This is to certify that the

dissertation entitled

SYNTHESIS AND CHARACTERIZATION OF AROMATIC

SUBSTITUTED POLYLACTIDES

presented by

Tara Simmons

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Major professor

Date Dec. 11, 2000

DATE DUE	DATE DUE	DATE DUE
APR 2 5 2002		

SYNTHESIS AND CHARACTERIZATION OF AROMATIC SUBSTITUTED POLYLACTIDES

By

Tara Simmons

A DISSERTATION

Submitted to
Michigan State University
In partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

2000

var
tran
pol
also
Poly
unsu
synt

for th
comp
or th
kineti
domi
longe

meth
degr
addi

SYNTHESIS AND CHARACTERIZATION OF AROMATIC SUBSTITUTED POLYLACTIDES

ABSTRACT

Polylactides are important biodegradable and biocompatible polymers with a variety of uses such as surgical sutures and bone fixation devices. However, its low glass transition temperature (T_g) limits the available uses. A biodegradable analog of polystyrene would be desirable for a number of packaging uses. Aromatic rings have also been shown to increase the T_g in the structurally similar poly(hydroxyalkanoate)s. Poly(2-hydroxy-5-phenylvalerate) has a T_g of 13 °C compared to −15 °C for the unsubstituted poly(hydroxyvalerate).[1] A variety of aromatic substituted lactides were synthesized based on phenyllactic acid, mandelic acid, and methylphenyllactic acid.

For all aromatic substituted polylactides, the polymerization rate is slower than for the polymerization of lactide. In addition, the solution polymerizations do not reach completion, indicating that there could be catalyst degradation, terminating the reaction, or that the reaction follows an equilibrium mechanism. Both models can be fit to the kinetic data obtained, but it appears both mechanisms take place, with equilibrium dominating at lower reaction times, and catalyst degradation dominating the kinetics at longer reaction times.

Degradation studies were carried out for poly(phenyllactic acid) and poly(*p*-methylphenyllactic acid) and compared to the degradation of poly(lactic acid). The degradation rate for the polymers were slower than polylactide, most likely because the addition of an aromatic ring causes the polymer to be more hydrophobic. The

degra

slowe

withi

polyr

degra

increa

conce

which

greate

produ

obtain

varied

polym

acids

relati

tempe

dem

arom

trans

1)

degradation for poly(phenyllactic acid) and poly(*p*-methylphenyllactic acid) is initially slower than the model because the hydrophobicity causes the concentration of water within the polymer sample to be relatively low, decreasing the rate of hydrolysis. As the polymer chains are hydrolyzed, the sample becomes more hydrophillic and the degradation rate increases. As the reaction approaches completion, the degradation rate increases. During the degradation reaction, the polymer sample aggregates, concentrating the acidic sites within the polymer, and catalyzing the hydrolysis.

Polyphenyllactide was found to have a glass transition temperature of 50 °C, which is nearly the same as polylactide. We believe that the methylene group allows for greater flexibility and prevents the T_g from being higher. By removing the methylene by producing polymandelide, we found a T_g of 96 °C. However, there were difficulties in obtaining high molecular weight materials.

A number of substituted polystyrenes have been synthesized and the properties varied by changing substituents. This idea was adapted to polyphenyllactide by polymerizing methyl-substituted phenyllactic acids. *o*-, *m*-, and *p*-Methylphenyllactic acids were synthesized from the corresponding methyl-substituted benzaldehyde in relatively low yields. Poly(*p*-methylphenyllactic acid) has the highest glass transition temperature, 59 °C, and poly(*m*-methylphenyllactic acid) the lowest, 42 °C. This demonstrates that poly(phenyllactic acid) can be modified through substituents on the aromatic ring. By choosing the correct substituent, a polymer with a higher glass transition temperature, like polystyrene's T_g of 100 °C, should be possible.

1) Fritzsche, K.; Lenz, R. W.; Fuller, R. C. *Makromol. Chem.* **1990**, *191*, 1957-1965.

To my grandmother, Olga Simmons

pos

defo

dep

mak

and

grou

Jing

abov

enjoy

Wald

miss

Biop

supp

of m

wasn

Acknowledgements

I wish to thank Professor Greg Baker, without whom this work would not be possible. I appreciate all of his help, encouragement, and assistance in organizing my defense while I was in West Virginia. I would also like to acknowledge the work of the department glass blowers, Manfred Langer and Scott Bankroff, for their assistance in making (and repairing) the custom glassware used in this work. Thanks for their time and patience in teaching me to make the sealed tubes used for the melt polymerizations.

I would like to acknowledge the assistance and support of current and past Baker group members Erin Paske, Chun Wang, Kirk Olson, J. B. Kim, Tianqi Liu, Gao Liu, Jingpin Jia, Susan Pasco, Cory Ruud, and Jun Hou. In addition to my friends listed above, I would like to thank my good friends that have made my stay at Michigan State enjoyable: Beth Gardner, Rob Gentner, Nadia Shams, Dalila Kovacs, Craig Shiner, Mike Waldo, Marie Migaud, Nancy Lavrik, and Diane Frost. My deepest apologies if I've missed anyone important.

I would like to thank the Corn Marketing Board of Michigan, the Crop and Food Bioprocessing Center, and the Center for Fundamental Materials Research for financial support for this research.

Lastly, and most importantly, I deeply appreciate the support and encouragement of my family: Michalina, Millie, and Steve Ostrander. They believed in me when I wasn't so sure of myself, and I could not have finished without them.

List o

List o

List o

Chapt

1

Table of Contents

Cha

Chap

3

3

Chap

Ch

Ta

Ta

Ta

List of Tables

List of Figures

Figu

Figu

Figu

Figu

Figu

Figu

Figu

Figur

Figur

Figur

Figur

Figur

Figur

List of Schemes

Al(C

BBA

DSC

GPC

LA

MD

Mn

mTLD

M_w

oTLD

PDI

PDLLA

PGA

PHB

PHBV

PhLA

PhLD

PLA

PLLA

PMA

PmTLD

List of Abbreviations

$Al(OiPr)_3$	Aluminum isopropoxide
BBA	*t*-Butylbenzyl alcohol
DSC	Differential scanning calorimetry
GPC	Gel permeation chromatography
LA	Lactic acid
MD	Mandelide
Mn	Number average molecular weight
mTLD	*m*-tolyllactide or *m*-methylphenyllactide
M_w	Weight average molecular weight
oTLD	*o*-tolyllactide or *o*-methylphenyllactide
PDI	Polydispersity
PDLLA	Poly(D,L-lactic acid) or Poly(D,L-lactide)
PGA	Poly(glycolic acid) or Polyglycolide
PHB	Poly(hydroxybutyrate)
PHBV	Poly(hydroxybutyrate-*co*-valerate)
PhLA	Phenyllactic acid
PhLD	Phenyllactide
PLA	Poly(lactic acid) or Polylactide
PLLA	Poly(L-lactic acid) or Poly(L-lactide)
PMA	Poly(mandelic acid)
PmTLD	Poly(*m*-tolyllactide) or Poly(*m*-methylphenyllactide)

PoTLD	Poly(*o*-tolyllactide) or Poly(*o*-methylphenyllactide)
PPhLA	Poly(phenyllactic acid)
PPhLD	Poly(phenyllactide)
PpTLD	Poly(*p*-tolyllactide) or Poly(*p*-methylphenyllactide)
pTLD	*p*-tolyllactide or *p*-methylphenyllactide
$Sn(Oct)_2$	Tin(II) 2-ethylhexanoate or Tin octoate
T_g	Glass transition temperature
TGA	Thermal gravametric analysis

1 l

conc

recyc

hydrc

Biod

either

Hydrc

photo

comb

and p

numb

degra

such

degra

alcoh

often

report

Chapter 1 – Introduction

1 Background

Most commercial plastics are resistant to degradation and as environmental concerns grow, there is an increasing emphasis on reducing waste through the use of recyclable and degradable polymers. Degradable materials include biodegradable, hydrolytically degradable, photodegradable, and oxidatively degradable materials. Biodegradable polymers and plastics are quantitatively converted by microorganisms to either CO_2 and H_2O, or to CH_4 and H_2O under aerobic or anaerobic conditions. Hydrolytically degradable polymers and plastics degrade via hydrolysis, while photodegradable polymers and plastics degrade by exposure to sunlight or by the combined action of sunlight and atmospheric oxygen. Oxidatively degradable polymers and plastics undergo an oxidative degradation process.[1]

These terms are often incorrectly applied to degradable polymers. For example, a number of polymers were previously reported to be biodegradable, but the observed degradation was due to the degradation of plasticizer[1] in the polymer. Other polymers such as polyethylene, polypropylene, polyacrylonitrile, and poly(vinyl chloride) undergo degradation (photodegradation), but at a slow rate. Poly(vinyl acetate) and poly(vinyl alcohol), having residual carbonyl groups, also photodegrade. Photodegradable polymers often persist as non-degradable oligomers, eliminating the major benefits of degradation.

The first synthetic biodegradable polymer was poly(glycolic acid) (PGA), reported in 1954.[2] Little work was initially done with PGA because of its poor thermal prop

degr

too

degr

the fi

curre

mater

acid),

polye

poly(h

these

PHB

for pa

and st

bacteri

bacteri

time.

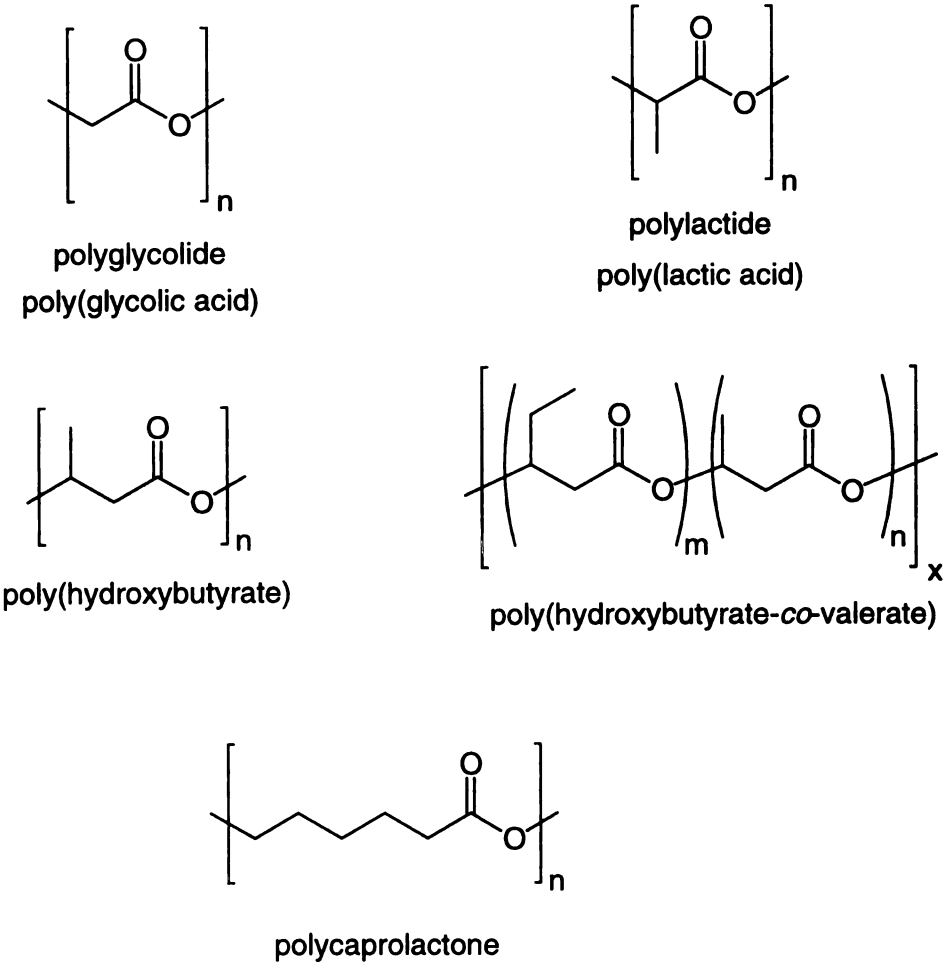
methyl

polylact

properties and its low hydrolytic stability. PGA's high crystallinity leads to a slow degradation rate. Its high melting temperature makes processing difficult because it is too close to the degradation temperature, causing the polymer to undergo thermal degradation during processing. Despite these limitations, two decades later PGA became the first biodegradable suture material that was unrelated to natural polymers.

Since then, a number of other synthetic polymers have been synthesized and are currently referred to as biodegradable, bioabsorbable, bioresorbable and bioerodible materials (Figure 1.1). The most important of these degradable polymers are poly(lactic acid), also called polylactide. Others include starch-based materials and variety of polyesters, such as polyglycolide, polycaprolactone, poly(hydroxybutyrate) (PHB) and poly(hydroxybutyrate-*co*-hydroxyvalerate) (PHBV). There is commercial interest in these materials for packaging, agricultural mulch films, fibers, and for medical uses. PHB has polypropylene-like properties and was sold under the commercial name Biopol for packaging applications. PHBs are unique in that a variety of microorganisms produce and store the polymer as an energy reserve. Commercial production of PHBs involves bacterial fermentation of alkanoic acids followed by harvesting of the polymer from the bacteria. PHBs are degraded by a wide range of bacteria, fungi, and algae.

Polylactide has been known to be bio- and environmentally degradable for some time. Polylactide is structurally similar to polyglycolide, differing only in the added methyl group α to the carbonyl. Depending on the stereochemistry of the polymer, polylactides can be either semicrystalline or amorphous, allowing for greater flexibility in



polyglycolide
poly(glycolic acid)

polylactide
poly(lactic acid)

poly(hydroxybutyrate)

poly(hydroxybutyrate-*co*-valerate)

polycaprolactone

Figure 1.1 Important biodegradable polymers contro

hydrol

by a

Polyla

polyla

surgica

polym

becau

polyla

packa

comm

additi

proce

polyl

1.1

dim

Poly

wa

controlling the degradation rate compared to PGA. Polylactides primarily degrade via hydrolysis of the polyester to the α-hydroxy acid, lactic acid. Biodegradation catalyzed by a variety of enzymes common in microorganisms has also been reported.[2] Polylactides are biocompatible, and there is a low chance of rejection or infection when polylactide is used inside the body. This has led to important medical applications as surgical sutures, bone fixture devices, and drug delivery systems. Upon degradation, the polymer forms lactic acid, which can be eliminated by the body.

Until recently, most uses for polylactide were limited to medical applications because of the high cost of the polymer. However, methods were developed to produce polylactide at lower costs, and polylactide can now compete with existing polymers as packaging materials and fibers. The Dow Cargill joint venture has announced a commercial polylactide plant with an announced capacity of 300 million lb./yr. In addition to reducing the cost of the polymer, improvements in the physical properties and processing characteristics have minimized earlier problems associated with crazing and polylactide's high melting temperature.

1.1 Polylactide Synthesis

Polylactides are most commonly synthesized by polymerization of the cyclic dimer of lactic acid. Direct polymerization of the the α-hydroxy acid by polycondensation gives low molecular weight polymer due to the difficulty of removing water during the reaction, which is necessary to drive the equilibrium-controlled reaction to completion. The polycondensation reaction is also much slower than the polymerization of the cyclic dimer. Polymerizations of the lactide dimer often have many of the characteristics found in living polymerizations, most importantly the ability to control the molecular weight by simple adjustments in the monomer-initiator ratio.

Lactide can be polymerized in solution or without solvent as a monomer melt. Melt polymerization has a number of advantages, such as a faster reaction rate than those in solution, due to both the higher reaction temperature and the higher monomer concentration. In addition, there is no solvent to dispose of after the reaction, an important consideration for commercial processes. There are also some disadvantages, such as less control over the polymer molecular weight. Because of the higher reaction temperature, transesterification reactions are more prominent, limiting the ability to control the molecular weight and increasing the polydispersity. If reactions are run for extended periods of time, molecular weights quickly decrease due to intramolecular transesterification, forming cyclic oligomers (Figure 1.7).

Solution polymerizations of lactide are commonly run in toluene, but the use of dichloromethane, THF, and a number of other solvents have also been reported. In many cases, the choice of solvent depends on the catalyst used for the polymerization. The largest disadvantage to solution polymerizations is the reaction time. Reactions that take minutes for melt polymerizations often take days.

1.2 Sy

availab

dimer.

esterifi

method

product

of low

catalyst

crackin

tempera

drives th

T

stereoce

meso la

Knowin

monome

Figure 1

1.2 Synthesis of Lactide

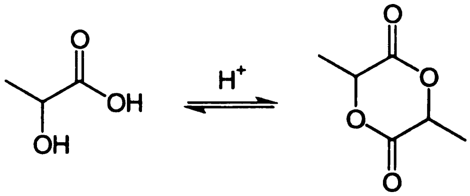


Figure 1.2 Synthesis of lactide via esterification.

There are a number of methods available for the preparation of the cyclic dimer. The simplest is acid-catalyzed self-esterification (Figure 1.2), however the method preferred for commercial production of lactide is thermal cracking of low molecular weight polymer (Figure 1.3) in the presence of a transesterification catalyst. Lactide is distilled out as it is produced, driving the reaction to completion. The cracking method is faster than self-esterification because of the higher reaction temperatures used and gives higher yields because removal of the lactide as it is produced drives the equilibrium towards the dimer.

Thermal cracking is usually accompanied by some racemization of the lactic acid stereocenter. Three lactide diastereoisomers are possible: (R,R), (S,S), and the (R,S) or *meso* lactide. A 1:1 mixture of the (R,R) and (S,S) diastereomers is termed *rac*-lactide. Knowing the stereochemistry of the monomer is important because of the effect that the monomer stereochemistry has on the resulting polymer's physical properties. For

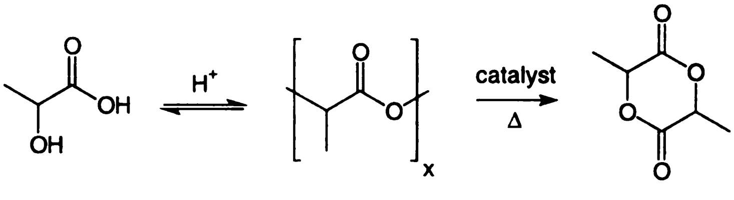


Figure 1.3 Synthesis of lactide via cracking method.

exam

acid)

1.3 P

1.3.1

(PLLA

(isotact

°C dep

involve

causing

degrada

plasticiz

by inclu

problem

amount

feed (fu

polymeriz

polymer.

polymer i

example, poly(L-lactic acid) (PLLA) is a semicrystalline polymer, where poly(*rac*-lactic acid) is amorphous.

1.3 Properties of Polylactide

1.3.1 Poly(L-lactide)

L-lactic acid is formed via fermentation of starch, and thus poly(L-lactic acid) (PLLA) is the most common polylactide produced. Because of its regular structure (isotactic), PLLA is semicrystalline, with T_gs ranging from 55-64 °C and T_ms of 159-215 °C depending on the degree of crystallinity in the polymer.[3] There is some difficulty involved in melt processing PLLA because the T_m is near the degradation temperature, causing the polymer to begin to thermally degrade during processing. Thermal degradation can produce small molecules such as dimer and oligomers that act as a plasticizer and alter the polymer's properties. Using a less crystalline copolymer, made by including a small amount of R,R-lactide in the polymerization, frequently solves this problem by decreasing T_m, allowing processing at a lower temperature and decreasing the amount of thermal degradation. Increasing the amount of R,R-lactide in the monomer feed (functionally equivalent to increasing the proportion of *rac*-lactide in a polymerization) will decrease polymer crystallinity and eventually lead to an amorphous polymer. Polymerization of *rac*-lactide gives poly(D,L-lactic acid) (PDLLA). The polymer is amorphous with reported T_gs varying from 50-57 °C.[3]

1.3.2 Poly(D-lactide)

Poly(D-lactide) (PDDLA) is isotactic and has identical properties to PLLA. However, since only L-lactic acid is typically obtained from fermentations, D-lactide is relatively rare and there are few reports of PDDLA. One interesting derivative of PDDLA is the polylactide stereocomplex, a 1:1 mixture of PLLA and PDDLA. The mixture co-crystallizes and melts at 230 °C, more than 30° higher than either homopolymers.

1.3.3 Syndiotactic Polylactide

The synthesis of syndiotactic polylactide (RSRSRSRS...) requires the stereospecific polymerization of *meso*-lactide. Coates[4] produced syndiotactic PLA by polymerizing *meso*-lactide with an optically active catalyst derived from BINAP (Figure 1.4). An enantiomorphic site-control mechanism is assumed where the catalyst selectively attacks one lactic acid residue of the R,S-lactide monomer, producing an enantiotopic selectivity of 96%. Syndiotactic PLA is crystalline due to the high degree of stereoregularity and has a T_g of 34 °C and T_m of 152 °C. The catalyst used by Coates is a variation of a catalyst used by Spassky and coworkers[5] for the enantioselective polymerization of D-lactide from *rac*-lactide. Spassky obtained

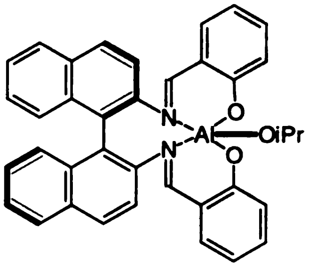


Figure 1.4 Catalyst used for the synthesis of syndiotactic PDLLA

88%

polyl

high

prefer

monor

rac-lac

catalys

1.3.4

A

polymer

segment

i.e. RR

referred

found th

conversic

t-butoxid

polylactid

lactide ste

stereoregul

where BDI

88% enrichment in D-units at low conversion, and at high conversions produced the polylactide stereocomplex because the removal of D-units leaves L-rich monomer pool at high conversions. The (-) form of Spassky's catalyst (the form used by Coates) preferentially polymerizes D-lactide and the (+) form preferentially polymerizes the L-monomer, a property which has been used to produce the polylactide stereocomplex from *rac*-lactide using a racemic mixture of the catalyst.[6] These examples show that Coates' catalyst should preferentially attack the D side of the *meso*-lactide.

1.3.4 Heterotactic Polylactide

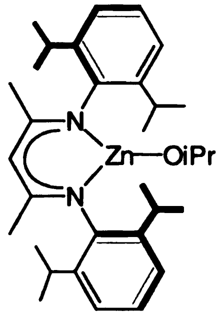


Figure 1.5 Catalyst for the synthesis of heterotactic PLA

A number of authors have reported the polymerization of lactide to produce enriched heterotactic segments[7-9] where pairs of stereogenic centers alternate, i.e. RRSSRRSS..., a stereochemical sequence also referred to as disyndiotactic. Kasperczek and coworkers found that heterotactic structures were preferred at low conversions when *rac*-lactide is polymerized using lithium *t*-butoxide, but the overall stereoregularity of the polylactide was poor.[10] This result illustrates the tendency for syndiotactic placement of lactide stereocenters during most lactide polymerizations. Coates recently produced a stereoregular heterotactic PLA using the sterically hindered zinc complex (BDI)ZnOiPr, where BDI is a 2,6-diisopropylphenyl-substituted β-diimine (Figure 1.5).[11] This hindered catalyst accentuates the chain-end control nature of the polymerization mechanism, enabling formation of the heterotactic polymer at room temperature.

1.4 Lactide Polymerization Mechanism and Catalysts

A number of catalysts are available for the polymerization of lactide, with tin(II) 2-ethylhexanoate (commonly called stannous octoate and abbreviated as $Sn(Oct)_2$) used most frequently. In recent years, there has been growing understanding of the polymerization mechanism (Figure 1.6). Most believe that a hydroxy-containing compound, such as water or an alcohol, first reacts with $Sn(Oct)_2$ to form a tin alkoxide, the active catalyst, and free 2-ethylhexanoic acid. After coordinating to the monomer, the tin alkoxide reacts by attacking the carbonyl of the lactide ring. The lactide ring opens, creating a new alkoxide. Other than polymerization, the growing polymer chain can exchange with free 2-ethylhexanoic acid to re-form $Sn(Oct)_2$ and the free polymer chain. There has also been some indication of decomposition of the catalyst to form solid precipitates,[12] which will be discussed in more detail later.

