Poly(β-Cyclodextrin) Prepared by Ring-Opening Metathesis Polymerization Enables Creation of Supramolecular Polymeric Networks

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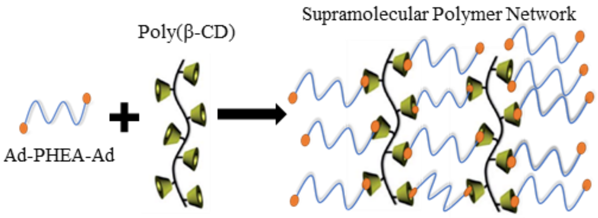
Abstract

The controlled synthesis of polymers containing densely grafted cyclodextrin units has proven challenging due to the steric hindrance of these cyclic oligosaccharides. In this study, we report the controlled synthesis of poly(β-cyclodextrin) [poly(β-CD)] through ring-opening metathesis polymerization (ROMP) using Grubbs third generation catalyst. Molecular weights of $>10^5$ g/mol were obtained with dispersity values (*Đ*) of ≤1.2. In aqueous solution, β-cyclodextrin forms a host-guest complex with adamantyl groups (Ad). These interactions were utilized to prepare supramolecular polymer networks (SPNs) made by adding poly(β-CD) to α,ω-adamantyl-functionalized poly(2-hydroxyethylacrylate) (Ad-PHEA-Ad). These poly(β-CD)/Ad-PHEA-Ad SPNs were prepared in aqueous solution and then dried to make homogenous, transparent films.

Varying the ratios of the two components enabled structure-property studies via tensile measurements.



Introduction

Supramolecular assemblies, which comprise two or more entities held together by means of noncovalent intermolecular binding interactions,[1] typically exhibit properties of polymers in bulk or in solution but may also be dynamic due to the inclusion of reversible, non-covalent bonds.[2-4] While all supramolecular assemblies rely on many synergistic noncovalent interactions, such as directional hydrogen bonds or metal coordination bonds, macrocycle-based host–guest interactions are of particular interest due to the potential for the formation of strong but dynamic complexes based on the shape and size of both partners.[5-7] Different types of supramolecular assemblies rely on macrocycle-based host–guest interactions, including polyrotaxanes,[8-11] linear polymers based on host–guest conjugates,[12-14] and supramolecular polymeric networks (SPNs).[15-18] Cyclodextrins, which are cyclic oligomers made of six, seven, or eight glucose units, were one of the earliest hosts discovered to form complexes with hydrophobic guests.[19] Specifically, β-cyclodextrin (β-CD) and adamantyl groups (Ad) form a host-guest complex with a high association constant in aqueous solution, making the β-CD/Ad pair a reliable tool for supramolecular polymer formation.[20]

Host-guest complexes comprised of Ad and β-CD units have been utilized to synthesize different types of supramolecular assemblies.[21-24] For example, Harada et al. found that mixing dimers of β-CD and with bis(Ad) compounds resulted in linear supramolecular assemblies when the linker was rigid, and supramolecular macrocycles when the linker was flexible.[25] In an example of SPNs, Ritter et al. used dimers of β-CD to crosslink poly(*N*-isopropylacrylamide) (PNIPAM) with pendant Ad groups, resulting in a decrease of the lower critical solution temperature (LCST) of the resulting PNIPAM hydrogel due to the limited mobility of the PNIPAM chains in the network.[26] Another approach is to attach Ad units and β-CD units to either the chain ends or backbones of two different polymers, generating complex polymer topologies or crosslinked networks.[27-29] Along these lines, Song et al. recently applied ring-opening metathesis polymerization (ROMP) to make a linear polymer containing pendant Ad units; adding poly(ethylene glycol) (PEG) with β-CD on one chain end resulted in a supramolecular graft polymer.[30] These examples of supramolecular assemblies based on β-CD and Ad highlight the great potential utility of these materials but also reveal that the preparation of polymers with controllable molecular weights and low molar-mass dispersity values (*Đ*) with densely packed pendant β-CD groups remains challenging.

