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Polyanhydrides: the effects of ring substitution changes on polymer properties

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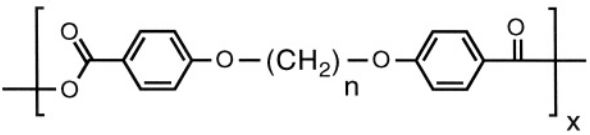
Summary

We synthesized polymers that overcome the processing problems associated with aromatic polyanhydrides. In this paper, we focus on the synthesis and characterization of *ortho*-substituted polyanhydrides, poly[1,3-bis(*o*-carboxyphenoxy)propane anhydride] (*o*-CPP) and poly[1,6-bis(*o*-carboxyphenoxy)hexane anhydride] (*p*-CPH). By lengthening the alkyl chain between aryl groups (from propane to hexane) and changing the ring substitution pattern from *para*- to *ortho*-, we observed enhanced solubility of aromatic polyanhydrides. Ultimately, these polyanhydrides may be useful as polymer scaffolds for use as functional soft tissue substitutes.

Introduction

In recent years, interest in polymers containing anhydride groups has been significant as the polymers can undergo non-enzymatic degradation more rapidly than other biodegradable materials.(1,2) In fact, aromatic polyanhydrides are one of the few synthetic degradable systems with regulatory approval from the Food and Drug Administration for use in human clinical trials. Polyanhydrides containing 1,3-bis(*p*-carboxyphenoxy)propane (*p*-CPP, where n=3 and the phenyl ring is *para*-substituted) (**1**) are currently used as implantable devices to control the delivery of chemotherapeutic drugs to treat brain cancer.(3)



1: n=3
2: n=6

These polymeric systems are unique as implantable drug delivery systems because they demonstrate near zero-order drug release.(2) Polyanhydrides of aromatic diacids offer several advantages over aliphatic derivatives including longer release and degradation times, higher mechanical strength and improved stability.(2,4,5) However, aromatic polyanhydrides are insoluble in common organic solvents and melt at high temperatures. These properties limit the applications of purely aromatic polyanhydrides as they cannot be fabricated into films using solvent or melt techniques.

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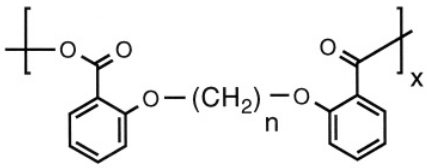
Despite interest and need, there has only been one report(6) on the synthesis and properties of anhydride homopolymers of aromatic diacids. Synthetic methods that allow for a broad variation of polymer properties are desirable, especially to obtain a polymer with a specific degradability based upon the polymer structure.

Our goal was to enhance the processibility of the polyanhydrides by changing the substitution of the phenyl rings from *para-* to *ortho*. Poly[1,3-bis(*o*-carboxyphenoxy)propane anhydride] (*o*CPP) (**3**) and poly[1,6-bis(*o*-carboxyphenoxy)hexane anhydride] (*o-CPH*) (**4**) were synthesized to overcome the solubility (or processing) problems associated with *p*-CPP (**1**) and *p*-CPH (**2**).



3: n=3
4: n=6

Desirable characteristics for implantable polymeric systems include biocompatibility, suitable physical properties for device fabrication (i.e., low melting point, solubility in common organic solvents), and flexibility before and during degradation so that the device does not fragment during use. We have synthesized polymers that maintain the desirable characteristics (biodegradability, biocompatibility, mechanical properties) and overcome the solubility (or processing) problems associated with aromatic polyanhydrides. In this paper, we focus on the synthesis and characterization of *ortho*-substituted polyanhydrides, **3** and **4**. For purposes of comparison, we also synthesized the related *para*-substituted compounds, *p*-CPP (**1**) and *p*-CPH (**2**).

Experimental

Materials

Except for acetic anhydride and ethyl ether (Fisher), all chemicals were purchased from Aldrich and used as received.

Methods

^{1}H NMR spectra were recorded on a Varian 200 MHz spectrometer. Samples (5 ~ 10 mg/ml) were dissolved in either $CDCl_3$ or DMSO-d_6 with the solvent used as an internal reference. IR spectra were measured on a Mattson Series spectrophotometer by solvent-casting samples onto a KBr pellet. Elemental analyses were provided by QTI, Inc. (Whitehouse, NJ).

