Aliphatic Polyesters with Pendant Cyclopentene Groups: Controlled Synthesis and Conversion to Polyester-*graft*-PEG Copolymers

Bryan Parrish and Todd Emrick*

Polymer Science & Engineering Department, University of Massachusetts Amherst, Conte Center for Polymer Research, 120 Governors Drive, Amherst, Massachusetts 01003

Received May 23, 2004

Revised Manuscript Received June 21, 2004

Aliphatic polyesters based on ϵ-caprolactone, lactide, and glycolide are of interest for medical and pharmaceutical applications for their biocompatible and biodegradable properties.[1−3] Current targets for these materials include degradable sutures, resorbable implant materials, tissue engineering scaffolds, and drug delivery vehicles.[4−7] While suitable for many applications, such polyesters are hydrophobic, semicrystalline solids that lack functionality for further modification and tailoring. The preparation of functionalized aliphatic polyesters is a synthetic challenge, whether the functionality is introduced at the monomer stage or in postpolymerization chemistry. In the former case, such functionality must be compatible with the polymerization conditions, while in the latter case the desired transformations must be achieved without degradation of the polyester backbone. While a number of groups in recent years have approached this problem with notable success,[8−12] the range of pendant-substituted aliphatic polyesters remains quite limited.

Here we target the pendant substitution of aliphatic polyesters by ring-opening polymerization of functionalized lactones. Subsequent poly(ethylene glycol) (PEG) substitution is of particular interest, as PEG-functionalized polymers can be used in aqueous media, are resistant to protein adsorption, and exhibit enhanced residence times in delivery applications.[13−15] PEG-functionalized aliphatic polyesters are typically block copolymers, prepared by the ring-opening polymerization of lactones initiated by the hydroxyl chain end, or chain ends, of PEG-monomethyl ethers or PEG-diols.[16,17] In such materials, the PEG chain imparts water solubility by forming a hydrophilic corona around the polyester core. While similar in composition, polyester-*graft*-PEG copolymers possess an inherent structural homogeneity, which unlike polyester-*block*-PEG copolymers is maintained upon degradation. In addition, the graft architecture allows for a controlled PEG density along the polyester backbone as well as the possibility for end-group functionalization of the PEG chains for targeting or recognition chemistry. While there have been a few recent reports on the synthesis of PEG-grafted polyesters,[18−20] to our knowledge the method presented here is the first controlled synthesis of such a structure giving materials with high grafting density, narrow polydispersity, and no apparent backbone degradation. We have presently focused on PEG grafts. However, this synthetic approach should provide a general method for the preparation of well-defined, aliphatic polyester biomaterials with numerous covalently bound pendant functionalities including chromophores, biomolecules, and drugs.

The synthesis of polyester-*graft*-PEG copolymers (**7**) described in Scheme 1 hinges on the preparation of the novel lactone α-cyclopentene−δ-valerolactone (**3**), accomplished in three steps from commercially available δ-valerolactone. Treatment of δ-valerolactone with lithium *N*,*N*-diisopropylamide followed by allyl bromide gave α-allyl-δ-valerolactone (**1**).[21] Lactone **1** was then subjected to a second allylation to afford α,α-diallyl-δ-valerolactone (**2**). Ring-closing metathesis of **2** using a ruthenium benzylidene catalyst recently reported by Grubbs and co-workers gave the cyclopentene-substituted monomer **3**.[22] Intramolecular ring-closing metathesis is favored over intermolecular cross-metathesis due to the proximity of the two allyl groups and the use of appropriate concentration (ca. 0.2 M). Successful ring-closing was confirmed in the ^{1}H NMR spectrum of **3** by the disappearance of the allyl signals from **2** (δ 5.75 and 5.11 ppm) and the appearance of a singlet (δ 5.61 ppm) corresponding to the cyclopentene unsaturation of **3**.

