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BLOCK COPOLYESTERS BASED ON POLY(LACTIDE) AND AROMATICALIPHATIC POLYESTERS OF THE AA/BB TYPE AND ACID FUNCTIONALIZED POLY (LACTIDE) AND POLY(ESTER-URETHANE)S THEREFROM

Timothy Russell Cooper
University of Southern Mississippi

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by

Timothy Russell Cooper

A Dissertation
Submitted to the Graduate Studies Office of The University of Southern Mississippi in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

August 2007
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ABSTRACT

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Aromatic-aliphatic poly[L-lactide-b-(ethyleneoxyethylene terephthalate-co-adipate)-b-L-lactide] triblock copolymers were synthesized and characterized. Hydroxy-telechelic poly(ethyleneoxyethylene terephthalate-co-adipate) (PEOETA) was first prepared via polycondensation and then utilized as an initiator for the ring opening polymerization (ROP) of L-lactide (LLA) in the presence of stannous octanoate (Sn(Oct)$_2$). Formation of the block copolymer was confirmed by $^1$H NMR spectroscopy, GPC, DSC and AFM. The polymerization rate induced by the PEOETA macroinitiator was comparable to that of a small molecule initiator. The mechanical and degradation properties failed to meet project objectives; therefore we focused more attention to the modification of $\alpha$-hydroxy acid polymers for use in the creation of degradable polyurethanes.

Linear poly(D,L-lactide) containing a single pendant carboxylic acid group (BHMBAB-PDLLA) was synthesized via ring opening polymerization (ROP) of D,L-lactide using 2,2-bis(hydroxymethyl) butyric acid (BHMBABA) as an initiator. Characterization of the BHMBAB-PDLLA using NMR spectroscopy and gel permeation chromatography confirmed the presence of the pendant carboxylic acid group and...
provided evidence of a linear architecture. Degradation studies were performed on
BHMBP-PDLLA polyesters by immersion into aqueous buffered solution (7.4 pH) held
at a constant temperature of 37°C. Complete degradation of the BHMBP-PDLLA
occurred at times much earlier than those of the controls. These poly(α-hydroxy acid)
polymers have shown promising degradation results when chain-extended using L-lysine
diisocyanate methyl ester as the chain-extending agent.
DEDICATION

I want to dedicate this manuscript to my parents Joe and Aileen Cooper of Morganton, NC for without their guidance and love I would not be the person I am today.

I additionally want to dedicate this research and all I will ever accomplish to my beautiful wife, Kristin.
ACKNOWLEDGEMENTS

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CHAPTER 1
INTRODUCTION

In recent years there has been a large amount of research focused on degradable plastics; this is due in part to the overwhelming quantity of consumer plastic that is being endlessly generated (100 million tons in 2001). Consumer plastic must be disposed of either through incineration, burial, or recycling, all of which adds considerable cost to the consumer. Degradable polymers are polymer materials that undergo bond scission of the backbone through chemical, biological and/or physical forces in the environment at a rate which leads to fragmentation or disintegration of the polymer. Thus, the primary structure of the polymer, especially side groups present, initial molecular weight, hydrophilic/hydrophobic balance, crystallinity, and glass transition temperature cooperatively dominate the degradability of the polymer and the time required for complete degradation.¹

There are significant challenges involved in the effort to replace existing non-degradable consumer plastics, such as poly(styrene) (PS) poly(ethylene), poly(propylene), poly(isobutylene) (PIB), and poly(butadiene) (PBD), with degradable alternatives. Degradable polyesters are at the forefront of this research due to their inherent ability to degrade by hydrolysis of the ester linkage.

Hydrolytic degradation occurs in two phases for semi-crystalline polyesters. First, water diffuses into the bulk of the polymer matrix, randomly attacking the ester bonds in the amorphous phase and causing scission of polymer chains into shorter water-soluble fragments. In the second phase, hydrolytic attack on the crystalline region occurs which leads to a prompt decrease in polymer mass.
Degradable polyester research is gaining interest due to the availability and declining cost of starting materials and the capability to create a diverse number of polymers that possess sufficient physical properties for use in a variety of applications.\textsuperscript{2,3} A large number of commercial-scale degradable polyesters have emerged into the market including Ecoflex® (BASF), Eastar® Bio (Developed by Eastman), Bionelle® (Showa Polymers), Biomax® (Dupont) and NatureWorks\textsuperscript{TM} PLA(Cargill-Dow).\textsuperscript{4,21} These materials are being investigated and marketed primarily for their degradation characteristic, which is influenced by many different factors.\textsuperscript{22,23}

Currently, research of degradable polyesters can be ultimately divided into two categories: polymers derived from non-renewable (petroleum) and renewable resources. Ecoflex®, Eastar®Bio, Bionelle® and Biomax® are degradable polymers that are synthesized from non-renewable resources and fall under the classification aromatic-aliphatic copolyesters (AAC).

Research involving AACs has shown that an increase in the proportion of aromatic units causes an increase in mechanical properties and a decrease in biodegradability. To counteract this decrease in biodegradability, aliphatic or hydrophilic monomers are incorporated into the polyester backbone. The most commonly used aromatic monomers are phthalic acid isomers, i.e. isophthalic and terephthalic acid. These aromatic monomers are produced commercially by the catalytic oxidation of \textit{p}-xylene or \textit{m}-xylene obtained from petroleum sources.\textsuperscript{24} Typical aliphatic monomers used include adipic acid, succinic acid, 1,4-butanediol and ethylene glycol. Again, these aliphatic monomers are manufactured from petroleum sources. The continuous rise in oil prices (25/barrel (July 2003) to 78/barrel (July 2006)) and the inevitable depletion of oil
reserves have provided a driving force for research aimed at copolymers of the above AACs and polymers that are derived from renewable resources.

Among degradable polymers from renewable resources, PLA is currently the most popular. In fact, it has been stated that PLA is a ideal candidate for the replacement of current non-degradable plastics.\textsuperscript{25} This is in part due to its physical and excellent degradation characteristics.\textsuperscript{23,26-28} In 2001, Cargill-Dow Corporation commercialized, NatureWorks™ PLA, a degradable, semi-crystalline aliphatic polyester synthesized from L-lactide, which is manufactured from corn, a renewable resource. Their process involves the fermentation of corn to produce lactic acid, which is then converted into the cyclic dimer, lactide; this conversion can be controlled to give three stereoisomers L-, D-, and meso-lactide. High molecular weight PLA can be synthesized from any lactide isomers via ring opening polymerization (ROP). PLA has gained tremendous attention in the past decade due to its desirable characteristics, namely, degradability under biotic or abiotic conditions, non-toxicity of polymer and degradation by-products, and adequate mechanical properties for use in select applications. A variety of degradable products derived from PLA, including clothing fibers, packaging applications, coatings, blow-molded bottles, and biomedical applications, are now a reality. Limitations of PLA with regard to degradation characteristics and mechanical and thermal properties have been documented. An extensive amount of research has been devoted to the modification of PLA, through copolymerization or chemical modification, in order to change degradation characteristics and/or enhance thermal and/or physical properties.\textsuperscript{29,30,31,32,33} Poly(L-lactide) (PLLA) has a $T_g$ of 50-59 °C and a $T_m$ of 130-196 °C, which tends to produce brittle and hydrolytically unstable materials in its crude state. As a result of its relatively
rapid degradation rate, its primary use has been in the medical industry as a copolymer with glycolide for bioresorbable surgical sutures, prosthetics, dental implants, pins, bone screws, plates for temporary internal fracture fixation, long-term delivery of antimalarial drugs, contraceptives and eye drugs, tissue supports, and controlled drug delivery systems.

Research into degradable polymers is growing due to the negative impact that non-degradable polymer have on the environment. This research is additionally fueled by the increased commercial availability of renewable monomers, such as lactide, in the past 10 years. Consequently, research in the field of degradable polyesters has grown drastically and remains a vanguard of polymer research. Most research in this field is concentrated on chemical manipulations of the polymer or copolymerization with other polymers in order to enhance the degradation and/or physical properties. Chemical modification of polymers that are prone to hydrolysis, such as poly(lactic acid), will enhance hydrolytic degradation by increasing their hydrophilic nature and/or impart a catalytic effect, for example addition of acid functionality. This document provides details concerning the synthesis and characterization of block AACs, acid-modified α-hydroxy acid polymers, i.e. poly(D,L-lactide) and poly (ester-urethanes). Kinetic investigation and hydrolytic degradation of the above polymers are also documented where applicable.
CHAPTER 2

BACKGROUND AND REVIEW

A. Degradable Polyesters and Modes of Degradation

In today's society consumer non-degradable plastic waste has grown to an unprecedented level. In fact, millions of tons of micro-plastic waste is accumulating in the oceans and is disrupting the stability of marine life and the devastating results could be irreversible if action is not taken soon. Solutions to control plastic waste have included recycling programs, incineration of plastic waste for energy production and alternative degradable plastics with benign degradation products. The necessity for degradable materials is an essential issue concerning a global society and has been a critical topic in the scientific community for the past three decades. The steady increase of scientific publications and the industrial surge to develop degradable polymers is a testament to the overall awareness of the benefits offered by environmentally friendly polymers. Many efforts into the search for degradable polymers have been concentrated on aliphatic polyesters. A number of aliphatic polyesters possess specific characteristics that make them ideal for environmental degradation, including susceptibility to hydrolysis and microbial attack. Additionally, degradable aliphatic polyesters can be created through natural, synthetic, and biosynthetic means and exhibit thermal and physical properties that are necessary for use in a variety of applications. Degradability can be engineered into polyesters by the astute introduction of chemical linkages such as anhydride, carbonate, or urethane bonds, or through modification of side groups contained on the polymer backbone. In addition, the nature of the polymeric substrate influences the degradability. Properties such as branching, hydrophilicity, molecular
weight, surface area, and crystallinity as well as the type of chemical bonds, stereochemistry, and interactions with other components play a vital role in polymer degradation.\textsuperscript{23} Similarly, enzymes can trigger degradation, which is effectively termed biodegradation. Biodegradation is governed by the type and level of enzyme, the location of the enzyme (intracellular vs. extracellular), and the presence of inhibitors or enzyme inducers.\textsuperscript{23} However, in order to successfully induce and control degradability of polymers, including polyesters, a number of aspects must be considered; such as hydrophobic/hydrophilic balance, molecular weight, and crystallinity all of which play a fundamental role in the polymer's overall degradability.

Due to the susceptibility of ester linkages to hydrolysis; the affinity of the polyester for water is a vital factor that leads to hydrolytic degradation. Accordingly, an increase in polymer hydrophilicity generally enhances degradability, therefore an extremely hydrophobic polyester such as poly(ethylene terephthalate) (PET) will inhibit degradation. Chu and coworkers demonstrated that PET under 100\% relative humidity (25°C) had a moisture gain of 0.8\%. This implies that only the surface of the polyester absorbed the water molecules, which is expected for a hydrophobic polymer.

Many studies concur that crystallinity plays a governing role in the hydrolytic degradation of polyesters.\textsuperscript{36-42} All studies thus far agree that water first, diffuses into amorphous regions of the polyester and randomly cleaves ester bonds causing fragmentation of the polymer, in turn creating hydroxy and carboxylic acid terminated fragments (Scheme 2.1), after which the crystalline regions undergo surface erosion leading to a rapid loss of molecular weight.
Scheme 2.1. Hydrolysis of ester linkage contained in a polyester.

\[
\begin{align*}
\text{O} & \quad \text{O} \quad + \quad \text{H}_2\text{O} \\
\text{OH} & \quad \quad \text{H} \quad \quad \text{HO}
\end{align*}
\]

Due to the organization or close packing of polyester chains in the crystalline regions hydrolysis is impeded due to the impermeability of water. Therefore, ester linkages embedded in a crystallite are more resistant to simple hydrolysis. Fukuzaki and coworkers demonstrated this behavior using low molecular weight copolymers of D- and L-lactide, whereby highly crystalline copolymers containing high feed ratios of one stereoisomer degraded more slowly in comparison to the totally amorphous racemic mixture.43

Molecular weight and chain flexibility, which are closely associated with glass transition temperature (\(T_g\)), also affects the rate of hydrolytic degradation. Negligible degradation is observed at temperatures below the glass transition of PET as determined by Hosseini and coworkers.44 Hydrolytic degradation of the PET increased as temperatures increased above \(T_g\) due to increased chain flexibility and diffusion of water.

B. Degradable Aromatic-Aliphatic Copolyesters

In the 1930s Carothers and coworkers at Dupont began work on synthesizing aliphatic polyesters. They established fundamental insights into the relationship between the extent of reaction and the influence of stoichiometric balance of functional groups and their affect on molar mass as pertaining to condensation and step growth polymerization.45 However, during early development of aliphatic polyesters only low molecular weight polymers with poor mechanical properties were possible. Eventually, new metal catalysts, thermal stabilizers and copolymerization with aromatic esters paved
the way for the synthesis of degradable aliphatic polyesters of higher molecular weight and improved physical properties.

Copolymerization of aromatic esters into the polyester chain proved to be successful in improving the mechanical and thermal properties of aliphatic polyesters. Lee and coworkers found that copolymerizing dimethyl terephthalate with succinic acid and 1,4-butane diol the elongation at break increases to 550 percent with 40 mole percent of butylene terephthalate. Ecoflex®, a commercialized AAC, comprised of adipic acid, terephthalic acid, 1,4-butanediol and a branching unit (proprietary) has a tensile strength of 32-36 N mm\(^2\) (50\(\mu\)m film) which is comparable to low density polyethylene. There is a trade off of degradability and physical properties of these polyesters; a decrease in degradability is observed when the aromatic content is increased. Consequently there has been research involved in obtaining a balance between degradability and physical properties by the variation of the aliphatic and aromatic content of a copolyester.

Haderlein et al. synthesized copolyesters containing bisphenol A-terephthalate/isophthalate (aromatic moieties) and lactide moieties.\(^{46}\) The sequencing of the aromatic/aliphatic segments was uncertain, and as a consequence the mechanical properties and degradation behavior were unpredictable; however, the authors concluded that the incorporation of the mesogenic aromatic moieties into the polylactide yielded some improvement in mechanical properties. In another, similar attempt to enhance the mechanical properties of polylactide, Haderlein et al. altered the comonomers employed. They chose phenylterephthaloyl dichloride, 2,2'-dimethyl-4,4'-dihydroxybiphenyl, and D,L lactide moieties for the purpose of obtaining a polyester with high molecular weight, which are crucial prerequisites for excellent mechanical properties. Even though the
copolymers obtained had promising properties, the block lengths of the aromatic and aliphatic segments still could not be determined accurately, which prohibited the ability to relate structural character to the physical properties of the polymer.\textsuperscript{47} Chen \textit{et al.} were able to increase the hydrophilicity of polyesters containing mesogenic aromatic segments and polylactide moieties by the incorporation of polyethylene oxide into the polymer backbone (Figure 2.1).

\begin{center}
\includegraphics[width=\textwidth]{figure2.1.png}
\end{center}

\textbf{Figure 2.1} Polycondensation reaction of phenylterephthaloyl dichloride (2), 2,2'-dimethyl-4,4'-dihydroxybiphenyl (1), \(\alpha\)-hydroxy-\(\omega\)-carboxyoligolactide (3), and \(\alpha\),\(\omega\)-dihydroxy poly(ethylene glycol) (4).

Incorporation of the ethyleneoxy moieties improved the hydrolytic degradability of the polylactide segments,\textsuperscript{48,49} however, in comparison to the polyesters synthesized by Haderlein \textit{et al.}, introduction of the polyethylene oxide decreased tensile properties significantly.\textsuperscript{47,49}
Jin et al. reported a similar polyester system to that of Haderlein and Chen; however, these authors chose \( p \)-hydroxybenzoic (PHBA) acid as the aromatic portion of the polyester, thereby incorporating a mesogenic segment.\(^{50}\) PHBA can be synthesized (microbial) from a renewable resource (glucose), and this feature fits well in to the proposed hybrid copolyester scheme.\(^{51}\) One obstacle that beset Jin et al., aside from poor copolymerizability of the aromatic and aliphatic monomers, was the thermal instability of the reaction products. The aliphatic (polylactide) portion of the polyester suffered thermal degradation during the reaction process, which prevented the production of high molecular weight polyesters.

