Design and Synthesis of a Novel Biodegradable Polymer for Biomedical Applications.

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INTRODUCTION

Thermoplastic elastomers based on biodegradable polymers such as poly(lactide), poly(glycolide) and poly(ε-caprolactone) posses great potential for biomedical applications[1]. The crystallinity of these polymers is critical for various properties such as degradability[2], shape memory behavior[3] and mechanical properties such as tensile strength, ultimate elongation, etc. Crystallinity in polymers can act as a crosslinking mechanism greatly affecting its properties. Variation of crystallinity can be achieved by chemical modification of the polymer backbone in a controlled manner and by different polymer architectures. ε-Caprolactone is a semicrystalline polymer with a high degree of crystallinity.[3] Modifying ε-caprolactone monomer with a functional group which can be crosslinked by UV and polymerized in a controlled manner can affect the crystallinity to enhance the mechanical properties and tensile strength of copolymers based on poly(ε-caprolactone), enabling their use in biomedical applications.[4] Among the recent efforts, Hillmyer and coworkers modified poly(lactide) with cyclopentadiene to synthesize a binary blend of poly(lactide) and poly(1,5-cyclopentadiene).[5] Crosslinking with UV radiation is also useful for biomedical applications as it does not involve any initiator or crosslinker which can remain in the polymer and leach out during degradation of poly(ε-caprolactone).

In this preprint, the functionalization of caprolactone with a cinnamoyl moiety (CCL) and synthesis of the corresponding copolymers are described. Funtionalization of caprolactone with a UV-curable moiety, such as cinnamoyl group and post-polymerization curing of the corresponding copolymer is expected to yield enhanced mechanical properties.

EXPERIMENTAL

Materials. Cinnamoyl chloride (Aldrich, 98%), 1,4-cyclohexanediol (Alfa Aesar, 98+%), Pyridinium chlorochromate (Alfa Aesar, 98%), Triethylamine(Alfa Aesar, 99%), 3-chloroperoxybenzoic acid (Alfa Aesar, 70-75%), ethyl acetate (Aldrich, ≥99.5%), triethylene glycol (Aldrich, 99.8%), Hydrochloric acid (Mallinckrodt chemicals, 36.5-38%) sodium chloride (Aldrich, ≥ 99.5%), methylene chloride (Aldrich, ≥ 99.5%), magnesium sulfate (Fluka analytical, 98%), 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%), tetrahydrofuran, (THF, Aldrich, 99.9%). THF and toluene were distilled over sodium metal and benzophenone under nitrogen atmosphere. Methylene chloride was distilled before the reaction. All other chemicals were used as received.

1. Synthesis of 3-Phenyl-acrylic acid 4-hydroxy-cyclohexyl ester

1,4-cyclohexanediol (20.0 g, 172.4 mmol) was dissolved in dichloromethane (200 mL). Cinnamoyl chloride (7.2 g, 43.1 mmol) dissolved in 50 ml dichloromethane was then slowly added. After 2 h of mixing, triethyl amine (5.3 g, 52 mmol) was added slowly. After 48 h of mixing, the solution was washed three times with dilute HCl (1 M) and two more times with H_2O before it was dried over $MgSO_4$ and filtered. The product was then dissolved in methanol which resulted in precipitation of the byproduct. After evaporating the solvents, the product was a yellow-orange viscous liquid, which was used without further purification. Yield: 25-40%.

2. Synthesis of 3-Phenyl-acrylic acid 4-oxo-cyclohexyl ester

Pyridinium chlorochromate (PCC) (19.7 g, 91.5 mmol) was added to a solution of **1** (15.0 g, 61 mmol) in dichloromethane (150 mL). The mixture was stirred for 12 h. The reaction mixture was then added to silica gel (30.0 g) and the solvent was evaporated. The product was purified using column chromatography (by silica gel using hexane/EtOAc gradient as eluent). The product was a white crystalline powder. Yield: 60%.

3. Synthesis of 3-Phenyl-acrylic acid 7-oxo-oxepan-4-yl ester

2 (10.0 g, 38.5 mmol) was dissolved in 50 mL of dichloromethane and added dropwise into a solution of 3-chloroperoxybenzoic acid (99.3 g, 42.4 mmol) in dichloromethane (50 mL). The mixture was stirred for 24 h and then filtered. The solution obtained was washed twice with $NaHCO_3$ (2 M) and once with brine. The extracted product was then purified by column chromatography (by silica gel using hexane/EtOAc gradient as eluent). The monomer was obtained as a white crystalline powder. Yield: 70%.

