# Amorphous Unsaturated Aliphatic Polyesters Derived from Dicarboxylic Monomers Synthesized by Diels−Alder Chemistry

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ABSTRACT: A versatile method for synthesizing functionalized amorphous degradable polyesters via step growth polycondensation was investigated. A series of dicarboxylic acids and anhydrides were synthesized by Diels−Alder reactions of fumaric acid and maleic anhydride, respectively, with various dienes. The resulting difunctional monomers were reacted with 1,8-octanediol in the presence of tin octanoate catalyst at 160 °C and 30 mmHg for 24 h to form new unsaturated aliphatic polyesters. Each polyester had molecular weight $\langle M_n \rangle$ between $1.0 \times 10^4$ and $2.0 \times 10^4$ g mol$^{-1}$ and a polydispersity index near 2.0. All of the materials were amorphous and had glass transition temperatures between −30 and −15 °C. Each polymer repeat unit necessarily featured a double bond, which was exploited to cross-link the materials yielding degradable elastomers. Amine- and ether-containing polyesters were synthesized by using monomers formed from the corresponding polar functionalized dienes. Using this broad cycloaddition scheme, a variety of amorphous, functionalized polyesters were successfully synthesized.

## Introduction

The use of aliphatic polyesters in biological and medical applications is well established because of their intrinsic biodegradability and biocompatibility. The most common materials are synthesized by ring-opening polymerization (ROP), including poly(L-lactic acid) (PLLA), poly(glyclolic acid) (PGA), poly($\epsilon$-caprolactone) (PCL), and their copolymers. Uses for these polyesters include drug delivery,[1] tissue engineering scaffolds,[2] stents,[3] and sutures.[4] The majority of these polyesters are semicrystalline, hydrophobic polymers that lack reactive functional groups along the backbone. This set of properties may limit their utility in certain applications. For example, the ideal drug delivery devices have a linear degradation and release profile over time. However, the semicrystalline, hydrophobic materials mentioned above have a nonlinear biodegradation profile due to poor water permeability and poor solubility in aqueous systems. Also, in tissue scaffolds, it may be necessary to have a soft, flexible matrix which mirrors the mechanical properties of the surrounding tissues. In these instances, the aliphatic polyesters mentioned fall short due to their relatively brittle, rigid nature in physiological environments.

Recent efforts have sought synthetic means to form amorphous aliphatic polyesters that will be able to meet these property requirements by changing the topology of the materials and by incorporating polar functional groups along the backbone of the polyesters. For example, Amsden has taken advantage of the amorphous nature of poly(DL-lactic acid) (PDLLA) and its copolymers by incorporating it into acrylate end-capped star copolymers.[5] These materials were completely amorphous and formed amorphous elastomers upon photocuring of the thermoplastic precursor. The cross-linking density was adjusted by varying the length of the arms of the stars. Langer described a tough biodegradable elastomer synthesized from the step growth condensation of glycerol and sebacic acid that, despite being semicrystalline, was above all thermal transitions and totally amorphous at the intended use temperature of 37 °C.[6] A similar elastomer was reported by Ameer, who used citric acid and 1,8-octanediol as the monomers.[7] The latter two examples rely on step growth condensations of monomers with an average monomer functionality greater than two ($f_{av} > 2$) to ensure that the thermoset materials were lightly cross-linked after the reaction proceeded to high conversion. This required the materials to be cured at high temperature under vacuum on the order of days. In addition, the final cross-linking density of the materials was difficult to control.

A significant advancement was realized by our group in this field with the design of new amorphous degradable elastomeric thermoset materials that combine the amorphous nature of thermoset materials with the synthetic and processing ease of thermoplastic elastomers.[8] The step growth polymerization of trans-$\beta$-hydromuconic acid and oligo(ethylene glycol)s yields unsaturated polyester materials (Scheme 2) that can be thermally cross-linked in the presence of a radical initiator. This approach relies on the use of an amorphous linear prepolymer that has a low glass transition temperature and is a liquid at room temperature. The cross-linking density of the material is easily modified to alter the mechanical properties ($G = 0.02-20$ MPa). The prepolymer composition is readily changed to tune the degradation rate of the material (linear mass loss up to 100% in as little as 30 days).