The synthesis of poly(β-CD), where β-CD units are either components of or attached to the polymer backbone, has been reported using multiple methods. The earliest and most widely used method to prepare a form of poly(β-CD) is through addition of epichlorohydrin to β-CD under basic conditions.[31] The resulting network polymer can exist as a either a soluble viscous liquid or an insoluble gel, depending on the ratio of β-CD to epichlorohydrin.[32-33] However, these highly branched structures lack the reproducibility and predictability of linear polymers. One method for linear poly(β-CD) synthesis is the step-growth polyaddition or polycondensation of bis-functionalized β-CDs with a second difunctionalized monomer, for example in the polycondensation of bis-amino β-CD and dimethylsuberimidate, which reached an average degree of polymerization of 8.[34] In related work, Barnes et al. functionalized γ-CD with 8 norbornenes and used it as a core initiator to polymerize hexaethylene glycol (HEG) and polyethylene glycol (PEG) to create diblock brush-arm star copolymers.[35] Perhaps the most controlled method for preparing linear poly(β-CD) thus far has been reported by Zhang et al. in their polymerization of a mono-methacrylate derivative of β-CD via atom transfer radical polymerization (ATRP).[36] The highest degree of polymerization reported was 17, with a monomer conversion of around 50% and *Đ* of 1.24.

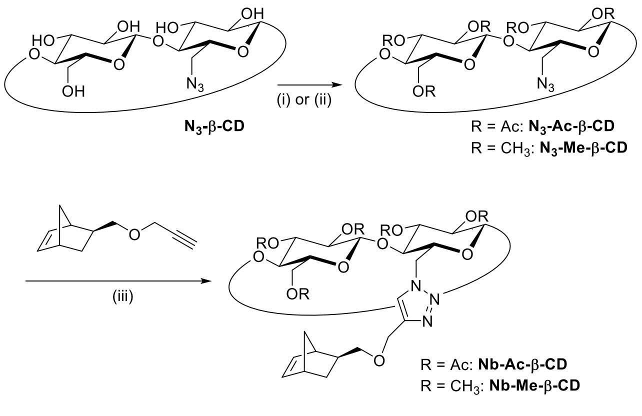
This lack of synthetic methods to prepare well-defined linear poly(β-CD) with controllable and high degrees of polymerization and low *Đ* values limits systematic studies on structure-property relationships of supramolecular structures based on the ubiquitous β-CD/Ad host-guest interaction. Therefore, in this study, we aimed to evaluate the use of ROMP to prepare well-defined acetylated, methylated, and native poly(β-CD) with degrees of polymerization of up to 150. We hypothesized that linear native poly(β-CD), but not acetylated or methylated poly(β-CD), could form SPNs with α,ω-Ad-functionalized poly(2-hydroxyethylacrylate) (Ad-PHEA-Ad). Finally, we sought to measure structure-property relationships in poly(β-CD)/Ad-PHEA-Ad SPNs by varying the ratios of the two components.

Results and Discussion

Installation of a single polymerizable group onto β-CD is necessary to prepare well-defined linear poly(β-CD) polymers. A well-known mono-functionalization approach for functionalizing just one of the 21 hydroxyl groups on β-CD is tosylation, which is documented in the literature through various reagents.[37-38] We opted to use tosyl imidazole, which cleanly produced the desired Mono-6-(*p*-toluenesulfonyl)-6-deoxy-cyclodextrin (Tos-β-CD) product in the presence of sodium hydroxide in aqueous solution.[39] Treatment of the resulting crystals with aqueous sodium azide afforded mono-6-azido-β-CD (N_3-β-CD) after precipitation from acetone. Finally, we employed the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction[40] to attach an alkyne-functionalized norbornene to N_3-β-CD, generating mono-6-norbornene-β-CD (Nb-β-CD). We attempted to directly polymerize Nb-β-CD using ROMP in polar solvents including DMSO and DMF, but we observed little to no conversion, likely because ROMP is mostly performed in less polar solvents.[41-43]

In order to achieve a high conversion in ROMP of Nb-β-CD, we aimed to make a hydrophobic derivative of the monomer to enhance solubility in moderately hydrophobic organic solvents (Scheme 1). Acetylation of the hydroxyl groups allowed us to achieve this goal, and the peracetylation of N_3-β-CD was carried out using acetic anhydride in pyridine, as reported previously[44], to generate fully acetylated N_3-β-CD (N_3-Ac-β-CD). We also carried out permethylation of N_3-β-CD using methyl iodide and sodium hydroxide to generate fully methylated N_3-β-CD (N_3-Me-β-CD).

