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ARTICLE TYPE

Cucurbit[6]uril–Cucurbit[7]uril Heterodimer Promotes Controlled Self-assembly of Supramolecular Networks and Supramolecular Micelles by Self-sorting of Amphiphilic Guests

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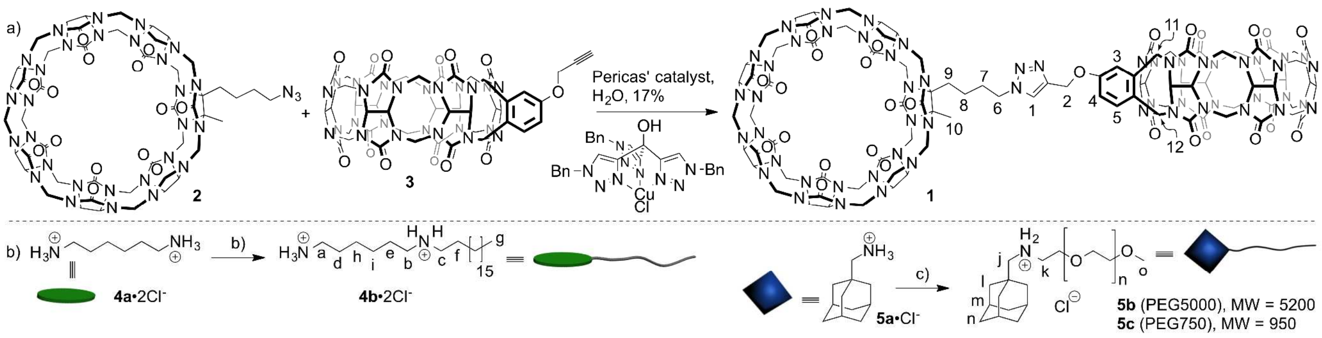
We report the synthesis of cucurbit[6]uril–cucurbit[7]uril heterodimer (1) by click chemistry of monofunctionalized CB[6] and CB[7] derivatives. Combinations of 1 with hydrophobic guest 4b or hydrophilic polymeric guests 5b and 5c deliver hydrophobic or amphiphilic supramolecular block copolymers which form supramolecular networks (6) and supramolecular micelles (7), respectively, in the solid state.

The cucurbit[n]uril (CB[n]) family of molecular containers has been the subject of numerous investigations over the past decade following the discovery of CB[n] homologues (n = 5, 6, 7, 8, 10, 14).[1,2] The high level of interest in the synthesis and supramolecular chemistry of CB[n]-type receptors can be traced to their ability to bind a wide array of cationic and even neutral guests with both high affinity and selectivity in water and the inherent stimuli responsiveness (e.g. chemical, photochemical, pH) of the resultant CB[n]•guest complexes.[3,4,5] Accordingly, CB[n]-type containers have been used to construct affinity separation phases, chemical sensing ensembles, drug solubilisation, delivery, and reversal agents, and as a porous material for gas uptake and purification.[6] Most relevant to the work described herein is the work of Kim, Urbach, Scherman, and Brunsveld who have exploited the ability of CB[8] to promote formation of hetero ternary complexes to construct stimuli responsive molecular machines, to trigger peptide and protein (hetero)dimerization, and to construct complex macromolecular systems.[5,7] Previously, our group has explored the related use of CB[10], bis-*ns*-CB[10], and most recently CB[6] homodimers to promote homo- and hetero-ternary complex formation and exploited these abilities for biomimetic (homotropic allostery, metalloporphyrin sensing)[2,8] and materials (supramolecular ladders and supramolecular polymers) applications.[9,10]

Block copolymers are a class of polymers in which two or more homopolymer units are linked together by chemical bonds.[11] The integration of different kinds of polymer segments endows them with tunable phase separation behavior that results in ordered self-assembled structures with various morphologies (e.g. spheres, lamellae, vesicles, micelles).[12] Accordingly, block copolymers can be used as templates for lithography, carriers for drug delivery, agents for diagnostic imaging, and nanoreactors.[13] Supramolecular block copolymers[14] are joined together by reversible non-covalent interactions. To date, H-bonding and metal coordination interactions are the most commonly used in the construction of supramolecular block copolymers.[15] Despite the range of methodologies to prepare supramolecular block copolymers, studies of their stimuli induced control over their morphologies are uncommon.[16] In this paper, we report the preparation of CB[6]–CB[7] heterodimer **1** and report the self-assembly behaviour of amphiphilic block co-polymers derived therefrom.