While these materials overcome many of the obstacles previously described, their thermal properties are intrinsically linked to their solubility via the nature of the ether-containing diol used in the polyester synthesis. Including the oligo(ethylene glycol) ensures that the material cannot crystallize and has a low glass transition temperature, while at the same time causing the material to be hydrophilic. It may be necessary to form materials whose thermal and solubility properties are independent of each other or to otherwise further modify the final properties of the elastomer. To do so, it is desired to modify the liquid polyester to contain various polar functional groups. Most previous examples of functionalized aliphatic polyesters are based on the ROP of a lactone or lactide containing the functionality.[9] Illustrative materials include those synthesized

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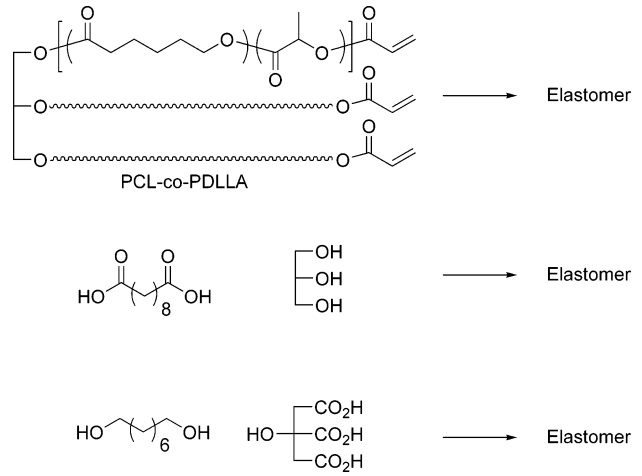
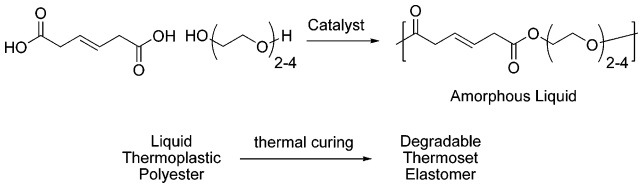
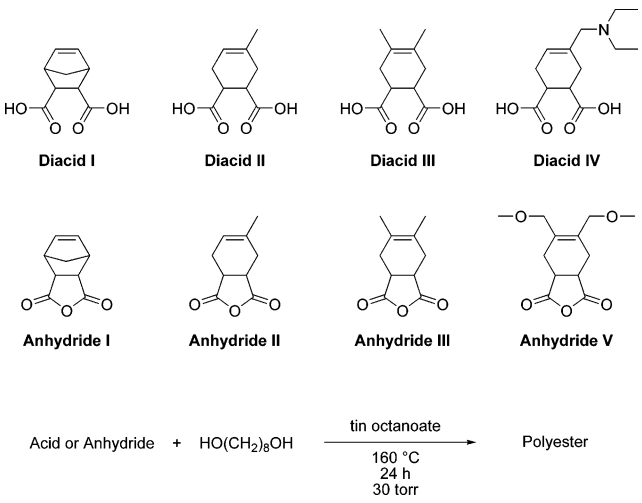
**Scheme 1. Examples of Amorphous Aliphatic Polyesters from Amsden, Langer, and Ameer**



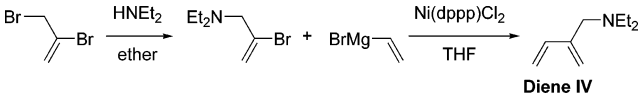

**Scheme 2. Rapidly Degrading Elastomeric Materials Synthesized by Olson et al.[8]**




**Scheme 3. Synthetic Strategy for Preparing New Unsaturated Aliphatic Polyesters**




**Scheme 4. Synthesis of Amine-Containing Diene IV**




to contain amino,[10,11] carboxyl,[12] and hydroxyl[13−15] groups. These functional monomers are often copolymerized with lactide or a lactone and thus have thermal properties that represent the average of the base material and the functionalized material. This approach makes it difficult to simultaneously target a specific degree of functionality and specific thermal transition temperatures.

In order to form a functionalized polyester that can serve as an amorphous, liquid precursor to degradable elastomers, a methodology needed to be developed that would meet several requirements. The first criteria is that the system allows for incorporation of a range of functional groups to be incorporated into the materials, while at the same time ensuring the polyesters are completely amorphous liquids at room temperature. Also, the materials must have a site of reaction for cross-linking. Last, each polyester must able to be synthesized to a targeted molecular weight. Herein, we describe a synthetic methodology that relies on Diels−Alder chemistry to meet these criteria and to achieve unsaturated, amorphous, functionalized polyesters.

## Experimental Section

**Materials.** All reagents were purchased from Aldrich and used without further purification unless otherwise noted. Pure 5-norbornene *cis*-2,3-dicarboxylic acid (diacid I) was recrystallized from ethanol and water. Pure 1,8-octanediol was recrystallized from tetrahydrofuran.

