Preparation of Unsaturated Linear Aliphatic Polyesters Using Condensation Polymerization

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ABSTRACT: A versatile method for preparing linear, unsaturated polyesters through condensation polymerization of *trans*-β-hydromuconic acid (HMA) with a variety of diols using $Sn(Oct)_2$ and Novozyme-435 as catalysts was explored. Poly(1,8-octanediol hydromuconoate) was the highest molecular weight homopolymer prepared with a $\langle M_n \rangle$ of 10.5×10^3 g/mol and polydispersity of 2.0. These materials showed unique melting behavior that was dependent on the number of carbons in the diol. Melting points ranged from 40 to 70 °C. Copolymers where the amount of HMA was diluted by adipic acid were prepared and had a $\langle M_n \rangle$ as high as 13.0×10^3 g/mol and polydispersities below 2.0. The double bonds of these materials were chemically modified through epoxidation in yields greater than 93% and with no degradation of the polymer backbone. Materials with hydroxyl end groups were prepared through stoichiometric mismatch. Unsaturated poly(ester ether)s that are amorphous liquids with T_g below −40 °C were prepared using diethylene glycol as the diol.

Introduction

Aliphatic polyesters continue to be of significant interest in biomedical applications ranging from drug delivery to medical devices and tissue engineering. Some of the most common examples include poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(ϵ-caprolactone) (PCL), and their copolymers.[1] Despite their utility, there remains a need to design materials with more variation in solubility, crystallinity, polarity, and reactivity. This need for an expanded set of properties has driven research in the area of preparing aliphatic polyesters with tunable properties.

Most examples of these functionalized materials have been prepared via ring-opening polymerization (ROP) of derivatized lactones or lactides and include materials with amino,[2−6] carboxyl,[4,7−10] and hydroxyl[4,11−13] groups. Although these are examples of useful materials, collectively they leave some issues to be addressed. First, a complex synthesis of the functionalized ring is required. Second, postpolymerization deprotection, which can often lead to degradation of the polymer backbone, is required. Third, a new cyclic monomer must be synthesized for each different kind of functional group to be incorporated into the material, limiting the ease of tunability.

Comparatively, there are fewer examples of functionalized materials being prepared via polycondensation of a diacid derivative with a diol. Poly(propylene fumarate) (PPF), one of the most well-known of these materials, has been studied by Mikos and co-workers using traditional metal catalysis.[14] The unsaturation allows for the materials to be cross-linked in situ. However, the highly reactive conjugated double bond gives rise to side reactions, which prevent the formation of high molecular weight linear prepolymers ($\langle M_n \rangle$ 1.5×10^3, PDI 2.8).[15] Higher molecular weight materials ($\langle M_n \rangle$ 4.6×10^3, PDI 2.3) were prepared, but hydroquinone was required as a cross-linking inhibitor.[16]

More recently, enzymes have been explored as polycondensation catalysts.[17,18] The inherent selectivity of the enzyme has been explored to polymerize functionalized monomers without the necessity for postpolymerization deprotection. Russell and Kobayashi have prepared hydroxyl-functionalized materials from trifunctional alcohols and divinyl acid derivatives.[19,20] Gross has demonstrated the direct condensation of a diacid with either sorbitol or glycerol to make similar hydroxyl-functionalized materials.[21] While these are examples of useful materials, they offer only hydroxyl functionality and are not completely linear. Sorbitol yielded 85% 1,6 regioselectivity, while glycerol only yielded 66% 1,3 regioselectivity.[21]

Our interest in the synthesis of aliphatic polyesters is focused on three objectives. First, the polymerization reaction must produce linear, unsaturated materials without the addition of cross-linking inhibitors. Second, the polymerization method must be versatile enough to allow for the facile preparation of a variety of different materials and the control of end groups. Third, the thermal and solubility properties of these materials must be easily varied. This paper describes a versatile route to functionalized aliphatic polyesters through polycondensation of an unsaturated diacid with a saturated diol, using metal and enzyme catalysts. The double bond can then be modified through epoxidation. Furthermore, variation of the diol or diacid allows for the preparation of different classes of materials while providing the ability to easily vary the thermal and solubility properties. Performing the polymerizations in bulk circumvents the use of an organic solvent. While ROP can produce molecular weights in excess of 100 000 g/mol in minutes, this polycondensation method offers a unique route to materials for specialty applications by using commercially available monomers and mild postpolymerization reactions that do not degrade the polymer chain. This method also offers an expanded ability to tune the solubility and thermal properties of the materials by varying the diol. *trans*-β-Hydromuconic acid (HMA) was used as the unsaturated diacid to eliminate the problems previously described with fumaric acid.

Experimental Section

Materials. All reagents were purchased from Aldrich and used without further purification, unless otherwise noted. Novozyme-435 was dried under vacuum at 25 °C for 24 h prior to use. *trans*-β-Hydromuconic acid (HMA) was purified by recrystallization from

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water and acetonitrile. 1,4-Butanediol, 1,5-pentanediol, and 1,7-heptanediol were distilled prior to use. 1,6-Hexanediol and 1,8-octanediol were recrystallized from tetrahydrofuran, and 1,9-nonanediol and 1,10-decanediol were recrystallized from ethanol prior to use. 3-Chloroperoxybenzoic acid (mCPBA) was rinsed with pH 7.4 buffer and dried under vacuum at 25 °C for 24 h prior to use.

