Combination of ROP and RAFT for synthesis of a novel biodegradable, stimuli responsive P(CL-*ran*-CCL)-*b*-PNIPAm-*b*-P(CL-*ran*-CCL) triblock copolymer

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INTRODUCTION

Amphiphilic block copolymers based on biodegradable segments have garnered immense research interest for their potential applications as numerous biomaterials.[1] For example, Molavi et al. reported control release of cucurbitacin from poly(ethylene oxide)-block-poly(ε-caprolactone) (PEO-*b*-PCL) micelles.[2] Poly(D,L-lactide) (PLA) and poly(ethylene glycol) (PEG) based multiblock copolymers were also studied for target drug delivery systems.[3] Incorporation of a thermoresponsive segment, such as poly(N-isopropylacrylamide) (PNIPAm) into the biodegradable block is particularly advantageous since it is expected to form a micelle in aqueous solution that will facilitate the solubilization of drug and will improve the drug release kinetics.[4] Also, using the lower critical solution temperature of PNIPAm which is close to body temperature has been used to prepare thermoresponsive gel valves[7] Hence several attempts have been made to synthesize block copolymers involving PCL or PLA and PNIPAm segments.[5] For example, Chang et. al. reported the synthesis of PCL-*b*-PNIPAm-*b*-PCL triblock copolymer using a combination of anionic ring opening and addition-fragmentation chain transfer (RAFT) polymerization.[6] These copolymers, however exhibited very low mechanical propoerties.

Enhancing the mechanical properties and tensile strength of triblock copolymers based on PCL and PNIPAm to enable their use in biomedical applications is the focus of our current research. One possible approach is cross-linking these copolymers to prepare a network or binary blend. This is expected to facilitate enhanced tensile properties and hence will broaden their scope for use in biomedical applications. Among the recent efforts, Hillmyer and coworkers modified PLA with cyclopentadiene to synthesize a binary blend of PLA and poly(1,5-cyclopentadiene).[8]

In this preprint, the functionalization of caprolactone with cinnamoyl moiety (CCL) and synthesis of the corresponding triblock copolymers of PCCL, PCL and PNIPAm blocks are described. Funtionalization of caprolactone with a UV-curable moiety, such as cinnamoyl group and post-polymerization curing of the corresponding P(CCL-*ran*-CL)-*b*-PNIPAm-*b*-P(CCL-ran-CL) triblock copolymer will combine enhanced mechanical properties with stimuli-responsive behavior of the networks based on PCL and PNIPAm respectively.

EXPERIMENTAL

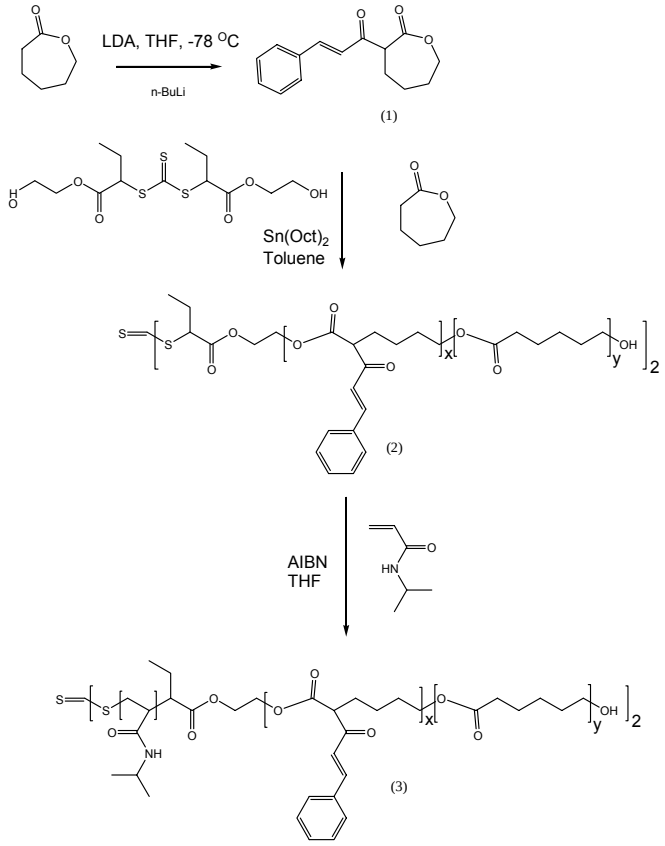
Materials. Butyllithium (Bu-Li, Aldrich, 2.4 M solution in hexane), diisopropylamine (Aldrich, redistilled, 99.95%), cinnamoyl chloride (Aldrich, 98%), ammonium chloride (Aldrich, ≥99.5%), ethyl acetate (Aldrich, ≥99.5%), ethylene glycol (Aldrich, 99.8%), 2-bromobutyric acid (Aldrich, 97%), *p*-toluenesulfonic acid (Aldrich, 98.5%), sodium chloride (Aldrich, ≥99.5%), methylene chloride (Aldrich, ≥99.5%), magnesium sulfate (Fluka analytical, 98%), Carbon disulfide (Aldrich, 99.9%) Caprolactone (Alfa Aesar, 99%), Toluene (Aldrich, 99.9%), Tin(II) 2-ethylhexanoate (Sn $(Oct)_2$, Aldrich, 95%), acetic acid (Aldrich, 99.7%), hexane (Aldrich, ≥99.8%), 2,2'-azobisisobutyronitrile, (AIBN, Aldrich, 98%), N-isopropylacrylamide (NIPAm, Aldrich, 97%), tetrahydrofuran, (THF, Aldrich, 99.9%), Benzene (Aldrich, ≥ 99.8%), Anionic exchange resin Amberlyst A26 (OH) form (Aldrich). THF and toluene were distilled over sodium metal and benzophenone under nitrogen atmosphere. Diisopropylamine was dried over calcium hydride under nitrogen atmosphere. Anionic exchange resin Amberlyst A26 (OH) was dried under vacuum at 60 °C till constant weight was obtained. All other chemicals were used as received.

