Polymer Architectures

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Supramolecular Block Copolymers with Cucurbit[8]uril in Water**

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Supramolecular polymers have expanded the scope of polymer science, allowing for the design and development of stimuli-responsive and dynamic materials.[1–3] Most prominently, hydrogen-bonding arrays[1,4] and metal–ligand interactions[5–9] have been used for the creation of supramolecular polymers. Utilizing metal coordinate bonds, block copolymers can be formed that are stable even in aqueous media.[10–13] In these instances, however, the metal–ligand interactions employed forfeit much of the dynamic nature of reversible binding, and their incorporation may curtail certain biological applications. Multiple hydrogen-bonding motifs in linear arrays have been utilized to achieve high association constants in common organic solvents;[4,14–18] however, they have not been replicated in aqueous environments, as the water molecules compete for the hydrogen-bonding sites.[19,20]

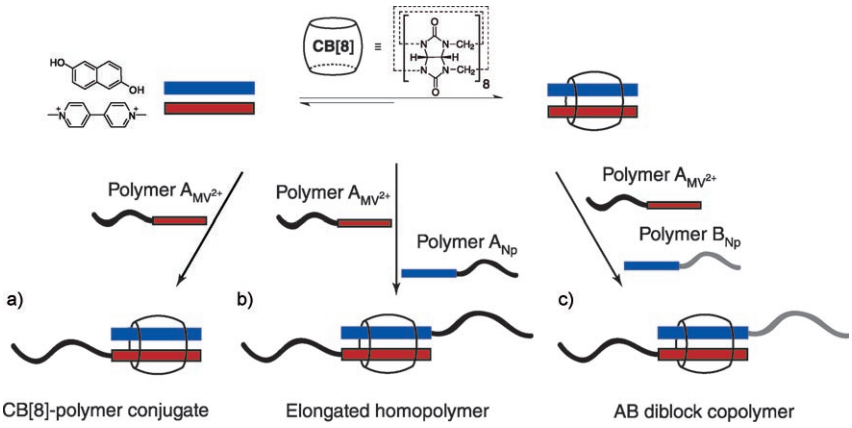
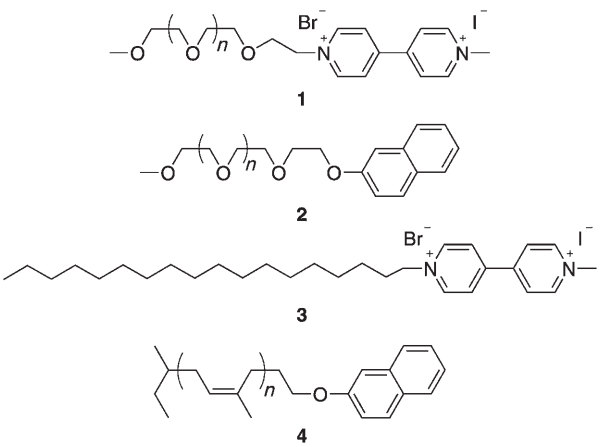


Figure 1. Formation of dynamic, noncovalent macromolecular architectures based on CB[8] CT complexes.

Herein we report a methodology for developing dynamic materials in aqueous media by interconnecting polymer chains through a ternary host–guest complex which can be controlled reversibly by an external stimulus. The host we have chosen to employ is the barrel-shaped container molecule cucurbit[8]uril (CB[8]),[21–24] which acts as a "supramolecular handcuff" for the polymer chains (Figure 1). Cucurbit[8]uril is a remarkable host molecule; it is able to bind two organic guest molecules simultaneously with high association constants ($K_a \geq 10^{11}\,\text{M}^{-2}$) in an aqueous environment.[25–27] Kim et al. have demonstrated that a stable charge-transfer (CT) complex is formed inside the cavity of CB[8] between viologen derivatives and hydroxynaphthalenes,[25] leading to the self-assembly of small molecular systems and architectures.[28–33] Kaifer et al. subsequently employed this principle to connect asymmetric dendritic units.[34,35]