Characterization. ^{1}H and ^{13}C NMR spectra were acquired in deuterated chloroform on a Bruker 400 AVANCE or Bruker 300 AMX spectrometer. Molecular weights, relative to narrow polystyrene standards, were measured using a Waters GPC system with a Wyatt Optilab DSP interferometric refractometer and a Wyatt Dawn EOS as the detector. The measurements were taken at 40 °C with tetrahydrofuran as the mobile phase on three columns (Waters Styragel HR2, HR4, and HR5). Glass transitions and melting points were measured with a Seiko 220C differential scanning calorimeter, using a heating rate of 10 °C/min and a cooling rate of either 10 or 100 °C/min. Three complete cycles were recorded with a 10 min annealing period between the second and third cycle. Thermogravimetric analysis was carried out using a Perkin-Elmer TGA 7 with a heating rate of 20 °C/min in a N_2 atmosphere. Elemental analysis was performed by Atlantic Microlab, Inc. Glass transitions were determined at the inflection point of the endotherm, and melting and crystallization points were determined at the peak of the endotherm or exotherm, respectively. FTIR spectra were acquired in a mull on a Mattson Galaxy Series 3000 instrument.

Homopolymer Synthesis. *Metal Catalyzed*. HMA (1.0 equiv) and diol (1.0 equiv) were stirred in a 10 mL round-bottom flask at 130 °C using magnetic stirring, until a homogeneous melt was formed. Upon formation, Sn(Oct)$_2$ (0.1 equiv) was added to the melt, and the flask was sealed with a rubber septum. The mixture was stirred for 1 h, when the pressure was reduced to 30 mmHg. The reaction was allowed to proceed at 30 mmHg for 5 h, when the polymer was precipitated into stirring methanol. Reactions were performed on a 5 g scale.

Enzyme Catalyzed. HMA (1.0 equiv) and diol (1.0 equiv) were stirred in a 10 mL round-bottom flask at 115 °C using magnetic stirring, until a homogeneous melt was formed. Upon formation, the temperature was slowly reduced in 10 °C increments to 90 °C. Novozyme-435 (10 wt % of the total monomer wt) was then added, and the flask was sealed with a rubber septum. The heterogeneous mixture was stirred for 2 h, when the pressure was reduced to 250 mmHg. The reaction was allowed to proceed at 250 mmHg for 22 h, when the pressure was further reduced to 40 mmHg. The reaction proceeded at 40 mmHg for an additional 24 h, for a total reaction time of 48 h. After 48 h, the mixture was diluted with 2 mL of chloroform and the Novozyme-435 was removed by filtration. The diluted melt was precipitated into stirring methanol. Reactions were performed on a 5 g scale.

Poly(alkyldiol hydromuconoate). ^{1}H and ^{13}C NMR data are give for poly(1,8-octanediol hydromuconoate). These data are representative of all materials prepared from diols 1,4-butanediol to 1,10-decane diol. ^{1}H NMR data vary only by the integration area under the peak at 1.30 ppm. ^{13}C NMR data vary only by the number of peaks less than 33 ppm. ^{1}H NMR: δ (ppm) = 5.67 (m, 1H), 4.04 (t, 2H, J = 6.8 Hz), 3.06 (dd, 2H, J = 1.6, 3.8 Hz), 1.60 (t, 2H, J = 6.7 Hz), 1.30 (s, 4H). ^{13}C NMR: δ (ppm) = 171.65 (CO_2), 125.94 ($-CH{=}CHCH_2-$), 64.89 ($-CH_2O$), 37.84 ($-CH_2CH{=}CH-$), 29.08 ($-CH_2CH_2CH_2CH_2O$), 28.51 ($-CH_2CH_2O$), 25.77 ($-CH_2CH_2CH_2O$). Elemental analysis is listed by the diol used to prepare the given polymer. Anal. Calcd for 1,4-butanediol $C_{10}H_{14}O_4$: C, 60.59; H, 7.12; O, 32.29. Found: C, 59.79; H, 7.02. Anal. Calcd for 1,5-pentanediol $C_{11}H_{16}O_4$: C, 62.25; H, 7.60; O, 30.15. Found: C, 61.36; H, 7.58. Anal. Calcd for 1,6-hexanediol $C_{12}H_{18}O_4$: C, 63.70; H, 8.02; O, 28.28. Found: C, 62.92; H, 7.91. Anal. Calcd for 1,7-heptanediol $C_{13}H_{20}O_4$: C, 64.98; H, 8.39; O, 26.63. Found: C, 64.11; H, 8.31. Anal. Calcd for 1,8-octanediol $C_{14}H_{22}O_4$: C, 66.12; H, 8.72; O, 25.16. Found: C, 65.98; H, 8.69. Anal. Calcd for 1,9-nonanediol $C_{15}H_{24}O_4$: C, 67.14; H, 9.01; O, 23.85. Found: C, 66.97; H, 9.12. Anal. Calcd for 1,10-decanediol $C_{16}H_{26}O_4$: C, 68.06; H, 9.28; O, 22.66. Found: C, 67.42; H, 9.33. Yields are listed by the diol used to prepare the given polymer and for metal catalysis, unless otherwise noted: 1,4-butanediol: 84% yield; 1,5-pentanediol: 89% yield; 1,6-hexanediol: 86% yield; 1,7-heptanediol: 89% yield; 1,8-octanediol: 98% yield (94% yield enzyme catalyzed); 1,9-nonanediol: 85% yield; 1,10-decanediol: 90% yield.

Poly(Diethylene glycol hydromuconoate). ^{1}H NMR: δ (ppm) = 5.65 (m, 1H), 4.19 (t, 2H, J = 4.6 Hz), 3.67 (t, 2H, J = 3.5 Hz), 3.07 (dd, 2H, J = 1.6, 3.7 Hz). ^{13}C NMR δ (ppm) = 171.35 (CO_2), 125.72 ($-CH{=}CHCH_2-$), 68.78 ($-CO_2CH_2CH_2O-$), 63.53 ($-CO_2CH_2CH_2O-$), 37.43 ($-CH_2CH{=}CH-$). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59; O, 37.34. Found: C, 55.98; H, 6.66. Yield 96%.

Copolymer Synthesis. A modified version of the homopolymer synthesis was used for the copolymer synthesis. This modified procedure is illustrated by a representative procedure for a 10% HMA copolymer. HMA (0.2 equiv), adipic acid (0.8 equiv), and diol (1 equiv) were added to a 10 mL round-bottom flask with a magnetic stir bar. The remainder of the procedure is identical to the metal- or enzyme-catalyzed homopolymer procedure, respectively. All reactions were performed on a 5 g scale.