Nagata approached the synthesis of biodegradable polyesters with aromatic segments using a fairly different system of diacid and diol monomers, including sebacid acid and hydroquinone.\(^{52}\) To avoid thermal degradation of the aliphatic segment of the copolymer during synthesis, a more thermally stable aliphatic unit, sebacic acid, was utilized in place of lactide. Similar to PHBA it has been reported that hydroquinone can also be obtained from a renewable process.\(^{53}\) Nagata found success in the degradation study of their polyesters noting that as the percentage PHBA increased, degradation rate decreased. Conversely, at lower percentages of PHBA (higher percentages of aliphatic units) the degradation rate decreased; this anomaly was attributed to increasing crystallinity associated with increasing lactide content. For all of the above syntheses, high temperatures (230-280°C) were necessary to achieve the “critical” molecular weight required to obtain polyesters with sufficient physical properties. The byproducts (\( \text{H}_2\text{O} \) and/or \( \text{HCl} \)) in combination with these temperatures can contribute to rapid hydrolytic cleavage of the ester linkages. This “premature degradation” and unwanted
transesterification of the aliphatic units accounts for the inconsistency in structural elucidation and control.

To alleviate the problems of uncontrollable structure, which greatly effect properties of the final polyester, copolymerization of aromatic and lactide segments will be carried out under milder conditions. One approach is to employ a synthetic route in which the copolymerization of the aromatic (or any polyester) segment and lactide segment are independent of one another. This is the basic concept governing the research involved in the synthesis of block copolyesters containing poly(lactide).

Kim et al. prepared a completely degradable poly(L-lactide-\(b\)-trimethylene carbonate-\(b\)-L-lactide) segmented block copolymer of the ABA type.\(^5^4\) The polymer was synthesized in a two-stage method in which the ABA block copolymer (hydroxy end-capped) was synthesized first, followed by chain extension with a diisocyanate. The mechanical properties (tensile strength and Young’s modulus) of the final product were improved in comparison to homopolymers of poly(lactide) and poly(trimethylene carbonate). Kim’s research is strong evidence that a block copolymer system-containing poly(lactide) will in fact bring about enhanced properties as compared to the respective homopolymers. In a more recent attempt to create block copolymers from two readily available biodegradable polymers, Ba et al. synthesized an ABA block copolyester of poly(lactide) and poly(butylene succinate).\(^5^5\) Poly(butylene succinate) has excellent elongation rate at break as well as other physical properties similar to those of polyethylene; this makes it a great copolymer candidate for a biodegradable polymer with enhanced physical properties.
C. Ring Opening Polymerization of Lactides Using Stannous Octoate as catalyst/coinitiator

Research into degradable polyesters has grown exponentially since the introduction of lactide derived from renewable resources to synthesize PLA, due to the potential impact this polyester will have on decreasing the amount of non-degradable plastic waste that makes it into the environment at the same time reducing dependency on petroleum-based polymers. PLA was considered for use as a biocompatible, biodegradable, and bioresorbable material as early as the 1960s and has received considerable attention ever since. A number of research groups developed homopolymers and copolymers of lactide and glycolide for use as surgical sutures, drug delivery devices, and other body implants. Vicryl, a blend of PGA (90%) and PLA (10%) was launched in the US in 1974 as a biodegradable suture. A vast number of researchers have significantly contributed to PLA research efforts in the past 15 years and have been instrumental in the pursuit to use biodegradable polyesters as an alternative to commodity plastics.

PLA can be synthesized by condensation, or alternatively by ring-opening polymerization (ROP) of lactide and advances via a chain growth process. ROP consists of initiation, propagation, chain-transfer, and termination. Propagation is governed by ring size; the presence, number and type of substituents; and ring strain. Conversion of medium-sized rings (5-7 atoms) rarely reaches 100% due to a thermodynamically controlled equilibrium between polymerization and depolymerization. ROP offers a major advantage over direct condensation in that high reaction conversion are relatively easy to achieve and this consequently results in high molecular weight polymer. ROP of lactides can be accomplished through four
mechanistic routes, namely cationic, anionic, nucleophilic and coordination-insertion polymerization. PLA is industrially produced by way of the coordination-insertion mechanism involving the complex tin(II) bis(2-ethylhexanoate) (Sn(Oct)$_2$) (Figure 2.2).

**Figure 2.2** Structure of tin(II) bis(2-ethylhexanoate) Sn(Oct)$_2$.

Sn(Oct)$_2$ has become the catalyst of choice due to its low cost, low toxicity, and high efficiency.$^{65}$ The first reports of Sn(Oct)$_2$-catalyzed polymerizations of lactones emerged in the late 1960s.$^{66,67}$ Dittrich and Schulz introduced the three step coordination-insertion mechanism of cyclic esters in 1971. Kricheldorf and Teyssié independently provided experimental proof of the mechanism with lactide in the late 1980s. The mechanism of Sn(Oct)$_2$-catalyzed polymerizations has been widely disputed over the past 30 years; cationic,$^{68,69}$ activated monomer,$^{70,71}$ direct Sn(Oct)$_2$ initiation$^{70}$, and Sn(Oct)$_2$/alcohol coinitiation$^{72-81}$ mechanisms have all been proposed. Kowalski and coworkers provided conclusive evidence supporting a coinitiation-type mechanism of Sn(Oct)$_2$ and an hydroxy containing species.$^{82}$ The Sn(Oct)$_2$ is converted into a tin(II) alkoxide that actually initiates polymerization.

Formation of initiating tin(II) alkoxide species and coordination-insertion mechanism for the ring opening polymerization of a cyclic ester, lactide, is illustrated in Figure 2.3 and Figure 2.4.
The alcohol initiator initially complexes and subsequently reacts with Sn(Oct)$_2$ producing a stannous alkoxide species (A) and liberates 2-ethylhexanoic acid (C) before polymerization commences (reaction 4, Figure 2.4). The stannous dialkoxide initiator (B) is created upon further reaction with a second equivalent of alcohol, simultaneously liberating another 2-ethylhexanoic acid (reaction 2). Competing reactions of adventitious water (or alcohol impurities) with (A) or (B) serve mainly to inhibit the catalytic activity via a reversible reaction (reaction 3) effectively reducing the concentration of active stannous alkoxide species and generating a stannous alcohol derivative (D), which is more thermodynamically stable than the stannous dialkoxide, but less efficient as an initiator.\textsuperscript{78}
Figure 2.4  ROP of lactide via coordination-insertion mechanism by way of tin(II) alkoxide.

The initial active propagating chain end (E) is generated by reaction of the first monomer unit and the stannous dialkoxide species (B) \textit{via} coordination-insertion (reaction 5). Subsequently, (E) either propagates or undergoes rapid intermolecular exchange of the stannous alkoxide moiety for a proton from either hydroxyl groups of initiator (if remaining) or another hydroxy chain end, which can also be polymeric in nature. Ultimately these processes establish a dynamic equilibrium between activated and deactivated chain ends such that R represents unreacted alcohol initiator or hydroxy chain ends generated \textit{in-situ} (reaction 5). Propagation proceeds through acyl oxygen cleavage of the cyclic monomer (reaction 6).
By far, Sn(Oct)$_2$ is the most commonly used co-catalyst for ROP of cyclic esters in both academia and industry, however, there are numerous other metal-based coordination catalysts that are being investigated. Complexes based on other metals such as Sn(IV)$_2$, Mg(II), Zn(II), Ti(IV)$_2$, Al(III)$_2$, have also been used in ROP of lactides.

ROP of lactides may be monitored in the mid-IR region by measuring the decrease in absorbance of the 933 cm$^{-1}$ peak (-CO-O- ring breathing mode) or the 1240 cm$^{-1}$ peak, (C-O-C stretch) of rac-lactide or L-lactide. Storey and Messman investigated the solution ROP of rac-lactide using in situ FTIR spectroscopy by monitoring the dissapperance of 1240 cm$^{-1}$ peak upon conversion of rac-lactide to polymer. The accuracy of the method was ensured by calibration using simulated polymerization mixtures consisting of known concentrations of monomer and polymer. Furthermore, the ATR-FTIR data were in good agreement with SEC measurements. The FTIR method using the 1240 cm$^{-1}$ peak proved to be accurate and convenient, and was used to study the effect of different experimental variables, e.g., initiator and catalyst concentration, on the rate of polymerization.

D. Improvement of PLA Through Functionalization or Copolymerization

The synthesis of functionalized polymers of a specific molecular weight is essential for any macromolecular engineering. Extensive research has been devoted to the modification of PLA in order to change degradation characteristics and/or enhance physical properties. One such modification involves the incorporation of carboxylic acid groups into the PLA backbone. Mullen and coworkers copolymerized D,L-lactide
(DLLA) with 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one, a cyclic carbonate containing a latent carboxylic acid group (benzyl ester). After deprotection to the carboxylic acid form, the resulting copolymers showed improved thermal characteristics, i.e., higher $T_g$; however, deprotection was incomplete and the degree of incorporation and sequencing of the acid pendant groups were subject to the comonomer reactivity ratios of the ring-opening copolymerization (ROP).

Kimura and coworkers synthesized a cyclic ester bearing protected carboxylic acid pendant groups, eventually obtaining a polyester containing glycolic and $\alpha$-malic acid units (Figure 2.5).  

![Figure 2.5](image)

**Figure 2.5** Synthesis of poly[(glycolic acid)-co-(a-(S)-malic acid)] from 3(S)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione.

The intended goal for poly[(glycolic acid)-co-(a-(S)-malic acid)] was to impart water solubility of $\alpha$-hydroxy acids and provide functional groups for the attachment of drugs for sustained release. While important efforts have been devoted to the synthesis of functionalized monomers, which is very often intricate and arduous, there are alternative routes to produce PLA with improved hydrophilicity and degradation profiles. Copolymers of PLA have been made by the incorporation of numerous other monomers such as cyclic carbonates, including trimethylene carbonate and 5,5-dimethyltrimethylene carbonate. Conceivably almost any PLA copolymer could in theory be synthesized given the right conditions.
An array of Al(III) alkoxides have been explored for their effectiveness in producing end-functionalized polymers\textsuperscript{118-124}. These polymers can be of use in and of themselves or utilized as macroinitiators in creating more elaborate polymeric systems. Other methods have been investigated, in which telechelic functionalized PLA is created either through direct or post polymerization syntheses\textsuperscript{125}. Lee and coworkers synthesized PLA with -Cl, -NH\textsubscript{2} and -COOH end groups from the product obtained by ROP of lactide, with an alcohol in the presence of Sn(Oct)\textsubscript{2}. Lee et al. and Wiggins et al. showed that PLA containing -COOH end groups had accelerated hydrolytic degradation when compared to PLA with -OH end groups.\textsuperscript{126,127} In fact, complete degradation of 5,000 g/mol PLA-COOH occurred in 55 days in contrast to 120 days for PLA-OH (Figure 2.6).

![Figure 2.6](image)

**Figure 2.6** Remaining mass percent vs. time for 5000 g/mol poly(D,L-lactide) diol (5K diol) and diacid (5K diacid).
Hiltunen and coworkers synthesized low molecular weight (~7000 g/mol) hydroxyl- and carboxyl-terminated PLA prepolymers by copolymerization with 1,4-butandiol and adipic acid, respectively (Figure 2.7).

They synthesized subsequent PLA prepolymers with varying Tgs and crystallinities for use in the formulation of degradable poly(ester-urethane)s.

\[ \text{Figure 2.7} \quad \text{Hydroxyl (A) and acid (B) terminated PLA synthesized by polycondensation of lactic acid, 1,4-butandiol and adipic acid.} \]

\[ \text{They synthesized subsequent PLA prepolymers with varying Tgs and crystallinities for use in the formulation of degradable poly(ester-urethane)s.} \]
CHAPTER 3
SYNTHETIC STRATEGIES AND RESEARCH GOALS AND OBJECTIVES

PLA and copolyesters of PLA have been at the forefront of scientific investigation with regard to degradable polymers that will potentially replace current petroleum based plastics. PLA has already proven useful in biomedical applications and currently is being utilized in food packaging and disposable utensils. PLA is typically synthesized from L-lactide and rac-lactide (racemic mixture of D- and L-lactide), where poly(L-lactide) is highly crystalline and rac-lactide is completely amorphous. PLA derived from these monomers are already approved by the United States Food and Drug Administration for a variety of applications including sutures, prostheses, and drug delivery.

A portion of PLA research focuses on adding functionality through backbone modification. This can be achieved by copolymerization or direct chemical alteration producing PLA with novel degradation and physical characteristics. A variety of PLA-containing copolyesters have been synthesized, in order to optimize the structure property relationships as well as providing predictable control of degradation. Copolyesters of PLA with blocky architectures are of particular interest due to the possibility of forming physical-type crosslinks resulting in a polymer with elastomeric unique physical properties and possess an avenue for hydrolytic degradation. PLA has been combined with a number of polyesters, including poly(butylene succinate) PBS, poly(ethylene terephthalate) PET and poly(butylene adipate) PBA in order to improve degradability of these materials. Additionally, the physical properties of PLA can be significantly improved when copolymerized with the before mentioned polyesters. Introduction of carboxylic acid moieties within PLA, through chemical modifications, during or post
polymerizations has been shown to increase the hydrophilicity of the polymer thereby
improving degradation rate in an aqueous environment. Functionalized PLA, containing
hydrophilic moieties could be used as a prepolymer in the formulation of poly(ester-
urethane)s that can be utilized in degradable packaging applications.

The goal of the research presented in this Ph.D. dissertation is to develop
degradable polymers based on rac- and L-lactide with unique structural, degradative, and
thermal properties. The objectives of the research include:

1. The synthesis of polyester macroinitiators of various molecular weights and
copolymer compositions, via polycondensation reaction utilizing
aromatic/aliphatic acids and alcohols of the AA/BB type.
2. Synthesis of ABA triblock copolyesters using the above polyester macroinitiators
in the ROP of L- and D,L-lactide.
3. Determination of structure-property and structure-degradation (via hydrolysis)
relationships of various ABA block copolymers consisting of different molecular
weights and copolyester compositions.
4. Synthesis of PLA prepolymers with improved hydrolytic degradation, by addition
of acid moieties.
5. Evaluation of the utility of PLA prepolymers for use in poly(ester-urethane)
systems by synthesizing chain-extended model polymers using a diisocyanate as
the chain-extending agent.
6. Determination of structure-property and structure-degradation (via hydrolysis)
relationship of PLA prepolymers synthesized from D,L-lactide of various
molecular weights, and chain-extended analogs.
CHAPTER 4

EXPERIMENTAL

A. Materials

Acetone-d (99.8% D, Aldrich Chemical Company) was used as received.

Argon (99.9%, Nordan Smith) was used as received.

Buffer Solutions, pH 4.00, 7.00, 7.40, 10.00 (Fisher Scientific) was used as received.

1,4-butanediol (99.5%, anhydrous, Aldrich Chemical Company) was used as received.

Calcium hydride (Aldrich Chemical Company) was used as received.

ε-Caprolactone (99+% Dow Chemical Company) was freshly distilled from CaH₂ under reduced pressure and stored under argon or nitrogen prior to use.

Chloroform (anhydrous, 99+, J.T. Baker Chemical Company) was used as received.

Chloroform-d (99.8% D, Aldrich Chemical Company) was used as received.

Dibutyltin dilaurate (98%, Aldrich Chemical Company) was used as received.

1,2-Dichloroethane (99%, Aldrich Chemical Company) was distilled from CaH₂ prior to use.

Dicyclohexylmethane 4,4'-diisocyanate (H₁₂MDI, Bayer Desmodur W) was used as received and stored under nitrogen.

Dimethyl sulfoxide-d₆ (99+, Aldrich Chemical Company) was used as received.

Ethylene glycol (99.8%, anhydrous, Aldrich Chemical Company) was used as received.

Hydrochloric acid (VWR) was used as received.

2,2-Bis-(hydroxymethyl)butyric acid (98%, Aldrich Chemical Company) was used as received.
2,2-Bis-(hydroxymethyl)propionic acid (98%, Aldrich Chemical Company) was used as received.

D,L-lactide or rac-Lactide (Ortec; Piedmont, SC) which is 50:50 mixture of D- and L-lactide isomers was used as received.

L-lactide (Ortec; Piedmont, SC) was used as received.

L-Lysine diisocyanate, methyl ester (Kyowa Hakko) was distilled under reduced pressure and stored under argon or nitrogen prior to use.