Our initial results of utilizing CB[8] as a linking unit for polymeric systems are described. In a first step, linear polymers were prepared that contained terminal groups, such as 2-naphthol and methylviologen derivatives, for selective encapsulation by CB[8]. Poly(ethylene glycol) (PEG) and *cis*-1,4-poly(isoprene) (PI) were chosen as the polymers (Scheme 1). Their combination allows for the formation of an amphiphilic block copolymer that is expected to exhibit higher order nanostructures in solution.[36]

Treatment of a 5000 g mol^{-1} methylviologen-terminated poly(ethylene glycol) monomethyl ether (**1**) with one equivalent of CB[8] in D_2O resulted in an upfield shift and broadening of the signals in the ^{1}H NMR spectrum arising from the aromatic protons on the viologen moiety. This result



Scheme 1. End-group functional polymers prepared based on monofunctional poly(ethylene glycol) monomethyl ethers (**1**, **2**) and *cis*-1,4-poly(isoprene) (**4**). Octadecyl methyl viologen (**3**) was prepared as a small-molecule hydrophobic guest.

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indicates the complexation of a methylviologen guest inside the cavity of the CB[8] host.[25] The steric bulk of **1** was therefore not prohibitive in host–guest molecular recognition. As CB[8] is able to simultaneously bind two guests forming a 1:1:1 ternary complex, the **1**⊂CB[8] complex was exposed to an aqueous solution of 2-naphthol. Formation of the ternary complex was confirmed by both ^{1}H NMR spectroscopy, exhibiting a further upfield shift and broadening, and UV/Vis spectroscopy, in which a strong charge-transfer (CT) band ($\lambda_{max} = 395$ nm, with a shoulder at 503 nm) was observed. Similar results were also obtained for several other polymer–small-molecule conjugates, such as a 5000 g mol^{-1} 2-naphthoxy-terminated poly(ethylene glycol) monomethyl ether (**2**), a methyl heptyl viologen (**8**), and CB[8] (see Figure S1 in the Supporting Information). In addition, complex formation was confirmed by ESI-mass spectrometry, by which the doubly charged **2** + **8**⊂CB[8] could be observed directly (see Figure S2 in the Supporting Information). All of these observations are in keeping with their small molecular analogues.[29]

To investigate CB[8] binding of two polymeric guests, **2** was added to a solution of **1**⊂CB[8] in D_2O. ^{1}H NMR spectroscopy again indicated complex formation. UV/Vis spectra of **1**, **2**, and CB[8] (Figure 2) show that solutions of both **1** and **2** alone have no appreciable absorption beyond

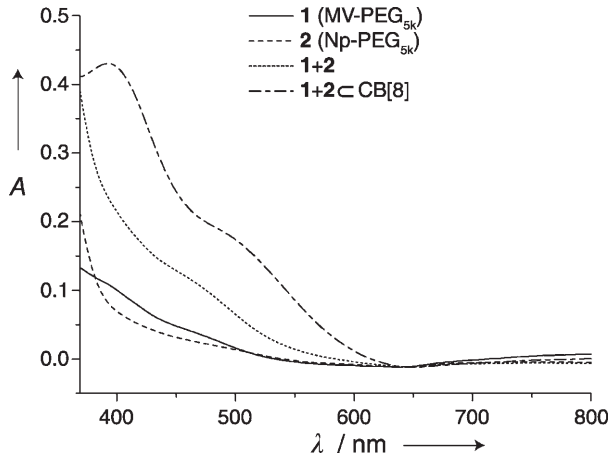

Figure 2. UV/Vis spectra in water (1.75 mM) of **1**, **2**, a 1:1 mixture of **1** and **2**, and the **1** + **2**⊂CB[8] complex mixture, illustrating the formation of a CT complex in the presence of CB[8] by the appearance of new charge-transfer bands.

400 nm. After both solutions were mixed together, a slight increase in UV/Vis absorption resulted, signifying a weak CT interaction of the respective polymer end groups. In the presence of CB[8], this CT interaction is enhanced and the emergence of a charge-transfer band beyond 500 nm provides evidence for complexation. This result demonstrates that polymer chains can be extended using CB[8] as a linking unit as depicted in Figure 1b.