Poly(1,8-octanediol hydromuconoate-*co*-1,8-octanediol adipate). ^{1}H NMR: δ (ppm) = 5.67 (m, 1H), 4.03 (t, 2H, J = 6.8 Hz), 3.06 (dd, 2H, J = 1.6, 3.8 Hz), 2.30 (t, 2H, J = 7.0 Hz), 1.63 (m, 4H), 1.30 (s, 4H). ^{13}C NMR: δ (ppm) = 173.44 (CO_2, AA), 171.66 (CO_2, HMA), 125.88 ($-CH{=}CHCH_2-$), 64.77 ($-CH_2O$, HMA:OD), 64.41 ($-CH_2O$, AA:OD), 37.79 ($-CH_2CO_2$, HMA:OD), 33.86 ($-CH_2CO_2$, AA:OD), 29.02 ($-CH_2CH_2CH_2CH_2O$), 28.50 ($-CH_2CH_2O$, HMA:OD), 28.44 ($-CH_2CH_2O$, AA:OD), 25.75 ($-CH_2CH_2CH_2O$, HMA:OD), 25.71 ($-CH_2CH_2CH_2O$, AA:OD), 24.34 ($-CH_2CH_2CO_2$, AA). ^{1}H NMR varies only by the relative integrated peak areas for all copolymers. ^{13}C NMR are identical for all copolymers. Elemental analysis is listed by mol percent HMA in the copolymer. Anal. Calcd 10% HMA: C, 65.70; H, 9.30; O, 25.01. Found: C, 65.44; H, 9.29. Anal. Calcd 20% HMA: C, 65.81; H, 9.15; O, 25.05. Found: C, 65.89; H, 9.29. Anal. Calcd 30% HMA: C, 65.91; H, 9.01; O, 25.08. Found: C, 65.89; H, 9.14. Anal. Calcd 40% HMA: C, 66.02; H, 8.86; O, 25.12. Found: C, 65.87; H, 8.94. Yields are listed by the diol used to prepare the given polymer and designated MC for metal catalysis and EC for enzyme catalysis. 10% HMA: EC 95% yield; MC 87% yield. 20% HMA: EC 94% yield; MC 88% yield. 30% HMA: EC 95% yield; MC 89% yield. 40% HMA: EC 96% yield; MC 86% yield.

Hydroxyl-Terminated Materials. HMA (0.918 or 0.880 equiv) and 1,8-octanediol (1.0 equiv) were stirred in a 10 mL round-bottom flask at 115 °C using magnetic stirring until a homogeneous melt formed. Upon formation, Sn(Oct)$_2$ (0.1 equiv) was added to the melt, and the flask was sealed with a rubber septum. The mixture was stirred for 1 h, when the pressure was reduced to 30 mmHg. After 5 h of total reaction time, the pressure was further reduced to 10 mmHg. The reaction was allowed to proceed at 10 mmHg for 1 h, for a total reaction time of 6 h. The polymerization was terminated by precipitating the mixture into stirring methanol. Reactions were performed on a 5 g scale.

Poly(1,8-octanediol hydromuconoate). ^{1}H NMR: δ (ppm) = 5.66 (m, 1H), 4.04 (t, 2H, J = 6.75 Hz), 3.61 (t, $-CH_2OH$ end group, J = 6.5 Hz), 3.06 (dd, 2H, J = 1.6, 3.8 Hz), 1.59 (t, 2H, 6.6 Hz), 1.29 (s, 4H). ^{13}C NMR: δ (ppm) = 171.65 (CO_2), 125.94 ($-CH{=}CHCH_2-$), 64.89 ($-CH_2O$), 62.01 ($-CH_2OH$ alcohol end group), 37.84 ($-CH_2CH{=}CH-$), 29.08 ($-CH_2CH_2CH_2CH_2O$), 28.51 ($-CH_2CH_2O$), 25.77 ($-CH_2CH_2CH_2O$). IR: 3398.45 cm^{-1}, ($HOCH_2-$ alcohol end group). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72; O, 25.16. Found: C, 65.98; H, 8.71. 99% yield.

Epoxidation. A representative example for epoxidation of poly(1,8-octanediol hydromuconoate) is as follows. Poly(1,8-octanediol hydromuconoate) (1.0 g, 3.9 mmol) was dissolved in 15 mL of methylene chloride in a 25 mL round-bottom flask. To the solution was added 3-chloroperoxybenzoic acid (1.36 g, 7.9 mmol), and the solution was allowed to stir under magnetic stirring for 12 h. At the end of 12 h, a white precipitate had formed. The precipitate was removed by filtration, and the filtered solution was washed twice with 1 M sodium bicarbonate solution. The solution was then concentrated and precipitated into cold methanol (−78 °C).

