Cucurbit[6]uril dimer induces supramolecular polymerisation of a cationic polyethylene glycol derivative

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Recently, we reported the synthesis of two new dimeric cucurbit[6]uril compounds (1 and 2). Herein, we describe the ability of compound 1 to undergo supramolecular polymerisation when combined with polyethylene glycol (PEG) derived divalent guests $3_{300}$ ($MW = 300, 1000, 3350, 10,000$). Interestingly, we find that the shorter PEG-derived guests $3_{300}, 3_{1000}$ and $3_{3350}$ lead to low degrees of oligomerisation based on the diffusion coefficients obtained by diffusion-ordered spectroscopy measurements. In contrast, when 1 was combined with the longest PEG-derived guest $3_{10,000}$, we observed the formation of a supramolecular polymer with a degree of oligomerisation of at least 36. We observe that the supramolecular polymer $L_c(3_{10,000})_n$ undergoes a slow decrease in its degree of oligomerisation to 22 over the course of 14 days controlled by the slow dissociation rate constant of the hexadennium unit of $3_{10,000}$ from the CB[6]-sized cavity of 1.

Keywords: cucurbituril; supramolecular polymer; polyethylene glycol; DOSY

Introduction

The cucurbit[n]uril (CB[n], $n = 5, 6, 7, 8, 10$; Figure 1) (1, 2) family of molecular containers has become the subject of intense investigation (3, 4) over the past decade as a result of the availability of a homologous series of molecular containers in a single step by the acid-catalysed condensation of glycoluril and formaldehyde. The confluence of several features distinguishes CB[n] from other molecular containers (e.g. cyclodextrins, calixarenes and crown ethers) (5). First, CB[n] forms remarkably tight ($K_a$ up to $10^{15}$ M$^{-1}$) host-guest complexes with cationic guests in water and display remarkable levels of selectivity among related guests (6, 7). Second, preference of CB[n] for cationic over neutral guests often results in substantial $pK_a$ shifts of the included guests (4, 8). Third, the CB[n] cavity constitutes a region of low polarisability which influences the photophysical properties of the included guests (9). Accordingly, CB[n] host-guest complexes are highly stimuli (e.g. pH, chemical, photochemical and electrochemical) responsive and have been exploited in the preparation of a number of application areas including chemical sensing systems (10), drug solubilisation and delivery (11–13), as a drug reversal agent (14), molecular machines (15), supramolecular materials (16–18), supramolecular catalysis (19), biomimetic systems (20), membrane protein fishing (21) and even underwater adhesion (22).

Over the years, our group has both developed the uses of these unique recognition properties of CB[n] molecular containers and also investigated the mechanism of CB[n] formation as a route towards the preparation of new CB[n]-type receptors with exciting new properties and applications including inverted CB[n] (23), CB[n] analogues (24), nor-seco-CB[n] (25, 26), glycoluril oligomers (27), acyclic CB[n]-type receptors (28) and CB[n] derivatives (29–32). Previously, we demonstrated that the double cavity host bis-nor-seco-CB[10] (Figure 1) forms ternary host-guest$_2$ complexes with a variety of guests. Even more interesting was the behaviour of bis-ns-CB[10] towards mixtures of small and large diammonium ions which results in the formation of ternary host-guest complexes comprising one bis-ns-CB[10] with two small or with two large guest but not with one small and one large guest; bis-ns-CB[10] displays size-selective homotropic allostery (25). More recently, we showed that bis-ns-CB[10] can be transformed into ethyleneurea-bridged bis-ns-CB[10] by reaction with ethyleneurea and formaldehyde in a precipitation-driven process under acidic conditions (33). The two cavities of ethyleneurea-bridged bis-ns-CB[10] are rigidified and bind preferentially to narrow diammonium guests. Most recently, we reported the synthesis of dimeric cucurbit[6]uril derivatives 1 and 2 (Figure 2) by the condensation of methylene-bridged glycoluril hexamer with aromatic tetraaldehydes (32). We showed that 2 – with its two CB[6] cavities connected by a rigid linker – forms discrete nanoscale supramolecular ladders when combined with oligomeric viologens connected by (CH$_2$)$_6$ linkers.

