Thermoplastic Poly(ester urethane)s with Novel Soft Segments

Benjamin F. Pierce, Andrew H. Brown, and Valerie V. Sheares*

Department of Chemistry, University of North Carolina at Chapel Hill, CB#3290, Caudill Hall, North Carolina 27599-3290

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ABSTRACT: A new class of thermoplastic poly(ester urethane)s containing novel soft segments are prepared using a one-step synthesis. Amorphous polyester prepolymers ($\langle M_n \rangle$ = 1.5 × 10^3−3.4 × 10^3 g/mol) were incorporated as soft segments in poly(ester urethane)s using an aromatic diisocyanate, 4,4′-methylenebis(phenylisocyanate), but with no chain extension. These completely amorphous materials had a wide range of mechanical properties (E = 0.86−29.3 MPa; γ_{max} = 2106%), and they possessed linear degradation profiles. A combination of contact angle studies, water uptake studies, and XPS analysis showed that these materials exhibited a surface segregation phenomenon upon contact with water. Kinetic analyses showed that three of the materials are among the fastest degrading poly(ester urethane)s reported in the literature to date. Initial cytotoxicity testing by minimum essential medium tests showed that only one of the nine new materials gave a cytotoxic response. Two separate sterilization methods did not elicit a cytotoxic response in the poly(ester urethane)s even after a 1 week incubation period.

Introduction

Polyurethane elastomers have been used in numerous biomedical applications over the past few decades.[1] Their broad range of mechanical properties enables them to be used as catheters,[1–9] heart valves,[1,10–14] bladders,[1,15] tubing,[1,15] blood filters,[1,16–20] and wound dressings.[1,21–24] The vast majority of biomedical polyurethane elastomers contain poly(tetramethylene oxide) (PTMO) as the soft segment, which makes these materials biocompatible, elastic, and hydrophilic. However, PTMO-based polyurethane elastomers are not biodegradable, a property that can be achieved when a biodegradable polymer, such as a polyester, is used as the soft segment. Some of the more common polyesters used as soft segments in biomedical polyurethane elastomers are poly(butylene adipate), poly(ethylene adipate), and poly(caprolactone),[1] which are all semicrystalline. Using semicrystalline prepolymers often results in semicrystalline poly(ester urethane)s (PEUs), as the thermal properties of the soft segment often dictate the overall morphology of the PEU. For example, Södergård et al. synthesized both semicrystalline PEUs (T_m = 125−138 °C) and amorphous PEUs by using a semicrysalline soft segment and an amorphous soft segment, respectively.[25] Although semicrystalline polymers possess many useful properties, they also exhibit drawbacks such as hydrophobicity, low resiliency, and swelling and deformation upon degradation. Semicrystalline materials also have lower diffusion constants, which slow the degradation rate. Furthermore, semicrystalline materials are not transparent, which is a requirement for applications such as ocular tissue replacements.[26–29] By using an amorphous polyester precursor, a transparent PEU that is more hydrophilic and resilient can be prepared. Moreover, a PEU containing an amorphous soft segment will also have a faster more linear degradation profile.

There are some examples of amorphous thermoplastic PEUs reported in the literature. Seppälä et al. synthesized amorphous soft segments of lactic acid[30–32] and comonomers[33,34] for PEUs and reported the biodegradation,[35–37] the effect of fillers,[38] and the rheological properties[39] of these amorphous materials. These PEUs have an extremely wide range of mechanical and thermal properties, yet they possess an unpredictable, nonlinear biodegradation profile. Poly(lactic acid)-based materials often possess nonlinear biodegradation profiles due to the autocatalysis of acidic byproduct trapped in the core of the devices. This can lead to an unpredictable burst of acidic residues from the materials.[40] Prasath et al. prepared amorphous calcium-containing PEUs by reacting 2,4-tolylene diisocyanate with a mixture of the calcium salt of mono(hydroxybutyl) phthalate [$Ca(HBP)_2$] and hydroxyl-terminated poly(1,4-butylene glutarate).[41] Although the modulus of these materials can be tuned very easily by varying the ionic content, they were not elastomeric. Synthetic elastic materials are useful as implants because they resemble tissues similar to elastin, for which Winlove et al. reported as having a breaking strain of 200%.[42] Marcos-Fernández et al. synthesized several amorphous poly(ester urethane urea)s with poly(caprolactone) as the soft segment and amino acid derivatives as the chain extenders.[43] These materials were durable and elastic, but they were synthesized using heterogeneous chain extension—an unnecessary synthetic step in preparing useful poly(ester urethane)s. Chain extension, whether heterogeneous or homogeneous, can be avoided altogether in synthesizing durable polyurethane elastomers, as Yilgor et al.[44,45] recently proved. Therefore, a more facile, one-step method that excludes the use of chain extenders can be employed to synthesize durable poly(ester urethane)s. Overall, the literature provides several amorphous poly(ester urethane)s that possess some beneficial characteristics for use as biodegradable materials in biomedical applications. However, they display at least one of the following features: (1) a nonlinear biodegradation profile, (2) low elasticity, or (3) unnecessary chain extension. Materials that possess the inherent attributes of PEUs, such as biocompatibility and biodegradability, along with hydrophilicity, more predictable biodegradation profiles, high elasticity, and facile synthetic procedures are very promising.

Recently, we reported the preparation of completely amorphous, degradable, elastomeric poly(ester ether)s.[46] The ether linkages ensured that the thermoset materials were hydrophilic and possessed very low glass transition temperatures, while the ester linkages ensured that the materials were degradable. Because of the high degree of hydrophilicity, these materials rapidly degraded and displayed linear degradation profiles. We have also reported the preparation of amorphous polyesters which were comprised of unsaturated cyclic moieties synthesized using Diels−Alder chemistry.[47] These monomers were designed to easily change the hydrophilicity/hydrophobicity of the

* To whom correspondence should be addressed.

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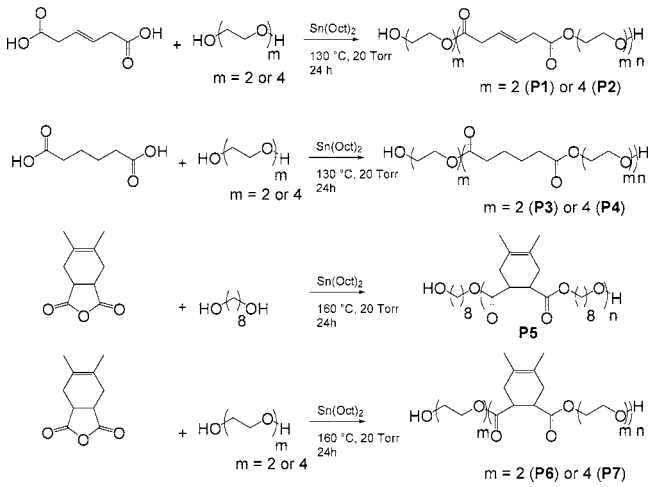
Scheme 1. Hydroxyl-Terminated Polyesters (P1−P7)



resulting polyester as well as to incorporate different functional groups. The cyclic monomers ensured that the polyesters were amorphous.