Viologen **3** was synthesized with an octadecyl chain. This only sparingly water-soluble guest can be drawn into water by **2** in the presence of CB[8], as observed by ^{1}H NMR spectrscopy. As Figure 3 illustrates, addition of CB[8] to a

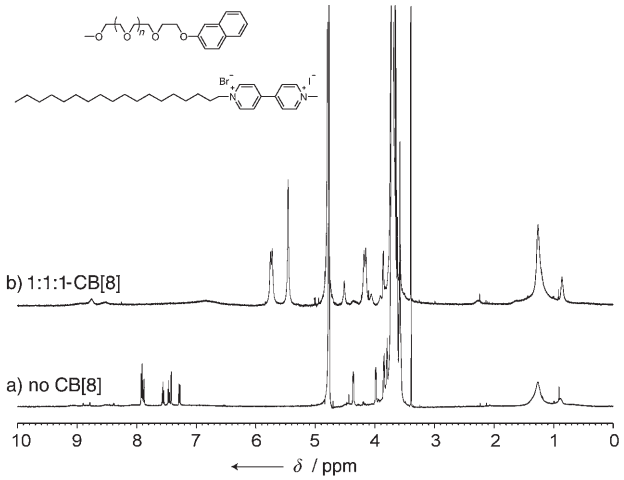

Figure 3. ^{1}H NMR spectra (500 MHz, D_2O) of **3** and polymer **2** a) before and b) after addition of CB[8], demonstrating that the solubility of a hydrophobic guest can be increased upon binding to the polymer.

solution of **2** and **3** led to complex formation, as seen by the upfield shift of aromatic proton signals. More impressively, the solubility of **3** increases notably, as the hydrophobic viologen is now noncovalently linked to **2** by CB[8].

Following the observation that the solubility of hydrophobic compounds in water can be enhanced by CB[8] complexation with PEG guests, it was envisioned that an amphiphilic diblock copolymer based on CB[8] could be created. Thus, 10500 g mol^{-1} 2-naphthoxy-terminated *cis*-1,4-poly(isoprene) (**4**) was prepared and added to a solution of **1**⊂CB[8] in D_2O followed by sonication and rigorous shaking for several hours. ^{1}H NMR spectra obtained from the filtered D_2O solutions indicated that a CT complex was indeed formed (Figure 4). Although no proton signals for the poly(isoprene) backbone were observed in the ^{1}H NMR spectrum, signals corresponding to the 2-naphthoxy end-group were visible, and are shifted considerably upfield, which is indicative of the 1:1:1 ternary CT complex with **1** and CB[8]. Upon successful complexation of the **1**⊂CB[8], an amphiphilic diblock copolymer with the hydrophobic PI should be formed. Subsequent self-assembly into a compartmentalized solution architecture, such as a micelle or vesicle, with **4**

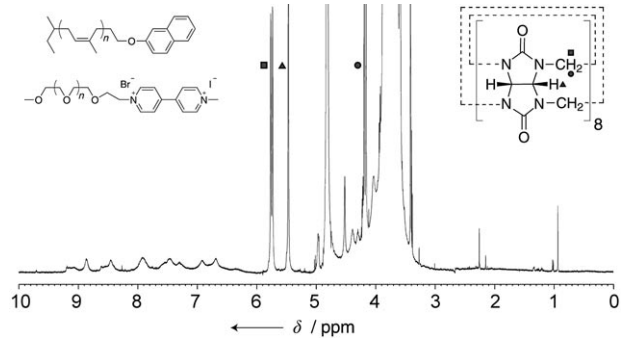

Figure 4. ^{1}H NMR analysis (500 MHz, D_2O) of the **1** + **4**⊂CB[8] system, indicating the existence of a CT complex, as viologen and naphthol end-group protons are shifted upfield.

existing as a non-solvated core domain, would then explain why the PI signals were absent in the NMR spectrum.[37]

Further evidence for the formation of a tertiary solution structure was provided by dynamic light scattering (DLS) measurements (Figure 5). In both volume and number distributions, the solution of **1**+**4**⊂CB[8] showed a peak centered around 244 nm. Control experiments using a commercial 5000 g mol^{-1} PEG monomethyl ether sample (**5**) and **1** alone, and using **1**⊂CB[8], appeared at much smaller size, namely, less than 5 nm. As can be seen in Figure 5, the trace for **1**⊂CB[8] is slightly shifted to a larger size than both **1** and **5**; this is expected, as the CB[8] container molecule is complexed with the polymer chain end. However, the dramatic shift of the size distribution in the presence of **4** supports the existence of a tertiary, compartmentalized solution structure. Studies to control the solution architecture by varying the hydrophilic versus hydrophobic domain size and to visualize them using microscopic techniques are currently underway.

