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. For example, Molavi et al. reported control release of curcubatin from poly(ethylene oxide)-block-poly(caprolactone) (PEO-b-PCL) micelles. 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. Also, using the lower critical solution temperature of PNIPAm, which is close to body temperature has been used to prepare thermoresponsive gel valves. Hence several attempts have been made to synthesize block copolymers involving PCL or PLA and PNIPAm segments. 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. These copolymers, however exhibited very low mechanical properties.

In this preprint, the functionalization of caprolactone with cinnamoyl moiety to the carbon α to carbonyl group (Scheme 1). The –COO-CH= resonance was observed as a multiplet at 4.4 ppm. Astrometric exchange resin Amberlyst A26 (OH) form (Aldrich). THF and toluene were distilled over sodium metal and benzophenone under nitrogen atmosphere. Disopropylamine 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 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 PNIPam 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), PCL (50.2 g, 0.177 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). H NMR spectrum showed peak at 3.9 ppm for -COO-CH= of caprolactone ring indicating successful synthesis of cinnamoyl-caprolactone (CCL)(1). The –COO-CH= resonated as a multiplet at 4.4 ppm.

EXPERIMENTAL

Materials. Butyllithium (Bu-Li, Aldrich, 2.4 M solution in hexane), disopropylamine (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, 96%), Carbon disulfide (Aldrich, 99.9%), Caprolactone (Alfa Aesar, 99%), Toluene (Aldrich, 99.9%), Tin(II) 2-ethylhexanoate (Sn (Oct), Aldrich, 95%), acetic acid (Aldrich, 99.7%), hexane (Aldrich, ≥99.8%), 2,2-azobis(isobutyronitrile, (AIBN, Aldrich, 98%), N-isopropylacrylamide (NIPAm, Aldrich, 97%), tetrahydrofuran, (THF, Aldrich, 99.9%), Benzene (Aldrich, ≥ 99.8%).
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
caprolactone (CCL) using S,S'-bis(2-hydroxyethyl-2'-butyrate)
trithiocarbonate as the initiator. The polymers were characterized by
NMR and GPC analysis. ¹H NMR spectrum showed a new resonance
at 4.1 ppm for –COOC₂H₂CH₂- of the caprolactone repeating unit. The
-C₂H₃OH 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-NIPAm-b-PCL and
P[CCL-ran-CL]-b-NIPAm-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 ¹H NMR spectrum showed new resonances at 4.0, 1.1 and 6.2 ppm for –CONH-CH₂(CH₃)₂, -NH-CH-
(CH₃)₂ and –CONHCH₂- 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 were 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.

Conclusion: Caprolactone can be successfully modified by cinnamoyl
group, a potential UV-curable unit. The triblock copolymer of PCL,
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.

Table 1. $M_n$ and PDI of PCL-b-PNIPAm-b-PCL and P[CCL-ran-CL]-
b-PNIPAm-b-P[CCL-ran-CL]

<table>
<thead>
<tr>
<th>Sample</th>
<th>$M_n$(GPC)</th>
<th>$M_n/M_w$(PDI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL-b-PNIPAm-b-PCL</td>
<td>15000</td>
<td>1.2</td>
</tr>
<tr>
<td>P[CCL-ran-CL]-b-PNIPAm-b-P[CCL-ran-CL]</td>
<td>7900</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Figure 2. GPC-RI traces of (A) PCL and (B) PCL-b-PNIPAm-b-PCL.

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REFERENCES