Magnesium sulfate (anhydrous, certified A.C.S., Fisher Scientific Company) was used as received.

Methyl alcohol (Fisher Scientific Company) was used as received.

Methylene chloride (99+%, J.T. Baker Chemical Company) was stored over 4A molecular sieves prior to use.

1-Methylimidazole (99+%, redistilled, Aldrich Chemical Company) was used as received.

Potassium Hydroxide (Fisher Scientific) was used as received.

1,2-Propanediol (99.5%, Aldrich Chemical Company) was used as received.

Sodium (20% suspension in toluene, Aldrich Chemical Company) was used as received.

Succinic anhydride (97%, Aldrich Chemical Company) was used as received.

Tetrahydrofuran (HPLC grade, J.T. Baker Chemical Company) was distilled from CaH2 prior to use.

Tin (II) bis(2-ethylhexanoate) (Alfa Aesar and Aldrich Chemical Company) was used as received.
Toluene (99+%, Aldrich Chemical Company) was refluxed over sodium for 24 h and distilled under N\textsubscript{2} and stored under Ar prior to use.

Water was filtered and deionized to a resistance value of > 10 M\textOmega\textperiodcentered cm prior to use.
B. Instrumentation

1. Size Exclusion Chromatography (SEC)

Molecular weights (number average and weight average) and molecular weight distributions (MWD) of the polymeric materials were determined using a SEC system consisting of a Waters Alliance 2690 Separations Module, an on-line multi-angle laser light scattering (MALLS) detector (MiniDAWN™, Wyatt Technology Inc.), an interferometric refractometer (Optilab DSP™, Wyatt Technology Inc.) and one of two sets of PLgel™ (Polymer Laboratories Inc.) SEC columns. Each set, consisting of two 3 μm mixed E or 5 μm mixed D PLgel™ columns connected in series, was attached in a separate switchable loop (Waters EV700-100-WA switching valve) with only one of the two sets active during data acquisition. The 3 μm particle-size columns were used for samples that did not contain molecules larger than ca. 10,000 g/mol; the 5 μm particle-size columns were used in separating molecules between ca. 10,000-2,000,000 g/mol. Freshly distilled THF served as the mobile phase and was delivered at a flow rate of 1.0 mL/min. Sample concentrations were ca. 7-40 mg of polymer/mL of THF, and the injection volume was 100 μL. The detector signals were simultaneously recorded using ASTRA™ 4.9 software (Wyatt Technology Inc.), and absolute molecular weights were determined by MALLS using a dn/dc value calculated from the signal response of the Optilab DSP and assuming 100% mass recovery from the columns.

2. Proton Nuclear Magnetic Resonance (1H NMR) Spectroscopy

1H NMR spectra were obtained using two different NMR spectrometers: Bruker AC-300 (300 MHz) or Varian 500 (500 MHz). The samples were prepared in 5-mm
(o.d.) glass tubes, and the concentration was approximately 5-25% (w/w) in d-
chloroform, d-acetone or d-DMSO. Proton signals were reported against the published
solvent lock resonances or an internal reference, tetramethylsilane (TMS) at 0 ppm. $^1$H
spin-lattice relaxation times ($T_1$) were determined using an inversion-recovery pulse
sequence (180°-τ-90°) with a delay of ~20-30 s between scans.

3. Carbon Nuclear Magnetic Resonance ($^{13}$C NMR) Spectroscopy

$^{13}$C NMR spectra were obtained using two different NMR spectrometers: Bruker
AC-300 system (300 MHz) or Varian Unity Inova 500 (500 MHz). The samples were
prepared in 5-mm (o.d.) glass tubes and the concentration was approximately 10-25%
(w/w) in d-chloroform, d-acetone or d-DMSO. Chemical shifts were referenced against
the published solvent lock resonances or an internal reference, tetramethylsilane
(TMS) at 0 ppm.

4. 2-Dimensional Nuclear Magnetic Resonance Spectroscopy

Nuclear Overhauser Enhancement SpectroscopY (NOESY) experiments were
performed using a delay time of $2 \times T_1$, obtaining 200 increments ($F_1$) and 16 scans per
increment, at a spectral width of 4000 Hz. Homonuclear Correlation Spectroscopy
(COSY) NMR experiments were performed using a delay time of $5 \times T_1$, obtaining 128
increments ($F_1$) and 8 scans per increment, at a spectral width of 3988 Hz operating at
499.77 MHz. Heteronuclear Single Quantum Coherence Spectroscopy (HSQC)
experiments were performed using a delay time of $5 \times T_1$, obtaining 200 increments and 16
scans per increment, within spectral widths of 7530 and 3988 Hz and operating at 125.7
and 499.7 MHz in the $^{13}$C and $^1$H domains, respectively.
5. Differential Scanning Calorimetry (DSC)

Glass transition temperatures ($T_g$) and the crystalline melting temperature ($T_m$) of the polymer samples were measured using a TA Instruments DSC Q100. Samples (10-15 mg) were heated from 25°C to 90-180°C at a heating rate of 10°C/min, quenched, and heated again from -50°C to 90-180°C at the same rate. The reported $T_g$ values represent the mid-point temperature for the glass-transition of the second heating cycle.

6. Monomer Conversion and Kinetic Measurements of PEOE/TA/Lactide Block Copolyesters by Real-time ATR-FTIR

A Bruker Equinox™ 55 FTIR (Bruker Optics, Inc., Billerica, MA), equipped with OPUS software, an Axiom Analytical Diamond Attenuated Total Reflectance (ATR) Probe DMD-270 (Axiom Analytical, Irvine, CA), and external mercury-cadmium-telluride (MCT) mid-band detector, and a silicone oil bath controlled using a DigiSense® 68900-01 temperature controller was used to collect real-time infrared spectra of the polymerization reaction. Spectra were acquired in the double-sided, forward-backward mode, with a phase resolution of 128 cm$^{-1}$ using a Mertz phase correction mode. Interferograms were truncated using the Norton-Beer medium apodization function with a zero-filling factor of 2. Once the reaction vessel was attached and its contents equilibrated spectra were acquired at 3.17 min intervals at a spectral resolution of 8 cm$^{-1}$ over the spectral range of 5000-2300 cm$^{-1}$ and 1800-600 cm$^{-1}$ each spectrum was an average of 8 scans. An interval as referred to here is the time period between the first scan of a spectrum and the first scan of the subsequent spectrum. A toluene background spectrum was taken prior to each polymerization and subtracted from all subsequent spectra. L-lactide (LLA) concentration was assumed to be proportional to
peak height of the 1240 cm\(^{-1}\) absorbance, measured between the limits of 1247 and 1236 cm\(^{-1}\), relative to a straight baseline from 1276 to 1034 cm\(^{-1}\) (OPUS method L) \(^{133}\). These reference points were chosen to obtain a baseline that was unchanging throughout the course of the polymerization reaction. The initial monomer concentration ([M]\(_0\)) was set proportional to the average 1240 cm\(^{-1}\) peak height of the first few spectra taken before addition of the catalyst. ATR-FTIR data files were selected and assembled into a GC or 3-D file using OPUS NT software.

Peak height values were copied into a Microsoft Excel spreadsheet and converted to concentration values based on the initial monomer concentration and the peak height of the first few spectra. Monomer conversions were monitored in real-time using the following equation, 

\[ c = 1 - \frac{[M]}{[M]_0} \]

where \(c\) represents monomer conversion, \([M]_0 = \) initial monomer concentration, \([M] = \) instantaneous monomer concentration.

Kinetic rate constants were determined from the monomer conversion data obtained using FTIR spectroscopic measurements. A plot of \(\ln ([M]_0/[M])\) vs. time yielded a slope equal to \(k_p[M^*]\), where \(k_p\) is the rate constant for propagation and \([M^*]\) is the concentration of actively growing chains. First-order (apparent) rate constants for propagation, \(k_{app} = k_p[M^*]\), were taken from the slopes of these plots. Due to a convoluting polymer peak \(^{134}\) centered at 1184 cm\(^{-1}\), peak height at 1240 cm\(^{-1}\) leads to an over-estimation of LLA concentration at high conversion. The effect of this error was minimized by extrapolating apparent rate constants over a limited conversion range (< 15\%).
7. *Atomic Force Microscopy*

A MultiMode AFM (Digital Instruments) with an ultra sharp silicon cantilever (MicroMasch Silicon Cantilevers NSC16/AIBS/15) having a resonant frequency of 166.9 kHz and force constant of approximately 40 N/m was used to phase image the polymer sample in hard-tapping mode. The full tip cone angle was less than 30°, and the radius of curvature at the apex was less than 10 nm. To minimize artifacts, all bulk sample surfaces were smoothed using a diamond knife prior to acquiring the phase images. The sample was prepared by solvent (chloroform) casting.

8. *Positron Anilation Lifetime Spectroscopy (PALS)*

The free volume of select PLA specimens was obtained using PALS. PLA was formed into discs having a diameter of 9 mm and a thickness of ~1.5 mm; a 30 μCi $^{22}$Na source was placed between two discs and the positron lifetime spectrum was constructed. The experiments were performed at a constant temperature of 37°C and under conditions set forth by Olson and coworkers.$^{135,136}$ The positron lifetimes and intensities were analyzed by PATFIT software. This analysis provides information concerning the average size of the holes ($\tau_3$), the concentration of holes ($I_3$) and the overall free volume ($\AA^3$) of the sample.

9. *Tensile Testing with Instron*

Tensile measurements were made using a Material Testing System Alliance RT/10 and analyzed using an MTS Testworks 4 software package. Stress vs. strain measurements was determined under ambient conditions according to ASTM D882-83. Test specimens (Type M-II) were prepared according to ASTM specifications. Specimens were clamped using AL 2000N pneumatic grips set at 40 p.s.i. and the tests
were conducted using a 2250 lbf load cell operating at 10% range. The draw rate for the experiments was 10 mm/min.

10. Mechanical Stirrer Assembly

Polycondensation reactions that produced high molecular polymers required the use of mechanical stirring due to an increase in viscosity. However, in order to achieve high molecular weight polymers a vacuum was employed; therefore the stirring assembly had to be vacuum tight (< 1 mm Hg). This was achieved using a stirrer assembly designed for flasks with a 24/40 joint (Figure 4.1). The vacuum tight seal was mainly achieved through a compression nut (B) that compressed a o-ring at the top of the Teflon sleeve (F) when the sleeve was fixed into a Teflon housing (C). The inner Teflon sleeve provided support for the polished glass rod (10 mm) and was equipped with an o-ring to help achieve an air tight seal. The assembly was then fitted to the flask using a threaded 24/40 adapter (E). A thrust nut (A) attached to the stir rod prevented it from slipping lower into the flask due to the high vacuum. The stirrer assembly held a vacuum down to ~0.05 mm Hg, which was adequate for all polycondensation reactions.
Figure 4.1  Stirrer Assembly:
Thrust nut (A); Compression nut (B); Teflon housing (C); 24/40 screw nut (D); 24/40 glass adapter (E); Teflon sleeve (F)
11. *pH Determination of Aqueous Solutions*

*pH* values were acquired using a Accumet AR20 pH meter equipped with an accuTupH probe (Ag/AgCl double junction) and a variable temperature reference. The pH meter was calibrated before each use by a 3 point calibration curve method including buffer solutions of pH 4.00, 7.00 and 10.00.
C. General Procedures

I. Synthesis of Polyester Macroinitiator Poly(ethyleneoxyethylene-terephthalate-co-adipate (PEOETA).

A polyester macroinitiator was produced using a 4-necked 250 mL round-bottom flask equipped with an overhead stirrer, nitrogen gas inlet tube, thermometer, and distillation head for removal of reaction by-products. A special stirrer bearing, of our own design, was employed to maintain a vacuum seal (< 0.20 mm Hg) at the stirrer shaft. To the flask were charged 60.76 g (0.313 mole) dimethyl terephthalate, 62.21 g (0.357 mole) dimethyl adipate and 74.28 g (0.700 mole) diethylene glycol. No catalyst was used in the synthesis. Under nitrogen, the mixture was slowly heated, with stirring, until all components became molten (150-170°C). Heating and stirring were continued and methanol was continuously distilled as the transesterification reaction proceeded. When no further methanol could be removed under atmospheric pressure, a slight vacuum (100 mm Hg) was applied until the theoretical amount of methanol had been approximately collected. The vacuum was then gradually increased until a final vacuum of 0.200 mm Hg was achieved. The reaction was maintained under these conditions, and molecular weight of the final polyester was controlled by careful removal of a theoretical amount of DEG. When the targeted amount of DEG had been collected, heating was discontinued, and the contents were allowed to cool to ~100°C under nitrogen flow. The molten polymer was then carefully poured into a receiving vessel, cooled to room temperature, dissolved in chloroform (~325 mL), and precipitated into a 10-fold excess of cold (~0°C), dry methanol. The precipitated polymer was then dried under vacuum for 24 h until a constant weight was obtained.
2. Synthesis of Poly(lactide)-b-PEOETA-b-Poly(lactide)

The following is a representative procedure for the synthesis of a PLA-b-PEOETAT-b-PLA triblock copolymer. A 100 mL 3-necked round-bottom flask, equipped with a magnetic stir bar, a rubber septum, a Liebig condenser, and an ATR-FTIR probe, was charged with polyester prepolymer (4.99 g, 0.394 mol), LLA (20.13 g, 0.140 mol), and 61.8 mL of anhydrous toluene. All glassware and stir bars were dried overnight in an oven at 113°C, and cooled to room temperature under a dry N₂ flow or under vacuum within the antechamber of the drybox prior to use. All reactions were formulated within the drybox and sealed from the atmosphere before attachment to the reaction probe. The mixture was heated to 100°C using a silicone oil bath controlled with a Digi-Sense® 68900-01 temperature controller and held at this temperature for ~30 min under an argon purge. Then, 0.0042 g (1.04x10⁻⁵ mol) of Sn(Oct)₂ catalyst was introduced into the flask. FTIR spectroscopy was used to monitor the disappearance of the 1240-cm⁻¹ peak associated with L-lactide monomer. The reaction was terminated by removal from the heat source upon attaining a specified monomer conversion as determined by real-time FTIR monitoring. The viscous liquid was allowed to cool to room temperature. The resulting crude polymer product was dissolved in 75 mL of chloroform and precipitated into a 10-fold volume excess of cold (~0°C), dry methanol. The precipitate was collected by filtration and washed with copious amounts of cold methanol and then dried under a vacuum at ambient temperature for 72 h until a constant weight was obtained.

3. Degradation Analysis of Polymers

Select polymers were hydrolytically degraded by immersion into a phosphate buffered solution at a pH of 7.4 (0.05M) held at a constant temperature of 37°C. Sample
disks of the polyesters were prepared by portioning an arbitrary amount of the polyester onto a mylar film, which was then placed into a vacuum oven. The polymer was then heated to 150 to 170° C, higher temperatures (170° C) were needed for the higher molecular weight materials, until a molten state was achieved, after which a vacuum was applied. The application of the vacuum removed all air pockets contained in the sample and the molten polymer was formed into disks using a circular die with a diameter of 2.54 cm. Disks with a mass of 0.5 to 1.1 gm were used for the study; this mass range corresponds to a disk thickness of ~2 to 3 mm.

A representative procedure for polymer degradation was as follows: A polymer disc was placed into a glass jar (125mL) filled with 100mL of buffered solution at a pH of 7.40. The jar and its contents were then placed into an incubator held at a constant temperature of 37° C. The discs were removed for analysis at predetermined time periods based on preliminary degradation rate studies. (This preliminary study was conducted in order to optimize the number of data points around critical events such as time of onset of degradation, i.e. the point at which the polymer sample begins to lose mass.)

Upon reaching a predetermined time a sample disk was removed from the buffered solution and placed into a preweighed polystyrene weighing dish. The disk was brought to constant mass in a vacuum oven, after which percent remaining mass ($m_r$) was calculated using Equation 4.1:

Equation 4.1

$$m_r = \left( \frac{m_{dry}}{m_0} \right) \times 100$$
where, $m_{\text{dry}}$ is the mass of the sample after drying and $m_0$ is the initial mass before immersion.

