Effect of Linker Structure on Salicylic Acid-Derived Poly(anhydride−esters)

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ABSTRACT: A series of salicylic acid-derived poly(anhydride−esters) were synthesized by melt polymerization methods, in which the structures of the molecule ("linker") linking together the two salicylic acids were varied. To determine the relationship between the linker and the physical properties of the corresponding poly(anhydride−ester), several linkers were evaluated including linear aliphatic, aromatic, and aliphatic branched structures. For the linear aliphatic linkers, higher molecular weights were obtained with longer linear alkyl chains. The most sterically hindered linkers yielded lower molecular weight polymers. The thermal decomposition temperature increased with the alkyl chain length, but the glass transition temperature decreased, due to the enhanced flexibility of the polymer. The highest glass transition temperatures were obtained by using aromatic linkers as a result of increased $\pi-\pi$ interactions. Water contact angles determined the relative hydrophobicity of the polymers, which correlated to hydrolytic degradation rates; i.e., the highest contact angle values yielded the slowest degrading polymers.

Introduction

Biodegradable polyanhydrides have been investigated for use in medical applications such as biomaterials[1−3] for tissue scaffolds[4,5] and drug delivery devices.[3,6−10] Polyanhydrides can undergo in vitro and in vivo hydrolytic bond cleavage to form water-soluble biocompatible degradation products.[11−13] In addition, the degradation rates of these polymers can be controlled by modifying the polymer composition.[14−16] Similar to poly(ortho esters), polyanhydrides generally undergo predominantly surface erosion,[13,17−20] in contrast to many other degradable polymers which are predominantly bulk-eroding.[15,16,21−23] This aspect is particularly relevant for controlled drug delivery as the degradation rate is surface area dependent and can be modified by manipulating the sample geometry.[14]

Previously, our laboratory reported the synthesis of poly(anhydride−esters) (**1f**) comprised of salicylic acid (**2**) as novel degradable biomaterials.[24−26] An important feature of homopolymer **1f** is that upon hydrolysis of the ester and anhydride bonds in the polymer backbone salicylic acid (**2**), a therapeutically active compound, and sebacic acid (**3f**) are released as outlined in Scheme 1.

Polymer **1f** is unique among polymeric biomaterials in that the drug is chemically incorporated into the polymer backbone, not attached as a side group.[27−32] This characteristic has three significant advantages. First, a high load of drug can be incorporated into the polymer; for example, ∼62 wt % for the polymer with sebacic acid linker (**1f**) is the drug, salicylic acid. Second, drug release is a function of the biocompatible linker[14] (e.g., compound **3f** in Scheme 1), which we define as the structure that connects the two salicylate units in polymer **1f**. Third, the polymer completely degrades because of the hydrolytically labile anhydride and ester bonds within the backbone. Examples of other salicylate-based polymers are found with low concentrations of salicylate (∼20 wt %) in the backbone[33] or which are simply homopolymers of salicylic acid[34,35] (i.e., no linker molecules) such that release of salicylate cannot be readily modified.

Based on our success with salicylic acid-derived poly(anhydride−esters),[5,24,25,36−43] alternate linkers to compound **3f** were investigated for inclusion into the polymeric backbone to modify the physical properties of the polymers as well as their degradation profiles. The linkers were chosen on the basis of their chemical structure and ranged from linear aliphatic and branched aliphatic to aromatic compounds (Table 1).

By incorporating these linker compounds, the polymer backbone delivers a high drug load of the chemically incorporated drug (salicylic acid), from 62 up to 74 wt %. This paper further describes how the polymers incorporating the linkers of Table 1 degraded into salicylic acid (**2**) and the corresponding carboxylic acid (**3a**−**j**) (Table 1) as a function of the linker molecule structure. The relationship between the linker structure and the physical properties of the corresponding polymer were assessed with respect to drug delivery; ultimately, our goal is to control polymer degradation and concurrent drug release by controlling the polymer composition.

Experimental Section

Materials. Tetrahydrofuran (THF), pyridine, acetic anhydride, methylene chloride, and diethyl ether were purchased from Fisher (Fair Lawn, NJ). All other fine chemicals and solvents were obtained from Aldrich (Milwaukee, WI) and used as received.

Methods. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian 200 MHz spectrometer. The samples (5−10 mg) were dissolved in deuterated solvents (DMSO-d_6), which was also used as the internal reference. Infrared (IR) spectra were measured on a Thermo Nicolet/Avatar 360 FT IR spectrometer, by depositing samples onto NaCl plates (if liquid) or solvent-casting samples from methylene chloride onto NaCl plates (if solid).

Weight-averaged molecular weights (M_w) were determined by gel permeation chromatography (GPC) on a Perkin-Elmer liquid chromatography system consisting of a series 200

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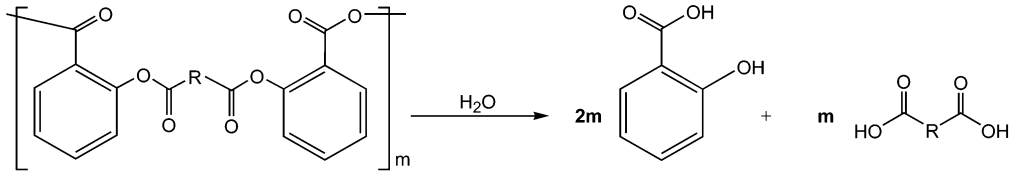
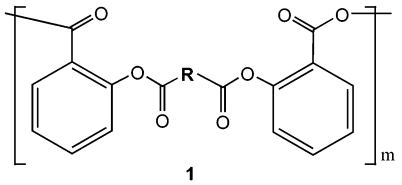
Scheme 1. Hydrolytic Degradation of Salicylic Acid-Derived Poly(anhydride−esters), 1

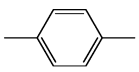
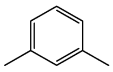


R = $(CH_2)_3$, **a**
$(CH_2)_4$, **b**
$(CH_2)_5$, **c**
$(CH_2)_6$, **d**
$(CH_2)_7$, **e**
$(CH_2)_8$, **f**
terephthalic, **g**
isophthalic, **h**
dimethylmalonic, **i**
diethylmalonic, **j**

Table 1. "Linker" Structures of R in Polymer 1



1

R		
Linear aliphatic	**Aromatic**	**Branched aliphatic**
$(CH_2)_3$ **a**		
$(CH_2)_4$ **b**	**g**	**i**
$(CH_2)_5$ **c**		
$(CH_2)_6$ **d**		
$(CH_2)_7$ **e**	**h**	**j**
$(CH_2)_8$ **f**		

refractive index detector, a series 200 LC pump, and an ISS 200 advanced sample processor. A Dell OptiPlex GX110 computer running Perkin-Elmer TurboChrom 4 software was used for data collection and processing and to automate the analysis via Perkin-Elmer Nelson 900 series interface and 600 series link. Polymers were dissolved in methylene chloride (5 mg/mL) and filtered through 0.45 μm poly(tetrafluoroethylene) (PTFE) syringe filters (Whatman, Clifton, NJ) before elution. Samples were resolved on a Jordi divinylbenzene mixed-bed GPC column (7.8 × 300 mm) (Alltech Associates, Deerfield, IL) at 25 °C, with methylene chloride as eluent at a flow rate of 0.5 mL/min. Molecular weights were calibrated relative to narrow molecular weight polystyrene standards (Polysciences, Dorval, Canada).