Previously, we have reported the preparation of monofunctionalized derivatives of CB[6] and CB[7].[17] For the synthesis of a CB[6]–CB[7] heterodimer we selected propargyloxy-CB[6] **2** and CB[7]-azide **3** as starting material and performed the 3+2 click reaction catalysed by Pericas' catalyst[18] in water at 80 °C (Scheme 1). The crude reaction mixture could be purified by Dowex ion exchange chromatography to deliver **1** in 17% yield. Compound **1** is poorly soluble (< 1 mM) in D_2O and is insoluble in common organic solvents, but its host-guest complexes are nicely soluble in D_2O. The spectroscopic data recorded for **1** as its **1**•(*p*-xylylenediammonium)$_2$ complex is in accord with the depicted structure including the observation of a 3^+ molecular ion peak at *m/z* 891.3233 (calc. 891.3204) and diagnostic ^{1}H NMR resonances for H1-H12 of host **1** and the two *p*-xylylenediammonium ion guests. We used hexanediamine **4a** as the starting material to prepare guest **4b** by alkylation with 1-bromooctadecane in CH_3CN in 95% yield. Guest **4b** with its hexanediammonium ion binding epitope was expected to be a good guest for both the CB[6] and CB[7] cavities of heterodimer **1**.[3] Conversely, we used adamantane derivative **5a** as the starting material to prepare guests **5b** and **5c** which contain hydrophilic poly(ethylene glycol) tails. Compounds **5b** and **5c** with their $AdCH_2NH_2$ binding sites were expected to function as potent guests for CB[7] cavities but not to undergo cavity binding with the CB[6] unit of **1**.[3]

Before proceeding to study the self-assembly behaviour of CB[6]–CB[7] heterodimer **1** with guests **4** and **5** we decided to simplify the system and study the binding processes of **4b** and **5b** toward CB[6] and CB[7] individually and collectively. First, we measured the ^{1}H NMR spectra for **4b**, CB[6]•**4b**, and CB[7]•**4b** (Figure 1a-c). Although both CB[6] and CB[7] bind



Scheme 1. Synthesis of: a) CB[6]–CB[7] heterodimer **1** and b) guests **4** – **5**. Conditions: a) Pericas' catalyst, H_2O, diethylimidazolium bromide, 80 ˚C, 5 days; 17%; b) $CH_3(CH_2)_{17}Br$, CH3CN, 35 ˚C, 95%; c) MeO-PEG-OTs, DMF, 70 ˚C, 46-58%.

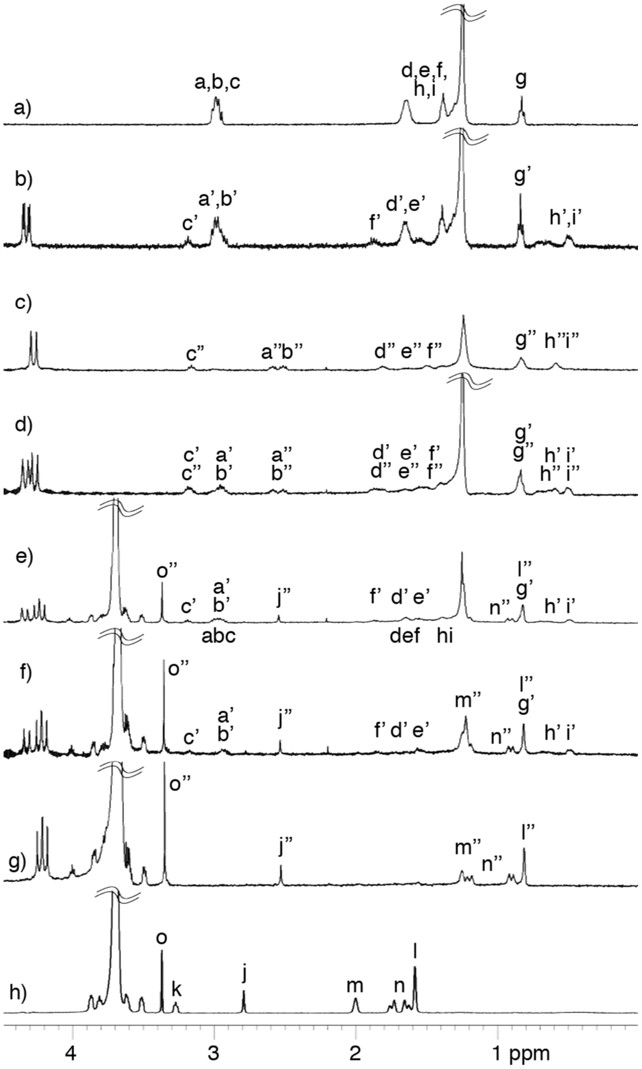
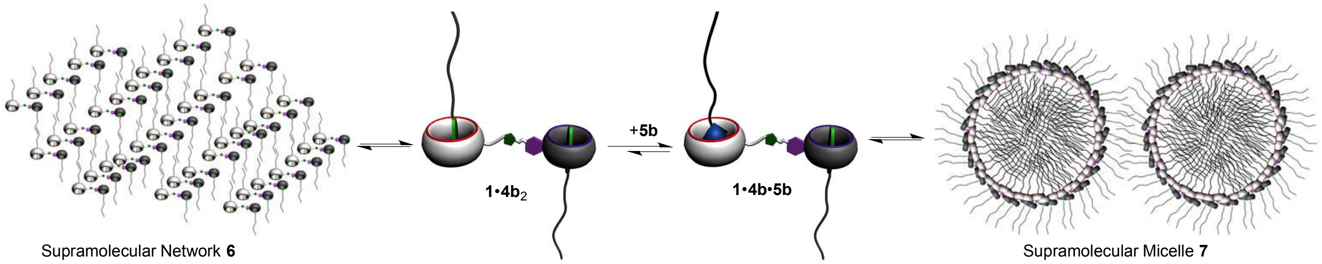