Figure 1

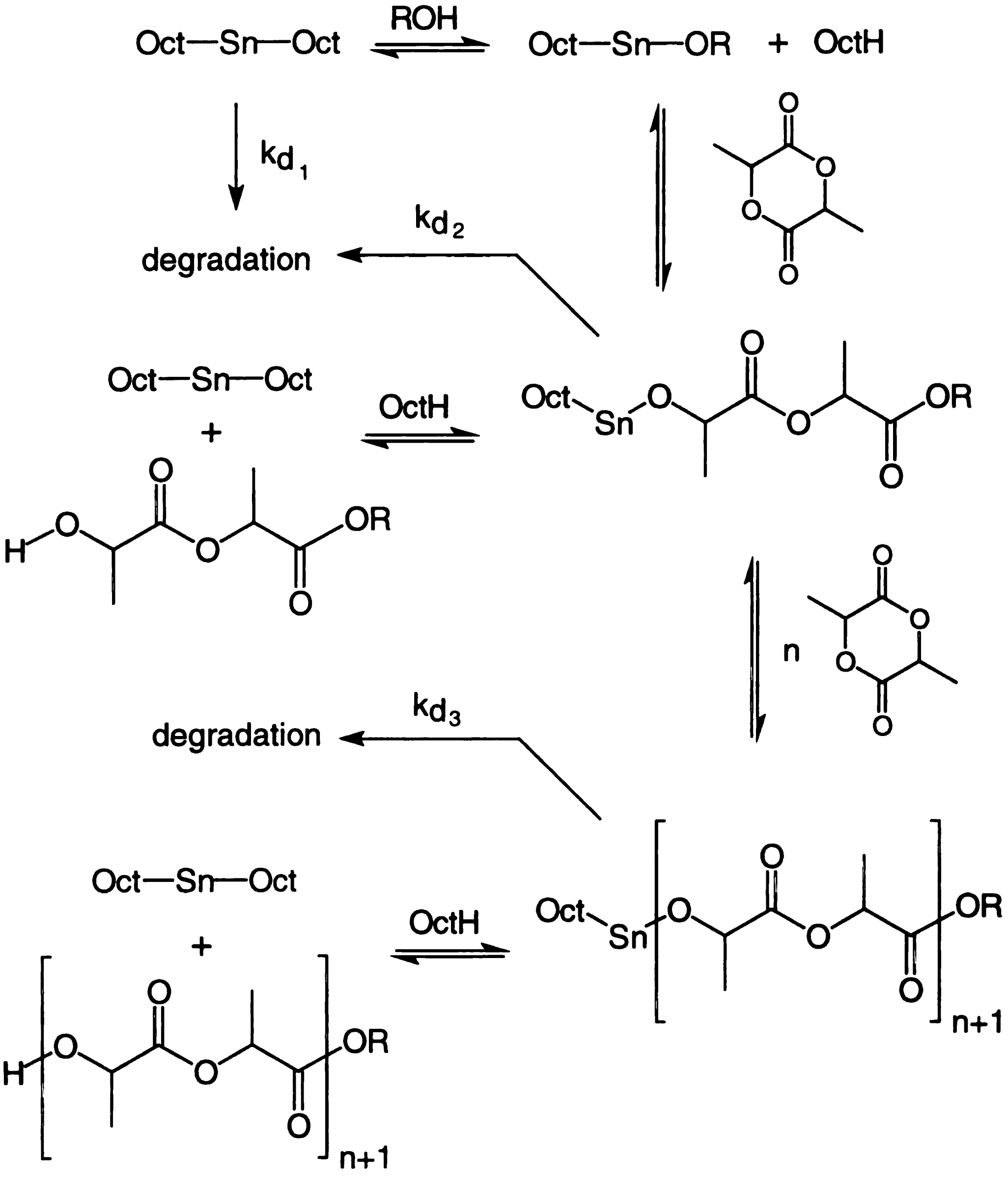


Figure 1.6 Mechanism for the polymerization of lactide using $Sn(Oct)_2$.

Support for this mechanism has been recently published in the literature. Using MALDI-TOF mass spectrometry, polymerization intermediates incorporating tin were detected by Kowalski, et al. that are consistent with the initiating species being a tin alkoxide.[13] Kricheldorf and coworkers have shown that reacting $Sn(Oct)_2$ with benzyl alcohol produces the free 2-ethylhexanoic acid, also supporting the formation of tin alkoxides.[12] A number of other tin compounds can be used for lactide polymerization including $SnCl_4$, $SnBr_2$, and $SnBr_4$. Except for the tin alkoxides, these tin compounds require an alcohol as an initiator.

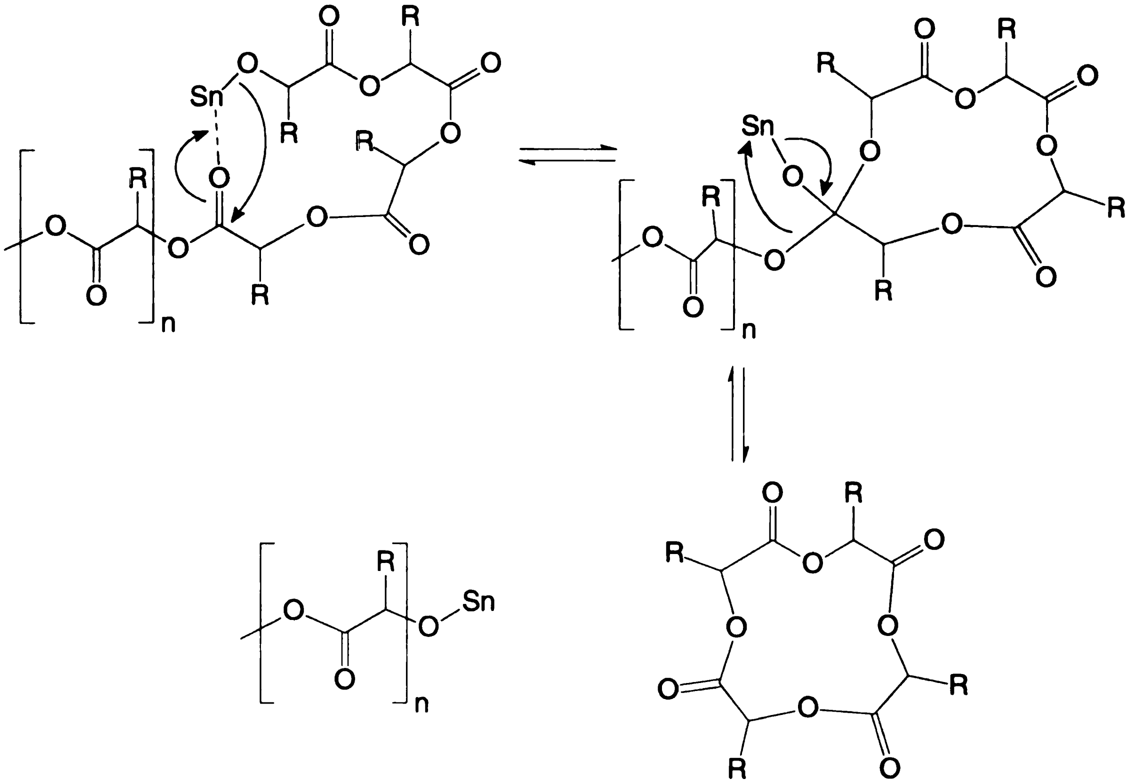


Figure 1.7 Mechanism for intramolecular transterification.

In addition to tin compounds, aluminum alkoxides such as $Al(OiPr)_3$ are commonly used catalysts for lactide polymerizations. These reactions typically use toluene as a solvent because more polar solvents decrease the rate of reaction,[14] most likely by competing with the monomer for coordination to the catalyst. There are some advantages to solution polymerizations. Because they are usually run at lower temperatures than melt polymerizations, there is less transesterification, and therefore greater control over molecular weights. Solution polymerizations using $Al(OiPr)_3$ are reported to be living polymerizations.[15] The proposed mechanism shown in Figure 1.8 is similar to that of tin-based catalysts, except there is no need to form an active catalyst before polymerization can begin.

The number of isopropoxide groups that initiate chains varies with different monomers. For example, only one isopropoxide group is active in ε-caprolactone polymerizations run at 0 °C. At 100 °C, the average number of active isopropoxides per aluminum is 1.4. When lactide is polymerized at 70 °C, all three isopropoxides initiate polymerization. Catalysis using aluminum isopropoxide is further complicated because it exists in two forms, a trimer and tetramer. The trimer is more active in initiating polymerization,[16] most likely due to reduced steric hindrance. It is believed that the aggregates dissociate after initiation of polymerization.[17]

Because the alkoxy group from the catalyst becomes the polymer end group, changing that group will change the end group. This led to the use of catalysts with the general form Et_2AlOR, where the alkoxide group becomes the polymer end group and can be varied to obtain polymers with different end groups. The ethyl groups are inactive

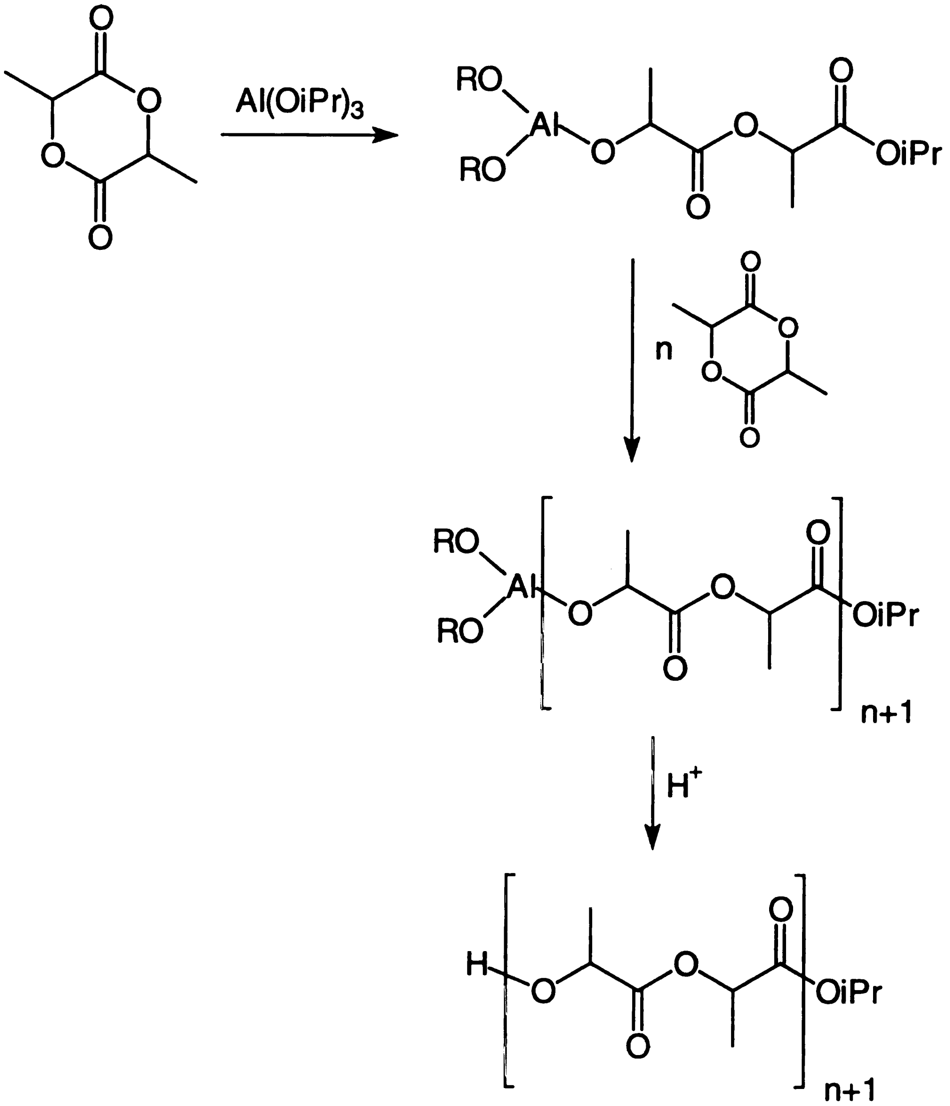


Figure 1.8 Synthetic scheme for the polymerization of lactide using $Al(OiPr)_3$.

and do not initiate polymerization. Examples of such initiators include Et_2AlOCH_2Br,[18] which has been used in the formation of star-branched polymers, and $Et_2AlO(CH_2)_2CH=CH_2$,[19] and $Et_2AlOCH_2OC(O)C(Me)=CH_2$,[20] which leave a polymerizable group at the end of the PLA chain, allowing it to be used as a macromonomer for the formation of comb polymers.

Another class of aluminum catalysts used for lactide polymerizations are aluminum porphyrins,[21-23] commonly TPP-Al-OMe (TPP = tetraphenylporphyrin). The advantage of these catalysts is that the polymerizations are "immortal," which is related to living polymerizations. "Immortal" polymerizations are especially resistant to termination, even in the presence of water or alcohols, which commonly terminate lactide polymerizations or cause chain transfer, decreasing molecular weights. Trofimoff reported that a lactide polymerization at room temperature gave an M_n of 16400 with a PDI of 1.12. No rate constant was given, but it was stated that the polymerization reached 94% conversion after 96 hours.[21] Aluminum porphyrin polymerizations[21-23] typically use CH_2Cl_2 since the higher solubility of the monomer in this solvent allows the use of lower reaction temperatures.

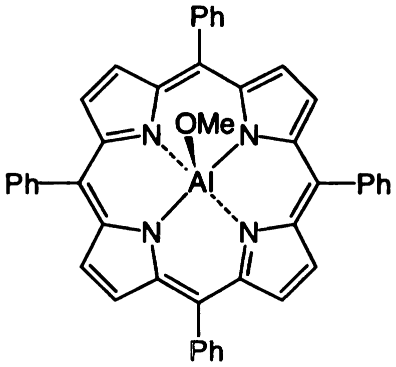


Figure 1.9 Aluminum porphyrin catalyst

Another important class of catalysts is based on lanthanides. Yttrium is one of the most popular metals, and a variety of yttrium alkoxide species have been used to polymerize lactide including $Y_5(O)(OiPr)_{13}$,[24] $Y(OCH_2CH_2NMe_2)_3$,[25,26] and $Y(OAr)_3$, where Ar= 2,6-di-*tert*-butylphenyl.[27] Polymerizations using these catalysts are reported to be much faster than aluminum-catalyzed polymerizations. $Y(OAr)_3$ requires an alcohol cocatalyst, such as iPrOH. An advantage of this system compared to $Y_5(O)(OiPr)_{13}$ is that mononuclear $Y(OiPr)_3$ is formed instead of the $Y_5(O)(OiPr)_{13}$ cluster. Because of the lower steric hindrance in $Y(OiPr)_3$, reaction times are reduced, and there is greater control over molecular weight because all isopropoxide groups are active toward polymerization, which is not the case for the cluster form. Polymerizations using the cluster catalyst takes 10 hours to reach complete conversion, compared to less than five minutes for $Y(OiPr)_3$.[27] $Y(OiPr)_3$ also gives a polymer closer to the molecular weight expected from the monomer to catalyst ratios. For example, a lactide polymerizations using $Y(OiPr)_3$ as the catalyst gave a M_n = 10,800 with a PDI of 1.14, compared to the theoretical value of M_n = 7200. A lactide polymerizations using the $Y_5(O)(OiPr)_{13}$ cluster gave M_n = 29300 and a PDI of 1.71, compared to 7600, the expected M_n assuming each isopropoxide group initiates a polymer chain. The rate constant for lactide polymerization catalyzed by $Y(OAr)_3$ is 0.076 L mol^{-1} min^{-1} at room temperature with an initiator concentration of 5.8 mM and 0.22 L mol^{-1} min^{-1} with an initiator ratio of 0.58 mM.[27]

The $Y(OCH_2CH_2NMe_2)_3$ catalyst is among the fastest known in the literature, with a rate constant of 30 min^{-1}, however some difficulty is observed in controlling the reaction due to slow initiation.[25] This causes the plot of molecular weight vs. monomer/ initiation ratio to be curved and increases the average number of polymer chains formed per initiator molecule.

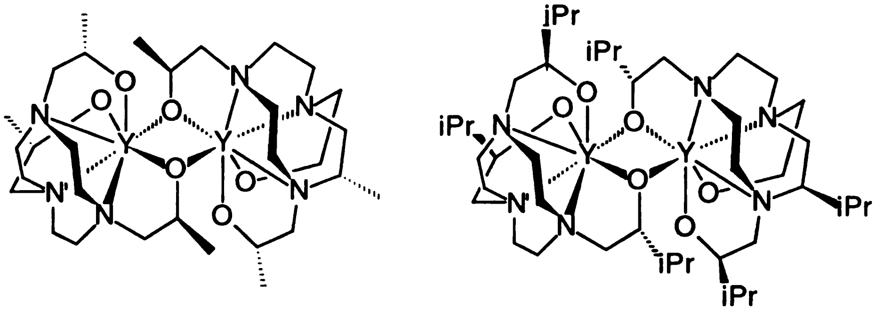


Figure 1.10 Tolman's yttrium catalysts.

Recently, Tolman et al. developed and evaluated new yttrium catalysts (Figure 1.10).[28] The greatest difficulty encountered with these two catalysts was control over the molecular weight as no control over the molecular weight was observed by changing the monomer to catalyst ratio. One advantage of these catalysts is that structural variations can be made to the catalyst to alter the polymerization rates and polymer molecular weights.[28]

1.5 Equilibrium Polymerizations

Many polymerizations reach equilibrium concentrations of monomer and polymer rather than 100 % conversion of monomer to polymer. In polymerizations, this can make it difficult or impossible to reach high molecular weights, especially under conditions such as high dilution which favor the reactants over polymer formation. An important concept related to this equilibrium is the ceiling temperature (T_c).[29,30] At T_c there is no progress in the polymerization because the rate of depolymerization is equal to the rate of polymerization. Because T_c will vary for different polymerization conditions (i.e. monomer concentration, solvent, pressure, etc.), standard conditions for reporting ceiling temperatures are 1 atm. pressure and either pure monomer (solvent-free polymerizations) or a 1 M solution of monomer.

As the monomer concentration decreases, the ceiling temperature also decreases because the initial monomer concentration is closer to the equilibrium monomer concentration. The ceiling temperature can be calculated using the relationship that at that the ceiling temperature, an equilibrium is established and the free energy equals zero:

$$\Delta G=\Delta H-T_c\Delta S=0, \tag{1-1}$$

and

$$T_c=\Delta H/\Delta S. \tag{1-2}$$

Expressing the relationship in terms of an equilibrium constant gives

$$\Delta G= -RT \ln K_{eq}=RT \ln [M]_{eq}, \tag{1-3}$$

which can be rearranged to give the equation:

$$T_c=\Delta H/(\Delta S + R \ln [M]_{eq}). \tag{1-4}$$

The effect of monomer concentration on ceiling temperature can be seen in figure 1.11 for the polymerization of α-methylstyrene in methylcyclohexane.[30] At temperatures greater than the T_c line, only monomer is present, while below T_c there is a polymer-monomer equilibrium. The bottom curve shows the upper limit of monomer solubility. Use of a better solvent, such as tetrahydrofuran, gives nearly the same polymerization line, but lacks the region where the monomer is not soluble in the solvent.[30]

The equilibrium monomer concentration, $[M]_{eq}$, varies with the solvent. For example, $[M]_{eq}$ for the polymerization of trioxane at 30 °C in benzene, 1,2-dichloroethane, and nitrobenzene, is 0.05 M, 0.13 M, and 0.19 M, respectively.[31] The concentration of dissolved polymer in the solvent can also affect $[M]_{eq}$. For the cationic

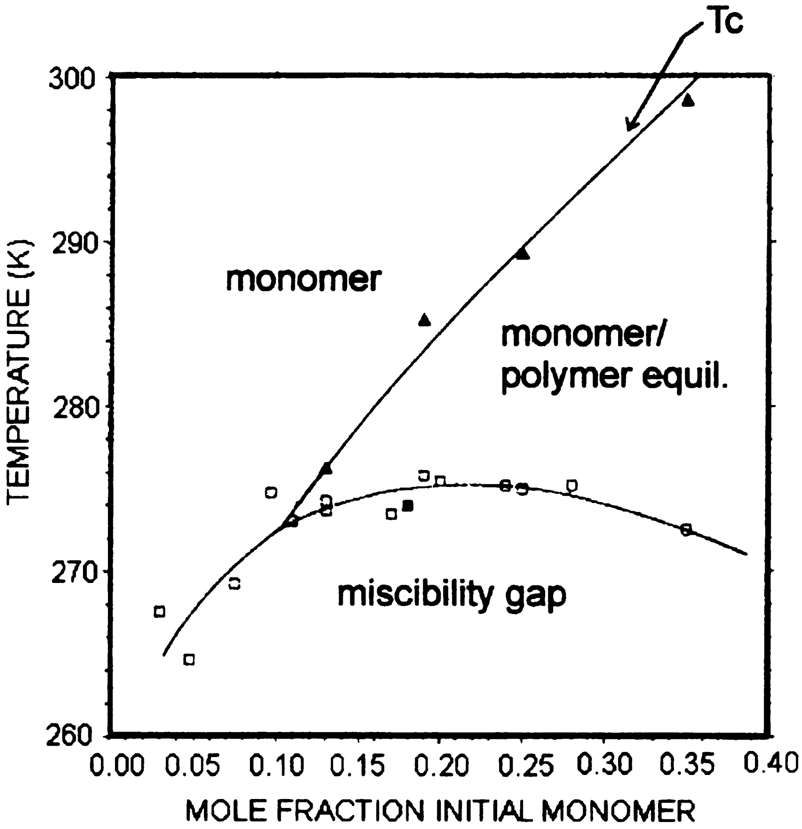


Figure 1.11 The effect of monomer concentration on ceiling temperature

polyme
contain
proport

decreas
from m
polymer
The effe

T
less freq
the free e
materials
which ha
positive.
at tempe
polymeri

E
depolyme
above th
degrade
monomer

polymerization of 1,3-dioxolane in CH_2Cl_2 at 60°C, $[M]_{eq}$ falls from 3.7 M for a solution containing a small amount of polymer to 2.8 M for a solution containing a large proportion of polymer.[32]

Pressure also can alter the ceiling temperature. Since increased pressure decreases the initial entropy, pressure decreases the overall change in entropy in going from monomer to polymer and increases T_c. The ceiling temperature for the polymerization of tetrahydrofuran changes from 81°C at 1 atm. to 129°C at 2500 atm.[33] The effect of pressure is given by

$$d \ln T_c/dP = \Delta V/\Delta H. \tag{1-5}$$

The floor temperature, a condition similar to ceiling temperatures is encountered less frequently. Instead of polymerization taking place below the temperature at which the free energy equals zero, as in ceiling temperatures, floor temperatures are found for materials that only polymerize above that temperature. Unlike most polymerizations which have a negative ΔH, the ΔH for polymerizations with floor temperatures is positive. For polymerization to occur, $-T\Delta S$ must be greater than ΔH, which is true only at temperatures greater than the floor temperature. A common example is in the polymerization of S_8, which only polymerizes above 159°C.[30]

Establishment of an equilibrium in a polymer requires that the polymerization and depolymerization reactions be kinetically accessible. Many polymers are useful materials above their ceiling temperature because they are kinetically stable and usually will not degrade to monomer. Many polymers, such as polyesters, only depolymerize to the monomer in the presence of a catalyst, and not all polymers return to the monomer. For example, polycaprolactone depolymerizes to cyclic oligomers from two to six repeat units instead of ε-caprolactone, with the major fraction being the dimer.[34]

An advantage made available by a monomer-polymer equilibrium is the ability to recycle the polymer to monomer via depolymerization. Ring-opening polymerizations are frequently reversible, the exception being radical reactions. Polyesters are easily depolymerized by intramolecular transesterification (also called backbiting reactions). The catalyst used can affect the amount of transesterification, with catalysts such as Et_2AlOMe used to retard the formation of cyclic oligomers, and tin compounds or alkali metals used to promote depolymerization.[35]

Lactide polymerizations are known to be reversible, and as described earlier, the lactide dimer is frequently produced via depolymerization of low molecular weight polymer. Another equilibrium effect in lactide polymerizations is unreacted monomer present after solution[36] and melt polymerization.[37] The calculation of the T_c is often based on measurements of $[M]_{eq}$ at a number of temperatures. From this data, ΔH and ΔS can be calculated, and since $T_c = \Delta H/\Delta S$ (equation 1-2), the ceiling temperature can then be calculated. Duda calculated a T_c of 641°C for melt polymerization of lactide by extrapolating from the data obtained from solution polymerizations in dioxane. ΔH was –22.9 kJ/mol and ΔS was –41.1 J/mol K.[36] The equation

$$[M]_{eq} = k_d/k_p = 1/K_{eq} \tag{1-6}$$

can be rewritten as

$$[M]_{eq} = \exp(\Delta H/RT - \Delta S/R). \tag{1-7}$$

Using non-linear regression, Witzke used equation (1-7) to calculate the ΔH (–23.3 kJ/mol) and ΔS (–22.0 J/mol K).[37] Using equation 1-2, this gives a T_c of 786 ± 87°C.