4. Synthesis of PLA Using 2,2-bis(hydroxymethyl) butyric acid and Stannous Octoate

Reaction mixtures were formulated within a Vacuum Atmospheres Company Dri-Lab glove box under an inert N$_2$ atmosphere. In a typical experiment, 40.00 g (0.28 mol) of D,L-lactide, 2.10 g (0.014 mol) of BHMBBA, and 0.043 g (0.106 mmol, 300 ppm Sn) of Sn(Oct)$_2$ were added to a 250 mL, 1-neck round bottom (Figure 4.2). The flask was then equipped with an overhead stirrer, and the polymerization was carried out by immersion of the flask in a 130°C thermostated oil bath contained within a dry N$_2$ glove box, for 2 hr, after which the molten reactor contents were poured into a Teflon dish to cool.

![Chemical structure of BHMBBA and D,L-Lactide](image)

**Figure 4.2** The synthetic route to pendant acid functionalized PLA.
5. Synthesis of Hydroxy-Terminated Telechelic PLA

Reaction mixtures were formulated within a Vacuum Atmospheres Company Dri-Lab glove box under an inert N₂ atmosphere. In a typical experiment, 150.01 g (1.04 mol) of D,L-lactide, 4.65 (0.056 mol) of 1,4-butanediol, and 0.162 g (0.40 mmol, 300 ppm Sn) of Sn(Oct)₂ were added to a 250 mL, 1-neck round bottom (Figure 4.3). The flask was then equipped with an overhead stirrer and the polymerization was carried out by immersion of the flask in a 130° C thermostated oil bath contained within a dry N₂ glove box, for a predetermined time (3-72 h), after which the molten reactor contents were poured into a Teflon dish to cool. Catalyst was removed by dissolving the crude polymer in CH₂Cl₂ (10%, w (g)/v (mL)) and washed three times with 100 mL of a 1.05 M HCl (aq) methanol solution. The polymer solution was then washed with 100-mL portions of de-ionized water until a constant pH was obtained. The pH of the polymer solution was roughly tested using Hydrion pH test paper (pH range of 0-13), in which we obtained a constant pH ensuring complete removal of residual HCl. The organic layer was collected and subsequently dried over MgSO₄ and filtered, and the excess solvent was removed by vacuum at ambient temperature.
6. Synthesis of (Carboxylic-Acid)-Terminated Telechelic PLA

Hydroxy-terminated telechelic PLA was reacted with succinic anhydride catalyzed by 1-methylimidazole (MIA) to generate (carboxylic-acid)-terminated telechelic PLA materials. A representative procedure was as follows: hydroxy-terminated PLA (26.00 g, 3.90 mmol) was dissolved in 50 mL dichloroethane at 60°C, followed by the addition of succinic anhydride (1.09 g, 0.011 mol). After complete dissolution of the succinic anhydride, MIA catalyst (0.738 g, 8.99 mmol) was added and the mixture was allowed to react for 48 h (Figure 4.4). The polymer solution was then allowed to cool to room temperature. Excess, unreacted succinic anhydride was removed by washing the polymer solution 3 times with 100 mL portions of 4.02 M HCl solution, followed by two consecutive washings with 100 mL saturated NaCl solution, and finishing with 100-mL portions of de-ionized water until a constant pH was obtained. The pH of the polymer solution was roughly tested using Hydrion pH test paper (pH...
range of 0-13), in which we obtained a constant pH ensuring complete removal of residual HCl and/or succinic acid. The organic layer was collected and subsequently dried over MgSO₄ and filtered, and the excess solvent was removed by vacuum at ambient temperature.

![Chemical structure](image)

Figure 4.4  Synthetic route to telechelic carboxylic acid PLA.

7. Synthesis of Poly(Lactide)/Diisocyanate-based Poly(Ester-Urethanes)

Synthesis of chain extended PDLLA prepolymers using LDI. Into a 1-neck round bottom flask were charged 16.05 g (2.30 mmols) of PDLLA prepolymer (6985 g/mol), 0.498 g (2.35 mmols) of LDI, 0.136 g (0.215 mmols) of DBTDL, and 60 mL of toluene. The flask was then equipped with an overhead stirrer and the polymerization was carried out by the immersion of the flask in a 40.0°C thermostated oil bath contained within a dry N₂ glove box, for 25 h, after which the contents were poured into a Teflon dish to
cool. The dish and its contents were then put into a vacuum oven, to remove toluene, for 72 h or until a constant weight was obtained.

*Synthesis of chain extended PDLLA prepolymers using H$_{12}$MDI.* Into a 1-neck round bottom flask equipped with an overhead stirrer were charged 10.00 g (2.83 mmols) of PDLLA prepolymer (3529 g/mol), 0.85 g (3.24 mmols) of H$_{12}$MDI, 0.181 g (0.29 mmols) of DBTDL, and 40 mL of toluene (Figure 4.5). The flask was then equipped with an overhead stirrer and the polymerization was carried out by the immersion of the flask in a 40.0°C thermostated oil bath contained within a dry N$_2$ glove box, for 25 h, after which the contents were poured into a Teflon dish to cool. The dish and its contents were then put into a vacuum oven, to remove toluene, for 72 h or until a constant weight was obtained.

![Chemical structure](image)

**Figure 4.5** Synthetic route to chain-extended PLA using diisocyanate as the chain-extending agent.
CHAPTER 5
AROMATIC-ALIPHATIC BLOCK COPOLYESTERS BASED ON AA/BB POLYMERS AND POLY(LACTIC ACID)

A. Objective

This chapter describes the investigation of a series of aromatic-aliphatic block copolymers for their potential use as a hydrolytically degradable packaging material. Research involving aromatic-aliphatic copolyesters has shown that an increase in the proportion of aromatic units causes an increase in mechanical properties and a decrease in biodegradability. A family of elastomeric aromatic-aliphatic polyesters that has grown to commercial-scale production is Ecoflex. These biodegradable plastics are produced through a statistical polymerization of 1,4-butanediol, adipic acid, terephthalic acid, and a modular unit. A “modular unit” is defined by the manufacturer as a monomer system that produces branching and/or chain extension in the end polymer product. To date, relatively few reports have appeared that investigate aromatic-aliphatic copolyesters containing lactic acid segments. The most common method of synthesis comprises a polycondensation polymerization in which hydroxy-terminated oligo(lactic acid) is used as a diol. Undesirable features common to the materials of these reports are high polydispersities and limited percentages of lactic acid within the final polyester. Ring opening polymerization (ROP) of lactide from telechelic polymers has proven to be a successful method for synthesizing PLA-based block copolymers with relatively narrow polydispersities; we have previously reported several instances of using a macroinitiator in the ROP of lactides and lactones. Ba and coworkers synthesized a unique block copolymer containing poly(butylene succinate) and poly(L-lactide) (PLLA). This was
done by using hydroxy-terminated poly(butylene succinate) as a macroinitiator in the ROP of L-lactide (LLA), creating PLLA-b-PBS-b-PLLA. The amount of PLLA could be regulated within the polymer with great precision.

Herein, we report the synthesis and characterization of ABA block copolyesters consisting of a poly(ethyleneoxyethylene terephthalate-co-adipate) center segment and PDLLA or PLLA outer segments: PDLLA-b-PEOETA-b-PDLLA or PLLA-b-PEOETA-b-PLLA. The method involves ROP of DLLA or LLA using hydroxy-terminated PEOETA as the (macro)initiator and stannous 2-ethylhexanoate as the catalyst/coinitiator. The terephthalate and adipate mole percent of the PEOETA macroinitiator was varied in an attempt to tune the physical properties of the final block copolymer. A comparison of kinetic parameters is presented, focusing on rate constants of polymerization of a small molecule initiator and a macroinitiator, ethylene glycol (EG) and PEOETA, respectively. Thermal analysis by differential scanning calorimeter (DSC) and atomic force microscopy (AFM) data suggest a phase-separated morphology.

B. Results and Discussion

Synthesis of poly(ethyleneoxyethylene terephthalate-co-adipate). Macroinitiators containing various molar percentages of terephthalate to adipate was prepared via polycondensation following the procedure described in chapter 4, these polymers are listed in Table 5.1.
Table 5.1  Number average molecular weight ($M_n$), molecular weight distributions (MWD) and glass transition temperatures ($T_g$) of polyesters.

<table>
<thead>
<tr>
<th>Copolyester</th>
<th>$M_n$ (g/mol)</th>
<th>MWD</th>
<th>$T_g$ ($^\circ$C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEOETA-50</td>
<td>12680</td>
<td>1.25</td>
<td>-28</td>
</tr>
<tr>
<td>PEOETA-25</td>
<td>13980</td>
<td>1.29</td>
<td>-40</td>
</tr>
<tr>
<td>PEOETA-75</td>
<td>15580</td>
<td>1.49</td>
<td>-4.4</td>
</tr>
</tbody>
</table>

The number average molecular weights ($M_n$), molecular weight distributions (MWD) and glass transition temperatures ($T_g$) of the PEOETA copolyester macroinitiators discussed herein are listed in Table 5.1. The 25, 50 and 75 denote the initial terephthalate feed ratio of the PEOETA polyesters. The copolyesters were purified by dissolution and precipitation in order to remove low-molecular weight components. The end groups of the low molecular weight macroinitiator PEOETA-50 were positively identified using \(^1\)H NMR. The proton resonance signals for the end groups were observed at 3.59 and 1.82 ppm, as shown in Figure 1, representing the $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ protons and the $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ proton of the PEOETA-50, respectively. A full assignment of the proton spectrum is found in Figure 5.1. Peak integration indicated a terephthalate/adipate ratio of 1.05.
Figure 5.1 $^1$H NMR assignment of PEOETA-50 end groups and components.

ROP of LLA using PEOETA as macroinitiator. The synthesis of PLLA-$b$-PEOETA-50-$b$-PLLA (2) was done in solution (toluene) at 100°C using PEOETA (1) as the initiator and Sn(Oct)$_2$ as a catalyst (Scheme 5.1). Reaction conditions are listed in Table 5.2.
Scheme 5.1 Synthesis of triblock copolymer PLLA-\textit{b}-PEOETA-50-\textit{b}-PLLA. Sequence distribution of PEOETA-50 is approximately random; \textit{m}=51; \textit{n}=49.

The conversion of LLA was monitored by following the disappearance of the 1240 cm\(^{-1}\) peak associated with the asymmetric C—O—C stretch of LLA as shown in Figure 5.2. This was accomplished by using an ATR-FTIR probe inserted into the reaction flask. The reaction was stopped by removing from heat and dissolving the resulting polymer product in chloroform. Reactions 2 and 4 (Table 5.2) displayed relatively rapid polymerization kinetics and were reacted to high conversion (80%). Reactions 1 and 3 were slower and arbitrarily terminated after 600 min (~22% conversion).

First order apparent rate constants (\(k_{\text{app}}\)) for various PLLA polymerizations are shown in Table 5.2; \(k_{\text{app}}\) was obtained from the slope of a plot of \(
\ln ([M]_0/[M])\) versus time (Figure 5.3).
Figure 5.2  Reduction of the 1240 cm\(^{-1}\) peak height with time for LLA polymerization initiated with PEOETA-50/Sn(Oct)\(_2\) (Reaction 4, Table 5.2).
Figure 5.3  First order kinetic plots of LLA polymerizations initiated with PEOETA-50/Sn(Oct)$_2$, illustrating the effect of changing Sn(Oct)$_2$ to account for acid end groups of PEOETA-50: (A) Reaction 3, Table 1, $k_{app}=3.2\times10^{-6}$ s$^{-1}$; (B) Reaction 4, Table 5.2, $k_{app}=1.47\times10^{-5}$ s$^{-1}$.
Table 5.2 Formulations and \( k_{\text{app}} \) values for LLA polymerizations using various initiators.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Initiator</th>
<th>Initiator(^b) ((\text{mol} \times 10^3))</th>
<th>( \text{Sn(Oct)}_2 ) Mass ((\text{g} \times 10^3))</th>
<th>( k_{\text{app}} ) ((s^{-1} \times 10^5))</th>
<th>Conv. (^d) (%</th>
<th>( Mn ) ((\text{g/mol}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{H}_2\text{O} )(^c)</td>
<td>------</td>
<td>4.2</td>
<td>0.30</td>
<td>22</td>
<td>3,100</td>
</tr>
<tr>
<td>2</td>
<td>( \text{EG} )</td>
<td>1.05</td>
<td>4.2</td>
<td>1.54</td>
<td>80</td>
<td>13,500</td>
</tr>
<tr>
<td>3</td>
<td>PEOETA-50</td>
<td>0.394</td>
<td>4.2</td>
<td>0.32</td>
<td>21</td>
<td>13,600</td>
</tr>
<tr>
<td>4</td>
<td>PEOETA-50</td>
<td>0.394</td>
<td>13.0</td>
<td>1.47</td>
<td>78</td>
<td>38,100</td>
</tr>
</tbody>
</table>

\(^a\) Reaction 1 and 2 were performed under the same conditions as described for PLLA-\(b\)-PEOETA-\(b\)-PLLA.

\(^b\) 0.0618 liters of toluene and 20.13 (0.140 mols) grams of LLA were used in each reaction. Average number molecular weight of PEOETA-50 12,680 g/mol.

\(^c\) Rate constant extraction was limited to conversion range of 0 to 15%.

\(^d\) The corresponding reaction time to obtain the above monomer conversions was \(~600\) min.

\(^e\) Adventitious water.
Reactions 1 and 2 (Table 5.2) are control polymerizations carried out in the absence of purposefully added initiator (adventitious water only) and in the presence of ethylene glycol initiator, respectively. The \( k_{\text{app}} \) for Reaction 3 was found to be very close to that obtained in the presence of adventitious water only (Reaction 1). The low \( k_{\text{app}} \) for Reaction 3 was attributed to the presence of acid end groups within the macroinitiator. Carboxylic acid groups are well known to cause lower rates of polymerization in stannous octoate-catalyzed ROPs of lactones. Acid end groups within the macroinitiator were quantified by measurement of acid number (ASTM 1639-90), as reported in Table 5.3. Using the acid number thus obtained, it was possible to calculate the moles of acid end groups contained in one gram of the macroinitiator. In Reaction 3 the concentration of acid end groups exceeded that of the catalyst, and a retardation of the polymerization rate was observed. Using this information and assuming that each acid end group removes one stannous octoate molecule, an adjustment of the catalyst concentration was made to provide a concentration of active sites that is equal to that used in Reaction 2. Once this was done, the \( k_{\text{app}} \) of the macroinitiator was very close the value obtained using the ethylene glycol as the initiator.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Acid Number (mgKOH/gPEOETA)</th>
<th>Acid End Groups (mols/g)((\times10^6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEOETA-50</td>
<td>0.245</td>
<td>4.36</td>
</tr>
</tbody>
</table>

\( ^1H\)-NMR and GPC spectroscopy were used to elucidate the structure of PLLA-\(b\)-PEOETA-50-\(b\)-PLLA triblock copolymers; this data is contained in Figure 5.4 and Figure 5.5, respectively. The hydroxy end groups associated with the PEOETA macroinitiator were no longer present in the proton NMR spectrum of PLLA-\(b\)-PEOETA-50-\(b\)-PLLA,
which indicated successful initiation and formation of the block copolymer (Figure 5.4). In addition, the methyne proton resonance of the ultimate repeat unit of the newly formed PLLA block segment was observed at 4.35 ppm.

Figure 5.4 $^1$H-NMR spectrum of PLLA-$b$-PEOETA-$50$-$b$-PLLA indicating location of terminal lactic acid unit methyne resonance (4.35ppm) and PLLA segment.

The GPC traces in Figure 5.5 show a clear shift to lower elution volume that occurred upon ROP of LLA from the PEOETA-$50$ macroinitiator; however, the traces also reveal the presence of PLLA homopolymer. This is indicated by a shoulder on the high elution time side of the block copolymer trace. PLLA homopolymer is thought to be formed from water or methanol remaining in the PEOETA-$50$ macroinitiator and/or the Sn(Oct)$_2$. 

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We, therefore, thoroughly dried the PEOETA macroinitiator under vacuum (~1 mm Hg) at 45°C for 1 week. Upon synthesis of PLLA-b-PEOETA-50-b-PLLA using rigorously dried PEOETA-50 we were able to eliminate the formation of PLLA homopolymer, as illustrated in Figure 5.6 by the disappearance of the shoulder in the GPC chromatogram of the triblock copolyester.
The morphology of the PLLA-b-PEOETA-50-b-PLLA (Table 5.2) was examined using AFM in hard-tapping mode. This mode was deemed particularly appropriate since it interrogates morphology on the basis of local viscoelastic properties (hard vs. soft regions) and preserves the surface topography of the sample so that results are reproducible. The AFM image (Figure 5.7) suggests the presence of a continuous phase and a discontinuous phase, which would be typical of a block copolymer.
Figure 5.7  AFM images of PLLA-b-PEOETA-50-b-PLLA. The white areas were assigned to the PEOETA block (discontinuous phase) and the darker regions to the PLLA block (continuous phase). These phase assignments were based on composition and viscoelastic properties.
Thermal properties of select block copolyesters (Table 5.4) were characterized by means of differential scanning calorimetry (DSC).

