Toward Cross-Linked Degradable Polyester Materials: Investigations into the Compatibility and Use of Reductive Amination Chemistry for Cross-Linking

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Introduction

The elegant design, functionalization, and thorough characterization of nanostructured materials allows for their investigation as biomedical devices such as drug delivery vessels,[1−3] biological sensors,[4,5] imaging agents,[6−8] and tissue culture matrices[9,10] and for many other applications. The abilities to construct precisely and characterize accurately these materials are of great importance as nanoobjects become tools for the investigation of complicated biological assemblies and important components of treatment strategies for various disease states.[11]

Nanomaterials have been synthesized through many clever routes and take the form of dendrimers,[12,13] star polymers,[14,15] branched and hyperbranched polymers,[16−18] micelles and cross-linked nanoparticles,[19−21] graft copolymers,[22] and single chain nanoparticles,[23−25] among others. Some strategies have allowed for the presentation of various functional groups that can be used for further modification including decoration of the nanostructures with biologically relevant drugs, imaging agents, antigens, proteins, and targeting ligands.

Significantly, the size, morphology, and chemical nature of these nanoconstructs have been shown to be factors in the biological function and fate of the materials, directing current syntheses to target specific size regimes and compositions. In addition, investigations into the *in vivo* fate of the nanostrucutres have shifted the synthetic focus toward biocompatible, biodegradable materials. To advance such materials toward being environmentally responsible, as well as having biologically inert and resorbable degradation products, compositions based on polyesters have received significant attention.

Poly(ϵ-caprolactone) (PCL), polylactide, and polyglycolide are commonly studied as materials to address the degradability, environmental waste, and biocompatibility of synthetic polymers. Our recent efforts have focused upon the transformation of PCL materials into discrete nanoscale objects. The mechanical and degradation properties of PCL can be tuned by the synthesis of random and block copolymers, blends and cross-linked materials. Given the breadth of synthetic variability and diversity of functional monomers[26−29] that have been demonstrated for PCL, it was an ideal material for the development and study of synthetic biodegradable nanostructures whose shape and morphology are stabilized by covalent cross-links. Cross-linked nanoparticles and gel materials have already been reported,[23,30−33] each resulting from the incorporation of a functional caprolactone monomer. Rather than developing a new synthetic monomer for each specific application, we sought to utilize the protected 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO) monomer reported by Jérôme and co-workers[34] to generate a platform PCL system[26] containing ketone carbonyls for post-polymerization modification by amino compounds (e.g., peptides or proteins containing lysine residues, amino-functionalized synthetic molecules, etc.) to yield a diverse array of functional and cross-linked materials through reductive amination. Described herein are results from polymer and small molecule studies that focus on evaluating the compatibility of reductive amination chemistry for the solution state synthesis and cross-linking of functional, hydrolytically degradable γ-keto ester containing PCL nanomaterials.

Results and Discussion

Overall Design Strategy. The general strategy for the preparation of well-defined and hydrolytically degradable nanoparticles was based upon the seminal developments of Hawker, Miller, and co-workers[23,24] for the preparation of well-defined nanoparticles via solution-state collapse and covalent stabilization of single polymer chains. Our intention was to produce intramolecularly cross-linked hydrolytically degradable random copolymers with incorporated functionality by reaction with nucleophilic difunctional small molecules that were commercially available or easily produced (Figure 1). The synthesis employed electrophilic ketone bearing repeat units distributed randomly along the backbone of PCL, which were designed to undergo subsequent reductive amination reactions with diamines to establish the intramolecularly cross-linked nanoparticles, **1** (Scheme 1). Control reactions were also conducted, between the keto-functionalized PCL and monoamines, to give alteration in the composition but with an absence of cross-linking.

A two step synthetic route involving ring opening copolymerization and deprotection was followed to construct the ketone-functionalized polyester, poly(ϵ-caprolactone-*co*-2-oxepane-1,5-dione) P(CL-*co*-OPD), which then served as the reactive polyester. Specifically, aluminum triisopropoxide was employed to initiate the ring-opening copolymerization of TOSUO,[34−37] a ketal-containing monomer, **2**, and ϵ-caprolactone to yield random copolymers **3**, of two different degrees of polymerization and each containing ca. 10% of the repeat units having latent functionality. Removal of the ketal protecting groups was achieved using triphenylcarbenium tetrafluoroborate to afford backbone ketone-bearing copolymers, **4a** and **4b**. The ketones of **4** were then used as reactive carbonyls to conduct the proposed intramolecular cross-linking of individual PCL chains in solution.

The accessibility and selective reactivity of the ketone units to attack by nucleophilic aminooxy-functionalized poly(ethylene oxide)s (mPEO−O−NH_2)[38] and various functional hydrazines[39] have been demonstrated, involving random copolymers of similar composition to those utilized in this work, to establish ketoxime ether- and hydrazine-linked graft copolymers. These

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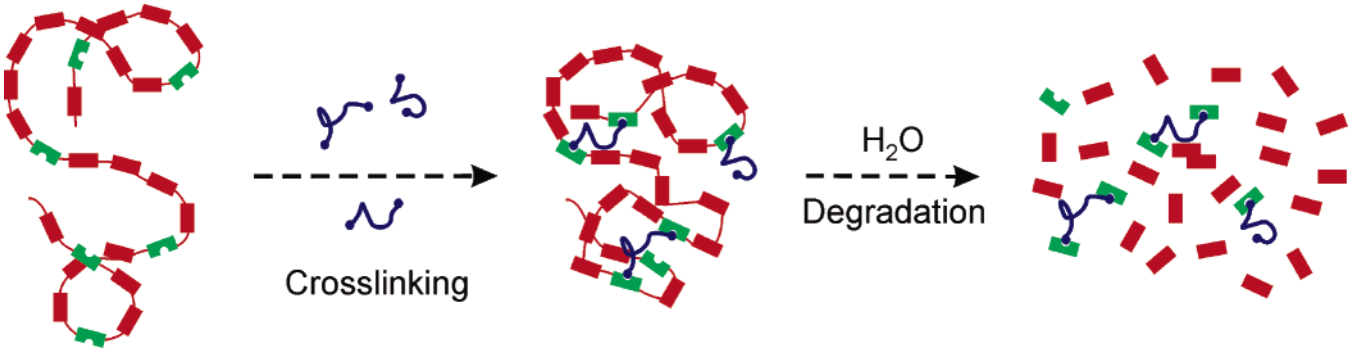
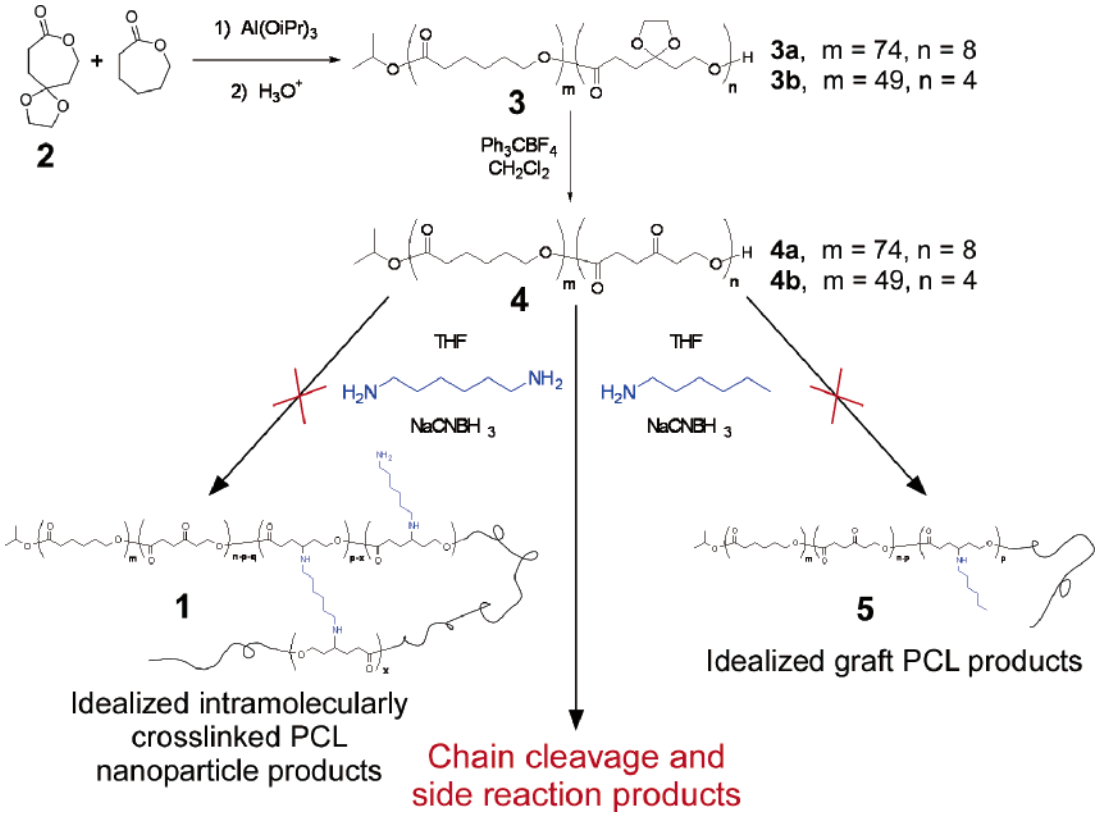


