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Supramolecular Hydrogel

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A Thermoresponsive Hydrogel Formed from a Star–Star Supramolecular Architecture**

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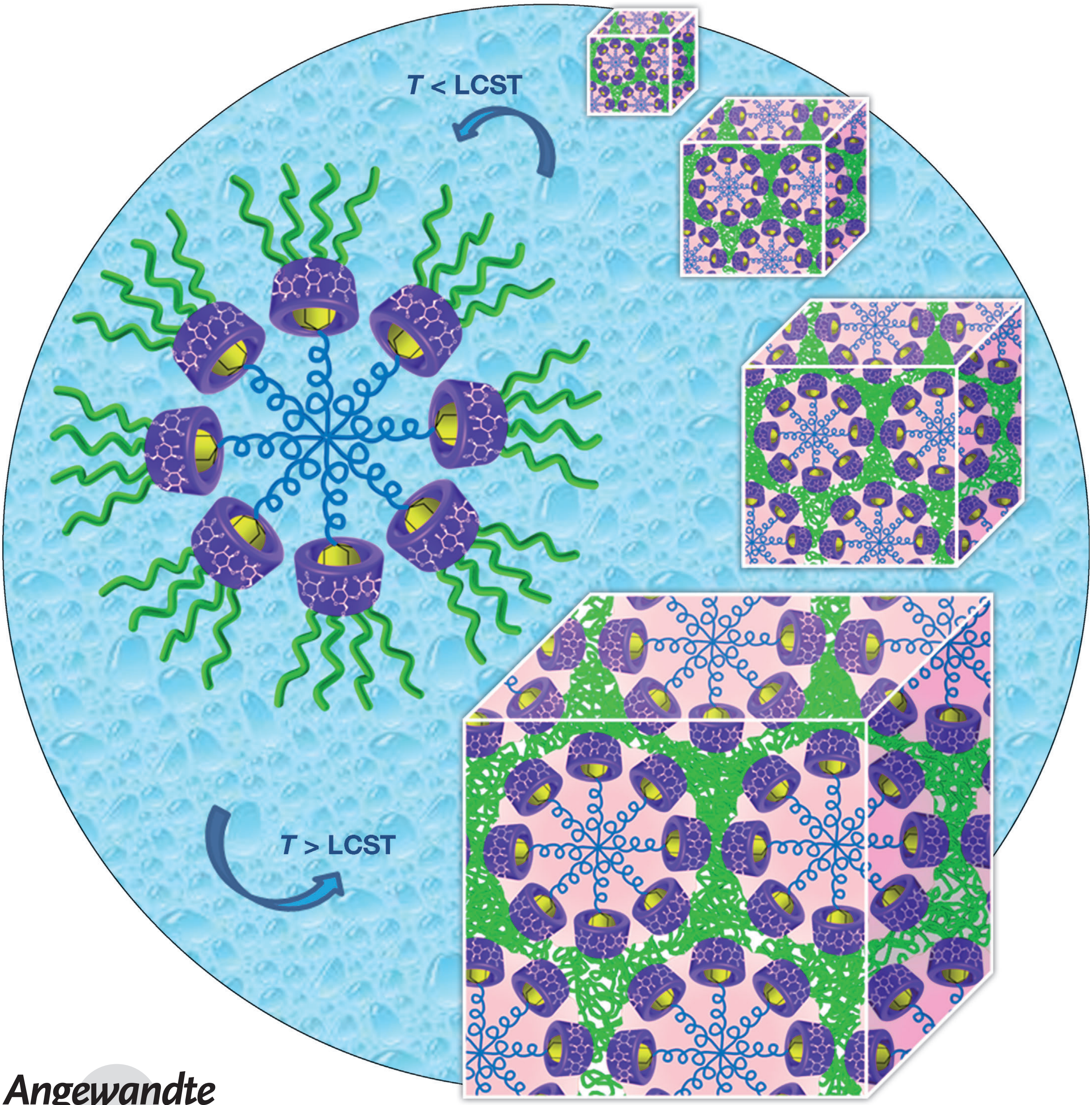

Polymers with novel architectures, such as star-shaped polymers and dendritic polymers, have attracted great interest in recent years because of their unique properties and functions, which polymers with conventional linear and branched structures may not have.[1–4] Cyclodextrins (CDs) have successfully been exploited to design and form self-assembled supramolecular polymer architectures owing to their unique complex-forming abilities,[5–11] which have inspired the interesting development of many supramolecular systems for biomedical and pharmaceutical applications.[12–19] We have previously demonstrated that a star-shaped poly(*N*-isopropylacrylamide) (PNIPAAm) with a β-CD core could form supramolecular self-assembled architectures with adamantyl-terminated linear poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG), which we termed "pseudo-block copolymers".[20,21] The self-assembling systems exhibited interesting properties, such as tunable thermoresponsivity and/or dually thermoresponsive micellization.