Table 5.4  Average molecular weights ($M_n$) of ABA block copolyesters synthesized from PEOETA macroinitiators and L- and D,L-lactide.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Macroinitiator</th>
<th>Monomer</th>
<th>$M_n$ (g/mol)</th>
<th>$ABA$ block copolymer $M_n$(g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>PEOETA-50</td>
<td>LLA</td>
<td>12680</td>
<td>39300</td>
</tr>
<tr>
<td>6</td>
<td>PEOETA-75</td>
<td>LLA</td>
<td>15580</td>
<td>44780</td>
</tr>
<tr>
<td>7</td>
<td>PEOETA-25</td>
<td>LLA</td>
<td>13980</td>
<td>39900</td>
</tr>
<tr>
<td>8</td>
<td>PEOETA-50</td>
<td>DLLA</td>
<td>12680</td>
<td>33400</td>
</tr>
</tbody>
</table>

Figure 5.8 shows the DSC curves of select block copolyesters (Table 5.4) bearing various PEOETA macroinitiators and lactide segments. The samples were quenched from 190°C and data was collected upon the second heating. We observed one glass transition temperature ($T_g$) for all block copolyesters except in the case of a PEOETA containing a 75:25 molar percentage of terephthalate to adipate (reaction 6, Table 5.4). Typically all PLLA-based block copolymers, where the attached block is another polyester, show only one $T_g$ over a wide range of compositions in DSC measurements. This is due to improved miscibility between the two components, at least in the amorphous domains.

For example one $T_g$ was observed for poly (L-lactide-b-butylene succinate-b-L-lactide) triblock copolyesters with various PLLA block lengths synthesized by Ba and coworkers. Therefore, the observance of two $T_g$s for reaction 6 (PEOETA-75) indicates that the two block segments are poorly miscible in the amorphous regions, which could be due to the high aromatic content of the PEOETA segment. As mentioned earlier PLLA-b-PEOETA-50-b-PLLA (reaction 5) is believed to have a two phase morphology; this is confirmed by DSC from the existence of an amorphous region ($T_g=19.2°C$) and a crystalline region ($T_c=70.6°C$ and $T_m=129.4°C$). However, these regions are not entirely

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segregated and some penetration of the segments into respective phases are evident due to the lower $T_m$ seen for the PLLA segment which is typically 150-170°C.\textsuperscript{151}

Figure 5.8 DSC traces of ABA block copolyesters as described in Table 5.4 (second heating).

Preliminary degradation test of PLLA-$b$-PEOETA-50-$b$-PLLA (reaction 4), performed in accordance with the procedure described in chapter 4, indicate no signs of fragmentation after 12 months. This degradation profile was not expected and more importantly does not meet the targeted degradation time of one month.
The targeted use for these block copolyesters is packaging applications, specifically stretch or pallet wrap. This type of material is characteristic of having high elongation (~500%) and high tensile strength, as shown in Figure 5.9.

Figure 5.9  Stress versus strain curve of LLDPE (stretch or pallet wrap) indicating elongation at break.

However, the percent elongation of PLLA-\(b\)-PEOETA-50-\(b\)-PLLA was determined and failed to meet the targeted physical properties (equivalent to LLDPE). The tensile test results (stress vs. strain curves) are presented in Figure 5.10; it can be observed that slippage occurred during testing of specimen 2, most probably due to high stress placed on the material (~10 MPa). All block copolyesters (reactions 5-8) exhibited brittleness and only PLLA-\(b\)-PEOETA-50-\(b\)-PLLA was tested for physical properties.
Figure 5.10  Stress versus strain curve of PLLA-b-PEOETA-50-b-PLLA indicating elongation at break.

C. Conclusions

PLLA-b-PEOETA-b-PLLA and PDLLA-b-PEOETA-b-PDLLA triblock copolyesters were synthesized by a combination of polycondensation and ROP polymerization techniques. The ROP polymerization of L- and D,L-lactide using a well-defined PEOETA macroinitiator yielded a triblock copolyester within proximity of the targeted molecular weight and a moderate MWD. The polymerization of LLA was retarded due to a presence of acid end groups contained in the PEOETA macroinitiator, consequently, a low $k_{app}$ value was observed. Once the catalyst/coinitiator (Sn(Oct)$_2$) concentration was adjusted to account for the acid end groups the $k_{app}$ of the
macroinitiator resembled that of a small molecule initiator (EG). The triblock copolymer forms a two phase morphology, which is confirmed from the AFM images and DSC analysis. Regrettably, the degradation profile and mechanical properties of PLLA-\textit{b-PEOETA-50-b-PLLA} did not meet targeted values.
CHAPTER 6

CHARACTERIZATION OF POLY(ETHYLENEOXYETHYLENE TEREPTHALATE-CO-ADIPATE) USING NMR SPECTROSCOPY

A. Objective

In the course of synthesizing A-B-A block copolyesters, where the middle block (B) is an AAC and the outer blocks (A) are poly(L-lactide), we found that a particular AAC, poly(ethyleneoxyethylene terephthalate-co-adipate) (PEOETA) displays a unique sensitivity of the terephthaloyl protons toward diacid comonomer sequence, as observed by nuclear magnetic resonance (NMR) spectroscopy. Upon examination of the \(^1\)H NMR spectrum it was discovered that a splitting occurs in the aromatic region, which has not been observed in previous studies of ACCs containing terephthoyl and adipoyl units, and moreover, would not be predicted due to the well-known insensitivity of \(^1\)H NMR spectroscopy toward long-range effects. We further concluded that the observed splitting was not due to the presence of dissimilar diol units, which might arise from impure diethylene glycol staring material or premature degradation of the copolyester. Supporting this conclusion is the fact that the \(^1\)H NMR spectrum of poly(ethylene/butylene terephthalate) exhibits only one peak representing the four protons of the aromatic ring of the terephthaloyl units. Subsequently, we have determined by 2D-NMR techniques that the splitting arises from spatial interactions of the aromatic ring protons with neighboring EOE and adipate units. These through-space interactions, which to our knowledge have not been previously reported, are thought to arise from the conformations created by the use of diethylene glycol in a polyester containing both terephthalate and adipate units.
$^1$H NMR spectroscopy has been previously used to determine the distribution of terephthalate (T) and adipate (A) units within poly(butylene terephthalate-co-adipate) (PBTA), in terms of the butylene (B)-centered sequences TBT, ABA, and ABT (=TBA). In this study we have similarly determined the sequence distribution of PEOETA, using the methylene proton resonance signals of the EOE units. In analogy to the definition of stereo sequences in vinyl polymers, we have defined such diacid-EOE-diacid sequences as a “dyad” and represented the four possible sequences within PEOETA as TT, TA (=AT), and AA. We have also identified and assigned multiple aromatic proton signals arising from dissimilar terephthalate-centered triads, ATA, TTA (=ATT), and TTT.

B. Results and Discussion

The number average molecular weights ($M_n$), molecular weight distributions (MWD) and glass transition temperatures ($T_g$) of the polyesters discussed herein are listed in Table 6.1.

<table>
<thead>
<tr>
<th>Copolyester</th>
<th>$M_n$ (g/mol)</th>
<th>MWD</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEOETA-50</td>
<td>8,600</td>
<td>1.25</td>
<td>-28</td>
</tr>
<tr>
<td>PEOETA-25</td>
<td>9,200</td>
<td>1.29</td>
<td>-40</td>
</tr>
<tr>
<td>PEOETA-75</td>
<td>18,600</td>
<td>1.49</td>
<td>-4.4</td>
</tr>
<tr>
<td>PEOET</td>
<td>7,600</td>
<td>1.45</td>
<td>16</td>
</tr>
<tr>
<td>PEOEA</td>
<td>8,300</td>
<td>1.64</td>
<td>-49</td>
</tr>
</tbody>
</table>

The proton NMR spectrum of PEOETA-50 (Chapter 5) copolyester is shown in Figure 6.1; for comparison the spectra of PEOEA and PEOET polyesters are also

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depicted. The complete carbon and proton resonance assignments of PEOETA-50 copolyester are specified in Figure 6.2 and Figure 6.3.
Figure 6.1 $^1$H NMR spectra of copolyesters PEOETA-50, PEOEA and PEOET.
Figure 6.2  Peak assignments of the proton resonance signals of PEOETA-50 copolyester.
Figure 6.3  Peak assignments of the carbon resonance signals of PEOETA-50 copolyester.

As shown in Figure 6.2, the aromatic protons (a) of PEOETA-50 copolymer appear as a triplet. This was unexpected since at least 12 covalent bonds separate a given aromatic proton from the nearest diacid structural unit. Furthermore, the terephthalate proton signal appears as a singlet in poly(butylene terephthalate-co-adipate) (PBTA) and poly(ethylene terephthalate-co-adipate) (PETA) copolyesters.\textsuperscript{157,158} The observed splitting cannot be due to structural variations in the diol units caused by impurities or side reactions, since the spectral region associated with the diol units in PEOETA-50, PEOEA and PEOET (Figure 6.1) shows no extraneous peaks. Additionally, if

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degradation of the diethylene glycol units to ethylene glycol was the cause of the unique splitting in PEOETA-50, one would also see similar splitting in the PEOET polyester, yet no such splitting is observed in the $^1$H NMR spectrum of PEOET (Figure 6.1). The splitting of the aromatic region shows no observable changes (Figure 3) upon heating of the copolyester in solution ($d$-DMSO) during $^1$H NMR experiments, except for broadening due to chemical shift anisotropy.$^{159}$ Persistence of the splitting phenomenon at higher temperatures suggests that splitting does not originate from slow exchange between different rotational states of the phenyl ring, but rather, the latter is a free rotor. Splitting associated with nonequivalent protons on a phenyl ring due to different rotational states has been observed in solid state NMR spectra for poly(phenylene-oxide).$^{160}$ This type of splitting is not typically observed in solution NMR. Additionally, we believe by heating the PEOETA-50 (in solution) all protons would become equivalent, if different rotational states are present, resulting in the formation of a singlet in the NMR spectrum.
Figure 6.4  $^1$H NMR spectra displaying aromatic region of PEOETA-50 at varying temperatures with triad sequences labeled.

Heteronuclear Single Quantum Correlation spectroscopy (HSQC) experiments (Figure 6.5) showed that the aromatic protons associated with the triplet are attached to four identical aromatic carbons ($C_4$ in Figure 6.3). Therefore the splitting must originate from through-space interactions of the aromatic protons with protons contained within or closely associated with nearest-neighbor diacid units. The relative intensities of the three aromatic proton peaks as a function of copolyester composition (Figure 6.6) allowed assignment of the peaks to the four identical protons within each of the terephthalate-centered triads as follows: ATA ($a_1$, 8.12 ppm), ATT and TTA ($a_2$, 8.08 ppm), and TTT...
($\alpha_3$, 8.03 ppm). Close inspection of the TTT proton peak ($\alpha_3$) revealed further higher-order sensitivity to sequence distribution, namely pentad sensitivity as tentatively assigned in Figure 6.7.
Figure 6.5 2D-HSQC spectrum of PEOETA-50 displaying cross peak of aromatic unsubstituted carbons of terephthalate unit and a. (128 increments, 16 scans per increment and a delay time of 4 s.)
Figure 6.6  Expansion of aromatic region of PEOETA-50, PEOETA-75 and PEOETA-25 showing triad sequence labels.

Figure 6.7  Proton resonance peak $a_3$ with pentad sequences labeled.
We used a NOESY pulse sequence to resolve the identity of the protons involved in the through-space interactions. The \( T_m \) chosen for the NOESY experiment was 800 ms, with a delay time of \( 2 \times T_1 \) of \( a \). \( T_1 \) relaxation times of aromatic and methylene protons are listed in Table 6.2.

**Table 6.2**  \( T_1 \) relaxation times for selected \(^1\text{H}\)

<table>
<thead>
<tr>
<th>(^1\text{H})</th>
<th>( T_1 ) (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a )</td>
<td>1.36</td>
</tr>
<tr>
<td>( b )</td>
<td>0.51</td>
</tr>
<tr>
<td>( d_{1,2}; e_{1,2} )</td>
<td>0.43; 0.62</td>
</tr>
</tbody>
</table>

The NOESY spectrum in Figure 6.8 reveals the existence of interactions that are responsible for the unique splitting of the aromatic protons. The expanded region of Figure 6.8 shows connectivity between the aromatic protons \( a \) and methylene protons \( b \), \( d_1, d_2 \), and \( e_1 \) of the EOE units and \( f \) and \( g \) of the adipate units.
Figure 6.8 2D-NOESY spectrum of PEOETA-50 copolyester showing magnification of $a$, $d_1$, $d_2$, $e_1$, $e_2$, $f$, and $g$. 

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This information was used to construct Figure 6.9, which shows the specific methylene protons associated with the central aromatic protons of each terephthalate-centered triad sequence. For example, the central aromatic protons ($a_3$) of a TTT pentad are associated only with $b$ and $d_1$ protons, since only these protons are proximate to the central aromatic ring. Likewise, it is perfectly sensible that $e_2$ protons are not associated with any of the three types of aromatic protons, since the former exist only between two consecutive adipate residues.

![Figure 6.9 Terephthalate-centered pentad sequences identifying those methylene protons with connectivity to the central aromatic protons as determined by NOESY pulse sequence experiments.](image)

Additional NOESY experiments using $\tau_{ms}$ between 200 and 700 ms revealed a nuclear Overhauser enhancement (nOe) for only the methylene protons $b$. This is conceivably due to the fact that the $b$ protons are spatially closer to the $a$ protons than the other methylene protons. The occurrence of the nOe between the $b$ and $a$ protons is to be expected, as described in the research performed by Spera and coworkers.\textsuperscript{161} They were able to add an additional constraint to the conformation of PET, as originally determined.
by Štokr and coworkers,¹⁶² which set the aromatic ring in a *cis* conformation about the ArCO-O bond. The exact conformations of the EOE and adipate units of PEOETA-50 that lead to the observed interactions is still in question and further NMR and IR studies will be necessary for a complete understanding of this phenomenon.

The inner methylene proton signals arising from the EOE units of PEOETA-50 copolyester have chemical shifts at 3.68, 3.74, 3.84, and 3.89 ppm. These peaks are associated with the four EOE-centered dyads AA (ε₂), AT (ε₁), TA (δ₂), and TT (δ₁), respectively. Figure 6.10 shows an expansion of this region of the ¹H NMR spectrum for PEOETA copolyesters PEOETA-25, PEOETA-50, and PEOETA-75.
Figure 6.10  Expanded $^1$H NMR spectra showing inner methylene proton signals of EOE units of PEOETA copolyesters with dyads labeled.
The fractions of adipate and terephthalate residues in the copolymer, $X_A$ and $X_T$ respectively, were calculated using equations (6.1) and (6.2),

**Equation 6.1**

$$X_A = \frac{A_{AA} + A_{AT}}{A_{AA} + A_{AT} + A_{TT} + A_{TA}}$$

**Equation 6.2**

$$X_T = 1 - X_A = \frac{A_{TT} + A_{TA}}{A_{TT} + A_{TA} + A_{AA} + A_{AT}}$$

where $A$ equals the area obtained by integrating the peaks associated with the respective dyads. The probability ($P$) of finding a terephthalate unit next to an adipate unit can be calculated by equation (6.3).

**Equation 6.3**

$$P_{TA} = \frac{A_{TA}}{A_{TA} + A_{TT}}$$

The probability of finding an adipate unit next to a terephthalate unit can be calculated using equation (6.4).