Ring-opening copolymerizations of **3** with ϵ-caprolactone were performed at room temperature as concentrated solutions in THF, using ethanol as initiator and $Sn(OTf)_2$ as catalyst. The polymerizations reached nearly full conversion (97% by ^{1}H NMR spectroscopy) after 48 h to yield copolymers of type **4**, with polydispersities typical of Sn(II)-mediated lactone polymerization (1.1−1.2) and controllable molecular weights in the range 5000−15 000 g/mol, as estimated by gel permeation chromatography. The presence of pendant cyclopentene in copolymer **4** was confirmed by ^{1}H NMR spectroscopy by the presence of a doublet at δ 2.85 ppm for the methylene protons α to the olefin, shifted slightly upfield relative to the corresponding protons in monomer **3**. The ^{13}C NMR spectrum of polymer **4** contains carbonyl resonances at δ 177.3 and 173.6 ppm, which appear broadened due to a generally random incorporation of the two monomer units.

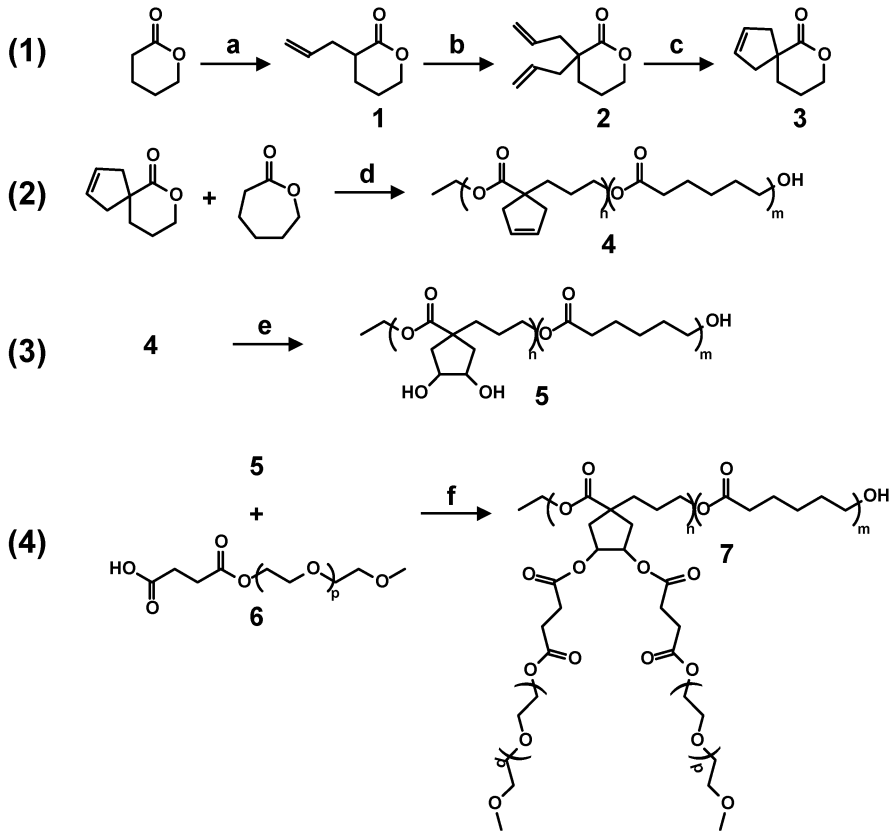
While we have thus far been unable to homopolymerize lactone **3**, copolymerization studies reveal an upper level of cyclopentene incorporation of about 20%, achieved when a 1:3 feed ratio of **3** to CL is used. This level of functionality significantly alters the properties of these aliphatic polyesters relative to their conventional counterparts. The pendant olefins of copolymer **4** were converted to *cis*-1,2-diols by dihydroxylation with osmium tetroxide and *N*-methylmorpholine-*N*-oxide to afford copolymers of type **5**. In the ^{1}H NMR spectrum of **5**, no residual olefin signals were observed, and a new signal centered at δ 3.41 ppm was found, corresponding to the methine protons α to the hydroxyls.