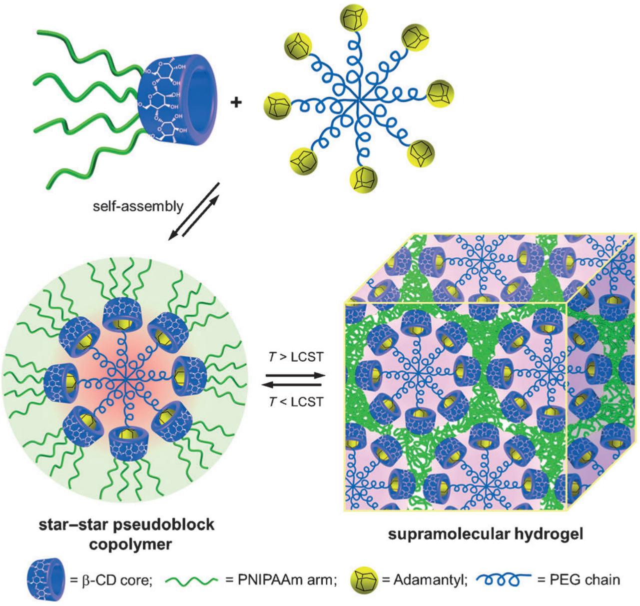

Figure 1. Formation of the star–star supramolecular architecture induced by the self-assembly of a polymeric star-shaped host and a polymeric star-shaped guest through inclusion complexation in aqueous solution and the formation of a supramolecular hydrogel at a temperature above the LCST.

Herein, we present the design of a novel star–star supramolecular architecture self-assembled between a star-shaped adamantyl-terminated 8-arm poly(ethylene glycol) and a star-shaped poly(*N*-isopropylacrylamide) with a β-CD core through inclusion complexation, which subsequently self-aggregated into a 3D network that induced thermoresponsive hydrogel formation. Figure 1 shows the self-assembling host–guest system that forms the novel star–star supramolecular architecture, in which the macromolecular host is star-shaped PNIPAAm with one β-CD core, and the macromolecular guest is an adamantyl-terminated 8-arm PEG star polymer. It is well known that PNIPAAm shows dramatic and reversible phase transition behavior in water with a lower critical solution temperature (LCST) at 32 °C.[22] When aqueous solutions of host and guest polymers were mixed together at 25 °C, a star–star pseudoblock copolymer was formed through inclusion complexation of the β-CD core and adamantyl end groups from the polymeric host and guest, respectively. Upon heating, this host–guest mixture changed from a clear solution with very low viscosity to a white stable hydrogel at around body temperature. This sol–gel transition was completely thermoreversible, rendering the hydrogel system unique and different from other reported β-CD/Ad-based gel-forming systems.[23–28] We hypothesize that the aggregation of PNIPAAm arm on the host polymer at temperature above its LCST results in physical cross-linking of the self-assembled star–star pseudoblock copolymer, thus forming a supramolecular 3D network that induces hydrogel formation.

The solution properties of the aqueous host–guest mixture were first investigated. At lower concentrations (typically, 1.0 wt % for the host polymer), the aqueous host–guest mixture showed tunable thermoresponsive behavior. The LCST of the aqueous host polymer solution shifted to a higher temperature upon the addition of the macromolecular guest. Figure S3 in the Supporting Information gives detailed information on the thermoresponsive behavior of a series of aqueous host–guest mixtures with varied guest/host ratios (such as Ad moiety/β-CD core), as investigated by the cloud-point technique. The LCST of the host polymer was ca. 33.5 °C. It shifted significantly, with an increase (ΔLCST, referenced to pure host polymer) of 2.1 °C when the guest/host ratio was 1:2. The ΔLCST further increased for another 1.7 °C, resulting in an LCST of ca. 37.3 °C when the guest/host ratio reached 1:1. However, the LCST became almost constant with further increase in the guest/host ratio beyond 1:1. This phenomenon was consistent with our previously reported observations,[20,21] which showed that the inclusion complexation that takes place between the polymeric host–guest pair and the self-assembling system involves a 1:1 complexation between the Ad moiety and β-CD core. In the following studies, a 1:1 host–guest mixture refers to an aqueous solution with a 1:1 molar ratio of Ad moiety to β-CD core.