Molecular weights were determined on a Perkin Elmer Series 200 LC system equipped with a PL-Gel column (5 µm, mixed bed) operated at 60°C, Series 200 refractive index detector, Series 200 LC pump and ISS 200 autosampler. A digital Celebris 466 computer was used to automate the analysis via PE Nelson 900 interface and PE Nelson 600 Link box. PE Turbochrom 4 software was used for data collection and processing. Tetrahydrofuran (THF) was used as eluent for analysis at a flow rate of 0.5 ml/min.

Samples (~ 5 mg/ml) were dissolved into THF and filtered using 0.45 μm PTFE syringe filters prior to column injection. Molecular weights were calibrated relative to narrow molecular weight polystyrene standards (Polysciences, Dorval, Canada).

Thermal analysis was determined on a Perkin Elmer system consisting of Pyris 1 DSC and TGA7 analyzers with TAC 7/7 instrument controllers. PE Pyris 1 and TGA7 software was used for data collection and processing on a digital Venturis 5100 computer. For DSC, samples (~ 5 mg) were heated under dry nitrogen gas. Data was collected at heating and cooling rates of 10°C/min with a two cycle minimum. For TGA, samples (~ 10 mg) were heated under dry nitrogen gas. Data was collected at a heating rate of 20 °C/min. Decomposition temperatures were defined as the onset of decomposition.

Sessile drop contact angle measurements were obtained with an NRL Goniometer (Rame-hart) using distilled water. Solutions of polymer in methylene chloride (10 %wt/vol) were spun-coat onto glass slips, except for *p*-CPP which was dissolved in DMSO, dropped onto glass slips, then vacuum dried overnight at 40°C. Spin-coating was performed at 5000 rpm for 30 sec.

Solubility measurements were carried out on a HP 8452A Diode Array Spectrophotometer. A calibration curve was constructed based on the relative UV absorptions at of four standard solutions of each polymer in each solvent ranging from 10^{-1} to 10^{-4} mg/ml. Saturated solutions of each polymer in THF were filtered, then multiply diluted until the absorbance values of the solutions were within the calibration range.

Synthesis

The polyanhydrides were synthesized according to methods established by Conix.(7) Briefly, melt condensation polymerizations were performed on the monomers (500 mg) at 260°C for 3.5 hr under vacuum (2 mmHg) in a side-armed test tube. The reaction mixture was flushed with dry nitrogen every 15 min. The polymers were isolated by precipitation into diethyl ether from methylene chloride. Polymerization reactions were performed in triplicate. Measurements for the optimization study were performed on crude (not purified by precipitation) polymers.

1,3-bis(o-carboxyphenoxy)propane diacid

To a mixture of salicylic acid (**5**) (40.0 g, 0.290 mol) and distilled water (44 ml), sodium hydroxide (23.2 g, 0.580 mol) was added. The reaction mixture was brought to reflux temperature before 1,3-dibromopropane (14.7 ml, 0.145 mol) was added dropwise. After 4 h, additional sodium hydroxide (5.79 g, 0.145 mol) was added to the reaction mixture. The mixture was heated to reflux temperature for another 4 h, cooled, and the product isolated by filtration. Purification involved recrystallization from water followed by a methanol wash. Yield: 37.7% (white solid). ^{1}H NMR (DMSO-d_6): δ 7.66 (d,2H,ArH), 7.50 (t,2H,ArH), 7.17 (t,2H,ArH), 4.26 (t,4H,CH_2), 2.20 (m,2H,CH_2). IR (KBr, cm^{-1}): 3200 (O-H), 1720 (C=O), 1240 (C-O). T_m: 153°C.

1,3-bis(o-carboxyphenoxy)propane monomer

The diacid (2.5 g, 7.9 mmol) was acetylated in an excess amount of acetic anhydride (36 ml) under nitrogen at reflux temperature. After 2.5 hr, the reaction mixture was filtered and the filtrate evaporated to dryness. Yield: 78% (white solid). ^{1}H NMR ($CDCl_3$): δ 7.85 (d,2H,ArH), 7.55 (t,2H,ArH), 7.03 (t,2H,ArH), 4.34 (t,4H,CH_2), 2.30 (m,2H,CH_2), 2.20 (s,6H,CH_2). IR (KBr, cm^{-1}): 2940 (C-H), 1800, 1740 (C=O), 1250 (C-O).