**Polymer Synthesis.** A 10 mL round-bottom flask was charged with dicarboxylic acid or anhydride (1.0 equiv) and 1,8-octanediol (1.0 equiv). The flask was sealed with a rubber septum, evacuated, and refilled with argon gas. A homogeneous melt was formed by heating the flask to 160 °C with magnetic stirring. Tin octanoate (0.01 equiv) was added to the melt. The reaction mixture was allowed to stir for 1 h, and then the pressure was reduced to 30 mmHg and stirred for an additional 23 h (24 h total reaction time). At this time, the reaction mixture was allowed to cool and dissolved in chloroform. This solution was precipitated into stirring methanol at −78 °C. Methanol was decanted from the polymer, and the oil was dried in a vacuum oven at 50 °C for 24 h. For each reaction, approximately 500−1000 mg of diacid or anhydride was used.

**Elastomer Synthesis.** Elastomer films were prepared by spreading a mixture of the liquid prepolymer (0.20−2.00 g) and AIBN (5.0 wt %) in a Teflon mold. The mixture was heated in an oven for 24 h at the desired temperature, after which the film was removed. Following removal, it was allowed to cool to room temperature and was removed from the mold.

**Characterization.** $^1$H and $^{13}$C NMR spectra were acquired in deuterated chloroform, deuterated acetone, or deuterium oxide on a Bruker 400 AVANCE spectrometer. Molecular weights, relative to narrow polystyrene standards, were measured using a Waters GPC system using RI detection. The measurements were taken at 35 °C with tetrahydrofuran as the mobile phase on three columns (Waters Styragel HR2, HR4, and HR5). Thermal transitions were measured with a Seiko 220C DSC on the second heat with a heating rate of 10 °C/min. Thermogravimetric analysis was carried out using a Perkin-Elmer TGA with a heating rate of 10 °C/min in a $N_2$ atmosphere. Mass spectra were recorded on a Bruker BioTOF II Reflectron time-of-flight mass spectrometer in high-resolution mode using electrospray ionization in the positive mode. Elemental analysis was conducted by Atlantic Microlab Inc. of Norcross, GA.

*Contact Angle Measurement.* A 5 wt % solution of the respective polymers were spin-coated onto a silicon wafer at 7000 rpm for 1 min. Contact angles measurements were performed on a KSV 200 optical contact angle meter. Water was used as the wetting liquid.

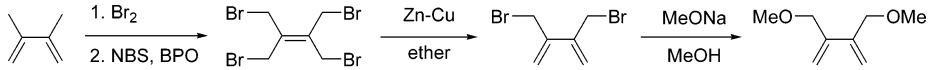
*Sol−Gel Analysis.* Sol−gel analysis was conducted by swelling a 0.15 g elastomer film in methylene chloride for 24 h at 25 °C. The solvent was removed, and the percent soluble fraction ($Q_s$) was determined according to the following equation

$$Q_s = \left(\frac{m_i - m_f}{m_i}\right) \times 100$$

where $m_i$ and $m_f$ represent the initial and final mass. Each measurement was performed on three separate samples. The value was reported as the average of the three measurements.

*Mechanical Analysis.* Elastomers for mechanical testing were synthesized by placing the prepolymer mixture in a dogbone-shaped Teflon mold with a test area 10 mm long, 3 mm wide, and 1.5 mm thicki. The mixture was cured as above. Mechanical data were collected on an Instron 5566 at a crosshead speed of 10 mm/min (∼100% extension per minute) at 25 °C. The Young's modulus ($E$) was calculated using the initial linear portion of the stress/strain

**Scheme 5. Synthesis of Ether-Functionalized Diene V**




**Diene V**

curve (0−5% strain). The cross-linking density $\nu$ was calculated according to the following equation

$$\nu = \frac{G}{3RT}$$

where $R$ represents the universal gas constant and $T$ is the temperature in K. Each measurement was performed on three separate samples. The value was reported as the average of the three measurements.

*Cytotoxicity Testing.* MicroMed Laboratories (Petaluma, CA) performed all cytotoxicity analysis. Minimum essential medium (MEM) elution tests were performed according to the USP ⟨87⟩ standard using L929 mouse fibroblast cells. Elastomer samples (0.20 g) were extracted in serum-supplemented medium (1.0 mL) for 24 h, and the medium was then exposed to confluent monolayers of cells. At the conclusion of 48 h, the cells were examined by light microscopy, and cytotoxicity was scored on a 0−4 scale, 0 being the least cytotoxic. Any material with a score less than or equal to 2 is considered to pass the assay.