Unfortuna
degradati

1.6 Deg

Se
on chang
polymer.
evolution
degradab
and degr
crystallin
morpholo

Th
bulk eros
molecula
of the su
scheme.
molecula
primary
chain en
chain en
Since the

Unfortunately the T_c cannot be measured directly because it is above the thermal degradation temperature of polylactide.

1.6 Degradation of Polylactides

Several methods are used for measuring polymer biodegradation. Many are based on changes in mechanical properties, morphology, and the chemical structure of the polymer. Microbial growth, measured by the uptake of oxygen by microorganisms or the evolution of carbon dioxide, has also been used. Various physical properties of degradable polymers have been studied to find correlations between polymer structure and degradation rates. Important properties include the glass transition temperature, crystallinity, initial molecular weight, hydrophilic/hydrophobic interactions, sample size, morphology, the availability of hydrolyzable groups, and surface area.

There are two limiting cases for the degradation of polyesters, surface erosion, and bulk erosion. In the first, the surface layers of a polymer sample are degraded to low molecular species by hydrolysis or enzymatic degradation, and as the molecular weight of the surface layer decreases, the layer is lost and a fresh surface is exposed. In this scheme, polymer samples slowly shrink in size as the samples degrade, while the overall molecular weight of the sample remains nearly constant. In the second scheme, the primary degradation reaction is the acid-catalyzed hydrolysis of polyester chains. The chain ends of polylactides often are carboxylic acids. As water diffuses into the sample, chain ends catalyze hydrolysis reactions which form an alcohol and a carboxylic acid. Since the local concentration of acid groups increases, the degradation rate of polyesters often increases because the acid groups formed catalyze further hydrolysis (autocatalysis). Polymers that degrade by this mechanism show uniform decreases in molecular weight, but little weight loss until the molecular weight reaches the point where the polymer chains are too short to provide the needed mechanical properties. Such samples disintegrate when the mechanical properties fall below a critical level.

Polymers degrade faster when there are at temperatures $>T_g$. Above T_g, the polymer chains are more flexible, increasing the diffusion rate of small molecules, such as water, and thus increasing the rate of hydrolysis in the interior of polymer samples. Increased polymer chain flexibility also promotes enzymatic degradation at the sample surface since the polymer chains can better adjust to an enzyme's active site, increasing the rate of biodegradation as well. The effect of T_g on the polymer degradation rate can be seen in the temperature dependent degradation of poly(glycolide-*co*-lactide) reported by Reed and Gilding.[38] They found that a plot of degradation (measured by tensile strength) vs. temperature shows a discontinuity at T_g.

Crystalline regions of polymers are inflexible and ordered. Diffusion of small molecules through a crystalline region generally is slow due to the high density of crystalline phases. Not surprisingly, the amorphous regions in semicrystalline polymers tend to degrade first, because their greater free volume enables diffusion of water into the polymer to support hydrolysis, and the polymer chains in amorphous regions have the flexibility to conform to an enzyme's active site for biodegradation. Therefore, the higher the crystallinity of a polymer, the lower the degradation rate.[39,40] Although PLLA is completely degradable, highly crystalline samples can take years to degrade.[41] Since crystallites are tie together by amorphous regions, hydrolysis of the amorphous regions leads to mechanical failure at low weight loss.

Other physical properties can also affect the sample degradation rate. Increasing the surface area of the sample increases the degradation rate by exposing more polymer exposed to either the water (hydrolysis) or enzymes (biodegradation). However, if the degradation mechanism is by hydrolysis, large samples often degrade faster than small samples due to autocatalysis of hydrolysis by the carboxyl groups that form as the polymer chain is hydrolyzed.[42] The initial molecular weight affects degradation by increasing the number of chain scissions that must take place before the polymer reaches the point where it loses mechanical stability. In addition, the number of carboxylic acid chain ends available to catalyze the degradation is related to the molecular weight. The diffusion rate of water into hydrophobic materials may be reduced and result in a slower degradation rate.

In addition to the physical properties of the polymer sample, degradation rates are strongly affected by degradation conditions. Important parameters include pH, ionic strength, temperature, and for the biodegradation of medical implants, the implantation site.[43] Both high and low pH increase the degradation rate, since both acidic and basic conditions catalyze hydrolysis. For the case of implants, it has been shown that certain implant sites put a greater mechanical stress on the implant, giving them a higher degradation rate.[44]

1.7 Methods for Controlling and Varying Physical Properties

1.7.1 Copolymerization

Polylactides have T_gs near 50 °C and melting transitions at 180 °C. From the previous sections, it is clear that having control over the chemical structure of polylactides could provide great flexibility in the physical properties of polylactides, and their degradation behavior. The most common method for controlling and varying physical properties is copolymerization. A number of monomers copolymerize with lactide, such as caprolactone, glycolide,[45-47] carbonates,[48] PEO,[49,50] isocyanates,[51,52] and a lactic acid/lysine cyclic monomer[53,54]. The physical properties of random copolymers fall between those of the parent homopolymers, and depend on the molar composition of the copolymer. Copolymers frequently degrade faster than the homopolymers due a decrease in crystallinity. For example the 50:50 copolymer poly(L-lactide-*co*-glycolide) degrades faster than both PLLA and PGA.[55] Both homopolymers are semicrystalline, but the copolymer is completely amorphous.

In addition, polymers with alcohol end groups can be used as an initiator to form block copolymers, which is frequently done with poly(ethylene glycol).[50,56,57] Block copolymers are formed by sequential additions of monomer to a living polymerization. These polymerizations can be carried out using catalysts such as $Al(OiPr)_3$, however the order in which the monomers are polymerized is sometimes limited. For example, poly(caprolactone) can initiate lactide polymerization, but not vice versa.[58] Comb block copolymers can be formed through the polymerization of macromonomers. The use of initiators like $Et_2AlO(CH_2)_2CH=CH_2$[19] places a polymerizable end group on the polymer chain, that can be polymerized in a later step. The polymer chains in block copolymers phase separate and thus have segments with properties of the homopolymers. Block copolymers have two T_gs corresponding to the parent homopolymers.

Many block copolymers are useful for the formation of micelles and microspheres. For example, a block copolymer of PLA and PEG forms a micelle with a PEG exterior. This is useful in drug delivery systems because PEG inhibits protein adhesion.[59]

1.7.2 Blends

Blending two or more polymers can give polymer mixtures with unique physical properties. This method is rather limited since polymers usually phase separate instead of forming homogeneous mixtures because the entropy of mixing for polymers is low. Blending causes the rates of degradation of the paired polymers to become more similar. For example, in a blend of poly(glycolide-*co*-lactide) and polycaprolactone, the rate of degradation of the PGA/LA slows and that of the PCL increases to nearly match the new rate of PGA/LA degradation.[60] This is true even though DSC measurements show the two polymers were phase-separated. The mechanism by which blending influences the degradation rate is unknown, but it is believed to be related to changes in the morphology and water content of the blend.[61] For PEO/PLA blends, the degradation rate increases with increasing amounts of PEO.[62] The two reasons for this behavior are the decreases in

T_g and increases the hydrophilicity caused by PEO. The T_gs of the blends are intermediate between the T_gs of PEO and PLLA.

1.7.3 Additives

Another method for changing polymer properties is the use of additives, such as plasticizers. Additives are commonly used materials such as poly(vinyl chloride) (PVC). PVC is a strong, but stiff and inflexible polymer, however, the addition of a plasticizer (commonly dioctyl phthalate) makes PVC more flexible. Unplasticized PVC is commonly used to form pipes used for plumbing (T_g = 80 °C), while plasticized PVC (often called "vinyl") has a T_g near 20 °C and is used for upholstery and car dashboards.[63] Plasticizers make polymers more flexible by decreasing the T_g, reducing crystallinity or decreasing the melting temperature. For PLA, common plasiticizers include unreacted monomer, whether left present deliberately or because of an incomplete reaction, and oligomeric PLA.[64]

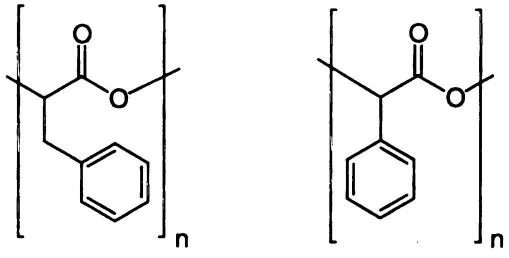
In the case of degradable polymers, additives can also be added to change the degradation rate. For polyesters, acids will catalyze hydrolysis, increasing the degradation rate. Additives that decrease the T_g also increase the rate of degradation by acting as plasticizers. Amino compounds have been shown to catalyze hydrolysis,[61] however they also neutralize carboxyl end groups, and thus decrease the degradation rate.[2] This accounts for some of the contradictions in the literature about the role of a number of additives. Because a number of drugs, such as methadone – a narcotic analgesic, contain amino groups, the plasticizing effect of these compounds is especially important when investigating materials for drug delivery systems. The increase in the degradation rate depends primarily on the nucleophilicity of the amine and not the pK_a or its concentration in the polymer.[65]

1.7.4 Substituted Lactic Acids

A more direct route to control over the physical properties of polylactides is the use of substituted lactides as monomer. In terms of physical properties, having only a methyl group pendant to the polymer backbone is limiting, and to obtain a broader range of physical properties for polyglycolides we can consider simple analogies based on polyolefins. Relatively minor changes in the substituents attached to the polymethylene chain of polyolefins drastically alter their physical properties, and thus analogous changes to the polylactide backbone should provide degradable polymers with a broad range of physical properties. For example, polystyrene has an aromatic ring directly attached to the polymer backbone and because the steric hindrance of the benzene ring limits the flexibility of the polymer backbone, polystyrene has a T_g of 109 °C. Having a polylactide with a T_g >100 °C would enable the use of polylactides use in applications such as disposable packaging.

Very few substituted poly(lactic acid)s are known in the literature, and those reported usually are used in copolymers with lactide. Known poly(substituted lactic acid)s include poly(phenyllactic acid) and poly(mandelic acid) (Figure 1.12). Although mandelic acid is not really a substituted lactic acid, it is included in this list because of its similarity in reactivity and polymerization mechanism. Phenyllactic acid has been polymerized previously by direct polycondensation of the α-hydroxy acid. This method only produces low molecular weight materials, and very little information is known about the polymer other than it is degraded by chymotrypsin.[66] L-Phenyllactic acid (L-PhLA) has also been copolymerized with lactic acid by the same method and the copolymer proven to be biodegradable by implantation in rats. The copolymers had a low molecular weight ($M_n = 3260$, and $M_w = 10400$), and a T_g of 47 °C. A monomer feed ratio of 70 mol % LA to 30 mol % L-PhLA resulted in a copolymer composition of 65 mol % LA to 35 mol % L-PhLA.

Several groups explored the preparation of the mandelic acid homopolymer, but the schemes reported to date resulted in polymers with number average molecular weights <5000, too low for most practical applications. Probably due to their low molecular weights, no glass transition temperatures were reported for these polymers. Mandelic acid also has been reported to have been copolymerized with lactide by first synthesizing the dimer, mandelide.[67] No physical data was reported on the polymer molecular weights, degradability, or other physical properties.



polyphenyllactide
poly(phenyllactic acid)

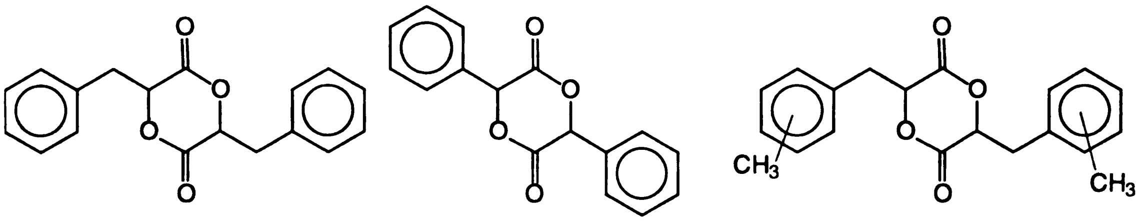
polymandelide
poly(mandelic acid

Figure 1.12 Structure of poly(phenyllactic acid) and poly(mandelic acid)

Literature data for substituted PHBs can be used to predict how the properties of polylactides might change with substitution. For alkyl-substituted poly(hydroxyalkanoates), the crystallinity and glass transition temperature decreases as the length of the sidechain increases. For example, poly(β-hydroxyvalerate) has a T_g of −15 °C, but poly(β-hydroxynonate), which has four more carbons in its side-chain, has a T_g of −37 °C.[68] Slow crystallization rates are reported for long side-chain PHBs.[43]

1.8 Goal of the Project

The purpose of this project is to synthesize a variety of aromatic substituted lactides in order to form new polymers and investigate the physical properties of those polymers. Aromatic substituents were chosen in the hope of developing a biodegradable substitute for polystyrene with a higher T_g than polylactide. Since a polymer softens and loses mechanical stablity at the glass transition, the T_g defines the upper limit for applications. This study will include polymers prepared from phenyllactide, mandelide, and methylphenyllactide (Figure 1.13).



phenyllactide mandelide methylphenyllactide

Figure 1.13 Aromatic substituted lactides.

1.8 Works Cited

1) Chiellini, E.; Solaro, R. *Adv. Mater.* **1996**, *8*, 305-313.

2) Li, S.; Vert, M. In *Degradable Polymers*; Scott, G., Gilead, D., Eds.; Chapman & Hall: London, 1995; pp 43-87.

3) Starkweather, H. W.; Avakian, P.; Fontanella, J. J.; Wintersgill, M. C. *Macromolecules* **1993**, *26*, 5084-5087.

4) Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 4072-4073.

5) Spassky, N.; Wisniewski, M.; Pluta, C.; LeBorgne, A. *Macromolecular Chemistry and Physics* **1996**, *197*, 2627-2637.

6) Radano, C. P.; Baker, G. L.; Smith III, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 1552-1553.

7) Kasperczyk, J. E. *Macromolecules* **1995**, *28*, 3937-3939.

8) Wisniewski, M.; LeBorgne, A.; Spassky, N. *Macromolecular Chemistry and Physics* **1997**, *198*, 1227-1238.

9) Kasperczyk, J.; Bero, M. *Polymer* **2000**, *41*, 391-395.

10) Bero, M.; Dobrzynski, P.; Kasperczek, J. *J. Polym. Sci., Pt. A: Polym. Chem.* **1999**, *37*, 4038-4042.

11) Cheng, M.; Attygalle, A. B.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 11583-11584.

12) Kricheldorf, H. R.; Kreiser-Saunders, I.; Stricker, A. *Macromolecules* **2000**, *33*, 702-709.

13) Kowalski, A.; Duda, A.; Penczek, S. *Macromolecules* **2000**, *33*, 689-695.

14) Ropson, N.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1995**, *28*, 7589-7598.

15) Dubois, P.; Jacobs, C.; Jerome, R.; Teyssie, P. *Macromolecules* **1991**, *24*, 2266-2270.

16) Duda, A.; Penczek, S. *Macromolecules* **1995**, *28*, 5981-5992.

17) Ropson, N.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1994**, *27*, 5950-5956.

18) Tian, D.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1994**, *27*, 4134-4144.

19) Dubois, P.; Jerome, R.; Teyssie, P. *Polymer Bulletin* **1989**, *22*, 475-482.

20) Dubois, P.; Jerome, R.; Teyssie, P. *Makromolekulare Chemie-Macromolecular Symposia* **1991**, *42-3*, 103-116.

21) Trofimoff, L.; Aida, T.; Inoue, S. *Chemistry Letters* **1987**, 991-994.

22) Aida, T.; Inoue, S. *Acc. Chem. Res.* **1996**, *29*, 39-48.

23) Endo, M.; Aida, T.; Inoue, S. *Macromolecules* **1987**, *20*, 2982-2988.

24) Simic, V.; Girardon, V.; Spassky, N.; Hubert-Pfalzgraf, L. G.; Duda, A. *Polymer Degradation and Stability* **1998**, *59*, 227-229.

25) McLain, S. J.; Ford, T. M.; Drysdale, N. E.; Jones, N.; McCord, E. F.; Shreeve, J. L.; Evans, W. J. *Abstracts of Papers of the American Chemical Society* **1994**, *208*, 360-POLY.

26) McLain, S. J.; Ford, T. M.; Drysdale, N. E. *Abstracts of Papers of the American Chemical Society* **1992**, *204*, 188-POLY.

27) Stevels, W. M.; Ankone, M. J. K.; Dijkstra, P. J.; Feijen, J. *Macromolecules* **1996**, *29*, 6132-6138.

28) Chamberlain, B. M.; Sun, Y.; Hagadorn, J. R.; Jemmesch, E. W.; Young Jr., V. G.; Pink, M.; Hillmyer, M. A.; Tolman, W. B. *Macromolecules* **1999**, *32*, 2400-2402.

29) Ivin, K. J. *Makromol. Chem., Macromol. Symp.* **1991**, *42/43*, 1-14.

30) Greer, S. C. *J. Phys. Chem. B* **1998**, *102*, 5413-5422.

31) Miki, T.; Higashimura, T.; Okamura, S. *J. Polym. Sci., A-1* **1970**, *8*, 157.

32) Kizub, L. I.; Markevich, M. A.; Berlin, A. A.; Yenikolopyan, N. S. *Polymer Sci. USSR* **1968**, *10*, 2332.

33) Rahman, M.; Weale, K. E. *Polymer* **1970**, *11*, 122.

34) Nelissen, M.; Keul, H.; Hocker, H. *Macromol. Chem. Phys.* **1995**, *196*, 1645-1661.

35) Hocker, H.; Keul, H. *Macromol. Symp.* **1995**, *98*, 825-834.

36) Duda, A.; Penczek, S. *Macromolecules* **1990**, *23*, 1636-1639.

37) Witzke, D. R.; Narayan, R.; Kolstad, J. J. *Macromolecules* **1997**, *30*, 7075-7085.

38) Reed, A. M.; Gilding, D. K. *Polymer* **1981**, *22*, 494-498.

39) Kanesawa, Y.; Tanahashi, N.; Doi, Y.; Saito, T. *Polym. Degrad. Stab.* **1994**, *45*, 179.

40) Kumagai, Y.; Doi, Y. *Makromol. Chem.* **1992**, *193*, 53.

41) Li, S. M.; Garreau, H.; Vert, M. *J. Mater. Sci. Mater. Med.* **1990**, *1*, 198-206.

42) Grizzi, I.; Garreau, H.; Li, S.; Vert, M. *Biomaterials* **1995**, *16*, 305-311.

43) Hammond, T.; Liggat, J. J. In *Degradable Polymers*; Scott, G., Gilead, D., Eds.; Chapman & Hall: London, 1995; pp 88-111.

44) Therin, M.; Christel, P.; Li, S. M. *Biomaterials* **1992**, *13*, 594-600.

45) Joziasse, C. A. P.; Veenstra, H.; Topp, M. D. C.; Grijpma, D. W.; Pennings, A. J. *Polymer* **1998**, *39*, 467-474.

46) Grijpma, D. W.; Nijenhuis, A. J.; Pennings, A. J. *Polymer* **1990**, *31*, 2201-2206.

47) Grijpma, D. W.; Pennings, A. J. *Polymer Bulletin* **1991**, *25*, 335-341.

48) Schmidt, P.; Keul, H.; Hocker, H. *Macromolecules* **1996**, *29*, 3674-3680.

49) Li, S. M.; Rashkov, I.; Espartero, J. L.; Manolova, N.; Vert, M. *Macromolecules* **1996**, *29*, 57-62.

50) Rashkov, I.; Manolova, N.; Li, S. M.; Espartero, J. L.; Vert, M. *Macromolecules* **1996**, *29*, 50-56.

51) Harkonen, M.; Hiltunen, K.; Malin, M.; Seppala, J. V. *Journal of Macromolecular Science-Pure and Applied Chemistry* **1995**, *A32*, 857-862.

52) Kylma, J.; Harkonen, M.; Seppala, J. V. *Journal of Applied Polymer Science* **1997**, *63*, 1865-1872.

53) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *J. Am. Chem. Soc.* **1993**, *115*, 11010.

54) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *Macromolecules* **1995**, *28*, 425-432.

55) Miller, R. A.; Brady, J. M.; Cutright, D. E. *J. Biomed. Mater. Res.* **1977**, *11*, 711-719.

56) Jin, X. M.; Carfagna, C.; Nicolais, L.; Lanzetta, R. *Macromolecules* **1995**, *28*, 4785-4794.

57) Li, Y. X.; Kissel, T. *Journal of Controlled Release* **1993**, *27*, 247-257.

58) Jacobs, C.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1991**, *24*, 3027-3034.

59) Shields, R.; Harris, J.; Davis, M. *Gastroenterology* **1968**, 54.

60) Cha, Y.; Pitt, C. G. *Biomaterials* **1990**, *11*, 108.

61) Pitt, C. G. In *Biodegradable Polymers and Plastics*; Vert, M., Feijen, J., Albertsson, A., Scott, G., Chiellini, E., Eds.; The Royal Society of Chemistry: Cambridge, 1992; pp 7-17.

62) Nijenhuis, A. J.; Colstee, E.; Grijpma, D. W.; Pennings, A. J. *Polymer* **1996**, *37*, 5849-5857.

63) Sperling, L. H. *Introduction to Physical Polymer Science*; John Wiley & Sons: New York, 1992.

64) Sinclair, R. G. *Journal of Macromolecular Science-Pure and Applied Chemistry* **1996**, *A33*, 585-597.

65) Cha, Y.; Pitt, C. G. *J. Controlled Release* **1988**, *7*, 69.

66) Tabushi, I.; Yamada, H.; Matsuzaki, H.; Furukawa, J. *J. Polym. Sci., Polym. Lett. Ed.* **1975**, *13*, 447-450.

67) Kimura, Y. In *Chem. Abst. 1993, 118, 255577r*: Japan, 1993.

68) Curley, J. M.; Hazer, B.; Lenz, R. W.; Fuller, R. C. *Macromolecules* **1996**, *29*, 1762-1766.

Chapter 2 – Phenyllactide

2.1 Introduction

Polylactide is a versatile polymer whose properties can be modified through control of the polymer stereochemistry and copolymerization. However, its low glass transition temperature (25-50 °C) makes it unsuitable for applications where clear, glassy materials are needed. Polymers such poly(methyl methacrylate) and polystyrene currently are used for such applications, but neither is degradable nor derived from natural sources. A degradable analog of polystyrene would be particularly attractive since it could have important applications as disposable food containers and packaging. Simple structural analogies to polystyrene can be made to try to identify the structural modifications needed to convert polylactide to a material that has a T_g similar to polystyrene's 109 °C. As shown in Figure 2.1, the lactide and polystyrene systems differ in the nature of their backbone and in the presence of an aromatic ring in the polystyrene structure. Two structural analogs of polystyrene, poly(phenyllactic acid) and poly (mandelic acid) are reasonable candidates. SciPolymer, a commercial software package, predicts that the T_g of poly(phenyllactic acid) should be near 60 °C, while that of poly(mandelic acid) should be near 100 °C. Both values are higher than that of polylactide, and we set out to prepare the polymers to evaluate their potential to serve as degradable analogs of polystyrene. In this chapter, we focus on the preparation and characterization of poly(phenyllactic acid).