Poly(alkyldiol 3,4-anhydro-2,5-dideoxyhexaroate). ^{1}H and ^{13}C NMR data are give for poly(1,8-octanediol 3,4-anhydro-2,5-dideoxyhexaroate). These data are representative of all materials prepared from diols 1,4-butanediol to 1,10-decane diol. ^{1}H NMR data vary only by the integration area under the peak at 1.29 ppm. ^{13}C NMR data vary only by the number of peaks less than 37 ppm. ^{1}H NMR: δ (ppm) = 4.08 (t, 2H, J = 6.8 Hz), 3.12 (t, 1H, J = 5.2 Hz), 2.57 (m, 2H), 1.60 (t, 2H, J = 6.5 Hz), 1.29 (s, 4H). ^{13}C NMR: δ (ppm) = 170.26 (CO_2), 65.02 ($-CH_2O$), 53.70 ($-C$HO, epoxide carbon), 37.31 ($-CH_2CO_2$), 29.02 ($-CH_2CH_2CH_2CH_2O$), 28.43 ($-CH_2CH_2O$), 25.71 ($-CH_2CH_2CH_2O$). Elemental analysis is listed by the diol used to prepare the given polymer. Any deviations that are larger than normal are accounted for by trace amounts of 3-chlorobenzoic acid. Anal. Calcd for 1,4-butanediol $C_{10}H_{14}O_5$: C, 56.07; H, 6.59; O, 37.34. Found: C, 55.07; H, 7.50. Anal. Calcd for 1,5-pentanediol $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; O, 30.05. Found: C, 56.12; H, 6.03. Anal. Calcd for 1,6-hexanediol $C_{12}H_{18}O_5$: C, 59.54; H, 7.49; O, 33.02. Found: C, 58.71; H, 6.51. Anal. Calcd for 1,7-heptanediol $C_{13}H_{20}O_5$: C, 60.92; H, 7.87; O, 31.21. Found: C, 59.21; H, 6.98. Anal. Calcd for 1,8-octanediol $C_{14}H_{22}O_5$: C, 62.20; H, 8.20; O, 29.59. Found: C, 61.42; H, 7.75. Anal. Calcd for 1,9-nonanediol $C_{15}H_{24}O_5$: C, 63.36; H, 8.51; O, 28.13. Found: C, 62.89; H, 8.49. Anal. Calcd for 1,10-decanediol $C_{16}H_{26}O_5$: C, 64.41; H, 8.78; O, 26.81. Found: C, 63.21; H, 8.12. Yields are listed by the diol used to prepare the given polymer: 1,4-butanediol: 98% yield; 1,5-pentanediol: 95% yield; 1,6-hexanediol: 94% yield; 1,7-heptanediol: 96% yield; 1,8-octanediol: 97% yield; 1,9-nonanediol: 98% yield; 1,10-decanediol: 96% yield.

Poly(1,8-octanediol 3,4-anhydro-2,5-dideoxyhexaroate-*co*-1,8-octanediol adipate). ^{1}H NMR: δ (ppm) = 4.08 (t, 2H, J = 6.8 Hz), 3.12 (t, 1H, J = 5.3 Hz), 2.57 (m, 2H), 2.29 (t, 2H, J = 7.0 Hz), 1.63 (m, 4H), 1.30 (m, 4H). ^{13}C NMR: δ (ppm) = 173.37 (CO_2, AA), 170.14 (CO_2, HMA), 64.90 ($-CH_2O$, HMA:OD), 64.33 ($-CH_2O$, AA:OD), 53.60 ($-C$HO, epoxide carbon), 37.19 ($-CH_2CO_2$, HMA:OD), 33.76 ($-CH_2CO_2$, AA:OD), 29.08 ($-CH_2CH_2CH_2CH_2O$), 28.40 ($-CH_2CH_2O$), 25.66 ($-CH_2CH_2CH_2O$), 24.24 ($-CH_2CH_2CO_2$, AA). ^{1}H NMR varies only by the relative integrated peak areas for all copolymers. ^{13}C NMR are identical for all copolymers. Elemental analysis is listed by mole percent HMA in the copolymer that was epoxidized. Any deviations that are larger than normal are accounted for by trace amounts of 3-chlorobenzoic acid. Anal. Calcd 10% HMA: C, 64.92; H, 9.19; O, 25.89. Found: C, 63.40; H, 8.64. Anal. Calcd 20% HMA: C, 64.24; H, 8.94; O, 26.82. Found: C, 63.71; H, 8.12. Anal. Calcd 30% HMA: C, 63.56; H, 8.70; O, 27.74. Found: C, 64.82; H, 8.21. Anal. Calcd 40% HMA: C, 62.88; H, 8.45; O, 28.67. Found: C, 63.91; H, 7.93. Yields are listed by the diol used to prepare the given polymer: 10% HMA: 95% yield; 20% HMA: 97% yield; 30% HMA: 95% yield; 40% HMA: 96% yield.

Solubility Testing. Solubility was characterized by placing 50 mg of polymer in a 5 mL tube. 1 mL of solvent was added to the tube, and the tube was shaken for 5 s. Materials were classified as freely soluble if the polymer had completely dissolved after 5 s. If the polymer did not dissolve after 5 s, the tube was heated and shaken for an additional 5 s. Materials were classified as insoluble if there was no visible amount of the polymer that dissolved. Materials were classified as partially soluble if the polymer dissolved after heating.

Cytotoxicity Testing. STS Duotek (Rush, NY) performed all cytotoxicity analysis. Minimum essential medium (MEM) elution tests were performed according to the ISO 10993-5 standard. 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.

Table 1. Characterization of *trans-β*-Hydromuconic Acid Polymerization with Various Diols

polymer	diol	$\langle M_n \rangle \times 10^{-3}$ (g/mol)^c	PDI^c	$\langle M_n \rangle \times 10^{-3}$ (g/mol)^d	5% wt loss^e	10% wt loss^e
1^a	C4	2.5	1.3	2.1	192	287
2^a	C5	3.4	1.9	5.7	327	335
3^a	C6	6.7	1.7	5.9	300	343
4^a	C7	7.2	1.6	6.0	327	338
5^a	C8	9.6	1.9	11.0	320	332
6^b	C8	10.5	2.0	13.0	328	340
7^a	C9	6.8	1.8	7.0	331	342
8^a	C10	6.0	1.8	6.7	334	346

[a] $Sn(Oct)_2$catalyst. [b] Novozyme-435 catalyst. [c] Determined by GPC. [d] Determined by ^{1}H NMR. [e] Determined by TGA in N_2.