Figure 1. Schematic representation of a collapsed random copolymer cross-linked and functionalized using a difunctional small molecule and subsequent degradation by hydrolysis.

Scheme 1. Proposed General Synthesis of Cross-Linked or Graft Materials from a Ketone-Containing Random Copolymer with Diamines or Monoamines, Respectively, by Reductive Amination



methods for selective post-polymerization modification through a single incorporated monomer unit exemplify the interesting kinds of macromolecular structures that can result from strategic combination of established chemistries and unique polymer templates.

Alternatively, reductive amination experiments have been conducted in our laboratory to explore the covalent functionalization and cross-linking of the polyester materials using commercially available and, potentially, biologically derived amines. The P(CL-*co*-OPD) copolymers, **4a** and **4b**, in 40−50 wt %[40] tetrahydrofuran (THF, which was selected due to its property of being a solvent for PCL but a partial solvent for CL−OPD copolymers[41]) were allowed to undergo reaction with 1,6-hexanediamine in the presence of $NaCNBH_3$. (The selective reductive abilities of $NaCNBH_3$ and $NaBH(OAc)_3$ are well documented in the literature,[42−44] with little or no direct reduction of ketones and esters at neutral pH, whereas the imine/iminium ion is easily reduced in the pH 6−8 range.) Additionally, an amine to ketone ratio range of 1.0−2.0 was explored to allow for the possible incorporation of residual amine groups after the diamine reactions, enabling further functionalization following cross-linking. In an effort to distinguish potential changes in the material properties arising from chemical differences due to reductive amination from those resulting from possible cross-linking, the P(CL-*co*-OPD) polymer **4a** was also functionalized with hexylamine under the same reductive amination conditions. Comparisons were made between the parent polymers and the products from reaction with either 1,6-hexanediamine or hexylamine. Characterization of the reaction mixtures and isolated products by a combination of ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopies, gel permeation chromatography (GPC), infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) allowed for determination of the composition and structure of the products, which included **1**, **5**, and several side products. The following discussion details the results that allowed for determination of the presence of unwanted products, resulting from side reactions and chain cleavage reactions, together with small molecule model studies that provided insight into the chemistries occurring.

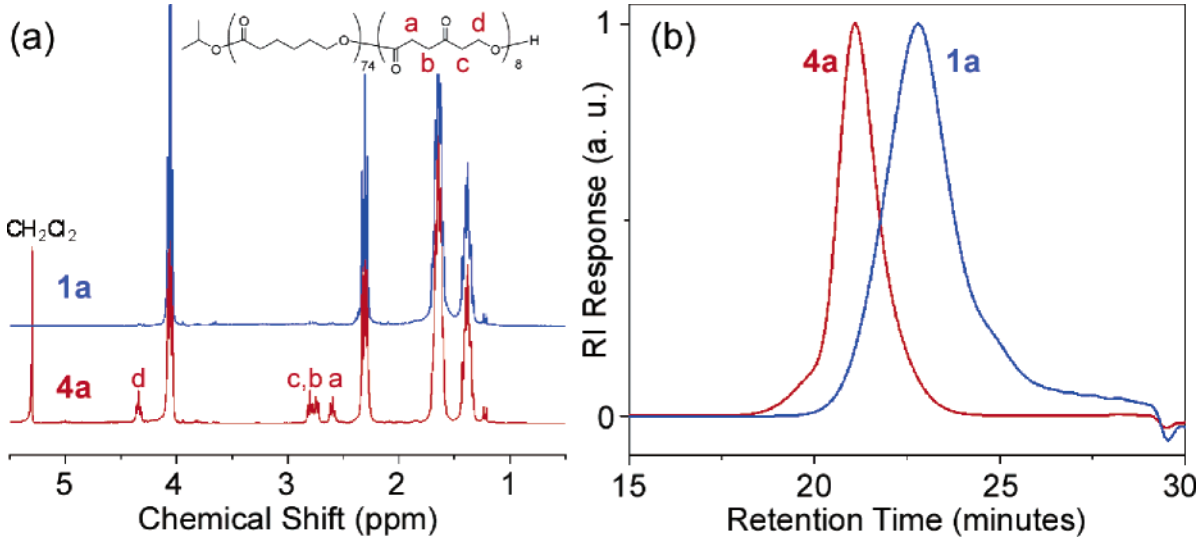


Figure 2. (a) ^{1}H NMR spectra overlay and (b) GPC traces for P(CL$_{74}$-*co*-OPD$_8$), **4a**, and products isolated by precipitation after reaction of **4a** with 1,6-hexanediamine and $NaCNBH_3$ to yield **1a**.