**Equation 6.4**

$$P_{AT} = \frac{A_{AT}}{A_{AT} + A_{AA}}$$

Using the results obtained from equations (6.3) and (6.4) the degree of randomness ($B$) can be described by,$^{163,164}$

**Equation 6.5**

$$B = P_{TA} + P_{AT}$$

where $B$ equals 1 for random copolymers, 2 for alternating copolymers, and 0 for block copolymers. The results for the degree of randomness are summarized in Table 6.3.
Table 6.3  Structural characteristics of homo- and copolyesters

<table>
<thead>
<tr>
<th>Copolyester</th>
<th>$\chi_T^a$</th>
<th>$B^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEOETA-50</td>
<td>52</td>
<td>1.01</td>
</tr>
<tr>
<td>PEOETA-25</td>
<td>35</td>
<td>0.97</td>
</tr>
<tr>
<td>PEOETA-75</td>
<td>78</td>
<td>0.95</td>
</tr>
</tbody>
</table>

\(^a\) Mole fraction of terephthalate units in copolymer (\(^1\)H NMR)

\(^b\) Degree of randomness (\(^1\)H NMR)

The copolyesters have an average value of 0.98 indicating that the sequence distribution is random. This is further confirmed by the presence of a single, sharp glass transition in the differential scanning calorimetry (DSC) thermogram (Figure 6.11).

**Figure 6.11**  DSC transition curve (second heating) at a heating rate of 10°C min\(^{-1}\) for PEOETA-50 with Mn of 19,270 g/mol.
A sample with nonrandom composition distribution would be expected to show a broad transition or possibly multiple transitions corresponding to each segment present.

C. Conclusions

Splitting of the terephthalate protons $a$ into a triplet is due to through-space interactions with principally the $b$ and $d$ protons and secondarily the $e, f,$ and $g$ protons of adjacent EOE and A units. Comonomer sequence distribution and chemical shift assignments were determined for PEOETA copolyesters of varying diacid composition using 500 MHz $^1$H NMR spectroscopy. An average value of 0.98 was found for the degree of randomness of the copolyesters, indicating that the sequence distribution is nearly completely random, which is typical of polyesterification.
CHAPTER 7
SYNTHESIS OF POLY(LACTIC ACID) AND CHAIN-EXTENDED POLY(LACTIC ACID)-POLYURETHANE FUNCTIONALIZED WITH PENDENT CARBOXYLIC ACID GROUPS

A. Objective

Poly(lactic acid) (PLA) plays a significant role in the field of degradable polymers. PLA is currently used in biomedical and packaging applications, including orthopedic implants and beverage containers. A number of factors contribute to the success of PLA in these applications, including its physical properties, favorable degradation characteristics, and benign degradation products. PLA is synthesized via two different polymerization mechanisms, direct polycondensation of lactic acid and ring opening polymerization (ROP) of the cyclic dimer, lactide. The latter method provides more precisely targeted and potentially higher molecular weight. Additionally, one can copolymerize a variety of lactones or carbonates with lactide using ROP.

Extensive research has been devoted to the modification of PLA, through copolymerization, in order to change degradation characteristics and/or enhance physical properties. One such modification involves the incorporation of carboxylic acid groups into the PLA backbone. In previous work, we copolymerized D,L-lactide (DLLA) with 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one, a cyclic carbonate containing a latent carboxylic acid group (benzyl ester). After deprotection to the carboxylic acid form, the resulting copolymers showed improved thermal characteristics, i.e., higher T_g; however, deprotection was incomplete and the degree of incorporation and sequencing of the acid pendant groups were subject to the comonomer reactivity ratios of...
the ring-opening copolymerization (ROP). Other methods have been investigated, in which telechelic carboxylic acid-terminated PLA is created through arduous multi-step syntheses.\textsuperscript{174,175}

To provide greater synthetic control and ease of synthesis we utilized a two step procedure involving the ROP of lactide initiated by 2,2-bis(hydroxymethyl)-butyric acid (BHMBA) to form hydroxyl-terminated prepolymers containing a single, pendant carboxylic acid group (BHMBA-PLA), followed by chain extension of the prepolymers with a diisocyanate such as L-lysine diisocyanate methyl ester (LDI) or dicyclohexylmethane 4,4'-diisocyanate (H\textsubscript{12}MDI) (Scheme 1). The carboxylic acid equivalent weight of the final chain-extended polymer is fixed by the molecular weight of the PLA prepolymer, which can be controlled with great precision. Since the molecular weight distribution of the PLA prepolymer is narrow, the spacing of the acid groups along the backbone is nearly constant. The method allows independent specification of molecular weight and carboxylic acid content and creation of PLA with tailored degradation characteristics and physical properties. Lee and coworkers have demonstrated that systematically adjusting the acid content of modified PLA will provide direct control of hydrolytic degradation.\textsuperscript{176} The chain-extended, acid-modified PLA may have utility in and of itself or as a prepolymer component in other polymer systems, such as segmented polyurethanes.

The presence of the carboxylic acid group within the BHMBA initiator creates the possibility for condensation side reactions during ROP. This would lead to branching and a decrease in acid functionality. In fact, for our system of interest, i.e., lactide/BHMBA/stannous octoate, it was recently claimed that ROP and
polycondensation will proceed simultaneously to create hyperbranched polymers. However, we are interested primarily in linear prepolymers with full retention of carboxylic acid functionality. Therefore, in this work we have established a method for characterization of the prepolymers with respect to the average number of branches per molecule using the integrated areas of select proton resonances within the NMR spectrum. We show that predominantly linear polymers result. And finally, we demonstrate that the prepolymers can be smoothly chain extended according to Scheme 7.1, to create high molecular weight PLA with regularly spaced carboxylic acid functionality.
B. Results and Discussion

Molecular weight and MWD values of BHMB A-PDLLA and comparative polymers are listed in Table 7.1.

<table>
<thead>
<tr>
<th>Exp. Number</th>
<th>Initiator</th>
<th>Monomer</th>
<th>Catalyst level (ppm Sn)</th>
<th>Rxn. Time (min)</th>
<th>( M_n,\text{theo} )</th>
<th>( M_n,\text{exp} )</th>
<th>MWD (Mw/Mn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BHMB A</td>
<td>DLLA</td>
<td>300</td>
<td>190</td>
<td>2970</td>
<td>3250</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>BHMB A</td>
<td>DLLA</td>
<td>800</td>
<td>185</td>
<td>2964</td>
<td>3440</td>
<td>1.03</td>
</tr>
<tr>
<td>3</td>
<td>BHMB A</td>
<td>DLLA</td>
<td>300</td>
<td>195</td>
<td>1006</td>
<td>1120</td>
<td>1.05</td>
</tr>
<tr>
<td>4</td>
<td>BHMB A</td>
<td>LLA</td>
<td>300</td>
<td>180</td>
<td>2964</td>
<td>3360</td>
<td>1.02</td>
</tr>
<tr>
<td>5</td>
<td>BHMB A</td>
<td>LLA</td>
<td>800</td>
<td>183</td>
<td>2970</td>
<td>3530</td>
<td>1.03</td>
</tr>
<tr>
<td>6</td>
<td>BHMB A</td>
<td>LLA</td>
<td>800</td>
<td>2076</td>
<td>2970</td>
<td>3440</td>
<td>1.17</td>
</tr>
<tr>
<td>7</td>
<td>1,4-butanediol</td>
<td>DLLA</td>
<td>300</td>
<td>186</td>
<td>2970</td>
<td>3420</td>
<td>1.08</td>
</tr>
<tr>
<td>8</td>
<td>1,4-butanediol</td>
<td>DLLA</td>
<td>300</td>
<td>338</td>
<td>2970</td>
<td>3430</td>
<td>1.10</td>
</tr>
<tr>
<td>9</td>
<td>BHMP A</td>
<td>DLLA</td>
<td>300</td>
<td>342</td>
<td>5041</td>
<td>5360</td>
<td>1.02</td>
</tr>
<tr>
<td>10</td>
<td>BHMB A</td>
<td>e-caprolactone</td>
<td>300</td>
<td>240</td>
<td>2999</td>
<td>2960</td>
<td>1.12</td>
</tr>
<tr>
<td>11</td>
<td>BHMB A</td>
<td>e-caprolactone</td>
<td>300</td>
<td>2000</td>
<td>2999</td>
<td>5250</td>
<td>1.18</td>
</tr>
<tr>
<td>12</td>
<td>1,2-propanediol</td>
<td>DLLA</td>
<td>300</td>
<td>198</td>
<td>2964</td>
<td>3370</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Theoretical number average molecular weights (\( M_n,\text{theo} \)) were calculated according to Equation 7.1, assuming full conversion of both monomer and initiator and a strictly linear prepolymer structure (Scheme 1).

Equation 7.1

\[
M_{n,\text{theo}} = \frac{\text{Mass of BHMB A} + \text{Mass of Lactide}}{\text{Moles of BHMB A}}
\]

We note that the latter assumption is contradictory to a recent report by Gottschalk and Frey,\textsuperscript{178} who claimed that the lactide/BHMB A/Sn(Oct)\textsubscript{2} system, under similar conditions, results in hyperbranched polylactides due to condensation between the carboxylic acid groups of BHMB A and the growing polylactide hydroxy end groups.

As shown in Table 7.1, the \( M_n,\text{exp} \) value (GPC) of BHMB A-PDLLA (exp. 1) is very close to \( M_n,\text{theo} \), which strongly suggests that little or no branching occurred. As a
control we synthesized PDLLA using 1,4-butanediol (exp. 7) under the same conditions. Based on the similar $M_n^{\text{exp}}$ and MWD data of exps. 1 and 7, it appears that the two initiators, BHMB, and 1,4-butanediol, produce similar PDLLA. Exps. 5 and 6 employed high catalyst levels and a long reaction time (exp. 6) in an attempt to force branching. However, no significant difference between $M_n^{\text{theo}}$ and $M_n^{\text{exp}}$ was observed for either experimental condition, and therefore it can be assumed that a trivial amount of branching occurred and that generating a branched polylactide using BHMB/Sn(Oct)$_2$ is extremely difficult.

In exp. 10, poly($\varepsilon$-caprolactone) was synthesized using BHMB as the initiator, and based upon the close agreement of $M_n^{\text{theo}}$ and $M_n^{\text{exp}}$ little to no branching occurred. However, in exp. 11 the $M_n^{\text{theo}}$ and $M_n^{\text{exp}}$ values are significantly different, demonstrating that branching can be induced in the poly($\varepsilon$-caprolactone) system through the use of long reaction times. Apparently, the primary hydroxyl group of poly($\varepsilon$-caprolactone) is more prone to condensation and branching compared to the secondary hydroxyl group of poly(D,L-lactide); however, it appears that branching is still controllable with the poly($\varepsilon$-caprolactone) system by careful management of reaction time, temperature and catalyst concentration.

We also used 2,2-bis(hydroxymethyl)propionic acid (BHMPA) in the synthesis of PDLLA (exp. 9) and observed that the $M_n^{\text{theo}}$ and $M_n^{\text{exp}}$ results are comparable, indicating insignificant branching. Therefore, either BHMB or BHMPA will produce pendant acid-functionalized PDLLA with a nearly linear structure.
$^1$H and $^{13}$C NMR data of BHMB A-PDLLA are presented in Figure 7.1 and Figure 7.2. The assignments of the carbon and proton resonances with the structures shown in Figure 7.1 and Figure 7.2 were confirmed by 2-D NMR.

![NMR spectrum of BHMB A-PDLLA](image)

<table>
<thead>
<tr>
<th>Proton ($^1$H)</th>
<th>Signal (ppm)</th>
<th>Multiplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>0.919</td>
<td>t</td>
</tr>
<tr>
<td>b</td>
<td>4.33</td>
<td>m</td>
</tr>
<tr>
<td>c</td>
<td>1.40</td>
<td>m</td>
</tr>
<tr>
<td>d</td>
<td>1.54</td>
<td>m</td>
</tr>
<tr>
<td>e</td>
<td>4.33</td>
<td>m</td>
</tr>
<tr>
<td>f</td>
<td>5.18</td>
<td>m</td>
</tr>
<tr>
<td>g</td>
<td>1.69</td>
<td>m or q</td>
</tr>
</tbody>
</table>

**Figure 7.1** $^1$H NMR spectrum of BHMB A-PDLLA.
Figure 7.2 $^{13}$C NMR spectrum of BHMB-A-PDLLA.

The COSY spectrum (Figure 7.3), which provides $^1$H-$^1$H connectivity of neighboring protons, shows correlations between $H_g$ and $H_a$, $H_c$ and $H_e$, and $H_d$ and $H_f$. These correlations are in good agreement with the labeled structure in Figure 7.1.
Figure 7.3 2D-COSY spectrum of BHMBPA-PDLLA.

Referring back to Figure 7.1, the peaks (~ 4.4 ppm) associated with H_e (methine proton of terminal lactic acid residue) and H_b (methylene protons of BHMBPA) overlap; the identification of these peaks was achieved using HSQC, which provides information regarding \(^1H-^{13}C\) pairs. Figure 7.4 is the HSQC spectrum showing the \(^1H-^{13}C\) pairs of BHMBPA-PDLLA (exp. 1).
Figure 7.4 2D-HSQC spectrum of BH MBA-PDLLA.

The connectivity of H\textsubscript{b} and C\textsubscript{4} and H\textsubscript{e} and C\textsubscript{11} provide the evidence necessary to accurately assign H\textsubscript{b} and H\textsubscript{e} to the multiplet centered at 4.4 ppm as revealed in Figure 7.2. Additionally, one can observe other \textsuperscript{1}H-\textsuperscript{13}C pairs, i.e., H\textsubscript{g}, C\textsubscript{2} and H\textsubscript{a}, C\textsubscript{1}, and especially the pairing of H\textsubscript{c} and C\textsubscript{10}, which confirms the identity of the methyl group associated with the terminal lactic acid residue.

If branching were taking place, as claimed by Gottschalk and Frey, one would expect to see a change in the intensity of the methine peak associated with the terminal
lactic acid residue and the formation of a new methine peak (H\textsubscript{branch}, Figure 7.5) arising from the condensation reaction.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figures/figure7.5.png}
\caption{Hypothetical structure of hyperbranched BHMBAPDLLA defining the methine proton (H\textsubscript{branch}).}
\end{figure}

Figure 7.6 displays the region in which the methine resonances are located. As the reaction progresses beyond a reaction time of 183 to 2076 min, as revealed in Figure 7.6, no appreciable change in intensity occurs and the formation of a new peak cannot be confirmed.
A comparison of the $^{13}$C NMR spectra of BHMBA-PDLLA (exp. 1) and 1,4-butandiol-PDLLA (exp. 7) in Figure 6 shows that a peak at 173.1 ppm is present in the former but not the latter; this provides support that the peak at 173.1 ppm is due to the carbonyl carbon of the BHMBA acid group.
1,4-butanediol-PDLLA (exp. 6)

BH MBA-PDLLA (exp. 1)

Figure 7.7 Comparison of the carbonyl regions of BH MBA-PDLLA (exp. 1) and 1,4-butanediol-PDLLA (exp. 7).

The presence of free acid within BH MBA-PDLLA is inconsistent with the hyperbranched structure proposed by Gottschalk and Frey. Free acid can be substantiated by titration (acid value). These results are contained in Table 7.2.
Table 7.2 Acid Values of Select Polyesters.

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Acid value (g KOH/g polymer)</th>
<th>Theoretical acid value (56.1/Mn,th.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHMBA-PDLLA (exp. 1)</td>
<td>6.73×10^2±6×10^-4</td>
<td>1.89×10^-2</td>
</tr>
<tr>
<td>1,4-butanediol-PDLLA (exp. 7)</td>
<td>1.54×10^3±2×10^-4</td>
<td>0</td>
</tr>
<tr>
<td>BHMBA-ε-caprolactone (exp. 10)</td>
<td>1.90×10^2±2×10^-4</td>
<td>1.87×10^-2</td>
</tr>
<tr>
<td>BHMBA-ε-caprolactone (exp. 11)</td>
<td>1.81×10^2±2×10^-4</td>
<td>1.87×10^-2</td>
</tr>
</tbody>
</table>

The high acid value of BHMBA-PDLLA compared with 1,4-butanediol-PDLLA indicates that BHMBA adds acid functionality to PDLLA. Depending on the amount of branching, the acid value would decrease accordingly as the acid residues are consumed in the condensation reaction; this type of behavior was observed for exp. 11 (branching), when compared to exp. 10 (no branching). It is important to note that the acid value of BHMBA-PDLLA is much higher than the theoretical value of 1.89×10^-2 g KOH/g polymer, which is based on Mn,th. This unusually high acid value is attributed to the testing conditions, which cause premature hydrolytic degradation of the BHMBA-PDLLA, increasing acid content. Modification of the acid value test would be necessary to eliminate premature degradation.