Results and Discussion

Materials with a double bond along the polymer backbone were desired, as the double bond could be used for future functionalization or cross-linking. As a result, the first issue addressed was the feasibility of polycondensation to produce linear, unsaturated materials. *trans-β*-Hydromuconic acid (HMA) was chosen as it is a commercially available unsaturated monomer that does not contain the conjugation that leads to the side reactions/branching associated with fumaric acid. Indeed, metal catalysis of fumaric acid and 1,8-octanediol (C8) produced low molecular weight materials ($\langle M_n \rangle$ 2.0 × 10^3 g/mol, PDI 1.2). Using the same reaction conditions, the polymer made from HMA and C8 gave linear material in 98% yield with a $\langle M_n \rangle$ near 10.0 × 10^3 g/mol. The polymerization was then extended to yield polyesters from straight chain aliphatic diols ranging from 1,4-butanediol to 1,10-decanediol (C4−C10). None of the materials had polydispersities greater than 2.0, and all materials had yields greater than 85% (Table 1). The catalytic behavior of Novozyme-435, consisting of lipase B from *Candida antarctica* immobilized on a Lewatit macroporous resin, was also examined. The enzymatic catalyst required a longer reaction time of 48 h, lower reaction temperature (90 °C), and an increased amount of catalyst (10 wt %). Polymers from HMA and all diols (C4−C10) with comparable molecular weights and properties were obtained. The data for the enzymatically catalyzed HMA-C8 material are given in Table 1 (polymer **6**). The fact that the highest molecular weights and yields were achieved when C8 was used as the diol is in agreement with the data of Gross.[22]

Several observations were made with regard to the thermal properties of these unsaturated materials. First, all polymers (**1**−**8**) demonstrate melting points ranging from 40 to 70 °C, as determined by differential scanning calorimetry (DSC). Furthermore, these melting points increase in an oscillatory fashion, with the melting point of a material prepared from a diol with an odd number of carbons always being lower than that of an even diol material with one more carbon. Second, regardless of the differences in molecular weight, all materials demonstrate either multiple or broad melting points (Figure 1), although this broadening may be due to a decreased interval between the transition temperatures.

There is precedence for the even−odd oscillatory increase in melting points for multiple classes of materials, such as aliphatic and aromatic polyamides,[23,24] poly(imide−ester)s,[25] and aromatic and aliphatic polyesters.[26,27] Specifically for aliphatic polyesters, melting points show a general increase as the ratio of ester groups to methylene units in the material decreases.

Table 2. Thermal Data of Homopolymers from Diols C4 through C10[a]

diol	T_{m2} (°C)	T_{c2} (°C)	$\Delta H_{m2}{}^{d}$ (J/g)	$-\Delta H_{c2}$ (J/g)	$\Delta T_{m2}{}^{e}$ (°C)	T_{m3} (°C)	T_{c3} (°C)	$\Delta H_{m3}{}^{d}$ (J/g)	$-\Delta H_{c3}$ (J/g)	$\Delta T_{m3}{}^{e}$ (°C)
C4[b]	36, 44	20	59	60	8	36, 45	21	58	60	9
C5[b]	33	5	51	55	0	33	5	51	53	0
C6[b]	44, 50	24	55	56	6	42, 50	22	55	56	8
C7[b]	36	13	66	67	0	36	13	66	67	0
C8[b]	60, 64	46	84	85	4	60, 64	46	83	85	4
C9[b]	57	41	88	88	0	57	41	88	89	0
C10[b]	66	52	91	93	0	66	52	90	92	0
C4[c]	34, 42	7	57	58	8	33, 42	8	57	59	9
C5[c]	31, 38	−10	63	64	7	31, 38	−11	62	64	7
C6[c]	39, 46	9	52	53	7	39, 45	8	52	53	6
C7[c]	33, 39	2	64	65	6	32, 39	1	64	64	7
C8[c]	59, 64	40	78	81	5	59, 64	40	81	83	5
C9[c]	56	36	85	85	0	56	36	86	87	0
C10[c]	66	48	88	91	0	66	47	88	90	0

[a] Determined by DSC with the subscript following the symbol indicating the DSC cycle. [b] Cooling rate 10 °C/min. [c] Cooling rate 100 °C/min. [d] Enthalpy of both transitions when two are observed. [e] ΔT_m is the difference in melting points when two transitions are observed.

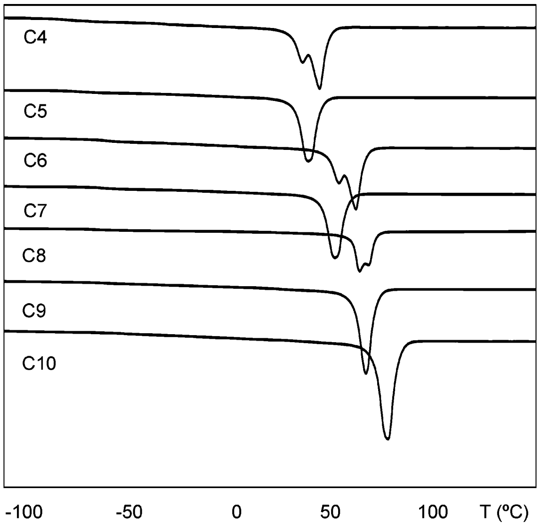


Figure 1. DSC thermograms of homopolymers from diols C4 through C10 using a 10 °C/min cooling rate.

The oscillatory nature of the increase is explained by differences in chain packing. Chains of materials with an even number of carbons between the ester groups pack in a planar fashion, with one chain above the other. Conversely, chains of materials with an odd number of carbons between the ester groups shift alongside one another, thus adopting a nonplanar arrangement. Our materials show the same trends as these similar polyester materials.

The second more unusual observation with regard to the melting points of our materials is that they demonstrate either multiple or broad melting points, while showing a single sharp T_c regardless of the cooling rate or heating cycle (Figure 1, Table 2). Melting points obtained from the second and third DSC heating cycles, with a 10 min annealing period at 125 °C in between the two cycles and a cooling rate of 10 °C/min, are nearly identical. Enthalpies of melting and of crystallization were also nearly equal for both the second and third cycles. At first glance, it appears that only materials prepared from diols with an even number of carbons demonstrate two melting points. However, it should be noted that the broad transitions of the other materials can be due to an unresolvable interval between the transitions. To further investigate the broad nature of these melting points, the cooling rate was increased to 100 °C/min. Just as the case was with the 10 °C/min cooling rate experiments, the melting points and enthalpies of melting and crystallization from the second and third heating cycles were nearly identical (Table 2). Additionally, the broad melting points for the C5 and C7 materials were resolved to two clearly visible melting points (Figure 2).