Polymer Characterization Studies. A comparison of the ^{1}H NMR spectra of P(CL-*co*-OPD) copolymers **4a** and **4b** before and after reaction with 1,6-hexanediamine in the presence of $NaCNBH_3$, with subsequent isolation by precipitation from MeOH (Figure 2a and Supporting Information Figure S1a, respectively), demonstrated that a reaction between the ketone bearing repeat units and the 1,6-hexanediamine had indeed occurred. The resonances of the methylene protons associated with the ketone bearing OPD units decreased in intensity, while other broad resonances from 2.5 to 3.5 ppm and from 1.5 to 2.0 ppm grew in. Interestingly, the GPC traces depicted in Figure 2b and Supporting Information Figure SI1b, respectively, showed apparent reductions in the molecular weights of the polymer products after reactions with the diamine. Such shifts to lower apparent molecular weight have been reported for other single chain cross-linking syntheses.[23−25] Infrared spectroscopy characterization of the copolymer **4a** and the corresponding product **1a** (Supporting Information Figure SI2) indicated perhaps a subtle presence of amine and/or amide groups, observed as a slight broadening and increased intensity of the N−H stretch in the 3000−3500 cm^{-1} region and a small peak at 1560 cm^{-1}. Changes in the carbonyl region of the IR spectrum also suggested reaction through the ketone bearing OPD units, as noted by a narrowing of the overall carbonyl peak with reductions in the ketone shoulder at 1713 cm^{-1} and the ester stretch at 1737 cm^{-1}. However, the breadth of the carbonyl band complicated further analysis to determine whether side reactions, for instance amide or lactam formation, had occurred in these polymer samples.

Comparison of the ^{1}H NMR spectra of the P(CL-*co*-OPD) polymer **4a**, 1,6-hexanediamine-functionalized sample **1a**, and hexylamine-grafted sample **5a** (Figure 3) illustrated reaction of both the diamine and monoamine through the ketone functional groups, as indicated by a loss of the parent methylene resonances. In the case of the hexylamine grafted material **5a**, two additional resonances were observed at 0.9 and 1.3 ppm, suggesting the presence of the aliphatic tails from the hexylamine units. Surprisingly, GPC analysis (Figure 4b−d) of the grafted material, **5a**, gave rise to a chromatogram peak of similar shape and polydispersity to the diamine reductive amination product **1a**, relative to the parent copolymer **4a**. This result led us to examine the MeOH filtrates of the precipitated polymer products by ^{1}H and ^{13}C NMR spectroscopies and GPC (Figure 4e). Complicated mixtures of small molecule byproducts and

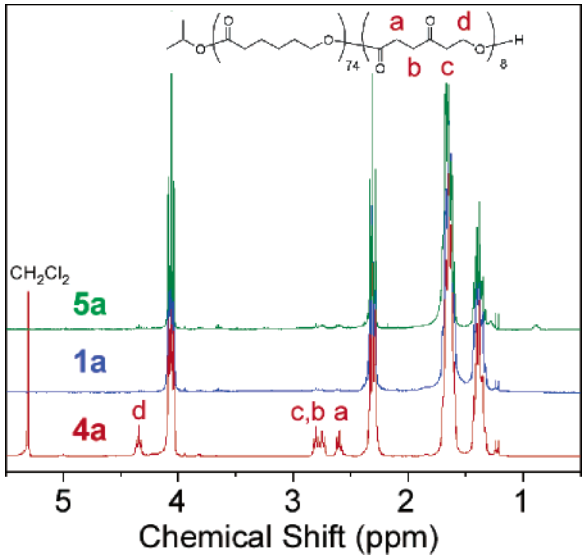


Figure 3. Overlay of ^{1}H NMR spectra of (a) P(CL$_{74}$-*co*-OPD$_8$), **4a**, and products isolated by precipitation after reaction of **4a** with (b) 1,6-hexanediamine and $NaCNBH_3$, **1a**, and (c) hexylamine and $NaCNBH_3$, **5a**.

oligomers were detected by these techniques, demonstrating that significant degradation of the polyester backbone was occurring for the P(CL-*co*-OPD) copolymer samples, affording product mixtures for **1a** and **5a**. Similar results were obtained for **4b**, giving product mixtures for samples isolated from reaction mixtures **1b** and **5b**.

Under the reductive amination conditions, several mechanisms that yield polymer backbone cleavage have been considered[45−47] including various inter- and intramolecular transesterifications and amidation. Further examination of the literature[48,49] revealed evidence for facile lactam formation after successful reductive amination of γ-keto ester units with primary amines, resulting in either chain cleavage (Scheme 2, route 1) or rearrangement of the polymer backbone (Scheme 2, route 2). Control reactions, detailed in the following paragraphs, were performed first on polymer samples and then on small molecules to eliminate and confirm the nature of the potential side reactions that could lead to degradation products.

As a model study to determine the stability of the PCL backbone under these reductive amination reaction conditions,

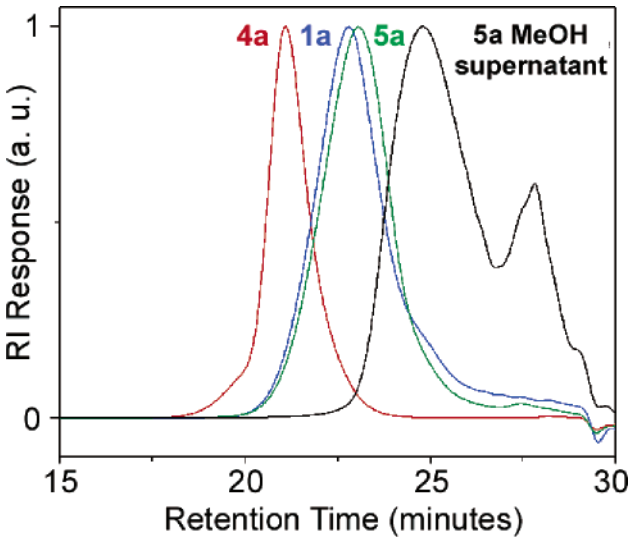


Figure 4. GPC traces for (a) P(CL_{74}-*co*-OPD_8), **4a**, and products isolated as the (b) precipitate after reaction of **4a** with 1,6-hexanediamine and $NaCNBH_3$, **1a**, (c) precipitate after reaction of **4a** with hexylamine and $NaCNBH_3$, **5a**, and (d) MeOH supernatant after reaction of **4a** with hexylamine and $NaCNBH_3$, **5a**.

a homopolymer of PCL was prepared of similar molecular weight to the P(CL-*co*-OPD) random copolymer **4b** and was tested using various combinations of amine, diamine and/or reducing agent. Results obtained from ^{1}H NMR and GPC analysis (Supporting Information Figure SI3) suggest that the PCL-rich segments of **4a** and **4b** would be stable under these conditions, and the observed degradation of the P(CL-*co*-OPD) polymers was selective for the OPD ester units.

The individual actions of the amine/diamine and reducing agent on the ketone bearing copolymers were then investigated. In two separate experiments, P(CL-*co*-OPD) copolymer **4a** was allowed to undergo reaction with a 10-fold excess of $NaCNBH_3$ and with 0.75−1.0 equiv of hexylamine, independently, in THF solution for 24 h. It was found that the reducing agent did not significantly degrade the polymer or reduce the ketone groups in the 24 h period. However, reaction of the OPD units with hexylamine did occur in the absence of the reducing agent to yield crude ^{1}H NMR spectra containing resonances associated with imine formation and GPC traces similar to the parent polymer.