## Results and Discussion

Amorphous aliphatic polyesters were designed, synthesized, and characterized that have unique solubility, functionality, and thermal properties relative to materials currently available for biomedical applications. The Diels−Alder reaction is the centerpiece of this methodology, as it was used to form new difunctional step growth monomers via the reaction of fumaric acid or maleic anhydride and a variety of dienes. These unsaturated dicarboxylate monomers were incorporated into high molecular weight aliphatic polyesters by step growth polycondensations with alcohols. The amorphous nature of these materials can be ascribed to the bulk of the cyclohexene ring in each repeat unit, which prevents the polymer from packing into crystallites. The Diels−Alder reaction allowed for a wide variety of dienes to be incorporated into the dicarboxylate monomers and thus into the polyesters.

**Monomer Design and Synthesis.** A series of unsaturated dicarboxylate monomers were synthesized, including two that include polar functionality, as shown in Scheme 3. Several of these compounds (mostly norbornene-based dicarboxylates) have been used for many years in polyester synthesis,[16−18] vinyl polymer synthesis,[19] and ROMP,[20] since they contain both an unsaturation and dicarboxylate groups. The Diels−Alder coupling of a diene with either fumaric acid or maleic anhydride was carried out in the absence of Lewis acid catalyst to prevent the diene from polymerizing by cationic chain-growth polymerization. Using cyclopentadiene as the diene led to polyesters that had a relatively reactive 1,2-disubstituted vinyl group in each repeat unit (diacid I and anhydride I). To control the reactivity of the double bond in the polyester backbone, isoprene and 2,3-dimethyl-1,3-butadiene were chosen to yield materials with 1,1,2-trisubstituted (diacid II and anhydride II) and 1,1,2,2-tetrasubstituted (diacid III and anhydride III) double bonds, respectively. These monomers were used to optimize the polymerization conditions and to understand the effect of the monomer structure on the final polymer properties. The information yielded in these studies was applied in the synthesis and polymerization of monomers containing amine and ether functional groups.

To synthesize monomers with these polar functional groups, dienes with the desired moiety were synthesized. Our group has synthesized a series of amine-functionalized dienes (Scheme 4) and polymerized them by chain-growth techniques.[21,22] One of these dienes, 2-(*N*,*N*-diethylaminomethyl)-1,3-butadiene (diene IV), was converted to a step growth monomer by reacting it with fumaric acid to form the dicarboxylic acid (diacid IV). The amine group was desired because materials containing this functionality have served as gene delivery vectors.[21]

We were also interested in synthesizing materials with ether functionality, as side chain ethers have been shown to decrease protein adhesion[23] and alter solubility with respect to their nonpolar counterparts. A methoxy-containing diene, 2,3-bis-(methoxymethyl)-1,3-butadiene (diene V), was synthesized using the procedure described by Gaoni (Scheme 5).[24] The resulting monomer (anhydride V) contains two side-chain ethers per repeat unit and a relatively unreactive 1,1,2,2-tetrasubstituted double bond. Each Diels−Alder reaction yielded the dicarboxylic monomer in good yield (51−80%) and in high purity.

**Polyester Synthesis.** With the monomers in hand, polymerization conditions were studied that rendered materials with high molecular weights. Allowing a dicarboxylate monomer to react with 1,8-octanediol (OD) in the presence of 1.0 mol % of tin-(II) 2-ethylhexanoate ($SnOct_2$) for 24 h at reduced pressure (30 Torr) at 160 °C was found to be the optimal method. The data are summarized in Table 1. All materials synthesized had number-average molecular weights of at least $1 \times 10^4$ g mol$^{-1}$ and polydispersity indices of ∼2.0 as predicted by step growth kinetics. With glass transition temperatures between −30 and −15 °C, all materials were amorphous oils that flowed at room temperature. Polyesters synthesized from the anhydride generally had higher molecular weights than the counterpart that was synthesized from the diacid. This is due to the fact that the anhydride is more reactive in the initial esterification reaction and because there is only one molecule of water that needs to be removed from the system for each repeat unit. In the diacid case, each repeat unit requires the removal of 2 equiv of water. Other advantages of the anhydride approach are that the anhydride monomers were generally easier to purify, had lower melting points, and were easily synthesized by refluxing the diene with maleic anhydride for only 1 h. One exception is the case of the norbornene-based monomers and polyesters (diacid I, anhydride I, polyesters 1 and 4). The polymerization of diacid I was conducted at 130 °C and yielded polyester with a number-average molecular weight of $1.44 \times 10^4$ and a polydispersity of 2.0 (polyester 1). In the case of anhydride I, polyesterification reactions conducted below 160 °C yielded polymers with molecular weights lower than $1.0 \times 10^4$, while polymerization reactions conducted at 160 °C yielded polymers with broad molecular weight distributions (polyester 4, PDI = 2.7). This is believed to be due to the steric differences in the monoester forms. Upon initial opening of the anhydride, the *cis*-dicarboxylate is more hindered to a second esterification reaction than the *trans*-dicarboxylate formed in the diacid case. This may allow for branching side reactions to dominate at higher temperatures, as discussed below in the copolymerization reactions.