Thermal analyses were performed on a Perkin-Elmer system consisting of Pyris 1 DSC and TGA 7 analyzers with TAC 7/DX instrument controllers. Perkin-Elmer Pyris software was used for data collection on a Dell OptiPlex GX110 computer. For DSC, samples (5 mg) were heated under dry nitrogen gas. Data were collected at heating and cooling rates of 10 °C/min with a two-cycle minimum. Glass transition temperatures were calculated as half Cp extrapolated. For TGA, samples (10 mg) were heated under dry nitrogen gas. Data were collected at a heating rate of 10 °C/min. Decomposition temperatures were defined as the onset of decomposition.

Elemental analyses were provided by QTI (Whitehouse, NJ). Melting points below 200 °C were obtained with a Mel-Temp apparatus at a heating rate of 1 °C/min, while those above 200 °C were determined on the Pyris 1 DSC (see above).

Sessile-drop contact angles were measured on polymer-coated coverslips with a model 100 goniometer (Rame-Hart, Mountain Lakes, NJ). Polymers (100 mg) were dissolved in methylene chloride (1 mL), and 2−3 drops were added to the glass coverslips that were spun at 1800 rpm for 40 s using a photoresist spinner (Headway Research, Garland, TX).

Poly(anhydride−esters) Precursors: Diacid Synthesis (5). Diacids were prepared by reaction of salicylic acid with the appropriate acyl chloride in the presence of a base (pyridine). The preparation of **5a** is provided as an example. Salicylic acid (**2**) (3.1 g, 22 mmol) was dissolved in THF (40 mL) and pyridine (3.6 mL, 44 mmol). Glutaryl chloride (**4a**) (1.4 mL, 11 mmol) dissolved in tetrahydrofuran (10 mL) was added dropwise over 5 min to the stirring reaction mixture at room temperature to afford a suspension. The reaction was stirred for 2 h at room temperature, poured over water (400 mL), and acidified to pH ∼ 2 using concentrated hydrochloric acid while stirring. The off-white solid (diacid, **5**) that formed was isolated by vacuum filtration, washed with water (3 × 100 mL), and dried overnight under vacuum at room temperature.

1,5-Bis(*o*-carboxyphenoxy)pentanoate (5a). Yield: 71% (off-white powder). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.65 (t, 2H, ArH), 7.40 (t, 2H, ArH), 7.25 (d, 2H, ArH), 2.75 (t, 4H, CH_2), 2.50 (m, 2H, CH_2). IR (NaCl, cm^{-1}): 3600−3100 (OH, COOH), 1760 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 61.3%; H, 4.3%; O, 34.4%. Found: C, 61.2%; H, 4.3%; O, 34.5%; mp 132−133 °C.

1,6-Bis(*o*-carboxyphenoxy)hexanoate (5b). Yield: 92% (white powder). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.65 (t, 2H, ArH), 7.40 (t, 2H, ArH), 7.20 (d, 2H, ArH), 2.65 (t, 4H, CH_2), 1.75 (m, 4H, CH_2). IR (NaCl, cm^{-1}): 3600−3000 (OH, COOH), 1730 (C=O, ester), 1650 (C=O, COOH). Anal. Calcd: C, 62.2%; H, 4.7%; O, 33.1%. Found: C, 61.6%; H, 4.8%; O, 34.0%; mp 174−176 °C.

1,7-Bis(*o*-carboxyphenoxy)heptanoate (5c). Yield: 80% (white powder). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.65 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.20 (d, 2H, ArH), 2.60 (t, 4H, CH_2), 1.70 (m, 4H, CH_2), 1.50 (m, 2H, CH_2). IR (NaCl, cm^{-1}): 3650−3100 (OH, COOH), 1700 (C=O, ester), 1650 (C=O, COOH). Anal. Calcd: C, 63.0%; H, 5.0%; O, 32.0%. Found: C, 62.8%; H, 5.0%; O, 32.3%; mp 131−133 °C.

1,8-Bis(*o*-carboxyphenoxy)octanoate (5d). Yield: 89% (white powder). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.65 (t, 2H, ArH), 7.40 (t, 2H, ArH), 7.20 (d, 2H, ArH), 2.60 (t, 4H, CH_2), 1.65 (m, 4H, CH_2), 1.40 (m, 4H, CH_2). IR (NaCl, cm^{-1}): 3650−3100 (OH, COOH), 1760 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 63.8%; H, 5.3%; O, 30.9%. Found: C, 63.5%; H, 5.4%; O, 30.3%; mp 141−143 °C.

1,9-Bis(*o*-carboxyphenoxy)nonanoate (5e). Yield: 90% (off-white powder). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.65 (t, 2H, ArH), 7.40 (t, 2H, ArH), 7.20 (d, 2H, ArH), 2.55 (t, 4H, CH_2), 1.65 (m, 4H, CH_2), 1.40 (m, 6H, CH_2). IR (NaCl, cm^{-1}): 3650−3100 (OH, COOH), 1760 (C=O, ester), 1700 (C=

O, COOH). Anal. Calcd: C, 64.5%; H, 5.6%; O, 29.1%. Found: C, 64.0%; H, 5.6%; O, 29.3%; mp 101−103 °C.

1,10-Bis(*o*-carboxyphenoxy)decanoate (5f). Yield: 91% (white powder). ^{1}H NMR (DMSO-d_6): δ 7.90 (d, 2H, ArH), 7.60 (t, 2H, ArH), 7.40 (t, 2H, ArH), 7.20 (d, 2H, ArH), 2.55 (t, 4H, CH_2), 1.65 (m, 4H, CH_2), 1.35 (b, 8H, CH_2). IR (NaCl, cm^{-1}): 3500−3000 (OH, COOH), 1760 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 65.2%; H, 5.9%; O, 28.9%. Found: C, 64.5%; H, 5.8%; O, 29.7%; mp 128−129 °C.