Important information regarding the composition and structure of the polymers were inferred from their thermal properties gathered through TGA and DSC for solid-state products isolated from MeOH precipitation of reaction mixtures from **1** and **5**. Specifically, higher thermal stability was exhibited by both the 1,6-hexanediamine-functionalized materials, **1a** and **1b**, and the hexylamine-functionalized polymers, **5a** and **5b**, during thermogravimetric analysis (Supporting Information Figure SI4). This change in the thermal degradation is likely due to the suppression of the lower temperature pyrolysis observed for the γ-keto ester groups in OPD containing copolymers, as was previously reported by Jérôme and co-workers.[41] Moreover, a significant fraction (5−10%) of the polymer mass degraded at higher temperatures (T_d maximum from the first derivative curve $\sim$ 450 °C) from the diamine functionalized materials **1a** and **1b**. The exact chemical nature of the component degrading at higher temperature has not been identified, but may result from the introduction of amides or lactams, exhibiting a thermal decomposition similar to aliphatic poly(ester amide) materials.[51] The melting transitions of the reaction products, as observed by DSC (Figure 5b), suggested a change in the material structure after reductive amination with the monoamine and diamine since lower temperatures induced melting in the polymers. It is also noteworthy that multiple melt transitions were observed for the diamine reductive amination products **1a** and **5a**, most likely the result of chain cleavage through the OPD repeat units and formation of smaller PCL crystallites from the lower molecular weight polymer products. Although more difficult to discern (Figure 5a), the presence of products resulting from cleavage/side reactions was also supported by effects upon the glass transition temperatures (T_g).

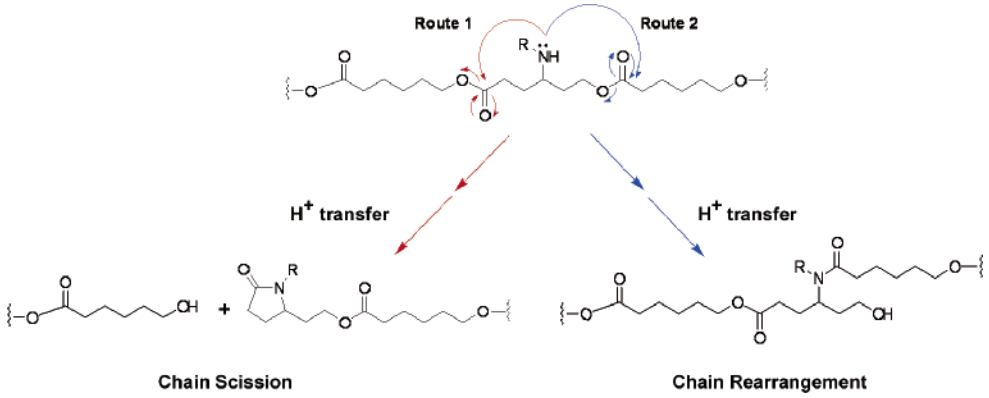
The data presented in this work have demonstrated the incompatibility of the OPD units with reductive amination chemistry, and, thereby, eliminated the original strategy for the preparation of intramolecularly cross-linked particles from commercially available primary amines. However, the characterization data obtained for the polymer systems are complicated by the remainder of the polymer backbone and the difficulties encountered when working with macromolecular species. To simplify the chemical reaction possibilities, to eliminate problems associated with populations of soluble and insoluble components, and to deduce the chemical reactions occurring for the γ-keto ester units, small molecule model studies were undertaken.

Small Molecule Model Studies. A series of small molecule model studies was conducted using 2-butanone, a model aliphatic ketone, and methyl levulinate, a model for a portion of the OPD unit with an aliphatic γ-keto ester combined functional group. Each model compound was allowed to undergo reaction with the reducing agent $NaCNBH_3$ alone or hexylamine alone or under the previously utilized hexylamine reductive amination conditions. The reaction mixtures were analyzed by ^{1}H and ^{13}C NMR spectroscopies to monitor the progress of each reaction and to resolve possible side reaction products. This subsection details the results of the small molecule studies and correlates the findings to the results of the polymer systems.

The extent of ketone and ester reduction by $NaCNBH_3$ was achieved through exposing 2-butanone and methyl levulinate, independently, to 0.2 and 1.0 equiv of $NaCNBH_3$ in THF solution. Neither compound was reduced extensively, even at 1.0 equiv, although various sharp doublets were observed between 1.0 and 1.5 ppm in the baseline of the ^{1}H NMR spectra, possibly arising from the methyl group adjacent to the formed secondary alcohol (Figure 6**a**).

In a similar fashion, 2-butanone and methyl levulinate were incubated, independently, with hexylamine at 0.2 and 1.0 equiv in THF solution to investigate imine formation. At low equivalents, no free hexylamine was detected by ^{1}H NMR spectroscopy (Figure 6b) after 24 h of reaction, and new resonances appeared at 3.2, 2.65, and 1.8 ppm for the two methylenes and the methyl group protons, respectively, in the newly formed methyl levulinate imine derivative. ^{13}C NMR spectroscopy further substantiated the imine presence, with a new ester carbon resonance at 173.7 ppm, an observed imine carbon resonance at 169.5 ppm, and new resonances for the α-methylene carbons of the two imine isomers at 51.1 and 50.9 ppm. The experiments performed at a stoichiometric equivalence of amine and ketone contained residual free amine in the reaction mixture and underwent little detected change after 12 h of reaction. Such an equilibrium position may be driven to completion through the use of drying agents (molecular sieves, drying salts, etc.), which may be important in the polymer modification strategy, but was not attempted in these model studies. Additionally, careful examination of the ^{1}H and ^{13}C NMR

Scheme 2. Proposed Side Reactions of the Secondary Amine Reductive Amination Product Leading to Chain Scission (Route 1) and Chain Rearrangement (Route 2) Products, Respectively



spectra did not yield evidence for significant aminolysis in the case of methyl levulinate, signifiying the stability of the ester moiety of this molecule to stoichiometric amine equivalents.

Combining the use of hexylamine in THF solution with the presence of $NaCNBH_3$ for model small molecules, 2-butanone and methyl levulinate, allowed for interrogation of the grafting reductive amination conditions. Even at low equivalents of amine and reducing agent, a mixture of products was observed for 2-butanone, including resonances from starting material, hexylamine, imine adduct, and possibly some reduced amine or secondary alcohol products, all of which were amplified at higher equivalents. Methyl levulinate is a more accurate model of the OPD repeat unit and, therefore, was of interest to probe the ketone and/or ester functional group selectivity and the potential for intramolecular aminolysis under the reductive amination conditions. Multiple products were detected by NMR spectroscopy with additional complexity being added by the possibility of forming amides and lactams and lactones from intermediate secondary amines and secondary alcohols, respectively.

Figure 6c depicts the ^1H NMR spectra for the low and stoichiometric equivalence reactions carried out for methyl levulinate and hexylamine in the presence of $NaCNBH_3$, along with the structures for some probable reaction products (for simplification, stereochemical differences are neglected). A significant fraction of imine product (~10%) was observed in aliquots for both reactions analyzed at the 12 h timepoint, but decreased in intensity after 24 h of reaction. Some small multiplet and broad resonances were visible between 4.5 and 5.0 ppm, although the chemical shift did not suggest that they were the result of a reduced imine to form a secondary amine, which would be expected to appear in the 2.7−2.9 ppm region. Similar resonances in the ^1H NMR spectra (Supporting Information Figure SI5) were observed while monitoring the crude mixtures of the polymer functionalization attempts and may result from ketone reduction to secondary alcohols followed by facile intramolecular cyclization to yield lactone products. Moreover, ^{13}C NMR spectroscopy of the reductive amination reaction mixture at 1.0 equiv of hexylamine to ketone lacked imine carbonyl and α-methylene resonances but contained many new resonances in the aliphatic region. Signals were detected near 54 and 47 ppm, possibly due to the formation of reduced secondary amine methine and methylene carbons, respectively.

