mathbf{1}\cdot\mathbf{15}_2$ (MW = 2857) and $\mathbf{1}_3\cdot\mathbf{17}_2$ (MW = 7389) we predict $D_{\mathbf{1}_3\cdot\mathbf{17}_2}/D_{\mathbf{1}\cdot\mathbf{15}_2} = 0.729$, which is very close to the experimental value of 0.732. For hypothetical assembly $\mathbf{1}_4\cdot\mathbf{18}_2$ (MW = 9933), we would predict $D_{\mathbf{1}_4\cdot\mathbf{18}_2}/D_{\mathbf{1}\cdot\mathbf{15}_2} = 0.660$. We can use the experimentally determined diffusion coefficients for $\mathbf{1}\cdot\mathbf{15}_2$ and the **1** + **18** (4:2) assembly along with the molecular weight of $\mathbf{1}\cdot\mathbf{15}_2$ to estimate the average molecular weight of the mixture of assemblies formed from **1** + **18** (4:2; MW ≈ 20169).