Herein, we describe the synthesis as well as thermal and mechanical properties, degradation rates, surface properties, hydrophilicity, and cytotoxicity of several poly(ester urethane)s based on novel oligomeric diols (Scheme 1). The poly(ester urethane)s and their corresponding prepolymers can be divided into two categories: those based on poly(ester ether) soft segments (**P1**−**P4**; **PEU1A**−**1C**, **PEU2**−**PEU4**) and those that contain soft segments bearing cyclic structures synthesized using Diels−Alder chemistry (**P5**−**P7**; **PEU5**−**PEU7**). First, incorporating such hydrophilic and amorphous soft segments in the PEUs induced a much more predictable and faster rate of degradation than previously made poly(ester urethane)s. Second, using 4,4′-methylenebis(phenylisocyanate) as the monodisperse hard segment gave the PEUs high elastic properties. Finally, these materials were synthesized using a simple one-step polymerization method, excluding the use of any chain extension.

Experimental Section

Materials. All reagents were purchased from Aldrich and used as received unless otherwise noted. Toluene and *N,N*-dimethylacetamide (DMAc) were dried over calcium hydride, distilled before use, and stored on 4 Å molecular sieves. Diethylene glycol was ≥99.0% pure, and tetraethylene glycol was ≥99.5% pure. *trans*-*β*-Hydromuconic acid (HMA) was purchased from TCI and recrystallized from water prior to use. 1,8-Octanediol (OD) was recrystallized from tetrahydrofuran. A film of poly(caprolactone) was formed thermally for contact angle measurements. 1,4-Butanediol (BD) was vacuum-distilled and stored on 4 Å molecular sieves. 4,5-Dimethylcyclohex-4-ene *cis*-1,2-dicarboxylic anhydride was synthesized according to the literature.[47]

Characterization. ^{1}H and ^{13}C NMR spectra were acquired in deuterated chloroform on a Bruker 400 AVANCE. Polymer molecular weights were determined by gel permeation chromatography using a Waters GPC system with a Wyatt Optilab DSP interferometric refractometer and a Wyatt Dawn EOS as the detector. Molecular weights were calculated using a calibration plot constructed from polystyrene standards. The measurements were taken at 35 °C with tetrahydrofuran or at 50 °C with *N,N*-dimethylformamide (0.05 M LiBr) as the mobile phase on three columns (Waters Styragel HR2, HR4, and HR5). Thermogravimetric analysis was performed on a Perkin-Elmer Pyris 1 TGA with a heating rate of 10 °C/min in a N_2 atmosphere. Glass transition temperatures were measured with a Seiko 220C differential scanning calorimeter, using a heating rate of 10 °C/min and a cooling rate of 10 °C/min in a N_2 atmosphere. Glass transitions were determined at the inflection point of the endotherm. FTIR spectra were acquired on a Perkin-Elmer Spectrum BX. Elemental analysis was performed by Atlantic Microlab, Inc., in Norcross, GA. Contact angle measurements were performed using a CAM 200 optical angle meter. Five frames were captured at a frame interval of 300 s. X-ray photoelectron spectroscopy data were taken using a Riber LAS-3000 with Mg Kα excitation (1254 eV). Energy calibration was established by referencing to adventitious carbon (C 1s line at 284.5 eV binding energy). The takeoff angle was ∼75° from surface, and the X-ray incidence angle was ∼20° and the X-ray source to analyzer ∼55°. The base pressure in the analysis chamber was in the 10^{-10} Torr range.

Mechanical Analysis. Mechanical analysis was conducted on an Instron 5566 at a crosshead speed of 10 mm/min at 25 °C. The Young's modulus (*E*) was calculated using the initial linear portion of the stress/strain curve (0−5% strain). Each measurement was performed on three separate samples. The value was reported as the average of the three measurements. Dynamic mechanical analysis was performed using a Perkin-Elmer Pyris Diamond DMA. The measurements were taken with the tension mode with a frequency of 1 Hz from −100 to 100 °C. The glass transition temperatures were recorded as the maximum of the loss modulus.

In-Vitro Degradation. Elastomer films (0.15 g) were placed in 0.01 M pH 7.4 phosphate buffer saline solutions at 37 °C. The films were removed from the buffer solution at the prescribed intervals and dried under vacuum for 24 h before their mass was measured. Each measurement was performed on three separate samples. All error bars represent a 50% confidence interval. Mass loss (ML) was calculated according to the following equation:

$$\mathrm{ML} = \frac{m_\mathrm{i} - m_t}{m_\mathrm{i}} \times 100 \qquad (1)$$

where m_i and m_t represent the initial mass and mass at time *t*. Kinetic analyses of degradation were calculated according to zero-order kinetics.

Water Uptake. Elastomer films (0.15 g) were placed in 0.01 M pH 7.4 phosphate buffer saline solutions at 37 °C. At the prescribed intervals, each swollen network was removed from the buffer solution and blotted dry, and the mass was recorded. Each measurement was performed on three separate samples. The water uptake (WU) was calculated according to the following equation:

$$\mathrm{WU} = \frac{m_\mathrm{s} - m_\mathrm{d}}{m_\mathrm{d}} \times 100 \qquad (2)$$

where m_s and m_d represent the swollen and dry mass, respectively. The value was reported as the average of three measurements. All error bars represent a 50% confidence interval.

Cytotoxicity Testing. Minimum essential medium (MEM) elution tests were performed according to the ISO 10993-5 standard by Micromed Laboratories in Petaluma, CA. Samples were extracted for 24 h at 37 °C and pH = 7.4 in minimal essential medium. Extracts were placed on cell monolayers for 48 h at 37 °C and pH = 7.4. L929 mouse fibroblast cells from the ATCC cell line were used. At the conclusion of 48 h, the cells were examined and cytotoxicity was scored on a 0 to 4 scale, 0 being the least cytotoxic. Cell growth and incubation were performed by the University of North Carolina Comprehensive Cancer Center Tissure Culture Facility. Samples were either autoclaved or chemically treated and then separately incubated in the presence of rabbit endothelial vascular cells (REVC) for 1 week. Imaging was taken with a Zeiss Axiovert 200 inverted microscope.

Polyester Syntheses. *Adipic Acid/HMA Polymerizations.* A 25 mL round-bottom flask was charged with the acid and a stoichiometric excess of diol, targeting molecular weights of 5000 g/mol. The contents of the flask were then placed under an argon atmosphere. The mixture was stirred at 130 °C using magnetic stirring until a homogeneous melt was formed. Stannous 2-ethylhexanoate (1.0 mol %) was added to the melt. The mixture was

stirred for 1 h, and the pressure was reduced to 20 mmHg. The reaction was allowed to proceed at 20 mmHg for 23 h, for a total time of 24 h. The polymerization was terminated by precipitating the polymer in cold diethyl ether (−78 °C). Reactions were performed on a 10−25 g scale.