Dihydroxyl copolymer **5** shows good bench-life stability and is not susceptible to rapid backbone degradation that was observed in our prior studies on the dihydroxylation of aliphatic polyesters with pendant allyl groups.[12] In this previous study, copolymers with as little as 5−10% pendant 1,2-diol functionality degraded to 50% of their original molecular weight within 2 weeks. The markedly enhanced stability of the present system is attributed to the absence of primary alcohols, as well as the steric constraints imposed by the cyclopentyl rings that prevent intramolecular cyclization and back-

* Corresponding author. E-mail tsemrick@mail.pse.umass.edu.

10.1021/ma048981d CCC: $27.50
Published on Web 07/10/2004

Scheme 1[a]



[a] Conditions: (a) LDA, −78 °C; allyl bromide/HMPA, 70% yield; (b) LDA, −78 °C; allyl bromide/HMPA, 90% yield; (c) [(H_2IMes)(3-Br-py)$_2$(Cl)$_2$Ru=CHPh], 90% yield; (d) EtOH/Sn(OTf)$_2$ 48 h, 97% yield; (e) OsO_4/NMO, 93% yield; (f) DCC/pyridine/DMAP, refluxing CH_2Cl_2 24 h, 78% yield.

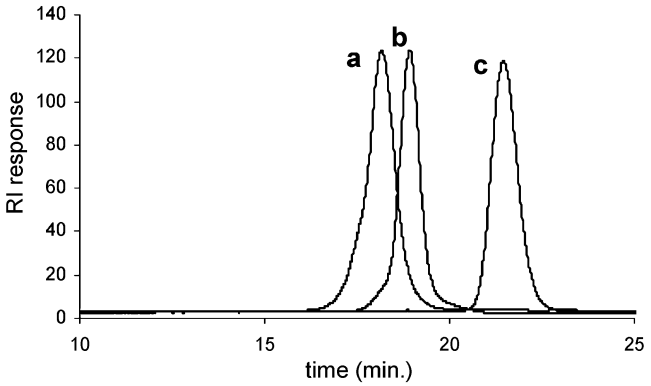


Figure 1. Overlaid gel permeation chromatographs of (a) polyester **7** with 1100 MW PEG grafts (**7$_{1100}$**); (b) copolymer **5** containing pendant cyclopentene moieties, and (c) succinic acid ester of PEG 1100 monomethyl ether (**6$_{1100}$**).

bone cleavage. The relative stability of 1,2-diol substituted polyesters **5** will allow for a variety of subsequent modifications. Here we present the synthesis of PEG-grafted aliphatic polyesters by dicyclohexyl carbodiimide-mediated coupling of **5** to succinic acid ester derivatives of various PEG monomethyl ethers **6** to give copolymers of type **7**. The coupling was performed in refluxing dichloromethane for 24 h, and the product was purified by dialysis in 95% ethanol (Spectra/Por Membrane MWCO 6−8000) to yield PEG-grafted polyesters with narrow molecular weight distributions (Figure 1).

The number of PEG grafts per polyester backbone (Table 1) was estimated by ^{1}H NMR spectroscopy by the relative integration of the signals at δ 4.01 ppm (−CH_2-OCO polyester) and δ 4.34 ppm (−CH_2OCO PEG). Grafting densities of 14−16 PEG chains per polymer were achieved, corresponding to a grafting efficiency of 70−80%. As expected, tetra(ethylene glycol) substitution of **5** to give **7$_{TEG}$** (using TEG-acid, denoted **6$_{TEG}$**) did not lead to water miscibility, while copolymer **7$_{750}$** formed stable dispersions in water, and copolymer **7$_{1100}$** formed optically clear solutions in water.

Table 1. Characterization of Polyester-*graft*-PEG Copolymers 7 and Precursors 4 and 5

copolymer	M_n[b] × 10^3	PDI[c]	no. of PEG grafts[d]
4[a]	8.5	1.12	N/A
5	8.6	1.16	N/A
7$_{TEG}$	11.7	1.20	16
7$_{750}$	15.5	1.21	14
7$_{1100}$	16.5	1.14	14

[a] With 14% incorporation of **3**. [b] Determined by gel permeation chromatography relative to polystyrene standards. [c] Polydispersity index, defined as weight-average molecular weight/number-average molecular weight (M_w/M_n). [d] Estimated by ^{1}H NMR spectroscopy.