4. Ring opening polymerization (ROP) of the monomers

The flask was first filled with nitrogen gas, triethylene glycol (6.3 mg, 0.042 mmol) and ε-caprolactone (5 g, 43.86 mmol) in toluene was added via a syringe into a 100 mL 3-neck round-bottom flask equipped with a stir bar. After a toluene solution of $Sn(Oct)_2$ (1 mol % of carbonyl group, 177.63 mg, 0.44 mmoles) was added, the flask was evacuated for more than 2 h. Toluene (10 mL per g of monomer) was then added and the reaction flask was immersed in an oil bath at 120 °C for 24 hours (48 hours for MCL) to allow the polymerization to occur. The reaction was quenched by the addition of 0.3 M acetic acid aqueous solution. The flask was then evacuated until a viscous solution was obtained. The reaction mixture was dissolved in tetrahydrofuran and the polymer was precipitated using cold methanol. After filtration and drying in a vacuum at room temperature for 48 hours, the polymer was characterized by NMR and DSC.

Table 1. ROP of modified ε-caprolactone (MCL) and copolymers of modified ε-caprolactone (MCL) and ε-caprolactone (CL).

No.	Polymer (CL:MCL)	Yield (Wt. %)	M_n (g/mol)	
			Theoretical	NMR
1	100:0	80	48,000	45,000
2	50:50 (random)	70	42,000	59,000
3	0:100	50	30,000	25,000

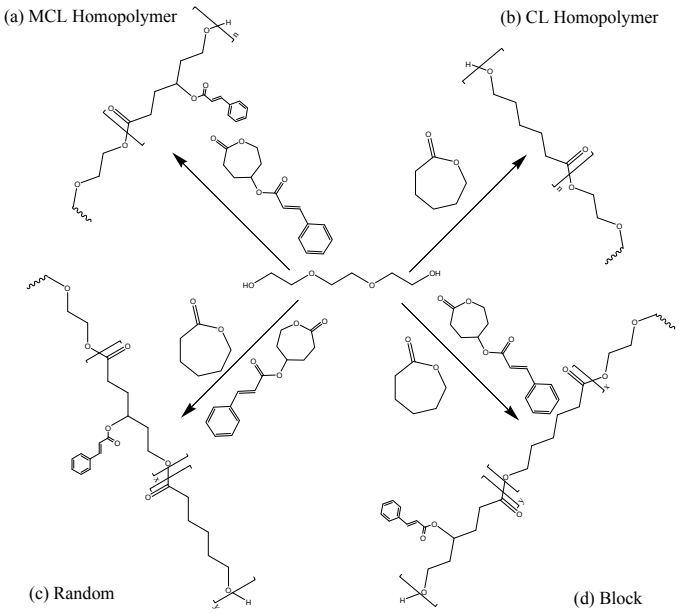

Figure 1. Polymerization scheme depicting the synthesis of homopolymers of (a) modified and (b) unmodified ε-caprolactone and the copolymers in a (c) random and (d) block architecture.

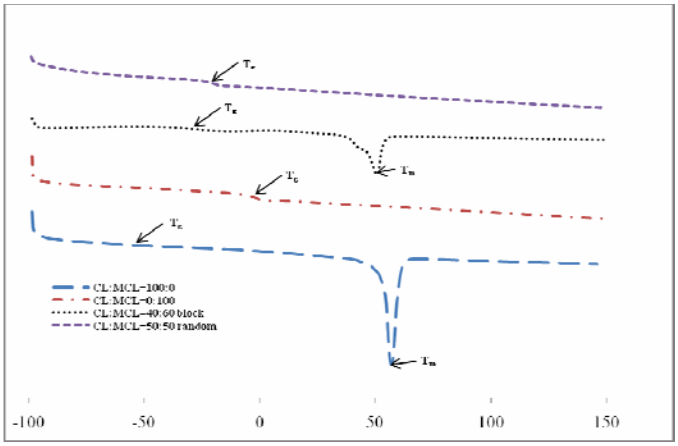

Figure 2. DSC traces of polymers showing their characteristic T_m and T_g.

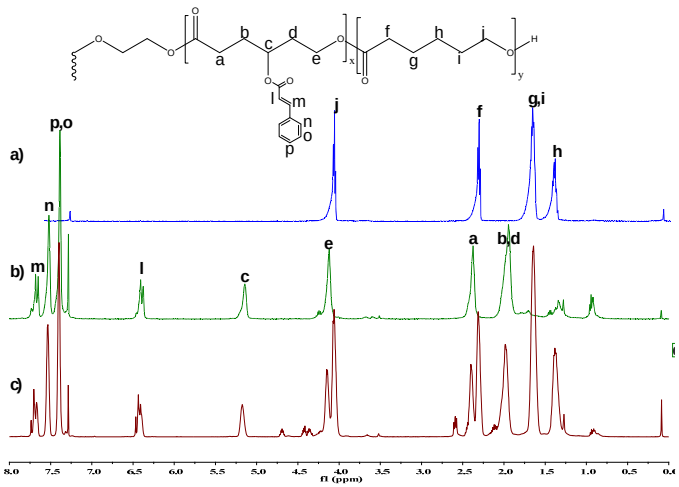

Figure 3. ^{1}H NMR spectra of the polymers a) CL:MCL = 100:0 b) CL:MCL = 0:100 c) CL:MCL = 50:50 random