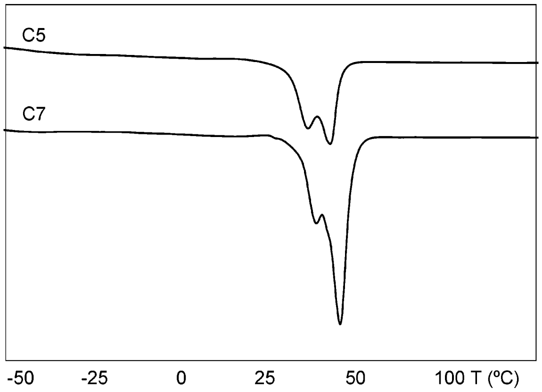
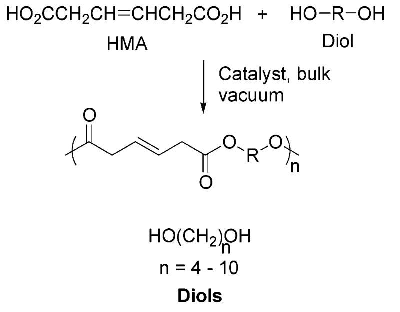


Figure 2. DSC thermograms of homopolymers from diols C5 and C7 using a 100 °C/min cooling rate.

Scheme 1. Synthesis of HMA Homopolymers



Careful analysis of the intervals between the two melting points shows that they decrease as the length of the diol increases, until they finally converge to an unresolvable interval (Table 2). Therefore, the peak broadening can indeed be attributed to closely located melting points. A possible explanation for this behavior is that the concentration of unsaturation in the material reduces the interval between melting points.

The ability to produce linear, unsaturated homopolymers and the question of how the relative concentration of unsaturation affected their melting behavior led to our extension of this chemistry to copolymers, where the amount of HMA in the C8 materials (polymers **5** and **6**) was diluted by adipic acid (Scheme 2, Table 3). These materials were prepared using the same polycondensation conditions that were used to prepare homopolymers. The ratio of HMA and adipic acid was varied so that the total amount of diacid was equimolar with the amount of diol. The ratio of HMA and adipic acid that was incorporated

Scheme 2. Synthesis of HMA−Adipic Acid Copolymers

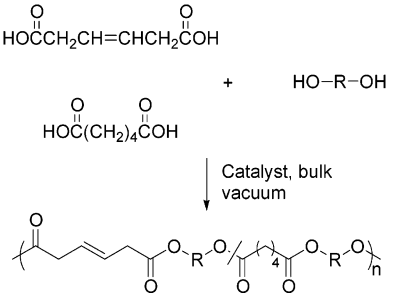


Table 3. Molecular Weight and Yield of HMA−Adipic Acid Copolymers Prepared Using Optimized Polycondensation Conditions

polymer	targeted HMA:AA:OD	observed[c] HMA:AA:OD	$\langle M_n \rangle \times 10^{-3}$ (g/mol)[d]	PDI[d]	$\langle M_n \rangle \times 10^{-3}$ (g/mol)[c]
9[a]	10:40:50	10:40:50	13.0	2.0	13.3
10[a]	20:30:50	20:30:50	10.2	1.8	11.8
11[a]	30:20:50	30:20:50	8.9	1.6	9.7
12[a]	40:10:50	40:10:50	9.9	1.8	9.3
13[b]	10:40:50	10:40:50	6.0	1.2	6.3
14[b]	20:30:50	20:30:50	6.3	1.2	7.0
15[b]	30:20:50	30:20:50	5.4	1.3	5.9
16[b]	40:10:50	40:10:50	4.7	1.3	4.4
17[e]	10:40:50	10:40:50	9.2	1.3	8.1
18[f]	10:40:50	10:40:50	11.6	1.4	12.0

[a] Novozyme-435 catalyst, 48 h. [b] $Sn(Oct)_2$ catalyst, 6 h. [c] Determined by ^{1}H NMR. [d] Determined by GPC. [e] $Sn(Oct)_2$ catalyst, 24 h. [f] $Sn(Oct)_2$ catalyst, 48 h.

into the polymer was characterized by ^{1}H NMR. Regardless of the catalyst used, the observed ratio was identical to the targeted ratio (Table 3). The catalyst choice, however, did affect the molecular weight of the materials. Novozyme-435 yielded materials with number-average molecular weights that were on average 3 × 10^3 g/mol higher than the $Sn(Oct)_2$-catalyzed polycondensations. Yields of the $Sn(Oct)_2$-catalyzed polymerizations were also 10−20% lower. Polymerization times of the $Sn(Oct)_2$-catalyzed 10% copolymers were extended to 24 and 48 h to investigate whether the number-average molecular weights and yields could be increased. Yields increased to ∼97% for both times, and number-average molecular weights increased to above 11.0 × 10^3 g/mol.

The thermal properties of polymers **9**−**16** were investigated to see how the relative concentration of the HMA double bond affected the melting behavior of the polymers. Materials using C8 as the diol were chosen because homopolymers derived from C8 and HMA (polymers **5** and **6**) display two melting points. As was the case with the homopolymer materials, copolymers **9**−**16** demonstrated melting points less than 70 °C, decreasing to near 60 °C as the mole percent concentration of HMA increased (Table 4). This shift to lower melting points seems to be an enthalpic effect as the values for ΔS_m are similar for all materials. A similar double melting point phenomenon was also seen in these copolymer materials. However, the data indicate that the molar concentration of HMA affects this double melting. Copolymers with less than 30 mol % HMA in the monomer feed only display a single melting point, although melting points for polymer **11** were broad compared to polymers **9** and **10**. It is not until the concentration of HMA is greater than or equal to 30 mol % that the polymers display two melting points.