Also significant for achieving insight into the polymer system chain cleavage and degradation, new ^{13}C NMR resonances were noted at 175.5 and 44 ppm and between 31 and 32 ppm, which were attributed to amide or lactam **C**ONR, CONR**C**H_2 and CONRCH$_2$**C**H_2 carbons, respectively. Unfortunately, corresponding proton signals were not easily resolved in the ^1H NMR spectra, due to overlap with the primary and secondary aliphatic amine resonances. Such aminolysis may be the result of intramolecular delivery of the amine group to the ester through initial imine formation, which allows for the establishment of a five-membered ring between the imine nitrogen and the carbonyl carbon of the corresponding ester. This mechanism was proposed previously for the unusually facile aminolysis of β-keto ester small molecule derivatives.[45] Even more likely is the intramolecular aminolysis reaction[46] for an intermediate γ-amino ester, which would afford 1-hexyl-5-methyl-2-pyrrolidinone by "reductive lactamization."[48] The presence of lactam/pyrrolidinone products was confirmed by column chromatography purification of the reaction mixture and characterization of the isolated products by ^1H and ^{13}C NMR and IR spectrocopies.

While characterization of the small molecule products was greatly simplified relative to the chemistry between 1,6-hexanediamine and P(CL-*co*-OPD) copolymers, the reductive amination of methyl levulinate with hexylamine and $NaCNBH_3$ in THF solution under ambient conditions did not deliver selective, clean, and complete conversion of the γ-keto ester functionality to a γ-amino ester without lactamization. Previous studies support the proposed lactamization side reactions. Specifically, reduction of the ketone moieties to afford secondary alcohols gamma to the ester linkages yields chain cleavage and rearrangement products through intramolecular lactone formation.[47,52] Therefore, reductive amination under these conditions using primary amines does not provide the requisite reactive discrimination and control demanded in the synthesis of PCL cross-linked materials from P(CL-*co*-OPD) precursors outlined in our strategy; functionalization using amines by reductive amination may be possible through α- and/or β-keto ester subunit incorporation within polyester materials, which do not readily cyclize to lactam products.

Experimental

Materials. The synthesis of 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO) (**1**) has been described elsewhere.[34,36,37] ε-Caprolactone (CL) (Aldrich) was distilled from CaH_2 and stored under argon. Toluene (Aldrich) was dried by heating at reflux over sodium and distilled under argon prior to use. Aluminum triisopropoxide (Al(OiPr)$_3$) (Aldrich) was purified by sublimation and dissolved in dry toluene prior to use. Tetrahydrofuran-d_8 (Cambridge Isotopes) was purchased as 0.75 or 1.0 mL ampules and used as received. All other reagents were purchased from Aldrich and used as received.

Instrumentation. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were acquired in $CDCl_3$ unless otherwise noted on a Varian Mercury 300 spectrometer using the solvent signal as the internal reference.

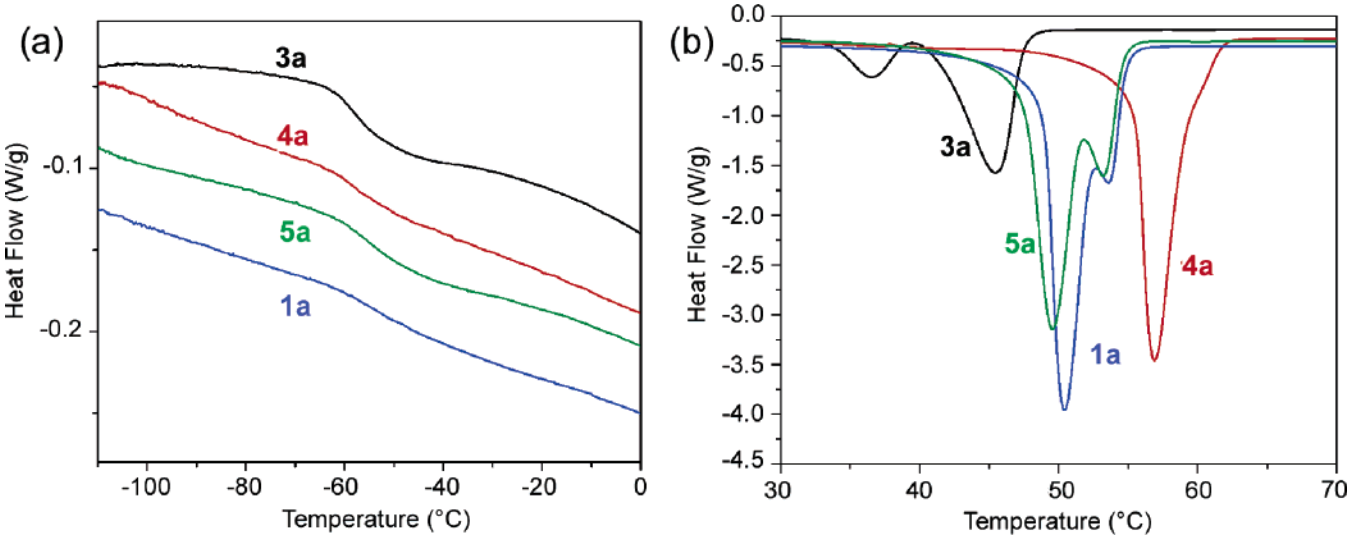


Figure 5. DSC second heating trace overlay of P(CL_{74}-*co*-$TOSUO_8$), **3a**, and P(CL_{74}-*co*-OPD_8), **4a**, products isolated by precipitation after reaction of **4a** with hexylamine and $NaCNBH_3$, **5a**, and products isolated by precipitation after reaction of **4a** with 1,6-hexanediamine and $NaCNBH_3$, **1a**, in the (a) glass transition temperature and (b) melt transition regions.