At higher concentrations (typically, 12.0 wt % for a 1:1 host–guest mixture), the aqueous host–guest mixture could form a stable supramolecular hydrogel at around body

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temperature (37 °C). Figure 2 shows the appearance of the host polymer, guest polymer and 1:1 host–guest mixture in water at 25 °C and 37 °C, respectively. At 25 °C, both host and guest polymers dissolved in water to give free-flowing solutions, which quickly settled at the vial bottom when the sample vials were inverted (Figure 2 a,b). When the two solutions were heated to 37 °C and equilibrated for 5 min, the host polymer solution changed into a free-flowing milky suspension, whereas the guest polymer solution had no change in appearance at 37 °C. For the 1:1 host–guest mixture, a clear and free flowing solution was observed at 25 °C, but a white hydrogel was formed when this solution was heated to 37 °C and equilibrated for 5 min, as shown in Figure 2 c.

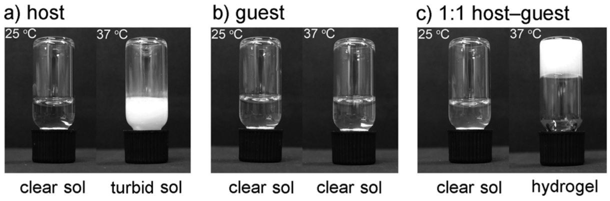

Figure 2. Representative photos of aqueous solutions of a) host polymer, b) guest polymer, and c) 1:1 host–guest mixture at 25 °C (left) and 37 °C (right). $C_{\text{solution}} = 12$ wt %.

To further confirm hydrogel formation and investigate the variation of G′ and G″ (representing the elastic modulus and viscous modulus, respectively) of the 1:1 host–guest mixture (12 wt %) upon temperature change from 25 °C to 45 °C, oscillatory temperature ramp experiments were carried out at an angular frequency of 1.0 rad s^{-1} and a shear stress of 2.0 Pa (Figure S4). At lower temperatures (25–34 °C), both the G′ and G″ of the host–guest mixture were quite low, with magnitudes on the order of 10^{-3} Pa and 10^{-2} Pa, respectively. The larger G″ over G′ throughout the temperature range indicated that the mixture was in a sol state (Figure S4a). When the temperature was raised to around 35 °C, both G′ and G″ increased dramatically. This phenomenon was related to the phase transition of PNIPAAm arms on the host polymer. The G′ increased even faster than G″. A G′/G″ crossover point was observed at 36.9 °C. At this point, the PNIPAAm arms on different host polymers collapsed into each other to form aggregates, which acted as physical cross-links for the formation of a supramolecular 3D network. As a result, a physical hydrogel was formed in situ. Above the gelling temperature (36.9 °C), the G′ and G″ continued to increase with increasing temperature, but the change slowed down when the temperature reached 45 °C. Over this temperature range (36.9–45 °C), the G′ was always much larger than G″, confirming a gel state. During the heating process, the G′ at 45 °C was found to be ca. five orders of magnitude higher than the original value at 25 °C. The cooling down process was also investigated (Figure S4b). It can be seen that the physical hydrogel formed at higher temperature completely reverted to a free-flowing solution at low temperatures.