Figure 1. Partial ^1H NMR spectra (400 MHz, D_2O, 22 °C): a) hexanediamine derivative **4b**; b) 0.5 mM CB[6] and **4b**; c) 0.5 mM CB[7] and **4b**; d) 0.5 mM CB[6], CB[7] and 1.0 mM **4b**; e) 0.5 mM CB[6], CB[7], 1.0 mM **4b** and 0.5 mM **5b**; f) 0.5 mM CB[6], CB[7], **4b** and **5b**; g) 0.5 mM CB[7] and **5b**; h) adamatanemethylamine derivative **5b**. Here ' and " denote protons binding with CB[6] and CB[7], respectively.

hexanediamine derivative **4b** as expected, the chemical shifts of certain protons within the CB[6]•**4b** and CB[7]•**4b** are distinct and serve as diagnostic signals to analyze the composition of the mixture. For example, for CB[6]•**4b** (Figure 1b) the methylene protons H_a and H_b do not undergo significant changes in chemical shift relative to **4b** whereas for CB[7]•**4b** they are observed to shift significantly upfield because of their inclusion in the larger CB[7] cavity. Similarly, H_h and H_i shift upfield within the CB[6]•**4b** and CB[7]•**4b** complex due to cavity inclusion but display slightly different chemical shifts in the ≈ 0.5 ppm region of the spectrum. Figure 1d shows the ^1H NMR spectrum of a 1:1:2 mixture of CB[6], CB[7], and **4b** which is essentially the superposition of the spectra in Figures 1b and 1c indicating the formation of CB[6]•**4b** and CB[7]•**4b** in the more complex mixture. The ^1H NMR spectra of hydrophilic guest **5b** and CB[7]•**5b** are shown in Figure 1h and 1g, respectively. As expected, upfield shifts are observed for protons H_j, H_l, H_m, and H_n of the adamantane ring system upon complex formation. The singlet for H_j at 2.52 ppm is particularly diagnostic for the formation of CB[7]•**5b**. Figure 1f shows the ^1H NMR spectrum recorded for an equimolar mixture of CB[6], CB[7], **4b**, and **5b** which establishes the formation of the self-sorting mixture comprising CB[6]•**4b** and CB[7]•**5b**. Finally, addition of one equivalent of **5** to the mixture comprising CB[6]•**4b** and CB[7]•**4b** (Figure 1d) triggers the transformation of the mixture into a new self-sorting state comprising CB[6]•**4b**, CB[7]•**5b**, and free **4b** (Figure 1e).