Many years ago, we recognised that the extremely high binding constants observed for CB[n]-guest complexes

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would promote the formation of supramolecular polymers with high degrees of oligomerisation provided that suitable divalent host–host, guest–guest or host–guest compounds were used. This general line of inquiry has been developed previously with other host systems based on metal–ligand coordination (34), hydrogen-bonding interaction (35, 36), aromatic stacking interaction (37) and host–guest interaction (17, 38, 39). Particularly noteworthy in this regard are the self-complementary A–A type ureidopyrimidinone dimers reported by Meijer, Sijbesma and co-workers that self-assemble by fourfold hydrogen-bonding interactions (36). The high affinity (≈10^4 M^{-1}) of ureidopyrimidinone dimerisation results in a high degree of polymerisation. In the area of host–guest-induced supramolecular chemistry, Harada has incorporated guest-derivatised cyclodextrins as A–B monomeric units to construct polymers of the (···A–B···A–B···)_n type (39). A limitation of these cyclodextrin-guest systems is their low binding constants (K_a ≈ 10^4 M^{-1}) which limit the overall degree of polymerisation. Within the CB[n] area, a number of groups have capitalised on the pioneering work of Kim which established that CB[8] forms ternary homomeric (CB[8]·guest_A·guest_B) or heteromeric (CB[8]·guest_A·guest_B) complexes (2, 40) to create supramolecular macromolecular and polymeric architectures. For example, Kim has combined CB[8] with divergent and trivalent building blocks in the construction of higher-order supramolecular oligomeric and dendritic complexes (41). Kaifer used the CB[8]-mediated dimerisation of viologen-derived dendritic wedges to prepare supramolecular dendrimers. Zhang has used CB[8] in a very elegant way to promote the supramolecular polymerisation of A–B–B–A type monomers (42). It is the Scherman group, however, who has contributed most substantially by using CB[8]-mediated processes to promote block copolymer formation, nanocapsule formation, stimuli-responsive hydrogels, self-folding polymers and CB[8]-containing plasmonic nanoconstructs (13, 17, 18).

Intrigued by the double cavity nature of bis-ns-CB[10] and its ability to bind two guests simultaneously, we have previously investigated its interactions with dumbbell-shaped divalent guests in hopes of forming supramolecular polymers (25, 43). Unfortunately, such systems deliver discrete self-assembled species rather than supramolecular polymers, although combinations of bis-ns-CB[10] with polymeric multivalent guests do result in more complex architectures (44). Our recent preparation of CB[6] dimers 1 and 2 rekindled our interest in supramolecular

Figure 1. Chemical structures of CB[n], bis-ns-CB[10] and ethyleneurea-bridged bis-ns-CB[10].
polymerisation (32). In this paper, we report that interaction between 1 and divalent polyethyleneglycol derivatives $3_{MW}$ result in the formation of supramolecular polymers with degrees of polymerisation of at least 36.

Results and discussion

This results and discussion section initially reviews some of the structural details and recognition behaviour of CB[6] dimer 1 (32). Subsequently, we describe the design, synthesis and characterisation of divalent PEG-derived guests $3_{MW}$. Finally, we describe the supramolecular oligomers and polymers formed by the interaction of 1 with $3_{MW}$ as studied by diffusion-ordered spectroscopy (DOSY).

Synthesis of CB[6] dimer 1

Previously, we synthesised the methylene-bridged glycoluril hexamer by the $p$-xylenediammonium ion-templated oligomerisation of glycoluril and paraformaldehyde on the gram scale in a single step in 10% yield and found that it undergoes macrocyclisation in the presence of substituted phthalaldehydes to give monofunctionalised CB[6] derivatives (29, 30). To prepare compounds containing two covalently connected CB[6] rings, we allowed hexamer to react with benzene-1,2,4,5-tetraaldehyde or biphenyl-3,3'4,4'-tetraaldehyde under acidic conditions (9 M $\text{H}_2\text{SO}_4$, RT, 24 h) to give 1 or 2 in 34% and 30% yield as described in our recent communication on the subject (32). Cucurbit[6]uril dimer 2 is very rigid and has poor solubility in water. The rigidity of 2 resulted in the formation of discrete supramolecular ladders rather than supramolecular polymers when 2 was allowed to interact with oligomeric viologens (32). In contrast, biphenyl linked CB[6] dimer 1 is nicely soluble ($=10$ mM in 0.2 M $\text{Na}_2\text{SO}_4$) in aqueous solution and can rotate around the Ar–Ar single bond which should promote the formation of supramolecular polymers at the expense of discrete self-assembled species.