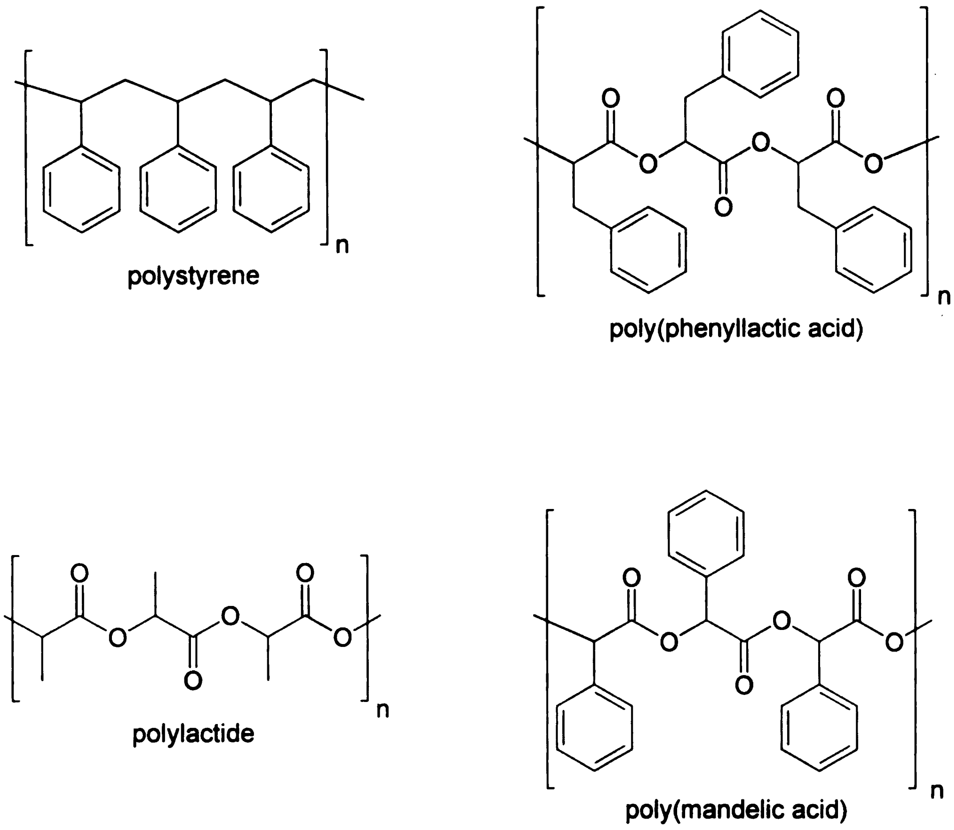
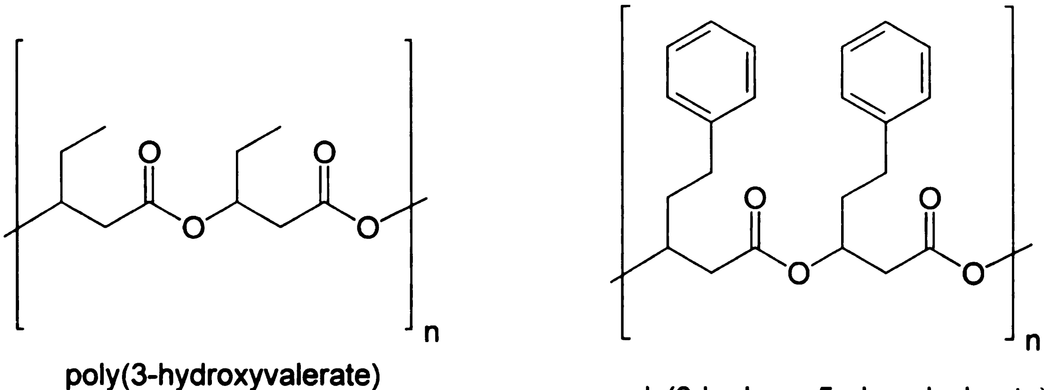


Figure 2.1 Structures of polystyrene, polylactide, and the lactide-based analogs of polystyrene, poly(phenyllactic acid) and poly(mandelic acid).

There are few reports of polymers based on phenyllactic acid. All known examples of poly(phenyllactic acid) were formed by the direct polycondensation of the α-hydroxyacid without a catalyst, a method that usually produces low molecular weight materials (M_n<10,000).[1] Little information was published on the physical properties of poly(phenyllactic acid), however, the polymers were shown to be biodegradable.[1,2] Copolymerizations involving phenyllactic acid are more common, especially those using lactic acid as the comonomer.[1,2] A poly(lactic acid-*co*-phenyllactic acid) copolymer with a 65% lactic acid content had a T_g of 47 °C.[1] Aromatic rings have also been added to the structurally similar poly(hydroxyalkanoate)s to alter their physical properties. As shown in Figure 2.2, adding an aromatic ring to poly(hydroxyvalerate) increased the T_g from –15 °C for the unsubstituted polymer to 13 °C for the aryl substituted polymer.[3] The polymer, poly(3-hydroxy-5-phenylvalerate) was produced biosynthetically by *Psuedomonas oleovorans* from 5-phenylvaleric acid and had a molecular weight (M_w) of 350,000.



poly(3-hydroxyvalerate)
T_g = -15 °C

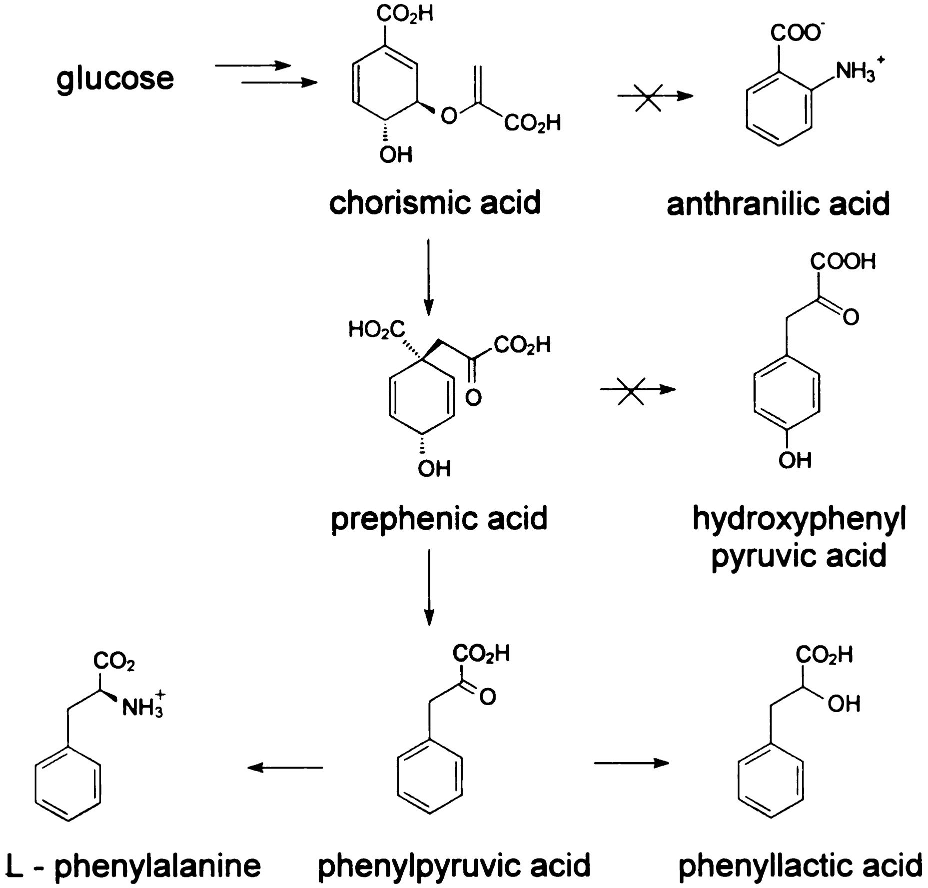
poly(3-hydroxy-5-phenylvalerate)
T_g = 13 °C

Figure 2.2 The effect of an aromatic substituent on T_g.

A practical synthesis of high molecular weight poly(phenyllactic acid) will likely mirror that of polylactide, and involve the ring opening polymerization of phenyllactide, the phenyllactic acid dimer. As described below, the dimer is readily prepared using the same route used to prepare lactide. Phenyllactic acid, the needed starting material, is commercially available, but expensive (approximately $12/g from Aldrich). However, Frost has shown that the biosynthetic pathway for the synthesis of phenylalanine (Scheme 2.1) can be harnessed for the bacterial production of phenyllactic acid.[4] The normal pathway leads from glucose to phenylpyruvic acid, which is converted by a transaminase into the amino acid. Interception of the pyruvate and reduction of the carbonyl produces phenyllactic acid from phenylpyruvic acid. Naturally occurring phenyllactic acid is racemic, although it should be possible to direct the synthesis of a particular phenyllactic acid enantiomer. Thus, fermentation may prove to be a low-cost source of phenyllactic acid.

2.2 Monomer Synthesis

Because the polymerization of phenyllactic acid produces low molecular weight material, we elected to prepare poly(phenyllactic acid) by ring-opening polymerization of the phenyllactic acid dimer. The easiest method for forming the dimer is acid-catalyzed self-esterification, removing the water as it is formed by azeotropic distillation. This method gives a mixture of the cyclic dimer, along with low molecular weight linear

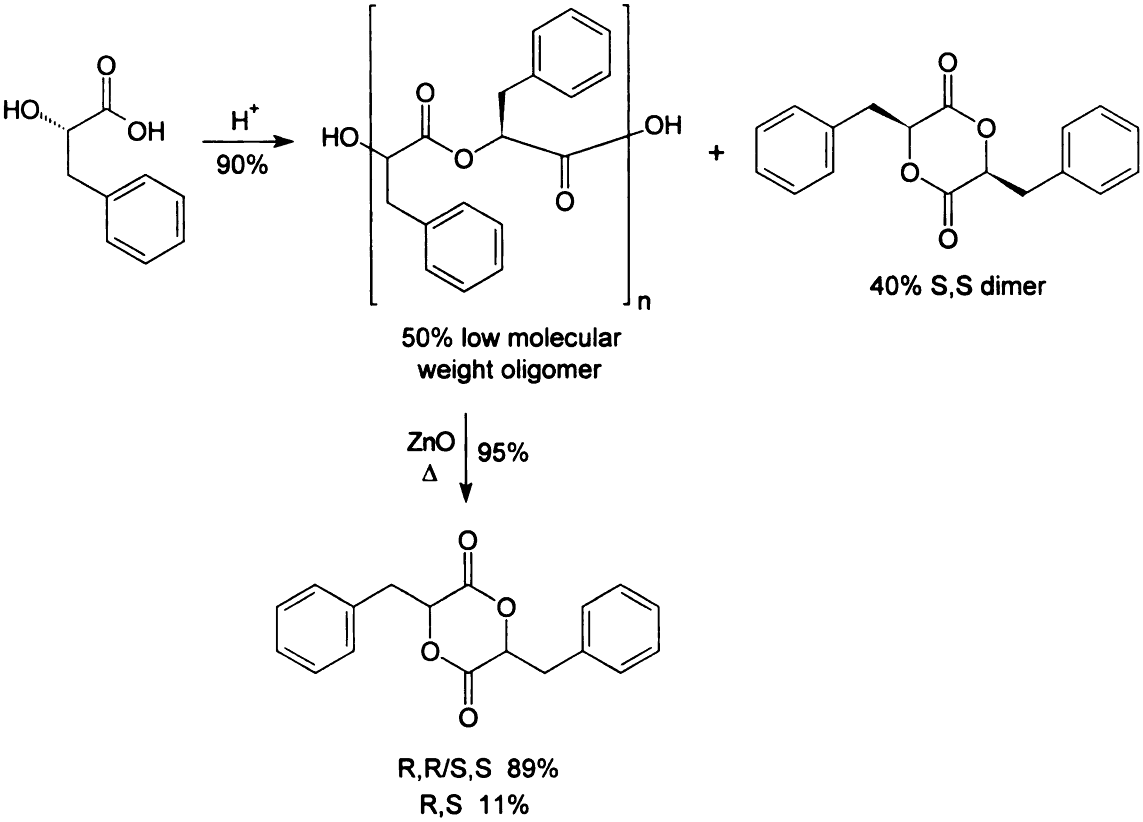


Scheme 2.1 Biosynthetic pathway for phenyllactic acid

oligomers. The dimerization reaction is run in dilute solution to favor production of the dimer over linear oligomers. This unfortunately causes the reaction to be rather slow, taking about one week to reach 90% conversion. Despite the slow rate of dimer formation, one advantage of this reaction is that there is no racemization of the stereocenters, allowing the formation of both the L,L- and D,D-stereoisomers simply by starting with the corresponding phenyllactic acid. The use of racemic phenyllactic acid as the starting material resulted in a mixture of all possible isomers (D,D; L,L; and D,L).

The product mixture (dimer vs. linear products) depended on the amount of *p*-toluenesulfonic acid used to catalyze the reaction. Increasing the amount of catalyst increased the rate of conversion, but had little effect on the absolute yield of dimer (typically near 40%) and increased the amount of oligomer formed. Interestingly, catalyzing the reaction with 4Å molecular sieves in place of *p*-toluenesulfonic acid gave higher conversions but the dimer yield was <10 %, with the remaining product being linear oligomers.

An alternative route to phenyllactide is the thermal cracking of low molecular weight polymer (Scheme 2.2). This method is widely used to prepare lactide. Acid-catalyzed condensation of phenyllactic acid at 120 °C without solvent produces low molecular weight polymer in high yields. When the unpurified polymer is heated under vacuum with ZnO, the dimer can be isolated by distillation. This method is faster and gives a higher yield (80 to 90%), but unfortunately the lower volatility of phenyllactide compared to lactide necessitates high temperatures (230 °C) during the cracking step, and



Scheme 2.2 Synthesis of phenyllactide

epimerization produces approximately 11% of the D,L-isomer and likely some amount of D,D-phenyllactide (starting from 100% L-phenyllactic acid). A method for separating the different isomers has not been found. As with polylactide, the properties of poly(phenyllactide) are expected to depend on the stereoregularity of the polymer, and thus having stereochemically impure monomer is not desirable.

2.3 Solution Polymerization

Solution polymerizations of lactide are slow, often taking days to reach high conversion even at elevated temperatures (70 °C is typically used). Lactide polymerizations are commonly run with a monomer concentration of 1 M, but phenyllactide's lower solubility forced the polymerizations to be run in dilute solution (0.1 M), further increasing the reaction time.

Phenyllactide polymerizations were run in toluene using $Al(OiPr)_3$ and $Sn(Oct)_2$ as the catalysts. Because lactide polymerizations catalyzed by $Sn(Oct)_2$ require an alcohol co-catalyst or residual water for initiation,[5] we used *t*-butylbenzyl alcohol as the initiator in $Sn(Oct)_2$ catalyzed polymerizations to maintain control over the molecular weights. *t*-Butylbenzyl alcohol was chosen because of its low volatility and because the *t*-butyl group provides a signal easily seen in ^1H NMR spectra.

Figure 2.3 shows typical results for phenyllactide polymerizations. The polymerizations are slow, taking weeks to reach conversions above 70%. In addition, the polymerizations typically did not reach high conversion but instead approached a limiting value of conversion. Two possibilities can explain this trend: catalyst degradation or

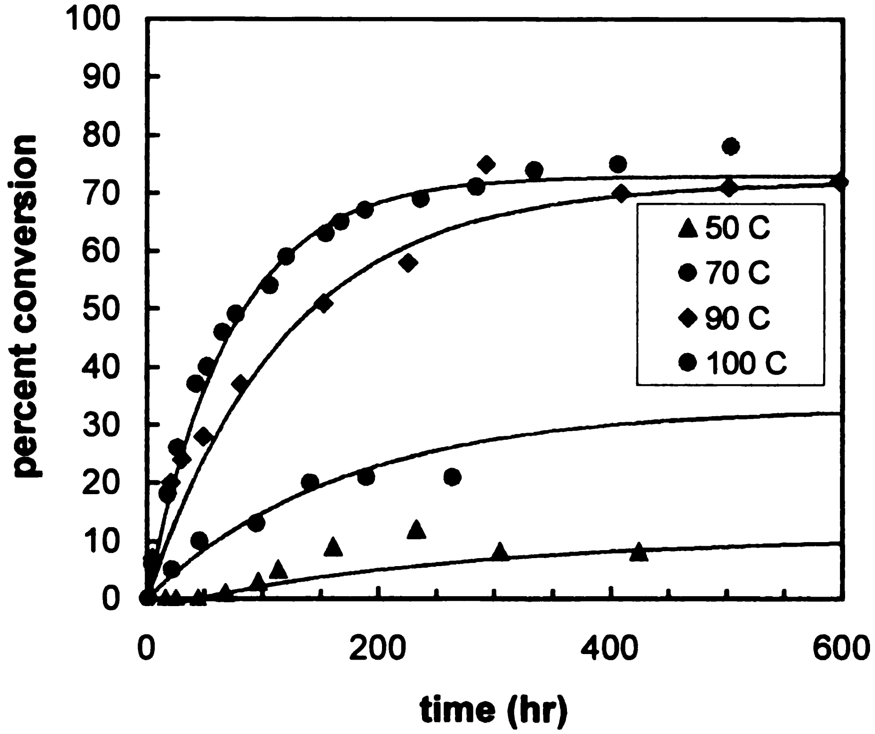


Figure 2.3 Solution polymerization of phenyllactide with $Sn(Oct)_2$ at various temperatures. All reactions were carried out using 0.1M L,L-phenyllactide in toluene with monomer to catalyst ratios of 100, and BBA as the initiator in a monomer to initiator ratio of 100. (Images in this dissertation are presented in color.)

equilibrium control of the polymerization. The former would result from slow degradation of the catalyst by an unknown process with the conversion achieved defined by the relative rates for propagation and catalyst degradation. Equilibrium control would imply that the rates of propagation and depropagation would be nearly equal, especially near room temperature. The solution polymerization data can be fit to equations that correspond to these two cases.

For termination due to catalyst degradation, the expression for the rate of propagation (equation 2.1):

$$-\frac{dM}{dt} = k_p [M^*] [M] \qquad (2.1)$$

where k_p is the rate constant for polymerization and [M*] is the concentration of active, growing chains, can be modified to include the loss of active propagation sites. Equation (2.2) assumes spontaneous loss of active sites,

$$-\frac{d[M^*]}{dt} = [M^*_0]\, e^{-k_d t} \qquad (2.2)$$

where k_d is the rate constant of decomposition. Integrating (2.2) and solving for [M*] gives equation (2.3),

$$[M^*] = A\, e^{-k_d t} \qquad (2.3)$$

where A is a constant. Substituting (2.3) into equation (2.1) and integrating gives equation (2.4)

$$-\ln\left(\frac{[M]}{[M]_0}\right) = -\frac{k_p A}{k_d}\left(e^{-k_d t} - 1\right) \qquad (2.4)$$

The case of equilibrium control has been studied previously,[6] and is described by equations 2.5 and 2.6:

$$[M]_t = [M]_{eq} + ([M]_0 - [M]_{eq})\, e^{-kp[I]t} \quad (2.5)$$

$$X = (1-[M]_{eq}/[M]_0)/(1-e^{kp[I]t}) \quad (2.6)$$

where $[M]_t$ is the monomer concentration at time = t, $[M]_{eq}$ is the monomer concentration at equilibrium, $[M]_0$ is the initial monomer concentration, k_p is the polymerization rate constant, [I] is the initiator concentration, and X is the conversion $(1-[M]_t/[M]_0)$.

The experimental data for $Al(OiPr)_3$ and $Sn(Oct)_2$ catalyzed polymerizations can be fit to both the catalyst degradation and equilibrium models. As shown in Figure 2.4, both models give reasonable fits to the data, but the catalyst degradation scheme seems more plausible. In an equilibrium polymerization, the equilibrium monomer concentration is expected to increase with increasing temperature,[7] decreasing the percent conversion at equilibrium. As shown in Figure 2.3, the opposite trend was observed, with the highest conversions seen at the highest temperatures. In solution polymerizations of alkyl-substituted lactides using the same $Sn(Oct)_2$ catalyst system, a solid precipitate was isolated which was proposed to be a 2:1 polymer formed from the alkyl-substituted lactic acid and Sn(II).[8] Similarly, a precipitate isolated from lactide polymerizations[9] was identified as a cyclic tin-lactic acid complex based on elemental analysis data. Loss of catalyst from polymerizations by precipitation would be consistent with the observed data. However, no precipitate was isolated from phenyllactide polymerizations.

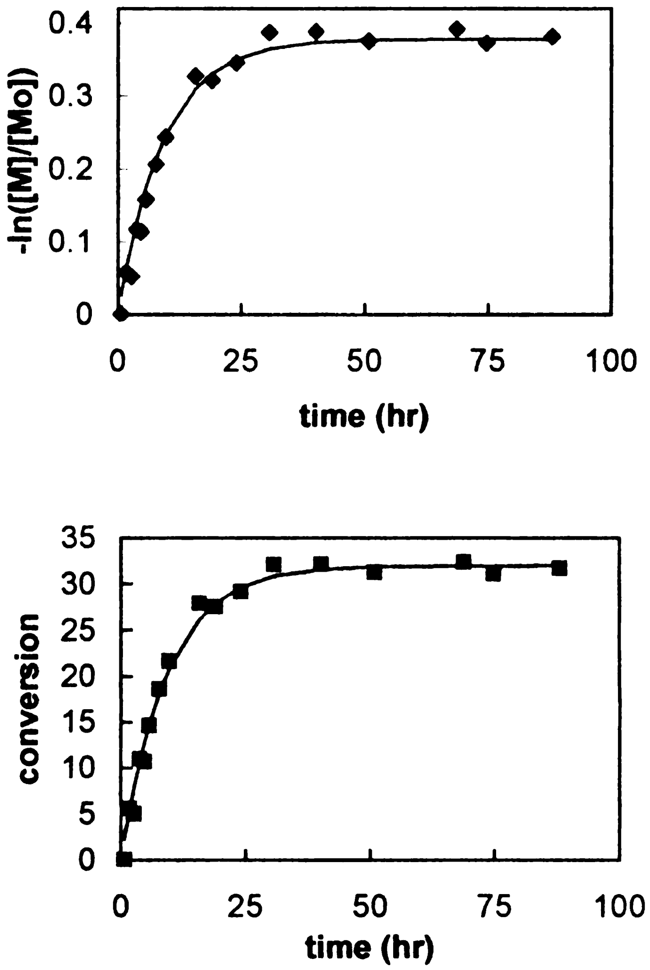


Figure 2.4 Both plots show the polymerization of phenyllactide in toluene solution at 0.1M and a temperature of 50 °C. In the top graph, the data are fit to the catalyst degradation model and, in the bottom graph, the same data are fit to the equilibrium model.

Solution polymerizations of phenyllactide provided poor control over polymer molecular weights. The extremely long reaction times (up to 600 h for $Sn(Oct)_2$ catalyzed reactions) allowed for a greater amount of intra- and inter-molecular transesterification to take place. Intermolecular transesterification tends to broaden the molecular weight distribution, but has no effect on the number average molecular weight. Intramolecular transesterification forms cyclic oligomers, which broaden the molecular weight distribution and decrease the number average molecular weight. As shown in Figure 2.5, the polymer molecular weights are lower than predicted by monomer/initiator ratios, suggesting that intramolecular transesterification is an important side reaction. In addition, intermolecular transesterification likely contributes to the polydispersities being >1. Thus, even though polymerizations at 100 °C reach 80 % conversion (Figure 2.3), the molecular weights remained below 8000 g/mol.

Aluminum isopropoxide is a better catalyst, in that it decreases the reaction time to approximately 200 hours, however it reaches even lower conversions (Figure 2.6). Increasing the temperature from 50 °C to 90 °C gives no reaction. This cannot be because of ceiling temperature behavior because phenyllactide is polymerized by $Sn(Oct)_2$ at 90 °C, and the catalyst does not change the ceiling temperature. A more likely reason is that the catalyst degrades quickly at the higher temperature leaving no $Al(OiPr)_3$ to catalyze the polymerization. The maximum conversion reached at 50 °C is 32 %, too low to have produced high molecular weights.

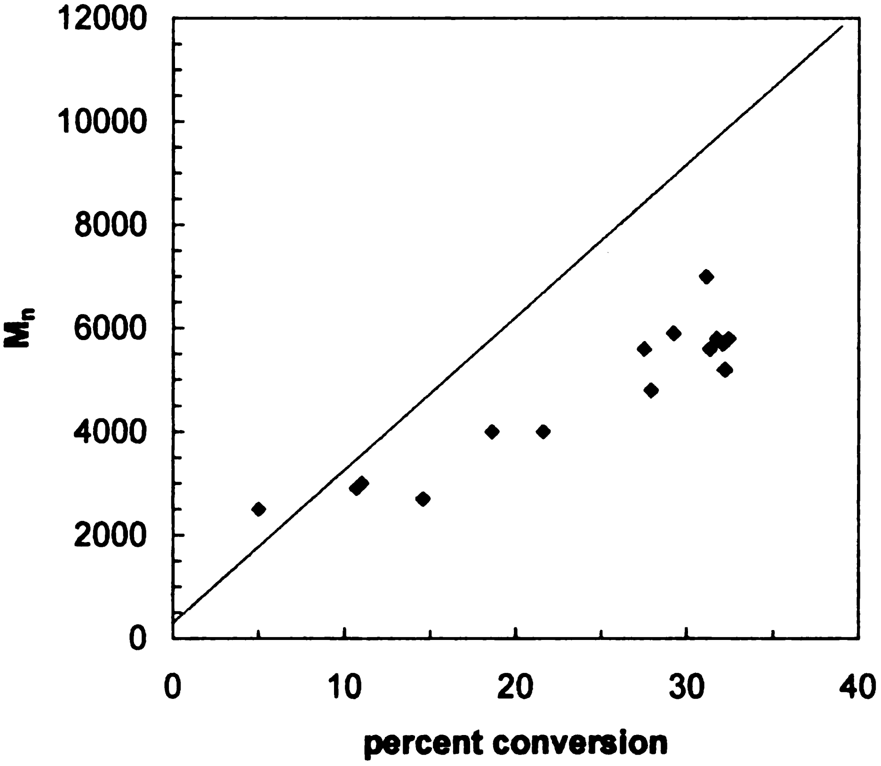


Figure 2.5 Plot of the number average molecular weight vs. conversion for the $Al(OiPr)_3$-catalyzed polymerization of L,L-phenyllactide in toluene (0.1 M) at 50 °C at a monomer to catalyst ratio of 304 (theoretical molecular weight of 30,000 g/mol). The line shows the theoretical molecular weight as a function of conversion.