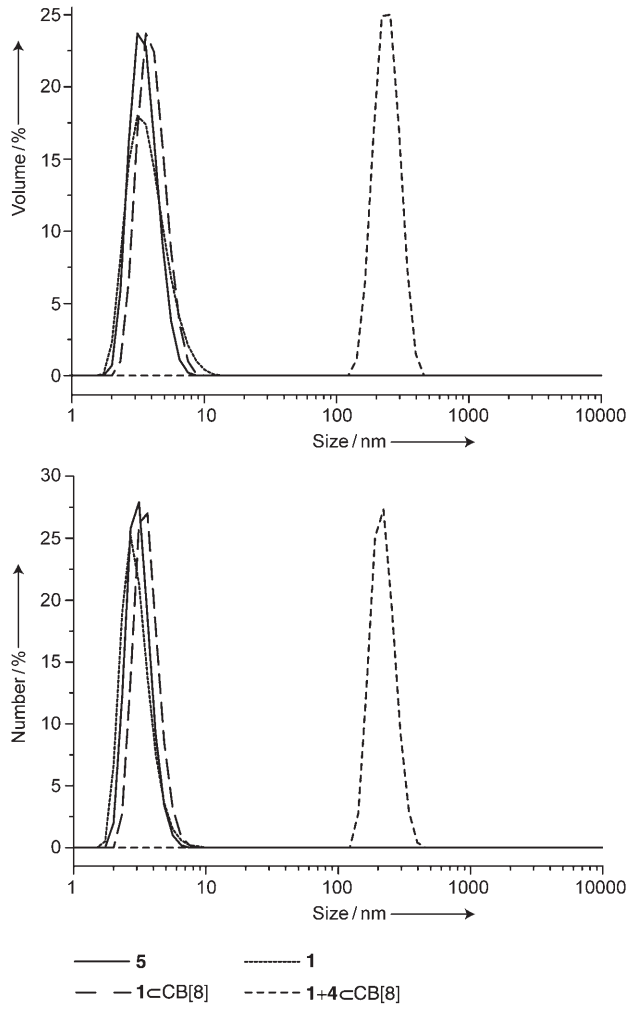

Figure 5. Dynamic light scattering results for the **1**+**4**⊂CB[8] system, indicating the formation of a tertiary structure in aqueous solution.

Cucurbit[8]uril is capable of recognizing specific polymer chain ends in aqueous media. Its capability to selectively bind two guest molecules by a dynamic interlink has been exploited in the design of new polymeric block copolymers. Polymer–small-molecule conjugates, elongated polymer chains, and amphiphilic diblock copolymers were all synthesized, showing the versatility of this approach. In comparison to existing strategies for noncovalent polymer preparation, CB[8] offers a strong yet dynamic binding profile in aqueous environments which is controllable by external stimuli. This approach will lead to potential applications in both the materials as well as the biomedical realm. In particular, it would allow for supramolecular polymers to interact with biomolecules, biomaterials, or drug molecules, giving rise to a potentially new class of stimuli-responsive drug-delivery systems. It is therefore believed that utilization of CB[8] as a supramolecular handcuff for interconnecting polymeric systems will allow for the building up of dynamic functional materials by a designed hierarchical self-assembly approach.

Experimental Section

Synthesis and characterization of compounds **1**–**4** and **6**–**9**, ^{1}H NMR spectra of **2** and **8** with and without CB[8], and the ESI mass spectrum of **2**+**8**⊂CB[8] complex can be found in the Supporting Information.

Supramolecular CB[8]-containing complexes were typically prepared by dissolving cucurbit[8]uril in aqueous solutions (millipore water, 18.2 MΩ cm, or deuterium oxide for NMR experiments) of the guest molecule(s) by sonication and with mild heating overnight, followed by filtration through 0.45 μm PVDF filters.

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