Basic recognition properties of CB[6] dimer 1

Previously, we have studied the ability of our CB[6] derivatives to bind to guests commonly used with CB[6] itself (29). For example, in our preliminary report, we showed that 1 and 2 bind to alkanediammonium ions 4–6, $p$-xylenediammonium ion 7, trans-1,4-cyclohexanediammonium ion 8 and spermine 9 with slow kinetics of exchange on the $^1$H NMR time scale (Figure 3) (32). Figure 4 shows the $^1$H NMR spectrum recorded for 1 on its own and as the 1·5$_2$ complex. Some features of these spectra are worth noting here because of their relevance to the spectra recorded for the supramolecular polymers described below. First, because 1 does not have a mirror plane running along the equator of each CB[6] subunit, protons $\text{H}_a$ and $\text{H}_b$ are not equivalent and appear as two singlets in the $^1$H NMR recorded for 1·5$_2$ (Figure 4(b)). Similarly, protons $\text{H}_c$, $\text{H}_d$ and $\text{H}_e$ also appear as distinct resonances as expected. Second, protons $\text{H}_f$ and $\text{H}_g$ on guest 5 undergo significant upfield shifts when bound within the cavity of 1, but do not split into two sets of resonances despite the lack of top–bottom symmetry of each subunit. In contrast, $\text{H}_h$ which is located at the ureidyl $\text{C}==\text{O}$ portal remains largely unchanged (7).

Design strategy

Based on our earlier studies, we knew that CB[6] derivatives bearing o-xylylene rings bind hexanediammonium ion tightly in aqueous solution ($K_a = 1.4 \times 10^7$ M$^{-1}$) and does so with slow exchange on the chemical shift time scale (29, 30, 32). Similarly, we knew from our earlier work that poorly soluble and relatively rigid hosts such as bis-ns-CB[10] and 2 promote the formation of discrete self-assembled species when used in combination with small divalent guests. Accordingly, to promote the formation of a supramolecular polymer, we selected to utilise 1 as our A–A divalent host because of its relatively high aqueous solubility (10 mM) and the free rotation around the Ar–Ar bond of 1. As the divalent B–B type guest we elected to prepare $3_{MW}$ (Scheme 1) which features terminal hexanediammonium units which are expected to bind tightly to the cavities of CB[6] dimer 1 and display diagnostic upfield shifts in the $^1$H NMR spectrum that are indicative of cavity inclusion of the hexanediammonium moiety. We selected to connect these

Figure 3. Chemical structures of selected guests for 1 and 2 that exhibit slow exchange on the NMR time scale.
two hexanammonium-binding groups by means of polyethylene glycol (PEG) chains. The PEG chains were selected for the following reasons: (1) to enhance the solubility of the resulting divalent guests, (2) because several molecular weight PEGs are commercially available, (3) PEG functionalisation chemistry is well established and (4) the large number of free rotors along the PEG chain should promote supramolecular polymerisation over discrete complex formation.

**Synthesis of polyethylene glycol-derived guests \(3_{\text{MW}}\)**

As starting material for the preparation of B–B type guests bearing terminal hexanammonium ion-binding sites, we chose PEG which is available in a variety of molecular weights (MW). First, we reacted PEG\(_{3350}\) with excess \(p\)-toluenesulfonyl chloride (TsCl) in the presence of NaOH in THF to form the TsOPEG\(_{3350}\)OTs derivative (Scheme 1) as shown in Scheme 1. Compound TsPEG\(_{3350}\) was then reacted with N-Boc-1,6-hexanedi-amine (10) in the presence of triethylamine in DMF to give the crude Boc-protected (BocNH(CH\(_2\))\(_6\)NH\(_2\))PEG\(_{3350}\) derivative. The crude material was subsequently stirred in a mixture of dichloromethane and trifluoroacetic acid to remove the Boc-protecting group to yield the crude (HO\(_n\) (CH\(_2\))\(_6\)NH\(_2\))PEG\(_{3350}\) derivative (3\(_{3350}\)) as its trifluoroacetate salt (Scheme 1). The crude material was dissolved in a minimal amount of H\(_2\)O and purified by size-exclusion chromatography (SEC, Sephadex G25) to give 3\(_{3350}\) in 30% yield. In an analogous manner, different molecular weight PEGs (PEG\(_{\text{MW}}\), MW = 300, 1000 and 10,000) were used as starting materials to synthesise 3\(_{300}\), 3\(_{1000}\) and 3\(_{10,000}\).