As with the homopolymer materials discussed above, melting points obtained from the second and third DSC heating cycles, with a 10 min annealing period at 125 °C in between the two cycles and a cooling rate of 10 °C/min, are nearly identical. Again, the enthalpies of melting and crystallization were also nearly identical from the second and third cycles. The cooling rate in the DSC experiments was increased to 100 °C/min, just as with the homopolymers, to see whether two melting points could be resolved for the materials with HMA concentrations less than 30. In contrast to the C5 and C7 homopolymers, the 10 and 20 mol % HMA materials did not show two melting points when the cooling rate was increased.

Analysis of the ratio of methylene units to double bond in the repeat unit shows that these findings are consistent with what was seen with the homopolymers. As this ratio increases, the concentration of double bonds in the material decreases. Polymer **7** (C9 material), the first material to show broad, but unresolvable double melting points, has a methylene unit to double bond ratio of 11, while polymer **6** (C8 material), the last material to show resolvable double melting points, has a ratio of 10. Copolymers **9** and **10** have methylene unit to double bond ratios of 11.6 and 11.2, respectively. Copolymer **11**, the first copolymer to show resolvable double melting points, has a ratio of 10.8. Therefore, these data together indicate that the methylene unit to double bond ratio must be less than 10.8 in order to see two melting points. The lower the value for this ratio, the more separated the two melting points are.

The next question to be examined was one of how chemical modification of the double bond affects the melting behavior of the materials. To address this issue, the unsaturated materials were epoxidized. Epoxidation was chosen because it was expected to be a high yield reaction that would introduce a polar functional group and simultaneously alter the crystallinity of the material. Morrow has previously prepared the epoxidixed C4 material from the bis(2,2,2-trichloroethyl) ester of HMA. Number-average molecular weights of 5.0 × 10^3 g/mol were obtained using lipase catalysis with a reaction time of 3.5 days.[28] Our epoxidation reaction was accomplished with 3-chloroperoxybenzoic acid (mCPBA) in methylene chloride for 12 h at room temperature. The reaction proved to be very mild and proceeded in greater than 93% yield. Number-average molecular weight and PDI of the materials before and after epoxidation were virtually unchanged by GPC, indicating little to no degradation of the polymer chain. Materials were characterized by ^{1}H and ^{13}C NMR in *d*-chloroform. Figure 3 illustrates the shift of the vinylic proton (b) from 5.7 to 3.1 ppm in the ^{1}H NMR spectrum.

Epoxidation dramatically affected the thermal properties of the materials. Melting points were reduced to near room temperature for the C8 homopolymers (materials prepared from polymers **5** and **6**). Homopolymers derived from diols C4 through C6 were made completely amorphous by epoxidation (Table 5). Copolymers had sharp melting points ranging from 50 °C to near room temperature. Again, three DSC cycles with varying cooling rates and annealing periods between cycles were collected. The second and third cycles showed similar results with regard to enthalpy of melting and crystallization and melting and crystallization points. Epoxidation dramatically lowered enthalpies of melting. Moreover, no materials showed two melting points in their thermograms, regardless of cooling rate, supporting the idea that the unsaturated double bonds of the unepoxidized materials affects the multiple or broad transition behavior of the materials. Materials displayed glass transition temperatures near negative 40 °C.

To further demonstrate the control of these condensation polymerizations, homopolymers with controlled end groups and molecular weights were prepared. Homopolymers of HMA and C8 were prepared with hydroxyl end groups through simple

Table 4. Thermal Properties of HMA−Adipic Acid Copolymer Materials

polymer	HMA:AA:OD	T_m[c] (°C)	ΔH_m[c] (J/g)	ΔS_m[d]	CH_2:DB[e]	5% wt loss[f]	10% wt loss[f]
19	0:50:0	67	120	1.8	0	370	391
9[a]	10:40:50	65	111	1.7	11.6	367	386
10[a]	20:30:50	63	105	1.7	11.2	358	378
11[a]	30:20:50	55, 58	95	1.7	10.8	365	386
12[a]	40:10:50	56, 60	88	1.5	10.4	379	392
5[a]	50:0:50	59, 64	80	1.4	10	320	332

[a] Novozyme-435 catalyst. [b] $Sn(Oct)_2$ catalyst. [c] Determined by DSC. [d] $\Delta S = \Delta H/T_m$. [e] Methylene unit to double bond ratio. [f] Determined by TGA in N_2.

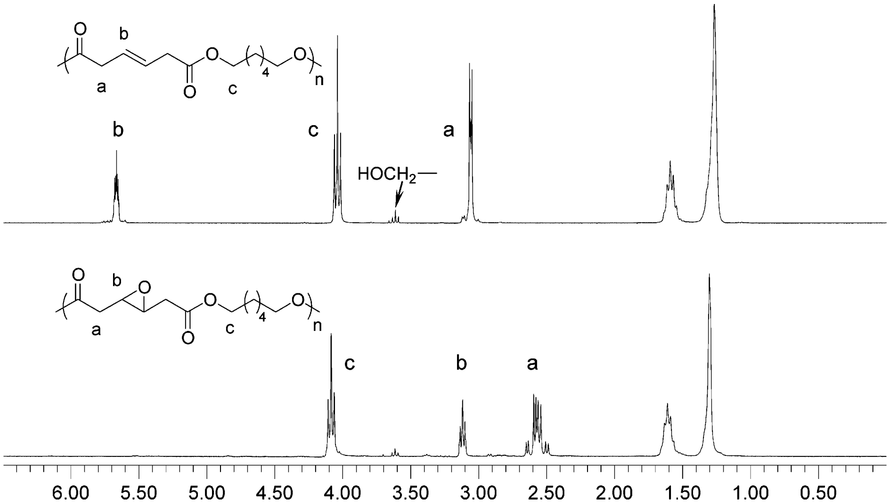


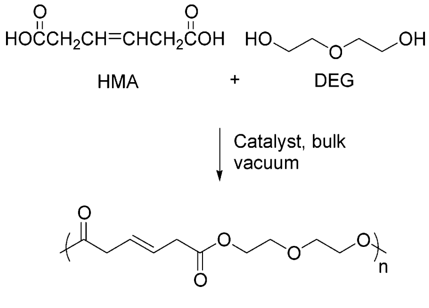
Figure 3. ^{1}H NMR of poly(1,8-octanediol hydromuconoate) before (top) and after (bottom) epoxidation.