*1,6-bis(o-carboxyphenoxy)hexane diacid (**6**)*

To a mixture of salicylic acid (**5**) (77.1 g, 0.558 mol) and distilled water (84 ml), sodium hydroxide (44.7 g, 1.12 mol) was added. The reaction mixture was brought to reflux temperature before 1,6-dibromohexane (44.2 g, 0.279 mol) was added dropwise. After 23 h, more sodium hydroxide (11.2 g, 0.279 mol) was added to the reaction mixture. The mixture was heated to reflux temperature for another 16 h, cooled, and the product isolated by filtration. Purification involved recrystallization from water followed by a methanol wash. Yield: 48.8% (white solid). ^{1}H NMR (DMSO-d_6): δ 12.5 (s,2H,COOH), 7.61 (d,2H,ArH), 7.46 (t,2H,ArH), 7.12 (d,2H,ArH), 6.99 (t,2H,ArH), 4.05 (t,4H,CH_2), 1.75 (m,4H,CH_2), 1.51 (t,4H,CH_2). IR (KBr, cm^{-1}): 3500 (O-H), 1770 (C=O), 1100 (C-O). T_m: 123°C.

*1,6-bis(o-carboxyphenoxy)hexane monomer (**7**)*

The diacid (**6**) (74.0 g, 0.136 mol) was acetylated in an excess amount of acetic anhydride (150 ml) under nitrogen at reflux temperatures. After 2.5 hr, the reaction mixture was filtered and the filtrate evaporated to dryness. The monomer was triturated with ethyl ether and precipitated upon cooling. Yield: 66.8% (white solid). ^{1}H NMR (DMSO-d_6): δ 7.83 (d,2H,ArH), 7.50 (t,2H,ArH), 7.25 (d,2H,ArH), 6.97 (t,2H,ArH), 4.04 (t,4H,CH_2), 2.26 (s,6H,CH_3), 1.82 (m,4H,CH_2), 1.57 (t,4H,CH_2). IR (KBr, cm^{-1}): 1770, 1720 (C=O), 1180 (C-O).

*Poly(p-CPH) (**2**)*

Yield: quantitative (tan solid). M_w: 19,200; PDI: 1.1.

*Poly(o-CPP) (**3**)*

Yield: quantitative (tan solid). ^{1}H NMR ($CDCl_3$): δ 7.90 (br,2H,ArH), 7.45 (b,2H,ArH), 6.90 (m,4H,ArH), 4.07 (t,4H,CH_2), 2.12 (m,2H,CH_2). M_w: 8,500; PDI: 1.3. Contact angle: 78°.

*Poly(o-CPH) (**4**)*

Yield: quantitative (tan solid). ^{1}H NMR (DMSO-d_6): δ 7.85 (d,2H,ArH), 7.45 (t,2H,ArH), 7.25 (s,2H,ArH), 6.93 (t,2H,ArH), 3.92 (br,4H,CH_2), 1.60 (br,4H,CH_2), 1.43

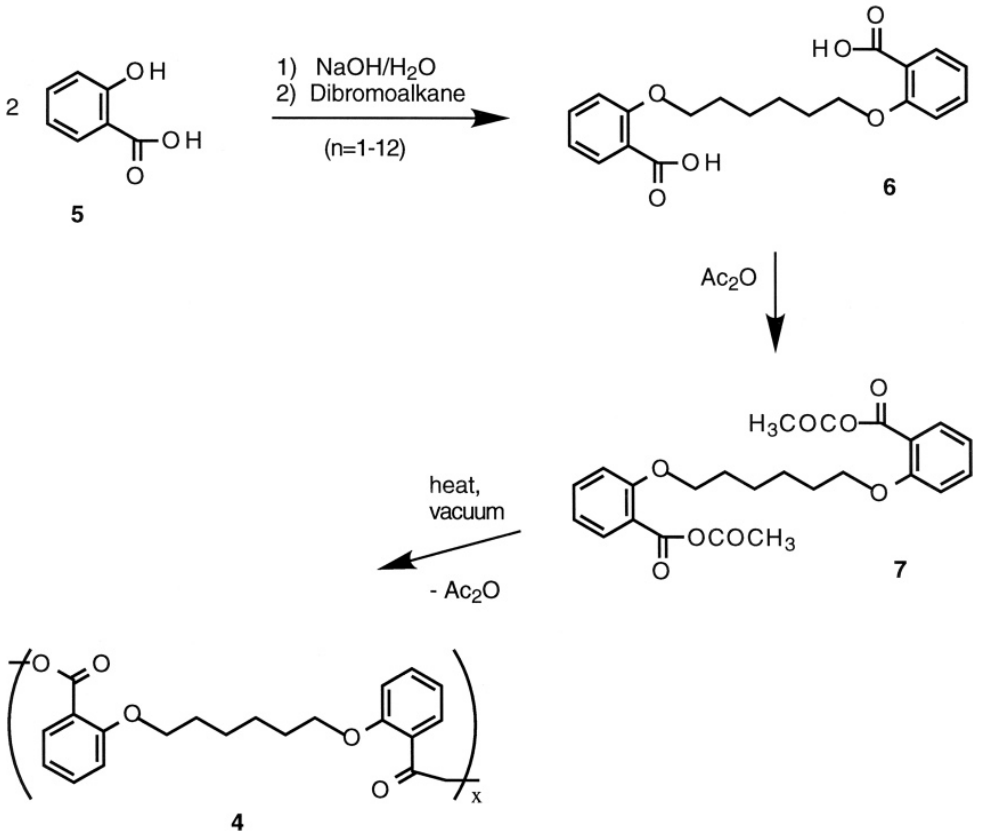
(m,4H,CH_2). Anal. Calc: C, 70.58; H, 5.92. Found: C, 70.47; H, 5.86. Mw: 19,900, PDI: 1.3. Contact angle: 84°.