Poly(diethylene glycol hydromuconate). ^{1}H NMR: δ (ppm) = 5.67 (m, 2H), 4.21 (t, 4H, J = 4.8 Hz), 3.71 (t, −CH_2CH$_2$OH end group, J = 4.3 Hz), 3.67 (t, 4H, J = 4.8 Hz), 3.57 (t, −CH$_2$CH_2OH end group, J = 4.3 Hz), 3.10 (dd, 4H, J = 1.6, 3.8 Hz). ^{13}C NMR: δ (ppm) = 171.36 (*C*O$_2$), 125.81 (−CH$_2$*C*H=*C*HCH$_2$−), 68.90 (−CO$_2$CH$_2$*C*H$_2$O−), 63.60 (−CO$_2$*C*H$_2$CH$_2$O−), 37.53 (−CO$_2$*C*H$_2$-CH=CH*C*H$_2$−). Anal. Calcd for $C_{124}H_{178}O_{63}$: C, 55.65; H, 6.66; O, 37.7. Found: C, 55.31; H, 6.70; O, 38.00.

Poly(tetraethylene glycol hydromuconate). ^{1}H NMR: δ (ppm) = 5.66 (m, 2H), 4.21 (t, 4H, J = 4.9 Hz), 3.67 (t, −CH_2CH$_2$OH end group, J = 4.9 Hz), 3.63 (s, 12H), 3.58 (t, −CH$_2$CH_2OH end group, J = 4.8 Hz), 3.09 (dd, 4H, J = 1.5, 3.9 Hz). ^{13}C NMR: δ (ppm) = 171.42 (*C*O$_2$), 125.82 (−CH$_2$*C*H=*C*HCH$_2$−), 70.47 (−CO$_2$CH$_2$*C*H$_2$O*C*H$_2$CH$_2$−), 68.95 (−CO$_2$*C*H$_2$CH$_2$O−), 63.71 (−OCH$_2$*C*H$_2$OH end group), 37.56 (−CO$_2$*C*H$_2$CH=CH*C*H$_2$−). Anal. Calcd for $C_{92}H_{150}O_{47}$: C, 55.03; H, 7.48; O, 37.49. Found: C, 54.83; H, 7.53; O, 37.95.

Poly(diethylene glycol adipate). ^{1}H NMR: δ (ppm) = 4.20 (t, 4H, J = 4.8 Hz), 3.71 (t, −CH_2CH$_2$OH end group, J = 4.3 Hz), 3.66 (t, 4H, J = 4.7 Hz), 3.57 (t, −CH_2OH end group, J = 4.3 Hz), 2.34 (t, 4H, J = 5.8 Hz), 1.64 (m, 2H). ^{13}C NMR: δ (ppm) = 173.12 (*C*O$_2$), 68.97 (−CO$_2$CH$_2$*C*H$_2$O−), 63.25 (−CO$_2$*C*H$_2$-CH$_2$O−), 33.64 (−CO$_2$*C*H$_2$CH$_2$CH$_2$−), 24.17 (−CO$_2$CH$_2$*C*H$_2$-*C*H$_2$−). Anal. Calcd for $C_{134}H_{218}O_{68}$: C, 55.18; H, 7.48; O, 37.34. Found: C, 54.52; H, 7.56; O, 37.04.

Poly(tetraethylene glycol adipate). ^{1}H NMR: δ (ppm) = 4.16 (t, 4H, J = 4.9 Hz), 3.63 (t, −CH_2CH$_2$OH end group, J = 4.8 Hz), 3.59 (s, 12H), 3.54 (t, −CH$_2$CH_2OH end group, J = 4.8 Hz), 2.29 (t, 4H, J = 5.7 Hz), 1.60 (m, 4H). ^{13}C NMR: δ (ppm) = 173.06 (*C*O$_2$), 72.32 (−*C*H$_2$CH$_2$OH end group), 70.34 (−O*C*H$_2$*C*H$_2$O−), 68.95 (−O*C*H$_2$CH$_2$CO$_2$−), 63.26 (−OCH$_2$*C*H$_2$CO$_2$−), 61.49 (−CH$_2$CH$_2$OH end group), 33.55 (−CO$_2$*C*H$_2$CH$_2$CH$_2$−), 24.08 (−CO$_2$CH$_2$CH$_2$*C*H$_2$−). Anal. Calcd for $C_{78}H_{138}O_{40}$: C, 54.61; H, 8.05; O, 37.34. Found: C, 54.09; H, 8.10; O, 37.93.

4,5-Dimethylcyclohex-4-ene *cis*-1,2-Dicarboxylic Anhydride Polymerizations. A 25 mL round-bottom flask was charged with the anhydride and a stoichiometric excess of diol, targeting molecular weights of 5000 g/mol. The contents of the flask were then placed under an argon atmosphere. The mixture was stirred at 160 °C using magnetic stirring until a homogeneous melt was formed. Stannous 2-ethylhexanoate (1.0 mol %) was added to the melt. The mixture was stirred for 1 h, and the pressure was reduced to 20 mmHg. The reaction was allowed to proceed at 20 mmHg for 23 h, for a total time of 24 h. The polymerization was terminated by precipitating the polymer in cold diethyl ether (−78 °C). Reactions were performed on a 10−25 g scale.

Poly(1,8-octanediol 4,5-dimethylcyclohex-4-ene cis-1,2-dicarboxylate). ^{1}H NMR: δ (ppm) = 4.05 (m, 4H), 3.62 (t, −CH$_2$CH_2OH end group, J = 3.62 Hz), 2.97 (t, 2H, J = 5.3 Hz), 2.42 (dd, 2H, J = 5.0, 16.0 Hz), 2.30 (dd, 2H, J = 4.0, 16.0 Hz), 1.60 (s, 6H), 1.29 (s, 10H). ^{13}C NMR: δ (ppm) = 173.39 (*C*O$_2$), 123.87 (−CH$_2$*C*(CH$_3$)=*C*(CH$_3$)CH$_2$), 64.50 (−CH$_2$CH$_2$*C*H$_2$CO$_2$−), 62.87 (−CH$_2$CH$_2$*C*H$_2$OH end group), 40.41 (−CO$_2$*C*H*C*HCO$_2$−), 32.68 (−CH$_2$*C*H$_2$CH$_2$OH end group), 31.87 (−*C*H$_2$C(CH$_3$)=C(CH$_3$)-*C*H$_2$−), 29.12 (−CO$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$−), 28.50 (−CO$_2$CH$_2$*C*H$_2$-CH$_2$−), 25.80 (−CO$_2$CH$_2$CH$_2$*C*H$_2$), 18.87 (−C(*C*H$_3$)=C(*C*H$_3$)−). Anal. Calcd for $C_{152}H_{242}O_{34}$: C, 69.89; H, 9.35; O, 20.84. Found: C, 69.45; H, 9.36; O, 21.16.