***p*-Bis(*o*-carboxyphenoxy)benzoate (5g).** Yield: 92% (white solid). ^{1}H NMR (DMSO-d_6): δ 8.35 (s, 4H, ArH), 8.05 (d, 2H, ArH), 7.75 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.45 (d, 2H, ArH). IR (NaCl, cm^{-1}): 3300−3000 (OH, COOH), 1740 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 65.0%; H, 3.5%; O, 31.5%. Found: C, 64.6%; H, 3.4%; O, 31.3%; mp 212 °C.

***m*-Bis(*o*-carboxyphenoxy)benzoate (5h).** Yield: 90% (white solid). ^{1}H NMR (DMSO-d_6): δ 8.80 (s, 1H, ArH), 8.45 (d, 2H, ArH), 8.00 (d, 2H, ArH), 7.85 (t, 1H, ArH), 7.75 (t, 2H, ArH), 7.45 (t, 2H, ArH), 7.40 (d, 2H, ArH). IR (NaCl, cm^{-1}): 3650−3100 (OH, COOH), 1740 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 65.0%; H, 3.5%; O, 31.5%. Found: C, 64.3%; H, 3.7%; O, 32.0%; mp 415 °C.

2,2′-Bis(*o*-carboxyphenoxy)isopropanoate (5i). Yield: 84% (white solid). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.70 (t, 2H, ArH), 7.45 (t, 2H, ArH), 7.25 (d, 2H, ArH), 1.70 (s, 6H, CH_3). IR (NaCl, cm^{-1}): 3300−3000 (OH, COOH), 1755 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 61.3%; H, 4.3%; O, 34.1%. Found: C, 61.2%; H, 4.3%; O, 34.1%; mp 188 °C.

3,3′-Bis(*o*-carboxyphenoxy)pentanoate (5j). Yield: 80% (white solid). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H, ArH), 7.65 (t, 2H, ArH), 7.45 (t, 2H, ArH), 7.25 (d, 2H, ArH), 2.20 (q, 4H, CH_2), 1.00 (t, 6H, CH_3). IR (NaCl, cm^{-1}): 3600−3100 (OH,-COOH), 1750 (C=O, ester), 1700 (C=O, COOH). Anal. Calcd: C, 63.0%; H, 5.0%; O, 32.0%. Found: C, 63.1%; H, 5.0%; O, 32.2%; mp 157−158 °C.

Monomer Synthesis (6). The diacid (**5**) (3.0 g) was activated with stirring in an excess of acetic anhydride (50 mL) at room temperature until the initial suspension becomes a clear solution (∼3−12 h). The excess acetic anhydride is removed by rotoevaporation at room temperature under vacuum to afford the monomer.

1,5-Bis(*o*-carboxyphenoxy)pentanoate Monomer (6a). Yield: quantitative (colorless oil). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.80 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.35 (d, 2H, ArH), 2.75 (t, 4H, CH_2), 2.40 (s, 6H, CH_3), 2.00 (m, 2H, CH_2). IR (NaCl, cm^{-1}): 1810 (C=O, anhydride), 1760 (C=O, ester). T_d = 217 °C.

1,6-Bis(*o*-carboxyphenoxy)hexanoate Monomer (6b). Yield: quantitative (yellowish oil). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.80 (t, 2H, ArH), 7.55 (t, 2H, ArH), 7.35 (d, 2H, ArH), 2.65 (t, 4H, CH_2), 2.35 (s, 6H, CH_3), 1.75 (m, 4H, CH_2). IR (NaCl, cm^{-1}): 1800 (C=O, anhydride), 1760 (C=O, ester). T_d = 274 °C.

1,7-Bis(*o*-carboxyphenoxy)heptanoate Monomer (6c). Yield: quantitative (yellow oil). ^{1}H NMR (DMSO-d_6): δ 8.05 (d, 2H, ArH), 7.80 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.35 (d, 2H, ArH), 2.65 (t, 4H, CH_2), 2.35 (s, 6H, CH_3), 1.70 (m, 4H, CH_2), 1.50 (m, 2H, CH_2). IR (NaCl, cm^{-1}): 1820 (C=O, anhydride), 1760 (C=O, ester). T_d = 310 °C.

1,8-Bis(*o*-carboxyphenoxy)octanoate Monomer (6d). Yield: quantitative (white solid). ^{1}H NMR (DMSO-d_6): δ 8.05 (d, 2H, ArH), 7.80 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.35 (d, 2H, ArH), 2.65 (t, 4H, CH_2), 2.35 (s, 6H, CH_3), 1.70 (m, 4H, CH_2), 1.45 (m, 4H, CH_2). IR (NaCl, cm^{-1}): 1810 (C=O, anhydride), 1760 (C=O, ester). T_d = 359 °C.

1,9-Bis(*o*-carboxyphenoxy)nonanoate Monomer (6e). Yield: quantitative (colorless oil). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.80 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.35 (d, 2H, ArH), 2.65 (t, 4H, CH_2), 2.35 (s, 6H, CH_3), 1.65 (m, 4H, CH_2), 1.35 (m, 6H, CH_2). IR (NaCl, cm^{-1}): 1820 (C=O, anhydride), 1730 (C=O, ester). T_d = 345 °C.

1,10-Bis(*o*-carboxyphenoxy)decanoate Monomer (6f). Yield: quantitative (colorless oil). ^{1}H NMR (DMSO-d_6): δ 8.05 (d, 2H, ArH), 7.80 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.30 (d, 2H, ArH), 2.65 (t, 4H, CH_2), 2.35 (s, 6H, CH_3), 1.65 (m, 4H, CH_2), 1.35 (b, 8H, CH_2). IR (NaCl, cm^{-1}): 1830 (C=O, anhydride), 1730 (C=O, ester). T_d = 345 °C.

***p*-Bis(*o*-carboxyphenoxy)benzoate Monomer (6g).** Yield: quantitative (white solid). ^{1}H NMR (DMSO-d_6): δ 8.35 (s, 4H, ArH), 8.05 (d, 2H, ArH), 7.75 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.45 (d, 2H, ArH), 2.25 (s, 6H, CH_3). IR (NaCl, cm^{-1}): 1810 (C=O, anhydride), 1740 (C=O, ester). T_d = 354 °C.