Figure 5(a),(c),(e) and (g) shows the \(^1\)H NMR spectra recorded for 3\(_{300}\), 3\(_{1000}\), 3\(_{3350}\) and 3\(_{10,000}\), respectively. The \(^1\)H NMR spectra for 3\(_{\text{MW}}\) are similar to one another except for the resonance due to the \((\text{OCH}_2\text{CH}_2)_n\) chain which increases in intensity as the chain length grows longer as expected. Of particular diagnostic utility for monitoring the complexation process are the resonances for protons H\(_5\)-H\(_6\) of the hexanammonium moiety. Protons H\(_1\) and H\(_4\) as well as H\(_3\) and H\(_4\) appear as two broadened multiplets in the upfield region of the \(^1\)H NMR spectrum. In contrast, the \(^1\)H NMR resonances for the symmetry non-equivalent protons H\(_n\), H\(_m\) and H\(_n\) on the C-atoms adjacent to N-atoms appear as triplets in the 3.3–2.9 region of the spectrum.

**Formation of supramolecular polymers between 1 and 3\(_{\text{MW}}\)**

To form supramolecular polymers, we separately dissolved host 1 and guest 3\(_{10,000}\) in 0.1 M Na\(_2\)SO\(_4\) solution in D\(_2\)O. Because the degree of polymerisation in A–A + B–B type supramolecular polymerisations is sensitive to the exact concentration of each component, and because CB\(_n\) compounds typically include numerous waters of solvation in their solid forms, we decided to separately measure the concentration of 1 and 3 in our stock solutions by \(^1\)H NMR spectroscopy. For this purpose, we spike an aliquot of each stock solution with a known concentration of 7 and compare the integrals of the peaks of 1 or 3 with the integrals of the peaks of 7. Aliquots of the stock solution of host 1 and guest 3\(_{\text{MW}}\) were then mixed together in a 1:1 molar ratio to obtain a concentration of 2 mM each in solution. Figure 5(b),(d),(f),(h) shows the \(^1\)H NMR spectra recorded for the self-assembled species comprising host 1 and the homologous series of guests 3\(_{\text{MW}}\). For all four complexes, the \(^1\)H NMR resonances for H\(_5\)-H\(_6\) undergo large upfield shifts whereas protons H\(_1\) and H\(_4\) undergo only slight changes in chemical shift, both of which are consistent with the binding of the hexanammonium moieties into the cavity of the two CB\(_6\) rings of 1 upon complexation. Somewhat surprisingly, however, the \(^1\)H NMR resonances of both host 1 and guest 3\(_{\text{MW}}\) remain quite sharp within the self-assembled species which led us to investigate the degree of oligomerisation of these systems by DOSY.

**Diffusion-ordered spectroscopy**

DOSY is an NMR technique that allows one to determine the diffusion coefficient of a species of interest in solution. By comparing the diffusion coefficient of the species of interest to model compounds or assemblies of known size – and making a few assumptions – it is possible to estimate the size of species of interest. Experimentally, a plot of the signal intensity versus the strength of the magnetic gradient can be fitted to Equation (1) to extract the diffusion coefficient (45). In Equation (1), \(I_0\) and \(I\) are...
signal intensities, $D$ is the diffusion coefficient measured in $m^2 s^{-1}$, $\gamma$ is the gyromagnetic ratio measured in $s^{-1} T^{-1}$, $g$ is the gradient strength measured in $G cm^{-1}$, $\delta$ is the length of the gradient measured in milliseconds and $\Delta$ is the diffusion time measured in milliseconds ($45$). Figure 6 shows the data that were collected to determine the diffusion coefficients for guest $3_{10,000}$ and complex $1 \cdot 3_{10,000}$. After fitting the data to Equation (1), we determined the diffusion coefficient ($D$) for free $3_{10,000}$ (Figure 6(a), $30.6 \pm 2.7 \times 10^{-12} m^2 s^{-1}$) and complex $1 \cdot 3_{10,000}$ (Figure 6(b), $6.00 \pm 0.06 \times 10^{-12} m^2 s^{-1}$).