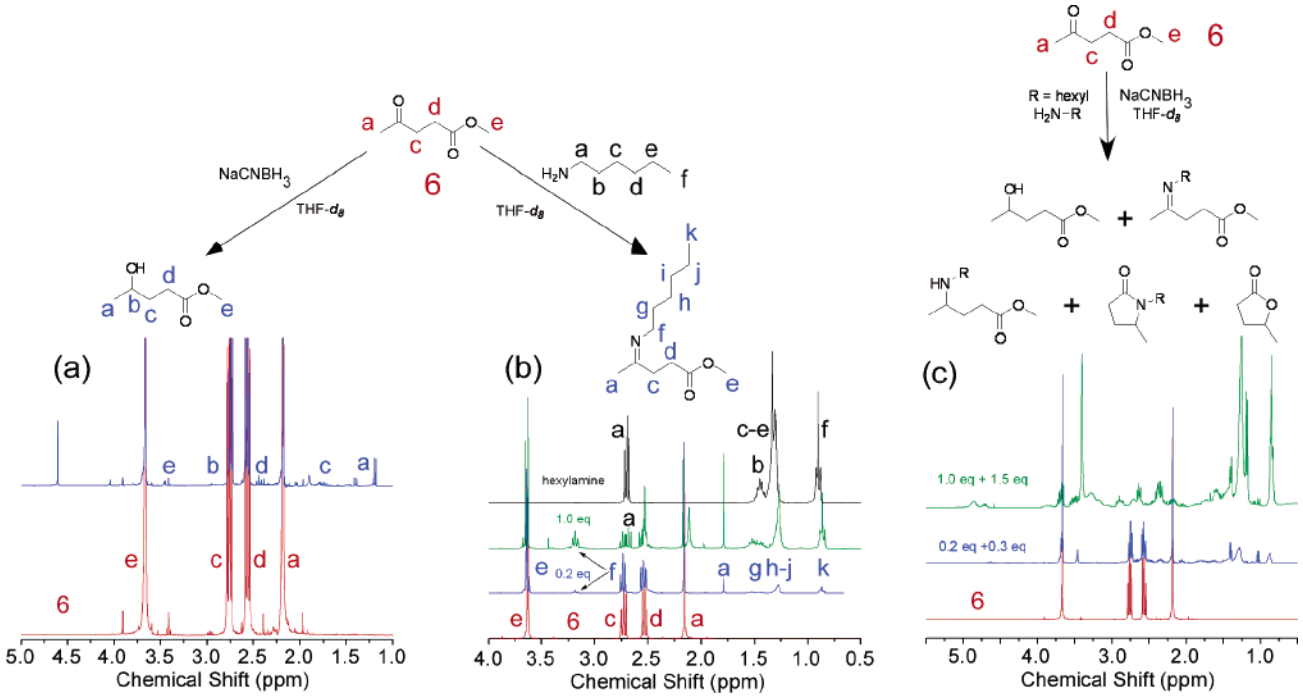


Figure 6. ^1H NMR spectra for the small molecule model studies with methyl levulinate: (a) reduction with $NaCNBH_3$ (1.0 equiv/ketone), (b) imine formation with hexylamine addition (0.2 and 1.0 equiv/ketone), and (c) reductive amination with hexylamine (0.2 and 1.0 equiv/ketone) and $NaCNBH_3$ (0.3 and 1.5 equiv/ketone), illustrating probable products (for simplification, stereochemical differences are neglected).

Infrared spectra were recorded in a Perkin-Elmer Spectrum RX FT−IR system by film deposition onto NaCl salt plates. Differential scanning calorimetry was performed under nitrogen atmosphere using 40 μL aluminum pans on a Mettler Toledo DSC822 with heating and cooling at 10 °C/min from −100 °C to 100 °C. T_m and T_g values were obtained from the third heating scan. Thermogravametric analysis data were obtained under nitrogen atmosphere using 100 μL aluminum open pans in a Mettler Toledo TGA/SDTA851^e thermogravimetric balance with heating rates of 10 °C/min from 25 to 550 °C. Gel permeation chromatography was performed on a Waters Chromatography, Inc., 1515 isocratic HPLC pump equipped with an inline degrasser, a model PD2040 dual-angle (15 and 90°) light scattering detector (Precision Detectors, Inc.), a model 2414 differential refractometer (Waters, Inc.), and four Plgel polystyrene-*co*-divinylbenzene gel columns (Polymer Laboratories, Inc.) connected in series: 5 μm Guard (50 × 7.5 mm), 5 μm Mixed C (300 × 7.5 mm), 5 μm 10^4 (300 × 7.5 mm), and 5 μm 500 Å (300 × 7.5 mm) using the Breeze (version 3.30, Waters Inc.) software. The instrument was operated at 35 °C with THF as eluent. Data collection was performed with Precision Acquire 32 Acquisition program (Precision Detectors, Inc.) and analyses were carried out using Discovery32 software (Precision Detectors, Inc.) with a system calibration using narrow polydispersity poly(styrene) standard (M_p = 90 000 g/mol, M_w/M_n < 1.04, Pressure Chemical Co.)

Synthesis. Random copolymers of CL and 2-oxepane-1,5-dione (OPD) were prepared by ring-opening polymerization of CL and the synthetic monomer TOSUO in the presence of $Al(OiPr)_3$, followed by deprotection using triphenylcarbenium tetrafluoroborate as reported elsewhere.[34−37,53,54]

Poly(CL_{74}-*co*-$TOSUO_8$) (3a). GPC: M_n = 19 100 Da, M_w = 25 700 Da, PDI = 1.3. M_n (^1H NMR) = 9890 Da. ^1H NMR (300 MHz, $CDCl_3$): δ 5.0 (septet, J = 6.3 Hz, 1 H of initiated chain end, $(CH_3)_2CHO$), 4.15 (t, J = 7.2 Hz, 2 H of TOSUO units, CH_2-

OCO), 4.05 (t, $J = 6.6$ Hz, 2H of CL units, C**H**$_2$OCO), 3.95 (br s, 4H of TOSUO units, CH$_2$C(OC**H**$_2$C**H**$_2$O)CH$_2$), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, C**H**$_2$OH), 2.37 (t, $J = 7.2$ Hz, 2 H of TOSUO units, C**H**$_2$COOCH$_2$), 2.3 (t, $J = 7.5$ Hz, 2H of CL units, C**H**$_2$COOCH$_2$), 2.0 (two t, $J = 7.2$ Hz, 4 H of TOSUO units, C**H**$_2$C(OCH$_2$CH$_2$O)C**H**$_2$), 1.65 (m, 4 H of the CL units, OCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$COO), 1.45 (m, 2 H of the CL units, C**H**$_2$CH$_2$CH$_2$COO), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, (C**H**$_3$)$_2$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 173.5, 109.5, 65.2, 64.3, 60.3, 36.1, 34.6, 34.3, 32.8, 28.8, 28.5, 25.7, 24.7 22.0, 19.9 ppm. IR (cm^{-1}): 3600−3000, 2944, 2866, 1732 (str, multiple modes), 1595, 1470, 1437, 1420, 1397, 1367, 1295, 1244, 1191 (br), 1108, 1065, 1046, 962, 933, 903, 841, 773, 732, 710 cm^{-1}. DSC: $T_g = -57.0$ °C, $T_{m1} = 36.6$ °C, $T_{m2} = 45.4$ °C. TGA: 25−267 °C, ∼0% mass loss; 309 °C, 10.0% mass loss; 380 °C, 93.0% mass loss; 4.1% mass remaining at 550 °C.

Poly(CL$_{49}$-*co*-TOSUO$_4$) (3b). GPC: $M_n = 13\,700$ Da, $M_w = 15\,300$ Da, PDI = 1.1. M_n (^{1}H NMR) = 6340 Da. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, (CH$_3$)$_2$C**H**O), 4.15 (t, $J = 7.2$ Hz, 2 H of TOSUO units, C**H**$_2$OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, C**H**$_2$OCO), 3.95 (br s, 4 H of TOSUO units, CH$_2$C(OC**H**$_2$C**H**$_2$O)CH$_2$), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, C**H**$_2$OH), 2.37 (t, $J = 7.2$ Hz, 2 H of TOSUO units, C**H**$_2$COOCH$_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, C**H**$_2$COOCH$_2$), 2.0 (two t, $J = 7.2$ Hz, 4 H of TOSUO units, C**H**$_2$C(OCH$_2$CH$_2$O)C**H**$_2$), 1.65 (m, 4 H of the CL units, OCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$COO), 1.45 (m, 2 H of the CL units, C**H**$_2$CH$_2$CH$_2$COO), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, (C**H**$_3$)$_2$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 173.5, 109.5, 65.2, 64.3, 60.3, 36.1, 34.6, 34.3, 32.8, 28.8, 28.5, 25.7, 24.7 22.0, 19.9 ppm. IR (cm^{-1}): 3600−3000, 2944, 2866, 1732 (str, multiple modes), 1595, 1470, 1437, 1420, 1397, 1367, 1295, 1244, 1191 (br), 1108, 1065, 1046, 962, 933, 903, 841, 773, 732, 710 cm^{-1}. DSC: $T_g = -60$ °C, $T_{m1} = 39.4$ °C, $T_{m2} = 46.7$ °C. TGA: 25−268 °C, ∼0% mass loss; 309 °C, 10% total mass loss; 380 °C, 93% total mass loss; 4.1% mass remaining at 550 °C.