Scheme 1. Synthesis of Nb-Ac-β-CD and Nb-Me-β-CD [a]

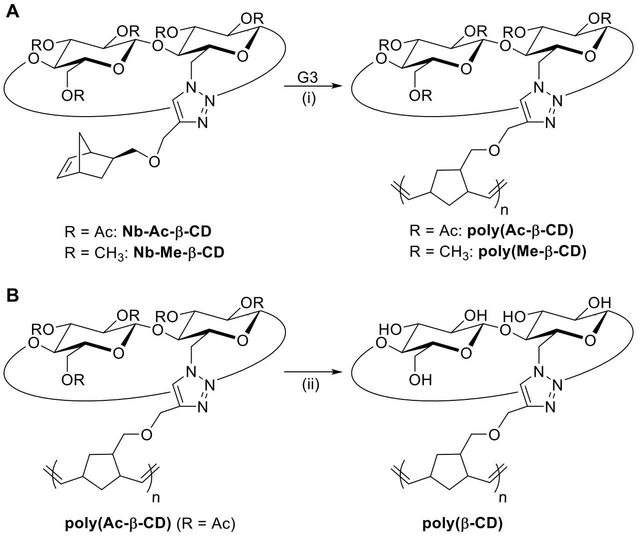


[a]Conditions: (i) for acetylation: acetic anhydride, pyridine, rt, 16 h. (ii) for methylation: NaOH, CH_3I, DMSO, rt, 48 h. (iii) CuBr, PMDETA, DMF, 40 ºC, 48 h.

Next, we set out to functionalize both N_3-Ac-β-CD and N_3-Me-β-CD with a norbornene group because it shows exceptional capabilities for polymerization of sterically bulky macromonomers (MMs) through ROMP.[42, 45-48] We designed a propargyl norbornene ether to include a norbornene group on one end and an alkyne group on the other end, enabling attachment of the acetylated or methylated N_3-β-CD through a CuAAC reaction to make norbornene functionalized compounds Nb-Ac-β-CD and Nb-Me-β-CD (Scheme 1). The triazole and ether connections were utilized due to their presumed stability to the reaction conditions used in the deacetylation step. According to ^{1}H NMR spectroscopy, norbornene functionalization reactions went to 77% functionalization for Nb-Ac-β-CD and 82% functionalization for Nb-Me-β-CD (Figures S9 and S11). Attempts to increase % functionalization were unsuccessful, but we envisioned that β-CD units lacking the norbornene functionality could be removed after ROMP due to their small size compared with the polymer.

Our first choice of solvent for the ROMP reactions of MMs Nb-Me-β-CD and Nb-Ac-β-CD was EtOAc because it provides fast reaction kinetics.[41] However, when EtOAc was used, the polymer formed a gel, meaning another solvent was needed that could keep the polymer product soluble at high concentrations. As a result, we performed test ROMP reactions using CH_2Cl_2 (Figure S16), THF (Figure S17), and acetone to see which solvent would best solubilize the reaction product, and we found that the product poly(Ac-β-CD) was soluble in all three solvents with ROMP in acetone resulting in polymers with the lowest dispersity. Use of acetone with MM/Grubbs 3rd generation catalyst (G3) ratios of 50, 100, and 150 led to full conversion of Nb-Ac-β-CD (or Nb-Me-β-CD) to poly(Ac-β-CD) [or poly(Me-β-CD)] (Scheme 2A), as followed by ^{1}H NMR spectroscopy (Figures S13 and S14). Moreover, the appearance of high molecular weight peaks in each of the six SEC traces demonstrated successful polymerizations (Figures S18 and S19).

Scheme 2. (A) Synthesis of poly(Ac-β-CD) and poly(Me-β-CD) through ROMP. (B) Synthesis of poly(β-CD) by deacetylation of poly(Ac-β-CD).[a]



[a] Conditions: (i) Acetone, rt, 2 h with MM/G3 ratios of 50, 100, and 150:1. (ii) KCN, THF/MeOH (3:2), rt, 10 min.