Table 1 gives the diffusion coefficients obtained in an analogous manner for the other PEG derivatives ($3_{MW}$) both as the free guest and as the material obtained from equimolar mixtures (2 mM) of $3_{MW}$ with host $1$.

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

**Determination of the degree of oligomerisation for systems comprising 1 and 3_MW by analysis of the diffusion coefficients**

The Stokes–Einstein equation (2) relates the diffusion coefficient ($D$) to the hydrodynamic radius ($R$) of a spherical molecule, where $k_B$ is the Boltzmann’s constant, $T$ is the temperature and $\eta$ is the viscosity. Equation (3) illustrates the inverse relationship between the diffusion
coefficients of two spherical species and their hydrodynamic radii. Equation (4) relates the volume of a sphere to its radius in the standard way. Accordingly, the ratio of the diffusion coefficients for two spherical species is inversely proportional to the cube root of their volumes \( V \) or their MW if one assumes that both species can be treated as uniform spheres (Equation 5).

\[
D = \frac{k_B T}{6\pi \eta R^2},
\]

\[
\frac{D_1}{D_2} = \frac{R_2}{R_1},
\]

\[
V = \frac{4}{3} \pi R^3,
\]

\[
\frac{D_1}{D_2} = \sqrt[3]{\frac{V_2}{V_1}} \approx \sqrt[3]{\frac{\text{MW}_2}{\text{MW}_1}},
\]

Equation (5) works well for systems that assume spherical shapes in solution. PEGs, however, tend to exist in multiple conformations in aqueous solution depending on the concentration and temperature of the solution (46). Previously, Shimada and co-workers studied the correlation between the diffusion coefficient of PEGs and their molecular weight for uniform PEG oligomers (47). They determined the scaling factor of the diffusion coefficient against the molecular weight for a given PEG molecule to be \(-0.43\) (Equation (6)) which is significantly different from the cube root dependence (e.g. \(-0.333\)) in Equation (5). Using the relationship given in Equation (6), we can then correlate the ratio of the diffusion coefficients of a free guest and a self-assembled species with their molecular weight (Equation (7)). We have used both models to estimate the degree of supramolecular oligomerisation as described below:

\[
D \propto \text{MW}^{-0.43},
\]

\[
\frac{D_1}{D_2} = \left(\frac{\text{MW}_1}{\text{MW}_2}\right)^{0.43}.
\]