Poly(CL$_{74}$-*co*-OPD$_8$) (4a). GPC: $M_n = 20\,000$ Da, $M_w = 24\,000$ Da, PDI = 1.2. M_n (^{1}H NMR) = 6170 Da. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, (CH$_3$)$_2$C**H**O), 4.25 (t, $J = 7.2$ Hz, 2 H of OPD units, C**H**$_2$OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, C**H**$_2$OCO), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, C**H**$_2$OH), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)CH$_2$C**H**$_2$COO), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)C**H**$_2$CH$_2$), 2.62 (t, $J = 7.5$ Hz, 2 H of OPD units, C**H**$_2$COOCH$_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, C**H**$_2$COOCH$_2$), 1.65 (m, 4 H of CL units, OCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$COO), 1.45 (m, 2 H of CL units, C**H**$_2$CH$_2$CH$_2$COO), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, (C**H**$_3$)$_2$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.9, 173.4, 172.7, 64.6, 64.2, 59.2, 41.6, 37.5, 34.2, 34.0, 28.4, 27.9, 25.6, 24.7, 24.5 ppm. IR (cm^{-1}): 3600−3000, 2946, 2866, 1727 (str, multiple modes), 1471, 1419, 1397, 1366, 1239, 1296, 1242, 1191, 1108, 1061, 1046, 962, 934, 842, 806, 771, 733, 707 cm^{-1}. DSC: $T_g = -56.7$ °C, $T_m = 57.2$ °C. TGA: 25−238 °C, 2.0% total mass loss; 348 °C, 10.0% total mass loss, 440 °C; 95.1% total mass loss; 2.4% mass remaining at 550 °C.

Poly(CL$_{49}$-*co*-OPD$_4$) (4b). GPC: $M_n = 11\,900$ Da, $M_w = 13\,600$ Da, PDI = 1.2. M_n (^{1}H NMR) = 6170 Da. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, (CH$_3$)$_2$C**H**O), 4.25 (t, $J = 7.2$ Hz, 2 H of OPD units, C**H**$_2$OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, C**H**$_2$OCO), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, C**H**$_2$OH), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)CH$_2$C**H**$_2$COO), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)C**H**$_2$CH$_2$), 2.62 (t, $J = 7.5$ Hz, 2 H of OPD units, C**H**$_2$COOCH$_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, C**H**$_2$COOCH$_2$), 1.65 (m, 4 H of CL units, OCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$COO), 1.45 (m, 2 H of CL units, C**H**$_2$CH$_2$CH$_2$COO), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, (C**H**$_3$)$_2$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.0, 173.7, 172.8, 64.7, 64.3, 59.2, 41.7, 37.6, 34.3, 34.1, 28.5, 27.9, 25.7, 24.7 ppm. IR (cm^{-1}): 3600−3000, 2946, 2866, 1727 (str, multiple modes), 1471, 1419, 1397, 1366, 1239, 1296, 1242, 1191, 1108, 1061, 1046, 962, 934, 842, 806, 771, 733, 707 cm^{-1} DSC: $T_g = -57$ °C, $T_{m1} = 56.0$ °C, $T_{m2} = 59.6$ °C. TGA: 25−235 °C, ∼0% total mass loss; 350 °C, 10.0% total mass loss; 430 °C, 88.6% total mass loss; 6.9% mass remaining at 550 °C.

General functionalization conditions involved dissolving the polymer and amine (hexylamine or 1,6-hexanediamine) in THF with mixing, and then adding 1.5 equiv of NaCNBH$_3$ and allowing the reaction to proceed for 24 h at room temperature, followed by precipitation in cold MeOH and drying of the isolated solid under vacuum to constant weight.

Poly(CL$_{74}$-*co*-OPD$_8$) Diamine Functionalized Polymer (1a). P(CL$_{74}$-*co*-OPD$_8$) (0.5204 g, 0.0546 mmol polymer, 0.437 mmol ketone groups) and 1,6-hexanediamine (36.4 mg, 0.313 mmol diamine, 1.44 equiv of amine/ketone) were massed into a 1 dram shell vial and allowed to dissolve with stirring in 1.18 g of THF for 30 min. Sodium cyanoborohydride (40.5 mg, 0.644 mmol, 1.47 equiv/ketone) was quickly added, and the reaction was allowed to proceed at room temperature for 24 h. The reaction mixture was diluted with an additional 0.25 mL of THF and the product was precipitated into cold MeOH, collected as a white powder by vacuum filtration, and dried under vacuum for 24 h. Isolated yield: 0.38 g, 68% GPC: $M_n = 6400$ Da, $M_w = 9800$ Da, PDI = 1.5. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, (CH$_3$)$_2$C**H**O), 4.25 (t, $J = 7.2$ Hz, 2 H of OPD units, C**H**$_2$OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, C**H**$_2$OCO), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, C**H**$_2$OH), 2.7−3.5 (very small, br), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)CH$_2$C**H**$_2$COO), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)C**H**$_2$CH$_2$), 2.62 (t, $J = 7.5$ Hz, 2 H of OPD units, C**H**$_2$COOCH$_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, C**H**$_2$COOCH$_2$), 1.65 (m, 4 H of CL units, OCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$COO), 1.45 (m, 2 H of CL units, C**H**$_2$CH$_2$CH$_2$COO), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, (C**H**$_3$)$_2$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 64.3, 34.3, 28.5, 25.7, 24.7 ppm. IR (cm^{-1}): 3600−3000, 2944, 2865, 1724, 1560−1540, 1470, 1419, 1367, 1295, 1243, 1190, 1108, 1047, 962, 934, 840, 732 cm^{-1}. DSC: T_g = (very weak) −53.0 °C, $T_{m1} = 50.3$ °C, $T_{m2} = 53.6$ °C. TGA: 25−295 °C, ∼0% total mass loss; 343 °C, 10.2% total mass loss; 417 °C, 78.9% total mass loss; 478 °C, 85.8% total mass loss; 12.7% mass remaining at 550 °C.