To further support our hypothesis on the mechanism of hydrogel formation, a series of control samples were investigated. They were an aqueous solution of pure guest polymer, an aqueous solution of pure host polymer, and a 1:1 aqueous mixture of host polymer and PEG-8 A-OH (the molar ratio of the hydroxyl end of PEG to the β-CD core was 1:1). The three controls had the same concentration (12 wt %) and were tested under the same conditions in oscillatory temperature ramp experiments as that of the 1:1 host–guest mixture of interest (Figure 3). At low temperatures (below 34 °C), all of the controls exhibited similar rheological properties to that of the 1:1 host–guest mixture (very low G′ and G″ with magnitudes in the order of 10^{-3} Pa and 10^{-2} Pa, respectively). Thus, the rheological curves of these samples in the temperature range 25–34 °C are not shown in Figure 3. At higher temperatures (above 34 °C), the guest polymer solution did not show any change in G′ and G″ (Figure 3 b), and the host polymer solution showed a slight increase in G″ (Figure 3 c), whereas the host-PEG-8A-OH mixture showed some increases in G′ and G″, but the mixture was still in the sol state (Figure 3 d). These small changes may be due to non-specific interaction and chain entanglement between the β-CD core and the PEG chain. For the three controls, the G″ values were always larger than the G′ values over the entire experimental temperature range (25–45 °C), which shows that there was no gelation taking place. Such fundamental differences in rheological properties between these controls and the 1:1 host–guest mixture indicates that the inclusion

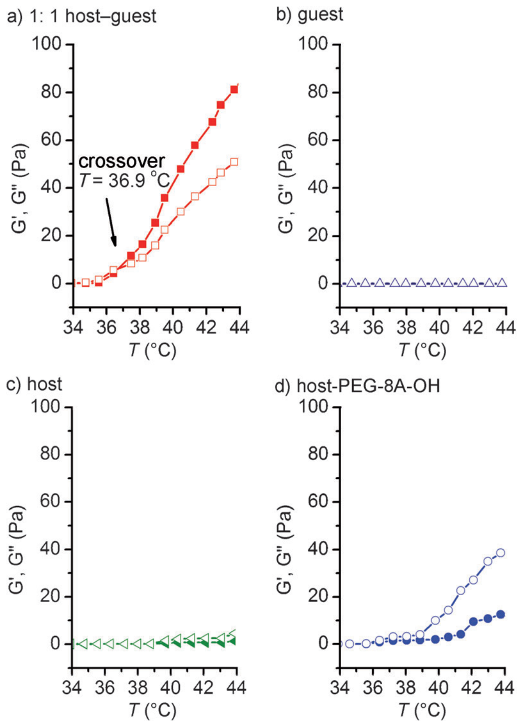

Figure 3. Oscillatory temperature ramp measurements of a) 1:1 host–guest mixture, b) guest polymer, c) host polymer and d) host-PEG-8A-OH mixture, showing variations of G′ (filled symbols) and G″ (open symbols) as functions of temperature during the heating process (selected range 34–44 °C). Shear stress $\tau = 2.0$ Pa, angular frequency $\omega = 1.0$ rad s^{-1}, heating rate 1 °C min^{-1}, and $C_{\text{samples}} = 12$ wt %.

complexation between the polymeric host and guest, as well as the reversible phase transition of the PNIPAAm arms on the host polymer are essential for the formation of supramolecular physical hydrogel in this study.

The supramolecular hydrogel formed from the 1:1 host–guest mixture (12 wt %) at 37 °C was subjected to a series of rheological measurements. From an oscillatory stress sweep at a constant angular frequency of 1.0 rad s^{-1}, the hydrogel was found to have a linear viscoelastic region (LVR) up to 20 Pa (Figure S5). Within this region, G′ and G″ were ca. 100 Pa and 50 Pa, respectively. An oscillatory frequency sweep test showed that the hydrogel was stable within the frequency region of 0.01–2.336 Hz under a shear stress of 2.0 Pa (Figure S6). In addition, the hydrogel demonstrated high reversibility and repeatability when subjected to repeated cycles of heating to 37 °C and cooling to 25 °C (Figure 4).

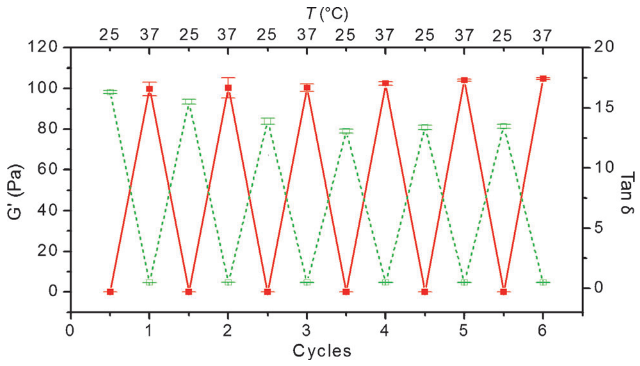

Figure 4. Variation of G′ (🟥) and Tan δ (□) of the 1:1 host–guest mixture at 25 °C and 37 °C, respectively, when subjected to repeated cycles of temperature change (25–37 °C). Shear stress $\tau = 2.0$ Pa, angular frequency $\omega = 1.0$ rad s^{-1}, and $C_{\text{mixture}} = 12$ wt %. δ = phase angle, Tan δ = G″/G′.