***m*-Bis(*o*-carboxyphenoxy)benzoate Monomer (6h).** Yield: quantitative (white solid). ^{1}H NMR (DMSO-d_6): δ 8.85 (s, 1H, ArH), 8.55 (d, 2H, ArH), 8.15 (d, 2H, ArH), 7.90 (t, 1H, ArH), 7.75 (t, 2H, ArH), 7.60 (t, 2H, ArH), 7.55 (d, 2H, ArH), 2.25 (s, 6H, CH_3). IR (NaCl, cm^{-1}): 1800 (C=O, anhydride), 1740 (C=O, ester). T_d = 329 °C.

2,2′-Bis(*o*-carboxyphenoxy)isopropanoate Monomer (6i). Yield: quantitative (white solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.85 (t, 2H, ArH), 7.55 (t, 2H, ArH), 7.35 (d, 2H, ArH), 2.35 (s, 6H, CH_3), 1.70 (s, 6H, CH_3). IR (NaCl, cm^{-1}): 1810 (C=O, anhydride), 1760 (C=O, ester). T_d = 275 °C.

3,3′-Bis(*o*-carboxyphenoxy)pentanoate Monomer (6j). Yield: quantitative (white solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.85 (t, 2H, ArH), 7.60 (t, 2H, ArH), 7.40 (d, 2H, ArH), 2.35 (s, 6H, CH_3), 2.20 (q, 4H, CH_2), 1.0 (t, 6H, CH_3). IR (NaCl, cm^{-1}): 1810 (C=O, anhydride), 1760 (C=O, ester). T_d = 284 °C.

Polymer Synthesis (1). Monomer (**6**) (3.0 g) was placed in a 100 mL two-necked round-bottom flask with 24/40 joints with a vacuum joint in one neck and a Teflon vacuum-stirring adapter in the other. The reaction flask was heated to 160−180 °C using a temperature controller (Cole Parmer) in a silicone oil bath under high vacuum (<2 mmHg). During this time, the melt was actively stirred at ∼100 rpm by an overhead stirrer (T-line Laboratory Stirrer, Talboys Engineering, Montrose, PA). Polymerization was complete when the viscosity of the melt remained constant and/or solidified (3−6 h). The polymer was cooled to room temperature and isolated by precipitation in methylene chloride/diethyl ether (5 mL/100 mL). Polymers were soluble in organic solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and chlorinated solvents such as chloroform and methylene chloride.

Poly[1,5-bis(*o*-carboxyphenoxy)pentanoate] (1a). T_{polym} = 160 °C. Yield: quantitative (brown solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (b, 2H, ArH), 7.80 (b, 2H, ArH), 7.45 (b, 2H, ArH), 7.35 (b, 2H, ArH), 2.65 (b, 4H, CH_2), 1.90 (b, 2H, CH_2). IR (NaCl, cm^{-1}): 1760, 1700 (C=O, anhydride), 1730 (C=O, ester). M_w = 12 600, PDI = 1.8. T_d = 243 °C, T_g = 50 °C. Contact angle: 75°.

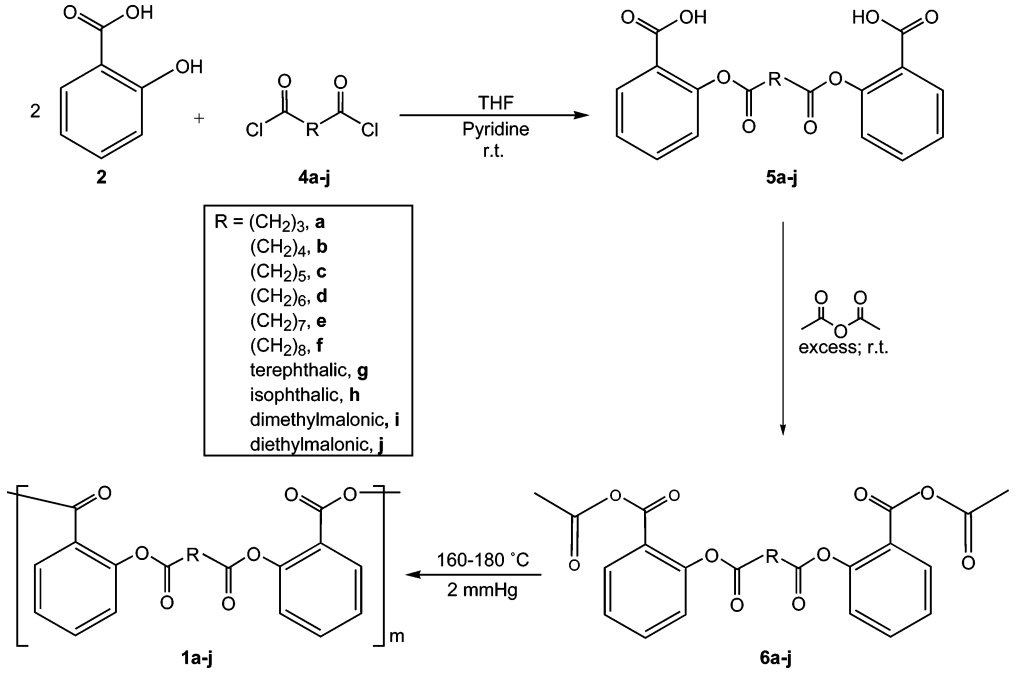
Poly[1,6-bis(*o*-carboxyphenoxy)hexanoate] (1b). T_{polym} = 160 °C. Yield: quantitative (brown solid). ^{1}H NMR (DMSO-d_6): δ 8.15 (b, 2H, ArH), 7.75 (b, 2H, ArH), 7.40 (b, 4H, ArH), 2.60 (b, 4H, CH_2), 1.60 (b, 4H, CH_2). IR (NaCl, cm^{-1}): 1780, 1700 (C=O, anhydride), 1740 (C=O, ester). M_w = 18 400, PDI = 2.6. T_d = 292 °C, T_g = 59 °C. Contact angle: 77°.

Poly[1,7-bis(*o*-carboxyphenoxy)heptanoate] (1c). T_{polym} = 180 °C. Yield: quantitative (light brown solid). ^{1}H NMR (DMSO-d_6): δ 8.15 (b, 2H, ArH), 7.75 (b, 2H, ArH), 7.40 (b, 2H, ArH), 7.25 (b, 2H, ArH), 2.60 (b, 4H, CH_2), 1.60 (b, 6H, CH_2). IR (NaCl, cm^{-1}): 1780, 1720 (C=O, anhydride), 1740 (C=O, ester). M_w = 29 700, PDI = 2.6. T_d = 313 °C, T_g = 40 °C. Contact angle: 88°.