SEC traces showed residual β-CD species of 25% and 15% for poly(Ac-β-CD) and poly(Me-β-CD), respectively (Figures S18 and S19, Table 1). These values were consistent across different MM/G3 ratios and similar to results from ^{1}H NMR spectroscopy mentioned above that revealed 77% norbornene functionalization in Nb-Ac-β-CD and 82% norbornene functionalization in Nb-Me-β-CD. In both cases, we attributed unreacted MM to N_3-Ac-β-CD or N_3-Me-β-CD (or related β-CD species lacking the norbornene unit) because there was no norbornene peak detected at ~6 ppm in the ^{1}H NMR spectra after the ROMP reaction (Figures S13 and S14). Investigations of complex formation of norbornene and Ac-β-CD or Me-β-CD using dynamic light scattering (DLS) showed no aggregates larger than 10 nm (Figures S27 and S28), suggesting that complexation of the norbornene unit with either Ac-β-CD or Me-β-CD in acetone did not occur. Instead, as noted above, we attribute the 15-25% residual β-CD species to incomplete functionalization in the CuAAC reaction of N_3-Ac-β-CD and N_3-Me-β-CD with propargyl norbornene ether. As a result, we adjusted the amount of G3 added to initiate ROMP to reflect the actual content of norbornene functionalized MM. Despite this drawback, we found that both poly(Ac-β-CD) and poly(Me-β-CD) could be easily isolated by removing unfunctionalized MM via passage through a plug of silica using CH_2Cl_2 as an eluent. SEC traces for the purified polymers showed no trace of the MMs after this simple processing step (Figure S20 and S21). In addition, the DPs of poly(Ac-β-CD) and poly(Me-β-CD) with MM/G3 ratios of 50, 100, and 150 were close to targeted values, and *Đ* values were all below 1.2, indicating the living characteristics of the ROMP reaction.

Table 1: Characterization of poly(Ac-β-CD) and poly(Me-β-CD) with varying MM/G3 ratios.

Polymer	Targeted[a] *DP*	M_n[b] (kg/mol)	*DP*[c]	*Đ*[d]	% Residual β-CD species[d]
Poly(Ac-β-CD)	50	117	54	1.08	25
Poly(Ac-β-CD)	100	242	112	1.11	25
Poly(Ac-β-CD)	150	367	145	1.13	25
Poly(Me-β-CD)	50	87	55	1.06	15
Poly(Me-β-CD)	100	173	108	1.13	15
Poly(Me-β-CD)	150	255	160	1.16	15

[a]Targeted DP values were calculated accounting for 25% residual β-CD species lacking the norbornene in Nb-Ac-β-CD and 15% in Nb-Me-β-CD, the presence of which is attributed to incomplete CuAAC reactions. [b]Measured by SEC in THF at 30 °C using light scattering and refractive index detectors. [c]Average degree of polymerization from SEC data using the formula DP = M_n/MW_{MM}. [d]Norbornene conversion was quantitative in all polymerizations as determined

by ^{1}H NMR spectroscopy (Figures S13 and S14); however, residual β-CD species lacking the norbornene were present. Estimates of amounts of these residual species were determined from SEC by comparing the integrations of the polymer peak and the residual β-CD species peak (Figures S18 and S19) based on measured d*n*/d*c* values for Nb-Ac-β-CD and poly(Ac-β-CD) (both 0.073) and Nb-Me-β-CD and poly(Me-β-CD) (both 0.084) (Figures S22–25). All polymerizations were conducted in acetone for 120 min and initiated by G3 catalyst.

Substituents on β-CD reduce the strength of the β-CD/Ad interaction, so we aimed to remove the Ac groups on poly(Ac-β-CD) to generate poly(β-CD). Deacetylation of Ac-β-CD can be accomplished using potassium cyanide.[49] We therefore aimed to use this deacetylation procedure in converting a sample of poly(Ac-β-CD) (targeted DP = 100) into poly(β-CD) (Scheme 2B). In order to ensure complete deacetylation, we needed a solvent capable of dissolving poly(Ac-β-CD) while also keeping the product polymer, poly(β-CD), soluble as long as possible. We found that a solvent mixture of THF and methanol, with a ratio of 3:2, worked well for this procedure, and even though the product polymer eventually precipitated, we observed complete deacetylation by ^{1}H NMR spectroscopy after dialysis and lyophilization (Figure S15).

Because poly(β-CD) is not soluble in THF, we could not directly run SEC on the polymer in the same solvent as the poly(Ac-β-CD) starting polymer. Instead, a small sample of poly(β-CD) was reacetylated to make it THF-soluble. The reacetylated poly(Ac-β-CD) showed a similar SEC trace to the polymer prior to deacetylation (Figure S26), albeit with a small shift to higher retention time likely due to loss of low molecular weight material in processing and a slight broadening of the peak, likely due to incomplete reacetylation (starting poly(Ac-β-CD) M_n = 284 kg/mol and $Đ$ = 1.15; reacetylated poly(Ac-β-CD) M_n = 291 kg/mol and $Đ$ = 1.28). This demonstrates that poly(Ac-β-CD) can be converted to poly(β-CD) without heavily affecting the polynorbornene backbone, the cyclodextrin moieties, or the linkages between them.