Poly(CL$_{49}$-*co*-OPD$_4$) Diamine Functionalized Polymer (1b). P(CL$_{49}$-*co*-OPD$_4$) (0.1744 g, 0.028 mmol polymer, 0.113 mmol ketone groups) and 1,6-hexanediamine (13.7 mg, 0.118 mmol diamine, 2.11 equiv of amine/ketone) were massed into a 1 dram shell vial and allowed to dissolve with stirring in 0.23 g of THF for 30 min. Sodium cyanoborohydride (9.5 mg, 0.15 mmol, 1.33 equiv/ketone) was quickly added, and the reaction was allowed to proceed at room temperature for 24 h. The reaction mixture was diluted with an additional 0.25 mL of THF, and the product was precipitated into cold MeOH, collected as a white powder by vacuum filtration, and dried under vacuum for 24 h. Isolated yield: 0.082 g, 44% GPC: $M_n = 6200$ Da, $M_w = 7300$ Da, PDI = 1.2. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, (CH$_3$)$_2$C**H**O), 4.25 (t, $J = 7.2$ Hz, 2 H of OPD units, C**H**$_2$OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, C**H**$_2$OCO), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, C**H**$_2$OH), 2.7−3.5 (very small, br), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)CH$_2$C**H**$_2$COO), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, C(O)C**H**$_2$CH$_2$), 2.62 (t, $J = 7.5$ Hz, 2 H of OPD units, C**H**$_2$COOCH$_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, C**H**$_2$COOCH$_2$), 1.65 (m, 4 H of CL units, OCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$COO), 1.45 (m, 2 H of CL units, C**H**$_2$CH$_2$CH$_2$COO), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, (C**H**$_3$)$_2$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.7, 64.3, 34.3, 28.5, 25.7, 24.7 ppm. IR (cm^{-1}): 3600−3000, 2944, 2865, 1724, 1560−1540, 1470, 1419, 1367, 1295, 1243, 1190, 1108, 1047, 962, 934, 840, 732 cm^{-1}. DSC: T_g = (very weak) −53.8 °C, $T_{m1} = 48$ °C, $T_{m2} = 52$ °C. TGA: 25−235 °C, 2.0% total mass loss; 334 °C, 10.2% total mass loss; 414 °C, 81.1% total mass loss; 6.1% mass remaining at 550 °C.

Poly(CL$_{74}$-*co*-OPD$_8$) Monoamine Graft Polymer (5a). P(CL$_{74}$-*co*-OPD$_8$) (0.2141 g, 0.0225 mmol polymer, 0.180 mmol ketone

groups) and hexylamine (21.1 mg, 0.209 mmol amine, 1.16 equiv of amine/ketone) were massed into a 1 dram shell vial and allowed to dissolve with stirring in 0.28 g of THF for 30 min. Sodium cyanoborohydride (16.1 mg, 0.26 mmol, 1.42 equiv/ketone) was quickly added and the reaction was allowed to proceed at room temperature for 24 h. The reaction mixture was diluted with an additional 0.25 mL of THF, and the product was precipitated into cold MeOH, collected as a whitish waxy solid by vacuum filtration, and dried under vacuum for 24 h. Isolated yield: 0.101 g, 43% GPC: $M_n = 6500$ Da, $M_w = 9100$ Da, PDI = 1.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, $(CH_3)_2CHO$), 4.25 (t, $J = 7.2$ Hz, 2 H of OPD units, CH_2OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, CH_2OCO), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, CH_2OH), 2.7−3.5 (very small, br), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2CH_2COO$), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2CH_2$), 2.62 (t, $J = 7.5$ Hz, 2 H of OPD units, CH_2COOCH_2), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, CH_2COOCH_2), 1.65 (m, 4 H of CL units, OCH_2CH_2 and CH_2CH_2COO), 1.45 (m, 2 H of CL units, $CH_2CH_2CH_2COO$), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, $(CH_3)_2CHO$), 0.9 (t, br, (CH_3 hexyl chain end). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 64.3, 34.3, 29.9, 28.5, 25.7, 24.7, 24.5 ppm. IR (cm^{-1}): 3600−3000 (str, br), 2944, 2896, 2865, 1738, 1723, 1649, 1644, 1470, 1461, 1436, 1418, 1398, 1367, 1295, 1244, 1193, 1176, 1107, 1065, 1046, 962, 934, 841, 806, 773, 732, 710 cm^{-1}. DSC: $T_g = -47.9$ °C, $T_{m1} = 49.5$ °C, $T_{m2} = 53.2$ °C. TGA: 25−261 °C, ∼0% total mass loss; 338 °C, 10.0% total mass loss; 430 °C, 87.6% total mass loss; 9.3% mass remaining at 550 °C.

Poly(CL_{49}-*co*-OPD_4) Monoamine Graft Polymer (5b). P(CL_{49}-*co*-OPD_4) (0.1930 g, 0.0313 mmol polymer, 0.125 mmol ketone groups) and hexylamine (25.8 mg, 0.255 mmol amine, 2.04 equiv of amine/ketone) were massed into a 1 dram shell vial and allowed to dissolve with stirring in 0.23 g of THF for 30 min. Sodium cyanoborohydride (10.8 mg, 0.172 mmol, 1.37 equiv/ketone) was quickly added, and the reaction was allowed to proceed at room temperature for 24 h. The reaction mixture was diluted with an additional 0.25 mL of THF, and the product was precipitated into cold MeOH, collected as a whitish waxy solid by vacuum filtration, and dried under vacuum for 24 h. Isolated yield: 0.0294 g, 13% GPC: $M_n = 7500$ Da, $M_w = 8500$ Da, PDI = 1.1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, $(CH_3)_2CHO$), 4.25 (t, $J = 7.2$ Hz, 2 H of OPD units, CH_2OCO), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, CH_2OCO), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, CH_2OH), 2.7−3.5 (very small, br), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2CH_2COO$), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2CH_2$), 2.62 (t, $J = 7.5$ Hz, 2 H of OPD units, CH_2COOCH_2), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, CH_2COOCH_2), 1.65 (m, 4 H of CL units, OCH_2CH_2,CH_2CH_2COO), 1.45 (m, 2 H of CL units, $CH_2CH_2CH_2COO$), 1.25 ppm (d, $J = 6.3$ Hz, 6 H of initiated chain end, $(CH_3)_2CHO$), 0.9 (t, br, CH_3 hexyl chain end). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 64.3, 34.3, 28.5, 25.7, 24.7 ppm. IR (cm^{-1}): 3600−3000 (str, br), 2943, 2865, 1723, 1470, 1436, 1419, 1397, 1368, 1295, 1244, 1192, 1107, 1066, 1046, 962, 934, 841, 773, 732, 710 cm^{-1}. DSC: $T_g = -58.5$ °C, $T_{m1} = 52.0$ °C, $T_{m2} = 54.0$ °C. TGA: 25−235 °C, 0% total mass loss; 336 °C, 10.0% total mass loss; 381 °C, 30.1% total mass loss; 425 °C, 87.3% total mass loss; 9.4% mass remaining at 550 °C.

Conclusions

The initial strategy, designed to employ keto functionalities along the backbone of PCL for a combined intramolecular cross-linking and introduction of reactive moieties, each accomplished via reductive amination with multifunctional amines, must be rethought, given the findings reported herein. Although some reductive amination occurred under the chosen conditions, the small molecule and polymer experiments performed suggest that the selectivity is not sufficient to allow for utilization in the preparation of well-defined macromolecular structures from P(CL-*co*-OPD) copolymers, which contain the γ-keto ester functional group present in methyl levulinate. However, interest in the PCL backbone remains strong, due to its use as a biodegradable material from which well-defined nanoparticles can be fashioned by this intramolecular chain collapse and cross-linking approach.[23−25] We continue to develop these materials, therefore, by utilizing alternative chemistry, which relies upon reaction of multifunctional amino−oxy and hydrazide cross-linkers to establish thermodynamically stable, acid-labile oxime and hydrazone linkages.[38]

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Supporting Information Available: Figures showing NMR and IR spectra for several control reactions and reductive amination reactions of the polymers and small molecules and TGA data for polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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