Next, we sought to prepare supramolecular block copolymers by combining CB[6]–CB[7] heterodimer **1** with guests **4b** and **5b** or **5c**. First, we combined **1** with two equivalents of **4b** which yields the hydrophobic homo-assembly **4b**•**1**•**4b**. The ^1H NMR spectrum of **4b**•**1**•**4b** (Figure 2b) shows diagnostic resonances for H_a, H_b, H_h, and H_i of the hexanediammonium ion unit of **4b** complexed within the CB[6] and CB[7] cavities of heterodimer **1**; similar chemical shifts were observed in the control experiments using CB[6], CB[7], and **4b** shown in Figures 1a-d. Separately, we found that an equimolar mixture of **1**, **4b**, and **5b** self-assembles to give amphiphilic block copolymer **4b**•**1**•**5b**. Figure 2d shows the ^1H NMR spectrum recorded for **4b**•**1**•**5b** which shows the diagnostic resonances for H_a, H_b, H_i, and H_j of the hexanediammonium ion unit of **4b** bound inside the CB[6] unit of **1** and also the diagnostic resonance for H_j of the adamantaneammonium ion unit of **5b** bound within the CB[7] unit of CB[6]–CB[7] heterodimer **1**. We also performed



Scheme 2. Depiction of the supramolecular network **6** and supramolecular micelles **7** formed by self-assembly of **1•4b**$_2$ and **1•4b•5b**.

diffusion ordered spectroscopy (DOSY)[19] to assess whether the assemblies **1•4b**$_2$ and **4b•1•5b** undergo further aggregation in aqueous solution (Table 1). By comparing the diffusion coefficient measured for **1•4b**$_2$ with that of a related CB[6]–CB[6] dimer complex (2.24×10^{-10} m^2 s^{-1})[9] suggests that **1•4b**$_2$ does not undergo further extensive aggregation in solution. Similar measurements for **5b** and **4b•1•5b** (Table 1) show that assembly **4b•1•5b** also remains largely monomeric. The diffusion coefficients measured for the complexes are dominated by the behavior of the PEG derivative **5b**.[19] Also conducted dynamic light scattering (DLS) measurements (Supporting Information) for **1•4b**$_2$ and **4b•1•5b** which suggest that larger assemblies coexist with their monomeric forms in solution.

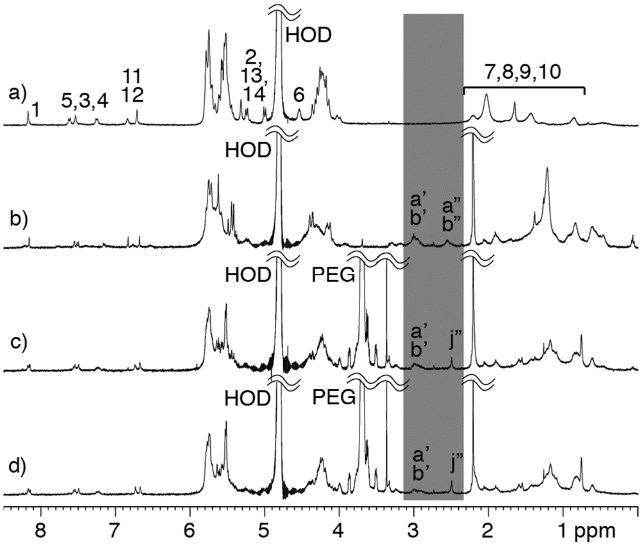


Figure 2. Partial ^{1}H NMR spectra (400 MHz, D$_2$O, RT): a) CB[6]/CB[7] heterodimer **1**; b) 0.5 mM **1** and 1.0 mM **4b**; c) 0.5 mM **1**, 1.0 mM **4b** and 0.5 mM **5b**; d) 0.5 mM **1**, **4b** and **5b**. Here primed (') and double primed (") denote protons binding with CB[6] and CB[7] moieties of **1**, respectively.

Table 1. Values of diffusion coefficients (m^2 s^{-1}) for different species.

4b	**1•4b**$_2$	**5b**	**1•4b•5b**	**1•4b•5b + 4b**
$2.93 \pm 0.06 \times 10^{-10}$	$1.84 \pm 0.11 \times 10^{-10}$	$1.13 \pm 0.06 \times 10^{-10}$	$1.22 \pm 0.20 \times 10^{-10}$	$1.18 \pm 0.18 \times 10^{-10}$