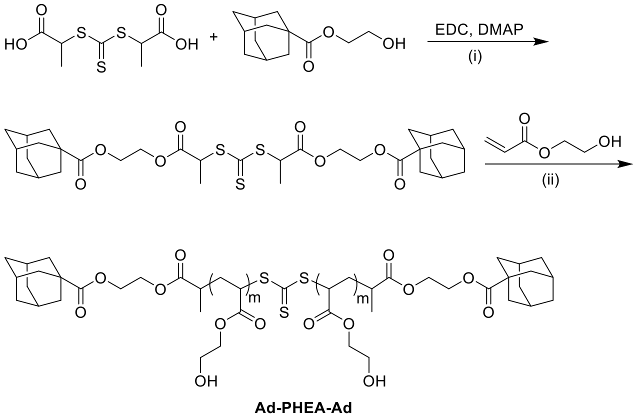
The host-guest interaction between β-CD and Ad has been extensively studied.[50-54] The stable inclusion complex can form with a 1:1 ratio with an association constant that exceeds 10^4 in aqueous solution due to the similar diameter and volume between Ad and the β-CD cavity.[20] However, the association constant between Ad and β-CD may change depending on chemical modifications done to either the host or the guest.[55]

Using this phenomenon, we studied the ability of poly(β-CD) to act as a crosslinker for linear polymer chains that contain Ad groups at both chain ends to prepare SPNs. For the linear polymer backbone, we selected PHEA because it is water-soluble and has a low T_g, which makes it a viscous liquid at room temperature. If functionalized with two Ad end groups, we envisioned that it would form an SPN with poly(β-CD) in water driven by the formation of β-CD/Ad inclusion complexes. Removal of water was expected to generate an elastomeric material crosslinked by host-guest interactions.

The preparation of PHEA functionalized with two Ad end groups (Ad-PHEA-Ad) started with synthesis of a chain transfer agent (CTA) capable of mediating reversible addition-fragmentation chain transfer (RAFT) polymerization of HEA. The synthesis of this bis-Ad-CTA started from bis-2-propionic acid trithiocarbonate, which was prepared according to a procedure published by Wooley et al.,[56] in order to have symmetric sites that allow for the attachment of Ad units on each end. As shown in Scheme 3, EDC coupling of bis-2-propionic acid trithiocarbonate with two equiv of 2-hydroxyethyl adamantane carboxylate was used to prepare the bis-Ad-CTA (Figures S3 and S4). Finally, RAFT polymerization of HEA initiated by AIBN and mediated by bis-Ad-CTA resulted in formation of Ad-PHEA-Ad with M_n = 5.0 kg/mol and $Đ$ = 1.16 (Figures S5 and S6). A control PHEA sample with a similar molecular weight was also synthesized using RAFT with 2-

(dodecylthio-carbonothioylthio)-2-methylpropanoic acid (DMPA) CTA (no Ad groups) to test the behavior of the polymer blends without the capacity for host-guest complex formation.

Scheme 2. Synthesis of bis-Ad CTA and Ad-PHEA-Ad[a]



[a]Conditions: (i) CH_2Cl_2, rt, 16 h. (ii) AIBN, DMF, 70 ºC, 3 h.

We then prepared a series of SPNs by combining Ad-PHEA-Ad with poly(β-CD) (DP = 100) which was synthesized on a large scale to be a representative sample of poly(β-CD) in the blends. The ratio of β-CD units to Ad units was varied to produce films using molar ratios of 25%, 35%, 50%, and 70% β-CD/Ad units. While Ad-PHEA-Ad behaved as a viscous liquid, all poly(β-CD)/Ad-PHEA-Ad blends formed creasable films after mixing the two polymers in water, followed by film-casting and drying. We then used a die-cutter to create dogbones for tensile testing. The dogbones were translucent and pale yellow due to the presence of the trithiocarbonate (Figure 1A). The preparation of poly(β-CD)/Ad-PHEA-Ad blends with higher than 70% β-CD/Ad units resulted in films that were too stiff to be processed into dogbones. Blends produced from the control PHEA and poly(β-CD) formed films that were sticky, opaque, and brittle. They also had visible phase-separation and lacked sufficient strength to prepare dogbones for tensile tests. Films formed from Ad-PHEA-Ad with either poly(Ac-β-CD) or poly(Me-β-CD) had similar properties. These observations highlight the importance of the β-CD/Ad host-guest interactions in the formation of robust films.