Table 5. Molecular Weight and Thermal Properties of Epoxidized Materials

diol	$\langle M_n \rangle \times 10^{-3}$ (g/mol)[a]	PDI[a]	$\langle M_n \rangle \times 10^{-3}$ (g/mol)[b]	T_g[c]	T_m[c] (°C)	ΔH_m[c] (J/g)	5% wt loss[e]	10% wt loss[e]
C4	2.3	1.3	2.1	1.2	*d*	*d*	161	183
C5	3.3	1.9	3.5	−13	*d*	*d*	179	224
C6	6.5	1.4	6.2	−29	*d*	*d*	188	211
C7	7.1	1.5	8.0	−33	−10	1.4	203	223
C8	8.2	1.8	8.8	−37	22	15	225	262
C9	6.9	1.7	7.3	−36	17	15	163	177
C10	6.1	1.7	6.9	−35	39	20	150	162

[a] Determined by GPC. [b] Determined by ^{1}H NMR. [c] Determined by DSC. [d] Polymer is amorphous. [e] Determined by TGA in N_2.

Scheme 3. Synthesis of Poly(ester ether)s from HMA and Diethylene Glycol



stoichiometric mismatch. The observed molecular weights, 4.5 and 6.7 × 10^3 g/mol determined by ^{1}H NMR were very close to the targeted values of 4.0 and 6.0 × 10^3 g/mol, respectively. The presence of hydroxyl end groups and absence of acid end groups were confirmed by ^{13}C NMR. Infrared data support the presence of hydroxyl end groups with a broad OH stretch at 3398 cm^{-1}, above where the acid OH stretch typically appears.

The versatility of this polymerization method was demonstrated by preparing a different class of materials, poly(ester ether)s, using diethylene glycol as the diol (Scheme 3). The same polymerization conditions as those described above were used. Materials with number-average molecular weights of 1.5 × 10^3 and PDI of 1.8 were prepared in 6 h using $Sn(Oct)_2$ as the catalyst, in over 80% yield. When polymerization times were extended to 18 and 24 h, number-average molecular weights increased to 6.9 × 10^3 (PDI 1.2, 95% yield) and 8.3 × 10^3 g/mol (PDI 1.3, 96% yield), respectively. When Novozyme-435 was used as the catalyst, materials with a number-average molecular weight of 6.4 × 10^3 g/mol (PDI 1.2, 88% yield) were produced. Thermal properties of these materials were very different from the previously described materials. The materials were completely amorphous with glass transition temperatures near negative 40 °C. These liquid materials allow for the facile preparation of elastomers through cross-linking, potentially making them unique biodegradable, biocompatible elastomers.

This versatile method of condensation polymerization allows for the ability to modify the thermal properties of the materials. Materials with melting points between 25 and 70 °C as well as completely amorphous materials can easily be prepared. Not surprisingly, these materials also display a wide range of solubility properties (Table 6). The solubility varies from water insoluble homo- and copolymers to partially water-soluble poly(ester ether)s.

Finally, given the potential use of these materials for biomedical applications, the cytotoxicity characteristics of these materials were tested. A minimum essential medium (MEM) elution test was performed on homopolymers, copolymers, and epoxidized materials. The materials were extracted with a minimal essential medium for 24 h at physiological conditions.

Table 6. Solubility Characteristics of Unsaturated and Epoxidized Materials[a]

material[b]	water	methanol	acetone	THF	DCM	hexanes
HMA−AA copolymer	−	−	−	+	+	−
HMA-C8 homopolymer	−	−	−	+	+	−
epoxidized homopolymer	−	=	+	+	+	−
DEG homopolymer	=	+	+	+	+	−

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

The extracts were then placed on monolayers of L929 mouse fibroblast cells from the ATCC cell line. Materials were scored after 48 h. All homopolymers and copolymers had toxicity scores of 0.0, indicating no cytotoxic response. As anticipated, all epoxidized materials had toxicity scores of 4.4, indicating severe cytotoxic response.

Conclusions

The use of HMA instead of fumaric acid as the diacid allowed for the preparation of linear, unsaturated materials without the need of a cross-linking inhibitor. Homopolymers with a variety of thermal properties were prepared through simple variation of the diol. This versatile method was extended to prepare HMA: adipic acid copolymers. These materials showed double melting behavior in their DSC thermograms, with the relative concentration of double bonds in the material determining the separation between these two melting points. A maximum methylene unit to double bond ratio of 10.8 was required to resolve this double melting behavior. Finally, this double melting behavior was not seen when the double bond was chemically modified. We believe these findings support the conclusion that the unsaturation in the material is causing two crystalline modifications, although X-ray analysis is required to confirm the exact origin of the two melting points. Variation of the diol allowed for facile tuning of thermal properties, with materials with a 45 °C range of melting points being prepared. This versatile method also allowed for the preparation of poly(ester ether)s. These materials are novel in that they are unsaturated, liquid, and completely amorphous. Further work is planned to use these three properties to prepare degradable elastomers using both thermal and photoinitiators for cross-linking.

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Supporting Information Available: Representative fully assigned ^{1}H and ^{13}C NMR spectra for each class of materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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