Results and discussion

Our preparation of *ortho*-substituted polyanhydrides addresses the issue of processibility; these polymers have high solubility in organic solvents and lowered glass transition temperatures. We hypothesized that two factors would affect solubility and thermal properties: i) changing the aromatic ring substitution pattern and ii) lengthening the alkyl chain between the aromatic rings. Although a longer alkyl chain would increase the overall flexibility of the polymer, the change from a *para* - to *ortho*-substituted aromatic repeat unit should more dramatically enhance the polymer flexibility.

Synthesis

Two new polymers were synthesized (**3** and **4**) along with two established polymer systems (**1** and **2**) for comparison. An example of the synthesis of poly[1,6-bis(*o*-carboxyphenoxy)hexane] (*o*-CPH) (**4**) is outlined in **Scheme 1**.



Scheme 1. Synthesis of polyanhydrides.

Salicylic acid (**5**) is reacted with 1,6-dibromohexane in the presence of aqueous sodium hydroxide solution at reflux temperatures to give 1,6-bis(*o*-carboxyphenoxy) hexane diacid (**6**). The diacid (**6**) is acetylated with acetic anhydride to form an activated mixed anhydride, **7** (i.e., the monomer). The monomer (**7**) is self-polymerized in a melt condensation reaction to give polymer **4** in quantitative yield. The procedure was similar for synthesis of *o*-CPP (**3**) except that 1,3-dibromopropane was used in place of 1,6-dibromohexane.

Processing characteristics

Qualitatively, the *ortho*-substituted polymers (**3** and **4**) were significantly more soluble in common organic solvents (e.g., methylene chloride, tetrahydrofuran, acetone) than the corresponding *para*-substituted polymers (**1** and **2**). For example, concentrations of polymers **1-4** in saturated solutions of THF were determined by diluting the solutions, measuring the absorbance using UV spectroscopy and comparing the values to calibration curves derived from known solutions. The *para*-substituted polymers, **1** and **2**, had solubilities near the limit of the spectrophotometer ($< 10^{-7}$ mg/ml) consistent with previously published values.(8) In contrast, polymers **3** and **4** had solubilities of 124 and 140 mg/ml, respectively. These results demonstrate that longer alkyl chains (n=6, for **4**) enhanced solubility but that aromatic ring substitution has a more significant effect on solubilities.

The *ortho*-substituted polymers were readily solvent-cast to make translucent films. Contact angle measurements on solvent-cast films demonstrated that the hexyl chains of **2** and **4** increased the surface hydrophobicity relative to the shorter, propyl chains of polymers **1** and **3**.

Comparison of thermal characteristics emphasized the effects of lengthening the alkyl chain and of changing the aromatic substitution pattern (**Table I**).

Polymer	**T_g (°C)**	**T_m (°C)**	**T_d (°C)**
p-CPP (**1**)	94	240	421
p-CPH (**2**)	48	147	439
o-CPP (**3**)	50	--	344
o-CPH (**4**)	34	--	410

Table I. Comparison of thermal transition temperatures for the aromatic polyanhydrides.

Hexyl chains decreased the glass transition temperatures (T_g) relative to the propyl chains reflecting the increased flexibility of the polymer chains. The opposite trend was observed for decomposition temperatures (T_d) - longer alkyl chains increased T_d's. Relative to the *para*-substituted compounds, the *ortho*-substituted polymers had lowered T_g's and displayed no melting transitions (T_m). Because the molecular weights for the polymers were similar, the observed effects are likely due to changes in chemical structure. As anticipated, the *ortho*-substituted polymers were also easily processed into films by compression-molding.