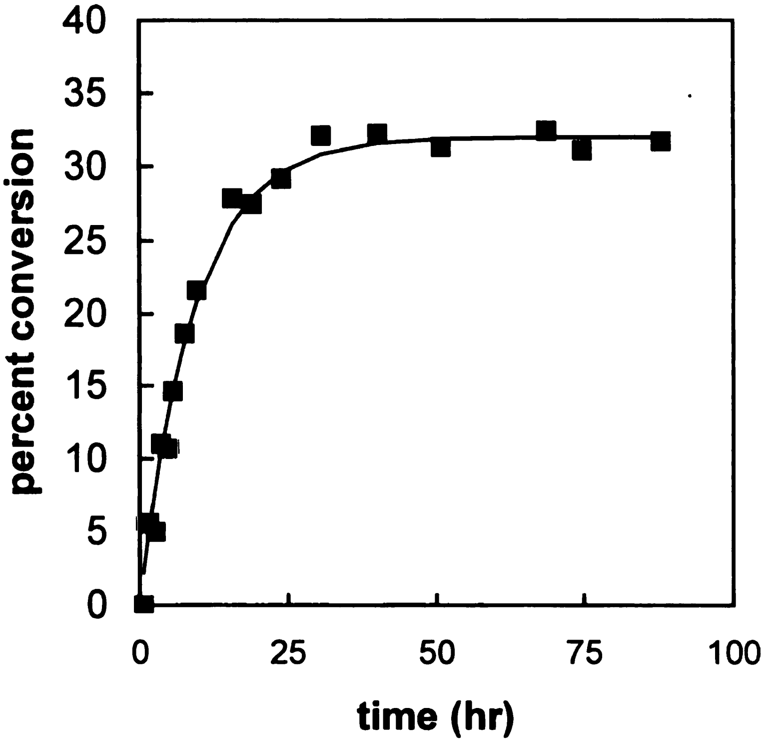
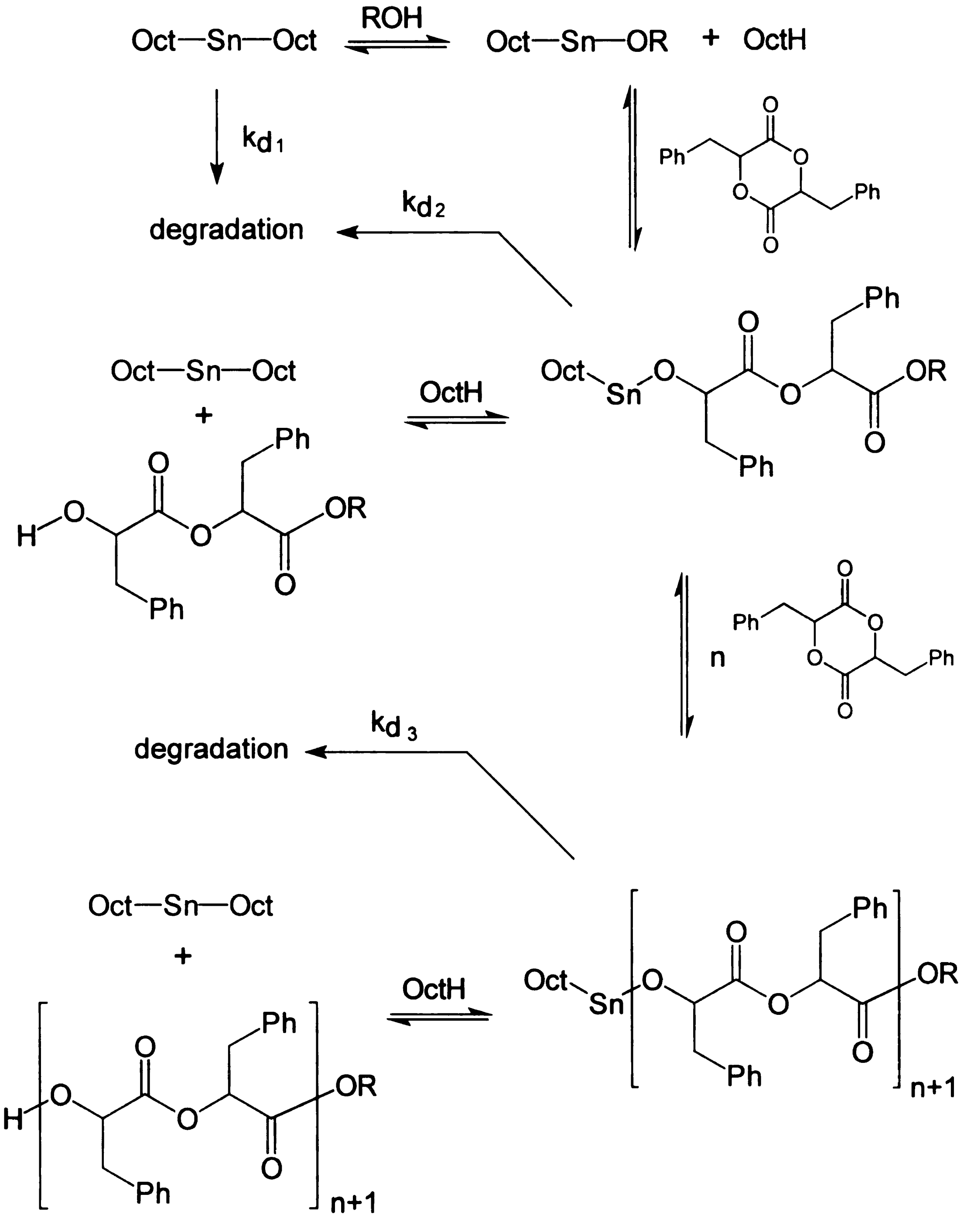


Figure 2.6 Solution polymerization of L,L-phenyllactide using $Al(OiPr)_3$. The reaction was run at 0.1 M in toluene at a temperature of 50 °C with a theoretical molecular weight of polymer of 30,000 g/mol.



Scheme 2.3 Mechanism of $Sn(Oct)_2$ catalyzed polymerization of phenyllactide.

As with $Sn(Oct)_2$ catalyzed polymerizations, transesterification occurs during the reaction, limiting molecular weights to approximately 6000 g/mol. It also should be noted that $Al(OiPr)_3$ catalyzed reactions are much faster than the tin-catalyzed ones.

$Sn(Oct)_2$ polymerizations were run both with and without alcohol cocatalyst. The reactions with alcohol are more predictable since those initiated by residual water in the monomer or catalyst solution lead to an unknown number of chains initiated. The proposed mechanism for $Sn(Oct)_2$-catalyzed polymerization is shown in Scheme 2.3. $Sn(Oct)_2$ first reacts with water or alcohol to form the active catalyst, which then reacts with the monomer to begin the polymerization. Like solution polymerizations using aluminum isopropoxide, transesterification becomes important at long reaction times or low monomer concentrations, preventing the formation of high molecular weight polymer. The M_n of polyphenyllactide obtained from solution polymerizations are typically less than 8000 g/mol, regardless of the catalyst used. Since stannous octoate catalyzed polymerizations are much slower than those using $Al(OiPr)_3$, it is not commonly used for solution polymerizations of lactide.

2.4 Melt Polymerization

Because melt polymerizations take place at much higher temperatures and have a higher monomer concentration (no solvent), the reactions are complete in minutes instead of hundreds of hours. Unlike solution polymerizations, the faster melt reaction allows much higher monomer conversion, but a small amount of monomer (3% at 180 °C) remains unreacted. Like the solution polymerizations, the kinetics can be fit to both equilibrium and catalyst degradation models. Reaction of pure polymer with catalyst produces the same amount of residual monomer as polymerization, providing support for the equilibrium model. Lactide polymerizations are reportedly equilibrium controlled.[6,10]

There are advantages and disadvantages to melt polymerizations. While the higher temperature allows for faster reactions and not having solvent is preferred for commercial processes in order to reduce cost and disposal of used solvent, there is greater transesterification and epimerization. Epimerization gives less control over the polymer structure, and therefore the final polymer properties. Transesterification reduces control over the molecular weight and increases the polydispersity. Reactions at extended times have decreasing molecular weights due to intramolecular transesterification, which forms cyclic oligomers.

A variety of catalysts were tested for their efficacy in melt polymerizations (Table 2.1) at both two hours and 48 hours. All reached high conversions after 48 hours, but the molecular weights were lower than calculated based on monomer to catalyst ratios. The longer reaction time increases the amount of intramolecular transesterification (also called backbiting) which forms cyclic oligomers, increases the number of polymer chains, and therefore decreases the molecular weight. The decrease in number average molecular weights at extended reaction times was monitored for phenyllactide polymerizations using $Sn(Oct)_2$ as the catalyst (Figure 2.7). The decrease in molecular weight is consistent with random chain scission, described by the following equation,[11] Reaction Time

	2 h				48 h			
catalyst	% conv	M_n	M_w	PDI	% conv	M_n	M_w	PDI
$Sn(Oct)_2$	96	12.7	28.6	2.26	98	6.7	10.8	1.50
$Al(OiPr)_3$	78	10.7	15.8	1.48	94	5.9	8.7	1.38
Ph_4Sn	91	13.3	20.5	1.54	95	4.6	5.7	1.23
$Bi(Oct)_3$	93	16.4	24.6	1.50	95	14.5	26.3	1.81
ZnO	16	2.8	3.5	1.25	88	11.0	19.5	1.77
SnO	24	5.6	8.0	1.43	90	9.7	16.6	1.71
PbO	96	11.9	26.7	2.25	95	6.7	9.6	1.42
Fe_2O_3	18	3.8	4.7	1.23	67	15.0	27.0	1.80
$SnCl_2$	88	12.0	17.0	1.42	96	4.7	5.5	1.16
$SnBr_2$	75	35.8	52.3	1.46	96	14.6	29.2	2.00
$SnBr_4$	26	6.3	7.9	1.26	97	11.4	22.1	1.94
Zn stearate	69	7.3	10.2	1.39	97	7.4	12.2	1.65

Table 2.1. Melt polymerization of phenyllactide with various catalysts. The first set of data is for a 2 h reaction time, and the data on the right is for 48 h. All reactions were carried out at 180 °C with monomer to catalyst ratios of 100.

$$DP_t = \frac{1}{k^*t + \frac{1}{DP_0}} \quad (2.7)$$

where DP_t is the degree of polymerization, k is a constant, and DP_0 is the initial degree of polymerization. A problem with this model and a reason that the fit is not ideal, is the assumption that the product of the chain scission reaction cannot react further (other than continued chain scission). This is not the case. For example, if the products of the chain scission reaction are cyclic oligomers, these can be monomers for the polymerization reaction. The amount of epimerization varied with the catalyst used but was less than 15%, with most samples being less than 10%, and was higher for longer reaction times (up to 30%, with the majority of samples being greater than 10%).

2.5 Polymer Properties

Differential scanning calorimetry (DSC) shows that the polyphenyllactide obtained from melt polymerizations is amorphous as demonstrated by its lack of a detectable melting point (Figure 2.8). Typically, polylactide produced from L-lactide is semicrystalline because of the regular tacticity. In the case of poly(L-phenyllactide) approximately 5-15 % epimerization takes place, disrupting crystallization and leading to an amorphous polymer. No DSC scans were run on the polymer produced by solution polymerizations because of their low molecular weights.

The T_g of polyphenyllactide is $50 \pm 3°C$, which is lower than expected when compared to polystyrene, and surprisingly near that reported for low molecular weight

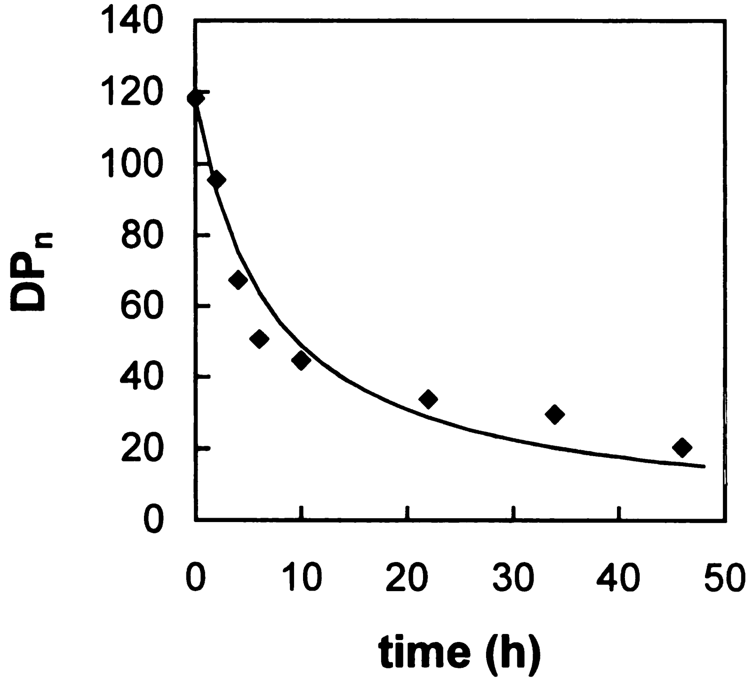


Figure 2.7 Melt polymerization of phenyllactide at longer reaction times. The reaction was carried out at 180 °C with $Sn(Oct)_2$ and BBA. The monomer to catalyst and monomer to co-catalyst ratios were 100. The curve is based on equation 2.7.

poly(lactic acid-*co*-phenyllactic acid).[1] We believe this is due to the added flexibility in the side-chain due to the methylene group between the main-chain and the aromatic ring, making the polymer more similar to poly(allylbenzene) (T_g=60 °C)[12] than polystyrene (T_g=110 °C). Polyphenyllactide can be processed into films by solution casting from cyclopentanone or melt pressed by heating above the T_g. The films are clear and colorless.

Thermal gravemetric analysis indicates that the polymer degrades at approximately 330 °C (Figure 2.9). The primary degradation pathway is believed to be cracking back to the cyclic monomer. To confirm this, a sample of polymer was degraded under vacuum and the products analyzed by ^{1}H NMR. The major product of this degradation (95 %) was phenyllactide, with 11% isomerization to produce the R,S isomer. Based on these results, we believe the degradation temperature to be related to the volatility of the lactide monomer. Its higher degradation temperature is consistent with the lower volatility of phenyllactide compared to lactide.

2.6 Polymer Degradation

Hydrolytic degradation of phenyllactide was carried out at a pH of 7.4 at 55 °C, the products being phenyllactic acid and low molecular weight oligomers. A number of factors can affect the degradation rate, such as crystallinity, T_g, and hydrophobicity. Since phenyllactide is amorphous, it has a faster degradation rate than poly(L-lactide), but a slower degradation rate than poly(D,L-lactide). Because the reaction was run above

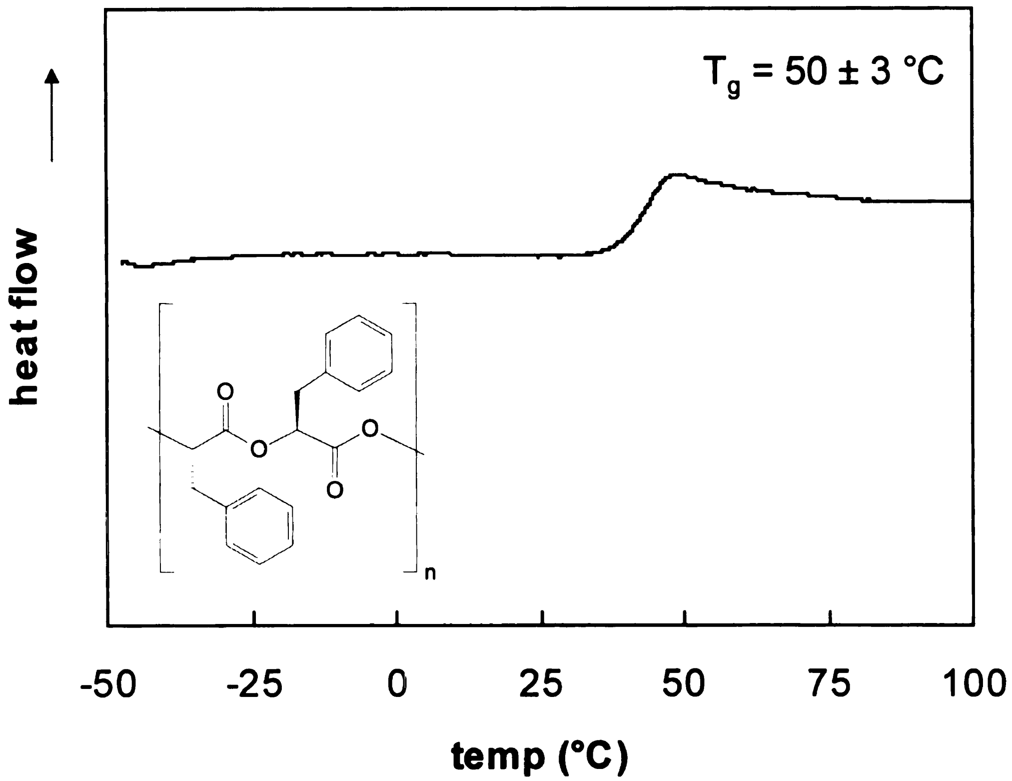


Figure 2.8 DSC scan of poly(L-phenyllactide). The sample was heated at a rate of 10 °C/min. in a helium atmosphere.

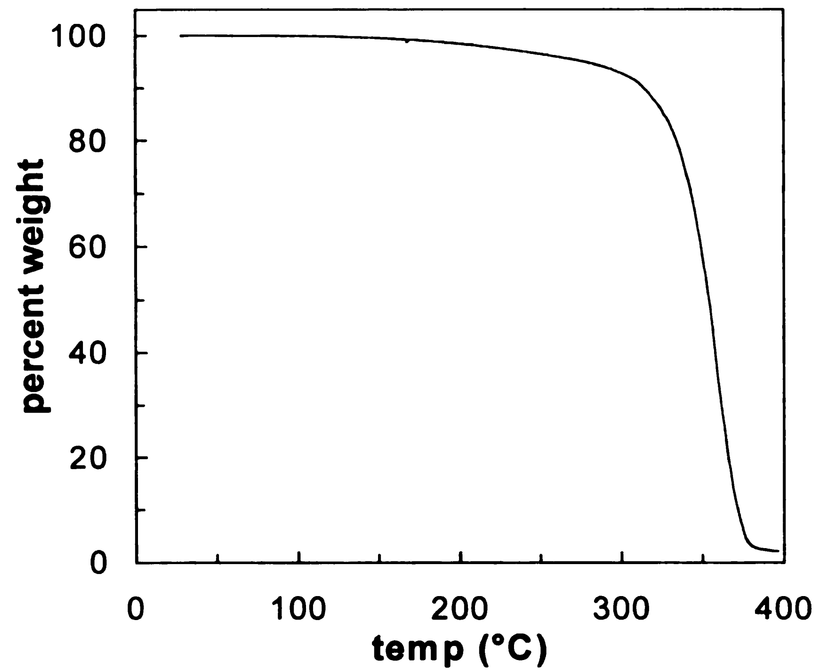


Figure 2.9 TGA of polyphenyllactide. The sample was heated at a rate of 10°C/min in a nitrogen atmosphere.

the glass transition temperature of both polymers, this is not a factor in the degradation rate, leaving polymer hydrophobicity as the major factor in the degradation rate. Polyphenyllactide, having a relatively large, non-polar side-chain, is more hydrophobic than polylactide, which explains the slower degradation rate. The calculated rate constant for the degradation is 0.0037 s^{-1} for polylactide and 0.00071 s^{-1} for polyphenyllactide.

The molecular weight curve (Figure 2.10) also displays an apparent induction time, and then follows the calculated curve based on random chain scission. The induction time is related to the hydrophobicity of the polymer. For a hydrophobic polymer, the concentration of water inside the polymer is relatively low, decreasing the rate of hydrolysis. This phenomenon was reported for the degradation of lactic acid/mandelic acid[13] and lactic acid/ phenyllactic acid copolymers.[1] There is a noticeable delay before the sample experiences weight loss (Figure 2.12). The molecular weight must decrease enough for the oligomers formed to be soluble.

Near the end of the experiment, polyphenyllactide degraded faster than predicted by the random chain scission model. Even though the samples were added to the tubes as small pieces, the pieces aggregate into one large piece because the reaction temperature is greater than the T_g. Because of this, once degradation begins, more acid end groups from the polymer are concentrated in the center of the sample, where they can catalyze the hydrolysis reaction and increase the degradation rate. Faster degradation in the center of large specimens of polylactide has been reported previously with the same explanation given.[14]

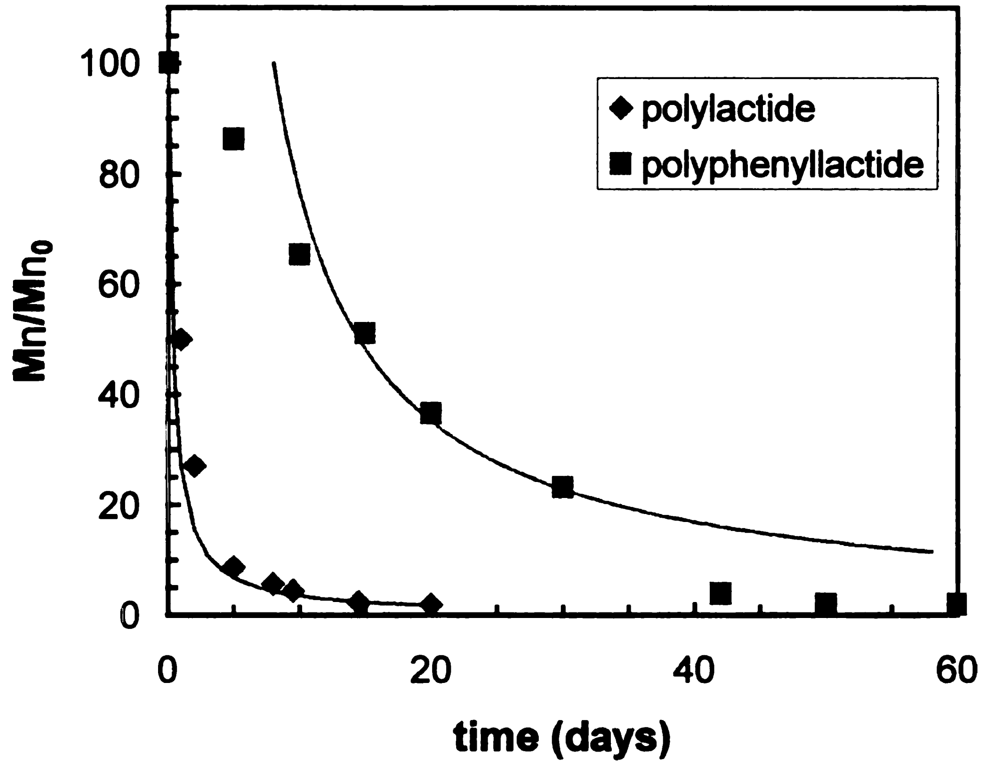


Figure 2.10 Degradation of polyphenyllactide and poly(lactide) 55 °C in a phosphate buffer solution at a pH of 7.4.