Poly[1,8-bis(*o*-carboxyphenoxy)octanoate] (1d). T_{polym} = 180 °C. Yield: quantitative (colorless solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (b, 2H, ArH), 7.80 (b, 2H, ArH), 7.50 (b, 2H, ArH), 7.30 (b, 2H, ArH), 2.60 (b, 4H, CH_2), 1.50 (b, 4H, CH_2), 1.20 (b, 4H, CH_2). IR (NaCl, cm^{-1}): 1775, 1725 (C=O, anhydride), 1760 (C=O, ester). M_w = 30 200, PDI = 1.6. T_d = 341 °C, T_g = 30 °C. Contact angle: 87°.

Poly[1,9-bis(*o*-carboxyphenoxy)nonanoate] (1e). T_{polym} = 180 °C. Yield: quantitative (pale yellow solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (b, 2H, ArH), 7.75 (b, 2H, ArH), 7.45 (b, 2H, ArH), 7.25 (b, 2H, ArH), 2.65 (b, 4H, CH_2), 1.55 (b, 4H, CH_2), 1.25 (b, 6H, CH_2). IR (NaCl, cm^{-1}): 1790, 1730 (C=O, anhydride), 1750 (C=O, ester). M_w = 35 700, PDI = 1.9. T_d = 342 °C, T_g = 24 °C. Contact angle: 88°.

Scheme 2. Synthetic Scheme for Salicylic Acid-Derived Poly(anhydride−esters), 1



Poly[1,10-bis(*o*-carboxyphenoxy)decanoate] (1f). T_{polym} = 180 °C. Yield: quantitative (pale tan solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (b, 2H, ArH), 7.75 (b, 2H, ArH), 7.30 (b, 4H, ArH), 2.45 (b, 4H, CH_2), 1.55 (b, 4H, CH_2), 1.25 (b, 8H, CH_2). IR (NaCl, cm^{-1}): 1790, 1740 (C=O, anhydride), 1760 (C=O, ester). M_w = 43 000, PDI = 1.6. T_d = 351 °C, T_g = 27 °C. Contact angle: 88°.

Poly[*p*-bis(*o*-carboxyphenoxy)benzoate] (1g). T_{polym} = 180 °C. Yield: quantitative (beige solid). ^{1}H NMR (DMSO-d_6): δ 8.15 (b, 6H, ArH), 7.80 (b, 2H, ArH), 7.50 (b, 4H, ArH). IR (NaCl, cm^{-1}): 1790, 1740 (C=O, anhydride), 1740 (C=O, ester). M_w = 17 100, PDI = 1.8. T_d = 403 °C, T_g = 118 °C. Contact angle: 81°.

Poly[*m*-bis(*o*-carboxyphenoxy)benzoate] (1h). T_{polym} = 180 °C. Yield: quantitative (beige solid). ^{1}H NMR (DMSO-d_6): δ 8.80 (s, 1H, ArH), 8.50 (d, 2H, ArH), 8.05 (d, 2H, ArH), 7.90 (t, 1H, ArH), 7.75 (t, 2H, ArH), 7.50 (t, 2H, ArH), 7.40 (d, 2H, ArH). IR (NaCl, cm^{-1}): 1800, 1740 (C=O, anhydride), 1740 (C=O, ester). M_w = 8800, PDI = 1.7. T_d = 405 °C, T_g = 106 °C. Contact angle: 77°.

Poly[2,2′-bis(*o*-carboxyphenoxy)isopropanoate] (1i). T_{polym} = 160 °C. Yield: quantitative (beige solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.95 (t, 2H, ArH), 7.55 (t, 2H, ArH), 7.45 (d, 2H, ArH), 1.70 (s, 6H, CH_3). IR (NaCl, cm^{-1}): 1780, 1720 (C=O, anhydride), 1760 (C=O, ester). M_w = 39 800, PDI = 1.5. T_d = 261 °C, T_g = 44 °C. Contact angle: 95°.

Poly[3,3′-bis(*o*-carboxyphenoxy)pentanoate] (1j). T_{polym} = 160 °C. Yield: quantitative (beige solid). ^{1}H NMR (DMSO-d_6): δ 8.10 (d, 2H, ArH), 7.90 (t, 2H, ArH), 7.60 (t, 2H, ArH), 7.40 (d, 2H, ArH), 2.20 (q, 4H, CH_2), 1.0 (t, 6H, CH_3). IR (NaCl, cm^{-1}): 1775, 1725 (C=O, anhydride), 1750 (C=O, ester). M_w = 16 500, PDI = 1.6. T_d = 276 °C, T_g = 23 °C. Contact angle: 93°.

Degradation Studies. *Sample Preparation.* Polymer pellets were prepared by pressing ground polymers (~150 ± 5 mg) into 13 mm diameter × 1 mm thick disks in an IR pellet die (International Crystal Laboratories, Garfield, NJ) with a benchtop hydraulic press (Carver model M, Wabash, IN). A pressure of 10 000 psi was applied for 5 min at room temperature. No change in polymer color was observed upon applying pressure.

Degradation Media Preparation. Degradation media consisted of phosphate buffer solution (PBS) containing 0.1 M potassium hydrogen phosphate and 0.1 M potassium dihydrogen phosphate. The pH was adjusted to 7.4 with 1 M sodium hydroxide and/or 1 N hydrochloric acid solutions, and pH measurements were performed on a pH meter (VWR Scientific, San Francisco, CA).

In Vitro Hydrolytic Degradation. Hydrolytic degradation of the polymers was performed by placing the disks in 20 mL Wheaton PET plastic scintillation vials (Fisher, Fair Lawn, NJ) with 10 mL of PBS and incubating them at 37 °C with agitation using a controlled environment incubator-shaker (New Brunswick Scientific Co., Edison, NJ) at 60 rpm for 30 days. Every 24 h, the buffer solution was replaced by fresh solution (10 mL), and the spent media was analyzed by UV (λ = 303 nm) with a DU 520 UV/vis spectrophotometer (Beckman Instruments, Fullerton, CA) to specifically monitor the release of salicylic acid. Measurements were taken at the maximum absorbance of salicylic acid (λ = 303 nm) that did not overlap with the UV absorbance of the linkers. UV data (average of three samples per time point) were calibrated against salicylic acid solutions of known concentrations (8.4×10^{-4}, 1.7×10^{-3}, 3.3×10^{-3}, and 6.7×10^{-3} mg/mL). For reference, solutions of the individual linkers (**4**) as well as the diacids (**5**) were measured to ensure that the UV spectra of the linkers (**4**) did not overlap with that of salicylic acid and that the diacids (**5**) were not present in the degradation media.