ROP of ε-caprolactone (CL) and Modified caprolactone (CCL) using the initiator BHBT: The flask was filled with nitrogen gas, and *S*,*S'*-bis(2-hydroxyethyl-2'-butyrate) trithiocarbonate (BHBT) (40 mg, 0.108 mmol) and Caprolactone (867 mg, 7.6 mmol) in toluene were added into a 100 mL 3-neck round-bottom flask equipped with a stir bar via a syringe. After a toluene solution of $Sn(Oct)_2$ (1 mol % of monomer) was added, the flask was evacuated more than 2 hours. The reaction flask was maintained at 120 °C and the reaction was continued for 12 hours. The reaction was quenched by the addition of 0.3 M acetic acid aqueous solutions, the reaction mixture was dissolved in chloroform, and the polymer was precipitated using cold methanol. After filtration and drying in a vacuum at room temperature for 24 hours, PCL was obtained in 90% yield.

RAFT polymerization of NIPAm with the RAFT macroinitiator: In a 5 mL 2-neck round-bottom flask with magnetic stirring bar, PCL (500 mg, 0.063 mmol) AIBN (0.67 mg, 0.004 mmol), NIPAm (2.0 g, 17.7 mmol), and THF (5 mL) were added, and then the flask was closed with rubber septa and stopcock. After being degassed by passing argon through the solution for 2 hours, the flask was sealed and then immersed in an oil bath at 100 °C while stirring. After 10 hour, the polymerization flask was cooled to room temperature rapidly, and the polymer was precipitated by pouring the solution in THF into hexane. After dried in a vacuum oven at 40 °C for 24 hour 2 g of triblock copolymer of PCL-*b*-PNIPAm-*b*-PCL was obtained

RESULTS AND DISCUSSION

The ε-caprolactone was modified by attaching a cinnamoyl moiety to the carbon α to carbonyl group (Scheme 1). ^{1}H NMR spectrum showed peak at 3.9 ppm for -CO-C***H***-CO- of caprolactone ring indicating successful synthesis of cinnamoyl-caprolactone (CCL)(1). The –COO-C$\boldsymbol{H}_2$- resonated as a multiplet at 4.4 ppm.



Scheme 1. Synthesis of P(CL-*ran*-CCL)-*b*-PNIPAm-*b*- P(CL-*ran*-CCL)

ROP of ε-caprolactone (CL) and Modified caprolactone (CCL)

A homopolymer PCL and random copolymer P[CCL(40 mol%)-*ran*-CL(60 mol%)] (2) was synthesized by anionic ring-opening copolymerization (ROP) of caprolactone or cinnamoyl substituted carpolactone (CCL) using *S*,*S'*-bis(2-hydroxyethyl-2'-butyrate) trithiocarbonate as the initiator. The polymers were characterized by NMR and GPC analysis. ^{1}H NMR spectrum showed a new resonance at 4.1 ppm for –COOC***H***$_2$CH$_2$- of the caprolactone repeating unit. The -C***H***$_2$OH of PCL end-group was observed at 3.7 ppm. According to end-group calculation, the M_n of PCL and P(CCL-*ran*-CL) was calculated to be 8000 and 3900 respectively. A typical GPC trace of PCL is shown in Figure 2. The GPC M_n = 7900 of PCL was similar to the NMR analysis data.