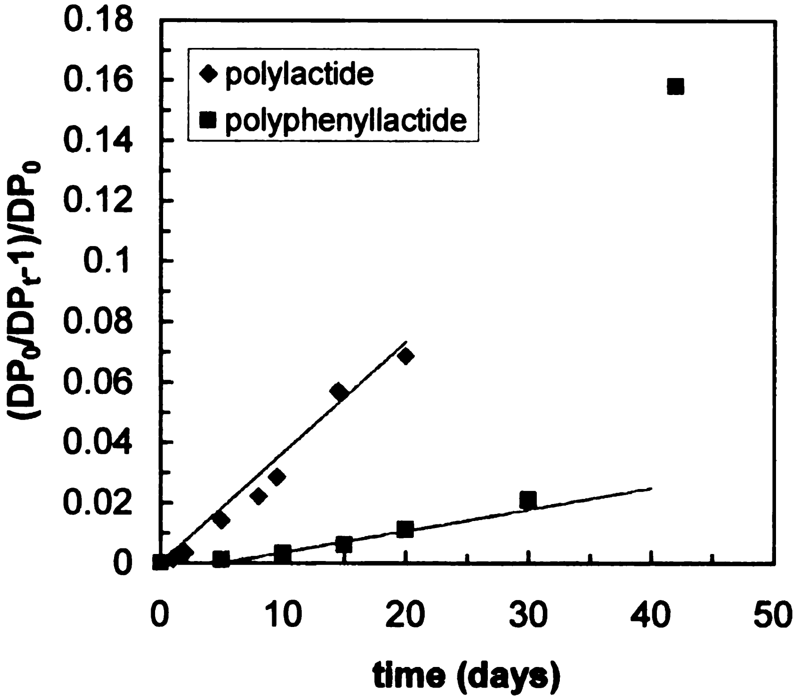


Figure 2.11 Degradation of polyphenyllactide and poly(lactide) 55 °C in a phosphate buffer solution at a pH of 7.4. The data are the same as plotted in Figure 2.10, but plotted to give a linear relationship.

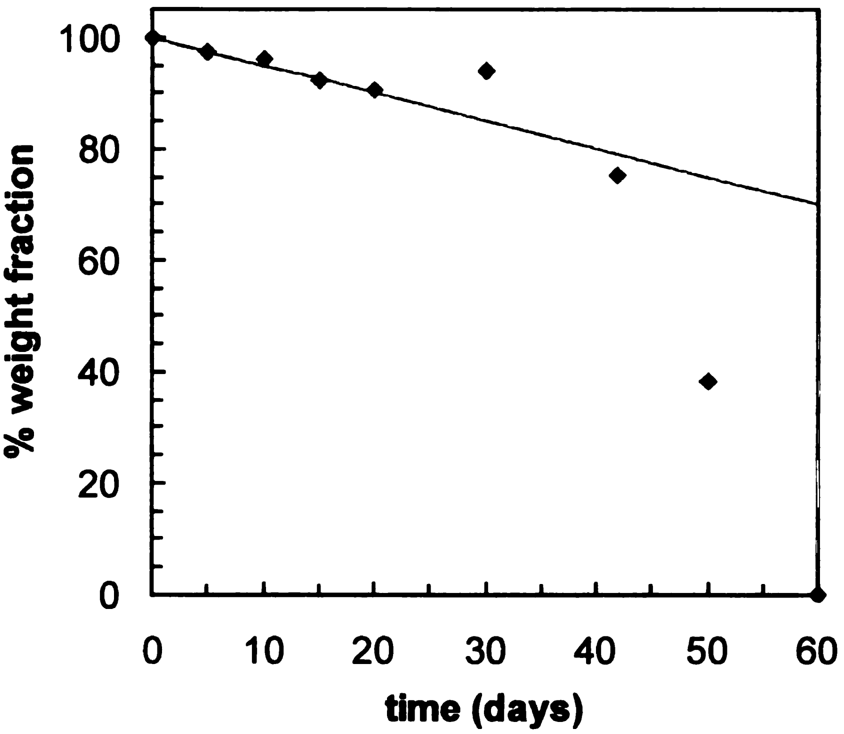


Figure 2.12 Weight loss during the degradation of polyphenyllactide. The degradation was run in a phosphate buffer solution at a pH of 7.4 and a temperature of 55 °C.

2.7 Summary

Solution polymerization of phenyllactide gives low conversions that depend on the catalyst ($Sn(Oct)_2$ or $Al(OiPr)_3$) and reaction temperature. For both catalysts, the conversion of monomer to polymer saturates due to catalyst degradation and the onset of a monomer-polymer equilibrium. Because of the limiting behavior of solution polymerization, melt polymerizations are the method of choice for obtaining high molecular weight poly(phenyllactide). A variety of catalysts polymerize phenyllactide under melt conditions, with repeatability and control over molecular weight best obtained through the use of an alcohol initiator. Longer polymerization times reduce the molecular weight through transesterification side reactions which broaden the molecular weight distribution.

Poly(phenyllactide) degrades at >300 °C to phenyllactide, which should enable simple recycling of the polymer. Polyphenyllactide has no measurable crystallinity. It can be processed into clear, colorless films by solution casting or by melt pressing the polymer above the T_g. Unfortunately, the T_g of polyphenyllactide is too low for it to be a suitable substitute for polystyrene. However, we expect that changing the substituents on the aromatic ring of polyphenyllactide could provide the desired properties.

2.8 Works Cited

1) Fukuzaki, H.; Yoshida, M.; Asano, M.; M., K.; Imasaka, K.; Nagai, T.; Mashimo, T.; Yuasa, H.; Imai, K.; Yamanaka, H. *Eur. Polym. J.* **1990**, *26*, 1273-1277.

2) Tabushi, I.; Yamada, H.; Matsuzaki, H.; Furukawa, J. *J. Polym. Sci., Polym. Lett. Ed.* **1975**, *13*, 447-450.

3) Fritzsche, K.; Lenz, R. W.; Fuller, R. C. *Makromol. Chem.* **1990**, *191*, 1957-1965.

4) Snell, K. D.; Draths, K. M.; Frost, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 5605-5614.

5) Nijenhuis, A. J.; Grijpma, D. W.; Pennings, A. J. *Macromolecules* **1992**, *25*, 6419-6424.

6) Witzke, D. R.; Narayan, R.; Kolstad, J. J. *Macromolecules* **1997**, *30*, 7075-7085.

7) Ivin, K. J. *Makromol. Chem., Macromol. Symp.* **1991**, *42/43*, 1-14.

8) Yin, M.; Baker, G. L. *Macromolecules* **1999**, *32*, 7711-7718.

9) Kricheldorf, H. R.; Kreiser-Saunders, I.; Stricker, A. *Macromolecules* **2000**, *33*, 702-709.

10) Duda, A.; Penczek, S. *Macromolecules* **1990**, *23*, 1636-1639.

11) Jellinek, H. H. G. In;; Jellinek, H. H. G., Ed.; Elsevier Sci. Rub. Co.: Amsterdam, 1978; pp 1-38.

12) Seefried Jr., C. G.; Koleske, J. V. *J. Polym. Sci.: Polym. Phys. Ed.* **1976**, *14*, 663-673.

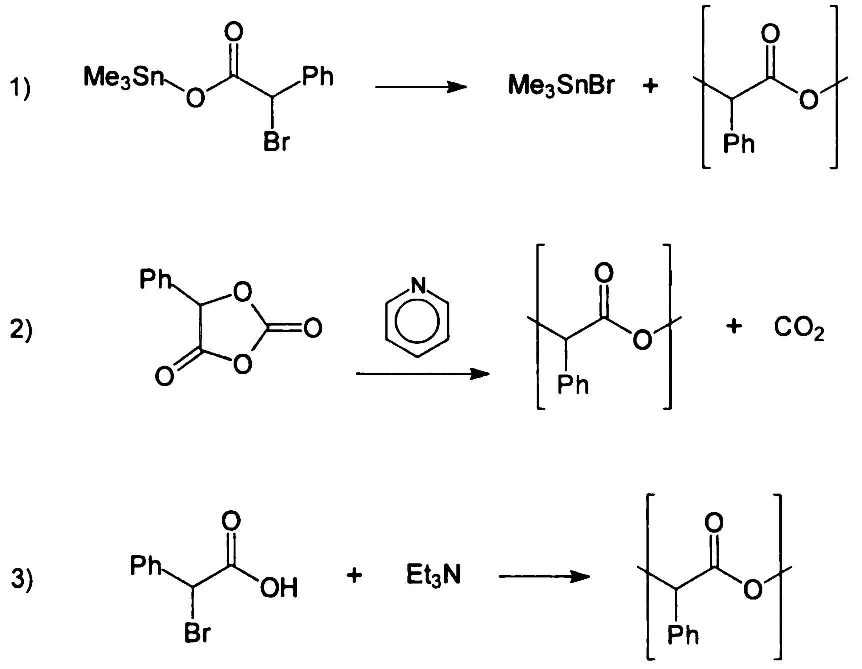
13) Fukuzaki, H.; Aiba, Y. *Makromol. Chem.* **1989**, *190*, 2407-2415.

14) Li, S. *J. Biomed. Mater. Res.* **1999**, *48*, 342-353.

Chapter 3 – Mandelide

3.1 Introduction

Like phenyllactic acid, there has been limited work on the synthesis of mandelic acid polymers. Most syntheses have produced low molecular weight materials, with the two most common methods being the polycondensation of mandelic acid,[1] and the transesterification of methyl mandelate[2] with removal of methanol. Poly(mandelic acid) was first synthesized by the pyrolysis of the trimethyltin ester of α-bromomandelic acid.[3] Kobayashi, et al. used deoxypolymerization of phenylglyoxylic acid with cyclic



Scheme 3.1 Syntheses of poly(mandelic acid). 1) Okada,[3] 2)Smith,[4] 3) Pinkus[5]

phosphates to prepare poly(mandelic acid).[4] Smith and Tighe used the pyridine-catalyzed ring-opening polymerization of 5-phenyl-1,3-dioxolane-2,4-dione to prepare poly(mandelic acid), which despite having the advantage of being a faster reaction than polycondensation, still gave molecular weights less than 4000 g/mol.[5] Pinkus and coworkers prepared poly(mandelic acid) by reacting α-bromophenylacetic acid with triethylamine to give polymers with degrees of polymerization between 12 and 20.[6]

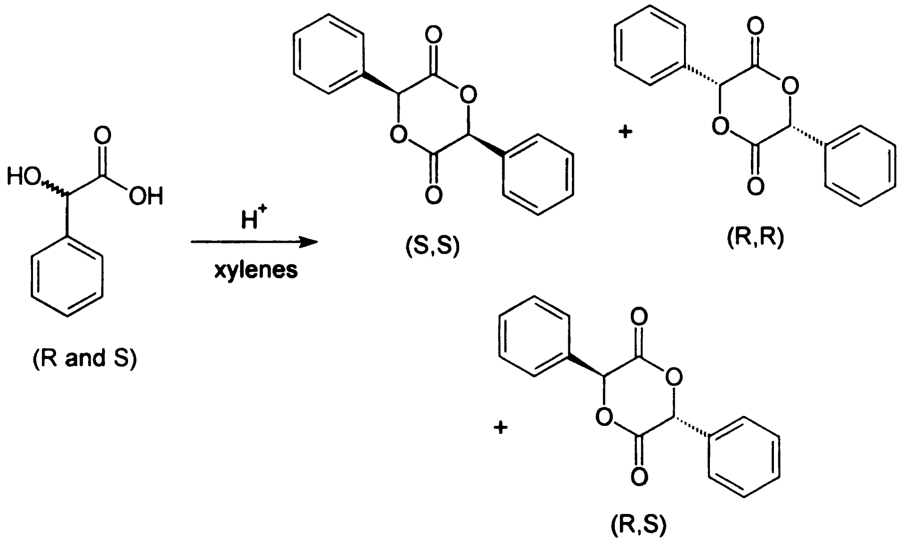
Mandelide, the cyclic dimer of mandelic acid, was synthesized previously.[1,7,8] The dimer structure was analyzed by x-ray crystallography,[7] but was rarely used as a monomer for polymerization. The only previous report of the polymerization of mandelide was as a comonomer polymerized with lactide.[9] The patent that describes this work provides little information regarding the polymer properties.

Little work has been done exploring the properties of polymandelide. The structures of polymandelide and poly(phenyllactide) differ only in that poly(phenyllactide) has a methylene that links the aromatic ring to the polymer backbone, and its removal should increase the T_g and give a biodegradable polymer with properties similar to polystyrene. It was reported that low molecular weight poly(mandelic acid) (2000 g/mol) has a T_g of 75 °C.[10]

Copolymers of mandelic acid and lactic acid are common, but all have relatively low molecular weights (<10,000 g/mol). The glass transition temperature of the copolymers increases with increasing mandelic acid content.[11] These copolymers degrade *in vitro*[10] and *in vivo*,[12,13] but no degradation of poly(mandelic acid) segments was detected during the length of the experiment (15 weeks).[10,12]

3.2 Monomer Synthesis

Previously reported syntheses of S,S-mandelide were all based on acid-catalyzed self-esterification reactions.[1,8,9] The major differences between the methods were the choice of solvent, mandelic acid concentration, and the choice of the acid catalyst. The reported yields were poor, less than 15%. The result for the synthesis of R,R-mandelide was similar, a 9% yield.[14] There are no reported syntheses of R,S-mandelide. The reactions described in the literature were carried out at relatively high concentrations, leading to high yields of low molecular weight oligomers. Whitesell and coworkers produced mandelide unintentionally during the polymerization of mandelic acid by polycondensation.[1]



Scheme 3.2 Synthesis of mandelide

When the same synthetic procedure used for the synthesis of phenyllactide was used for the preparation of mandelide, there was little product after two weeks.

Increasing the reaction temperature by using a higher boiling solvent (xylenes, instead of toluene) increased the rate of product formation, leading to a 50 % yield of mandelide as a mixture of the R,R; S,S; and R,S diastereomers (Scheme 3.2). Reducing the mandelic acid concentration decreased the proportion of oligomers formed, and provided much greater yields of the cyclic dimer than had been previously reported. The R,S diastereomer can be separated from the R,R and S,S isomers by recrystallization from chloroform. Being less soluble, the R,R and S,S isomers crystallize leaving the R,S diastereomer in solution. After removing the R,R and S,S isomers by filtration, the R,S isomer is isolated by crystallization from ethyl acetate and hexanes.

3.3 Polymerization

Solution polymerizations of mandelide gave no polymer, most likely due to low reaction rates, with additional problems caused by mandelide's low solubility in toluene. Solution polymerization of the less hindered phenyllactide also was slow, and transesterification side-reactions prevented formation of high molecular weight products. For these reasons, mandelide was polymerized exclusively using melt polymerization. The R,R and S,S isomers of mandelide decompose at 210 °C instead of melting,[8] making them unsuitable for melt polymerizations. Therefore, all melt polymerizations of mandelide used the R,S diastereomer, which melts at 137 °C.

The kinetics for the $Sn(Oct)_2$/BBA catalyzed melt polymerization of mandelide follow the same trends seen in phenyllactide polymerizations, and reach a limiting conversion of 96%. Polymerizations were run at 180 °C in order to make direct comparisons with phenyllactide polymerizations, although lower temperatures can be used. As might be expected, the rates of mandelide polymerizations are slightly slower due to increased steric hindrance (Figure 3.1). The rate constant for polymerization of mandelide is about 90% of that for phenyllactide polymerization. In addition, a fraction of the R,S monomer epimerized to the R,R and S,S form (approaching 50% of the remaining monomer during the reaction), however, the presence of small amounts of the R,R and S,S diastereomers does not appear to interfere with the polymerization because

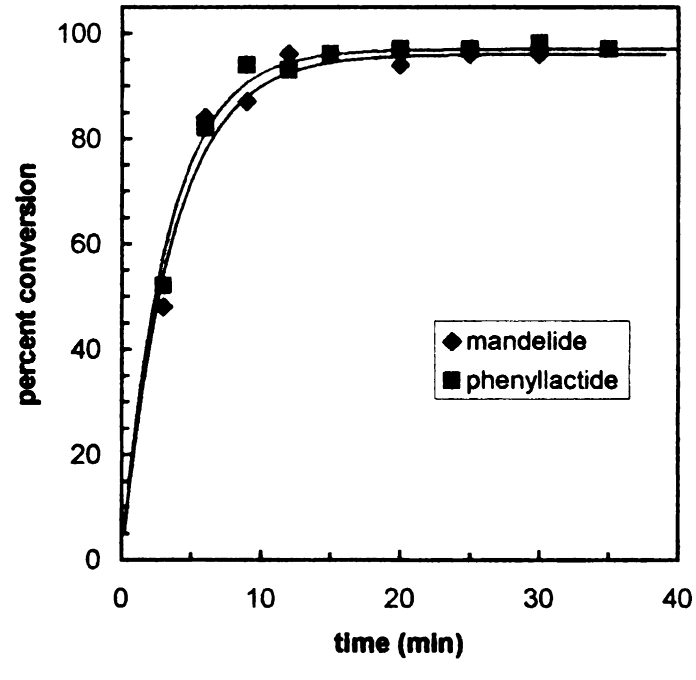


Figure 3.1 Melt polymerization of R,S-mandelide and S,S-phenyllactide at 180 °C using $Sn(Oct)_2$ and BBA with monomer to catalyst and monomer to cocatalyst ratios of 100. The lines are fits using the equilibrium model.

both isomers are soluble in the molten R,S-mandelide.

Unfortunately, while the reactions reach high conversions, the molecular weights were low: typically less than 15,000 g/mol compared to 27,000 g/mol predicted from the monomer to catalyst ratio. Excess initiator in the form of water or alcohol, or a chain transfer step could increase the number of polymer chains formed. Monomer degradation at the high reaction temperature (180 °C) could also lead to reduced molecular weights, but no degradation products were detected by ^{1}H NMR spectroscopy after polymerization or when monomer was heated without catalyst. It is more likely that water is present as an impurity, and it is more difficult to remove from mandelide than from phenyllactide.

Comparisons of a variety of polymerization catalysts gave similar results: the molecular weights were well below the values expected from the monomer to catalyst

catalyst	% conversion	M_n	M_w	PDI
$Sn(Oct)_2$	96	1200	1500	1.29
$Al(OiPr)_3$	25	2400	3000	1.26
$Bi(Oct)_3$	64	7100	15,400	2.15
Ph_4Sn	-	1100	1500	1.33
PbO	-	1100	1500	1.30
$SnCl_2$	-	1000	1400	1.31
$SnBr_2$	76	15,800	42,700	2.69
Zn stearate	51	5400	7400	1.38

Table 3.1 Melt polymerization of R,S-mandelide with a variety of catalysts. All reactions were carried out at 180 °C for two hours with monomer to catalyst ratios of 100.

ratio (Table 3.1). The results parallel those obtained when the same catalysts were used to polymerize phenyllactide. Similar conversions were obtained, except that $Al(OiPr)_3$ was a less efficient catalyst for converting mandelide to polymandelide. It is possible that steric hindrance has a greater effect on $Al(OiPr)_3$ catalyzed polymerizations than those catalyzed by $Sn(Oct)_2$, because $Al(OiPr)_3$ exists as an aggregate in solution. However, the state of aggregation is not known for melt polymerizations. One run with $SnBr_2$ gave the highest molecular weight, but attempts to repeat that result were unsuccessful. This would support the assumption of water in the monomer controlling initiation.

Repeat polymerization reactions at the same monomer to catalyst ratios using the catalysts that gave the best results in terms of molecular weight ($Sn(Oct)_2$, $Bi(Oct)_3$, $SnBr_2$, and Zn stearate), gave higher molecular weights for $Sn(Oct)_2$, $Bi(Oct)_3$, and Zn stearate, but lower molecular weights for $SnBr_2$. These results show that the results vary for reactions run under the same conditions. Polymerizations catalyzed by $Sn(Oct)_2$ were repeated at different monomer to catalyst and monomer to initiator ratios. While larger ratios did produce higher molecular weight materials, the increase in molecular weight was not linearly related to the change in ratios. In other words, doubling the monomer initiator ratio did not double the molecular weight of the polymer (Table 3.2)

The inconsistent results, while frustrating, would be expected if the monomer was impure. The quantity of the impurity could vary from one batch of monomer to the next, giving inconsistent polymerization results. Evacuating the polymerization samples overnight before use showed no significant improvement in molecular weight, but later work by others showed that higher molecular weights are obtained with monomer dried under vacuum for a period of many days.

3.4 Initial Polymer Properties (based on low molecular weight materials)

DSC measurements on a low molecular weight sample of polymandelide indicate a T_g of 96 °C. This increase of 46 °C compared to polyphenyllactide is most likely due to the removal of the methylene group between the polymer chain and the aromatic ring, which reduces some of the flexibility of the polymer backbone. Later work on high molecular weight samples gave a T_g of 100°C. The polymer is amorphous, as expected because epimerization during polymerization renders the polymer atactic.

TGA measurements of polymandelide show that the polymer degrades at a slightly lower temperature than polyphenyllactide. The degradation pathway is believed to be the same for both polymers: intramolecular transesterification (backbiting) to give the cyclic monomer, as demonstrated in the controlled thermal degradation of polyphenyllactide.

The degradation temperature likely is related to the relative volatility of the monomer. Since mandelide is more volatile than phenyllactide, as expected due to its lower molecular weight, the onset for the degradation of polymandelide is ~30 °C below that for polyphenyllactide.

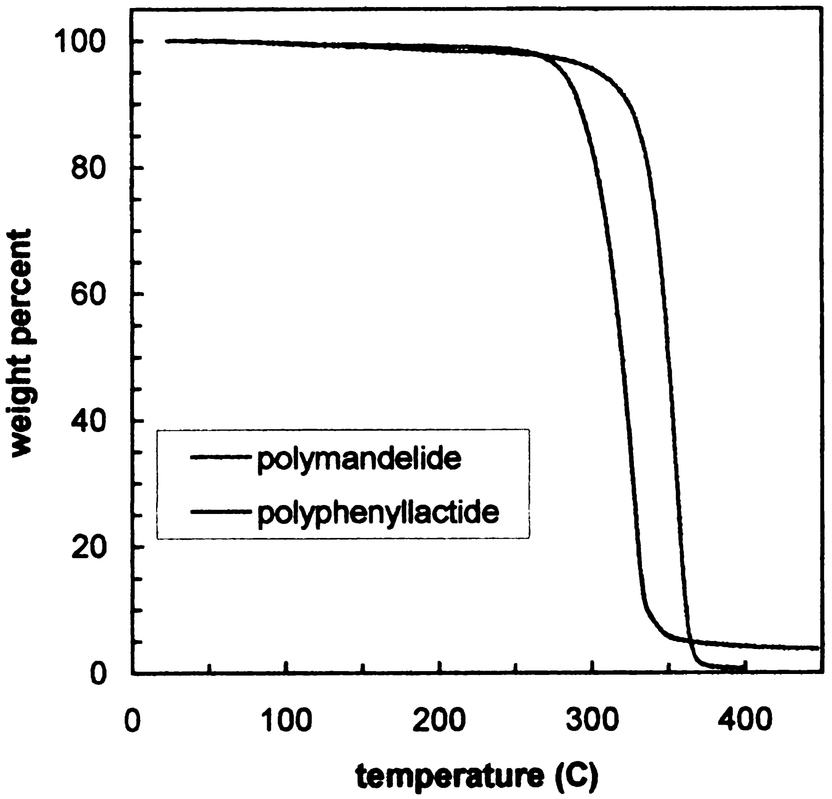


Figure 3.2 TGA of polymandelide and polyphenyllactide. Both scans were carried out under a nitrogen atmosphere at a heating rate of 10 °C/min.

3.5 Copolymers

The principal limitation of polymandelide is its low molecular weight. In hopes of increasing the molecular weight, copolymers of D,L- mandelide and L,L-phenyllactide were synthesized via melt polymerization using $Sn(Oct)_2$ as the catalyst. As expected, the molecular weight of the copolymers decreased with increasing proportions of mandelide in the copolymer (see Table 3.2). Since polyphenyllactide has a lower T_g than polymandelide, the T_g of the copolymers decreased with increasing amounts of the phenyllactide comonomer. By synthesizing copolymers, we were able to obtain materials containing mandelide with higher molecular weights, but they were still below 20,000 g/mol.

PhLD:MD	M_n	M_w	PDI	T_g
0:100	6600	9400	1.42	87
10:90	7600	11,400	1.50	86
25:75	8700	14,200	1.63	79
50:50	8300	13,100	1.57	45
75:25	11,100	19,600	1.77	42
100:0	21,300	46,800	2.20	50

Table 3.2 Copolymerization of R,S-mandelide. All reactions were carried out at 180 °C using $Sn(Oct)_2$ and BBA with monomer to catalyst and monomer to cocatalyst ratios of 100.