Results and Discussion

Diacid Synthesis. An outline of the poly(anhydride−ester) (**1**) synthesis, starting from salicylic acid (**2**) and the appropriate acyl chloride of the linker (**4**), is shown in Scheme 2.

The salicylate-based monomer precursor (**5**) was formed by direct coupling of salicylic acid (**2**) with the corresponding diacyl chloride (**4**) in an appropriate solvent (THF) containing pyridine at room temperature.[26] Pyridine deprotonates salicylic acid (**2**) and also acts as a catalyst to form an acylpyridinium ion,[44] which reacts with the free phenolate. Thus, formation of the acylpyridinium ion, which is known to react more rapidly with alcohols than acyl chlorides,[44,45] eliminates the need to protect the carboxylic acid of the salicylic acid. This method also eliminates further purification, except for washing with the appropriate solvent to remove starting materials and reaction's byproducts, because of the large solubility differences. This one-step

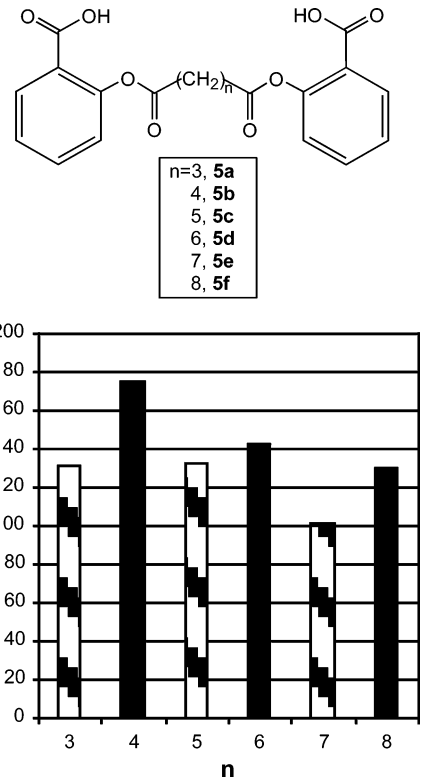


Figure 1. Melting point temperatures of diacid (**5a**−**5f**) as a function of alkyl chain length, $(CH_2)_n$.

method[26] was used to prepared a variety of diacids (**5**) with different linkers that will ultimately undergo melt condensation to yield poly(anhydride−esters). Three classes of linker molecules (Table 1) were evaluated to assess the role of the linker chemical structure in the polymer properties: (1) linear aliphatic, (2) branched aliphatic, and (3) aromatic compounds.

Isolated yields for the diacids (**5**) based on linear aliphatic linkers (**5a**−**5f**) ranged from 71 to 91%, and an odd/even effect was observed in the melting point (Figure 1). The trend of odd-membered alkanes displaying slightly lowered melting points than even-membered systems is well documented in simple alkyl chains.[46]

For the diacids based on aromatic and branched aliphatic linkers (**5g**−**5j**), the yields ranged from 80 to 92%. As anticipated, diacids with aromatic linkers (**5g**, **5h**) displayed higher thermal stabilities (i.e., melting points) than the diacids with aliphatic linkers (**5a**−**5f** and **5i**, **5j**). Melting points decreased with increased steric hindrance of the linker molecule due to less effective intermolecular interactions.

Influence of Linear Aliphatic Linkers on Poly(anhydride−ester) Properties. The activation of the diacid (**5a**−**5f**) with acetic anhydride yielded the anhydride monomer (**6a**−**6f**), which was melt-polymerized at 160−180 °C under vacuum (<2 mmHg) for 3−6 h to yield the poly(anhydride−ester) (**1a**−**1f**). The chemical, physical, and thermal properties of polymers with linear alkyl chain linkers are summarized in Figure 2.

Molecular weights significantly increased as the alkyl chain length of the linker increased from three to eight methylenes, while the polydispersity index (PDI) remained relatively unchanged due to homogeneous mixing of the polymer melt.[26] Similarly, decomposition temperatures (T_d) for the polymers are influenced by the alkyl linker chain length, increasing from 243 °C

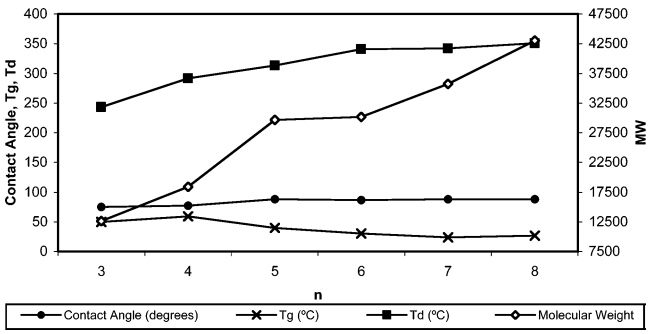
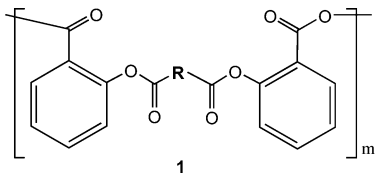


Figure 2. Influence of linear aliphatic chain length, $(CH_2)_n$, on poly(anhydride−ester) **1a**−**1f** properties.

Table 2. Influence of Aromatic and Branched Linker Structures on Poly(anhydride−esters) 1g−1j



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R	salicylic acid (%)	contact angle (deg)	T_g (°C)	T_d (°C)	mol wt
terephthalic, **g**	67.5	81	118	403	17 100
isophthalic, **h**	67.5	77	106	405	8 800
dimethylmalonic, **i**	73.6	95	44	261	39 800
diethylmalonic, **j**	68.5	93	23	276	16 500

for the glutaric linker (three methylenes) to 351 °C for the sebacic linker (eight methylenes) (Figure 2).

Glass transition temperatures decreased as the linear linker length increased due to the enhanced flexibility, ranging from 59 to 24 °C. The drug loading of the polymer was also modified; drug loads ranged from 60 to 74% for the longest alkyl chain (Figure 1, $n = 8$) to the shortest alkyl chain (Figure 1, $n = 3$), respectively. As the number of methylenes increases, the amount of salicylic acid chemically incorporated in the polymer backbone decreases.

Influence of Aromatic/Branched Linkers on Poly(anhydride−ester) Properties. Polymers with aromatic (**1g**, **1h**) and branched alkyl linker structure (**1i**, **1j**) were also synthesized and their properties evaluated. For consistency, similar polymerization conditions were used rather than optimizing the reaction conditions for each polymer. As previously demonstrated[5] by our laboratory and expected for melt condensation polymerization, molecular weights can be optimized for each polymers by systematically modifying polymerization time and temperature. Among these systems, the polymers with the most sterically hindered linker groups were the most difficult to polymerize (**1h**, **1j**), thus yielding lower molecular weights as shown in Table 2.