RAFT polymerization of NIPAm with the RAFT macroinitiator

The corresponding triblock copolymers, PCL-*b*-PNIPAm-*b*-PCL and P(CCL-ran-CL)-*b*-PNIPAm-*b*-P(CCL-*ran*-CL) were synthesized by RAFT polymerization of NIPAm. Successful incorporation of a PNIPAm moiety into PCL and PCCL-*ran*-PCL was confirmed by NMR and GPC analysis. A typical ^{1}H NMR spectrum showed new resonances at 4.0, 1.1 and 6.2 ppm for –CONH-C***H***-$(CH_3)_2$, -NH-CH-$(C\boldsymbol{H}_3)_2$ and –CON***H***CH- respectively indicating incorporation of PNIPAm segment into the block copolymer (Figure 1). GPC analysis of the resulting triblock copolymers were carried out using tetrahydrofuran as the eluant. The M_n and PDI are described in Table 1 below. The M_n data were close to the theoretical value suggesting, triblock copolymers with controlled molecular weight can be synthesized.

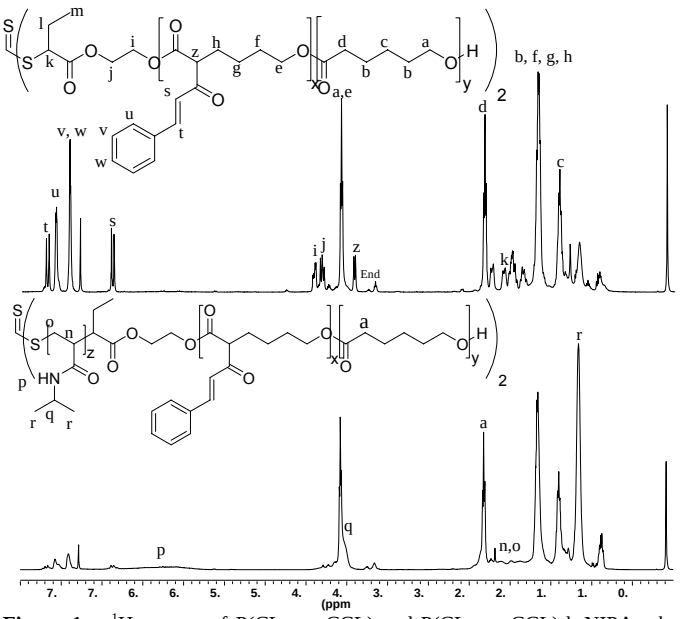


Figure 1. ^{1}H spectra of P(CL-*ran*-CCL) and P(CL-*ran*-CCL)-b-NIPAm-*b*-P(CCL-*ran*-CL) in $CDCl_3$.

Table 1. ***M*$_n$ and PDI of PCL-*b*-PNIPAm-*b*-PCL and P(CCL-*ran*-CL)-*b*-PNIPAm-*b*-P(CCL-*ran*-CL)**

Sample	M_n(GPC)	M_w/M_n (PDI)
PCL-*b*-PNIPAm-*b*-PCL	15000	1.2
P(CCL-ran-CL)-*b*-PNIPAm-*b*-P(CCL-*ran*-CL)	7900	1.3

Conclusion: Caprolactone can be successfully modified by cinnamoyl group, a potential UV-curable unit. The triblock copolymer of PCCL, PCL and PNIPAm was successfully synthesized with controlled molecular weight by a novel combination of anionic ring-opening and RAFT polymerization. The curing of the resulting triblock copolymer and analysis of their mechanical properties are currently under progress.

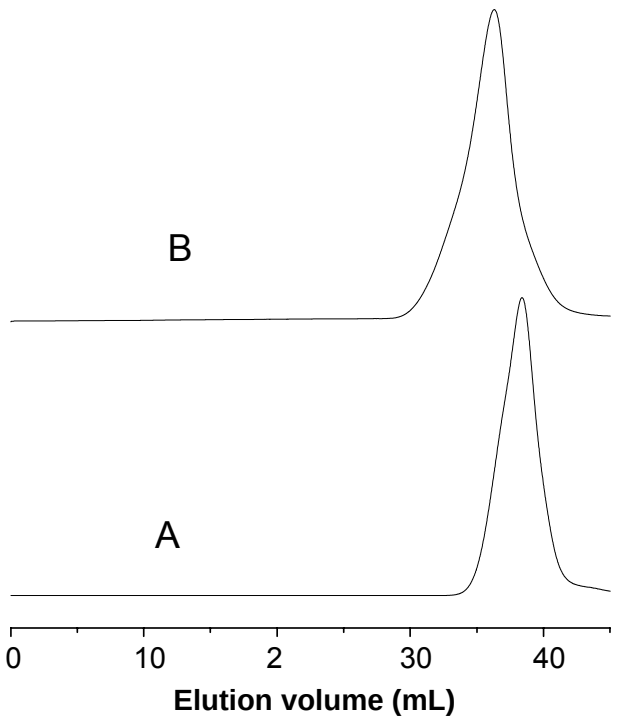


Figure 2. GPC-RI traces of (A) PCL and (B) PCL-*b*-PNIPAm-*b*-PCL.

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