Poly(diethylene glycol 4,5-dimethylcyclohex-4-ene cis-1,2-dicarboxylate). ^{1}H NMR: δ (ppm) = 4.21 (m, 4H), 3.71 (t, −CH_2CH$_2$OH end group, J = 3.6 Hz), 3.64 (m, 4H), 3.56 (t, −CH$_2$CH_2OH end group, J = 4.6 Hz), 3.01 (t, 2H, J = 5.1 Hz), 2.44 (dd, 2H, J = 4.7, 15.7 Hz), 2.24 (d, 2H, J = 15.7 Hz), 1.60 (s, 6H). ^{13}C NMR: δ (ppm) = 173.19 (*C*O$_2$), 123.80 (−CH$_2$-*C*(CH$_3$)=*C*(CH$_3$)CH$_2$−), 68.89 (−CO$_2$CH$_2$*C*H$_2$O−), 63.45 (−CO$_2$-*C*H$_2$CH$_2$O−), 40.27 (−CO$_2$*C*H*C*HCO$_2$−), 31.70 (−*C*H$_2$C(CH$_3$)=C(CH$_3$)*C*H$_2$−), 18.87 (−CH$_2$C(*C*H$_3$)=C(*C*H$_3$)CH$_2$−). Anal. Calcd for $C_{130}H_{190}O_{48}$: C, 61.95; H, 7.54; O, 30.5. Found: C, 61.62; H, 7.77; O, 30.8.

Poly(tetraethylene glycol 4,5-dimethylcyclohex-4-ene cis-1,2-dicarboxylate). ^{1}H NMR: δ (ppm) = 4.20 (m, 4H), 3.69 (t, −CH_2CH$_2$OH end group, J = 4.1 Hz), 3.62 (m, 12H), 3.00 (m, 2H), 2.42 (dd, 2H, J = 4.7, 15.9 Hz), 2.22 (dd, 2H, J = 4.0, 15.6 Hz), 1.59 (s, 6H). ^{13}C NMR: δ (ppm) = 173.17 (*C*O$_2$), 123.76 (−CH$_2$*C*(CH$_3$)=*C*(CH$_3$)CH$_2$−), 70.50 (−CO$_2$CH$_2$CH$_2$O*C*H$_2$−), 68.99 (−CO$_2$*C*H$_2$CH$_2$O−), 63.52 (−CH$_2$*C*H$_2$OH), 40.23 (−CO$_2$*C*H-*C*HCO$_2$−), 31.67 (−*C*H$_2$C(CH$_3$)=C(CH$_3$)*C*H$_2$−), 18.83 (−C(*C*H$_3$)=C(*C*H$_3$)−). Anal. Calcd for $C_{100}H_{162}O_{41}$: C, 59.46; H, 8.03; O, 32.5. Found: C, 58.95, H, 8.16; O, 32.89.

Poly(ester urethane) Syntheses. A typical poly(ester urethane) synthesis with 20 or 10 wt % hard segment is as follows. All glassware was flame-dried. A solution of the polyester in 10 mL of DMAc was prepared and cannulated to an addition funnel connected to a 100 mL 3-necked round-bottom flask equipped with a mechanical stirrer. The appropriate amount of 4,4′-methylenebis-(phenylisocyanate) (MDI) (20 or 10 wt % of the prepolymer) was weighed and added to the 100 mL flask. DMAc (5 mL) was added to the flask. The prepolymer solution was added dropwise to the reaction flask with constant stirring. The reaction was heated at 80 °C for 2 h. The reaction was precipitated at 0 °C water and dried at 70 °C for 2 days. Films were solution cast from DMAc and dried at 50 °C for 1 day and then at 80 °C in a vacuum oven for 4 days.

Poly(ester urethane) with 40 wt % Hard Segment Polymerization. The reaction which utilized 40 wt % MDI required chain extender and was monitored by FTIR (disappearance of strong isocyanate signal at 2270 cm^{-1}). This reaction was terminated by 1-butanol near the completion of the reaction. No gelation occurred during any of the poly(ester urethane) syntheses.

Results and Discussion

Polyester Prepolymers. Seven polyester prepolymers were prepared for this study (Scheme 1). The first and second polymers were derived from *trans*-β-hydromuconic acid (HMA) and a calculated excess of diethylene glycol or tetraethylene glycol (**P1** and **P2**, respectively). The third and fourth prepolymers were derived from adipic acid (AA) and a calculated excess of diethylene glycol or tetraethylene glycol (**P3** and **P4**, respectively). The final three prepolymers were derived from polymerizing 4,5-dimethylcyclohex-4-ene *cis*-1,2-dicarboxylic anhydride with a stoichiometric excess of 1,8-octanediol (**P5**), diethylene glycol (**P6**), or tetraethylene glycol (**P7**) (Scheme 1). The molecular weight, polydispersity, and thermal data for these prepolymers are shown in Table 1.

The molecular weights of **P1**−**P7** based on gel permeation chromatography were within a 2 × 10^3 g/mol window, ranging from 1.5 × 10^3 to 3.4 × 10^3 g/mol. The molecular weights were all lower than the target molecular weight (5.0 × 10^3 g/mol) due to the loss of monomers under reduced pressure. These molecular weights are in a range that is well-suited for soft segments in thermoplastic polyurethanes,[1] and the polydispersities were close to 2.0 (1.7−2.1) as expected by step growth kinetics. All NMR spectra indicated that these prepolymers were terminated only by hydroxyl groups, and these end-group signals were used to calculate the $\langle M_n \rangle$. Overall there was a relatively lower molecular weight estimation by NMR analysis when compared to the GPC-based $\langle M_n \rangle$ calculations for all of the samples except **P6**. In most of the ^{1}H NMR spectra (Supporting Information), end-group signals partially overlapped with signals that corresponded to hydrogens in the polymer backbone or residual monomer, which effectively lowered the $\langle M_n \rangle$ calculations. End-group signals were clearly discernible in the ^{1}H NMR spectrum of **P6**, however, which resulted in a higher estimation of $\langle M_n \rangle$ by NMR analysis. The ^{1}H NMR spectrum of **P5** displayed the most discernible end-group signals

Table 1. Polyester Prepolymers Synthesized at 130 °C (P1−P4) or 160 °C (P5−P7), 20 mmHg, and 24 h

sample	$\langle M_n \rangle \times 10^{-3}$ (g/mol)[a]	$\langle M_n \rangle \times 10^{-3}$ (g/mol)[b]	PDI[a]	5% wt loss (°C)[c]	10% wt loss (°C)[c]	T_g (°C)[d]	yield (%)
P1	3.37	2.67	2.05	270	292	−29.2	80.4
P2	3.41	2.00	1.90	288	307	−39.3	85.2
P3	3.23	2.91	2.11	280	302	−47.2	80.2
P4	2.53	1.71	1.87	241	265	−50.0	79.5
P5	2.76	2.61	1.96	327	349	−23.9	81.6
P6	1.51	2.52	1.88	268	313	−5.0	80.5
P7	1.96	*e*	1.69	283	320	−26.4	88.3

[a] Based on GPC analysis. [b] Based on NMR analysis. [c] Based on TGA analysis. [d] Based on DSC analysis. [e] End-group signals not discernible in ^{1}H NMR spectrum.