Polymers with aromatic linkers showed the highest decomposition temperatures likely due to the increased $\pi-\pi$ interactions between the polymer chains. Steric bulk decreased the packing efficiency of the polymer chains, resulting in greater free volume and lowered glass transition temperatures for the polymers with the more sterically bulky linker groups. Thus, for the aromatic linkers, changing the linker substitution pattern from *para*-substitution (**1g**) to *meta*-substitution (**1h**) decreases the T_g by 12 °C.

Degradation Studies. In vitro hydrolytic degradation of the polymers was measured by quantifying the

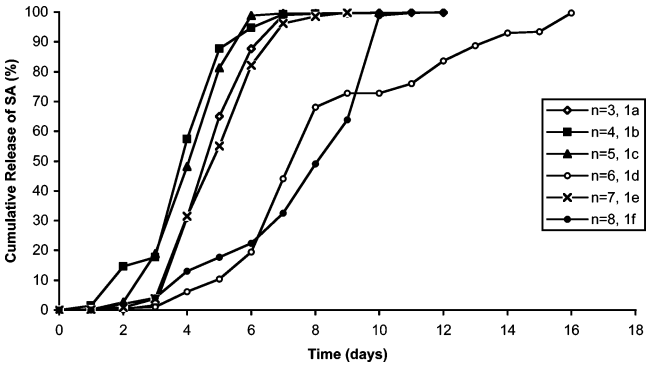

Figure 3. In vitro degradation profile of poly(anhydride−esters) with linear aliphatic linkers, **1a**−**1f**.

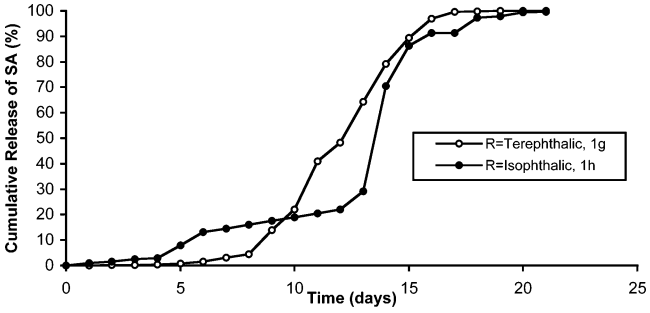

Figure 4. In vitro degradation profile of poly(anhydride−esters) with aromatic linkers, **1g** and **1h**.

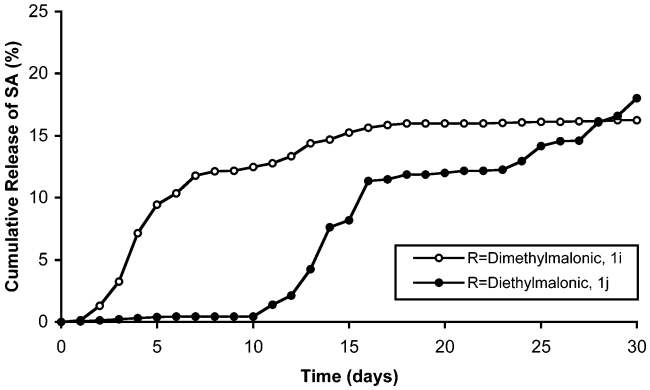

Figure 5. In vitro degradation profile of poly(anhydride−esters) with branched aliphatic linkers, **1i** and **1j**.

salicylic acid concentration in the degradation media using UV spectrometry. Polymers **7a**−**7j** were compressed into disks and then degraded at 37 °C in pH 7.4 phosphate buffered solution over 30 days. Polymers with linear aliphatic linkers (**1a**−**1f**) showed similar release profiles (Figure 3): short lag times (0−3 days) before salicylic acid was detected in solution and complete degradation of the disk within 8−16 days. In contrast to polymers with linear aliphatic linkers (**1a**−**1f**), polymers with aromatic linkers (**1g**, **1h**) required longer degradation time (up to 20 days) (Figure 4) and also displayed a longer lag time (4 days). Polymers with branched aliphatic linkers (**1i**, **1j**) degraded much slower and were only partially degraded in 30 days, with less than 20% of the drug released at this time point (Figure 5).

Water contact angles were measured to evaluate the relative hydrophobicity of the polymers as a factor that may influence hydrolytic degradation rate of the polymers. Indeed, polymers containing the branched aliphatic linkers (**1i**, **1j**) displayed the highest contact angle values and also displayed the slowest degradation relative to the other poly(anhydride−esters) (**1a**−**1h**).

Conclusion

The specific biomedical application for which a polymer is suited depends on several factors, including in vitro degradation rate, thermal and mechanical properties, and biocompatibility of the polymer.[47] This work demonstrates that the properties of salicylate-derived poly(anhydride−esters), **7**, were readily modified by varying the compound linking together the salicylic acids as summarized below. First, polymers with higher molecular weight values were obtained by using longer linear aliphatic linkers. This effect is likely due to enhanced mobility in the molten state during polymerization. Second, the glass transition temperature (T_g) concurrently decreased with increasing aliphatic chain length. Overall, polymers containing aromatic linkers (**1g** and **1h**) displayed the highest T_g values, even relative to polymers with branched aliphatic molecules (**1i** and **1j**). Third, the drug loading of the polymer was modified by changing the linker, obtaining drug loads ranging from 60 to 74 wt %. Fourth, hydrolytic degradation of the polymers to release salicylic acid was demonstrably a function of the linker structure; polymers with aliphatic linkers generally degraded faster in vitro than polymers comprised of aromatic or branched aliphatic linkers. Last, water contact angle values of the undegraded polymer is a good indicator of in vitro degradation rate; the polymer (**1i**) with the highest contact angle (i.e., most hydrophobic) degraded over a longer time period.

We are currently evaluating specific parameters such as water solubility and log *P* values of the polymer degradation products to further optimize the polymer degradation profiles.