We used the spherical model described above (Equation (5)), the known diffusion coefficients and the molecular weight of \( \text{MW} \) to solve for the molecular weight of the self-assembled species.\(^1\) Using the calculated molecular weight of the self-assembled species divided by the sum of the MW of host \(1\) (2138) and guest \( \text{MW} \) allowed us to calculate the number of host-guest units that comprise the self-assembled species. In this manner, we calculated that the assemblies formed by host \(1\) (2 mM) and guest \( \text{MW} \) (2 mM) comprise on average 1.7, 2.3, 4.1 and 110 host-guest units, respectively, for \( \text{MW}_{1000}, \text{MW}_{10000}, \text{MW}_{2138}\) and \( \text{MW}_{100000} \). However, this model is based on the idea that host and guest are of similar structure and volume which is not necessarily true. Therefore, we also determined the ratio of the molecular weight for the self-assembled species to the molecular weight of guest (\( \text{MW}_{\text{MW}} \)) using the PEG model.
For the self-assembled species formed from host 1 and guest $3_{300}$, we determined that the self-assembled species comprises on average 1.03 host-guest units. Similarly, we determined that the self-assembled species formed from host 1 and guests $3_{1000}$, $3_{3350}$ or $3_{10,000}$ comprise 1.5, 2.7 and 36.5 host-guest units, respectively. Although the precise degree of oligomerisation values obtained from the spherical and the PEG models are not in close agreement, they do exhibit common trends. For example, the degree of oligomerisation of the system increases as the molecular weight of PEG guest $3_{nMW}$ increases. Scheme 2 presents cartoon representations of some of the classes of species that might be formed by the self-assembly of 1 with $3_{nMW}$. For example, interaction of one molecule of host 1 with one molecule of guest $3_{nMW}$ can yield the cyclic monomer, although three diastereomers are possible because the ureidyl $\text{C}==\text{O}$ portals of each CB[6] unit of 1 are not equivalent. When two ($n$) molecules of host 1 interact with two ($n$) molecules of guest $3_{nMW}$, the formation of cyclic dimer (cyclic $n$-mers) is possible. Finally, the combination of $n$-molecules of host 1 with $n$-molecules of guest $3_{nMW}$ can also yield the linear supramolecular polymers (Scheme 2). For such supramolecular polymeric systems, it is known that increasing the overall concentration tends to favour the linear supramolecular polymer whereas, at low concentrations, the effective molarity of the intra-aggregate cyclisation process tends to favour the formation of cyclic oligomers (36, 48). Based on the DOSY data, we believe that the self-assembled species based on $3_{500}$ forms cyclic monomer probably in mixture with cyclic dimer. For the longer guests $3_{1000}$ and $3_{3,350}$, the DOSY data suggest the formation of mixtures of short cyclic oligomers (e.g. up to tetramer). In contrast, it is clear that the self-assembled species formed from 1 and $3_{10,000}$ is polymeric in nature with a degree of polymerisation of at least 36. As would be expected, the short and flexible PEG chains used in $3_{300}$ or $3_{1000}$ are able to adjust their conformation to allow for small (cyclic) oligomers. In contrast, for $3_{10,000}$ which features a long PEG chain, supramolecular polymers are formed presumably because of the entropic costs associated with conformational restriction of $3_{10,000}$ within smaller (cyclic) oligomers.

**Scheme 2.** (Colour online) Possible self-assembled species formed when the CB[6] dimer (1) is mixed with the polyethyleneglycol divalent guest ($3_{nMW}$).

**Time dependence of supramolecular polymerisation of 1 and $3_{10,000}$**

Given the known slow dissociation kinetics exhibited by many CB[6] guest complexes (7, 49), we wondered whether the degree of polymerisation observed for mixtures of 1 and $3_{10,000}$ would be time dependent. For example, higher degrees of polymerisation might be observed at short times in kinetically controlled processes whereas shorter supramolecular polymers might be observed as the system rearranges towards equilibrium. To determine the time dependence, the host and guest were first mixed in an equimolar ratio with a concentration of 2 mM for both host and guest. After 30 min, the diffusion coefficient was determined by DOSY NMR to be $(6.6 \pm 0.3) \times 10^{-12}$ m$^2$ s$^{-1}$. A minimum diffusion coefficient of $(6.0 \pm 0.2) \times 10^{-12}$ m$^2$ s$^{-1}$ was obtained after 4 h. After 5 days, the diffusion coefficient had increased to $(6.8 \pm 0.2) \times 10^{-12}$ m$^2$ s$^{-1}$ and, after 14 days, to $(8.1 \pm 0.3) \times 10^{-12}$ m$^2$ s$^{-1}$. After 14 days, the degree of polymerisation was calculated to have decreased from a 36-mer to a 22-mer based on the PEG model. These small but meaningful changes in diffusion coefficient indicate that an interplay between kinetics and thermodynamics is operating in this polymerisation process; we attribute this slow decrease in oligomerisation to slow dissociation kinetics for the 1-guest complex.

**Conclusion**

In conclusion, we have shown that the water-soluble CB[6] dimer 1 undergoes self-assembly with low molecular weight hexanediamine-derivatised PEG guests ($3_{300}$, $3_{1000}$ and $3_{3,350}$) to form (cyclic) oligomers with low degrees of polymerisation. Conversely, host 1 self-assembles with high molecular weight guest $3_{10,000}$ to form a polymer with a degree of polymerisation of at least 36 as revealed by analysis of the data from DOSY.
measurements. An investigation of the degree of polymerisation of the supramolecular polymer formed from 1 and 300000 shows a maximum degree of polymerisation of 36 after 4 h which decrease to 22 after 14 days. This observation highlights the potential for dynamic changes in CB[n] -derived supramolecular systems because of the inherently slow kinetics of association and dissociation commonly observed for CB[n] -guest complexes. A significant limitation of the current system is the relatively low solubility of 1 which prevents us from further promoting linear supramolecular polymerisation over cyclisation by using higher concentrations. Another limitation of the present system is that it is composed of A–A and B–B type monomers which can lead to lower degrees of polymerisation if perfect 1:1 stoichiometry is not achieved. With recent advances in the synthesis of monofunctionalised CB[7] derivatives (22, 31), we expect that both of these issues can be addressed in future work on this subject.