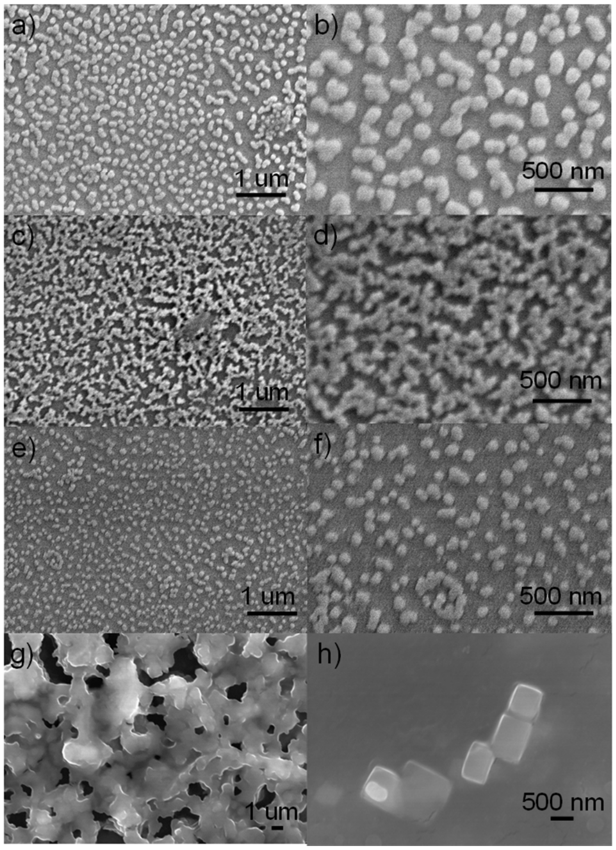


Figure 3. SEM images of a&b) 0.01 mM heterodimer **1**, **4b** and **5b**; c&d) 0.01 mM **1** and 0.02 mM **4b**; e&f) 0.01 mM **1**, 0.02 mM **4b** and 0.01 mM **5b**; g) 0.01 mM **1** and **5b**; h) 0.01 mM **1** and 0.02 mM **4a**.

Given the observation of larger assemblies by DLS we decided to examine the self-assembled structures formed from supramolecular block copolymers **1•4b**$_2$ and **1•4b•5b** in the solid state by scanning electron microscopy (SEM). The samples were prepared by dropping their aqueous solution onto a silica wafer followed by freeze drying. We find that amphiphilic supramolecular block copolymer **1•4b•5b** self-assembles into nearly uniform supramolecular micelles (**7**) with diameter of 125 (±7.6 nm) (Scheme 2, Figs. 3a, 3b, S12 and S19). We believe that the micelles were formed with hydrophobic octadecyl chains of **4b** as core and hydrophilic PEG chains of **5b** or **5c** as corona (Scheme 2), which has precedent in the behavior of conventional amphiphilic block copolymers.[12] In contrast, the homomeric assembly **1•4b**$_2$ self-assembled into supramolecular networks (Figs. 3c, 3d and S13) likely because of the physical entanglements of octadecyl tails and the linking of hexanediamine heads by heterodimer **1** (Scheme 2). Interestingly, addition of 1 equivalent of **5b** to **1•4b**$_2$ resulted in self-sorting transformation to **1•4b•5b** and free **4b** which results in the formation of supramolecular micelles with diameter of 108 (± 8.9 nM) (Figs. 3e, 3f and S14). The smaller diameter of the micelles formed from this self-sorting transformation is probably due to the incorporation of excess **4** into the core structure of micelles, leading to more compact arrangement of the polymers on their surface. As control experiments, we investigated the self-assembled structures formed from **1•5b** (Figs. 3g and S17) and **1•4a**$_2$ (Figs. 3h and S18). Complex **1•5b** forms smooth networks with large pores was due to the coil of PEG chains whereas **1•4a**$_2$ forms crystallites that display cube-like structures. Overall, these results indicate that the hydrophobic octadecyl chains play a significant role in the formation of supramolecular micelles.

In summary, we have synthesized the first CB[n]-type receptor containing two different covalently linked cavities, namely CB[6]–CB[7] heterodimer **1**. By virtue of the high affinity and selectivity displayed by the CB[6] and CB[7] cavities of **1**, it is able to undergo self-sorting assembly of hydrophobic hexanediammonium ion guest **4b** and hydrophilic poly(ethylene glycol) derived guests **5b** and **5c**. The resulting complexes undergo further self-assembly (Scheme 2) to yield supramolecular networks (**6**) and supramolecular micelles (**7**). Transformation between networks and micelles is possible by the addition of guest **5b**. The amphiphilic nature of the **1•4b•5b** complex and the packing of the hydrophobic octadecyl chains into the core of supramolecular micelle **7** were crucial for the self-assembly process. Given their high stimuli responsiveness, we believe that the ability to control the morphology of supramolecular block copolymers assembled using double cavity CB[n]-type receptors holds significant promise for future biological and technological application.

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Notes and references

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