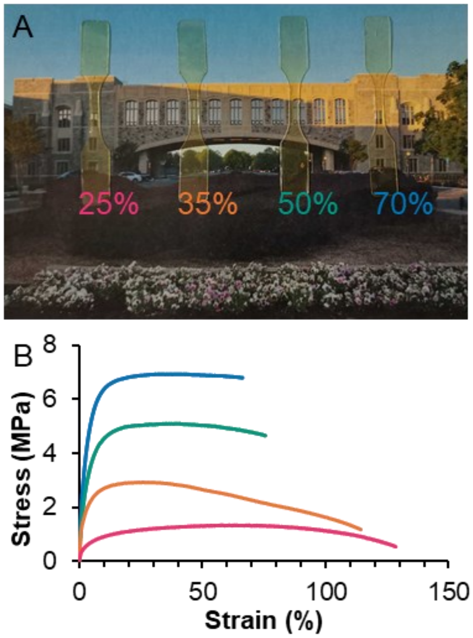


Figure 1. (A) Dogbones cut from films with β-CD/Ad. (B) Tensile measurements of SPNs of poly(β-CD) and Ad-PHEA-Ad with β-CD/Ad ratios of 25% (magenta), 35% (orange), 50% (teal) and 70% (blue). The tensile curves show representative samples of each poly(β-CD)/Ad-PHEA-Ad blend.

We carried out tensile tests on at least five samples of each poly(β-CD)/Ad-PHEA-Ad blend on an Instron at 30 mm/min. Stress-strain curves revealed several trends (Figure 1B, Table 2). Increased loading of poly(β-CD) in the blend increased the strength of the films and reduced their elongation at break: At a β-CD/Ad molar ratio of 25%, samples reached 130% strain at an average ultimate stress of 0.6 MPa. Increasing the ratio to 35% yielded samples that reached just over 100% strain before breaking at average ultimate stress of 1.5 MPa. When the β-CD/Ad ratio reached 50%, the material became significantly stronger and required more force to prepare the dogbones.

This observation is supported by tensile test results as the average stress at break increased to 4.6 MPa at a 50% β-CD/Ad ratio and 6.8 MPa at a 70% β-CD/Ad ratio, with elongation at break values dropping correspondingly. Young's modulus values increased similarly to ultimate stress, ranging from 0.5 MPa for the 25% molar ratio samples to 2.0 MPa for the 70% molar ratio samples.

Table 2: Tensile results for poly(β-CD)/Ad-PHEA-Ad SPNs based on β-CD/Ad ratios.

β-CD/Ad (Molar %)	Young's modulus[a] (MPa)	Stress at break[a] (MPa)	Strain at break[a] (%)
25	0.5±0.1	0.6±0.1	130±20
35	1.1±0.4	1.5±0.2	110±20
50	1.7±0.3	4.6±0.9	80±10
70	2.0±0.4	6.8±1.0	70±10

[a] Determined from an average of 5 runs using an Instron5500R at a strain rate of 30 mm/min.

Conclusions

In summary, we developed a method to prepare methylated, acetylated, and native poly(β-CD) through the ROMP of norbornene-functionalized β-CD derivatives. Molecular weights were controllable up to degrees of polymerization exceeding 150, and dispersities were less than 1.2, demonstrating living characteristics and high molecular weights with a substantially greater level of control over molecular weight and dispersity than previous methods. KCN served as a mild reagent for the deacetylation of poly(Ac-β-CD) to prepare native poly(β-CD). After deacetylation, poly(β-CD) was utilized to prepare SPNs by mixing with Ad-PHEA-Ad in water, which resulted in elastic films after drying. When a control polymer lacking Ad end groups was utilized, only brittle films that could not be analyzed by tensile testing were produced, demonstrating the importance of the host-guest complex in these materials. We observed a trend of higher stress and lower strain at break when the loading of poly(β-CD) increased relative to Ad-PHEA-Ad. Moving forward, several related systems can be envisioned, including poly(β-CD)-based SPNs with other low T_g polymers, polymer blends (miscible or immiscible), or copolymers (block, multiblock, statistical, or random). In addition, the ability to synthesize acetylated, methylated, and native poly(β-CD) with controlled molecular weights and low molecular weight distributions might be broadly useful beyond SPNs in constructing a variety of supramolecular assemblies.

Acknowledgements

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