**Experimental details**

Starting materials were purchased from commercial suppliers and were used without further purification. Host 1 was synthesised following a known procedure in the literature (32). Compound 10 was synthesised following a literature procedure (50). Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. Thin layer chromatography was measured on a Meltemp apparatus in open capillary tubes and are uncorrected. Thin layer chromatography (Sephadex G25, H2O mobile phase, 3 x 30 cm column, spotted on glass plate) to yield 300004 TFA as a nearly colourless oil (0.126 g, 16%). 1H NMR (400 MHz, D2O, RT): 3.77 (t, J = 5.1, 4H), 3.70–3.65 (m, 20H), 3.24 (t, J = 5.1, 4H), 3.05 (t, J = 8.0, 4H), 2.97 (t, J = 8.0, 4H), 1.75–1.60 (m, 8H), 1.45–1.30 (m, 8H). 13C NMR (125 MHz, D2O, RT, 1,4-dioxane as external standard): δ 162.4, 162.2, 117.1, 114.8, 69.2, 69.1, 69.0, 64.9, 63.6, 53.4, 52.3, 46.9, 46.3, 38.9, 26.0, 26.0, 24.8, 24.7, 24.7, 24.6, 22.2. MS (ESI): m/z 479.40 (M+)..

Compound TsPEG1000: To a stirring solution of PEG(1000) (Sigma-Aldrich, St Louis, MO, USA, Part # P3515, 1.00 g, 1.0 mmol) in THF (5.0 ml) at RT was added NaOH (0.16 g, 4.0 mmol) in H2O (1.0 ml) and stirred for 20 h. The reaction mixture was slowly poured into stirring H2O (30 ml) and stirred for 30 min. The product was then extracted from the solution with CH2Cl2 (3 x 20 ml). The organics were collected and concentrated by rotary evaporation and dried under high vacuum to yield TsPEG1000 as a white solid (1.22 g, 93%). M.p. 260–265°C.

Compound TsPEG1000·4 TFA: A solution of 10 (0.248 g, 1.145 mmol, 0.26 ml) and triethylamine (0.232 g, 2.29 mmol, 0.32 ml) in DMF (2.0 ml) was heated and stirred at 70°C. A solution of compound TsPEG1000 (0.500 g, 0.822 mmol) in DMF (2.0 ml) was then added to the reaction mixture dropwise and stirred at 70°C for 20 h. The reaction mixture was cooled, diluted with CH2Cl2 (15 ml) and then washed with NaHCO3 solution (15 ml) and H2O (15 ml). The organics were isolated and concentrated by rotary evaporation, then dried under high vacuum. The crude mixture was then dissolved in CH2Cl2 (5.0 ml) and TFA (5.0 ml) was added to the solution and stirred at RT for 1 h. The solution was then concentrated by rotary evaporation and dried under high vacuum. The crude product was purified by gel permeation chromatography (Sephadex G25, H2O mobile phase, 3 x 25 cm column, spotted on glass plate) to yield 3100004 TFA as an off-white solid (0.147 g, 23%). M.p. 260–265°C (dec.). IR (cm⁻¹): 3448br, 2913s, 2870s, 1696s, 1643m, 1470m, 1348m, 1234m, 1080m, 835m, 726m, 652s, 622s. 1H NMR (400 MHz, D2O, RT): 3.78 (t, J = 5.0, 4H), 3.75–3.60 (m, 136H), 3.26 (t, J = 5.0,
Compound TsPEG3350: To a stirring solution of PEG3350 (Sigma-Aldrich, Part # 202444, 5.00 g, 1.49 mmol) in THF (15.0 ml) at RT was added NaOH (0.239 g, 5.97 mmol) in H2O (1.50 ml) and then washed with NaHCO3 solution (1.0 g, 0.097 mmol) in DMF (1.50 ml) was then added to the reaction mixture which was then stirred at RT for 18 h. The reaction mixture was slowly poured into stirring H2O (100 ml) and stirred for 30 min. The crude mixture was then dissolved in CH2Cl2 (3 × 50 ml) and then washed with NaHCO3 solution (1.0 g, 0.097 mmol) in DMF (1.50 ml) was then added to the reaction mixture dropwise and stirred at 70ºC. The reaction mixture was cooled, diluted with CH2Cl2 (15.0 ml) and then washed with NaHCO3 solution (1.0 g, 0.097 mmol) in DMF (1.50 ml) was then added to the reaction mixture dropwise and stirred at 70ºC for 18 h. The reaction mixture was then added to the reaction mixture which was then stirred at RT for 18 h. The reaction mixture was slowly poured into stirring H2O (100 ml) and stirred for 30 min. The crude mixture was then dissolved in CH2Cl2 (3 × 50 ml). The organics were collected and concentrated by rotary evaporation and dried under high vacuum to yield TsPEG10,000 as a white solid (4.5 g, 87%). M.p. 41–44ºC. IR (cm⁻¹): 2944s, 2889s, 2742m, 1470s, 1344s, 1331s, 1299s, 1277s, 1268s, 1246s, 1113s, 959s, 847s. ¹H NMR (400 MHz, D2O, RT, 1,4-dioxane as external standard): δ 7.86 (d, J = 8.2, 4H), 7.52 (d, J = 8.2, 4H), 4.28 (t, J = 4.2, 4H), 3.75–3.50 (m, 3H, 3H), 2.46 (s, 6H). ¹³C NMR (125 MHz, CDCl3, RT): δ 144.8, 133.13, 129.9, 128.1, 127.8, 126.4, 126.3, 70.6, 69.3, 68.8, 21.7.