Physical hydrogels formed through non-covalent interactions have various advantages over conventional covalently cross-linked hydrogels for practical biomedical and pharmaceutical applications.[29–34] Owing to non-covalent crosslinking, physical hydrogels often exhibit a reversible sol–gel transition upon exposure to external stimuli, such as temperature, pH, and shear force, which make them capable of being used as smart materials for sensing and controlled release applications,[35–37] as well as for self-healing materials.[38–41]

The specific and strong host–guest inclusion complexation between the β-CD cavity and the adamantyl (Ad) moiety has been used as a physical cross-link to obtain β-CD-based supramolecular networks and hydrogels. Examples include hydrophilic polymers bearing pendant β-CD moieties or β-CD polymers physically cross-linked with adamantane end-capped linear polymers,[23,24] hydrophilic polymers bearing adamantane moieties cross-linked by β-CD dimers,[25] and systems containing β-CD modified polymers and adamantane modified polymers.[26–28] However, these physical hydrogels usually lack the ability for reversible sol–gel transition, owing to the stable β-CD/Ad links in water. A PEG hydrogel based on inclusion complexes of β-CD and cholesterol, where β-CD and cholesterol were conjugated to the ends of star-shaped PEG, was reported.[42,43] Hydrogels based on inclusion complexation between β-CD and ferrocene (Fc) were also reported recently, taking advantage of the reversible association–dissociation of β-CD/Fc complexes controlled by the redox state of Fc.[44,45] For the larger γ-CD, it can complex two molecules of certain compounds in a single cavity to form dimer inclusion complexes. By utilizing this property, we recently reported that γ-CD can be directly used as a supramolecular cross-linking reagent to induce hydrogel formation of pyrene-terminated PEG star polymers.[46] None of these CD-based supramolecular host–guest complexes form the dendritic star–star architecture demonstrated in this work. More importantly, such a star–star architecture allows for further self-assembly in response to temperature changes, thus producing a thermosensitive reversible “smart” hydrogel. Recently stimuli-responsive supramolecular polymer gels formed by crown-ether-based host–guest interactions were also reported.[47–50]

In summary, a novel star–star supramolecular architecture was assembled through inclusion complexation between a star-shaped adamantyl-terminated 8-arm PEG and a star-shaped PNIPAAm with a β-CD core. The star–star supramolecules further self-aggregated into a 3D network in response to temperature change, forming a thermoresponsive reversible “smart” hydrogel. In view of its interesting rheological properties, this system could potentially be used as injectable vehicle for drug delivery applications. Therapeutic agents could be conveniently mixed with the star-shaped host–guest polymer mixture at room temperature and injected into the body by virtue of the low solution viscosity. Once in the body, the mixture undergoes a temperature triggered gelation, forming a hydrogel that is able to encapsulate and sustain the release of the therapeutic agents in a controlled fashion.

Experimental Section

The macromolecular guest (PEG-8A-Ad) used in this work was synthesized by coupling the molecular recognition moiety, adamantane, with 8-armed PEG star polymer, PEG-8A-OH (Scheme S1). The conversion of hydroxyl end groups of 8-armed PEG to adamantyl groups was quantitative, as confirmed by ^{1}H NMR spectroscopy and GPC analysis (see the Supporting Information). The macromolecular host (β-CD-(PNIPAAm)$_4$) was obtained by growing PNIPAAm arms from a β-CD-based macroinitiator by copper(I)-mediated ATRP, according to our previous report (Scheme S2).[20,21] The host polymer was endowed with a β-CD core as a molecular recognition moiety and multiple PNIPAAm arms as actuation parts. The number-average molecular weight (M_n) of the host polymer calculated based on ^{1}H NMR and elemental analysis measurements was 10300 Da and 10330 Da, respectively. These values were found to correlate well with the predicted molecular weight (10350 Da) calculated from monomer/initiator ratio and monomer conversion. The polydispersity index (M_w/M_n) is ca. 1.2 by GPC (see the Supporting Information).

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