**Ether-Functionalized Polyester Characterization.** Particularly notable is the successful synthesis of the side-chain ether

**Table 1. Polyesters Formed from the Reaction of the Indicated Monomer with 1,8-Octanediol in the Presence of 1 mol % of Tin Octanoate Catalyst for 24 h at 160 °C and 30 mmHg**

| | | | | | weight loss (°C)[c] | | |
|---|---|---|---|---|---|---|---|
| polyester | monomer | $\langle M_n \rangle$[a] (g mol$^{-1}$) | PDI[a] | $T_g$[b] (°C) | 5% | 10% | yield (%) |
| 1 | diacid I[d] | 14 400 | 2.0 | −22 | 268 | 289 | 92 |
| 2 | diacid II | 17 000 | 1.7 | −20 | 326 | 349 | 96 |
| 3 | diacid III | 11 500 | 1.7 | −16 | 318 | 365 | 92 |
| 4 | anhydride I | 13 400 | 2.7 | −21 | 231 | 273 | 92 |
| 5 | anhydride II | 20 100 | 1.8 | −19 | 299 | 339 | 91 |
| 6 | anhydride III | 18 300 | 2.2 | −15 | 351 | 370 | 87 |
| 7 | anhydride V | 16 600 | 1.9 | −26 | 336 | 362 | 93 |

[a] Determined by GPC. [b] Determined by DSC, second heat, 10 °C/min. [c] Determined by TGA in $N_2$, 10 °C/min. [d] Reaction temperature 130 °C.

**Table 2. Solubility Characteristics of Unsaturated Polyester and Ether-functionalized Unsaturated Polyester[a]**

| material | water | methanol | acetone | THF | DCM | hexanes |
|---|---|---|---|---|---|---|
| polyester 6 | − | − | = | + | + | − |
| polyester 7 | − | = | + | + | + | − |

[a] Symbols: −, insoluble; =, partially soluble; +, freely soluble. [b] 50 mg of polymer in 1 mL of solvent, 25 °C.

containing polyester derived from anhydride V. The ether functionality was expected to be well tolerated in the reaction conditions, as poly(ester ether) materials have been produced by us under similar conditions.[8] In this case, each repeat unit contains 2 equiv of the polar functionality, which make the polymer more hydrophilic than the corresponding polyester that does not contain these groups. The increased hydrophilicity of the ether-containing polymer (polyester 7) is evidenced qualitatively by the differences in solubility between this polymer and the polyester derived from anhydride III and octanediol (polyester 6), as shown in Table 2.

Further evidence that the ether groups make the material more hydrophilic is shown by water contact angle data. Uniform films of each of the two materials were spin-coated onto silicon wafers for water contact angle measurements. The initial contact angles were similar (∼90°), but over time the water droplet spread across the surface. This behavior is depicted in Figure 1, which compares the mean water contact angles as they decrease with time. The water droplet spread very quickly across the ether-containing polyester 7, stabilizing to a contact angle of about 45° within 15 min. The control material, polyester 6, also showed that the droplet could spread across its surface, but at a slower rate and to a lesser extent. In a further control experiment, a commercial sample of poly($\epsilon$-caprolactone) (Aldrich, $\langle M_n \rangle$ = 10 000 g/mol, PDI = 1.4) was also analyzed in the same manner. It can be seen that the PCL displayed an

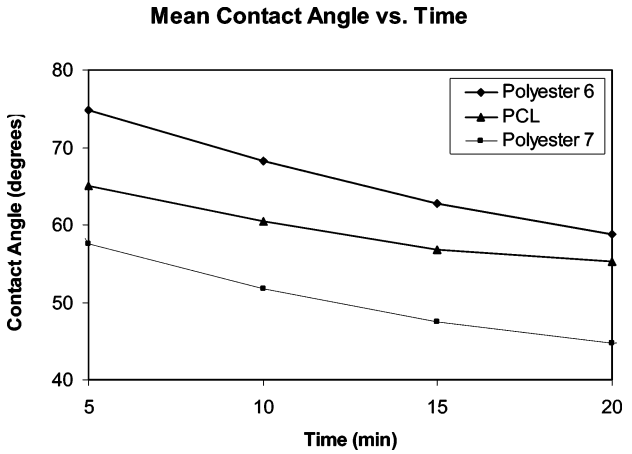



**Figure 1.** Comparison of water droplet spreading between unsaturated polyester and ether-functionalized unsaturated polyester.