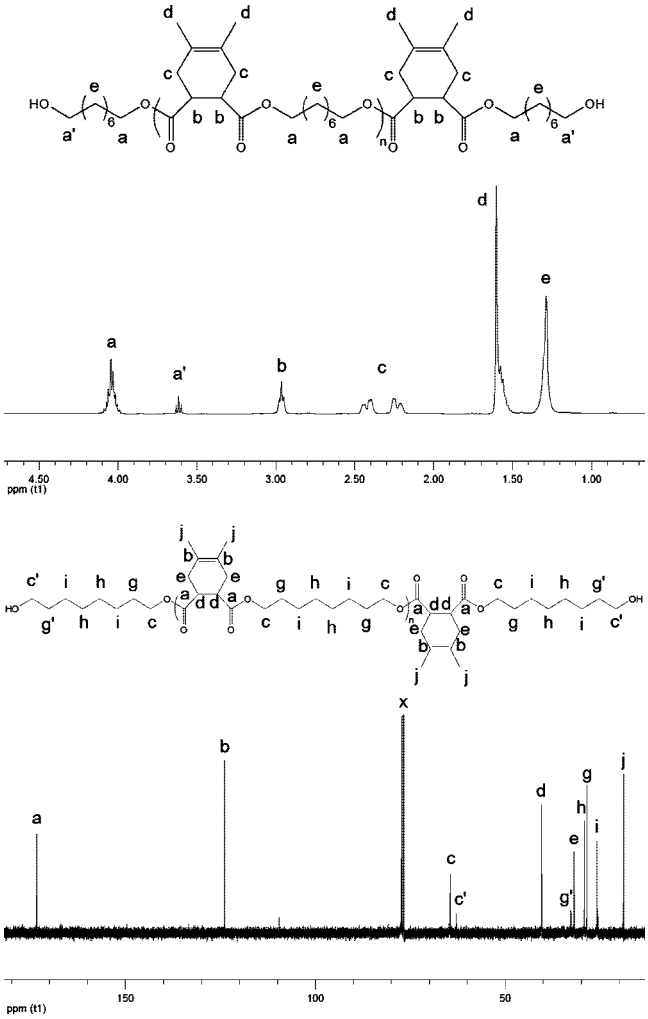
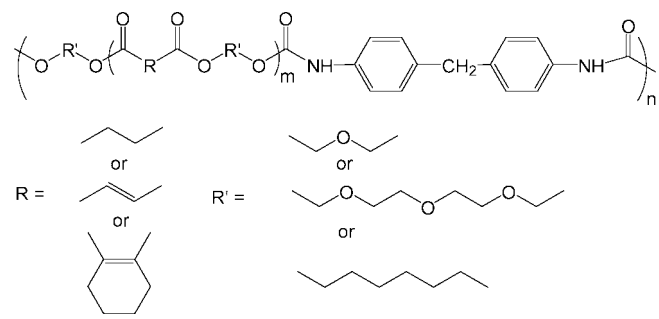


Figure 1. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **P5** (4,5-dimethylcyclohex-4-ene *cis*-1,2-dicarboxylic anhydride-1,8-octanediol prepolymer).

(δ = 3.62 ppm), which were also present in the ^{13}C NMR spectrum (δ = 62.9 and 32.7 ppm) (Figure 1). Hydroxyl end-group signals for TEG-based polymers were either absent or difficult to visualize using ^{1}H NMR analyses, yet the signals were quite evident in the ^{13}C NMR spectra (δ = 63.5 ppm). The end-group signals for the DEG-based prepolymers, although present in the ^{1}H NMR spectra, were not present in the ^{13}C NMR spectra. There was no indication of any carboxyl-terminated prepolymers using NMR analyses. Infrared spectroscopy was also used to determine that the polyester prepolymers had only hydroxyl-terminated end groups (Supporting Information). A broad peak at 3500 cm^{-1} and a sharp peak at 1735 cm^{-1} corresponded to hydroxyl groups and (ester) carbonyl groups, respectively. Stretching absorptions corresponding to carboxyl groups (3300 and 1700 cm^{-1}) were not present in the FTIR spectra. The combination of ^{1}H NMR, ^{13}C NMR, GPC, and FTIR analyses indicated that low molecular weight hydroxyl-terminated polyester prepolymers were successfully synthesized.

Scheme 2. General Structure of Poly(ester urethane)s PEU1−PEU7



All glass transition temperatures were significantly below 0 °C, with the AA-based polymers (**P3** and **P4**) having the lowest values (−47.2 and −50.0 °C). As expected, each DEG-based polymer had a higher glass transition temperature than its corresponding TEG-based polymer [T_g(**P1**) > T_g(**P2**), T_g(**P3**) > T_g(**P4**), and T_g(**P6**) > T_g(**P7**)]. While the T_g of **P6** (−5 °C) was higher than expected, it was also reproducible. Seppälä et al. demonstrated that glass transition temperatures of amorphous PEUs are dictated by the thermal transitions of their prepolymers.[33] By using 1,6-hexamethylene diisocyanate as the hard segment, a number of poly(ester urethane)s were synthesized that possessed a relatively narrow range of glass transition temperatures higher (5−15 °C) than their prepolymers. In this work, every prepolymer possessed a relatively low glass transition temperature (T_g = −50.0 to −5.0 °C). This ensures that the resulting poly(ester urethane)s have glass transition temperatures below body temperature (37 °C), meaning that the PEUs are elastomeric at physiological conditions.

Poly(ester urethane)s. A one-step method where an aromatic diisocyanate, 4,4′-methylenebis(phenylisocyanate) (MDI), reacted with the hydroxyl-terminated polyester prepolymer was utilized for our study. **PEU1A−1C** and **PEU2−PEU7** were successfully synthesized by this method (see Scheme 2). Prepolymers **P1−P7** were used to prepare poly(ester urethane)s **PEU1B** and **PEU2−PEU7**, which all contain 20 wt % hard segment. The effect of the MDI was studied by varying its content (10, 20, and 40 wt %; **PEU1A**, **PEU1B**, and **PEU1C**, respectively) for prepolymer **P1**. Because FTIR showed no strong isocyanate signal (2270 cm^{-1}) after 2 h of reaction time for those reactions using 10 and 20 wt % MDI, no chain extenders were used. A strong isocyanate peak was present, however, after 2 h of reaction time for **PEU1C**, the polyurethane which comprised 40 wt % hard segment. Therefore, 1,4-butanediol, a very common chain extender,[1] was employed, and the disappearance of the isocyanate peak was monitored using FTIR. 1-Butanol was used to terminate this reaction near its completion to avoid any gelation. The thermal and mechanical properties of the poly(ester urethane)s are shown in Table 2.