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References and Notes

(1) Uhrich, K.; Gupta, A.; Thomas, T.; Laurencin, C.; Langer, R. *Macromolecules* **1995**, *28*, 2184−2193.
(2) Uhrich, K.; Larrier, D.; Laurencin, C.; Langer, R. *J. Polym. Sci., Polym. Chem. Ed.* **1996**, *34*, 1261−1269.
(3) Langer, R. *Acc. Chem. Res.* **2000**, *33*, 94−101.
(4) Burkoth, A.; Anseth, K. *Biomaterials* **2000**, *21*, 2395−2404.
(5) Campo, C.; Anastasiou, T.; Uhrich, K. *Polym. Bull. (Berlin)* **1999**, *42*, 61−68.
(6) Anastasiou, T.; Uhrich, K. *Macromolecules* **2000**, *33*, 6217−6221.
(7) Mathiowitz, E.; Jacob, J.; Jong, Y.; Carino, G.; Chickering, D.; Chaturvedi, P.; Santos, C.; Vijayaraghavan, K.; Montgomery, S.; Bassett, M.; Morrell, C. *Nature (London)* **1997**, *386*, 410−414.
(8) Chasin, M.; Langer, R. *Biodegradable Polymers as Drug Delivery Systems*; Marcel Dekker: New York, 1990.
(9) Brem, H.; Piantadosi, S.; Burger, P.; Walker, M.; Selker, R.; Vick, N.; Black, K.; Sisti, M.; Brem, S.; Mohr, G.; Muller, P.; Morawetz, R.; Schold, S. *Lancet* **1995**, *345*, 1008−1012.
(10) Hanes, J.; Chiba, M.; Langer, R. *Biomaterials* **1998**, *19*, 163−172.
(11) Leong, K.; Kost, J.; Mathiowitz, E.; Langer, R. *Biomaterials* **1986**, *7*, 364−371.
(12) Leong, K.; D'Amore, P.; Maletta, M.; Langer, R. *J. Biomed. Mater. Res.* **1986**, *20*, 51−64.
(13) Sanders, A.; Li, B.; Bieniarz, C.; Harris, F. *Polym. Prepr.* **1999**, *40*, 888.
(14) Whitaker-Brothers, K.; Uhrich, K. E. *J. Biomed. Mater. Res., Part A*, in press.
(15) Gopferich, A.; Tessmar, J. *Adv. Drug Del. Rev.* **2002**, *54*, 911−931.
(16) Gopferich, A. *Biomaterials* **1996**, *17*, 103−114.

(17) Von Burkersroda, F.; Schedl, L.; Gopferich, A. *Biomaterials* **2002**, *23*, 4221−4231.
(18) Tamada, J.; Langer, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 552−556.
(19) Quick, D.; Macdonald, K.; Anseth, K. *J. Controlled Release* **2004**, *97*, 333−343.
(20) Park, E.; Maniar, M.; Shah, J. *J. Controlled Release* **1996**, *40*, 111−121.
(21) Gopferich, A. *Macromolecules* **1997**, *30*, 2598−2604.
(22) Vogelhuber, W.; Rotunno, P.; Magni, E.; Gazzaniga, A.; Spruss, T.; Bernhardt, G.; Buschauer, A.; Göpferich, A. *J. Controlled Release* **2001**, *73*, 75−88.
(23) Uhrich, K.; Cannizzaro, S.; Langer, R.; Shakesheff, K. *Chem. Rev.* **1999**, *99*, 3181−3198.
(24) Erdmann, L.; Uhrich, K. *Biomaterials* **2000**, *20*, 1941−1946.
(25) Erdmann, L.; Macedo, B.; Uhrich, K. *Biomaterials* **2000**, *21*, 2507−2512.
(26) Schmeltzer, R.; Anastasiou, T.; Uhrich, K. *Polym. Bull. (Berlin)* **2003**, *49*, 441−448.
(27) San Roman, J.; Bujan, J.; Bellon, J.; Gallardo, A.; Escudero, M.; Jorge, E.; de Haro, J.; Alvarez, L.; Castillo-Olivares, J. *J. Biomed. Mater. Res.* **1996**, *32*, 19−27.
(28) Sato, H.; Kojima, J.; Nakajima, A.; Morita, T.; Noishiki, Y.; Gu, Z.; Li, F.; Feng, X. *J. Biomater. Sci. Polym. Ed.* **1991**, *2*, 1−13.
(29) Elvira, C.; Gallardo, A.; San Roman, J. *Polymer* **1999**, *40*, 6911−6924.
(30) Chafi, N.; Montheard, J.; Vergnaud, J. *Int. J. Pharm.* **1989**, *52*, 203-211.
(31) Rivas, B.; Moreno-Villoslada, I.; Elvira, C.; San Roman, J. *J. Membr. Sci.* **2001**, *192*, 187−191.
(32) Elvira, C.; San Roman, J. *J. Mater. Sci.: Mater. Med.* **1997**, *8*, 743−746.
(33) Kricheldorf, H.; Gerken, A.; Yulchibaev, B.; Friedrich, C. *J. Polym. Sci., Polym. Chem. Ed.* **2000**, *38*, 2013−2022.
(34) Liming, T.; Rabenstein, M.; Kricheldorf, H. *Macromol. Chem. Phys.* **2001**, *202*, 1497−1504.
(35) Shalaby, S.; Koelmael, D.; Arnold, S. U.S. Patent 5,082,925, 1992.
(36) Schmeltzer, R.; Schmalenberg, K.; Uhrich, K. *Biomacromolecules* **2005,** *6*, 359−367.
(37) Kim, Y.; Uhrich, K. *Polym. Prepr.* **2004**, *45*, 505.
(38) Whitaker-Brothers, K.; Uhrich, K. E. *J. Biomed. Mater. Res.* **2004**, *70A*, 309−318.
(39) Anastasiou, T.; Uhrich, K. *J. Polym. Sci., Polym. Chem. Ed.* **2003**, *41*, 3667−3679.
(40) Anastasiou, T.; Beaton, M.; Uhrich, K. *Polym. Prepr.* **2001**, *42*, 121.
(41) Bedell, C.; Deng, M.; Anastasiou, T.; Uhrich, K. *J. Appl. Polym. Sci.* **2001**, *80*, 32−38.
(42) Anastasiou, T.; Uhrich, K. *Polym. Prepr.* **2000**, *41*, 1366.
(43) Krogh-Jespersen, E.; Anastasiou, T.; Uhrich, K. *Polym. Prepr.* **2000**, *41*, 1048.
(44) Fersht, A.; Jencks, W. *J. Am. Chem. Soc.* **1970**, *92*, 5442−5452.
(45) Hoefle, G.; Steglich, W.; Vorbrueggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.
(46) Solomons, T. *Organic Chemistry*; Wiley & Sons: New York, 1980.
(47) Jagur-Grodzinski, J. *J. React. Funct. Polym.* **1979**, *39*, 99−138.

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