In summary, we have presented a novel approach to amphiphilic graft copolymers with narrow molecular weight distributions by the synthesis of aliphatic polyesters with pendant cyclic olefins, followed by conversion of the olefins to 1,2-diols, and coupling of the hydroxyl groups to PEG-carboxylic acid derivatives. This study provides a novel route to amphiphilic graft copolyesters that can be prepared without backbone degradation. Our current efforts target exploitation of the amphiphilic nature of the PEGylated polyesters described here

as well as an investigation of cell−polymer interactions and the use of these polyesters as novel biomaterials.

Acknowledgment. The authors gratefully acknowledge the financial support of the University of Massachusetts Amherst through start-up funds, a Faculty Research Grant in the form of a Healey Award, and facilities support from the National Science Foundation-sponsored Materials Research Science and Engineering Center (MRSEC) at the University of Massachusetts Amherst (DMR-9400488). Kurt Breitenkamp is acknowledged for help with early experiments.

Supporting Information Available: Synthetic procedures and characterization for monomers and polymers 2−7. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181−3198.
(2) Albertsson, A.-C.; Varma, I. K. *Biomacromolecules* **2003**, *4*, 1466−1486.
(3) Jones, D. S.; Djokic, J.; McCoy, C. P.; Gorman, S. P. *Biomaterials* **2002**, *23*, 4449−4458.
(4) Langer, R. *Acc. Chem. Res.* **2000**, *33*, 94−101.
(5) Hoffman, A. S. *Adv. Drug Delivery Rev.* **2002**, *43*, 3−12.
(6) Ihre, H. R.; Padilla De Jesús, O. L.; Szoka, F. C., Jr.; Fréchet, J. M. J. *Bioconjugate Chem.* **2002**, *13*, 443−452.
(7) Han, D. K.; Hubbell, J. A. *Macromolecules* **1996**, *29*, 5233−5235.
(8) Trollsås, M.; Lee, V. Y.; Mecerreyes, D.; Löwenhielm, P.; Möller, M.; Miller, R. D.; Hedrick, J. L. *Macromolecules* **2000**, *33*, 4619−4627.
(9) Latere, J.-P.; Lecomte, P.; Dubois, P.; Jérôme, R. *Macromolecules* **2002**, *35*, 7857−7859.
(10) Mecerreyes, D.; Miller, R. D.; Hedrick, J. L.; Detrembleur, C.; Jérôme, R. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 870−875.
(11) Liu, M. J.; Vladimirov, N.; Fréchet, J. M. J. *Macromolecules* **1999**, *32*, 6881−6884.
(12) Parrish, B.; Quansah, J. K.; Emrick, T. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1983−1990.
(13) Prime, K. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 10714−10721.
(14) Gan, D.; Lyon, L. A. *Macromolecules* **2002**, *35*, 9634−9639.
(15) Li, S.; Garreau, H.; Pauvert, B.; McGrath, J.; Toniolo, A.; Vert, M. *Biomacromolecules* **2002**, *3*, 525−530.
(16) Lee, S.-H.; Kim, S. H.; Han, Y.-K.; Kim, Y. H. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2545−2555.
(17) Ferruti, P.; Mancin, I.; Ranucci, E.; De Felice, C.; Latini, G.; Laus, M. *Biomacromolecules* **2003**, *4*, 181−188.
(18) Chung, Y.-M.; Simmons, K. L.; Gutowska, A.; Jeong, B. *Biomacromolecules* **2002**, *3*, 511−516.
(19) Renard, E.; Ternat, C.; Langlois, V.; Guerin, P. *Macromol. Biosci.* **2003**, *3*, 248−252.
(20) Ikeda, I.; Simazaki, Y.; Suzuki, K. *J. Appl. Polym. Sci.* **1991**, *42*, 2871−2877.
(21) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716.
(22) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

MA048981D