Table 2. Thermal and Mechanical Data for Poly(ester urethane)s Synthesized at 80 °C in DMAc for 2 h

sample	$\langle M_n \rangle^a \times 10^{-4}$ (g/mol)	PDI[a]	$T_g{}^b$ (°C)	$T_g{}^c$ (°C)	G^c −100 °C (GPa)	G^c 25 °C (MPa)	G^c 37 °C (MPa)	E^d (MPa)	$\gamma_{max}{}^e$ (%)
PEU1A[f]	2.7	1.5	−25.0	*j*	*j*	*j*	*j*	*j*	*j*
PEU1B[g]	6.1	1.9	−17.6	−23.0	5.82	21.1	17.6	3.44	2106[l]
PEU1C[h]	2.3	1.7	−16.0	−21.5	3.24	26.8	17.9	*j*	*j*
PEU2[i]	4.3	1.5	−28.2	−43.8	3.68	14.1	11.6	4.68	133
PEU3	6.4	1.4	−34.6	−52.1	3.43	18.1	16.0	4.41	375
PEU4	2.9	1.4	−46.2	*j*	*j*	*j*	*j*	*j*	*j*
PEU5	3.4	1.5	−0.2	−9.2	4.00	9.70	1.70	0.86	*k*
PEU6	2.5	1.4	18.5	*j*	*j*	*j*	*j*	29.3	281
PEU7	3.3	1.6	−8.0	−14.8	6.04	3.56	1.89	1.12	*k*

[a] Based on GPC analysis. [b] Based on DSC analysis. [c] Based on DMA analysis; storage modulus. [d] Young's modulus. [e] Ultimate strain. [f] 10 wt % MDI. [g] 20 wt % MDI. [h] 40 wt % MDI. [i] Number denotes which prepolymer is used as soft segment (**P2** is prepolymer for **PEU2**); **PEU2**−**PEU7** contain 20 wt % MDI. [j] Could not determine using DMA analysis or Instron analysis. [k] Mechanically failed. [l] 50 mm/min.

Molecular Weight Analysis. The molecular weights and polydispersity of these samples were measured using gel permeation chromatography with *N*,*N*-dimethylformamide as the mobile phase. All PEUs were of high molecular weights, falling within a range of $\langle M_n \rangle = 2.3-6.4 \times 10^4$ g/mol. A broad range of molecular weights for polyurethane elastomers is certainly not uncommon,[33,48] and because they were all relatively high molecular weight and above the critical molecular weight of entanglement, any differences in mechanical properties should not be due to differences in molecular weight. The polydispersity of each sample was lower than the theoretical value (PDI = 2.0). This is most likely due to these polymers being highly soluble in DMAc, the solvent used in the polymerization conditions. Upon precipitation, the lower molecular weight chains remained soluble in the good solvent, which resulted in lower PDI values.

Thermal Analysis. The one-step polyurethane synthetic method resulted in thermoplastic elastomers with a relatively broad range of thermal and mechanical properties. The glass transition temperatures of the PEUs correlated well with the thermal properties of their corresponding prepolymers and were ~15 °C higher than the glass transition temperatures of the corresponding prepolymers. The glass transition temperatures for the PEUs ranged from −46.2 to 18.5 °C. **PEU6** (4,5-dimethylcyclohex-4-ene *cis*-1,2-dicarboxylic anhydride−diethylene glycol prepolymer) displayed the highest glass transition temperature in this study (T_g = 18.5 °C), which was anticipated as its prepolymer (**P6**) also possessed a relatively high glass transition temperature (−5.0 °C). **PEU4** (adipic acid−tetraethylene glycol prepolymer) possessed a relatively low glass transition temperature (−46.2 °C) as did the prepolymer **P4** (−50.0 °C). All of the materials are in the rubbery phase at body temperature (37 °C). Using the one-step polymerization method for prepolymers with glass transition temperatures greater than ~22 °C would result in glassy poly(ester urethane)s at physiological conditions. Consequently, this method has potential use for preparing amorphous shape-memory materials for biomedical applications, which require very precise thermal transitions.[49–51]

Mechanical Analysis. The mechanical properties of these materials were quantified by DMA and Instron analysis. The storage moduli (MPa) at −100, 25, and 37 °C are listed in Table 2. The storage moduli of the PEUs were in the 10^3 MPa range at temperatures lower than the glass transition temperatures. All PEUs showed a distinct decrease in storage modulus near the glass transition temperature. The storage moduli then formed a rubbery plateau in the 10^1 MPa range at temperatures above the glass transition as shown in Figure 2, which is the DMA data generated for **PEU1B** (HMA−diethylene glycol prepolymer/20 wt % hard segment). The glass transition for **PEU1B** is clearly visible from the sharp decline in *G* and the peak in tan δ. The glass transition temperatures were measured as the maximum value of the loss modulus (not shown), which is −23.0 °C for **PEU1B**.

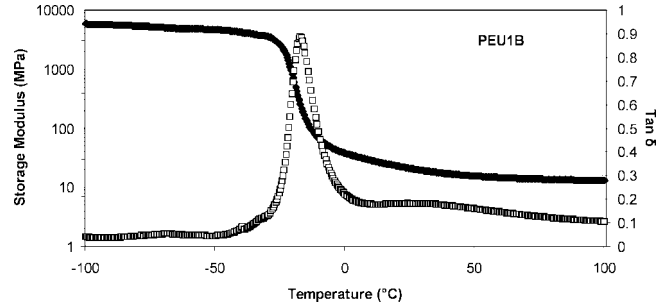


Figure 2. Storage modulus (*G*) and tan δ plotted vs temperature for **PEU1B**.

Poly(ester urethane)s with high moduli at lower temperatures did not necessarily possess good mechanical properties at higher temperatures. For example, **PEU7** possessed the highest storage modulus at −100 °C of the measurable samples, but this material had the lowest modulus at 25 and 37 °C. **PEU1A** (HMA−diethylene glycol prepolymer/10 wt % hard segment) and **PEU4** (adipic acid−tetraethylene glycol prepolymer) were too soft for DMA analysis, while **PEU6** (4,5-dimethylcyclohex-4-ene *cis*-1,2-dicarboxylic anhydride−diethylene glycol prepolymer) was too brittle for DMA analysis. It seems that a PEU containing 20 wt % hard segment possesses optimum mechanical properties because **PEU1B** (20 wt %) had sufficient mechanical properties for DMA analysis, but both **PEU1A** (10 wt %) and **PEU1C** (40 wt %) were unsuitable for DMA analysis. The DMA analyses also supported the evidence that these materials are completely amorphous, as semicrystalline polyurethanes display changes in the storage modulus and tan δ at higher temperatures.[45] The DMA data for these poly(ester urethane)s showed no such transitions at higher temperatures.

Instron analysis measured the mechanical properties using isothermal analysis. The Young's moduli of the measurable materials ranged from 0.86 MPa (**PEU5**) to 29.3 MPa (**PEU6**). **PEU1B** has remarkable elasticity with a high ultimate strain (γ_{max} = 2106%). This material did not break at a crosshead speed of either 10 or 30 mm/min and retained its original shape in a matter of seconds following those trials. This material broke only after increasing the crosshead speed to 50 mm/min. Both Seppälä[33] and Hilborn[52] synthesized amorphous poly(ester urethane)s with high elasticity (>1000%). **PEU2**, **PEU3**, and **PEU6** had ultimate strains ranging from γ_{max} = 133 to 281%, which are similar to the ultimate strain of pure elastin (γ_{max} = 200%).[42] **PEU1A**, **PEU1C**, and **PEU4** were too soft for Instron analysis while **PEU5** and **PEU7** did not give a clean break under high strain. A typical stress−strain curve obtained by Instron analysis is shown for **PEU3** (AA−diethylene glycol prepolymer/20 wt % hard segment) (Figure 3). **PEU3** had an average Young's modulus of 4.41 MPa and an ultimate elongation of 375%. When compared to standard poly(ether urethane)s

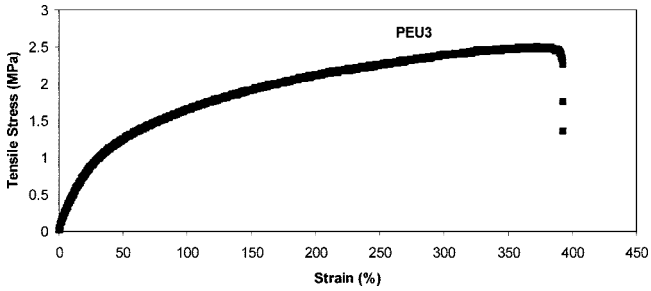


Figure 3. Tensile stress (MPa) plotted vs strain (%) for **PEU3**.