RESULTS AND DISCUSSION

The synthesis of the new lactone monomer modified with cinnamoyl moiety was performed in three steps. The cinnamoyl moiety was attached to the carbon γ to carbonyl group (Scheme 1). ^{1}H NMR spectrum showed a peak at 5.3 ppm for –CH_2-C***H***-CH_2- of caprolactone ring indicating successful synthesis of cinnamoyl-caprolactone (MCL). The –COO-C***H***$_2$- resonated as a multiplet at 3.0 and 2.6 ppm. Homopolymer of MCL and copolymers of MCL and ε-caprolactone with different architectures were prepared by anionic ring opening polymerization (ROP). The synthesis scheme and the polymerization data is described in Figure 1 and Table 1 respectively. The conversions reported are the extracted weight fraction of the polymer from the polymer work-up.

^{1}H NMR spectrum showed a new resonance at 4.2 ppm for –COOC***H***$_2$$CH_2$- of the carpolactone repeating unit. The -C***H***$_2$OH of PCL end-group was observed at 3.8 ppm. Using end-group analysis, the number average molecular weight, M_n of PCL was calculated to be 45,000.

^{1}H NMR spectrum of the random copolymer of CL and MCL showed a new resonance at 4.3 ppm for –COOC***H***$_2$$CH_2$- of the modified carpolactone (MCL) repeating unit. The -C***H***$_2$OH of copolymer end-group was observed at 3.8 ppm. Again, using end-group analysis, the M_n of PCL was calculated to be 59,000. The mole fraction of monomer in the feed was 1:1 i.e. CL:MCL = 1:1 but the final polymer contains monomers in ratio of CL:MCL = 0.65:0.35. MCL has the cinnamoyl group at the γ position and its effect on the ring carbonyl was assumed to be low. Hence, the reactivity of the CL and MCL was expected to be same.

For the MCL homopolymer, the –COOC***H***$_2$$CH_2$- resonance of the modified carpolactone (MCL) repeating unit was seen at 4.1 ppm. The resonance of –CH_2C***H***CH_2– and –C***H***$_2$CHC***H***$_2$– of PMCL was observed at 5.1 ppm and 2.3 ppm respectively. The low yield of the polymer can be attributed to a low concentration of the co-catalyst. It is speculated that the co-catalyst may be coordinating with the carbonyl of the cinnamoyl group resulting in low overall concentration of the co-catalyst available for the polymerization. This effect is also seen with the decrease in yield of the polymer with increasing concentration of MCL.

The DSC traces of the un-crosslinked polymers are shown in Figure 2. The second heating cycle is taken so as to neglect any thermal history due to processing seen in the first heating cycle. PCL gave a glass transition temperature (T_g) at -62 °C and a melting transition (T_m) at 57 °C. With the incorporation of MCL, the Tm completely disappeared. This can be seen in both the homopolymer of MCL and random copolymer of MCL and CL. In the random copolymer the pendant cinnamoyl group affects the crystalline packing of the chains resulting in amorphous polymers with T_g at -25 °C. The homopolymer of MCL gave no T_m but has a T_g at 0 °C. With the incorporation of the MCL, the T_g increased due to the increase in the aromatic character of the polymers which decreased the mobility of the chains and hence, increased the T_g. The block copolymer gave the T_m at 51 °C. The decrease in melting point is expected due to a decrease in the order of chains at the ends due to MCL and smaller crystalline domains in the copolymer.

CONCLUSION

The synthesis of a new lactone monomer modified with cinnamoyl moiety, a potential UV-curable unit was successfully accomplished. Homopolymer of MCL and copolymers of MCL and ε-caprolactone with different architectures were prepared by anionic ring opening polymerization (ROP). The curing of the resulting copolymer and the analysis of their mechanical properties are currently in progress.

ACKNOWLEDGEMENTS

We are thankful to Dr. Umaprasana Ojha for fruitful discussions. This work was supported by the National Science Foundation as a Nanoscale Science and Engineering Centers Program (Award # NSF-0425826).

REFERENCES

1) Coombes, A.; Rizzi, S.; Williamson, M.; Barralet, J.; Downes, S.; Wallace, W. Biomaterials, **2004**, 25, 315.
2) Lam, C.; Savalani, M.; Teoh, S.; Hutmacher, D. *Biomed. Mater.*, **2008**, 3, 034108, 15.
3) Nagata, M.; Yamamoto, M.; *J. Poly. Sci. Part A: Poly. Chem.*, **2009,** 47, 2422.
4) Semba, T.; Kitagawa,K. ; Ishiaku, U.; Hamada, H.; *J. App. Poly. Sci.*, **2006,** 101, 1816.
5) Jing F.; Hillmyer M.; *J. Am. Chem. Soc.*, **2008**, *130*, 13826.