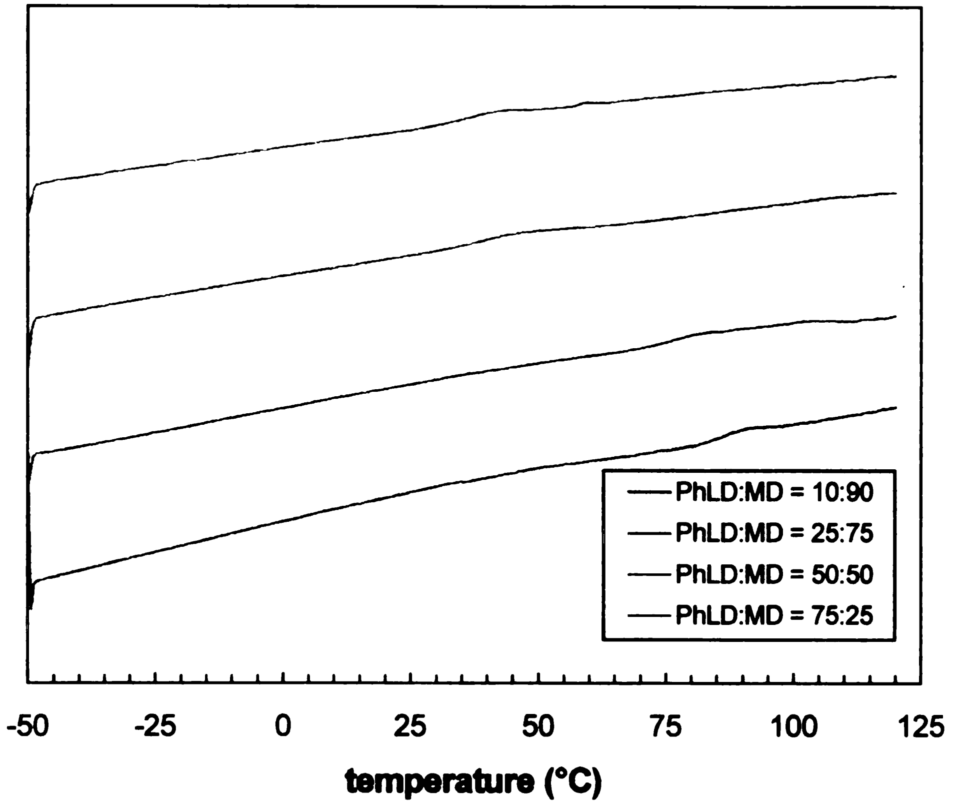


Figure 3.3 DSC of copolymers of R,S-mandelide and S,S-phenyllactide. All were run under He atmosphere with heating rates of 10 °C/min.

3.6 Summary

The properties of polymandelide indicate that it could be a biodegradable substitute for polystyrene. Modification of polyphenyllactide by removing the methylene between the aromatic ring and the polymer chain increases the glass transition temperature by approximately 50 °C, however there are consistent difficulties in obtaining high molecular weight polymandelide. This led us to explore modification of polyphenyllactide by adding substituents to the aromatic ring, which is covered in Chapter 4.

3.7 Works Cited

1) Whitesell, J. K.; Pojman, J. A. *Chemistry of Materials* **1990**, *2*, 248-254.

2) Domb, A. J. *Journal of Polymer Science Part a-Polymer Chemistry* **1993**, *31*, 1973-1981.

3) Okada, T.; Okawara, R. *J. Organometal. Chem.* **1973**, *54*, 149-152.

4) Kobayashi, S.; Yokoyama, T.; Kawabe, K.; Saegusa, T. *Polymer Bulletin* **1980**, *3*, 585-591.

5) Smith, I. J.; Tighe, B. J. *Makromol. Chem.* **1981**, *182*, 313-324.

6) Pinkus, A. G.; Subramanyam, R.; Clough, S. L.; Lairmore, T. C. *Journal of Polymer Science; Part A:Polymer Chemistry* **1989**, *27*, 4291-4296.

7) Lynch, V. M.; Pojman, J.; Whitesell, J. K.; Davis, B. E. *Acta. Cryst.* **1990**, *C46*, 1125-1127.

8) Schoberl, A.; Wiehler, G. *Ann. Chem.* **1955**, *595*, 101-130.

9) Kimura, Y. In *Chem. Abst. 1993, 118, 255577r*: Japan, 1993.

10) Fukuzaki, H.; Aiba, Y. *Makromol. Chem.* **1989**, *190*, 2407-2415.

11) Kylma, J.; Harkonen, M.; Seppala, J. V. *Journal of Applied Polymer Science* **1997**, *63*, 1865-1872.

12) Fukuzaki, H.; Yoshida, M.; Asano, M.; M., K.; Imasaka, K.; Nagai, T.; Mashimo, T.; Yuasa, H.; Imai, K.; Yamanaka, H. *Eur. Polym. J.* **1990**, *26*, 1273-1277.

13) Imasaka, K.; Yoshida, M.; Fukuzaki, H.; Asano, M.; Kumakura, M.; Mashimo, T.; Yamanaka, H.; Nagai, T. *International Journal of Pharmaceutics* **1992**, *81*, 31-38.

14) Toniolo, C.; Perciaccante, V.; Falcetta, J.; Rupp, R.; Goodman, M. *J. Org. Chem.* **1970**, *35*, 6-10.

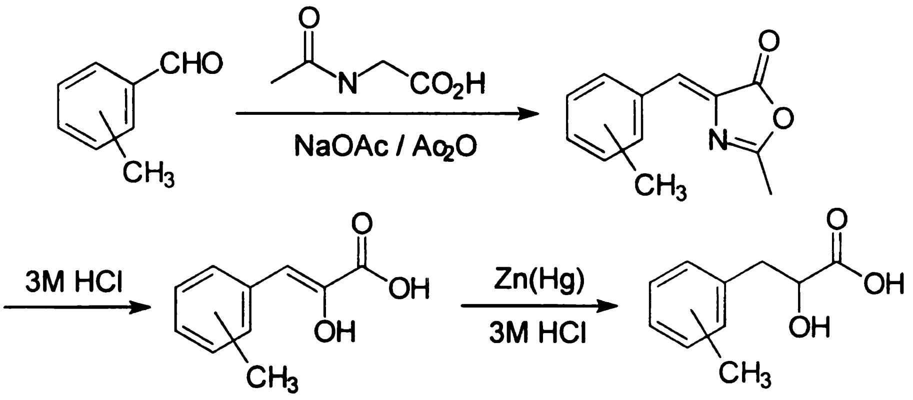
Chapter 4 – Methylphenyllactides

4.1 Introduction

A degradable glassy polymer with properties similar to polystyrene would be a valuable addition to the family of environmentally degradable polymers. Previously, the similarities in structure between polystyrene and poly(phenyllactide) prompted us to investigate poly(phenyllactide) as a potential polystyrene mimic. The polymer proved to be glassy, but the T_g of the polymer was 50 °C, less than the 88 °C predicted by computer modeling and nearly 50 ° below that of polystyrene. One strategy used to raise the T_g in styrenic polymers is to add substituents to the aromatic ring. The addition of polar groups such as Cl and CN tend to increase the T_g of the polymer by increasing dipole-dipole interactions between chains. Small alkyl groups also increase the T_g, in this case by increasing the rotational barriers and decreasing the flexibility of the polymer backbone. Thus, adding a methyl group to the *ortho* position of the polystyrene ring increases the polymer T_g from 109 °C to 136 °C, while substitution at the *meta* and *para* positions has little effect on T_g. Similar trends in T_g might also be obtained in the polyphenyllactide system. Following this analogy, poly(*o*-methylphenyllactide) (or poly(*o*-tolyllactide) and abbreviated as PoTLD) would have the highest T_g.

However, it is possible that the methylene group that connects the aromatic ring and the main polymer chain may minimize the steric effects of *ortho* substitution, resulting in small increases in T_g. Ideally the best analogy to the polymers of substituted phenyllactic acids would be substituted poly(allylbenzene)s, but these polymers have not yet been synthesized. Several aryl-substituted substituted poly(hydroxyalkanoate)s have been reported. Poly(3-hydroxy-5-phenylvalerate) (PHPV) has a T_g of 19 °C and is amorphous even though the polymer backbone is stereochemically regular.[1] Its methyl substituted analog, poly(3-hydroxy-5-(4'-tolyl)valeric acid) (PHTV) has a T_g of 17 °C,[1] demonstrating that a *para* methyl group has little effect on the glass transition temperature. However, unlike PHPV, PHTV is semicrystalline with a T_m of 95 °C.[1] Based on this example, stereoregular PpTLD might exhibit some crystallinity, even though poly(L-phenyllactide) is amorphous.

In this chapter, the preparation of *ortho*, *meta*, and *para*-substituted poly(methylphenyllactide) is described. Like other lactide polymerizations, the polymers were synthesized by the Sn-catalyzed ring opening polymerization of the corresponding cyclic dimer. The monomer synthesis, polymerization, polymer properties, and preliminary degradation data for the polymers will be described.

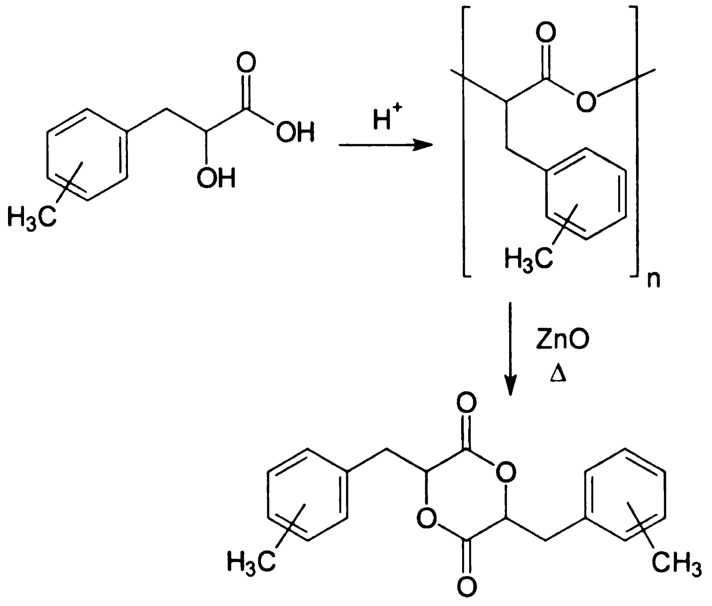


Scheme 4.1 Synthesis of methylphenyllactic acids.

4.2 Synthesis of Substituted Phenyllactic Acids

Methyl substituted phenyllactic acids have not been reported, but Wong and coworkers[2] described a general route to hydroxy and methoxy substituted phenyllactic acids that can be adapted to the synthesis of methyl-substituted phenyllactic acids. Starting from the corresponding benzaldehydes, we prepared the oxazolones using N-acetylglycine (Scheme 4.1). The yields were modest, with the highest yield for the *para* substituted oxazolone (46%) and lowest for the *ortho* derivative (16%). These yields are considerably lower than Wong reported for the methoxy and hydroxy substituted compounds (64-90%). Since the formation of oxazolone involves nucleophilic attack at the benzaldehyde carbonyl, any electron-donating group on the aromatic ring would make the reaction more difficult. While methoxy, hydroxy, and methyl groups are all electron donating, the acidic conditions of the reaction could protonate the hydroxy and methoxy groups. Once protonated, these groups would now be electron withdrawing and make the addition more favorable. Since the methyl group cannot be protonated, it remains electron donating and causes the lower yield. The low yields for the *ortho* substituted product were likely due to the steric hindrance of the *ortho* methyl group. During purification, the *ortho* and *meta* oxazolones often hydrolyzed to give the α-keto acid, the product of the next step in the reaction scheme.

Hydrolysis of the oxazolone in refluxing 3 M HCl overnight gave the acid. For these compounds, the enol is more stable than the keto form because the enol double bond is conjugated with both the aromatic ring and the acid carbonyl. Clemmensen reduction of the crude hydrolyzed product gave the methyl-substituted phenyllactic acid



Scheme 4.2. Synthesis of methylphenyllactide *via* cracking

in high yield (80-90%). The *meta* and *ortho*-substituted compounds were difficult to purify due to formation of oligomers (frequently near 50 %). These compounds were used for the formation of the cyclic dimer without further purification.

4.3 Synthesis of Phenyllactides

There are two general routes to the dimer, acid-catalyzed condensation of the α-hydroxyphenyllactic acid and thermal cracking of low molecular weight oligomers and isolation of the more volatile cyclic dimer by distillation. The former method is slow but can be carried out without loss of stereochemical purity, while the latter is fast but is always accompanied by some degree of racemization. The starting α-hydroxyphenyllactic acids were racemic, and thus avoiding racemization was not a consideration in this case. This also allowed us to use unpurified methylphenyllactic acid for the preparation of the monomers because the major impurity was the corresponding oligomer.

The hydroxyacid was oligomerized (Scheme 4.2) by stirring in 2-5 mL of 3M HCl at 120 °C overnight. ZnO was added to the oligomer, and after heating the mixture at 220 to 240 °C under vacuum, the crude lactide was isolated by distillation/sublimation as it formed. The crude lactide was purified by washing with aq. $NaHCO_3$ and recrystallized from ethyl acetate/hexanes. Purification of the *ortho* and *meta*-methylphenyllactides required column chromatography using silica gel eluted with 75/25 hexanes/ethyl acetate to produce dimer suitable for polymerization. Typical yields were 50 % for pTLD, with lower yields for oTLD and mTLD (20-40%) because of the extra purification step.

Self-esterification, used previously to prepare phenyllactide and mandelide, was also used for the synthesis of the *para*-substituted dimer. Refluxing the hydroxyacid for seven days in xylenes with a catalytic amount of *p*-toluenesulfonic acid gave the dimer in 36% yield, compared to a 50 % yield via the thermal route. Monomer from both methods behaved identically in polymerizations.

4.4 Polymerizations

Since only melt polymerizations of phenyllactide gave high molecular weight materials in reasonable times, melt polymerization was used exclusively for the polymerization of the methylphenyllactides. Initially, the molecular weights of the polymers were consistently lower than those obtained for phenyllactide under the same

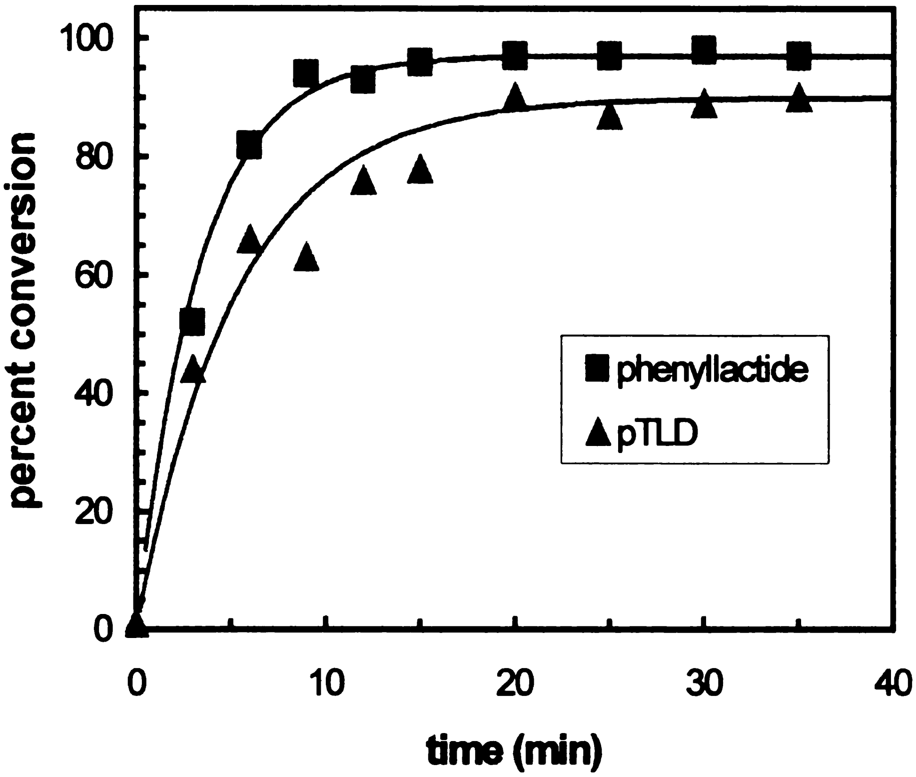


Figure 4.1. Melt polymerization kinetics of pTLD using Sn(Oct)$_2$ and BBA at 180 °C. The monomer to catalyst and monomer to cocatalyst ratios were 100.

conditions. Phenyllactide prepared via the oxazolone (beginning with benzaldehyde) also gave low molecular weights, indicating residual impurities from the monomer synthesis. After purification by column chromatography, the monomers gave polymers that were close to the molecular weights predicted by the monomer/initiator ratios.

Kinetic results for the melt polymerization of pTLD using $Sn(Oct)_2$ and BBA are shown in Figure 4.1. The propagation rates were extracted from pTLD and phenyllactide polymerizations run under identical conditions using an equilibrium model for the polymerization, and indicate that the polymerization rate for pTLD is 60% of the rate for phenyllactide. In addition, the reaction equilibrates at 90% conversion, compared to 97% with PhLD. Kinetic experiments were not run for the ortho and meta methylphenyllactides, but we expect similar behavior, with slower rates likely for the *ortho* compound because of increased steric hindrance.

4.5 Polymer Properties

Differential scanning calorimetry shows that all three poly(methylphenyllactide)s are amorphous, which is expected because the polymers were made from racemic lactides. Polylactide made from racemic monomer is also amorphous. PpTLD has the highest T_g at 59 °C, followed by PoTLD (51 °) and PmTLD (42 °C). Having the methyl group in the *para* position inhibits bond rotation the most, which is why the *para* substituted polymer has the highest T_g.

Thermogravimetric analysis shows that PpTLD has nearly the same degradation temperature as PPhLD (Figure 4.2). Since the degradation mechanism for degradation of

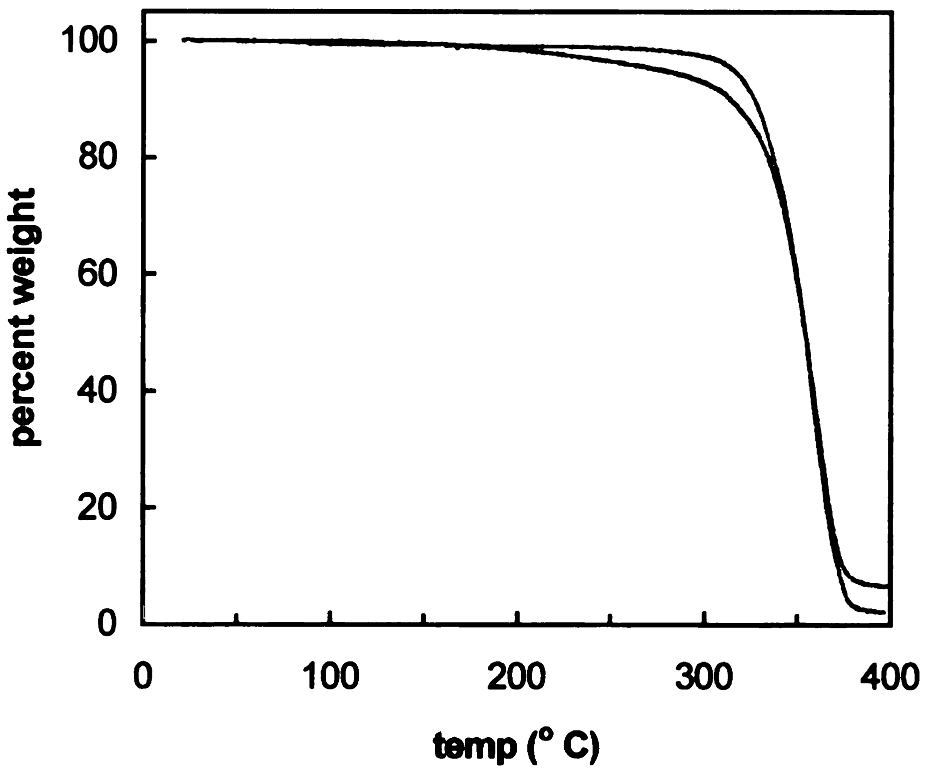


Figure 4.2. TGA of poly(methylphenyllactide) (blue) and polyphenyllactide (red). The TGA scans were run under nitrogen with a heating rate of 10 °C/min.

substituted lactides is depolymerization, the onset for degradation should be related to the volatility of the monomers. Phenyllactide and methylphenyllactide have similar volatilities, and thus have similar degradation profiles.

4.6 Degradation

Degradation experiments were run on poly(*p*-methylphenyllactic acid), and reveal similar degradation rates for PPhLD and PpTLD. The data were fit to a degradation model based on random chain scission, and the degradation rates were extracted from the fit. The relative rates were 9.8×10^{-4} for PPhLD and 1.2×10^{-3} for PpTLD. The results of the weight loss experiments were very different. The weight of the PPhLD samples decreased to nearly 0 at 60 days, while the PpTLD samples retained >80% of their weight. These results can be explained by the additional methyl group of PpTLD, which increases the hydrophobicity of the polymer and decreases the solubility of low molecular weight oligomers in the buffer solution. In addition, the initial molecular weight of PpTLD was higher than the initial molecular weight of PPhLD, meaning that PPhLD would require fewer breaks in the polymer chain to become soluble in the buffer solution. The initial M_n of the PpTLD was 63,600 g/mol and the initial M_n of PPhLD was 46,500 g/mol. Thus, the mass losses are smaller for PpTLD even though the rates for the decrease in molecular weight of PpTLD and PPhLD are similar. It is expected that the *ortho* and *meta* substituted polymers would degrade faster than the para substituted because of the lower glass transition temperatures. The T_g of the para substituted

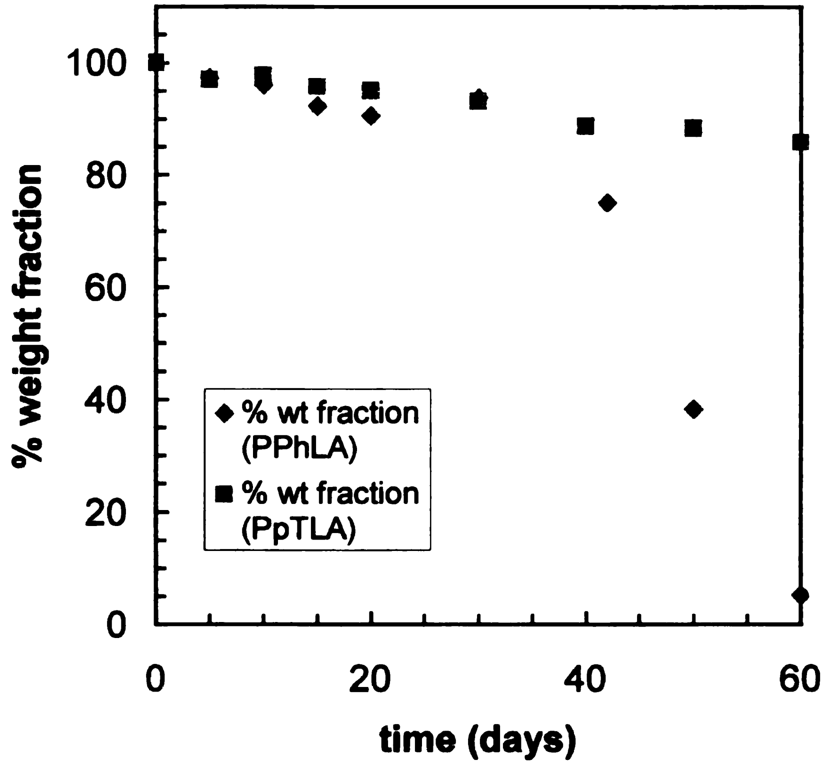


Figure 4.3. Weight loss during the degradation of PpTLD compared to PPhLD. Both degradations were carried out in a phosphate buffer solution at a pH of 7.4 and a temperature of 55 °C.