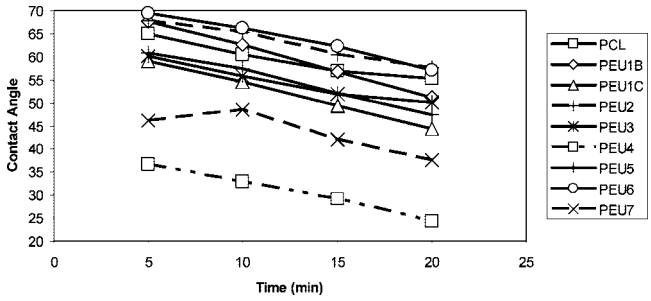


Figure 4. Contact angles of all polymer samples and poly(caprolactone) vs time.

(PTMO soft segment, MDI hard segment; $E = 18.1$ MPa, $\gamma_{max} = 675\%$),[53] **PEU1B** ($\gamma_{max} = 2106\%$) had superior elasticity and **PEU6** ($E = 29.3$ MPa) had a superior Young's modulus. Poly(ester urethane) samples **PEU1B**, **PEU2**, **PEU3**, and **PEU6** had excellent mechanical properties and are promising for use in biomedical applications.

Surface and Bulk Characterization. Thus far, we have shown a method that produces completely amorphous poly(ester urethane)s that are elastomeric at 37 °C and display excellent mechanical properties such as high elasticity and resiliency. As these materials are designed as biodegradable devices, an understanding of their surface and bulk properties is important. Previously, we have shown that the rates of degradation for poly(ester ether)s are affected by the materials' hydrophilicity and water uptake.[46] Here, we measured the contact angles formed by water droplets placed on the PEU surfaces over a 20 min time period. The contact angle measurements for the PEUs were compared with that of poly(caprolactone) (PCL) (Figure 4).

For the purpose of clarity, the PEUs are divided into two groups: those that derive from poly(ester ether) prepolymers (**PEU1B**, **PEU1C**, **PEU2**, **PEU3**, and **PEU4**) and those that derive from the polyesters bearing cyclic moieties (**PEU5**, **PEU6**, and **PEU7**). The contact angles differ as such: [**PEU2** (most hydrophobic) > **PEU1B** > **PEU3** > **PEU1C** > **PEU4** (most hydrophilic)] and [**PEU6** (most hydrophobic) > **PEU5** > **PEU7** (most hydrophilic)]. Most of these materials were hydrophobic, as they were in the same range as PCL ($\theta_{5min} = 65°$). All contact angles decrease as time increases due to the droplets spreading on the polymer surfaces. To compare the surface properties with the bulk properties of these materials, water uptake data were recorded over a 3 day period (Supporting Information). The water uptake data differ as such [**PEU2** (most water uptake after 3 days) > **PEU1B** ~ **PEU3** > **PEU1C** > **PEU4** (least water uptake after 3 days)] and [**PEU7** (most water uptake after 3 days) > **PEU5** > **PEU6** (least water uptake after 3 days)]. These results certainly show that, for the poly(ester urethane)s containing poly(ester ether) soft segments, the surface properties differ from the bulk properties. The components for all of these materials include hydrophilic soft segments and hydrophobic aromatic hard segments,[41] and the relative amounts of each may differ at the polymer surface and in the bulk when wet. Previous studies have shown that copolymers or polymer blends often exhibit the surface segregation phenomenon, a process in which lower energy constituents adsorb preferentially at the surface in order to lower the overall surface free energy.[54–60] Other studies have confirmed that polyurethanes exhibit surface restructuring upon contact with water.[61,62]

Although the contact angle measurements indicated unique surface properties, further experiments were required to determine whether any phenomenon was occurring during the contact angle measurements. Contact angle measurements are rather qualitative and time-dependent; therefore, X-ray photoelectron spectroscopy (XPS) analysis of the surface was obtained to further elucidate the surface properties of the materials discussed here. Because there were no nitrogen atoms in the prepolymers, the nitrogen content of the samples shows the relative urethane concentrations (hydrophobic hard segments) at the surface of dry PEU films. The XPS data revealed that the nitrogen content for **PEU2** = 1% and **PEU4** = 2%. These data support that the materials derived from the poly(ester ether) prepolymers are in fact undergoing the surface segregation phenomenon during the contact angle measurements. If this phenomenon was not present, **PEU4** would have a higher contact angle than **PEU2** because the hard segment content in **PEU4** is relatively more concentrated at the surface of a dry sample. The class of poly(ester urethane)s which derive from prepolymers bearing cyclic moieties are slightly more complicated due to the relatively high T_g of **PEU6**. Contact angle measurements are affected at temperatures near the glass transition temperature,[63] and the interfacial energy and glass transition temperature for polymer films are directly proportional.[64] Because of this, it is still not yet determined whether the second class of materials exhibit the surface segregation phenomenon as well as whether it is the soft segment cyclic moieties or the thermal properties that most affect the surface properties of **PEU5**, **PEU6**, and **PEU7**.

Degradation Studies. As these poly(ester urethane)s differ in terms of thermal properties, mechanical properties, and hydrophilicity, they degraded at different rates in an in-vitro degradation study. Samples were left in a phosphate buffer medium (pH = 7.4) at 37 °C for 6 weeks, and the medium was changed weekly. Three PEUs (**PEU1A**, **PEU2**, and **PEU4**) degraded within that time period (Figure 5).

Kinetic analysis was conducted using zero-order kinetics in addition to first-order kinetics because hydrolysis of polyesters have been explained using both methods.[46,65] Both **PEU1A** and **PEU2** degraded according to zero-order kinetics; however, **PEU4** did not degrade according to either zero-order or first-order kinetics for the entire degradation study. The degradation profile of **PEU4** exhibited a sharp increase in mass lost for the first week followed by a more linear increase for the remainder of the experiment. The nonlinear degradation profile of **PEU4** can best be explained using the results from the contact angle studies, water uptake studies, and XPS studies. These studies showed that these materials exhibited a surface segregation phenomenon, meaning that a material's surface was quite different from its bulk in an aqueous environment. The degradation profile indicates that the surface of **PEU4** degraded at a faster rate than the bulk. Gardella, Jr., et al. demonstrated how the surface degradation kinetics differ from that of the bulk for biodegradable polyesters.[66] During a material's degradation time, an initial "induction" period is present that is dominated by surface and interfacial reactions until the equilibration of water penetration and absorption leads to bulk degradation processes. This "induction" period is present for all samples; thus, the discrepancy in the profile of **PEU4** during the first 7 days is more likely due to the low mechanical properties of the