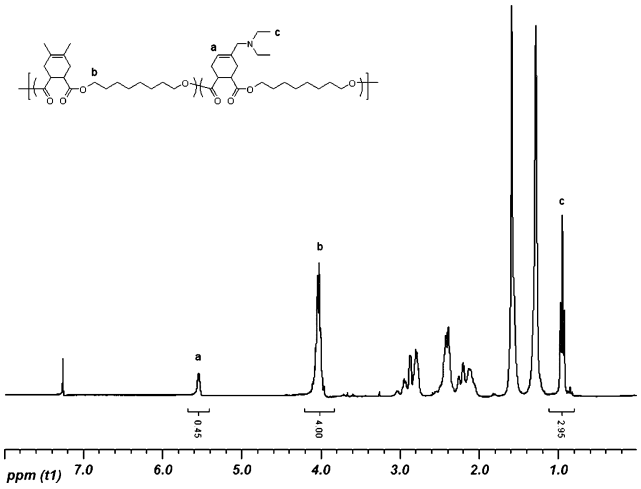



**Figure 2.** $^1$H NMR spectra of copolymer 5, 50:50 feed ratio of diacid III:IV.

intermediate hydrophilicity between the two samples tested. These data show that modifying the polymer structure with two ether groups per repeat unit significantly changes the solubility and hydrophilicity of the material.

**Amine-Containing Copolyester Synthesis.** Given the successful synthesis of the ether-containing material, attempts were made to synthesize amine-containing polyester in a similar manner. The amine-containing diacid IV was subjected to the same synthetic conditions as all of the other monomers in an attempt to form amine-containing homopolymers. When the polymerization reaction was attempted at 160 °C, the reaction product did not dissolve in chloroform; rather, it swelled in the solvent, an indication that a cross-linked material was produced. If the reaction temperature was lowered to 130 °C, only oligomers were isolated. In order to incorporate diacid IV into polyesters, a series of copolymerizations with diacid III and octanediol were carried out. All mixtures were polymerized at 160 °C for 24 h in the presence of tin octanoate (1 mol %). The feed ratio of diacid III to diacid IV was studied in increasing increments of 10%, as shown in Table 3.

The amount of amine monomer that was incorporated in the copolyesters was determined by integrating the peak for the methyl group (−$NCH_2CH_3$,0.95 ppm, peak c) and the peak for the methylene protons adjacent to the ester group (−$CO_2$−$CH_2$−, 4.02 ppm, peak b) in the $^1$H NMR spectra of the polymers (Figure 2). The amount of amine monomer in the feed correlated well to the amount incorporated in the polymer. However, the integration of the vinyl peak (5.54 ppm, peak A) showed some discrepancies which indicated that amine was incorporated into the polyesters but that some of the double bonds had been consumed. The molecular weights of all of the materials were in the range of (1.0−2.0) × $10^4$ g mol$^{-1}$, but as the amount of amine monomer in the feed is increased, the

**Table 3. Polyesters Formed from the Reaction of the Indicated Monomers with 1,8-Octanediol in the Presence of 1 mol % of Tin Octanoate Catalyst for 24 h at 160 °C and 30 mmHg**

| copolymer | feed ratio of diacid III:IV | polymer composition[a] | mol % of vinyl proton[a] | $\langle M_n \rangle$[b] (g mol$^{-1}$) | PDI[b] | $T_g$[c] (°C) | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | 90:10 | 90:10 | 7 | 11 400 | 1.9 | −19 | 89 |
| 2 | 80:20 | 81:19 | 18 | 15 000 | 2.1 | −21 | 88 |
| 3 | 70:30 | 73:27 | 27 | 16 200 | 3.3 | −28 | 94 |
| 4 | 60:40 | 60:40 | 37 | 12 000 | 2.1 | −26 | 90 |
| 5 | 50:50 | 51:49 | 45 | 18 400 | 3.2 | −28 | 75 |

[a] Determined by $^1$H NMR. [b] Determined by GPC. [c] Determined by DSC, second heat, 10 °C/min.