Compound 3₅₀₀₀₀: A solution of 10 (0.063 g, 0.291 mmol, 0.07 ml) and triethylamine (0.059 g, 0.582 mmol, 0.08 ml) in DMF (1.0 ml) was heated and stirred at 70ºC. A solution of compound TsPEG10,000 (1.0 g, 0.097 mmol) in DMF (1.50 ml) was then added to the reaction mixture dropwise and stirred at 70ºC for 18 h. The reaction mixture was cooled, diluted with CH2Cl2 (15.0 ml) and then washed with NaHCO3 solution (15.0 ml) and H2O (15.0 ml). The organics were isolated and concentrated by rotary evaporation, then dried under high vacuum. The crude mixture was then dissolved in CH2Cl2 (5.0 ml) and TFA (5.0 ml) was added to the solution and stirred at RT for 1 h. The solution was then concentrated by rotary evaporation and dried under high vacuum. The crude product was purified by gel permeation chromatography (Sephadex G50, H2O mobile phase, 3 × 25 cm column, spotted on glass plate) to yield 3₅₀₀₀₀ as an off-white solid (0.228 g, 22%). M.p. 42–44ºC. ¹H NMR (400 MHz, D2O, RT): 3.76 (t, J = 5.0, 4H), 3.80–3.60 (m, 478H), 3.24 (t, J = 5.0, 4H), 3.05 (t, J = 7.8, 4H), 2.98 (t, J = 7.8, 4H), 1.75–1.60 (m, 8H), 1.45–1.35 (m, 8H). ¹³C NMR (125 MHz, D2O, RT, 1,4-dioxane as external standard): δ 7.14, 69.3, 65.0, 60.1, 46.5, 24.8, 24.8.

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Note

1. For the molecular weights of PEG oligomer minus two OH groups, we used the average molecular weight of the PEG oligomer minus two OH groups (3000) as an off-white solid (0.228 g, 22%). M.p. 42–44ºC. ¹H NMR (400 MHz, D2O, RT): 3.76 (t, J = 5.0, 4H), 3.80–3.60 (m, 478H), 3.24 (t, J = 5.0, 4H), 3.05 (t, J = 7.8, 4H), 2.98 (t, J = 7.8, 4H), 1.75–1.60 (m, 8H), 1.45–1.35 (m, 8H). ¹³C NMR (125 MHz, D2O, RT, 1,4-dioxane as external standard): δ 7.14, 69.3, 65.0, 60.1, 46.5, 24.8, 24.8.

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