Average Number of Branches per Molecule. Hawker et al.\textsuperscript{179} introduced the following definition for “degree of branching” (DB) with specific reference to dendritic and hyperbranched polymers created via step-growth polymerization of AB\textsubscript{2} monomers,

Equation 7.2

\[
DB = \frac{D + T}{D + L + T}
\]

where, D, L, and T are the fractions of dendritic (both B groups reacted), linear (one B group reacted), and terminal (neither B group reacted) structural units, respectively, within a distribution of polymer molecules.

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For copolymerization systems of AB and AB₂ monomers, to which the lactide/BHMBA system formally belongs, Frey and Hölter¹⁸⁰ defined DB according to the following equation,

**Equation 7.3**

\[
DB_{AB:AB_2} = \frac{2D}{2D + L_{co}}
\]

where, \( L_{co} \) is the sum of L units (as defined above) and \( L_1 \) units, which are defined as non-terminal structural units from the AB monomer. They also proposed that DB can be predicted as a function of conversion in such a system provided that all B-groups are of equal reactivity and the reaction proceeds as a random, one-pot copolymerization. Based on these assumptions, they offered the following predictive relationship,

**Equation 7.4**

\[
DB_{AB:AB_2} = 2 \frac{p(1 - x_{AB})}{(2 - x_{AB})^2}
\]

where, \( p \) is the reaction conversion of the A groups and \( x_{AB} \) is the molar fraction of AB monomers in the feed.

Gottschalk and Frey¹⁸¹ used Equation 7.4 to calculate DB for the lactide/BHMBA system, catalyzed with Sn(Oct)₂, but they did not offer direct evidence that their polymers were actually branched. Polymerization of lactide initiated by BHMBA is not a random polycondensation, but rather a ring-opening polymerization that proceeds by a chain-growth mechanism. Furthermore, the primary hydroxyl groups of BHMBA are more reactive than the secondary hydroxyl groups derived from lactic acid units. Finally, our results show that the rate of polycondensation is significantly slower than the rate of ring opening polymerization under these conditions. Thus, this polymerization system abjectly fails to meet the assumptions upon which Equation 7.4 is based, and predictions derived from it are meaningless. Even if the assumptions of Equation 7.4 had been met,
Gottschalk and Frey calculated $x_{AB}$ as the mole fraction of lactide (i.e., two AB units) in the feed; whereas the derivation of Equation 7.4 demands that $x_{AB}$ be calculated as the mole fraction of lactic acid (i.e., one AB unit) in the feed.

Rather than relying on theoretical predictions of branching, we set out to directly measure the extent of branching in our polymers. However, DB as defined by Equation 7.3 was intended for true hyperbranched or dendritic molecules and is not particularly appropriate to the lactide/BH MBA system. For example, if the latter system were reacted to produce perfectly linear molecules, each with exactly two lactic acid-based hydroxyl end groups and one unreacted BH MBA carboxylic acid group (i.e., no polycondensation reactions whatsoever involving the carboxylic acid group of the BH MBA residue and 100% initiation efficiency of the BH MBA hydroxyl groups), these molecules would logically possess a degree of branching of zero. However, Equation 7.3 would still yield a non-zero DB for this system. In fact, for a degree of polymerization $= 2x$ (original lactide/BH MBA ratio $= x$), Equation 7.2 would yield DB $= 1/x$. In view of this, we have chosen to measure the average number of branches per polymer molecule, $\overline{N_{br}}$, rather than the average number of branches per repeat unit. This reduces to a measurement of the number of hydroxyl groups per BH MBA residue. $^1H$ NMR spectroscopy of our BH MBA-PDLLA polymers indicates that all BH MBA hydroxyl groups are fully reacted; however, the following analysis is easily adapted to account for these groups, should they begin to appear at low lactide/BH MBA ratios. $\overline{N_{br}}$, which yields a value of zero for our targeted structure, but would increase with polycondensation, is defined as,

**Equation 7.5**

$$\overline{N_{br}} = \frac{N_{BH MBA}}{N} - 1$$
where, $N_{BHMBA}$ is the number of BHMBA structural units and $N$ is the number of polymer molecules in the sample. $N_{br}$ can be measured using $^1$H NMR. The number of BHMBA structural units remains constant throughout the reaction and is proportional to the area of the $H_a$-proton signal, $A_a$ (Figure 7.1):

$$N_{BHMBA} = \frac{k}{3} A_a$$

Equation 7.6

The number of hydroxyl end groups, $N_{OH}$, is proportional to the area of the $H_c$-proton signal, $A_c$. If unreacted BHMBA hydroxyl groups were present, they could also be counted by integration of the adjacent methylene protons, which would appear at 3.7 ppm.

$$N_{OH} = \frac{k}{3} A_c$$

Equation 7.7

Prior to the occurrence of any condensation reactions, the initial number of hydroxyl groups, $N_{OH}^0$, and the initial number of polymer molecules, $N^0$, possess the following relationship to $N_{BHMBA}$:

$$\frac{N_{OH}^0}{2} = N^0 = N_{BHMBA}$$

Equation 7.8

During the process of condensation, the number of polymer molecules and the number of hydroxyl end groups are reduced by equivalent amounts. Thus, the following relationship always holds:

$$N_{OH}^0 - N_{OH} = N^0 - N$$

Equation 7.9

Combination of eqs. 7.6-7.9 yields the following relationship:

$$N = \frac{k}{3} (A_c - A_a)$$

Equation 7.10

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And, finally we have an expression for $\overline{N}_{br}$ in terms of signal areas in the $^1$H NMR spectrum that are readily integrated:

**Equation 7.11**  

$$ \overline{N}_{br} = \frac{2A_s - A_c}{A_c - A_s} $$

Figure 7.8 shows the expanded $^1$H NMR spectrum of a representative BH MBA-PDLLA (exp. 1).
Figure 7.8  Expanded $^1$H NMR spectrum of BHMB-A-PDLLA (exp. 1) showing integrated peak areas of protons $H_c$ and $H_a$.

One can see that the relevant end group resonances are entirely resolved and that the foregoing analysis can be successfully completed. Values of $\bar{N}_{be}$ for several BHMB-A-PDLLA and BHMB-A-PLLA polyesters are listed in Table 5.1.
Table 7.3  Average Number of Branches per Molecule, $\bar{N}_{br}$, for Select Polyesters.

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>$\bar{N}_{br}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHMBA-PDLLA (exp. 1)</td>
<td>0.020</td>
</tr>
<tr>
<td>BHMBA-PDLLA (exp. 2)</td>
<td>0.041</td>
</tr>
<tr>
<td>BHMBA-PLLA (exp. 4)</td>
<td>0.043</td>
</tr>
<tr>
<td>BHMBA-PLLA (exp. 5)</td>
<td>0.080</td>
</tr>
<tr>
<td>1,4-butanediol-PDLLA (exp. 7)</td>
<td>0.032</td>
</tr>
<tr>
<td>BHMBA-PDLLA (exp. 3)</td>
<td>0.047</td>
</tr>
<tr>
<td>1,2-propanediol-PDLLA (exp. 12)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

It would appear that minute amounts of branching occurred since the $\bar{N}_{br}$ values in Table 7.3 are non-zero. However, these branching degrees are insignificant and would constitute a loss of only 2-4 mole percent of the acid groups in the samples produced under our standard conditions of catalyst concentration and reaction time (e.g. exp. 1), assuming $H_c$ protons reacted with an acid group of BHMBA. When comparing exp. 1 to exp. 2 or exp. 4 to exp 5 one can see that an increase in catalyst concentration increases $\bar{N}_{br}$ as expected.

At higher BHMBA/lactide feed ratios, the likelihood of branching via condensation should increase and consequently higher $\bar{N}_{br}$ values might be observed. Therefore, we synthesized BHMBA-PDLLA (exp. 3) having a 15/85 molar ratio of BHMBA/lactide. This is one of the intermediate feed ratios used by Gottschalk and Frey and in the absence of condensation reactions, will produce PDLLA with a Mn of $\sim$1000 g/mol, which is the lowest $M_n$ of PDLLA prepolymers that we anticipate using in the formulation of hydrolytically degradable polyurethanes. The $\bar{N}_{br}$ value of this polyester was 0.047 (Table 7.3), which falls in the same range as the BHMBA-PDLLA polymers produced at lower BHMBA/lactide ratio.
As a control experiment, we extended our NMR analysis to polylactides synthesized using 1,4-butanediol or 1,2-propanediol. For 1,4-butanediol-PDLLA, we determined the peak area, $A_h$, of the inner methylene protons ($H_h$) of the initiator residue vs. $A_c$ (Figure 7.9) and used the following equation:

**Equation 7.12**

$$N_{br} = \frac{6A_h - 4A_i}{4A_i - 3A_h}$$

![Figure 7.9](image)

**Figure 7.9** $^1$H NMR spectrum of 1,4-butanediol-PDLLA (Exp. 7) with methylene protons of initiator ($H_h$ 1.75 ppm) and methyl protons ($H_c$ 1.40 ppm) of terminal lactide residue labeled.

For 1,2-propanediol-PDLLA, we determined the area of the methyl protons of the initiator residue and used eq. 11. These control polymers (exp. 7 and 12, respectively,
Tables 7.1 and 7.3) do not contain a pendent carboxylic acid group and therefore cannot undergo branching via condensation. Consequently, they should yield values for $\bar{N}_{br}$ of approximately zero. As shown in Table 7.3, both control polymers yielded about the same $\bar{N}_{br}$ (0.032-0.035), and this value is in the same range as all the other polymers. This suggests a minor, systematic error in the measurement that is biased toward higher $\bar{N}_{br}$. Most likely this is caused by slight underestimation of $H_c$, perhaps because the ultimate methyl groups of very short chains (1-3 lactoyl residues) have a chemical shifts that are slightly away from the main resonance at 1.4 ppm. In any case, the fact that the control polymers, which cannot be branched, yield the same $\bar{N}_{br}$ as the BHMBAPDLLAs-polyactides, strongly supports our proposition that the latter polymers are predominantly linear.

*Chain extension of BHMBAPDLLA via LDI.* Chain-extended PDLLAs (CE-PDLLA) containing pendant acid groups were synthesized using various BHMBAPDLLA prepolymers of differing molecular weights as outlined in Table 7.4.

Table 7.4 Prepolymers and Chain Extenders Used in the Synthesis of CE-PDLLAs.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Prepolymer$^a$</th>
<th>Prepolymer $M_n$ (g/mol)$^b$</th>
<th>Chain Extender</th>
<th>$M_n$ (g/mol)</th>
<th>MWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>BHMBAPDLLA</td>
<td>1170</td>
<td>LDI</td>
<td>8670</td>
<td>1.29</td>
</tr>
<tr>
<td>14</td>
<td>BHMBAPDLLA</td>
<td>6740</td>
<td>LDI</td>
<td>51100</td>
<td>1.35</td>
</tr>
<tr>
<td>15</td>
<td>BHMBAPDLLA</td>
<td>14200</td>
<td>LDI</td>
<td>206000</td>
<td>1.38</td>
</tr>
<tr>
<td>16</td>
<td>BHMBAPDLLA</td>
<td>6740</td>
<td>$H_{12}$MDI</td>
<td>47200</td>
<td>1.38</td>
</tr>
<tr>
<td>17</td>
<td>1,2-propanediol-PDLLA</td>
<td>5550</td>
<td>LDI</td>
<td>49500</td>
<td>1.39</td>
</tr>
<tr>
<td>18</td>
<td>BHMBAPDLLA</td>
<td>3340</td>
<td>$H_{12}$MDI</td>
<td>Table 5</td>
<td>Table 5</td>
</tr>
<tr>
<td>19</td>
<td>1,4-butanediol-PDLLA</td>
<td>3530</td>
<td>$H_{12}$MDI</td>
<td>Table 5</td>
<td>Table 5</td>
</tr>
</tbody>
</table>

$^a$ Prepolymers used in the synthesis of CE-PDLLAs (exps. 13-19) are not listed in Table 1, but were synthesized according to the procedure described in the experimental with a catalyst level of 300 ppm and a reaction time of ~180 min.

$^b$Molecular weight analysis accomplished by MALLS.
The polymers were synthesized via step growth polymerization using LDI or H12MDI as the chain extending agent (Scheme 7.1).

Scheme 7.1 Ring-opening polymerization of D,L-lactide using BHMBA as an initiator. Chain extension of BHMBA-PDLLA with a diisocyanate.

The CE-PDLLA synthesized in Exp. 13 was used for characterization purposes, in order to identify formation of urethane linkages (Figure 7.10).
Figure 7.10 $^{13}$C NMR spectrum of CE-BHMBAPDLLA (exp. 13) showing urethane linkage and acid functionality.

The disappearance of the isocyanate peaks and formation of the peaks characteristic of urethane linkages is consistent with the data reported by Wiggins and coworkers.$^{183}$ CE-PDLLA polymers (exps. 14 and 15) were synthesized using prepolymer having $M_n$s of 6740 and 14200 g/mol, resulting in chain-extended molecular weights of 51,100 (MWD=1.35) and 206,000 (MWD=1.38), respectively. These chain-extended polymers on average contain 9-17 pendant acid groups along the polymer backbone. Their synthesis demonstrates the ability to create linear PDLLA polymers of high molecular weight and poly(ester-urethane)s whose potential degradation can be tuned by the presence of a controlled number of pendant carboxylic acid groups. exps. 14, 15, 16 and 17 will be the focus of future studies and will provide information.
concerning the effect of the acid functionality, introduced by BHMB, and the choice of diisocyanate on hydrolytic degradation.

A series of CE-PDLLA polyesters were synthesized based on exps. 18 and 19, in which the NCO/OH ratio was varied; these data are presented in Table 7.5.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>NCO/OH (mol/mol)</th>
<th>( M_n ) (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td>0.93</td>
<td>22900</td>
</tr>
<tr>
<td>18b</td>
<td>0.96</td>
<td>23900</td>
</tr>
<tr>
<td>18c</td>
<td>0.99</td>
<td>29200</td>
</tr>
<tr>
<td>18d</td>
<td>1.00</td>
<td>36100</td>
</tr>
<tr>
<td>18e</td>
<td>1.02</td>
<td>30000</td>
</tr>
<tr>
<td>18f</td>
<td>1.05</td>
<td>31300</td>
</tr>
<tr>
<td>18g</td>
<td>1.08</td>
<td>54100</td>
</tr>
<tr>
<td>18h</td>
<td>1.14</td>
<td>96300</td>
</tr>
<tr>
<td>18i</td>
<td>1.18</td>
<td>62000</td>
</tr>
<tr>
<td>18j</td>
<td>1.22</td>
<td>54800</td>
</tr>
<tr>
<td>18k</td>
<td>1.30</td>
<td>47800</td>
</tr>
<tr>
<td>18m</td>
<td>1.40</td>
<td>38100</td>
</tr>
</tbody>
</table>

\( ^a \) Molecular weight analysis accomplished by GPC-MALLS.

From Table 7.5 one can observe that as the NCO/OH ratio of exps. 18 and 19 increases the \( M_n \) values increase to a maximum value but then decrease. This trend can be easily distinguished in Figure 7.11.
Figure 7.11  $M_n$ versus NCO/OH ratio for exps. 18 and 19 (Table 7.4).

The maximum $M_n$ obtained in both series (18 and 19) was achieved at a NCO/OH ratio of 1.14. This suggests that the OH content, as determined from GPC-MALLS data, is under-estimated or that side reactions are present that reduce the available NCO. The $M_n$ as determined by $^1$H NMR is 2558 and 2708 g/mol for the prepolymer used in Exp 18 and 19, respectively. These values are very different from those obtained by GPC-MALLS, and using these values will over estimate OH content. Using the NCO content of exps. 18h and 19h and assuming this is where NCO/OH equals ~1, prepolymer $M_n$s were calculated to be 2920 and 3100 g/mol, respectively. These $M_n$ values are very close.
to $M_n$ (2964 g/mol) based on initiator/monomer feed ratios for prepolymers used in Exps. 18 and 19. This suggest that hydroxyl groups from the initial feed are conserved throughout the polymerization of DLLA using BHMB as the initiator and therefore provides additional evidence that little to no branching exists in the BHMB-PDLLA prepolymer. The $M_n$s are consistently higher in series 18, which uses BHMB-PDLLA as the prepolymer, than series 19, which uses 1,4-butanediol-PDLLA. The $M_n$ increase is possibly caused by branching that is occurring through the acid pendant group during the CE reaction in series 18 to form an amide linkage. Additionally, it is possible that side reactions, leading to branching, caused by moisture are more prevalent in series 18 due to the increased hydrophilic nature of BHMB-PDLLA compared to 1,4-butanediol-PDLLA.