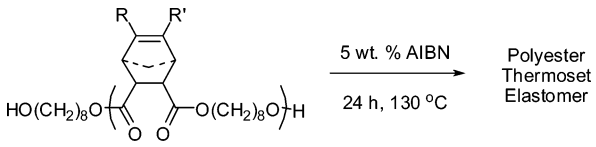
molecular weights and polydispersities of the resulting copolymers generally increased, which indicates some degree of uncontrolled branching in the reaction. Also, in the case of the 50:50 copolymer, a low yield resulted due to some intractable material left in the reaction vessel. At higher loadings, completely insoluble cross-linked gels resulted.

These observations may likely be explained by analogy to the Ordelt reaction, which has been studied in the synthesis of unsaturated polyester resins from diol maleates or fumarates.[25−28] This reaction involves the addition of an alcohol across the double bond of the dicarboxylate. This leads to a branch point and an increase in molecular weight and polydispersity. Experiments are underway to further understand the exact nature of the branching and cross-linking in the Diels−Alder system in an effort to synthesize amine-containing polyesters in a well-controlled manner.

**Elastomer Synthesis and Characterization.** All of the materials synthesized feature a double bond in each repeat unit and are amorphous liquids that flow at room temperature, which make them suitable candidates as thermoplastic precursors to polyester elastomers. As shown previously,[8] when a liquid, unsaturated polyester is reacted with a radical initiator, a degradable amorphous elastomer results. In the cross-linking of the Diels−Alder-based materials, it was anticipated that the polyester with disubstituted double bonds (polyester 1 or 4) would be more reactive toward cross-linking than the tri- or tetra-substituted materials (polyester 2, 3, 5, or 6). This was tested by thermally cross-linking the materials under the same conditions. To facilitate ease of processing, low molecular weight prepolymers were synthesized by condensing anhydrides I−III with an excess of octanediol. The stoichiometric imbalance led to materials with lower $\langle M_n \rangle$ ($(3.0-5.0) \times 10^3$ g mol$^{-1}$), lower $T_g$ (−40 to −30 °C), and 100% hydroxyl end groups. Each polyester was mixed with 5 wt % AIBN and heated at 130 °C for 24 h. The resulting elastomers were swollen in methylene chloride for 24 h to find the soluble fraction ($Q_s$) as an indication of the reactivity of the olefins toward the cross-linking reaction. The results follow the expected trend (Table 4). The fully substituted olefins are not reactive under the conditions studied (elastomer A), while the trisubstituted material showed moderate reactivity (elastomer B). The norbornene-based polyester was the most reactive and formed the elastomers with the lowest sol fraction (elastomer C).

The elastomer that resulted from the cross-linking of polyester 4 was then evaluated further for its mechanical properties. To vary the mechanical properties of the material, a series of cross-linking reactions were conducted at different temperatures. The resulting materials showed a broad range of properties, as shown in Table 5. Elastomer C was a very soft material, as shown by its low Young's modulus value (0.05 MPa) and its ability to stretch to nearly 200% its original length before failure. Elastomer D was an intermediate material synthesized at 145 °C and was slightly stiffer ($E$ = 0.44 MPa) with good ultimate strain ($\epsilon$ = 161%). A much stiffer material was synthesized at 160 °C (elastomer E, Young's modulus = 11.5 MPa, $\epsilon$ = 87%).

**Table 4. Sol−Gel Data for Elastomeric Materials**



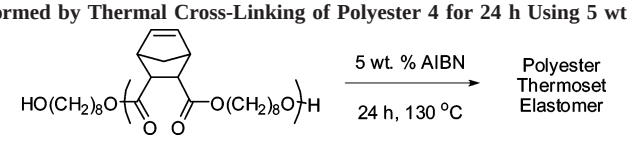

| elastomer | prepolymer[a] | R | R′ | $Q_s$ (%)[b] |
|---|---|---|---|---|
| A | polyester 4 | H | H | 51 |
| B | polyester 5 | H | Me | 58 |
| C | polyester 6 | Me | Me | 100 |

[a] Polymer listed was combined with 5 wt % of AIBN and cured for 24 h at 130 °C. [b] Extracted in methylene chloride for 24 h at 25 °C.

Given the high sol content of the materials, the mechanical properties were measured for the insoluble portion that remained after the neat materials were extracted with methylene chloride for 24 h at 25 °C (sol-removed samples). In general, these elastomers were more brittle than their precursors, so much so that the sample cross-linked at 130 °C was too brittle to test. The samples cross-linked at 145 and 160 °C each had higher Young's moduli, similar ultimate strain, and lower ultimate stress values than the neat elastomers (Table 6). This is expected since the removal of the soluble portion will increase the overall cross-link density, which gives a higher Young's modulus. The high sol content of these elastomers must also be considered in the processing and degradation of these materials and may be a limitation to the utility of these materials. Further cross-linking methods, such as (meth)acrlyate end-capping the polyols, may be explored to yield materials with a lower sol content and better mechanical properties.