Optimization of polymerization conditions

The polycondensation conditions were optimized using monomer **7**, the activated form of 1,6-bis(*o*-carboxyphenoxy) hexane diacid (**Scheme 1**). For biomaterial applications, it is frequently preferable to have glass transition temperatures (T_g's) above body temperature (37°C). Therefore, we defined optimal conditions as those that yielded a crude polymer with the highest glass transition temperature. As expected for a condensation polymerization, longer reaction times yielded polymers with higher molecular weights and a general increase in T_g (**Figure 1**).

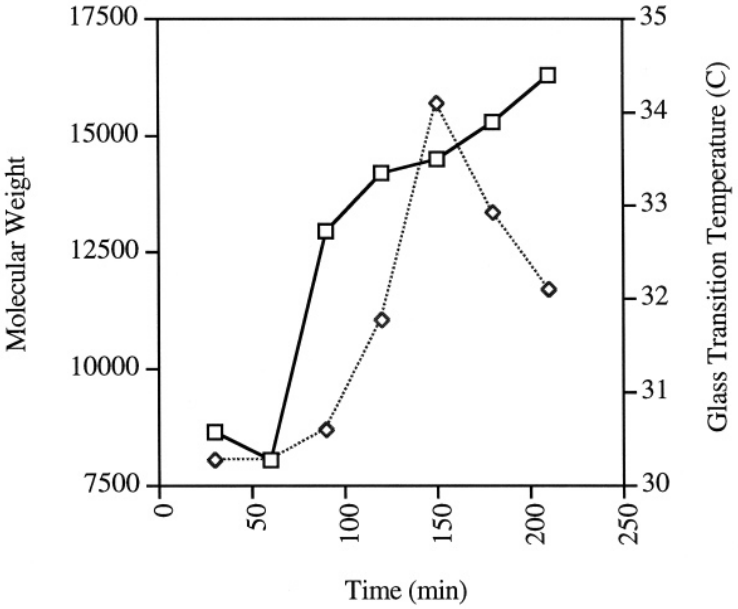


Figure 1. Comparison of changes in molecular weight and glass transition temperature (˚C) with polymerization time.

However, over longer reaction times there appeared a subsequent decrease in glass transition temperatures (T_g). Higher reaction temperatures decreased the M_w values (measured by GPC) with a concurrent increase in polydispersity (**Figure 2**). The decrease in T_g is thus a result of the rapid increase in polydispersity at higher temperatures. Based on these results, the optimal conditions were defined as temperatures of 220°C for 150 min under vacuum.

By lengthening the alkyl chain between aryl groups (from propane to hexane) and changing the ring pattern from *para-* to *ortho*-substitution, we observed enhanced solubility of aromatic polyanhydrides. Ultimately, these polyanhydrides may be useful as drug delivery systems because of their tensile modulus (200 MPa) and fast degradation characteristics (week time-scale). *In vitro* studies examining the degradation and mechanical characteristics in depth will be published elsewhere.(9)

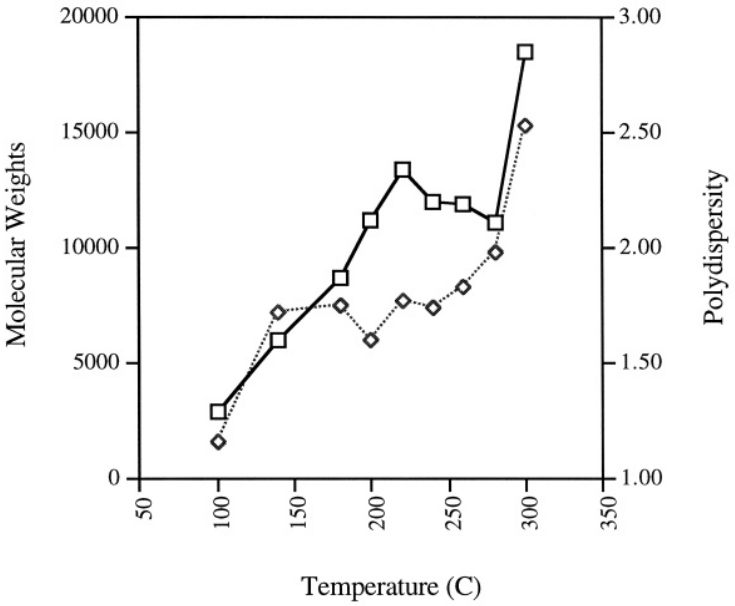


Figure 2. Comparison of changes in molecular weight and polydispersity with polymerization temperature.

Acknowledgments

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