C. Conclusions

Contrary to a recent literature report, the lactide/BHMB/stannous octoate polymerization system yields polymers exhibiting a predominantly linear architecture. End group residues and backbone units were defined with great certainty using $^1$H and $^{13}$C NMR spectroscopy. Molecular weight data, in combination with a measure of branching density obtained by $^1$H NMR end group analysis, provided convincing evidence that branching due to condensation reactions between hydroxyl end groups and the carboxylic acid of BHMB residues is insignificant under our conditions. An insignificant degree of branching was further confirmed by the absence of resonances in the $^{13}$C NMR spectrum representing likely branching structures. Chain-extended BHMB-PDLLA of high molecular weight (51,100 and 206,000 g/mol) and moderately narrow molecular weight distribution (1.35 and 1.38) containing a controlled number (~9
and 17) of acid pendant groups per polymer chain were synthesized, providing PDLLA with enhanced and tunable rate of degradation. Additionally, maximum $M_n$ for chain extended PDLLA was obtained at a nominal NCO/OH ratio of 1.14, and this corresponds to prepolymer $M_n$ values close to $M_{n,\text{tho}}$, assuming maximum chain extension occurs at a true NCO/OH ≈1. Hydrolytic degradation studies of BH MBA-PLA and chain-extended derivatives will follow in future publications.
CHAPTER 8
HYDROLYTIC DEGRADATION OF PENDENT-ACID FUNCTIONALIZED POLY(LACTIC ACID)

A. Objective

The objective for this research is to investigate routes to enhance the hydrolytic degradation of poly (α-hydroxy acid)s, i.e. L- and D,L-lactic and glycolic acid, by tailoring the functionality of the backbone, which will be used in the formulation of thermoplastic poly(ester-urethane)s. In this study we investigated the hydrolytic degradation of pendent-acid-functionalized PDLLA (PDLLA-BH MBA) synthesized via ring opening polymerization of D,L-lactide using 2,2-bis(hydroxymethyl)butyric acid as the initiator. We compare the degradation profile of pendent acid-functionalized PDLLA having number average molecular weights ($M_n$)s of approximately 5000, 20000 and 40000 g/mol with hydroxyl and acid terminated PDLLA of the same $M_n$s. We additionally, evaluated the hydrolytic degradation of model chain-extended (CE) poly(ester-urethane)s made from PDLLA-BH MBA prepolymers and L-lysine diisocyanate methyl ester (LDI) or dicyclohexylmethane 4,4'-diisocyanate ($H_{12}$MDI) as the chain-extending agent.
B. Results and Discussion

Pendent carboxylic acid functionalized PDLLAs (PDLLA-BHMBAs-5K, PDLLA-BHMBAs-20K, PDLLA-BHMBAs-40K) of three different molecular weights were synthesized according to conditions previously described\textsuperscript{184}; details of these polyesters are given in (Table 8.1).

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Polymer Name\textsuperscript{a}</th>
<th>Rxn. Time (min)</th>
<th>(M_n)\text{theo}</th>
<th>(M_n)\text{exp}</th>
<th>MWD (Mw/Mn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PDLLA-BHMBAs-5K</td>
<td>198</td>
<td>5500</td>
<td>5727</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>PDLLA-BHMBAs-20K</td>
<td>246</td>
<td>20597</td>
<td>21400</td>
<td>1.05</td>
</tr>
<tr>
<td>3</td>
<td>PDLLA-BHMBAs-40K</td>
<td>542</td>
<td>41697</td>
<td>39900</td>
<td>1.09</td>
</tr>
</tbody>
</table>

Reaction times of PDLLA-BHMBAs polymers were adjusted accordingly to accommodate for the increase in viscosity, i.e. the higher the viscosity the longer the reaction time needed to achieve targeted molecular weight (\(M_n\)\text{theo}). PDLLA, synthesized via ring opening polymerization (ROP) of DLLA using 1,4-butanediol as the initiator and Sn(Oct)_2 as the catalyst, was used in the synthesis of hydroxyl- and carboxylic acid-telechelic polyesters. Hydroxyl-telechelic PDLLA (PDLLA-OH) was prepared by washing a solution of PDLLA/CHCl\textsubscript{3} with an HCl (aq) methanol mixture; this was done to remove catalytic stannyl ether endgroups formed during ROP. Carboxylic acid-telechelic PDLLA (PDLLA-COOH) was synthesized by end-capping PDLLA-OH with succinic anhydride as shown in Figure 4.4.
Number average molecular weights and polydispersities of PDLLA-BHMBMA, PDLLA-OH and PDLLA-COOH polyesters are presented in Tables 8.1 and Table 8.2.

**Table 8.2.** Number average molecular weights ($M_n$) and molecular weight distributions (MWD) for hydroxyl- and carboxylic acid telechelic-poly(D,L-lactide).

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Polymer Name</th>
<th>$M_n$ theo</th>
<th>$M_n$ exp</th>
<th>MWD (Mw/Mn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>PDLLA-OH-5K</td>
<td>5423</td>
<td>5350</td>
<td>1.03</td>
</tr>
<tr>
<td>5</td>
<td>PDLLA-OH-20K</td>
<td>20597</td>
<td>21500</td>
<td>1.14</td>
</tr>
<tr>
<td>6</td>
<td>PDLLA-OH-40K</td>
<td>41697</td>
<td>38000</td>
<td>1.18</td>
</tr>
<tr>
<td>7</td>
<td>PDLLA-COOH-5K</td>
<td>5615$^a$</td>
<td>5510</td>
<td>1.04</td>
</tr>
<tr>
<td>8</td>
<td>PDLLA-COOH-20K</td>
<td>20789$^a$</td>
<td>21100</td>
<td>1.09</td>
</tr>
</tbody>
</table>

$^a$ Theoretical $M_n$ calculated from PDLLA-OH plus the addition of succinic acid endgroups.

The $^{13}$C NMR spectra of the carbonyl region showing the conversion of hydroxy (PDLLA-OH-5K) to carboxylic acid (PDLLA-COOH-5K) end-group functionalized PDLLA is shown in Figures 8.1 and 1.2. Prior to end-capping with succinic anhydride (Figure 8.1), the carbonyl carbon resonance associated with the terminal lactic acid unit of PDLLA-OH-5K is present at 174.9 ppm. Upon reaction with succinic anhydride three new peaks appear at 173.2, 172.2 and 170.5 ppm which are identified in Figure 8.2. The peaks at 173.2 and 172.2 ppm are associated with the carbonyl carbon resonances of the newly formed succinic acid end-groups. The peak at 170.5 ppm corresponds to the carbonyl carbon of the ultimate lactic acid unit directly bonded to the succinic acid units.
Figure 8.1  $^{13}\text{C}$ NMR spectrum of hydroxy-telechelic PDLLA-OH-5K showing carbonyl region.
Degradation studies were performed on samples 1-8 following the method described in Chapter 4. Number average molecular weights ($M_n$) and molecular weight distributions (MWD) were obtained for the polyesters after being formed into disks and showed no appreciable change from the $M_n$ and MWD values listed in Tables 8.1 and 8.2. Figure 8.3 shows the percent remaining mass versus time of exps. 1 (PDLLA-BHMB-5K), 4 (PDLLA-OH-5K), and 7 (PDLLA-COOH-5K).
Figure 8.3 Remaining Mass of dry samples vs. immersion time for exps. 1 (PDLLA-BHMBA-5K), 4 (PDLLA-OH-5K) and 7 (PDLLA-COOH-5K).

The data indicate that mass loss occurs much sooner for the acid-functionalized PDLLA’s (PDLLA-BHMBA-5K and PDLLA-COOH-5K) compared to the control polymer containing only hydroxyl groups (PDLLA-OH-5K). Moreover, the PDLLA-BHMBA-5K, with the single pendent acid group per molecule, shows a slightly earlier mass loss (11 days) than the PDLLA-COOH-5K (18 days). Rapid degradation of the acid-containing polymers relative to PDLLA-OH-5K was predicted on the basis of a catalytic affect and increased water uptake caused the presence of the hydrophilic carboxylic-acid groups. The more rapid degradation of PDLLA-BHMBA relative to PDLLA-COOH, however, was not necessarily expected. We first attributed this phenomenon to a free

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volume effect; we hypothesized that PDLLA-BHMB HA possessed a higher free volume and that higher free volume leads to an increase in the rate of water diffusion and consequently an increase in the rate of hydrolytic degradation. However, upon examination of the glass transition temperatures ($T_g$) in Table 8.3, which would provide insight into the variation in free volume of the samples, we observed that the diacid has a lower $T_g$ value indicating it possesses the highest content of free volume. PALS was used to confirm the $T_g$ data as it relates to free volume ($\AA^3$) (Table 8.3).

From these data we concluded that free volume is not the primary factor that contributes to the unique degradation characteristics of PDLLA-BHMB HA-5K. We now suspect that the location of the acid functionality is the primary reason for the increased hydrolytic degradation.

Figures 8.4 and 8.5 show the percent remaining mass vs. time of exps. 2 (PDLLA-BHMB HA-20K), 5 (PDLLA-OH-20K) and 8 (PDLLA-COOH-20K) and exps. 3 (PDLLA-BHMB HA-40K) and 6 (PDLLA-OH-40K), respectively. From Figures 8.4 and 8.5 we again observe the enhanced hydrolytic degradation of PDLLA with $M_n$s of 21400 and 39900 g/mol when synthesized using BHMB HA as the initiator. It should be noted that in

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Polymer Name</th>
<th>$T_g$</th>
<th>$\tau_3$</th>
<th>$I_3$</th>
<th>$\AA^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>PDLLA-OH-5K</td>
<td>42.5</td>
<td>1.96</td>
<td>8.93</td>
<td>93.3</td>
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<td>1</td>
<td>PDLLA-BHMB HA-5K</td>
<td>39.0</td>
<td>1.99</td>
<td>11.12</td>
<td>96.0</td>
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<tr>
<td>7</td>
<td>PDLLA-COOH-5K</td>
<td>37.8</td>
<td>2.15</td>
<td>9.58</td>
<td>111.6</td>
</tr>
</tbody>
</table>

Table 8.3 Glass transition temperatures ($T_g$) and PALS data for a series of 5000 g/mol PDLLA polyesters.
Figure 8.3 the onset of degradation of PDLLA-OH-20K and PDLLA-COOH-20K are virtually the same. This trend was observed in a similar study carried out by Wiggins et al. This phenomenon is contrary to what is observed for PDLLA-OH-5K and PDLLA-COOH-5K in Figure 8.3 and supports our hypothesis that location of the acid functionality plays an important role in hydrolytic degradation of PDLLA polyesters. It should be noted that the conversion of PDLLA-OH-20K to PDLLA-COOH-20K could not be confirmed by NMR spectroscopy as in the case of PDLLA-COOH-5K and based on their degradation profiles we suspect that total acid end group functionalization was not achieved. The degradation profile of high molecular weight PDLLA-BHMB-40K compared to PDLLA-OH-40K illustrates the remarkable degradation characteristics caused by the addition of a single pendant acid group.
Figure 8.4  Remaining Mass of dry samples vs. immersion time for exps. 2 (PDLLA-BHMBA-20K), 5 (PDLLA-OH-20K) and 8 (PDLLA-COOH-20K).

Figure 8.5  Remaining Mass of dry samples vs. immersion time for exps. 3 (PDLLA-BHMBA-40K) and 6 (PDLLA-OH-40K).

It is inherent that as PDLLA hydrolytically degrades it forms an acid-terminated fragment and a hydroxy-terminated fragment (Scheme 8.1).
Scheme 8.1 Hydrolysis of PDLLA showing formation of hydroxyl and acid terminated fragments.

The presence of these acid terminated fragments can be followed by monitoring the pH of the buffer solution vs. time. Figures 8.6, 8.7 and 8.8 contain pH vs. time data for PDLLA-5K, PDLLA-20K and PDLLA-40K series. Comparison of the pH data with the mass loss data shows a correlation between the onset of fragmentation and drop in pH.
Figure 8.6  Change in buffer solution pH vs. time of exps. 1 (PDLLA-BHMBA-5K), 4 (PDLLA-OH-5K) and 7 (PDLLA-COOH-5K).
Figure 8.7  Change in buffer solution pH vs. time of exps. 2 (PDLLA-BH MBA-20K), 5 (PDLLA-OH-20K) and 8 (PDLLA-COOH-20K).
The utility of pendant acid PDLLA polyesters as prepolymers has been established in the formulation of poly(ester-urethane)s.\textsuperscript{184} Details of select chain-extended PDLLAs (CE-PDLLA) are contained in Table 8.4.

Table 8.4 Prepolymers and Chain Extenders used in the synthesis of CE-PDLLAs (reproduced from ref. 15).

<table>
<thead>
<tr>
<th>Prepolymer</th>
<th>Prepolymer $M_n$ (g/mol)</th>
<th>Chain Extender</th>
<th>Polymer Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDLLA-BHMBA</td>
<td>6740</td>
<td>LDI</td>
<td>51100</td>
</tr>
<tr>
<td>PDLLA-BHMBA</td>
<td>6740</td>
<td>$H_{12}$MDI</td>
<td>47200</td>
</tr>
<tr>
<td>PDLLA-1,2-propanediol</td>
<td>5550</td>
<td>LDI</td>
<td>49500</td>
</tr>
</tbody>
</table>
The hydrolytic degradation of these poly(ester-urethane)s are presented in Figure 8.9. Compared to the control (CE-1,2-propanediol-PDLLA) the CE-BHMBA-PDLLA polymers show an earlier mass loss.

![Figure 8.9 Remaining Mass of dry samples vs. immersion time for exps. 3 (PDLLA-BHMBA-40K) and 6 (PDLLA-OH-40K).](image)

**Figure 8.9** Remaining Mass of dry samples vs. immersion time for exps. 3 (PDLLA-BHMBA-40K) and 6 (PDLLA-OH-40K).

Furthermore, when L-lysine diisocyanate methyl ester (LDI) was used as the chain-extending agent the degradation of CE-BHMBA-PDLLA was enhanced when compared to CE-BHMBA-PDLLA using 4,4'-diisocyanate dicyclohexylmethane (H_{12}MDI); we propose this degradation enhancement was due to an increase in hydrophilicity of CE-BHMBA-PDLLA caused by incorporation of LDI, containing a methyl ester group.
Figure 8.10 Change in buffer solution pH vs. time of CE-PDLLA polymers.

In Figure 8.10 we see the pH vs. time data for the CE-PDLLA polymers. We can observe the curves for the CE-BHMBA-PDLLA polymers are very similar, indicating fragmentation of the polymers occurs at approximately the same time. However, the complete fragmentation and dissolution of the CE-PDLLA-BHMBA (LDI) polymer occurs much earlier (62 days vs. 82 days) and to a greater extent than the CE-PDLLA-BHMBA (H_{12}MDI). Again, we attribute this rapid degradation to the CE-PDLLA-BHMBA (LDI) being more hydrophilic due to the presence of the LDI moiety.

C. Conclusions

The onset of degradation of the PDLLA-BHMBA occurs a great deal sooner than the diol analogs (PDLLA-OH) of all series tested. Therefore, using our synthetic route, we have provided a pathway to enhance the hydrolytic degradation of PDLLA up to a M_n.
of ~40000 g/mol. This synthetic route can be applied any α-hydroxy acid polymers to improve degradation characteristics, such as, poly(L-lactic acid), poly(glycolic acid) and copolyesters, including poly(D,L-lactic acid), made therefrom. Additionally, we are confident that using pendent acid functionalized poly(lactic acid) (PLA), prepared using BHMBDA, as a prepolymer in the formulation of poly(ester-urethane)s will enhance their hydrolytic degradation.
REFERENCES

9. Gruber, P. R., et al. USP 5,142,023.
15. Gruber, P. R., et al. USP 5,484,881.
17. WO 96/15174.
18. WO 96/21689.

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