Since these materials are intended for biomedical applications, each of the cured elastomers was screened for cytotoxic response according to the current USP ⟨87⟩ standard. The neat elastomers and the sol-removed samples were both subjected to the assay. Each material was extracted with minimum essential medium for 24 h, at which point the medium was then added to a confluent monolayer of L-929 mouse fibroblast cells. After incubation for 48 h, the cells were visually graded for cell morphology and monolayer confluence. Under the guidelines of this test, a grade of 0 indicates a noncytotoxic material, a grade of 4 indicates a severely cytotoxic material, and a grade of 2 or less indicates a material that passes the assay. As Table 7 indicates, all of the materials were not cytotoxic, with the exception of elastomer C. This material is the most lightly cross-linked and leaches a larger amount of oligomeric materials, which contribute to the high toxicity. If this material is extracted in methylene chloride before being subjected to the cytotoxicity assay and the oligomers are separated from the elastomer, then the toxicity is eliminated.

**Table 5. Properties of Elastomers Formed by Thermal Cross-Linking of Polyester 4 for 24 h Using 5 wt % AIBN at the Given Temperature**




| | | | weight loss (°C)[b] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| elastomer | $T_{cure}$ (°C) | $T_g$[a] (°C) | 5% | 10% | $E^c$ (MPa) | $\sigma^c$ (MPa) | $\epsilon^c$ (%) | $\nu^c$ (mmol/L) | $Q_s$[d] (%) |
| C | 130 | −16 | 243 | 264 | 0.05 | 0.08 | 195 | 7.0 | 51 |
| D | 145 | −12 | 263 | 288 | 0.4 | 0.4 | 161 | 60.4 | 41 |
| E | 160 | −15 | 266 | 291 | 11.5 | 1.5 | 87 | 1560 | 27 |

[a] Determined by DSC, second heat, 10 °C/min. [b] Determined by TGA in $N_2$, 10 °C/min. [c] Determined by Instron, 10 mm/min crosshead speed. [d] Extracted in methylene chloride for 24 h at 25 °C.

**Table 6. Properties of Sol-Removed Elastomers**

| | | | weight loss (°C)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| elastomer | $T_{cure}$ (°C) | $T_g$[a] (°C) | 5% | 10% | $E^c$ (MPa) | $\sigma^c$ (MPa) | $\epsilon^c$ (%) | $\nu^c$ (mmol/L) |
| C[d] | 130 | −16 | 242 | 266 | | | | |
| D[d] | 145 | −14 | 260 | 283 | 1.1 | 0.4 | 105 | 149 |
| E[d] | 160 | −14 | 262 | 292 | 40.6 | 2.1 | 12 | 5510 |

[a] Determined by DSC, second heat, 10 °C/min. [b] Determined by TGA in $N_2$, 10 °C/min. [c] Determined by Instron, 10 mm/min crosshead speed. [d] Extracted in methylene chloride for 24 h at 25 °C.

**Table 7. Cytotoxicity Results of Elastomers Formed by Thermal Cross-Linking**

| material tested | cytotoxicity grade[a] |
|---|---|
| elastomer C | 4 |
| elastomer D | 0 |
| elastomer E | 0 |
| elastomer C[b] | 0 |
| elastomer D[b] | 0 |
| elastomer E[b] | 0 |
| negative control, HDPE | 0 |
| reagent control, medium | 0 |
| positive controls, high [salt] | 4 |

[a] According to USP ⟨87⟩ standard. [b] Extracted in methylene chloride for 24 h at 25 °C.

## Conclusions

We have introduced a new monomer family based on cyclohex-4-ene 1,2-dicarboxylates synthesized from Diels−Alder chemistry that permit a variety of functional groups in good yields. Subsequent polymerization of these novel monomers was achieved under step growth conditions to yield high molecular weight amorphous polyesters. The thermal cross-linking of these materials allowed for the creation of degradable nontoxic elastomers. The scope of this method includes, but is not limited to, variation in the diene to yield new functionalized dicarboxylate monomers, incorporation of different diols or co-diols in the polyester synthesis, and variation of the cross-linking strategies to yield materials with an even wider range of mechanical properties. This new approach should allow for the solubility, mechanical properties, thermal properties, and topology of polyester materials to be designed and evaluated in a controlled manner as a means to study aliphatic polyesters intended for biomedical applications.

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**Supporting Information Available:** Detailed synthetic procedures and characterization data, including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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