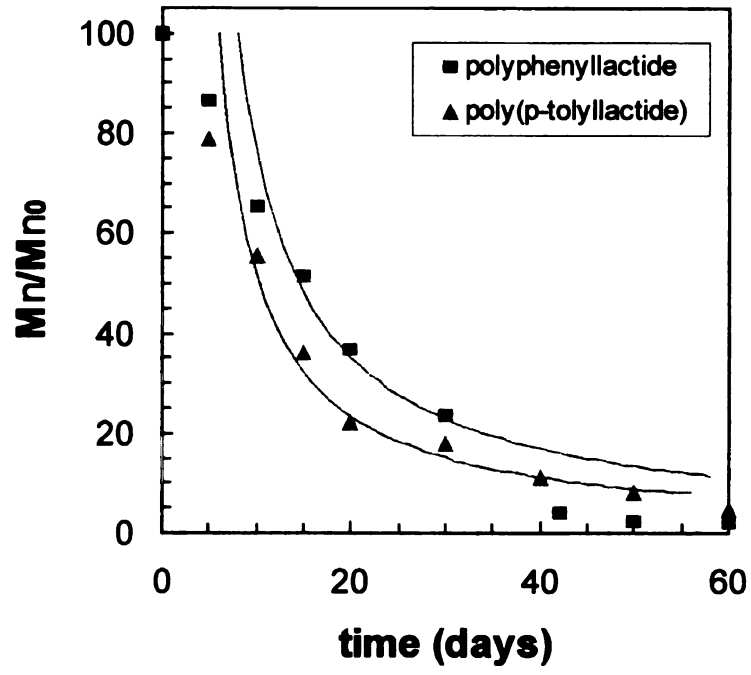


Figure 4.4. Decrease in molecular weight decrease during the degradation of PpTLD and PPhLD. The degradations were carried out at 55 °C in phosphate buffer solutions at a pH of 7.4.

polymer is slightly above the temperature of the experiment, causing the degradation to occur more slowly than polyphenyllactide. These factors combined cause PpTLD to lose weight more slowly than PPhLD (Figures 4.3). The rates of molecular weight decrease for both polymers are nearly the same (Figure 4.4).

4.7 Summary

Based on this work with methyl-substituted phenyllactides, we have demonstrated that substitutions on the aromatic ring can be used to modify the physical properties of poly(phenyllactic acid). In addition, the choice of the position for the substituent also affects properties. Unlike poly(methylstyrene), the *ortho* substituted polymer has the lowest T_g instead of the highest. The additional methylene between the ring and the chain changes how the substitution location affects physical properties, such as glass transition temperatures.

4.8 Works Cited

1) Curley, J. M.; Hazer, B.; Lenz, R. W.; Fuller, R. C. *Macromolecules* **1996**, *29*, 1762-1766.

2) Wong, H. N. C.; Xu, Z. L.; Chang, H. M.; Lee, C. M. *Synthesis* **1992**, 793-797.

Chapter 5 – Conclusions

This work presents modifications on the basic structure of polylactides by adding substituents to the side chain in order to modify the physical properties. By choosing aromatic substituents, we expect to be able to obtain a biodegradable polymer with properties similar to polystyrene. The basic property we have measured is the glass transition temperature, although the degradation rates were also studied. The T_g has a large effect on the potential uses for a polymer. For example, if one wishes to use polylactide in place of a Styrofoam cup, the addition of a hot beverage such as coffee will increase the temperature of the cup above the T_g of polylactide, causing the cup to soften and be useless. If the addition of an aromatic group to polyethylene increases the T_g for polystyrene, one would expect that an aromatic group added to polylactide would also increase the T_g.

The polymer initially chosen was polyphenyllactide. The major difference between our analogy using polyethylene and polystyrene is that there is a methylene group between the aromatic ring and the main polymer chain. This makes the polymer more similar to poly(allyl benzene). While polystyrene has a T_g of 100 °C, poly(allyl benzene)'s is 60 °C. Based on this information, it is not surprising that the T_g of polyphenyllactide (50 °C) is not substantially different than that of polylactide.

What may not have been expected is that poly(L-phenyllactide) is amorphous, while poly(L-lactide) is crystalline. This is explained by the small, but significant, amount of epimerization occurs during the polymerization of phenyllactide. Less epimerization typically occurs during the polymerization of L-lactide because the reaction is run at a lower temperature. The high melting point of L-phenyllactide necessitates a higher temperature during polymerization (180 °C), increasing the amount of epimerization.

The next logical action in developing a polystyrene-like lactide-based polymer would be to remove the methylene between the aromatic ring and the polymer chain, producing polymandelide. While polymandelide does have a higher glass transition temperature of nearly 100 °C, there was some difficulty in obtaining high molecular weight materials.

To work around the problems with mandelide polymerizations and to also give greater possibilities for modification, we chose to work with substituted phenyllactides. The addition of a methyl group to the aromatic ring provides a slight modification, producing relatively minor changes to the T_g relative to that of polyphenyllactide (± 10 °C). We also determined that the position of the methyl group was important in determining the T_g. Poly(*o*-methylphenyllactide) has a glass transition temperature nearly the same as polyphenyllactide, while poly(*m*-methylphenyllactide) has a T_g of 42 °C and poly(*p*-methylphenyllactide) has a T_g of 59 °C. While not quite as high as polystyrene or polymandelide, this proves that the addition of substituents to the aromatic ring of polyphenyllactide can be used to further modify the properties of polylactide.

Based on this work, one would expect that continued modification by the addition of a larger group, such as *t*-butyl would increase the glass transition even further. Because substituted phenyllactides are relatively easily synthesized, they are likely to have the most flexibility for modification in order to obtain a variety of polymers with varying properties. Another possibility is the use of reactive groups, such as bromine, which can be used to modify the material after polymerization. For example, one possibility would be to copolymerize *p*-bromophenyllactic acid with lactic acid, then replace the bromine with a crosslinkable group to produce an even wider variety of materials. A large number of options for modifications to the basic structure of polyphenyllactide are available.

Experimental

General. L-Phenyllactic acid was purchased from Aldrich and used as received. THF and toluene were distilled over CaH_2, then distilled under nitrogen from sodium benzophenone ketyl. CH_2Cl_2 was distilled over CaH_2. All reactions requiring anhydrous or inert conditions were carried out in oven-dried glassware under a positive atmosphere of argon or nitrogen. Solutions or liquids were introduced using oven-dried syringes or cannula through rubber septa. All reactions were stirred magnetically using Teflon-coated stir bars unless otherwise noted. For reactions requiring heating, electrically heated silicon oil baths were used, and the stated reaction temperature is either the temperature of the bath or the reflux temperature. In the cases requiring -78°C cooling, the reactions were chilled with a dry ice/acetone bath. Organic solutions obtained after an aqueous work-up were dried over $MgSO_4$. Removal of solvents was accomplished using a Büchi rotary evaporator at water aspirator pressure. Proton nuclear magnetic resonance spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Gemini 300 or VXR 500S spectrometer. ^1H NMR spectra were recorded at 300 and 500 MHz. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded at 75 MHz and chemical shifts are reported (as ppm) relative to $CDCl_3$ ($\delta = 77.0$ ppm). Melting points were taken using an Electrothermal Melting Point Apparatus. Low resolution electron impact (EI) mass spectra (MS) were recorded on a Finnigan 4000 mass spectrometer and high resolution mass spectra (HRMS) were recorded on Kratos MS50 or MS25 mass spectrometers. Molecular weights were obtained by gel permeation chromatography (GPC) using a PLgel 20μ Mixed A column from Polymer Laboratories with THF at a flow rate of 1.0 mL/min and are reported relative to polystyrene standards. Detection was by a Waters R401 Differential Refractometer, Waters 996 Photodiode Array, or Waters W410 Differential Refractometer operating at 35 °C with a column oven heated to the same temperature. Thermogravimetric analysis (TGA) results were obtained from a Perkin Elmer TGA7 with a heating rate of 10 °C/min in a nitrogen atmosphere unless otherwise stated. Differential scanning calorimetry (DSC) was performed in aluminum pans under a helium atmosphere on a Perkin Elmer DSC7 with a heating rate of 10 °C/min. The instrument was calibrated with indium and cooled with liquid nitrogen.

Synthesis of L,L-Phenyllactide. L-Phenyllactic acid (3.69 g, 12.5 mmol) and a catalytic amount of *p*-toluenesulfonic acid (0.02 g, 0.1 mmol) were dissolved in toluene (600 mL). The solution was refluxed for eight days, removing the water by a Dean Stark trap filled with 4Å molecular sieves. After washing three times with saturated aqueous $NaHCO_3$, the solvent was removed and the crude crystals were recrystallized twice from ethyl acetate and hexanes to afford the dimer (1.40 g, 42%) as white crystals. ^1H NMR: 3.0 (dd, J=8, 15 Hz, 1 H), 3.4 (dd, J=4, 15 Hz, 1H), 5.0 (dd, J=4, 8 Hz, 1 H), 7.2-7.4 (m, 5 H). ^{13}C NMR: 36.6, 76.6, 127.5, 128.7, 129.7, 134.6, 165.5. MS *m/z* (rel inten) EI 91 (100), 104 (15), 131 (11), 148 (25), 161 (10), 296 (M^+, 10), 297 ($M+H^+$, 6); HRMS (EI) calcd. for $C_{18}H_{16}O_4$ (M^+) 296.1049, found 296.1048. mp 165 °C.

Catalyst solutions. Commercially available (Aldrich) aluminum isopropoxide ($Al(OiPr)_3$) was distilled under reduced pressure and then dissolved in freshly distilled toluene. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) (Aldrich) and bismuth(III) 2-ethylhexanoate ($Bi(Oct)_3$) (Alfa Aesar) were dissolved in freshly distilled toluene before use.

Tetraphenylporphyrin aluminum methoxide was prepared following the procedure outlined by Endo, Inoue, and Aida.[1] 4-*t*-butylbenzyl alcohol (BBA) was purchased from Aldrich and dried over 4 Å molecular sieves, then dissolved in distilled toluene before use.

Solution Polymerization - General Procedure. To a custom-made flask containing a glass-covered stir bar, L,L-phenyllactide (0.50 g, 1.7 mmol) was added and the apparatus was assembled and evacuated overnight with a diffusion pump. The empty flask was filled with argon and 17 mL of freshly distilled toluene was added. Styrene (0.5 mL, 4 mmol) was added and polymerization initiated with 0.25 mL of 1.6 M *n*BuLi (0.40 mmol). After one hour, the solution was degassed and the solvent was vacuum transferred to the flask containing the phenyllactide monomer. Upon completion of the transfer the solution was placed under argon and heated to 50 °C. $Al(OiPr)_3$ (207 µL of a 27.0 mM solution in toluene) was added by syringe. The polymerization was terminated with an excess of 2 N HCl (1 mL, 2.0 mmol). The polymer solution was washed with water until neutral and the solvent removed. The polymer obtained had too low a molecular weight to be precipitated. ^{1}H NMR: 3.0 (dd, J=8, 14 Hz, 1 H), 3.2 (dd, J=4, 14 Hz, 1 H), 5.3 (dd, J=4, 8 Hz, 1 H), 7.0-7.3 (m, 5 H).

For solution polymerization in THF, a similar procedure was followed except the styrene was polymerized at -78 °C for 2 hours.

Melt Polymerization - General Procedure. A Schlenk flask containing L,L-phenyllactide (0.25 g, 0.85 mmol) was evacuated and refilled with argon three times, and then $Sn(Oct)_2$ (49 µL of a 51.5 mM solution in toluene) was added. The flask was placed under vacuum and heated to 180 °C. Upon completion of the reaction, the flask was allowed to cool and the polymer dissolved in toluene (2 mL), then precipitated twice into cold methanol to give 0.23 g (92 %) of polyphenyllactide.

Melt Polymerization - Catalyst study. L,L-Phenyllactide (100 mg, 0.34 mmol) was added to glass tubes sealed at one end. Inside a drybox, catalyst was added to give a monomer:catalyst mole ratio of 100:1. Vacuum adapters were connected to the tubes, the tubes were connected to a vacuum line, and evacuated. The tubes were then sealed and placed into an oil bath heated to 180 °C. After two hours, the tubes were removed and placed in cool water to quench the reaction. The tubes were broken open and the contents dissolved in THF. The solvent was then removed to yield the polymer.

Melt Polymerization - Kinetics. The procedure described in the catalyst study was followed using 50 mg of L,L-phenyllactide (0.17 mmol) and $Sn(Oct)_2$ as the catalyst for all samples in a molar ratio of 100:1 (monomer: catalyst). A tube was removed at the desired times and handled as outlined previously.

Solution Polymerization with Added Alcohol. The same procedure as outlined above was followed, except that a solution of 4-*t*-butylbenzyl alcohol (BBA) in toluene was added to the reaction flask before the addition of catalyst to give a monomer: alcohol mole ratio of 100:1.

Melt Polymerization with Added Alcohol - Catalysts. The procedure described above was followed, with a solution of 4-*t*-butylbenzyl alcohol in toluene added to give a monomer: alcohol mole ratio of 100:1. The reaction tube was then evacuated and sealed.

Melt Polymerization with Added Alcohol - Kinetics. The procedure described above was followed, with 4-*t*-butylbenzyl alcohol at amolar ratio of 100:1 (monomer:

alcohol). A solution of the alcohol in toluene was added to the reaction tube, then evacuated and sealed.

Synthesis of Mandelide. R,S-Mandelic acid (6.03 g, 39.7 mmol) and a catalytic amount of *p*-TsOH (0.20 g, 1.2 mmol) were dissolved in xylene (600 mL). The solution was refluxed for six days, removing the water by a Dean Stark trap filled with 4Å molecular sieves. The solution was then washed three times with saturated aqueous $NaHCO_3$ and the solvent removed. The crude solid was recrystallized repeatedly from ethyl acetate and hexanes to separate the diastereomers. Combined yield of the R,R and S,S isomers : 1.3 g (47 %). mp 193 °C (decomp). ^1H NMR: 6.1 (s, 1 H), 7.2-7.3 (m, 5 H). Yield of R,S isomer: 1.5 g (53 %). mp 135 °C. ^1H NMR: 5.9 (s, 1 H), 7.4-7.5 (m, 5 H).

Melt Polymerization of Mandelide - Catalyst Study. The procedure used for L,L-phenyllactide was followed.

Melt Polymerization of Mandelide - Added Alcohol. To a Schlenk flask containing R,S-Mandelide (0.5075 g, 1.89 mmol), $SnBr_2$ was added to give a monomer to catalyst ratio of 400:1. One equivalent of distilled methanol was then added. The flask was moved to a vacuum line, placed under a positive pressure of argon, and heated with an oil bath at 180 °C. After four hours, the flask was removed and allowed to cool. The product was analyzed without purification.

Melt Polymerization of Mandelide – Kinetics. The procedure used for phenyllactide with *t*-butylbenzyl alcohol was followed.

Synthesis of (TPP)Al-OCH$_3$ Initiator. Tetraphenylporphyrin was obtained from C.K. Chang and was used without further purification. The catalyst was prepared following the procedure outlined by Endo, Inoue, and Aida.[1]

Synthesis of Oxazolones.

2-Methyl-4(p-methylbenzal)-5-oxaazolone. *p*-Tolualdehyde (12.5 g, 104 mmol), N-acetylglycine (8.26 g, 71.2 mmol), acetic anhydride (17.55 g, 172.1 mmol), and sodium acetate (4.94 g, 60.2 mmol) were added to a 250-mL round bottom flask fitted with a condenser. The mixture was heated at 100 °C in an oil bath for 5 hours, and then 50 mL of ice water was added. The crude product was collected by filtration, washed four times with 50 % aq. ethanol, and dried overnight under vacuum. After recrystallization from acetone, chloroform and petroleum ether, the oxazolone was obtained in 46.1 % yield (6.60 g). mp 135-136 °C (lit[17] 133-135 °C). ^{1}H NMR: δ 2.38 (s, 6H), 7.11 (s, 1 H), 7.23 (d, J=8 Hz, 2 H), 7.26 (d, J=8 Hz, 2 H). ^{13}C NMR: δ 15.7, 21.7, 129.7, 130.5, 131.7, 132.2, 142.0, 165.5, 168.0. Elemental analysis: calc'd 71.33% C, 5.49% H, 6.94% N. Found: 71.16% C, 5.75% H, 6.75% N.

2-Methyl-4(m-methylbenzal)-5-oxazolone. Yield 36 %. mp 106-108 °C ^{1}H NMR: δ 2.39 (s, 6 H), 7.10 (s, 1 H), 7.23 (d, J=7 Hz, 1 H), 7.32 (t, J=8 Hz, 1 H), 7.87 (d, J=9 Hz, 2 H). ^{13}C NMR: δ 15.7, 21.4, 128.8, 129.4, 131.8, 132.1, 12.3, 132.7, 133.0, 138.6, 165.9, 167.9. Elemental analysis: calc'd (for the hydrolyzed oxazolone) 65.72% C, 5.98% H, 6.39% N. Found: 66.19% C, 6.02% H, 6.20% N.

2-Methyl-4(o-methylbenzal)-5-oxazolone. Yield 16.3 %. mp 106-108 °C. ^{1}H NMR: δ 2.39(d, J=1 Hz, 3 H), 2.47 (s, 3 H), 7.20-7.31 (m, 3 H), 7.42 (s, 1 H), 8.51-8.54 (m, 1 H). ^{13}C NMR: δ 15.7, 20.0, 126.5, 128.4, 130.7, 131.0, 131.6, 131.7, 132.5, 139.6, 166.3, 167.9. Elemental analysis: calc'd (for the hydrolyzed oxazolone) 65.72% C, 5.98% H, 6.39% N. Actual: 66.73% C, 5.92% H, 6.39% N.

Synthesis of Methylphenyllactic Acids.

p-Methylphenyllactic acid. 2-Methyl-4(*p*-methylbenzal)-5-oxazolone (13.76 g, 68.5 mmol) was added to a 1-L round bottomed flask and 3 M HCl (500 mL) was added. A condenser was attached and the reaction refluxed overnight. Zn (62.0 g, 0.95 mol) and $HgCl_2$ (10.00 g, 36.8 mmol) were added to a separate flask, 3 M HCl (12 mL) and water (100 mL) were added and the mixture was stirred for five minutes to form the Zn(Hg) amalgam. The solution was drained off and the amalgam rinsed with water. The amalgam was the added to the hydrolyzed oxazolone and refluxed for 4 hours. The reaction mixture was filtered while hot into a separatory funnel, extracted five times with 100 mL portions of ethyl acetate, and the solvent removed. Recrystallization of the crude product from ethyl acetate and hexanes yielded 10.60 g of *p*-methylphenyllactic acid (86.0 %). mp 98-100 °C. ^{1}H NMR: δ 2.31 (s, 3 H), 2.95 (dd, J=7, 14 Hz, 1 H), 3.15 (dd, J=4, 8 Hz, 1 H), 4.48 (dd, J=4, 7 Hz, 1 H), 7.12 (s, 4 H). ^{13}C NMR: δ 21.1, 39.7, 71.0, 129.3, 129.4, 132.5, 136.8, 178.2.

m-Methylphenyllactic acid. mp 70-72 °C. ^{1}H NMR: δ 2.32 (s, 3 H), 2.94 (dd, J=7, 14 Hz, 1 H), 3.16 (dd, J=4, 14 Hz, 1 H), 4.49 (dd, J=4, 7 Hz), 1 H), 7.02-7.22 (m, 4 H). ^{13}C NMR: δ 21.4, 40.1, 71.0, 126.4, 128.0, 128.5, 130.3, 135.7, 138.3, 178.4.

o-Methylphenyllactic acid. mp 70-73 °C. ^{1}H NMR: δ 2.45 (s, 3 H), 2.94 (dd, J=9, 14 Hz, 1 H), 3.26 (dd, J=4, 14 Hz, 1 H), 4.47 (dd, 4, 9 Hz, 1 H), 7.13-7.21 (m, 4 H). ^{13}C NMR: δ 19.6, 34.5, 70.6, 126.1, 127.2, 130.0, 130.6, 134.5, 136.9, 178.6.

Synthesis of Methylphenyllactides.

p-Methylphenyllactide. *p*-Methylphenyllactic acid (0.515g, 2.86 mmol) was added to a 50-mL round bottom flask and heated to 120 °C in an oil bath for 2 days. The flask was removed from the oil bath and ZnO (0.05 g, 0.61 mmol) was added. The flask was connected to a Kugelrohr distillation apparatus and heated to 220 °C. The crude product was dissolved in toluene and washed three times with aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvent removed. The residue was recrystallized twice from ethyl acetate and hexanes to give 0.233 g (50.2 %) of the product as a mixture of the RR, SS, and RS isomers. mp 157-164 °C. ^{1}H NMR: δ 2.30 (s, 6 H), 2.31 (s, 6 H), 2.93 (dd, J=8, 15 Hz, 2 H), 3.12 (d, J=5 Hz, 4 H), 3.29 (dd, J=4, 15 Hz, 2 H), 4.24 (t, J=5 Hz, 2 H), 4.97 (dd, J=4, 8 Hz, 2 H), 6.99-7.12 (m, 16 H). ^{13}C NMR: δ 21.1, 36.2, 38.0, 76.7, 76.9, 129.4, 129.6, 129.8, 130.6, 131.6, 137.1, 137.6, 165.0, 165.6. Elemental analysis: 74.04% C, 6.22% H. Actual: 74.14% C, 6.33% H.

m-Methylphenyllactide. *m*-Methylphenyllactide was prepared and purified following the procedure used for the *para* compound except that before recrystallization, the crude lactide was further purified using a silica gel column eluted with 25% ethyl acetate/75% hexanes. mp 121-123 °C. ^{1}H NMR: δ 2.27 (s, 6 H), 2.32 (s, 6 H), 2.90 (dd, J=8, 15 Hz, 2 H), 3.12 (t, J=4 Hz, 4 H), 3.30 (dd, J=4, 15 Hz, 2 H), 4.24 (t, J=5 Hz, 2 H), 5.00 (dd, J=4, 8 Hz, 2 H), 7.02-7.22 (m, 16 H). ^{13}C NMR: δ 21.4, 36.7, 126.7, 128.2, 128.6, 130.4, 134.6, 138.4, 165.5. Elemental analysis: 74.04% C, 6.22% H. Actual: 74.16% C, 6.46% H.

o-Methylphenyllactide. *o*-Methylphenyllactide was synthesized and purified following the same procedure as that used for the *para* compound, except that before recrystallization, the crude lactide was purified further using a silica gel column eluted with 25% ethyl acetate/75% hexanes. mp 127-131 °C. ^{1}H NMR: δ 2.23 (s, 6 H), 2.32 (s, 6 H), 3.02 (dd, J=9, 15 Hz, 2 H), 3.12 (dd, J=6, 15 Hz, 2 H), 3.32 (dd, 4, 15 Hz, 2 H), 3.44 (dd, J=4, 15 Hz, 2 H), 4.35 (dd, J=4, 6 Hz, 2 H), 4.98 (dd, J=4, 9 Hz, 2 H), 7.14-7.24 (m, 16 H). ^{13}C NMR: δ 19.5, 19.6, 33.6, 35.2, 76.4, 76.8, 126.3, 126.5, 127.6, 127.7, 130.2, 130.3, 130.6, 130.9, 132.5, 133.3, 136.7, 137.2, 165.2, 165.8. Elemental analysis: 74.04% C, 6.22% H. Actual: 73.91 % C, 6.50% H.

Melt Polymerization - Catalyst study. Methylphenyllactide (100 mg) was added to glass tubes sealed at one end. Inside a drybox, the catalyst was added to give a molar ratio of 100:1 (monomer: catalyst). Vacuum adapters were connected, the tubes connected to a vacuum line, and evacuated. A solution of *t*-butylbenzyl alcohol (BBA) in toluene was added to give a monomer:alcohol mole ratio of 100:1, and the solvent was removed by vacuum. The tubes were then sealed and placed into an oil bath heated to 180 °C. After two hours, the tubes were removed and placed in cool water to quench the reaction. The tubes were broken open and the contents dissolved in THF. The polymer was isolated by removal of the solvent.

Melt Polymerization - Kinetics. The procedure used for the catalyst study was followed using 50 mg of monomer, $Sn(Oct)_2$ as the catalyst,and *t*-butylbenzyl alcohol as the cocatalyst for all samples at a molar ratio of 100:1 (monomer: catalyst/ monomer: alcohol). A tube was removed at the desired times and handled as outlined previously.

Melt Depolymerization. A sample (100 mg) of well-purified polyphenyllactic acid (containing no residual monomer as detected by ^{1}H NMR) was added to glass tubes sealed at one end. Vacuum adapters were connected, the tubes moved to a vacuum line, and evacuated and filled with argon three times. $Sn(Oct)_2$ and BBA solutions were added to give the equivalent of a monomer to catalyst ratio of 100, assuming all of the polymer is converted to monomer. The tubes were then sealed and placed into an oil bath heated to 180 °C. Tubes was removed at the desired times and handled as outlined in the polymerization procedure.

Hydrolytic Degradation of Polymers. A sample of approximately 50 mg of the polymer that had been well purified was accurately weighed and the weight recorded. The sample was then placed inside a test tube with a screw cap and 15 mL of pH of 7.4 phosphate buffer solution was added. The degradation was carried out at 55 ± 0.2 °C. At the desired time, the sample was removed, rinsed repeatedly with distilled water and dried under vacuum overnight. The sample was weighed to determine the weight loss and the molecular weight was determined by GPC.

Works Cited

1) Endo, M.; Aida, T.; Inoue, S.; **1987**, *20*, 2982-2988.