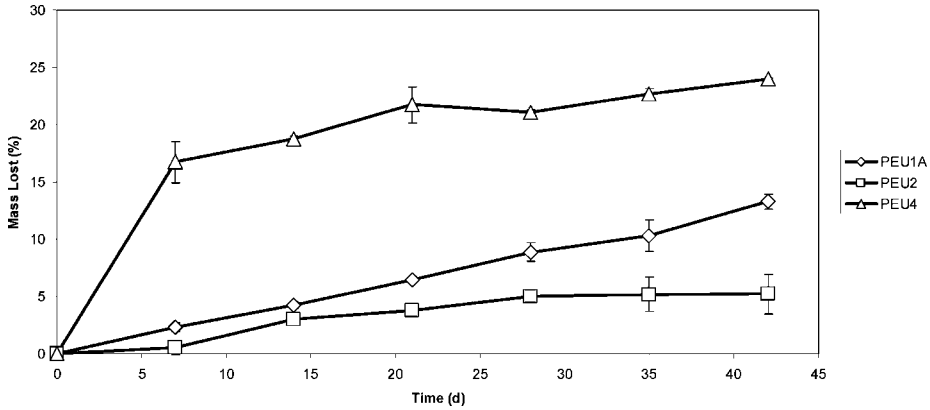


Figure 5. Mass lost (%) plotted vs time (d) for **PEU1A**, **PEU2**, and **PEU4**.

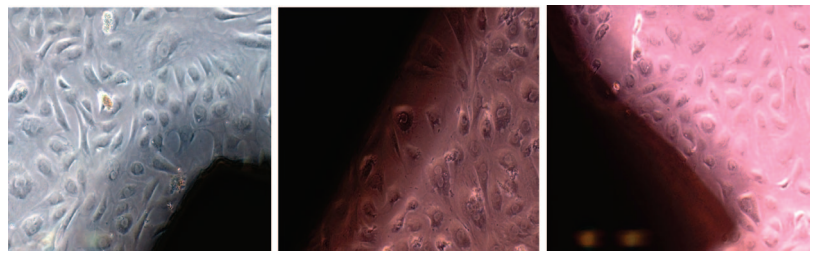


Figure 6. Autoclave-sterilized **PEU2** (left), autoclave-sterilized **PEU3** (middle), and ethanol-sterilized **PEU3** (right). Darker portions of image(s) are the polymer sample(s).

hydrophilic surface (4.5% mass lost by simply washing a 0.15 g of sample with H_2O). Because both zero-order or first-order rate laws do not apply for the entire span of the experiment for **PEU4**, zero-order rate laws were applied to each profile following the first week (0.31, 0.13, and 0.19% mass lost/day for **PEU1A**, **PEU2**, and **PEU4**, respectively). The rate of **PEU1A** may be explained by its relatively lower content of hydrophobic hard segment. The % mass lost for **PEU2** and **PEU4** measured after 100 days was 12.2% and 29.9%, respectively, which correlate well with what the zero-order kinetic analyses predicted (13.3% and 35.5%). None of these materials displayed a "burst effect", which is prevalent in many poly(ester urethane)s.[33,37] **PEU2** is an extremely promising material as it possesses good mechanical properties ($E = 4.68$ MPa, $\gamma_{max} = 133\%$) and a linear degradation profile. **PEU1A**, **PEU2**, and **PEU4** are among the fastest degrading poly(ester urethane)s recorded to date.

Cytotoxicity Studies. Studies have shown that aromatic-based polyurethanes, if treated under harsh, basic conditions, can produce aromatic amines, which are highly toxic. There has been contradictory evidence disputing (1) whether this happens in the human body and (2) whether the amounts are at toxic levels.[1] The alternative to this possibility is the use of an aliphatic isocyanate, as aliphatic amines are less detrimental in biological environments. However, by using an aliphatic diisocyanate, there is loss in mechanical and thermal properties. Our studies have shown that aliphatic diisocyanates are unsuitable for our one-step method of preparing amorphous poly(ester urethane) thermoplastic elastomers with high mechanical integrity.

Because of the evidence indicating that aromatic-based polyurethanes are cytotoxic, the cytotoxicity characteristics of these materials were tested using two methods. The first being a minimum essential medium elution test. The materials were extracted with a minimum essential medium for 24 and 48 h at physiological conditions. The extracts were then placed on confluent monolayers of L-929 mouse fibroblast cells. All poly(ester urethane)s scored 0, indicating no cytotoxic response, with the exception of **PEU7**. **PEU7** was repeatedly characterized as severely cytotoxic even after rigorous drying or several extractions. It is still not well understood as to why this particular sample was cytotoxic. There was no difference in the cross-link density of **PEU7** when compared to the other materials in this study, as all reactions containing 20 wt % hard segment were carried out to completion. Also, the molecular weight, mechanical properties, or structural features of this material give no further reasoning as to why this particular sample was cytotoxic. Further testing is required to better explain this anomaly.

The second method was used only for samples **PEU2**, **PEU3**, and **PEU7** and was designed to test how these materials responded under different sterilization methods. **PEU2** and **PEU7** were autoclaved; **PEU3** was partitioned into two samples: one was chemically treated (ethanol), and the other was autoclaved. They were then separately incubated in the presence of rabbit endothelial vascular cells (REVC) for 1 week. **PEU7** could not be tested because autoclaving proved too harsh of a sterilization method, which made this sample unsuitable for handling. This was not surprising as **PEU7** had a relatively low modulus, even at 37 °C (Table 2). The autoclave-sterilized **PEU2**, autoclave-sterilized **PEU3**, and ethanol-sterilized **PEU3** are all nontoxic, as shown in Figure 6. The figure clearly shows that autoclaving methods of sterilization are not detrimental to those samples with sufficient moduli. There are no signs of either sterilization method inducing any cytotoxic response from the materials, as there was zero cell death. This test demonstrated that two poly(ester urethane)s, **PEU2** and **PEU3**, show no cytotoxicity even after 1 week of incubation with the REVC cells. These initial cytotoxicity tests indicate that these materials are promising for biomedical purposes; however, further testing is required for these materials to ascertain whether they are biocompatible.

Conclusions

A one-step method has been used to prepare versatile degradable, amorphous poly(ester urethane) thermoplastic elas-

tomers with novel soft segments without the use of a chain extender. These materials show a wide range of mechanical properties, including materials that have a high modulus (E = 29.3 MPa) and high elasticity (γ_{max} = 2106%). These materials displayed a surface segregation phenomenon when in contact with aqueous solutions. Three poly(ester urethane)s, **PEU1A**, **PEU2**, and **PEU4**, showed appreciable degradation at 37 °C during the 6 week study and possessed relatively fast degradation rates. Studies on **PEU2** and **PEU3** showed that different methods of sterilization do not induce cytotoxic behavior in these materials. Current efforts are being made toward synthesizing amorphous degradable thermoplastic poly(ester urethane)s with shape-memory properties.

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Supporting Information Available: Detailed characterization data, including NMR spectra, IR spectra, Instron analysis, water upate data, XPS data, and kinetic analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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